

OXIDATIVE STRESS AND DIABETIC NEUROPATHY: CURRENT STATUS OF ANTIOXIDANTS

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ABSTRACT

There are many studies which advocate the role of amplified production of reactive oxygen species (ROS) in the development and progression of various diseases affecting human being. Diabetic neuropathy which is one of the common and most troublesome complication of diabetes have also got oxidative stress as unifying mechanism associated with nerve damage followed by structural and functional loss. Oxidative stress forms a common platform where majority of pathophysiological pathways like aldol pathway, advanced glycation end products formation, poly ADP-ribose polymerase (PARP), protein kinase c (PKC) and mitogen activated protein kinase (MAPK) overactivation converge. Since oxidative stress leads such a major role in the development of diabetic neuropathy, a large number of antioxidants have been tested in experimental models, many of which have reached clinical trials as well. Moreover, novel strategies such as employing antioxidant which specifically reduce mitochondrial ROS generation, increasing the expression of antioxidant enzymes or externally supplying the antioxidants to strengthen the innate antioxidant defense rekindle the interest in oxidative stress as a fruitful target for the treatment of diabetic neuropathy. In this review, we have updated the present status of pharmacological intervention targeted at oxidative stress in diabetic neuropathy. We have also tried to delineate the futuristic strategies against oxidant induced damage in diabetic neuropathy.

Keywords: Diabetic neuropathy; oxidative stress; biomarkers; antioxidants; mitochondria

[1] INTRODUCTION

Hyperglycemia-induced overproduction of free radicals is widely recognized as the link between diabetes and diabetic complications. Diabetic neuropathy (DN) is the most common cause of non-traumatic amputations and unfortunately, to date, except the tight glycemic control, treatment for DN is not available. Considering the epidemic of diabetes throughout the world and the fact that diabetic neuropathy is one of the most common long-term complications of diabetes, it is important to look into details of its pathophysiology. Oxidative stress resulting from enhanced free-radical formation has been implicated in the pathogenesis of diabetic neuropathy. Research over many years has identified major pathways leading to microvascular complications of diabetes. These include increased polyol pathway activity leading to sorbitol and fructose accumulation, nonenzymatic glycation of proteins forming advanced glycation end-products (AGEs), activation of protein kinase C (PKC) and other cascades of stress responses and increased hexosamine pathway flux. Oxidative stress rooting from long term hyperglycemia has been established as a link that provides a unified mechanism of tissue damage [1]. Besides hyperglycemia, other factors, such as endoneurial hypoxia, transition metal

imbalances and hyperlipidemia play a key role in inducing oxidative stress in the diabetic nerve. ROS-induced damage to proteins affects the function of receptors, enzymes, transport proteins etc. causing damage of other biomolecules. An assemblage of ongoing research and future development of antioxidant for diabetic neuropathy in both pre-clinical and clinical phases is discussed in the present review.

1.1. Innate antioxidant mechanisms

Antioxidants are defined as substances which inhibit or impede the oxidative damage to subcellular proteins, carbohydrates, lipids and DNA by getting oxidised themselves. In response to excess ROS production during respiration and metabolism, mammals have evolved numerous antioxidant processes and systems. These mainly involve the redox reaction in which oxidation and reduction occurs simultaneously via transfer of hydrogen or a pair of electrons. Free radicals are unstable molecules and get stabilized after donating electrons; as for example donation of hydrogen atom by ascorbate or tocopherol to

a free radical. Steric interference by compounds such as tocopherols can prevent attack of ROS on the target cell and thus can provide enhanced stability to cellular membranes [2]. In order to maintain the levels of antioxidants in the cells, dietary uptake or de novo synthesis is necessary. Even fleeting episodes of acute hyperglycemia can blunt the antioxidant capacity of body and increase oxidative stress in diabetics. The warriors of body's antioxidants defense are superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx). SOD catalyses the dismutation of superoxide (O_2^-). Since in the process of dismutation hydrogen peroxide (H_2O_2) is generated, this enzyme bands together with other two antioxidant enzymes catalase and glutathione peroxidase, the H_2O_2 removing enzymes, to avert cellular damage by H_2O_2 . Criticality of this enzyme for survival is highlighted by the fact that complete knockout of SOD is lethal within days of birth in mice [3]. Catalase and glutathione peroxidase are other antioxidant enzymes that detoxify H_2O_2 to water and therefore their activity needs to be present when SOD is active. Glutathione peroxidase equally protects against the oxidation of dihydrorhodamine 123 (an indicator dye) by peroxynitrite ($OONO^-$), requiring glutathione as reductant indicating that it also acts as a defense line against peroxynitrite-mediated oxidations [4].

In addition to the antioxidant enzymatic defense, mammalian cells also possess small non protein molecules which quench free radicals and dampen the injurious effects of ROS; these include glutathione (reduced form), thioredoxin, vitamin C and vitamin E. Of particular mention among these molecules is glutathione, a tripeptide (γ -Glu-Cys-Gly) which is present ubiquitously in mammalian cells. Depletion of glutathione stores in the cell draws it indefensible to oxidative injury. It has been demonstrated that neuroblastoma cells show magnified resistance

to oxidative stress when glutathione-S-transferase is overexpressed [5]. Redox activity of endogenous antioxidant agents can be helpful in designing the useful therapy of antioxidants in diabetic neuropathy. Another endogenous antioxidant is melatonin, which is a neurohormone synthesized by the pineal gland and is involved in regulation of circadian rhythms and also possesses a powerful antioxidant capacity in vitro. In vivo, the concentrations of melatonin are relatively low and its antioxidant action can be attributed to its modulation of secretion of other antioxidants [6, 7].

1.2. Biomarkers for oxidative stress

The exact status of antioxidant defense and oxidative stress can be measured by employing series of biomarkers studies which can provide information, which can be crucial in selection of proper antioxidant, dose, duration of intervention and most importantly the efficacy of intervention in a given set of conditions. Biomarker study also serves to analyze whether oxidative stress has developed and whether the prospective interventions are capable of attaining anticipated biochemical or physiological endpoint. There are many experimental tools to study oxidant damage in biological systems which include HPLC, gas chromatography, mass spectroscopy and protein expression studies by immuno-blotting and ELISA protocols. Oxidative stress exerts its devastating effects directly by damaging cellular proteins, lipids, and DNA, or indirectly by affecting normal cellular signaling and gene regulation. The damage to various biological macromolecules ends up in genesis of various malicious substances which serve as biomarkers of oxidant induced damage. Based on their sources, these can be sub-classified as given in [Table-1](#).

Table 1: Categorization of different biomarkers of oxidative stress used as experimental tools

Type of Damage	Parameters
Biomarkers of lipid damage	TBARS, MDA, isoprostanes, various HETEs
Biomarkers for damage of proteins	Protein carbonyls, nitrosylated proteins
Biomarkers for oxidant induced DNA damage	8-OHdG, Comet and TUNEL assay
Endogenous antioxidants	Tocopherols, Ascorbic acid, GSH
Antioxidant enzymes	SOD, Catalase

TBARS: Thiobarbituric acid reacting substance; MDA: Malondialdehyde; HETE: 20-hydroxyeicosatetraenoic acid; 8-OHdG: 8-hydroxy-2'-deoxyguanosine; TUNEL: Terminal deoxynucleotidyltransferaseUTP nick end labeling; GSH: Reduced glutathione; SOD: Superoxide dismutase.

There are marked changes in the biomarkers oxidative stress in diabetic neuropathy. The excessive production of superoxide and peroxynitrite in sciatic nerve has been linked with altered vaso-relaxation responsible for nerve perfusion irregularities [8]. In addition to this, superoxide can cause decreased vascular reactivity which further contributes toward impediment of nutritive supply to sciatic nerve. Reduction in glutathione levels and levels of antioxidant enzymes has also been well documented in experimental diabetic neuropathy [9]. Lipid

peroxidation and oxidative damage to DNA measured by 8-OHdG has been correlated with diabetes associated damage. Hyperglycemia independently increases 8-OHdG in patients with type 2 diabetes which is a useful biomarker of not only oxidative stress but also of microvascular and macrovascular complications in patients with type 2 diabetes [10]. Whether or not hyperglycemia induced oxidative stress culminates into apoptosis and cell death is still controversial among researchers. Many groups found that oxidative stress is manifested as excessive

DNA fragmentation in nerve microsections of diabetic animals [11, 12]. Guo et al. observed apoptosis in dorsal root ganglion (DRG) and vagus nodose ganglion in STZ-diabetic rats [13]. However, in other studies it was demonstrated that oxidative stress resulting from hyperglycemia did not cause apoptosis in peripheral neuron [14-16]. Zhrebetskaya et al. found that hyperglycemia does lead to the depletion of antioxidant enzymes and increased oxidative damage in DRG but this was not associated with increased cell death or apoptosis [16]. Since apoptotic cell death in peripheral nerves remains a disputed outcome of diabetes, many advocate it be avoided while assessing diabetic nerve degeneration. However it is clear that long term hyperglycemia results in ROS production and exploiting the oxidative stress biomarkers which appear early in the condition may present new possibility in the early detection and treatment of diabetic neuropathy.

[II] PATHOPHYSIOLOGY OF DIABETIC NEUROPATHY: INTERACTION OF OXIDATIVE STRESS WITH OTHER PATHOPHYSIOLOGICAL PATHWAY

Elevated hyperglycemia in diabetes leads to a range of microvascular and macrovascular complications. As a result of

microvascular complication in retina, renal glomeruli and peripheral nerves, diabetic patients suffer from blindness, end stage renal disease and a variety of debilitating neuropathies. There are many hypotheses which support the hyperglycemia induced damage in nerves resulting in diabetic neuropathy. These include aldol reductase pathway, increased advanced glycation end product pathway, oxidative-nitrosative stress, PARP overactivation, activation of PKC, increased hexosamine pathway, MAPK activation and inflammatory damage. All of these pathways have been extensively studied and have generated large volume of data and several clinical trials based on the specific inhibitors of these pathways have been conducted. Out of many of these evidences it has emerged that oxidative stress is a feature common to all the pathways. Inhibitors of these specific pathways have also been demonstrated to reduce the levels of reactive oxygen species and alleviate oxidative stress.

2.1. Polyol pathway

Majority of glucose is phosphorylated to glucose-6-phosphate by hexokinase and only a meagre fraction (3%) is converted to sorbitol via polyol pathway. This reaction is catalyzed by aldose reductase. Sorbitol is subsequently oxidized to fructose by

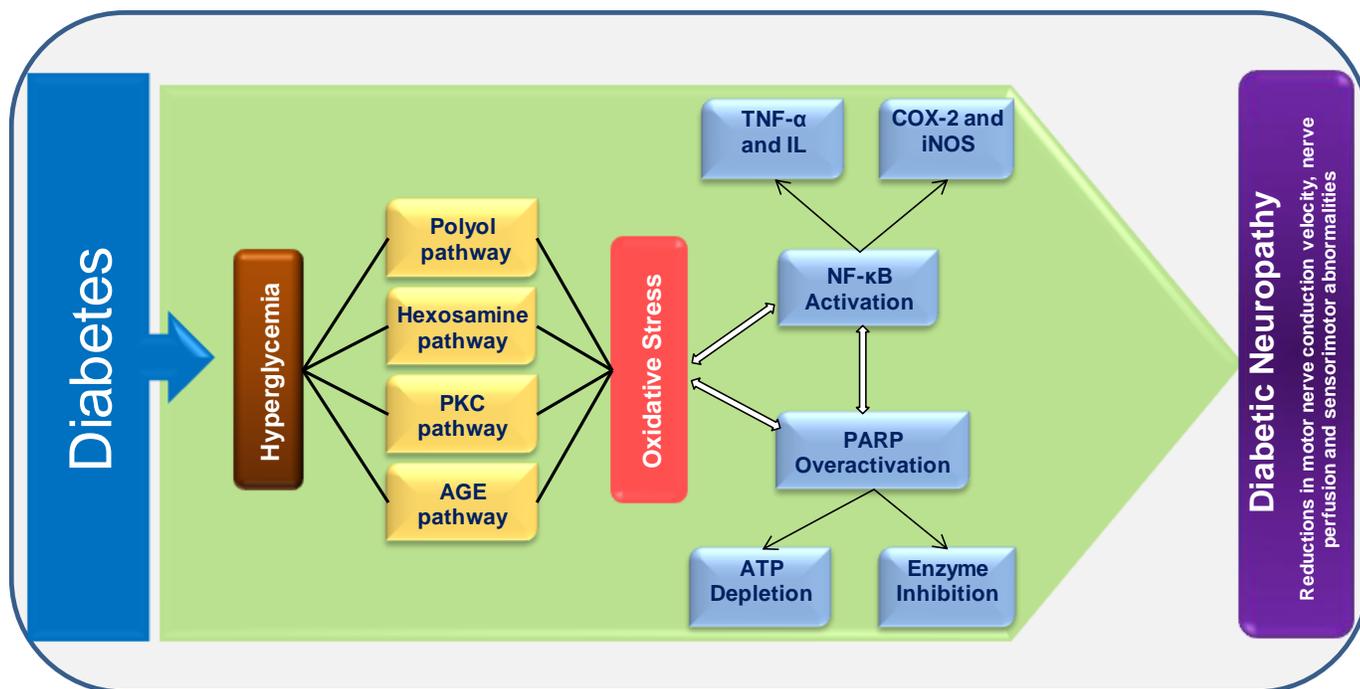


Fig: 1. Chronic presence of glucose in diabetic conditions results in the activation of various pathways which ultimately culminates in producing oxidative stress in cells. Oxidative stress leads to activation of various secondary cascades such as overactivation of PARP and NF- κ B which results in dysregulated cellular functions and transcription of an array of proteins ensuing the development of neuropathy..

sorbitol dehydrogenase and requires NAD⁺ as cofactor. But in hyperglycemic condition, hexokinase is saturated and excess

glucose is metabolized by polyol pathway (30%) which leads to overt production of sorbitol and fructose which can lead to

metabolic disturbances and causing tissue damage to various target organs including peripheral nerves leading to diabetic complications [17]. Polyol pathway coactivates two other pathophysiological pathways (AGE formation and PKC activation) which contribute to etiology of diabetic neuropathy [17]. However complete inhibition of aldose reductase to prevent polyol pathway is also not desirable as it is also involved in detoxification of lipid peroxidation products.

2.2. Advanced glycated end products (AGE)

Reducing sugars like glucose undergo non-enzymatic reactions with the primary amino groups of proteins to form glycated residues called “Amadori products”. These early glycation products undergo further complex reactions such as dehydration, condensation, and crosslinking to form stable covalent adducts called advanced glycated end products (AGE). RAGE (receptor for AGE) employs reactive species to act as second messengers, thus contributing towards oxidative stress. Studies using knockout animal models have strengthened the concept that the AGE-RAGE interaction plays a crucial role in the development and progression of diabetic neuropathy [18]. Modifying the AGE formation process can also alleviate different outcomes of diabetic neuropathy which reconfirms the role of AGE formation in its pathogenesis. LR-90 [4-(2-chlorophenylureidophenoxyisobutyric acid)] a scavenger of AGE precursor and ALT-711 (alagebrium chloride) an agent that disrupt the cross-links have been shown to reduce AGE formation and oxidative stress in STZ induced diabetes rat model [19].

2.3. Protein kinase C (PKC) activation

PKC is a family of eleven isoforms, 9 of which are activated by lipid second messenger di-acyl glycerol (DAG). DAG led activation has been seen in cultured vascular, retina, glomeruli and nerve cells. Activation of PKC pathway modulates various transcription factors like NF- κ B signaling causing inflammation. PKC activation can contribute to blood flow abnormalities, increase in vascular permeability, angiogenesis and various other effects leading to development and progression of diabetic complication [20]. The involvement of PKC in diabetic neuropathy is supported by studies in STZ animal model where inhibition of PKC with LY333531 improved the sciatic nerve blood flow and nerve conduction and ameliorated diabetic hyperalgesia [21]. PKC has a unique structural feature that facilitates its regulation according to redox status of cell. Prooxidants react with regulatory domain to stimulate its activity while antioxidant reacts with catalytic domain and inhibits its activity. On activation, it triggers stress genes that phosphorylates transcription factors and thus alters the balance of gene expression. It also activates hsp and c-jun kinases that can lead to apoptosis. As with some aldose reductase inhibitors, some of the PKC inhibitors have been shown to exhibit antioxidant effects.

2.4. Hexosamine pathway

During hyperglycemia fructose 6-phosphate is converted to glucosamine 6-phosphate by an enzyme- glutamine fructose 6-phosphate aminotransferase (GFAT). Further processing to UDP-N-acetylglucosamine aids proteoglycan synthesis and formation of O-linked glycoproteins. This pathway leads to increased transcription of transforming growth factors (TGF- α and TGF- β 1) and plasminogen activator inhibitor-1 (PAI-1) and has been implicated in insulin resistance. Inhibition of GFAT blocks the transcription of TGF- α , TGF- β and PAI-1. Glucosamine has been shown to elevate H₂O₂ levels and antioxidants tend to inhibit this effect [22]. Overt expression of both TGF- β and PAI-1 has been reported to contribute to pathogenesis of diabetic complications. Both of these factors are affected by increased hexosamine shunt as well as by PKC activation. So it can be said that increased flux through hexosamine pathway contribute to multitude of effects in diabetes and diabetic complications [17].

2.5. PARP over-activation

Poly (ADP-ribose) polymerase (PARP EC 2.4.2.30) is a nuclear enzyme catalyzing the addition of ADP-ribose units to DNA, histones and various DNA repair enzymes, which affects cellular processes such as replication, transcription, differentiation, gene regulation, protein degradation and spindle maintenance. PARP deficient cells are more prone to DNA damage by various ionizing radiations and alkylating agents which proves the crucial role of PARP in DNA repair mechanisms. PARP metabolizes NAD⁺ into polymers of ADP-ribose and nicotinamide after getting activated, which leads to the depletion of the pyridine nucleotide pool. Therefore, cellular metabolic pathways using NAD⁺ as cofactor are compromised and end up in irregularities such as function loss followed by cell death. Recently it has been proved that PARP overactivation and oxidative stress are two inseparable pathways. Under physiological conditions, PARP activity is relatively low. However, under conditions of oxidative stress, excessive DNA single-strand breakage is triggered by ROS leading to overactivation of PARP [12].

2.6. Miscellaneous

Numerous studies indicate ROS as powerful activators of three subfamilies of mitogen activated protein kinase (MAPK) i.e c-Jun N-terminal kinases (JNK), extracellular signal-regulated kinases (ERK) and p38 MAPK. In addition, oxidative stress affects multiple signal transduction pathways- arachidonic acid cascade, phosphoinositide, Ca²⁺ signaling as well as neurotransmission. Oxidative stress has also been implicated in myelin fiber atrophy and other morphological changes characteristic of advanced diabetic peripheral neuropathy [22].

[III] ANTIOXIDANT THERAPY: CURRENT STATUS

Considering the imperative role of oxidative stress in mediating nerve dysfunction in diabetes, a large number of antioxidants have been tested in an equally large number of animal models [Table-2]. Based on these preclinical findings antioxidants vitamins are expected to perform same in human trials. A number of antioxidants have reached phase 3 of clinical trials. These include vitamin E, curcumin, ascorbic acid and lipoic acid. Two 52-week randomized placebo-controlled diabetic neuropathy trials demonstrated that acetyl-L-carnitine produced

significant improvements in sural nerve fiber numbers and regenerating nerve fibers [23]. A combination of allopurinol, alpha lipoic acid and nicotinamide is under phase 3 clinical trials for diabetic autonomic neuropathy.

Although many in vivo and in vitro studies have explicitly identified ROS as a key player in the pathophysiology of diabetic neuropathy; the clinical outcomes of antioxidant therapy have been disheartening. No antioxidant therapy is approved by the FDA for diabetic neuropathy in the USA. Lipoic acid is only member of this list which has been approved for treating diabetic neuropathy in some European countries [Table-3].

Table 2. Effect of various antioxidant therapies in in vivo/in vitro model of experimental diabetic neuropathy

Drug	Exp. Model	Parameter	References
Melatonin	STZ induced diabetes in rats	Corrected motor nerve conduction velocity (MNCV) and nerve blood flow(NBF) deficits. Improved Nrf2 and HO1 level, decreased NF-κB, iNOS and COX-2 levels	[6, 24]
FeTMPyP and FeTPPS	STZ induced diabetes in rats	Corrected MNCV and NBF deficits. Protection against nitrosative stress	[25, 26]
Resveratrol	STZ induced diabetes in rats	Ameliorated the alterations in MNCV and NBF, significant reduction in DNA fragmentation, Abrogation of NF-κB, iNOS and COX-2 levels	[27, 28]
Edaravone	STZ induced diabetes in rats	Protection against MNCV and NBF deficits, restored antioxidant enzyme levels	[29]
Curcumin	STZ induced diabetes in mice	Attenuation of thermal hyperalgesia Inhibition of TNF-α and NO production	[30]
Trolox	STZ induced diabetes in rats	Ameliorated the alterations in MNCV, NBF, hyperalgesia, MDA levels and antioxidant enzymes in diabetic rats	[31]
U83836E	STZ induced diabetes in rats	Ameliorated the alterations in MNCV, NBF, hyperalgesia, MDA levels and antioxidant enzymes	[32]
Apocynin	STZ- induced diabetes in rats	Protection against MNCV and NBF deficits, restored blood glucose.	[33]
Tempol	STZ- induced diabetes in rats	Corrected MNCV,NBF and SNCV deficits	[8]
DL-α-Lipoic acid	STZ- induced diabetes in rats	NBF and MNCV deficits restored	[9]
Probucol	STZ- induced diabetes in rats	Corrected NBF, normalized MNCV and SNCV	[34]

[IV] ANTIOXIDANTS THERAPY: EXPANDING SPHERE

4.1. Antioxidant targeted at mitochondria

Mitochondrial ROS generation in response to hyperglycemia can be considered as chief contributor to the development and progression of diabetic neuropathy and thus can be targeted for therapeutic benefit. Mitochondria-targeted antioxidants have displayed the protective abilities against toxic oxidative stress in experimental models. These agents selectively concentrate in the inner membrane of mitochondria and thus scavenge ROS at the site of production thereby curbing mitochondrial oxidative damage and death of neuron.

A known antioxidant of mitochondrial origin Coenzyme Q10 (CoQ10) was evaluated in various models of diabetes and

related complications [35], but its potential was marred by the fact that its bio-availability is very less. To obviate bio-availability problems associated with the natural antioxidant CoQ10, it was covalently linked to a lipophilic triphenylphosphoniumcation (MitoQ10). Once it enters mitochondria, MitoQ10 is reduced to its native ubiquinol form, acting as a powerful antioxidant preventing mitochondrial damage. When compared to non-targeted CoQ10 analogue decylubiquinone, MitoQ has been shown to be a more potent antioxidant and moreover it concentrated several-fold within mitochondria [36]. Another novel class of cell-permeable antioxidant peptides that selectively partition into the inner mitochondrial membrane has been reported. These peptides, known as Szeto-Schiller (SS) peptides, are nontoxic and have been shown to protect against oxidative stress in a range of neurodegenerative diseases [37]. Redox state of mitochondria is largely controlled by thiol proteins of mitochondria. Thus employing such thiol containing chemical moieties for targeted delivery to mitochondria may be a useful

therapy for oxidant-induced pathophysiologies. Triphenylphosphonium cations attached to a thiol-reactive moiety like 4-thiolbutyltriphenyl phosphonium and 4-iodobutyltriphenyl phosphonium are under investigation for mitochondria-targeted thiol delivery [38].

Although mitochondria-targeted antioxidants are in the embryonic stage of their development, they vouch for potential therapy for the treatment of not only diabetic neuropathy but also of other disease conditions associated with oxidative stress. A myriad of preclinical studies support their potential use for ischemia-reperfusion injury and neurodegenerative disorders

Table 3. Summary of clinical trials of antioxidants in diabetic neuropathy

Drug	Phase	Sponsor	Age group/ gender	Purpose
Ascorbic acid (Vitamin C)	Phase I	Washington State University	50 Years to 70 Years/Both	Primary Outcome Measures: Changes in intracellular erythrocyte sorbitol levels Secondary Outcome Measures: Changes in Neuropathic Pain Scale (NPS) measurement
N-acetylcysteine (Diabetic foot)	Phase III	University of Turin, Italy	45 Years to 70 Years/ Both	Primary Outcome Measures: Tissue oxygenation improvement Secondary Outcome Measures: Improvement of the endothelial function, Oxidation status reduction
Lipoic acid	Phase III	MEDA Pharma GmbH & Co. KG	18 Years to 74 Years/ Both	Primary Outcome Measures: Absolute change in the neuropathy impairment score
Metanx (a medical food)	Phase IV	Pamlab, L.L.C., USA	25 Years to 80 Years/ Both	Primary Outcome Measures: Determine improvement in vibration perception threshold Secondary Outcome Measures: evaluated by the Neuropathy Total Symptom Score-6, improvement in clinical examination as determined by the Neuropathy Disability Score (NDS)
Haemoderivative of calf blood (Actovegin)	Phase III	Nycomed, Denmark	18 Years to 65 Years/ Both	assess clinical efficacy and safety of Actovegin in type 2 diabetic patients with symptomatic diabetic peripheral polyneuropathy
Allopurinol, alpha lipoic acid (ALA), nicotinamide (for diabetic autonomic neuropathy)	Phase III	University of Michigan	18 Years to 65 Years/ Both	Primary Outcome Measures: Retention Index (RI) Secondary Outcome Measures: Endothelial function, 8-epi prostaglandin F2alpha, CRP
Controlled nitric oxide releasing patch (for diabetic foot)	Phase III	Fundación Cardiovascular de Colombia	18 Years and older/ Both	Primary Outcome Measures: Ulcer reduction percentage Secondary Outcome Measures: Complete cure of the infection that was present before the treatment
BK-C-0701	Phase III	Bukwang Pharmaceutical	18 Years and older / Both	Primary end point: change of Total symptom score Secondary end point: neurological test

4.2. Increasing the expression of antioxidant enzymes

Expression and induction of enzymes that protect against ROS induced damages, play an important role in determining the risk of neuropathy in human. Many experimental evidences have thrown light on the potential of innate antioxidant enzyme system against oxidative stress induced cellular damage. A torrent of scientific groups is studying about possibilities for such an antioxidant therapy. One of the best-characterized protective genes proven to be effective in ameliorating neurovascular complication of diabetes and associated oxidative stress is SOD. Adenovirus containing manganese superoxide dismutase cDNA (AdMn-SOD) are being tried in vitro and in vivo in the treatment of diabetes related complications [39]. Endothelial dysfunction in diabetes mellitus is one of the

important reasons for loss of nerve function and nerve conduction deficits. Gene transfer of Cu/Zn SOD and Mn/SOD to diabetic aorta improved endothelium-dependent relaxation [39]. Gene therapy with organ-specific targeting of Mn-SOD plasmid liposome accords a valuable technique for increasing the levels of SOD in specific organs at high risk of oxidative damage [4].

However experimental evidences indicating that over-expression of these enzymes can protect neurons against oxidative injury are still lacking. Moreover whether this approach can be exploited clinically in neuropathy is still under the layers of doubt as at the time of diagnosis of neuropathy in diabetic patients massive turnover of ROS had already occurred. Under oxidative stress, whether these antioxidant enzymes can surmount oxidative stress is still a question.

4.3. External supply of antioxidants

One of the most applicable approaches of combating oxidative stress is to increase antioxidant defense of the body by supplying them externally. Although antioxidants are already in clinical use, but limitations encountered with conventional antioxidant therapy calls for some more effective alternative. SOD which is frontline defense against H₂O₂ have been tested but was found inadequate as being a peptide it was unstable, did not permeate cell membrane, and provoked an immune response. SOD liposome infusions have been reported to render protection against superoxide toxicity. A plethora of Cu, Zn-SOD conjugates are available, including polyethylene glycol (PEG)-SOD, Ficoll-SOD, lecithinized SOD, polyamine conjugated SOD, cationized SOD, genetically engineered SOD polymers, pyran-SOD and albumin-SOD complexes. Lecithinized SOD contains four phosphatidylcholine (PC)-derivative molecules covalently attached to SOD. PC-SOD has a long half-life and high affinity for plasma membranes. It exhibited beneficial effects in animal models of various diseases like ulcerative colitis [40].

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[V] CONCLUSIONS

The Diabetic neuropathy is still one of the unmet medical challenges. Several studies have demonstrated that oxidative stress play an imperative role contributing towards various deficits associated with diabetes and its complications. With the advent of technologies more specific targeting may produce different results as seen in earlier trials. The novel agents modulating specific targets like mitochondrial stress and innate antioxidant defense can also pave their way to clinics and can become a part of preventive or adjuvant therapy for diabetic neuropathy. The future of targeted antioxidant therapy in diabetes and related complication including neuropathy is bright, but there is still a long way to go.

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