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Mechanisms of Diabetic Neuropathies and Antioxidant Therapy

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Diabetic neuropathy is very common and affects half of patients with either type 1 or type 2 diabetes mellitus. It is the leading cause of diabetes-related hospital admissions and nontraumatic amputations. Currently, the keys to management are maintaining blood glucose concentration within the normal range and treatment of symptoms. Despite many studies of chronic pain associated with diabetic neuropathy, few improvements have been made.
Main Finding: This is a review of the classification of diabetic neuropathy, molecular mechanisms, and treatment options focusing on antioxidants.
Conclusion: As oxidative stress may play a significant role in the pathophysiology of diabetic neuropathy, the study of molecular mechanisms by which hyperglycemia induces oxidative stress is important. New targets for disease-modifying drugs could be elucidated.

Keywords: Antioxidants; diabetic neuropathy; oxidative stress; molecular mechanisms; pharmacotherapeutic targets.

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1. INTRODUCTION

Diabetic neuropathies (DN) are defined as "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes" [1]. It is very common and affects half of patients with either type 1 or type 2 diabetes mellitus (DM) [2,3]. Table 1 presents the prevalence of DN among different types of DM in different countries. Approximately 10% of patients with newly diagnosed DM have DN [4], which increases morbidity, distress, and healthcare cost [5]. In the USA, the cost of DN is $4.6–13.7 billion which represents a quarter of the total cost of DM [6]. Many risk factors contribute in DN development, such as the level and duration of hyperglycemia, abdominal obesity, creatinine level, and high white blood cell count [7].

The clinical manifestations of DN depend on the affected nerve fibers [8]. Small nerve fibers are affected first, and symptoms are characterized by hyperalgesia and allodynia. As the disease progresses, the degradation and dysfunction may involve large myelinated nerve fibers, resulting in a loss of Achilles reflex, sensory ataxia, and diminished perception. Subsequently, patients may develop hypoalgesia and experience complete loss of sensation [8]. Long-term DM in rodents is associated with thermal and mechanical hypoalgesia [9], motor incoordination, nerve degeneration, and demyelination [9,10]. Due to sensory loss, the risks of delayed treatment, foot injury, foot and leg ulceration, and infections are increased. Unfortunately, recurrent infections and ulcers may lead to amputation of the lower extremities [11].

2. CLASSIFICATION OF DIABETIC NEUROPATHIES

DNs are classified as *general*, *focal*, and *multifocal* polyneuropathies [12]. Other types of diabetic peripheral neuropathy include small nerve fiber neuropathy, autonomic neuropathy, mononeuropathy, radiculoplexopathy (diabetic amyotrophy), and treatment-induced neuropathy [6], which are presented in Fig. 1. However, several patients may have asymptomatic neuropathy [13].

General neuropathies follow *typical* or *atypical* patterns [3,14]. *Typical* diabetic peripheral neuropathy is the most common subtype and is defined by the Toronto Diabetic Neuropathy Expert Group as: "Typical DN, also known as chronic distal symmetrical polyneuropathy (DSPN), is a symmetrical, length-dependent sensorimotor polyneuropathy attributable to metabolic and microvessel alterations as a result of chronic hyperglycemia exposure and cardiovascular risk covariates." Nerve conduction (NC) tests revealed [15] that the sensory neurons are the ones affected, not the motor neurons [6], and autonomic nerve fibers can be involved [15]. DSPN is associated with metabolic disorders secondary to chronic hyperglycemia, including oxidative stress [16]. Microvascular alterations are manifested as diabetic nephropathy and retinopathy [17]. As a result, patients with DSPN suffer from one or more of pain, numbness, tingling, or weakness [6]. These symptoms usually begin in the feet and spread lengthwise proximally, which is known as glove and stocking distribution [6] (Fig. 1a). Many patients complain of poor shoe fit and constriction by shoes and socks [6]. Some patients suffer from numbness and sensitivity at the same time [6], and symptoms are variable from patient to patient [6]. Numbness associated with DSPN may contribute to loss of balance which increases the risk of falls by two- to threefold [18]. The risk of developing foot ulceration and lower limb amputation is 15 times higher in patients with DM compared with those without [19], and 15% of patients with severe DSPN develop ulceration [20]. Also, many patients have asymptomatic diabetic neuropathy and develop insensate foot injury [1].

Atypical diabetic peripheral neuropathy is characterized by acute, subacute, or chronic onset and either a monophasic or relapsing course [17]. Symptoms are burning pain, contact hyperalgesia, and a mild sensory loss that may resolve within months. Usually, other microvascular complications go undetected. Deterioration in nerve conduction velocity (NCV) is mild and often absent [17]. Moreover, inflammation may be involved in the pathogenesis, and hyperglycemia may not be the cause, unlike in the typical pattern [17].

Small nerve fiber neuropathy is an early presentation and can progress to DSPN [6]. It is difficult to diagnose because both electrodiagnostic test and clinical examination for absent reflexes, impaired vibration, and weakness may be normal [6].

Diabetic autonomic neuropathy (DAN) occurs if hyperglycemia affects the autonomic nerves [3] and may represent a subtype of small nerve fiber neuropathy [6]. However, DAN increases the

risks of morbidity and mortality [6], especially for cardiovascular autonomic neuropathy [21]. The clinical manifestations of DAN include cardiac arrhythmias, constipation, gastroparesis, erectile dysfunction, and urinary retention [6].

Mononeuropathy is common among patients with DM and is secondary to ischemic injury or a compressive mechanism [6], and its symptoms develop suddenly [22]. Focal and multifocal mononeuropathies can affect the median, ulnar, radial, common peroneal, or oculomotor nerves. The most common nerves that are affected are the oculomotor or median nerves [6]. Cranial nerve neuropathy is rare (0.05%) [1].

Radiculoplexopathy is a neuropathy affecting the lumbar, sacral, or cervical plexuses [6]. The symptoms include weight loss, pain, and weakness [6].

Treatment-induced neuropathy is acute pain or autonomic symptoms occurring after insulin therapy or after a rapid correction of the blood glucose concentration [6,23].

Diabetic neuropathy has been further classified as follows: (1) *generalized symmetric polyneuropathies*, including acute sensory, chronic senso-motor, and autonomic forms; (2) *focal/multifocal neuropathy*, including cranial, truncal, focal limb, proximal motor (amyotrophy), and chronic inflammatory demyelinating polyneuropathy [1].

Acute sensory neuropathy is rare and results from a sudden change in blood glucose level (insulin neuritis) and poor metabolic control (diabetic ketoacidosis) [1]. Contrarily, the chronic type is the most common, with 50% of patients developing symptoms, including burning pain, electrical sensations, paresthesia, and hyperalgesia [1].

3. MOLECULAR MECHANISMS OF DIABETIC NEUROPATHIES

Several mechanisms are involved in the pathogenesis of hyperglycemia-induced microvascular complications in patients with DM. Oxidative stress, inflammation, and mitochondrial dysfunction are the main pathogenic factors, as summarized in Fig. 2.

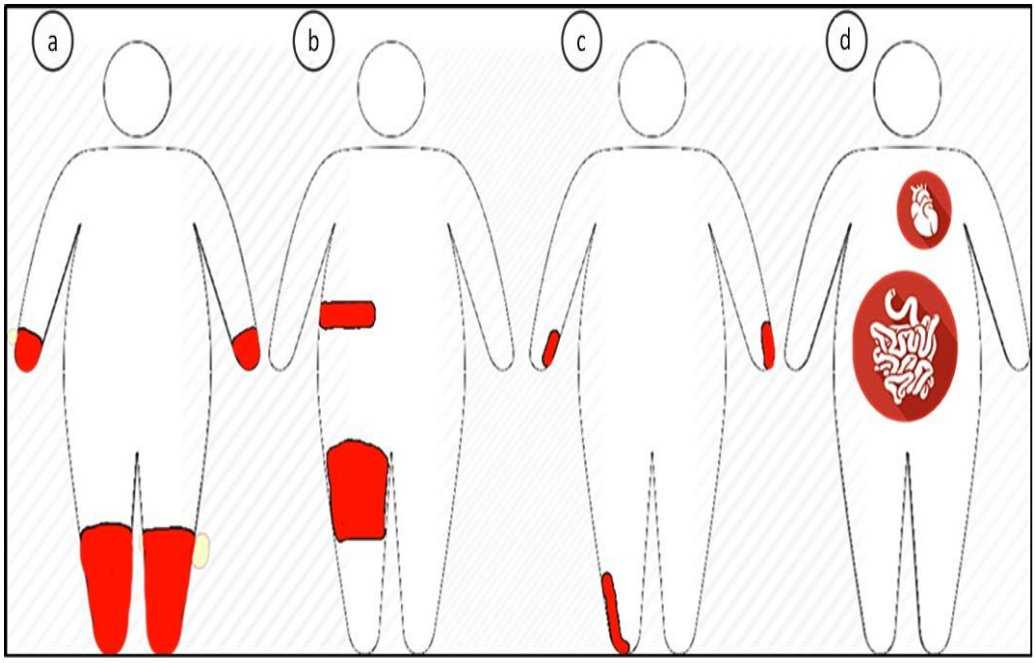

Fig. 1 Patterns of nerve injury among DNs

Patients with DM can have more than one pattern of nerve injury. The pattern shown in (a) can be observed in distal symmetrical polyneuropathy, small fiber predominant neuropathy, and treatment-induced neuropathy. The pattern shown in (b) can be observed in radiculoplexopathy and radiculopathy. The pattern shown in (c) can be observed in mononeuropathy and mononeuritis. The pattern shown in (d) can be observed in autonomic neuropathy and treatment-induced neuropathy The figure modified [6] .

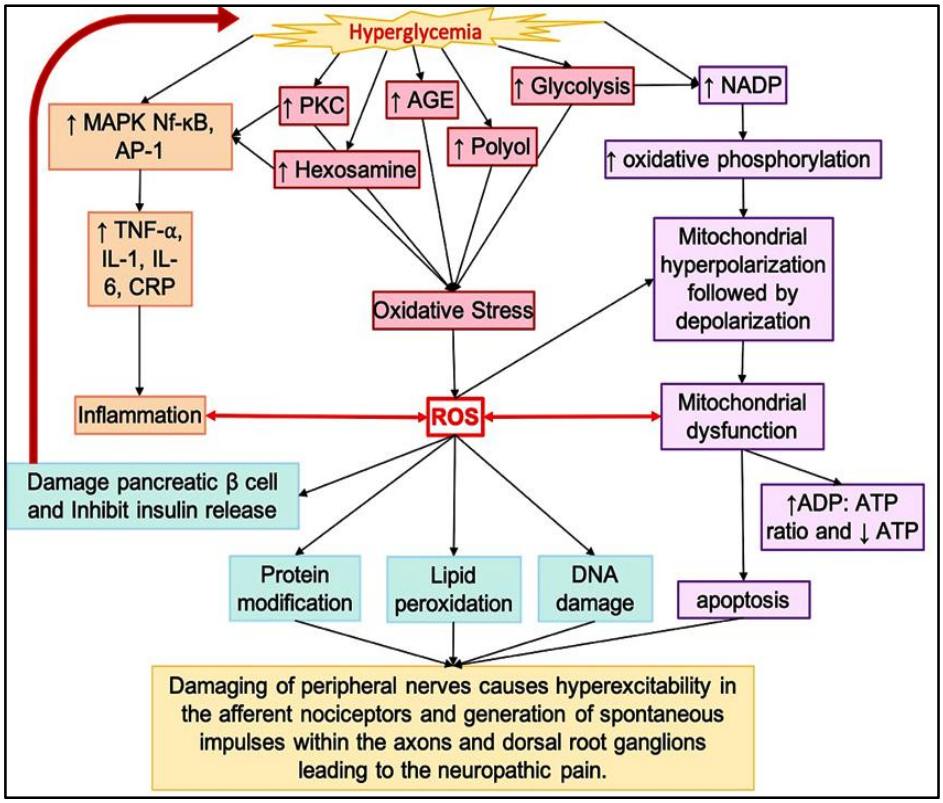

Fig. 2. Molecular mechanisms of hyperglycemia-induced diabetic neuropathy

A schematic diagram representing the role of oxidative stress, inflammation, and mitochondrial dysfunction in the pathogenesis of diabetic neuropathy. AGE, advanced glycation end product; AP-1, activator protein 1; CRP, C-reactive protein; MAPK, mitogen-activated protein kinases; NADH, nicotinamide adenine dinucleotide; NF-κB, nuclear factor-kappa B; PKC, protein kinase C; RAGE, receptor of advanced glycation end; ROS, reactive oxygen species The figure modified [24]

3.1 Oxidative Stress

Oxidative stress plays a significant role in cellular injury [25], and in diabetic neuropathy, it can result from overproduction of reactive oxygen species (ROS) or impairment of endogenous antioxidant defense mechanisms [26].

A small variation in basal glucose concentration induces ROS that can result in neuronal injury [27]. *In vitro* and *in vivo* studies have shown that an increase in glucose concentration leads to overproduction of oxidative stress biomarkers, such as thiobarbituric acid-reactive substances, malondialdehyde (MDA), and advanced glycation end products (AGEs), along with the inhibition of endogenous antioxidant synthesis [28]. ROS generation in patients with DM results from the factors summarized in Fig. 3.

The most important factor is endoneurial hypoxia [29] that may arise from the decrease in neural blood flow and increased resistance of neural blood vessels [29]. Hyperglycemia can contribute to hypoxia through rheological mechanisms, and AGEs are produced as a result of glycation of different structural proteins. AGE can interact directly with the extracellular receptor (RAGE), thus initiating inflammatory signaling cascades, activating Nicotinamide adenine dinucleotide phosphate reduced form (NADPH) oxidases, and generating oxidative stress [30]. ROS may further contribute to vascular disorders in patients with DM by interfering with nitric oxide (NO)-induced vasodilation [31]. Moreover, reduction of nerve perfusion may contribute to neuronal hypoxia and diminished nerve conduction velocity (NCV), which is an early sign of neuropathy in experimentally induced DM [31]. Several peripheral vasodilators have been identified, which partially prevent or correct nerve function in diabetic rats by improving nerve perfusion and oxygen delivery [31]. Prolonged hyperglycemia is associated with an increase in

glycolysis and the polyol hexosamine pathways; these trigger the production of ROS [24]. Modifying these pathways, as described in Fig. 4, may prevent the development of DN.

After the glucose enters the cell, most of it is metabolized *via* glycolysis to pyruvate. In DM, as glucose levels increase intracellularly, glycolysis is increased, which can result in the overload of the mitochondrial electron transport chain and generation of ROS [32]. An increase in intracellular glycolysis also leads to the formation of diacylglycerol (DAG), an important activator of protein kinase C (PKC); this then triggers the intracellular proinflammatory signaling cascade [33]. Similarly, some of the intracellular glucose is converted to sorbitol *via* the polyol pathway; its activity is increased by 30% during hyperglycemia. Sorbitol accumulation intracellularly results in an increase in cellular osmolarity that can lead to a reduction in the level of NADPH oxidase required for reduced glutathione synthesis. This inhibits cellular antioxidants and contributes to ROS generation [34,35]. Hyperglycemia results in the activation of the hexosamine pathway that produces uridine diphosphate-N-acetylglucosamine. Glucosamine increases oxidative stress in cells by hydrogen peroxide (H_2O_2) production while increasing the expression of inflammatory vascular growth factors (such as transforming growth factor-beta (TGFβ1) and plasminogen activator inhibitor-1 (PAI-1)) that are known to be involved in the pathogenesis of diabetic microvascular complications [24].

Excessive production of ROS leads to the destruction of the cell membrane, cell proteins, and nucleic acid, which finally causes cell death [26]. ROS and reactive nitrogen species interact with the lipids of myelin sheath of neuronal cells, thus destroying the axon of nerve and the microvascular blood supply to the peripheral nerves [36]. A reduction in the total number of sensory neuronal cells and sural nerve myelinated fibers has been reported but was not statistically significant [37].

Nuclear-related factor-2 (Nrf-2) is an important pathway involved in the expression of the endogenous antioxidant system as a defense mechanism against oxidative stress [38]. Nrf-2 presents at the cells in an inactive state. In case of stress or increased ROS generation, Nrf-2 is activated then transferred to DNA, where it binds to antioxidant response elements; this results in the transcription of antioxidant protein and subsequent reduction of ROS and oxidative stress [39]. In persistent hyperglycemia, the level of Nrf-2 is decreased, resulting in the development of neuropathy, as presented in Fig. 4. [40]. A preclinical study has demonstrated that dietary components can activate Nrf-2, with significantly improved renal function, and amelioration of oxidative stress and metabolic upset in diabetic mice [41].

3.2 Inflammation

Overexposure to hyperglycemia results in the overproduction of ROS, which activates proinflammatory mediators, such as nuclear factor-kappa B (NF-κB) [42], activator protein 1 (AP-1), and mitogen-activated protein kinases (MAPKs) [24]. These mediators may further activate cytokines that increase the inflammatory response [43]. A clinical study of 227 patients with type 2 DM found that IL-6 and C-reactive protein (CRP) levels increased significantly with the severity of DN compared with those with type 2 DM without DN [44].

3.3 Mitochondrial Dysfunction

Glucose in neuronal cells undergoes glycolysis to produce nicotinamide adenine dinucleotide (NADH) that is transported into the mitochondria through complexes I–IV to produce adenosine triphosphate (ATP) *via* oxidative phosphorylation. This reaction results in the ROS from the mitochondria that are neutralized by intracellular antioxidants. However, in hyperglycemia, excess glucose leads to the overactivation of oxidative phosphorylation, resulting in an increase in ROS production. ROS coupling with mitochondrial cell membranes results in hyperpolarization, followed by depolarization; this is associated with an increase in adenosine diphosphate (ADP): ATP ratio and a decrease in ATP level [1,45]. Eventually, the mitochondrion releases cytochrome c and cleaves the caspases that cause dorsal root ganglion apoptosis [27].

4. TREATMENT OF DIABETIC NEUROPATHIES

Non-pharmacological treatments of DN that are important in preventing diabetic complications include diet control, regular exercise, and foot care [11]. Pharmacological management of DN comprises three approaches: glucose control, pain management [6], and disease-modifying therapy (Fig. 4).

4.1 Glycemic Control

Previous clinical studies have shown that tight glycemic control in patients with type 1 DM is associated with a 60% reduction of the risk of developing clinical signs of neuropathy [46] but is less effective in patients with type 2 DM [6]. The duration and severity of hyperglycemia are risk factors for the severity of DN in patients with type 2 DM [47], in whom the prevalence of neuropathy increases for up to 10 years [48].

Insulin exerts a neurotrophic effect through the delivery of glucose to the neuronal cells which promotes their growth and survival [49,50]. Insulin deficiency (type 1) or insulin resistance (type 2) can lead to a reduction of insulin and neurotrophic signals that contribute to the development of neuropathy [51]. C-peptide prevents peripheral and autonomic nerve dysfunction in type 1 DM [52], and a reduction of C-peptide may contribute to the development of DN.

A meta-analysis was conducted in 2012 to determine the role of glucose control in preventing the progression of DN [53]. In type 1 DM, enhanced glucose control significantly prevented the development of clinical neuropathy and reduced nerve conduction and vibration threshold abnormalities. In type 2 DM, vibration and conduction threshold abnormalities were significantly reduced; however, although the incidence of DN was reduced, it was not significant. A possible explanation could be that there were differences in baseline glucose, measurement technique, or treatment regimens. This meta-analysis had significant limitations because the targeted glucose levels, therapeutic strategies, outcome measures, trial designs, and follow-up durations differed between the studies. In particular, the majority of these studies utilized crude neuropathy end points, including monofilament thresholds, foot examination, and vibration perception; these end points cannot be expected to detect an improvement in the underlying neuropathy [5].

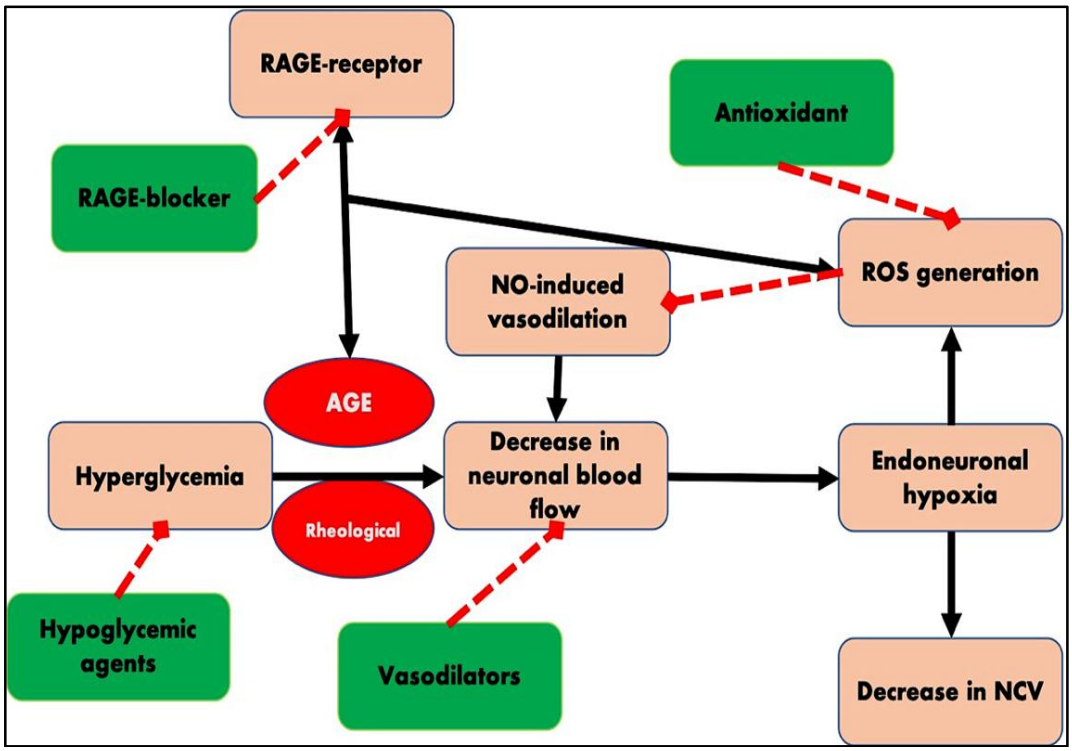

Fig. 3. Mechanisms of hyperglycemia-induced oxidative stress and possible therapeutic targets

This illustration describes hyperglycemia-induced advanced glycation end product (AGE) which alters the rheological properties of blood, leading to a decrease in blood flow and nerve conduction velocity (NCV) and endoneurial hypoxia. Reactive oxygen species (ROS) generation is enhanced, and nitric oxide (NO)-induced vasodilation is reduced. Hypoglycemic agents block the receptor of advanced glycation end product (RAGE), vasodilators improve neuronal blood flow, and antioxidant medications inhibit ROS generation

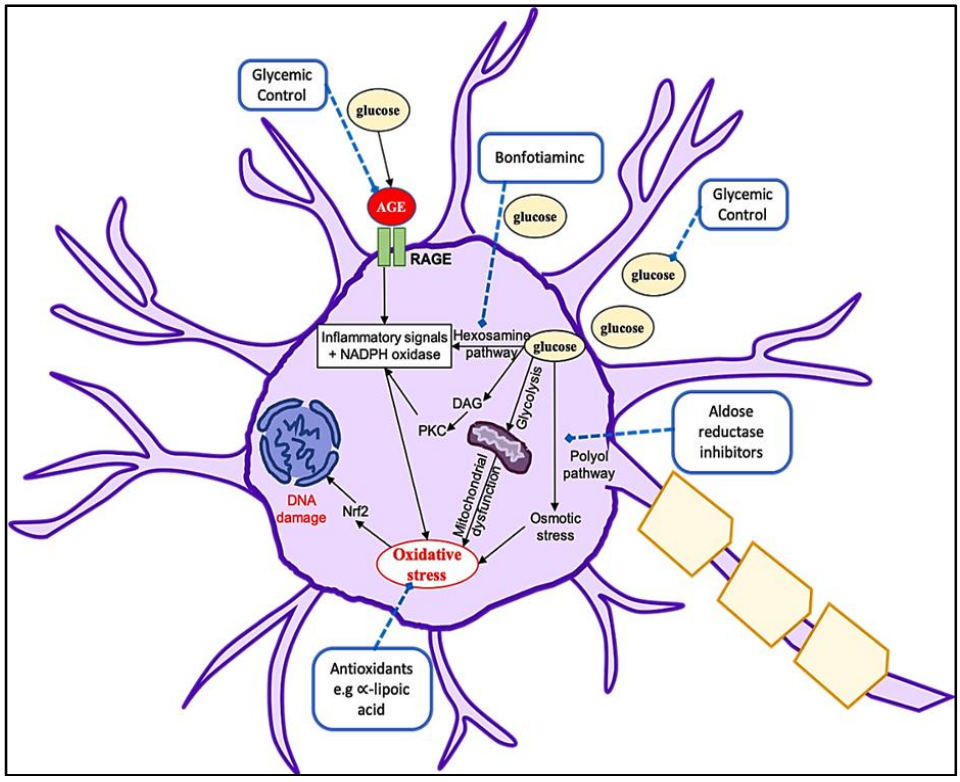

Fig. 4. Mechanisms of hyperglycemia-induced oxidative stress in neurons and therapeutic targets

Schematic diagram presenting the main pathways involved in the pathogenesis of diabetic neuropathy. AGEs, advanced glycation end products; DAG, diacylglycerol; NADPH, nicotinamide adenine dinucleotide phosphate; Nrf-2, nuclear-related factor-2; PKC, protein kinase C; RAGE, receptor of advanced glycation end product.

Table 1. The prevalence of diabetic neuropathy among patients with DM in different regions

Type of DM	Participants (n)	Prevalence	Region	Reference
Type 1	5936	11%	United States	[54]
Type2	2453	71.2%	China	[55]
Type 2	959	55%	China	[56]
Type2	552	19.9%	Saudi Arabia	[7]
Type 2	3359	33%	China	[57]
Type 1&2	1039	65%	Saudi Arabia	[58]
Type 2	132	8%	Finland	[59]
Type 1&2	6487	28.5%	United Kingdom	[60]
Type 1	382	10.7%	United States	[61]

Intensive glucose control results in the improvement in electrophysiological measurements in type 1 DM, but not in type 2 DM. Neither somatic neuropathy nor autonomic neuropathy could be prevented by intensive glucose therapy (INT) compared with conventional therapy, despite a decrease in HbA1c of 2.07%. However, there was a decreased frequency of cranial neuropathy and better preservation of touch sensation with INT [62]. Another study was conducted to investigate the effect of intensive multifactorial cardiovascular therapies, including glucose control. These did not prevent the progression of somatic neuropathy compared with the conventional therapy group but significantly reduced the autonomic neuropathy risk [63]. However, according to the UKPDS study, INT reliably decreased the overall risk of microvascular complications in type 2 DM [64]. A

similar beneficial effect of INT was observed in more recent trials [65].

4.2 Diabetic Neuropathic Pain Management

Diabetic neuropathic pain is the most disabling symptom associated with DSPN [6]. The prevalence of pain symptoms was 26% among DM patients without neuropathy [66] but 60%–65.3% among patients with severe neuropathy [58].

The characteristics of neuropathic pain include burning, electrical, and stabbing sensations, with and without numbness [6]. Over time, patients can develop allodynia (pain sensation in response to non-painful stimuli) and hyperalgesia (very severe pain sensation in response to normally painful stimuli) [6].

Agents used to control the pain are essential in improving the patients' quality of life [6]. Many agents have been approved by the US Food and Drug Administration, Health Canada, and the European Medicines Agency for the treatment of neuropathic pain [67]. Gabapentin, pregabalin, tricyclic antidepressants, venlafaxine, and duloxetine are first-line treatments [6].

Pregabalin is a gamma aminobutyric acid analog that acts on alpha-2/delta receptors in the central nervous system to decrease neuronal calcium influx and the release of some excitatory neurotransmitters [68]. It can relieve pain by 30%–50% [69]. To prevent its side effects, especially in the elderly, it must be started at a low, gradually increasing dose as tolerated by the patient [70, 67].

Duloxetine is a reuptake inhibitor of both serotonin and norepinephrine [67]. It relieves pain in DN and improves the patients' quality of life [71], but it can increase HbA1c [72].

Tapentadol is a mu-opioid receptor agonist and noradrenaline reuptake inhibitor. It is approved by the US Food and Drug Administration for the treatment of diabetic neuropathic pain, but is not generally recommended as first- or second-line treatment due to a high risk of addiction [73].

Local lidocaine therapy can be used in patients who have localized neuropathic pain [6].

The drug of choice depends on the comorbidities, side effect profiles, and cost-effectiveness [6]. Tricyclic antidepressants are the cheapest drug of the first-line medications. Gabapentin and venlafaxine are cheaper than pregabalin and duloxetine, respectively [6].

Opioid analgesics and tramadol are second-line agents [6]. However, long-term use of this group is not recommended due to addiction, side effects, and reduction of effectiveness over time.

Disease-modifying therapy aims to prevent, slow, or reverse DN progression through the reduction of oxidative stress and inhibition of polyol, hexosamine, protein kinase, AGE, and poly(ADP-ribose) polymerase pathways [74].

5. ANTIOXIDANT THERAPY OF DIABETIC NEUROPATHIES

DM complications can result from excessive production of ROS with depletion of endogenous antioxidant, as mentioned above [75,76].

5.1 α-Lipoic Acid

α-Lipoic acid is a racemic organosulfur compound [77]. The R-stereoisomer is present in natural plants, animals, and the human body. The S-stereoisomer is synthesized by chemical procedures. In the Krebs cycle, α-lipoic acid plays a significant role as a coenzyme in energy production [77]. It covalently binds with some proteins and has therapeutic potential [77]. Both α-lipoic acid and its reduced form, dihydrolipoic acid (DHLA), have positive effects on health [78,79], including antioxidant activity, detoxification, and metal chelation. They can both reduce the oxidized form of endogenous molecules, such as vitamins C and E and glutathione [78,79], and can modulate different signaling pathways, such as insulin and NF-κB [78,79]. They also have anti-aging, anti-cancer, and neuroprotective properties [77].

5.1.1 The beneficial mechanisms of α-lipoic acid in diabetes mellitus

α-Lipoic acid has strong antioxidant activity by scavenging ROS, regenerating endogenous antioxidants, repairing oxidation damage [80], and decreasing the proinflammatory pathways [81]. Also, α-lipoic acid in both *in vitro* and *in vivo* studies produced an increase in the synthesis of glutathione through its ability to increase cystine uptake, which is essential in the biosynthesis of glutathione [82]. α-Lipoic acid decreased iron in the epithelial cells due to the thiol group in its

structure. These changes were associated with an increased resistance against free radicals [83]. It is a water- and fat-soluble antioxidant, so it has the ability to neutralize ROS both inside and outside cells [84,85]. α-Lipoic acid used as an adjuvant in DM had a decreased glycation and free radical generation [86]. Overall, α-lipoic acid blocks the oxidative stress inflammatory pathway [74] and can be used in the prevention and treatment of neuropathy [86]. It has the ability to increase glucose uptake [87,88], and it improves glucose utilization by the repartition of glucose transporters to the plasma membrane, tyrosine phosphorylation of insulin receptor substrate-1, and activation of AMP-activated protein kinase (AMPK) [89]. It increases NO bioavailability and thus improves endothelial function [86].

However, the pharmacokinetic profile of α-lipoic acid affects its therapeutic efficacy. A low bioavailability of 30% is caused by the decreased solubility, instability at the low pH of the stomach, and extensive first-pass hepatic clearance [90]. To enhance the intestinal absorption of α-lipoic acid, a complex adjuvant with γ-cyclodextrins has been used [91]. A clinical study that was conducted on 18 subjects to assess the bioavailability of α-lipoic acid combined with lecithin demonstrated that bioavailability was higher compared with a normal less-soluble form [92]. The dose and duration of lipoic acid used in clinical trials ranged from 200 to 1800 mg, either parentally or orally [74].

5.1.2 Effect of lipoic acid as a treatment in diabetic neuropathy

A-Lipoic acid is used as a treatment for neuropathy in many countries but is not approved in the UK or the United States [5]. A randomized double-blinded clinical trial conducted on 460 patients suffering from mild to moderate DN for over 4 years found that α-lipoic acid at a dose of 600 mg/day exhibited meaningful improvement and prevented the progression of neuropathy [93]. Another open-label clinical trial enrolled type 2 DM patients with DN. Forty-five patients were allocated to receive α-lipoic acid, 600 mg three times a day for over 4 weeks, followed by 600 mg once a day for 16 weeks. The study found that the total symptom score was significantly reduced in the group who received α-lipoic acid [94].Another clinical trial of 600 mg lipoic acid per day over 40 days in patients suffering from diabetic neuropathy revealed a significant reduction of neuropathic symptoms with an improvement in the quality of life [95]. Intravenous α-lipoic acid 600 mg significantly improved clinical symptoms of DN for over a 3-week duration [96,97]. A multicenter double-blind randomized placebo controlled study reported that administration of α-lipoic acid 600 mg orally exhibited no improvement compared with placebo [97].

5.2 Aldose Reductase Enzyme Inhibitors

5.2.1 Aldose reductase enzyme inhibitors

During hyperglycemia, glucose converts to sorbitol catalyzed by aldose reductase. Cellular accumulation of sorbitol is associated with myo-inositol deficiency, protein kinase C and Na/K ATPase activity depletion, and changes in NAD/NADP ratio [98]. Consequently, there is an increase in osmotic pressure of sorbitol [99] and oxidative injury [100]. Nitric oxide (NO) levels are reduced, leading to ischemic injury to the nerve [5], and a reduction of NCV occurs [101]. Aldose reductase activity increases, but there is only minimal change in sorbitol dehydrogenase expression in the peripheral nerves [102]. An increase in blood glucose level enhances the flux to the polyol pathway [103]. An increase in the polyol pathway increases cellular osmolarity and reduces the level of NADPH oxidase that contributes to ROS generation [6]. Also, an increase in the oxidation pathway to form fructose is associated with an increase in NADH/NAD ratio, which also increases diglycerol formation, activates protein kinase C, inhibits Na/K ATPase, enhances prostaglandin synthesis, and increases ROS production [104]. Additionally, the decrease in NADPH/NADP ratio is associated with increasing diabetic complications through impairment of the scavenger function for oxygen free radicals [105], inositol depletion, and impaired Na+/K+-adenosine triphosphatase or the reduction of nitric oxide production [106].

Therefore, aldose reductase enzyme inhibitors block the rate-limiting step in the polyol pathway. Subsequently, they prevent the accumulation of sorbitol, which could improve nerve dysfunction. However, most of these compounds have been shown to be effective only in animal models [103]. Unfortunately, clinical trials were inconclusive [103]. Aldose reductase enzyme inhibitors have shown improvement in nerve conduction velocity (NCV) and prevent and reverse both sorbitol accumulation and myo-inositol depletion in the sciatic nerve of diabetic

rats [107]. Also, it has been shown to restore antioxidant reduced glutathione (GSH) molecules and prevent lipid peroxidation and was effective at least in early diabetic neuropathy [34].

5.2.2 Aldose reductase enzyme inhibitors and diabetic neuropathy

Several aldose reductase enzyme inhibitors have reached phase II and III clinical trials but were withdrawn before reaching the market due to lack of efficacy or serious adverse effects [103]. A systematic review found that the effects of aldose reductase inhibitors were no better than placebo. Although the majority of the reported adverse effects were infrequent and minor, some were serious, including severe hypersensitivity associated with sorbinil, renal impairment associated with zenarestat, and liver toxicity associated with tolrestat [108].

Ponalrestat failed to exert any beneficial effect, except in one study in which it enhanced the vibration perception threshold after 52 weeks. This unexpected result can be explained by its poor penetration into the nerve tissue, which is manifested by a nonsignificant reduction in the sorbitol level on nerve biopsy [103]. Together, no clinically important side effects attributable to ponalrestat were found [109].

Only epalrestat has been passed and approved for the treatment of DN [110]. It significantly improved motor NCV, vibration sensation threshold, and diabetic autonomic neuropathy compared with placebo [110]. Neuropathy symptoms and test results were improved in more than 5000 patients with diabetic neuropathy [111], and it prevented the deterioration of motor NCV without serious adverse events [112]. Conversely, other studies revealed an increase in aminotransferase levels in 0.63% of 5249 patients, and in rare cases, hepatic damage could be serious [111,103].

6. CONCLUSIONS AND FUTURE DIRECTIONS

Diabetic neuropathy is one of the most common complications of DM and affects the patients' quality of life. Although the exact mechanisms of DN are still not fully understood, oxidative stress plays a major role in its patogenesis. Antioxidants could inhibit the pathogenesis of DN rather than its symptoms. Current antioxidant therapy provides promising results, but a further large-scale research is needed.

CONSENT AND ETHICAL APPROVAL

It is not application.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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