Newer Treatment Horizons of Diabetic Peripheral Neuropathy: From Bench to Bed Side

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Abstract

Diabetic peripheral neuropathy (DPN) is most crippling disease worldwide, and its incidences are increasing with rising prevalence of diabetes mellitus prevalence among the population. It is causing substantial morbidity and in severe cases mortality along with posing economic burden. DPN needs a new understanding of its mechanism and associated clues for pathogenesis. Many biochemical pathways contribute in progression of DPN such as polyol, hexosamine, advanced glycation end product pathway etc. Besides the understanding, newer therapies and interventions are emerging, as a strong tool for supporting patient’s healthcare. Apart from conventional therapies, new therapeutic approaches need to be explored. The present review is focused on the detailed mechanism of DPN and newer therapeutic tools for the treatment of DPN in clinics.

1. Introduction

The nervous system plays a vital and crucial role in maintaining human biological events such as cognition and individual cell function. Neuropathy is characterized by pathological, cellular and non-cellular changes in peripheral nerves (PN). PN degeneration has found increased affecting 2.8% of trauma subjects annually [1]. A statistical number quoted by the previously published literature showed that in general population the prevalence of about 8% and the counting increases up to 15% in the population over the age of 40 years [2]. DPN is a common disorder with prevalence rate ranging from 10-26% in the adult population with diabetes mellitus (DM). DPN is associated with de-myelination and axonal atrophy that leads to nerve degeneration [3]. The pathomechanistic approach leading to damage of PN plexus in DPN occurs via two main phenomena, first is the impairment of endoneurial circulation following ischemia [4] and second is the abrupt axon-glia relationship followed by segmental or paranodal demyelination Wallerian degeneration and neuroma. Previously published report showed the worldwide cases of pre-diabetes and T2DM are 316 million and 387 million respectively [5]. The United States of America (USA) and Europe presume that pre-diabetes (PD) is also contributing towards progression of PN [6]. Twenty million subjects in USA currently have neuropathic related secondary complications and this number progressively doubles as the incidences of PD and type 2 diabetes mellitus (T2DM) increases [6]. DM leads to several acute, chronic, diffuse and focal neuropathy syndromes. In DM, peripheral nervous system (PNS) degeneration includes, symmetric and bilateral damage to feet nerves also known as stocking-glove neuropathy [7]. DPN is defined as a “symmetrical, length-dependent sensorimotor polyneuropathy attributable to metabolic and microvessel alterations due to chronic hyperglycemia exposure and cardiovascular risk covariates” [8]. DPN typically creates positive sensory symptoms
including pain, tingling, and prickling sensations (paresthesias) along with negative symptoms like numbness, sensation loss (disordered sensory processing), episodes of pain in the feet region when touched (allodynia) and elevate sensitivity to noxious stimuli (hyperalgesia). DPN is also associated with morbidity, lower limb fractures, ulceration and amputations. Diabetes neuropathy is broadly classified into (1) Diffuse neuropathy (2) Mononeuropathy and (3) Non-diabetic neuropathies. Several studies published on economic burden due to DPN showed that the patients bore high cost to manage the detrimental effects of the disease. In a study, the healthcare budget of UK accounted for nearly £2,511 out of which 41% budget accounted for patient’s care [9]. In another study, it was found that diabetic peripheral painful neuropathy (DPPN) is significantly associated with discontinuous employment and work productivity [10].

Despite the advancement in research, the medical community still lacks an effective therapeutic approach for DPN besides strict glycemic control and lifestyle interventions. A Cochrane review composing of clinical analysis dealt with DPN revealed that strict glucose control in T1DM subjects showed decrease DPN progression, but this has little effect in T2DM subjects despite long-term glycemic control [11]. This difference in incidences of DPN is extensively informative and favours the hypothesis that different pathophysiological mechanisms underlie in T1DM and T2DM associated DPN, considered as two diseases with the similar clinical presentation.

Previously published study has demonstrated repair of peripheral nerve damage by regeneration of nerve fibres and maintaining the functional recovery [12]. Implantation of autografts, allografts and xenografts from donor subjects are few strategic approaches available at present. The few limitations associated with these grafts primarily include loss of function or sensation at the donor nerve graft site, mismatch of the damaged nerve and the abrupt dimension of nerve graft [12].

Furthermore, the xenogenic and allogenic also showed disease transmission and immunological complications [12]. DPN related research in the last decades has focused on therapeutic potentials of newer approaches that directly improve the severity of the complications. In present work, the pathophysiological mechanism of DPN with up to date understanding, and most importantly, newer therapeutic approaches is covered.

1.1 Key players in pathogenesis of DPN

Over the last few decades, studies in the sector of DPN has focused the detailed mechanisms and biochemical pathways linked with the nervous system damage. The studies focused on enhancing the pathological relevance with polyol pathway activation, hexosamine/protein kinase C (PKC) isof orm activation, and accumulation of advanced glycation end products (AGEs) in the peripheral nerves plexus during diabetic state.

1.1.1 Polyol pathway

The polyol pathway is most highlighted biochemical mechanism in diabetic neuropathy. During hyperglycemia, surplus glucose is converted into sorbitol (alcohol) by aldose reductase (AR) (EC No. 1.1.1.21), leading to increased sorbitol level and osmotic imbalance. A pre-clinical rodent study performed on streptozotocin (STZ) rat model with T1DM showed the relation of polyol pathway and impairment in PNS structure and function [13]. Exploiting this information, several AR inhibitors (ARI) have been developed and tested for pre-clinical aspects, but the clinical trials have failed to show promising results because of adverse effects at the clinical endpoint of studies. Epalrestat (ONO2235) is the only licensed ARI, currently used in Japan as it was approved after the 3 months double-blind trial which showed promising improvement in nerve function [14]. In additional study conducted for ARI, it was demonstrated that it ameliorates the nerve conduction velocity (NCV) and nerve makeover in diabetes state [15]. The failure of ARI in treatment has been attributed to experimental design, inaccessibility to PNS, dose range and secondary hepatotoxicity [15]. The advent of recent and promising transgenic technology has revealed the tales of this pathway.

1.2 Hexosamine/PKC pathway

Increased glycolysis pathway in retort to surplus glucose impairs the metabolic pathways and also promotes neuronal injuries. The fructose-6-phosphate is a glycolytic intermediate which enters into this pathway and follows a sequence of reactions to form uridine-5-diphosphate-N-acetylglucosamine (GlcNac). GlcNac has a binding affinity for serine/threonine amino acids on transcription factors particularly Sp-1 resulting in lipid dyshomeostasis, injury to peripheral nerves along with inflammation.
Dihydroxy-acetone phosphate (DHAP), another glycolytic intermediate converted into diacylglycerol (DAG) for the initiation of tissue complications especially of nerves due to instigation of neuronal PKC.

PKC inhibitors have also been tested for promising therapeutic results in PDN. There are various isoforms of PKC that includes α, βI, βII, δ, ε, ζ, θ, μ, ι, λ and γ. STZ persuaded diabetic rat, it was found that there is an improvement in nerve physiology and function with PKC inhibitors in the treatment of DN [16]. In another landmark study, the PKC-β inhibitor (ruboxistaurin) showed beneficial role in diabetic neuropathy, but unfortunately not for diabetic retinopathy (DR) and nephropathy [16].

PKC is a crucial player in the pathogenesis of DN [16]. Nakamura and their co-workers did not find any significant changes in PKC activity in the tissue homogenate of whole peripheral nerve of diabetic model induced by STZ, though there is an improvement in nerve conduction velocity (NCV) and blood circulation to nerve upon using PKC-β inhibitors [17]. In a pre-clinical study performed on animal models, PKC-β inhibitors have beneficial effects on neuropathic changes in STZ induced diabetic rats [18].

1.4 Oxidative stress
Enhanced glycolytic flux in hyperglycemia primes generation of free radicals, which are primarily responsible for DN. Numerous studies prove that oxidative stress (OS) induces peripheral nerve damage in diabetes [22,23]. In the state of high glucose and excess fatty acid flux, the excess substrate is metabolized through glycolysis and TCA cycle respectively enriching the dorsal root ganglion (DRG) neuron with an ample amount of FADH₃ and NADH electron donors. This increases the proton gradient and hence ROS generation. Mitochondrial damage causes decreased neurotrophin-3 (NT-3) and NGF (nerve growth factor) that disturbs the neurotrophic support. It is being noted that a small amount of insulin, insufficient for lowering systemic glycemic levels and is capable of enhancing the NCV delay [24]. Moreover, in-vitro-oxidative stress activates poly ADP-ribose polymerase (PARP) initiation in combination with sustained hyperglycemia [25], which results in cellular dysfunction and programmed cell mortality that can be inhibited by using PARP inhibitors.

1.5 Insulin physiology
T1DM and T2DM exhibit different presentation of DN with a dissimilar mechanism for its occurrence in each disorder. In T1DM subjects, the DN improvement relies on insulin dose and is suggestive of the fact that one or more-insulin dose do not show glycemic control but has an optimistic impact on PNS [26]. Insulin receptors (IRs), present on sensory and motor neurons that showed enriched presence within SC membranes along with nodes of Ranvier. Insulin binding to IRs activates the signalling cascade of intracellular mechanisms that are helpful in maintaining normal cell homeostasis [27]. In previous literature in T1DM with DN complications it was concluded that failure of insulin signalling exhibit cell injury and promotes apoptosis [28]. The progress in PNS in DN is whether due to normoglycemia or insulin-mediated neuronal signalling is a matter of debate.

2. Conventional therapeutic approaches to manage DPN

2.1 Metabolic control
Strict glucose control in T1DM dramatically reduces the episodes of distal symmetric polyneuropathy.
(DSPN) to 78% (relative risk reduction) 29-30. Contrastingly, there is 5-9% relative risk reduction of DSPN in T2DM [31]. Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial on T2DM subjects also showed a mild reduction in DSPN episodes [31]. In one small trial performed on Japanese population with T2DM, intensive insulin treatment was associated to the improvement in DSPN [32]. Specific glucose control approach also had some discrepancy associated with it. Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) trial showed that male patients given with insulin sensitizers have lower DSPN episodes over 4 years compared to those who received sulfonylurea/insulin [33]. Although, none randomized, controlled trials of intensive insulin therapy in DPN management is present, however, the data available showed that strict glycemic control is of greatest use in the management of DPN.

2.2 Lifestyle modification

The appropriate model for controlling of DPN includes intensive lifestyle interventions as suggested by American Diabetes Association (ADA) guidelines [34]. The programs launched for lifestyle interventions are the Diabetes Prevention Program (DPP), the Steno-2 Study, the Italian supervised treadmill study and the University of Utah type 2 diabetes study [34]. All these studies suggested that lifestyle modification reduces the incidences of DPN/DSPN. In the previously published study, nerve fiber regeneration occurs prominently in T2DM patients engaged in exercise [34]. This conventional approach has much affected in the reduction of DSPN incidences.

2.3 Cytoprotective therapies

2.3.1 Lowering cell apoptosis

There are controversial opinions in DPN that whether neuronal loss occurs or not, if so then whether the cells are undergoing death/apoptosis, non-apoptotic programmed cell mortality or necrosis. Previously in-vitro studies performed on rodents and in-vitro models of developed neuropathy demonstrated the phenomenon of apoptosis [35,36]. Mitochondria play an imperative role in a neuronal injury, results in depletion of DRG neurons [37]. In DN models, activation of caspases 3, apoptotic pathway component contributes in this mechanism.

2.3.2 Poly ADP-ribose polymerase inhibition

Oxidative damage to DNA induces the release of PARP factor. This enzyme is involved in DNA repair by addition of poly (ADP-ribose) subunits to DNA strand breaks and base-excision pathway. It is evident from the previous study that reticence of PARP may delay the event of DN by inhibiting the PARP-mediated depletion of NAD$^+$ and ATP [38].

2.4 Supplementation of alpha lipoic acid

Alpha lipoic acid (ALA) is a naturally occurring thiol compound commonly used as a dietary supplement also called thiocystic acid. ALA is popularly known to perform antioxidant defense, metal chelating attribute, increasing expression of endogenous antioxidants and stimulating cellular glucose uptake. It is proved from earlier in-vitro studies that ALA along with dihydrolipoic acid (DHLA) has the ability to quench ROS, singlet oxygen along with free radicals (hydroxyl) [39]. In-vivo studies on ALA demonstrate its role in lowering pro-inflammatory responses, restoring antioxidant defense and lowering OS (Oxidative Stress) [40]. The oxidative stress is among the leading causes of DPN, therefore ALA can be explored as a new choice for treatment of DPN. In the previously published literature, ALA showed insulin-mediated glucose transport thereby backing to glycemic control. Moreover, setting a goal for newer treatment approach, ALA might be the clinical candidate in DPN. ALA is proved beneficial in several studies performed on the peripheral, central nervous system and cardiovascular complications. It is effectively cure pain allied with sciatica, diabetic neuropathy and carpel tunnel syndrome.

Interestingly, ALA has a neuroprotective effect in disorders allied with central nervous system including brain ischemia, subarachnoid haemorrhage, spinal cord injury and several others [41]. Melli, et al. studied the protective role of ALA on mitochondrial damage along with neurotoxicity induced by some chemotherapeutic agents [41]. Peripheral nerve injury caused by chronic constriction also showed a decrease in trend due to ALA application [41]. A recently published study therapeutic effect of ALA on peripheral crush injury studied and found its protective role [41]. It believed that the ALA/DHLA act as strong metal ion chelators and antioxidants modulate signalling pathways like nuclear factor associated mechanisms. Nuclear factor erythroid 2-related
factor 2 (Nrf-2)-mediated antioxidant gene expression is actively initiated by ALAc. It activates the 5′AMP-activated protein kinase (AMPK) and significantly inhibits the nuclear factor-κB. ALAc controls the peroxisome proliferators-activated receptors (PPARs) and activate the PPAR-α and -γ, that further initiate the expression acetyl-CoA synthase and carnitine palmitoyltransferase IA, that upshots in expression of lipoprotein lipase along with several fatty acid binding protein (FABPs) [42]. ALA effectively reduces the oxidative stress by inhibiting lipid peroxidation. Multifunctional ALA inhibits non-enzymatic glycation reaction that contribute in reduction of diabetes associated macro-and microvascular complications. Both ALA and DHLA reduces protein glycation, lesser lipid peroxidation and increases Na⁺ /K⁺ -ATPase activity in hyperglycemia. In previous study done on a diabetic neuropathy rat model, ALA promoted glucose uptake by nerve cells, increased intracellular nerve myoinositol, GSH concentration, Na⁺ /K⁺ -ATPase activity and nerve blood flow thereby proving beneficial to nerves, especially in diabetes-associated complications [43]. Peripheral nerve injury is characterized by cell death (apoptosis) of several cells like axons, Schwann cells, macrophages. ALA plays a significant role in decrease events of apoptosis in nerve injury [43]. In one of the recent study, supplementation of 600 mg/day of ALA proved beneficial in DPN [44].

3. Newer future therapies for the treatment of diabetic peripheral neuropathy

3.1 Long non-coding RNA’s

Long noncoding RNA’s (LncRNA) are small RNAs which have a molecular length of >200 nucleotides [45]. LncRNA’s are produced during RNA polymerase II transcription and it was believed earlier that they have no biological function [46]. However, recent studies showed the role of LncRNAs in regulatory processes, such as, transcriptional activation, chromatin modification, genomic imprinting transcriptional interference, and intranuclear transport, X-chromosome silencing and involvement of lncRNA in such a wide plethora of processes has intrigued the scientific world [47]. LncRNAs interact with transcription factors, coactivators, and/or inhibitory factors to affect various aspects of gene transcription [48]. The misexpression of LncRNAs occurs in many human diseases including DM and its complications [49]. Past studies exhibited that LncRNAs are involved in the occurrence and progression of DM and interact with transcription factors in T1DM to give rise to a complex regulatory network [50,51]. Human β cell transcriptome uncovered tissue specific LncRNAs, dynamically regulated, and abnormally expressed in T2DM [52]. These moieties are also involved in the pathological progression of the nervous system and have numerous effects on neurogenic pain [53]. LncRNAs such as MIAT and PVT1 were found to mediate high glucose-induced renal injury, and MEG3 was involved in diabetic microvascular dysfunction and the aberrant expression of MALAT1 was found both in diabetic retinopathy and cardiomyopathy. Si Yang et al. showed that Knockdown of lncRNA AK139328 assuages myocardial ischaemia (MI)/reperfusion injury (RI) through miR-204-3p and inhibiting autophagy [54]. NR_033515 also accelerated the expression levels of fibrogenesis-related genes [55]. In spite of several studies, which have given us some insights on the participation of lncRNA in DN, still much exploration is required through research to answer the questions associated with DN and lncRNA.

3.2 HGF gene therapy

At the time when any peripheral nerve injury occurs Schwann cells undergo dedifferentiation, many cytokines, chemokines and neurotrophic factors are secreted by SCs for nerve repair. Several neurotrophic factors are involved in nerve regeneration. A previously published study indicated towards the involvement of Hepatocyte growth factor (HGF), an angiogenic factor, on the nervous system [56]. HGF has been known to enhance angiogenesis, cell survival, cell migration and anti-inflammation in a variety of cell types. Until, the only known cellular receptor for this protein is receptor tyrosine kinase c-met [57]. During peripheral nerve injury, HGF has shown to enhance survival and axon outgrowth of cultured motor neurons [58]. It works together with NGF to exert neurotrophic effects on sensory neurons. In a recent study Ko, et. al. have reported that that HGF and its receptor c-met involved in Schwann cell-mediated nerve reparation [59]. Gene therapy efficiency was tested with HGF-bearing plasmid (pC4W-hHGF) to improve consequences of traumatic nerve injury in mice [60]. Their findings suggest that plasmid-constructed HGF gene therapy is a possible action for traumatic injury of
3.3 Long-acting C-peptide

During insulin biosynthesis, proinsulin is cleaved into insulin and C-peptide. Both insulin and C-peptide are secreted in pancreatic beta cells. C-peptide aids in the proper folding of insulin peptide chains along with formation of its disulfide bridges [62]. C-peptide binds with membrane-bound receptors to start signalling cascades within the cellular system. This signalling behaviour may result in protection or amelioration of complications that result from the chronic hyperglycaemia of diabetes, particularly T1DM. It was found that C-peptide administration stimulated the nerve conduction velocity (NCV) when the peptide was given from one week after the onset of diabetes. In addition, C-peptide elicited a marked increase in NCV and partially corrected the NCV deficit [63]. In another study once-weekly subcutaneous administration of long-acting C-peptide for 52 weeks resulted in marked improvement of vibration perception threshold compared with placebo [64]. C-peptide and insulin delivery for 3 months showed improvement in renal function in T1DM. Treatment with native C-peptide helped in alleviating these conditions. Probable reasons behind helpful effects of C peptide in neuropathic conditions due to increase in eNOS expression in the presence of C-peptide which in turn improves the endothelial function and improves the nerve blood flow. C-peptide exerts a direct stimulatory effect on Na+, K+ -ATPase which improves the energy conditions. Both of this phenomenon leads to an improved nerve function. C peptide also elevates neurotropic factors such as NGF, IGF-1 and NT3, they result in amelioration of nerve structural abnormalities. However much research needs to be done to explore and establish the role of C-peptide in neuropathic conditions developed during diabetes.

3.4 Platelet-rich plasma (PRP)

Platelet-rich plasma (PRP) promotes tissue regeneration through release of varied growth factors and cytokines contained in platelet granules. These molecules control angiogenesis, remodelling of the extracellular matrix along with the necessary recruitment of cells. PRP also mediate the proliferation and differentiation of stromal cells [65]. PRP therapy is economically beneficial to the clinics as it not require sophisticated techniques and instrumentation. PRP therapy is autologous and hence does not possess immunological complications. In the current scenario, PRP is of a good choice for post-surgical recoveries, bone repair, diabetic foot ulcers, burns and rheumatoid arthritis. In several pioneer studies, PRP has proved to reduce pain in osteoarthritis with the promotion of healing related to soft tissues like tendon, ligament and connective tissues. PRP also reduces neuropathic pain and stimulate axon regeneration as proved by previously published literature [66]. Axon regeneration inducing ability of PRP was tested in various animal studies in neuropathic pain reduction [67]. In another cell culture study, PRP assists the release of IGF-1 and VEGF factors that help in axon growth [68]. PRP is rich in MSCs fractions and hence may promote the axon regeneration due to release of NGF and BDNF factors promoting angiogenesis. PRP is rich in platelets complemented with clotting and growth factors. The α-granules of platelets contain platelet-derived growth factor, TGF-β (transforming growth factor β), IL-1 (Interleukin-1), PDAF (platelet-derived angiogenesis factor), and VEGF, EGF, PDEGF (platelet-derived endothelial growth factor), IGF, fibrinogen, vitronectin, osteocalcin, fibronectin, osteonactin and thrombospondin-1 [69]. PRP, suppress inflammatory responses and improves the tissue regeneration by promoting neo-epithelialization and capillaries growth factors [69].

3.5 Mesenchymal stromal cells

Mesenchymal stromal cells (MSCs) are a group of stem cells contained in several tissues including adipose tissue, bone marrow and spinal ligaments [70]. The surface marker proteins present in these cells include CD44, CD90, or CD105 [70]. Two predominant types of MSCs explored for their therapeutic potential without phenotypic differences (a) bone marrow (bone marrow-derived MSC; BMSC) and (b) adipose tissue (adipose tissue-derived MSC: ASC, migrated BMSC into adipose tissues). Shibata and their co-workers disclosed the therapeutic effect of MSCs on diabetic neuropathy in STZ induced animal model [71]. Transplantation of BMSCs presented significant improvement in motor nerve conduction velocity (MNCV), sciatic nerve blood flow (SNBF) along with the increased expression of VEGF, bFGF and neurofilament proteins [71]. Another study also presented expression of NT-3 and NGF in
3.6 Yang-warming method

Chinese medicines (TCM) are of popular choice in countries, especially in China [78]. Several clinical trials have checked the efficiency of TCM therapies in along with EGFR-TKIs [79,80]. Prior execution of the TCM therapy, one should differentiate not only Yin and Yang, cold and heat but also Interior and Exterior, excess and deficiency diseases into 6 meridians and 12 zang-fu organs. It is quoted in the textbook Huangdi Neijing to differentiate between Yin-cold (YC) and Yang-heat (YH) types of diseases [79]. In another study, it was shown that TCM could be effective in DPN treatment [80]. In a recently published meta-analysis, it was demonstrated that yang-warming Chinese medicines formula alone without western medicines could recover NCV [80]. This group found a significant difference between the efficacy of western medicines and yang-warming Chinese medicines (p<0.001) without any adverse effects [80]. Both animals and clinical investigations verified the efficacy of TCM in the management of DPN [80]. It is proposed that Chinese herbs are a rich source of antioxidants and reduce the oxidative stress via Nrf2 and Bcl2 expression [80] complemented with a decrease in neuropathic pain and autonomic nerve damage [80]. The previous study showed that Chinese herbs are involved in peripheral nerve regeneration and its nourishment via improved microcirculation [80]. Yang-warming method is also a prospective therapy for DPN and can be exploited for mankind.

3.7 A pulsed electromagnetic field (PEMF)

One of the recent clinically proven approaches named as a pulsed electromagnetic field (PEMF) of low-frequency have analgesic, neuroprotective, vasoactive and neurostimulatory effect during DPN [81]. It was quoted that low-frequency exogenous application of non-thermal electromagnetic pulsed field upregulates NGF, IGF-1, IGF-2, fibroblast growth factors, VEGF and also reorganized Schwann cells with the decrease of OS, claiming that PEMF reduces DPN symptoms [82]. Lei et al. also published the therapeutic role of PEMF in DPN [158]. It is proposed that PEMF improves the 1a afferent state and reduces the reflex excitability [83]. In previously published literature, PEMF controls the hormones, antibodies and neurotransmitters. These alterations cause impairment in the electrons transfer during electron exchange taking place in chemical reactions [84]. PEMF induced hyperpolarization of -90 mV may block the pain signal transmission in DPN [84]. It is also evident that PEMF alters the
ATP invention that in turn improves the oxygen and nutrients cargo and decreases the pain or muscles spasm in DPN [85]. PEMF is not associated with any harmful effect, is safer for DPN patients, effectively implicated in clinics nowadays.

4. Conclusion

DPN is an unadorned complication-affecting people with huge economic and health burden. It effects peripheral nerves resulting into their dysfunction and pain episodes. Despite the advancement in research, the medical community still lacks an effective therapeutic approach for DPN [86] besides strict glycemic control with lifestyle interventions. Over the last few decades, research in the sector of DPN has focused to exploit the detailed mechanisms and biochemical pathways associated with the nervous system damage for the treatment. There are many conventional therapies for DPN such as metabolic control, lifestyle modification, cytoprotective therapies, ALA supplement [87]. Apart from these Long Non-Coding RNAs, HGF gene therapy, Long-Acting C-Peptide, Platelet-rich plasma (PRP), Mesenchymal stromal cells, Yang-warming method, PEMF are some of the newer therapies which are emerging for DPN which might be more helpful in lowering the disease burden.

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