Oxidative stress at the crossroads of diabetic neuropathy: Mechanisms and implications of antidiabetics (Review)

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Abstract. Diabetic neuropathy (DNP) is among the most common complications of diabetes, affecting the majority of individuals with long-standing diabetes. This painful microvascular condition is associated with a high risk of morbidity. While multiple factors are considered to contribute to the development of DNP, its exact cause remains unclear, although several theories have been proposed. Despite ample research aimed at detecting and attenuating the progression of DNP, effective treatment options remain limited. The present review delves into the connection between oxidative stress and neuropathy in patients with diabetes, with particular focus on the mechanisms through which antidiabetic medications may influence oxidative stress to help attenuate the advancement of DNP. For the purposes of the review, a search for relevant articles was performed using online sources, including the PubMed and Google Scholar databases, using key words, such as antidiabetics, antioxidant effects, diabetes, diabetic neuropathy and oxidative stress. It is currently considered that hyperglycemia and complex metabolic imbalances, particularly oxidative stress, play central roles in the development of DNP. Some antidiabetic drugs have antioxidant properties, either by boosting the body's own antioxidant enzymes or by reducing the production of harmful reactive oxidants. These antioxidant effects are linked to a lower risk of developing diabetic complications, including DNP. While certain antidiabetic medications may help prevent DNP from becoming more severe, others may have no effect or may even exacerbate the condition.

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Abbreviations: AGEs, advanced glycation end products; AMPK, adenosine monophosphate-activated protein kinase; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; DAG, diacylglycerol; DM, diabetes mellitus; DNP, diabetic neuropathy; DPP IV, dipeptidyl peptidase IV; DSPN, distal symmetric polyneuropathy; GFAT, glutamine-fructose-6-phosphate aminotransferase; GlcNAc, N-acetylglucosamine; GLP-1, glucagon-like peptide 1; HBP, hexosamine biosynthetic pathway; MDA, malondialdehyde; NAD^+; nicotinamide adenine dinucleotide; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor κB; Nrf2, nuclear factor erythroid 2-related factor 2; OS, oxidative stress; PARP; poly(ADP-ribose) polymerase; PGC-1α; peroxisome proliferator-activated receptor coactivator 1α; PKC, protein kinase C; PPAR-γ, peroxisome proliferator-activated receptor γ; RAGE, receptor of advanced glycation end products; RNS, reactive nitrogen species; ROS, reactive oxygen species; SGLT-2, sodium-glucose co-transporter; SOD, superoxide dismutase; STZ, streptozotocin; TZD, thiazolidinedione; UDP-GlcNAc, uridine-5-diphosphate-N-acetylglucosamine

Key words: antidiabetics, antioxidants, diabetes, diabetic neuropathy, oxidative stress

Contents

1. Introduction

Morbidity and mortality rates associated with diabetes mellitus (DM) are high and result from hyperglycemia-related complications that can develop in various organ systems. The mechanisms involved in the development of complications are versatile and varied, with each complication being organ-specific (1). Diabetic neuropathy (DNP) is one of the most prevalent complications of DM, which affects >50% of individuals with long-standing DM. It is a microvascular complication characterized by pain and high morbidity rates, mostly caused by damage to the somatosensory nervous system. The longevity of diabetes and hemoglobin A1c levels are two key predictors of DNP. The latter is often linked to poor glycemic control, genetic predisposition, environmental variables, metabolic factors and cardiovascular risk factors (2).

Even though there are several factors at play in the development of DNP and the precise pathogenic process remains unknown, numerous theories can be described. Hyperglycemia and a complex metabolic imbalance, primarily oxidative stress (OS), are current hypotheses (3). Since neurons obtain glucose via facilitated concentration-dependent transport, they are probably more vulnerable to glucose flow, which leads to elevated levels of OS. The polyol pathway, diacylglycerol (DAG)/protein kinase C (PKC), hexosamine biosynthetic pathway (HBP), advanced glycation end products (AGEs)/inflammation and nitric oxide all play critical roles in DNP. Evidence suggests that OS plays a role in each of the aforementioned pathways (4-6).

Despite concerted efforts to detect and prevent the progression of DNP, there are presently only a limited number of alleviative medications available; the remainder essentially provide symptomatic improvement. In the meantime, the present objective of DNP treatment is to improve quality of life and functionality of patients, while reducing pain. However, beyond glycemic control, several antidiabetic medications can alleviate DNP and prevent its progression (7-9). The aim of the present review was to synthesize currently available knowledge on OS-related mechanisms in DNP, while critically appraising the evidence on the antioxidant potential of various antidiabetic drug classes. By integrating mechanistic insights with clinical outcomes, the present review aimed to bridge the gap between basic the pathophysiological understanding and therapeutic applications for this condition. Unlike prior reviews, the present review discusses antidiabetic agents, such as metformin, pioglitazone, dapagliflozin and others, with emphasis on OS modulation and mechanistic pathways linked to diabetic neuropathy and integrates clinical prescribing recommendations, providing a practical translation of mechanistic insights into the management of diabetes.

2. Clinical spectrum of DNP

The dorsal root ganglia neurons are subjected to systemic metabolic and hypoxic stresses, rendering them very sensitive to damage. The structure of the sensory system outside the blood-brain barrier may also explain its extraordinary vulnerability. DNP presents as a diffuse neuropathy (distal symmetrical polyneuropathy or autonomic neuropathy), as well as mononeuropathy or radiculopathy/polyradiculopathy. Distal symmetric polyneuropathy (DSPN), the most common form of DNP, is mostly accompanied by pain and distal sensory loss. However, approximately half of the patients do not experience any symptoms (10). The symptoms are usually manifested as a perception of tingling, numbness, sharpness, or burning that begins in the feet and extends proximally. The clinical feature of DSPN is that symptoms manifest in the lower extremities at rest and worsen at night. Paresthesia, hyperesthesia and dysesthesia may also occur. The pain becomes less severe over time with DSPN; however, there is still a loss of sensory function, and motor dysfunction may appear (11).

Another form of DNP is autonomic neuropathy, which is presented as autonomic dysfunction and is manifested in patients with long-term DM, affecting both the parasympathetic and sympathetic nervous systems. Thus, it can affect a number of systems, including the cardiovascular system. Complications of cardiac autonomic neuropathy include resting tachycardia, exercise intolerance, orthostatic hypotension associated with dizziness, silent myocardial ischemia and an increased risk of sudden death syndrome. Other systems that are also affected include the gastrointestinal (bloating, diarrhea, or constipation), genitourinary (infections, bladder dysfunction, or sexual dysfunction) and metabolic (sweating abnormalities, and trouble identifying low blood sugar) systems (12). Mononeuropathy, a less prevalent form of DNP, manifests as a painful sensation and a lack of strength in the muscles along with motor dysfunction in a particular nerve. Mononeuropathy involves the malfunctioning of isolated cranial or peripheral nerves and may be non-compressive or arise at entrapment sites such as as the carpal tunnel. Other examples of peripheral mononeuropathies include ulnar neuropathy at the elbow, peroneal neuropathy at the fibular head, radial neuropathy causing wrist drop, and femoral neuropathy with quadriceps weakness (13).

3. Oxidative stress in diabetes

OS describes a condition when there is an imbalance between the generation of oxidants inside the body and the endogenous antioxidant system. Free radicals or other oxidants mediate OS. Free radicals include reactive oxygen species (ROS), which are the most critical, and reactive nitrogen species (RNS). Previous population studies on DM and its chronic complications have provided evidence of an association between DM and OS (14-16).

ROS are naturally occurring oxygen-containing free radicals that result from oxygen metabolism as a byproduct. These include hydrogen peroxide, superoxide anion radicals, hypochlorite, oxygen singlet and hydroxyl radicals. They arise inside organelles, such as the mitochondria, endoplasmic reticulum and peroxisomes. Mitochondrial OS impairs insulin signaling, leading to insulin resistance, and contributes to pancreatic β-cell dysfunction and death (15). When the protein folding capacity of the endoplasmic reticulum is overwhelmed, it triggers an unfolded protein response that, if prolonged, can lead to inflammation and the apoptosis of insulin-producing cells and insulin resistance. The dysfunction of peroxisomes worsens the metabolic imbalances observed in diabetic patients and interferes with insulin secretion. However, RNS comprise nitric oxide, the nitroxyl ion, peroxynitrite anion, nitrosyl-containing compounds, and organic hydroperoxide (17).

To blunt or scavenge the excessive generation of ROS, and consequently OS, cells have a variety of defensive mechanisms. Antioxidant enzymes, such as glutathione peroxidase, catalase, and superoxide dismutase (SOD) are among these (18). Glutathione peroxidase eliminates hydrogen peroxide and lipid peroxides via detoxification, whereas SOD scavenges superoxide radicals by promoting their conversion into hydrogen peroxide. Catalase catalyzes the decomposition of hydrogen peroxide into oxygen and water. Hyperglycemia can suppress the endogenous antioxidant defense system, which may alter the activity of antioxidant enzymes. For instance, SOD is known to be inactivated by increased hydrogen peroxide concentration, although its activity may also be reduced by glycosylation of the enzyme and/or loss of copper,

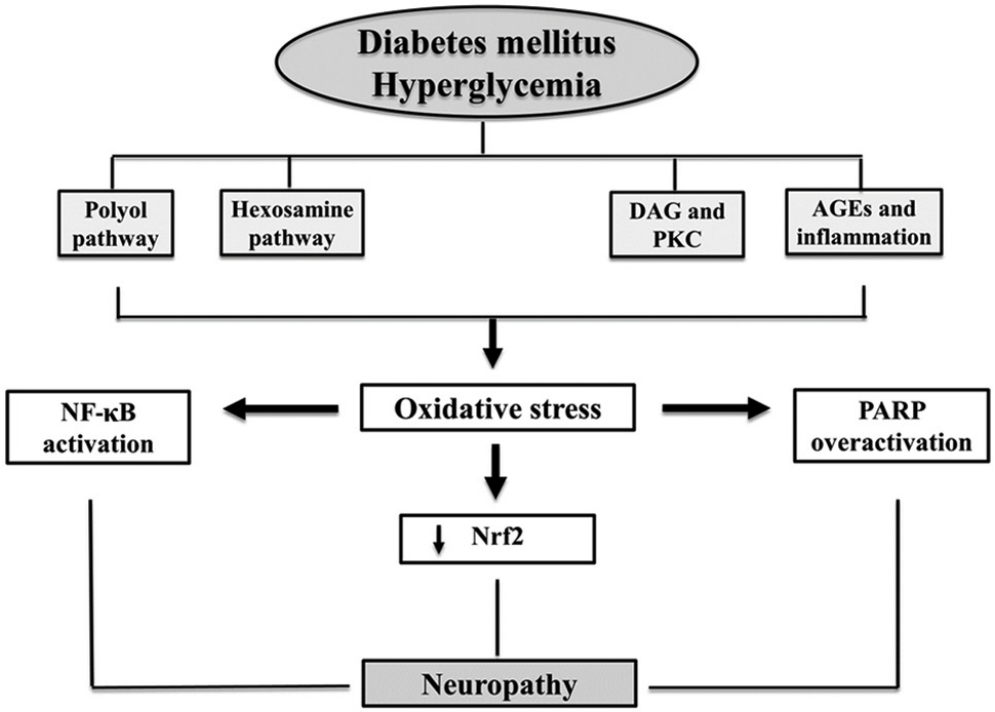

Figure 1. Mechanisms of oxidant generation in diabetic neuropathy: Hyperglycemia activates four main pathways that lead to the formation of ROS and ultimately oxidative stress. Oxidative stress leads to the activation of PARP along with inflammatory process activation and reduces the level of Nrf2. With time, these pathways lead to neuropathy (98,99). AGEs, advanced glycation end products; DAG, diacylglycerol; NF-κB, nuclear factor κB; Nrf2, nuclear factor 2; PARP, poly(ADP-ribose) polymerase.

an essential cofactor. OS in diabetic patients may arise due to either an increase in the generation of free radicals or a decline in the protective mechanisms of antioxidants (19). Another mechanism for scavenging the excessive generation of ROS is the non-enzymatic antioxidants. These include metal-binding proteins such as ferritin, which sequester pro-oxidant metals; glutathione, a primary cellular reductant that neutralizes free radicals; uric acid, a potent scavenger of hydroxyl radicals; melatonin, a potent antioxidant and free radical scavenger that easily crosses cell membranes; bilirubin, which provides lipophilic antioxidant protection; and polyamines, which stabilize cellular structures and directly scavenge ROS (20).

4. Mechanisms of oxidant generation in DNP

Evidence is presented to support the hypothesis that both chronic and acute high blood sugar levels lead to OS in the peripheral nervous system, which may contribute to the onset of DNP. Various damaging molecular mechanisms may clarify the adverse consequences of reactive oxidants in DNP generated by hyperglycemia (Fig. 1). These mechanisms include the polyol pathway and HBP, which have consistently been recognized in patients with DNP. The AGE and PKC pathways exert direct or indirect effects on proteins, lipids, and DNAs via glucose. All these are associated with DNP through the excessive production of ROS, a distinguishing characteristic found in all cell types affected by hyperglycemia (21).

OS, when combined with hyperglycemia, triggers the induction of poly(ADP-ribose) polymerase (PARP), which then breaks down nicotinamide adenine dinucleotide (NAD^+) into nicotinamide and ADP-ribose fragments. This process proceeds via the interaction with nuclear proteins, leading to alterations in gene expression and transcription, depletion of NAD^+, and the redirection of glycolytic products towards other disease-causing mechanisms, such as PKC and AGEs (21,22).

Activated polyol pathway. Under conditions of hyperglycemia, excess glucose saturates glycolysis in nerve cells, diverting it into the polyol pathway (Fig. 2). This pathway, involving aldose reductase and sorbitol dehydrogenase, converts glucose to sorbitol and then fructose, consuming nicotinamide adenine dinucleotide phosphate (NADPH) and generating NADH. This process markedly contributes to ROS production, driving OS (23).

The polyol pathway results in a decline in intracellular NADPH levels and an accumulation of NADH. The greater production of NADH serves as a substrate for NADH oxidase, leading to the production of ROS. Intracellular hyperosmolarity occurs due to an elevated polyol flow, which leads to the buildup of impermeable sorbitol and the efflux of other osmolytes. Consequently, the inhibition of adenosine triphosphate (ATP) production occurs (24). The conversion of glucose to sorbitol by the action of aldose reductase leads to the utilization of NADPH. Since NADPH is necessary for the reformation of reduced glutathione, this process directly adds to OS generation. Furthermore, the conversion of sorbitol into fructose contributes to glycation, leading to reduced NADPH availability and elevated AGEs, all of which contribute to a significant disruption in redox balance (25).

As regards DNP, the peripheral nerves of diabetic patients have been shown to exhibit an accumulation of sorbitol and

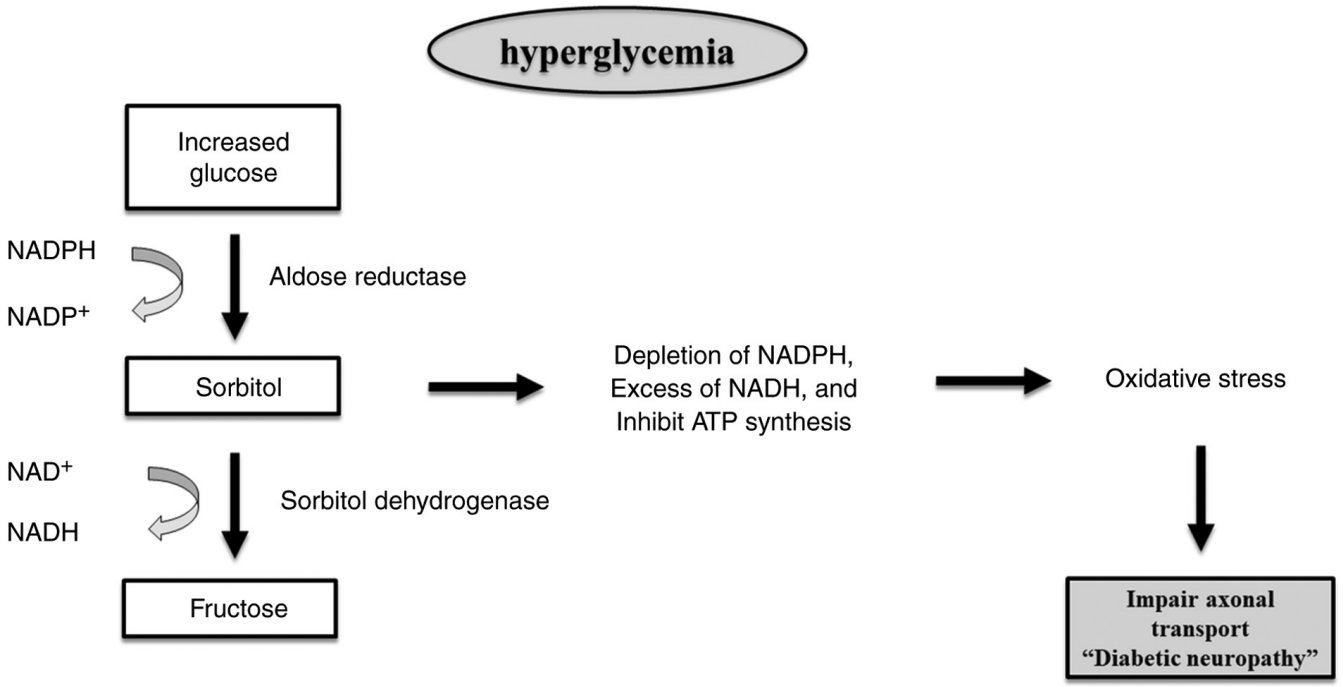

Figure 2. Contribution of the polyol pathway in diabetic neuropathy: Hyperglycemia associated with diabetes results in the shifting of normal glucose metabolic pathways, activating the polyol pathway as an alternative pathway. The polyol pathway converts glucose into sorbitol which is in turn converted to fructose. This results in NADPH depletion and excess of NADH, causing a decrease in ATP synthesis and an increase in ROS production. As a result, nerve function is impaired, and this results in DNP (100,101). NADPH, nicotinamide adenine dinucleotide phosphate; NADH, nicotinamide adenine dinucleotide; ATP, adenosine triphosphate.

fructose. Additionally, the shunting of glycolytic intermediates to the polyol pathway increases glycation and the generation of DAG in the dorsal root ganglia. These processes minimize the activity of Na^+/K^+-ATPase, suppressed axonal transport and the structural deterioration of nerves, ultimately manifesting as an abnormal action potential. Therefore, the suppression of the polyol pathway remains a focal point for therapeutic development in the control of diabetic neuropathy (26,27).

HBP. Diabetic complications, including DNP, may be caused by the shunting of excess glucose in nerve cells into another pathway rather than glycolysis, including the HBP, in addition to the polyol pathway (28). The most commonly proposed mechanism by which HBP contributes to DNP is the effect of intracellular uridine-5-diphosphat-N-acetylglucosamine (UDP-GlcNAc) on the modification of proteins (Fig. 3). Under healthy conditions, the HBP represents a minor pathway of the glycolytic system, with glutamine-fructose-6-phosphate aminotransferase (GFAT), the rate-limiting enzyme, converting only 2 to 5% of fructose-6-phosphate to glucosamine-6-phosphate (29).

However, under conditions of hyperglycemia, the increased generation of ROS inside the mitochondria hinders the action of the glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase, which inhibits fructose-6-phosphate from flowing through glycolysis (30). Subsequently, UDP-GlcNAc is established from glucosamine-6-phosphate, acetyl-CoA, and uridine-5-triphosphate. UDP-GlcNAc regulates the activity of *O*-linked *N*-acetylglucosamine transferase, which is present in both the nucleus and cytosol. The latter is an enzyme that transfers N-acetylglucosamine (GlcNAc) to certain serine and threonine residues on proteins, allowing for a reversible posttranslational modification. Notable proteins that have undergone O-GlcNAcylation, including glucose transporter 4 and insulin receptor substrates 1 and 2, result in insulin resistance (31,32).

Concerning DNP, there was a noticeable increase in GFAT activity and UDP-GlcNAc levels in the muscle of ob/ob mice. By contrast, mice with continuous caloric restriction exhibit a decrease in the UDP-GlcNAc concentration, which is accompanied by an improvement in insulin sensitivity in their muscles (33). Since peripheral nerves are highly metabolically active and insulin-dependent, this disruption directly links insulin resistance to neuronal injury, leading to axon degeneration, demyelination, and ultimately, DNP. However, the particular peripheral nerve proteins that can be altered by the activated HBP in response to DM have yet to be identified. Therefore, further investigations are required to fully elucidate the interplay between HBP and DNP (21).

AGEs and inflammation. Hyperglycemia increases the formation of AGEs by non-enzymatic reactions between reducing sugars and proteins, nucleic acids, or lipids. These groups tend to impair the biological activity of proteins, affecting cellular function. AGEs promote modification through glycation of the extracellular matrix protein laminin, which causes impaired regenerative activity in DNP. In addition, AGEs induce segmental demyelination; as a result, the nerves become susceptible to phagocytosis by macrophages. Axonal atrophy, degeneration and impaired axonal transport are consequences of AGE-modified major axonal cytoskeletal proteins such as tubulin, neurofilamen and actin (34).

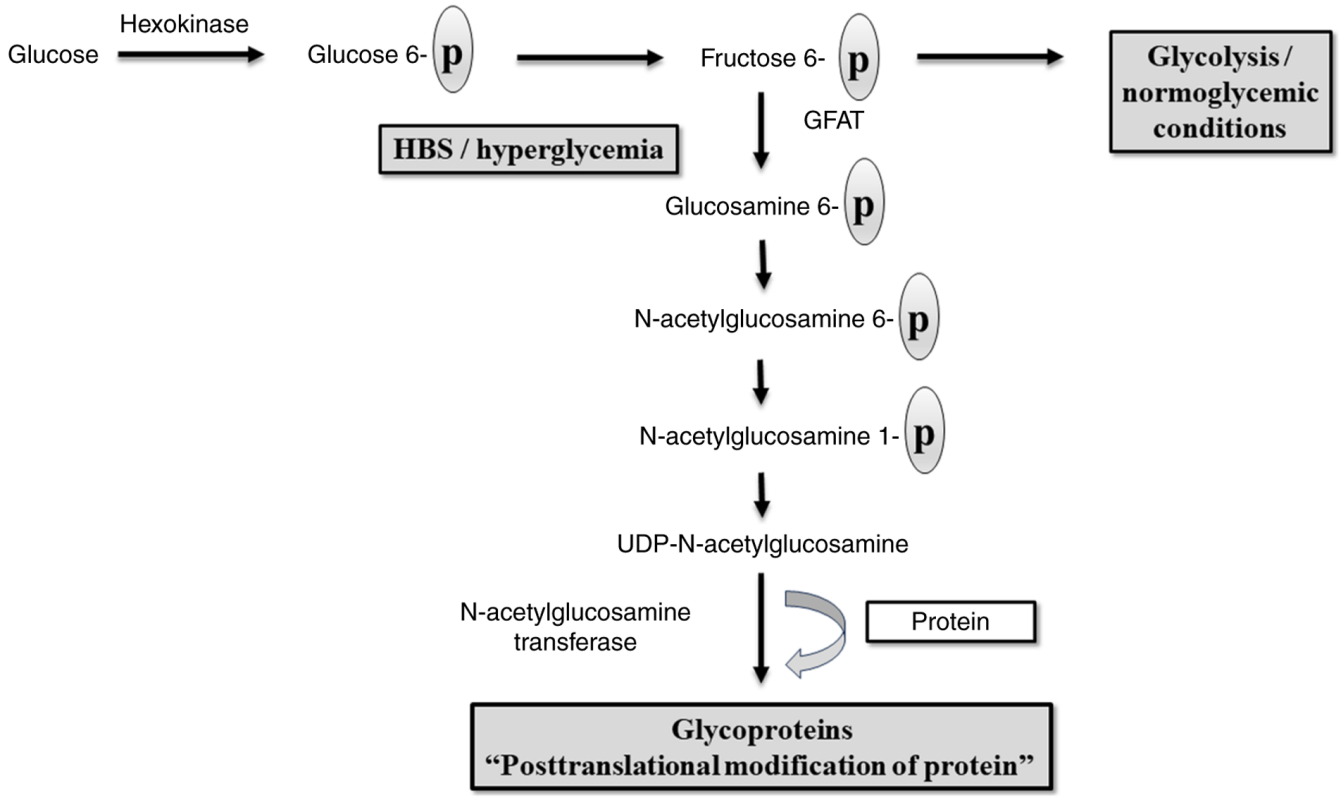

Figure 3. Hexosamine biosynthetic pathway: Under normal conditions, glucose undergoes a phosphorylation process catalyzed by hexokinase, and phosphorylated glucose is formed which is then converted to fructose that undergoes glycolysis. In hyperglycemia, shifting from glycolysis into a hexosamine biosynthetic pathway occurs resulting in the formation of UDP-N-acetylglucosamine, the rate-limiting step is catalyzed by GFAT. UDP-N-acetylglucosamine interferes with the action of N-acetylglucosamine transferase, an enzyme that interferes with the action of a number of proteins, including insulin receptor substrate and glucose transporter protein (102,103). GFAT, glutamine-fructose-6-phosphate aminotransferase; HBS, hexosamine biosynthetic pathway; UDP, uridine diphosphate.

In the peripheral nerves of diabetics, the AGE receptor [receptor of advanced glycation end products (RAGE)] has been shown to colocalize with AGEs. It appears that AGEs and their interactions with RAGE cause OS in DNP (35). Consequently, this leads to an increase in nuclear factor κB (NF-κB) and numerous pro-inflammatory genes regulated by NF-κB. Furthermore, the blood of individuals with DM contains inflammatory mediators, such as C-reactive protein and TNF-α (5,36). The combined effects of AGE-induced biochemical damage include reduced neurotrophic support, nerve blood flow impairment, neuronal integrity disruption and compromised repair mechanisms (37).

DAG and PKC pathway. Chronically increased levels of DAG occur in hyperglycemia as a result of an increased glycolytic intermediary, dihydroxyacetone phosphate. This intermediate is converted into glycerol-3-phosphate, which then enhances the production of DAG by *de novo* synthesis. The PKC family consists of 11 isoforms, of which nine are activated by DAG. The activation of the DAG-PKC pathway increases ROS production via NADPH oxidase, reinforcing OS, while simultaneously disrupting mitochondrial electron transport, uncoupling endothelial nitric oxide synthetase and influencing transcription factors, such as NF-κB, which promotes pro-inflammatory signaling (38).

Animal studies support the role of PKC in DNP, as inhibition using LY333531 has been shown to improve sciatic nerve blood flow, conduction and hyperalgesia (39). PKC activation contributes to neuropathy via two mechanisms: Reduced activity limits blood flow and alters conduction, while excessive activity disrupts neuronal function by affecting neurochemical signaling. Several PKC inhibitors, similar to aldose reductase inhibitors, also demonstrate antioxidant properties antioxidant (40).

PARP overactivation. PARP is a nuclear enzyme that facilitates the attachment of ADP-ribose units to DNA, histones and other DNA repair enzymes. This process has an impact on cellular functions (41). Recent evidence indicates that the overactivation of PARP and the occurrence of OS are two interconnected pathways. PARP activity is minimal under normal physiological circumstances. Nevertheless, in the presence of OS, DNA single-strand breaks become abundant and result in excessive activation of PARP. As regards DNP, research has demonstrated that the overactivation of PARP may contribute to the development of DNP, whereas preventing its function may impede the progression of this condition (42). PARP is found in both endothelial cells and Schwann cells inside the peripheral nerve. The activation of PARP is evident in DM and plays a role in diabetic endothelial dysfunction, which is a key contributor to DNP. Activation of PARP induces marked metabolic alterations and influences the expression of genes. Furthermore, PARP is necessary for the translocation of apoptosis-provoking

factors from the mitochondria to the nucleus. This process plays a crucial role in PARP-mediated programmed cell death, which has recently been linked to the development of DNP (43).

Nuclear factor erythroid 2-related factor 2 (Nrf2) in DNP. Nrf2 is a major leucine zipper protein that mainly acts as a defense mechanism against cellular OS. It functions as a transcription factor to regulate the development of cytoprotective enzymes. Typically, Nrf2 is not active within cells; however, it becomes activated when there is stress or an increase in the generation of free radicals (44). Upon activation, Nrf2 translocates to the cell nucleus and selectively interacts with the DNA at the antioxidant response element, decreasing free radicals and OS. Similarly, in the presence of DM, elevated blood sugar levels lead to the activation of several neuroinflammatory pathways and the generation of free radicals. During the first phases of hyperglycemia, Nrf2 signaling plays a crucial role in controlling the activation of several cytoprotective genes. However, in cases of prolonged hyperglycemia, the levels of Nrf2 decline, leading to the development of DNP via linked neuroinflammatory pathways (3).

5. Impact of antidiabetics on DNP and oxidative stress

Generally, antidiabetics cannot interfere directly with the polyol pathway or HBP, which are the main pathways of the generation of free radicals in DNP (45). Nevertheless, antidiabetic medications can decrease the production of AGEs and disrupt the activation of the PKC pathway. In addition, antidiabetics tend to suppress the inflammatory condition that often induces OS (46-48). Some antidiabetics exert antioxidant effects either by improving the endogenous antioxidant enzymes, such as SOD and catalase, or by reducing the production of ROS. The antioxidant effects of antidiabetics are accompanied by a reduction in the occurrence of diabetic complications, including DNP. Thus, in the case of DNP or high-risk conditions, some antidiabetics may be recommended over others (Table I) (49).

Metformin. Metformin, a biguanide derivative, is primarily used for controlling type 2 DM. Adenosine monophosphate-activated protein kinase (AMPK) is a key prospective target of metformin since it serves as a cellular energy sensor that becomes activated in response to metabolic stress, leading to improved glucose uptake (50). Metformin can significantly reduce the OS associated with diabetic patients. Previous studies have demonstrated that metformin has the ability to inhibit mitochondrial complex I (NADH:ubiquinone oxidoreductase), which contributes to the antioxidant effect of metformin (51-53).

The cellular production of ROS may be greatly influenced by mitochondrial complex I. There is much documentation indicating that a blockage of this complex results in a decrease in the generation of reactive species. This is caused by a reduction in the transportation of electrons from NADH plus hydrogen. In addition, metformin has been demonstrated to scavenge oxygenated free radicals produced *in vitro* directly and to inhibit the opening of the mitochondrial permeability transition pore in both intact and permeabilized human epithelial carcinoma cells (KB cells), as well as in permeabilized human microvascular endothelial cells (HMEC-1 cells) (51,54).

The use of metformin for the treatment of the manifestations of DNP in both animals and humans has yielded inconclusive results to date. Several studies have proven the positive benefits of metformin on DNP (55-58). Metformin has been shown to reduce the accumulation of AGEs in the sciatic nerves of rats with streptozotocin (STZ)-induced diabetes by activating AMPK, leading to improved nerve conduction velocity, and the attenuation of heat and mechanical hyperalgesia (59). It has also been shown to decrease serum malondialdehyde (MDA) levels and enhance SOD activity, highlighting its role in counteracting diabetes-induced OS (59).

Conversely, other studies suggest that metformin may worsen neuropathic outcomes, with reports of it functioning as an iatrogenic factor contributing to more severe neuropathy in type 2 DM (60). This negative effect has been partly attributed to the association of long-term metformin use with vitamin B12 deficiency, a known risk factor for DNP. These contrasting findings underscore the complexity of the effects of metformin on DNP, indicating a dual role where protective mechanisms against OS may be counterbalanced by adverse effects under certain conditions (61).

Sulfonylureas. Sulfonylureas promote insulin secretion by their interaction with the ATP-sensitive potassium channel located on the β-cell of the pancreas. Sulfonylureas decrease the level of AGEs indirectly by controlling blood glucose levels (62). The administration of glimepiride has been shown to cause a decrease in the levels of peroxides and MDA, and an increase in the activity of SOD and glutathione peroxidase in rats following the administration of STZ; this suggests that glimepiride may effectively inhibit the development of OS in DM (63). Gliclazide also exerts a prominent antioxidant effect mainly due to the free radical scavenging effect. The main mechanism for this effect is not yet clearly understood; however, the characteristic of an azabicyclo-octyl ring grafted on a hydrazide group, a structure unique to gliclazide, may provide the compound with free radical scavenging properties (64). Glibenclamide, glipizide, tolazamide and other sulfonylureas do not exert antioxidant effects. Similar to sulfonylureas, meglitinides such as repaglinide and nateglinide form a bond with the KATP channel on the pancreatic beta cells, but at a different binding location. However, it has not been shown that these medications have any antioxidant properties (65).

In the aspect of DNP control, gliclazide is a novel sulfonylurea that inhibits the development of DNP. Regardless of blood glucose levels in mice with STZ-induced diabetes, gliclazide considerably reduces peripheral nerve morphological alterations and improves the slowing of motor nerve conduction velocity. The morphological alterations observed in diabetic rats compared to non-diabetic rats include an increase in nerve fiber density and a reduction in fascicular area, axon/myelin ratio and nerve fiber area (66). Animal research has demonstrated that potassium-ATP channel blockage by sulfonylurea may enhance glutamate-induced superoxide generation and neurotoxicity by selectively intensifying mitochondrial inhibitors; however, no such data have

Table I. Effects of antidiabetics on diabetic neuropathy along with antioxidant effects.

Drug group	Antioxidant effect	Effect on diabetic neuropathy	(Refs.)
Metformin	Present	Inconclusive effects: Several studies have proven positive benefits; on the other hand, it may be an iatrogenic cause of DNP exacerbation	(55-58,60)
Sulfonylurea	Present	Beneficial effects (gliclazide)	(66)
Thiazolidinediones	Present	Beneficial effects	(7,71)
SGLT-2 inhibitors	Present	Beneficial effects	(75)
DDP-IV inhibitors	Present	Beneficial effects	(91-93)
GLP-1 receptor agonists	Present	Inconclusive effects: Some studies have proven positive effects, while others have failed to demonstrate improvements in the clinical presentations of DNP	(80,81,83-85)
Alpha-glucosidase inhibitors	No effect	No effects	(65)
Meglitinides	No effect	No effects	(65)

SGLT-2, sodium-glucose co-transporter; DPP IV, dipeptidyl peptidase IV; GLP-1, glucagon-like peptide 1.

been reported for humans, at least to the best of our knowledge (67).

Thiazolidinediones (TZDs). TZDs exert their insulin-sensitizing effects through the activation of the peroxisome proliferator-activated receptor γ (PPAR-γ) nuclear receptor, hence reducing insulin resistance. TZDs possess exert antioxidant effects. The potential mechanism may be attributed to the triggering of the transcription of several genes, including NADPH, SOD and catalase, via the activation of PPAR-γ receptors, resulting in the improvement of mitochondrial health (68). Some TZDs, such as troglitazone, provide direct antioxidant effects via a side chain that resembles α-tocopherol, in addition to their ability to indirectly upregulate antioxidant genes. Due to their ability to decrease NO production via the trans-repression of inducible nitric oxide synthetase, all TZDs exert intracellular antioxidant effects. Pioglitazone is beneficial in reducing OS via correction of the PKC pathway and pro-inflammatory process (69).

It has been shown that the administration of pioglitazone improves biochemical markers via reduced MDA levels and improved GSH and SOD activities (70). Pioglitazone has also been shown to be more effective than metformin in reducing OS, as seen by a decrease in MDA levels. However, only metformin exerts an antioxidant effect through an increase in SOD levels. The distinct mechanisms of action of the two medications on OS support the concurrent prescription of both treatments to enhance the result in ameliorating insulin resistance and diabetes complications (49). TZDs are associated with increased total serum soluble RAGE levels that may lead to a decrease in the harmful effects of AGEs. Furthermore, TZDs reduce the tissue expression of RAGE, resulting in decreased proinflammatory effects of AGEs (62).

Several studies have been conducted to demonstrate the efficacy of TZD in slowing or preventing the progression of DNP. In STZ-treated rats, troglitazone protected against nerve conduction velocity slowing and maintained normal myelinated fiber architecture and number (71). Pioglitazone has the triple advantage of lowering central sensitization, hyperglycemia and hyperalgesia; hence, TZDs are a desirable pharmacotherapy for those with neuropathic pain related to type 2 DM (7). Furthermore, pioglitazone has neuroprotective properties by enhancing nerve conduction velocity and diminishing macrophage infiltration in the sciatic nerve (72). Rosiglitazone reduces the OS in the sciatic nerve, thus reducing the progression of DNP (73).

Sodium-glucose co-transporter (SGLT-2) inhibitors. SGLT-2 inhibitors block SGLT2, which are responsible for glucose reabsorption in renal proximal convoluted tubules, leading to glycosuria and a reduction in blood glucose level. Recently, SGLT-2 inhibitors have been identified as potent antioxidant agents that can prevent oxidative damage to tissues by lowering glucose levels, generating fewer free radicals, or by potentiating the antioxidant system (Table II). The observed therapeutic advantages of SGLT-2 inhibitors in diabetic complications may be attributed to the reduction of OS (74).

A previous meta-analysis of 89 articles in the field of DNP demonstrated that SGLT-2 inhibitors have the potential to preserve the nerves by significantly enhancing the speed at which sensory and motor nerves conduct signals (75). This improvement in nerve function leads to improved clinical manifestations for patients with DNP, with a reduction in the activity of the sympathetic nervous system (75). A follow-up study demonstrated that the use of SGLT-2 inhibitors for >3 years led to significant improvements in certain measures of neuropathy (76).

Combining dapagliflozin and mecobalamin may considerably reduce clinical symptoms in patients with DNP. This combination may lower blood glucose, control MDA, SOD and cyclooxygenase 2 levels, and prevent nerve cell damage. Additionally, it promotes sensory and motor nerve transmission. The approach of using dapagliflozin and mecobalamin is safe and warrants clinical promotion (77).

Glucagon-like peptide 1 (GLP-1) agonists. GLP-1 receptor agonists, as a class of antidiabetic medications, have been

Table II. Mechanisms of SGLT-2 inhibitors in reducing oxidative stress (74).

Effect	Mechanisms
Reduction of free-radical generation	Decreasing the level of prooxidant enzymes, such as Nox and eNOS Reduction of levels of AGEs Lowering the level of proinflammatory cytokines Improvement of insulin sensitivity Normalization of hemodynamic condition Enhancement of mitochondrial function
Antioxidant effect	Directly via increasing the endogenous antioxidant system and scavenging the free radicals or indirectly by inducing normoglycemia.

eNOS, endothelial nitric oxide synthase; RAGE, the receptor for advanced glycation end product, Nox; nitrous oxide, AGEs, advanced glycation end products.

observed to enhance the secretion of insulin in response to glucose stimulation, inhibit the release of glucagon, and delay the process of stomach emptying. GLP-1 can reverse the oxidative action, as the administration of GLP-1 or its receptor agonist has been found to have a beneficial effect on OS markers, such as SOD, glutathione peroxidase, glutathione amount, glutathione reductase, catalase, lipid peroxidation and non-enzymatic glycosylated proteins, stimulated by different stress factors (78). The mechanism by which GLP-1 reduces OS in DM involves the activation of cyclic adenosine monophosphate (cAMP), PI3K and PKC pathways via receptors, as well as the activation of Nrf-2, increasing antioxidant capacity. These findings indicate that activating Nrf2 by GLP-1 and its subsequent antioxidative effects may have potential benefits in preventing and treating DM, as well as reducing the likelihood of complications. Also, GLP-1 receptor agonists were suggested to suppress OS generation induced by AGEs-RAGE and reduce tissue expression of RAGE via activation of cAMP pathways (79).

However, the effect of GLP-1s receptor agonists in DNP remain uncertain. Some clinical studies support the role of GLP-1 receptor agonists in improving DNP through a number of mechanisms including the antioxidant effect, the anti-inflammatory signaling through microglia/astrocyte modulation, improvement in peripheral nerve blood flow and endothelial function, and metabolic improvement (80,81). The antioxidant effect is one of the most effective mechanisms. GLP-1 receptor agonists activate SOD; however, they do not cause alterations in the distribution pattern of neuronal markers. Exenatide protects cells against apoptosis caused by OS and promotes neurite. These findings suggest that GLP-1 receptor agonists function as neuroprotective agents, considering their direct effects on neurons (82). Another study documented that the use of liraglutide alleviated DNP through antioxidant and anti-inflammatory effects, as well as via the remodeling of the extracellular matrix (81).

On the other hand, other research has demonstrated that GLP-1 receptor agonists have no significant effect in improving DNP (8). Despite the anti-inflammatory and antioxidant effects of liraglutide, no clinical improvement in autonomic neuropathy or polyneuropathy has been observed (83). In addition, exenatide has failed to provide a significant effect on DNP (84,85).

Dipeptidyl peptidase IV (DDP-IV) inhibitors. DPP-IV inhibitors prevent the breakdown of endogenous GLP-1, consequently enhancing the incretin action. DPP-IV, a cell surface enzyme found in endothelial cells and some lymphocytes, is responsible for the degradation of various peptides. DPP-IV inhibitors have been observed to stimulate insulin secretion without causing hypoglycemia or weight gain (86). Clinical studies have demonstrated that DPP-IV inhibitors exert antioxidant effects by reducing ROS generation and promoting the activity of antioxidant enzymes, including increased nitric oxide, SOD, catalase and reduced glutathione (87,88).

Furthermore, it has been discovered that the production of ROS caused by the AGE-RAGE interaction leads to the release of DPP-4. DPP-4 inhibitors prevent this release (89). Additionally, another study demonstrated that the use of vildagliptin, a DPP-4 inhibitor, was associated with decreased AGEs to a certain extent (90).

As regards DNP, sitagliptin plays protective roles on neurons via activating GLP-1 receptor, resulting in an anti-apoptotic effect, improving microtubule stabilization and axon regeneration, ameliorating mitochondrial dysfunction, and promoting locomotor functional recovery. The mechanism of action of sitagliptin in DNP is related to AMPK/peroxisome proliferator-activated receptor coactivator 1α (PGC-1α) signaling pathway. The activation of the AMPK/PGC-1α signaling pathway results in the development of neurites and the regeneration of axons (9). It is well-established that when teneligliptin is orally administered, it produces analgesic properties in humans specifically against thermal pain. It has been demonstrated that teneligliptin exerts mild antinociceptive effects in response to acute pain; however, it exerts, significant analgesic effects against DNP. Furthermore, teneligliptin can improve the synthesis of glutathione antioxidants inside the cellular environment (91,92). Vildagliptin improves glucose intolerance and increases serum insulin and GLP-1 levels, accompanied by the amelioration of delayed nerve conduction velocity and neuronal atrophy (93).

Alpha-glucosidase inhibitors. Alpha-glucosidase inhibitors attenuate the process of starch digestion in the gastrointestinal tract, resulting in a slow release of glucose into the circulation. The currently used alpha-glucosidase inhibitors consist of acarbose and miglitol. Thus far, there have been no documented antioxidant properties observed for these medications (65). However, a previous study demonstrated that miglitol improved the activity of catalase, SOD, glutathione peroxidase, glutathione reductase and thioredoxin reductase (94).

6. Clinical significance, prescribing recommendations and future directions

Clinical significance. Glycemic control is the primary goal of DNP treatment. The pathogenesis of the complication is regarded as the primary focus of interest while developing pharmaceutical DNP targets. Although there is no curative treatment for DNP, several medications can alleviate the symptoms. When managing diabetic neuropathy, it is important to select antidiabetics with antioxidant properties that attenuate the progression of the disease, in addition to controlling the blood sugar levels (75-77,95).

Prescribing recommendations. The use of metformin should be accompanied by routine vitamin B12 monitoring and supplementation to maximize its benefit in DNP, while minimizing deficiency-related risks. The use of pioglitazone may be considered in patients with neuropathic pain due to its neuroprotective potential, although caution is advised due to its side-effect profile. Combination therapy with metformin, pioglitazone and vitamin B12 supplementation may provide the most prominent protective effect against DNP (7,49,72,96). Concerning sulfonylureas, gliclazide is a novel sulfonylurea that inhibits the development of DNP (65). However, the use of sulfonylureas or insulin in combination with metformin and pioglitazone may worsen DNP (75,76,97). SGLT-2 inhibitors, particularly dapagliflozin, may be incorporated into diabetes therapy where neuropathy is a concern, with potential added benefit when combined with cobalamin (77).

The effect of GLP-1 receptor agonists in DNP is uncertain, and the use of such medications in DNP requires further investigations (8,80,81,83-85). Sitagliptin, as a DPP-IV inhibitor, on the other hand, plays a protective role in neurons by improving the actions of GLP-1. The administration of sitagliptin in conjunction with metformin leads to enhanced grip strength and increased pain sensitivity, while also demonstrating neuroprotective effects (95).

Future directions. Future studies for the management of DNP are required to focus on identifying medications that can directly interfere with the main pathways of ROS generation, including the polyol pathway and HBP. Furthermore, additional studies may be required to provide sufficient insight into the role of antidiabetic combinations in preventing DNP, and to determine which combinations are the most effective.

7. Conclusion

Hyperglycemia and a complex metabolic imbalance, primarily OS, are current hypotheses for the progression of DNP. A number of antidiabetics exert antioxidant effects that can reduce OS in patients with DM. The antioxidant effects of antidiabetics are accompanied by a reduction in the occurrence of diabetic complications, including DNP. Some antidiabetics may be beneficial in preventing the progression of DNP, while others have no effect or could trigger or worsen the existing DNP. Thus, in the case of DNP or high-risk conditions, some antidiabetics may be recommended over others.

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Authors' contributions

KAH and MKZ were involved in the writing, reviewing and editing of the manuscript, as well as in the writing and preparation of the original draft of the manuscript, and the conceptualization of the study. FAA and MNA supervised the study, and were also involved in project administration, in the literature search and in the conceptualization of the study. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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