

REVIEW

How inflammation dictates diabetic peripheral neuropathy: An enlightening review

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Abstract

Background: Diabetic peripheral neuropathy (DPN) constitutes a debilitating complication associated with diabetes. Although, the past decade has seen rapid developments in understanding the complex etiology of DPN, there are no approved therapies that can halt the development of DPN, or target the damaged nerve. Therefore, clarifying the pathogenesis of DPN and finding effective treatment are the crucial issues for the clinical management of DPN.

Aims: This review is aiming to summary the current knowledge on the pathogenesis of DPN, especially the mechanism and application of inflammatory response.

Methods: We systematically summarized the latest studies on the pathogenesis and therapeutic strategies of diabetic neuropathy in PubMed.

Results: In this seminal review, the underappreciated role of immune activation in the progression of DPN is scrutinized. Novel insights into the inflammatory regulatory mechanisms of DPN have been unearthed, illuminating potential therapeutic strategies of notable clinical significance. Additionally, a nuanced examination of DPN's complex etiology, including aberrations in glycemic control and insulin signaling pathways, is presented. Crucially, an emphasis has been placed on translating these novel understandings into tangible clinical interventions to ameliorate patient outcomes.

Conclusions: This review is distinguished by synthesizing cutting-edge mechanisms linking inflammation to DPN and identifying innovative, inflammation-targeted therapeutic approaches.

KEYWORDS

diabetic neuropathy, inflammatory response, metabolic changes, molecular mechanism

The first three authors contributed equally to this work.

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1 | INTRODUCTION

Diabetic neuropathy is one of the significant complications of diabetes and occurs in approximately 50% of diabetes patients.^{1,2} Diabetes is a global epidemic, its prevalence continues to increase, and it is expected to affect 693 million adults by 2045,^{3,4} which means a corresponding increase in the incidence of diabetic neuropathy. Diabetic neuropathy affects different parts of the nervous system and presents multiple manifestations. The common forms of diabetic neuropathy are distal symmetric polyneuropathy (DSPN) and autonomic neuropathy.⁵ The past decade has seen rapid developments in understanding the complex etiology of diabetic neuropathy.

The pathogenesis of diabetic neuropathy is very complex. Hyperglycemia, dyslipidemia, and insulin resistance trigger a cascade of responses, activating pathways such as the polyol pathway, glycolysis pathway, hexosamine pathway, and advanced glycation end-product pathway. These activations enhanced oxidative stress and inflammatory signals, leading to endoplasmic reticulum stress, mitochondrial dysfunction, DNA damage, and elevated inflammatory factor levels. Ultimately, this complex process substantiates the onset of diabetic neuropathy.^{2,5-7} Despite the confirmation of these mechanisms through clinical and experimental studies, the quest for effective treatments remains ongoing. Therefore, clarifying the

pathogenesis of diabetic neuropathy and finding effective therapies are crucial issues for diabetic neuropathy.

In this review, we summarize the current knowledge on the pathogenesis of diabetic neuropathy, especially how metabolic factors affect the course of the disease and the indispensable role of the inflammatory response. Furthermore, we touch on recent advances in therapeutic strategies.

2 | PATHOGENESIS OF DIABETIC NEUROPATHY

The pathogenesis of diabetes involves insulin resistance in tissues (such as adipose tissue, muscle, and liver) and insufficient insulin secretion in pancreatic cells,^{8,9} which may lead to hyperglycemia. Thus, hyperglycemia is associated with the development of diabetic neuropathy. However, the cause of diabetic neuropathy is very complex and involves hyperglycemia, dyslipidemia, and insulin resistance (Figure 1).

High blood sugar, or hyperglycemia, is a crucial contributor to diabetic neuropathy, primarily through its damaging effects on nerves. This damage is propagated via multiple biological pathways (Figure 2).^{3,10-12} First, hyperglycemia excessively activates the glycolytic pathway in nerve and Schwann cells, leading to an accumulation

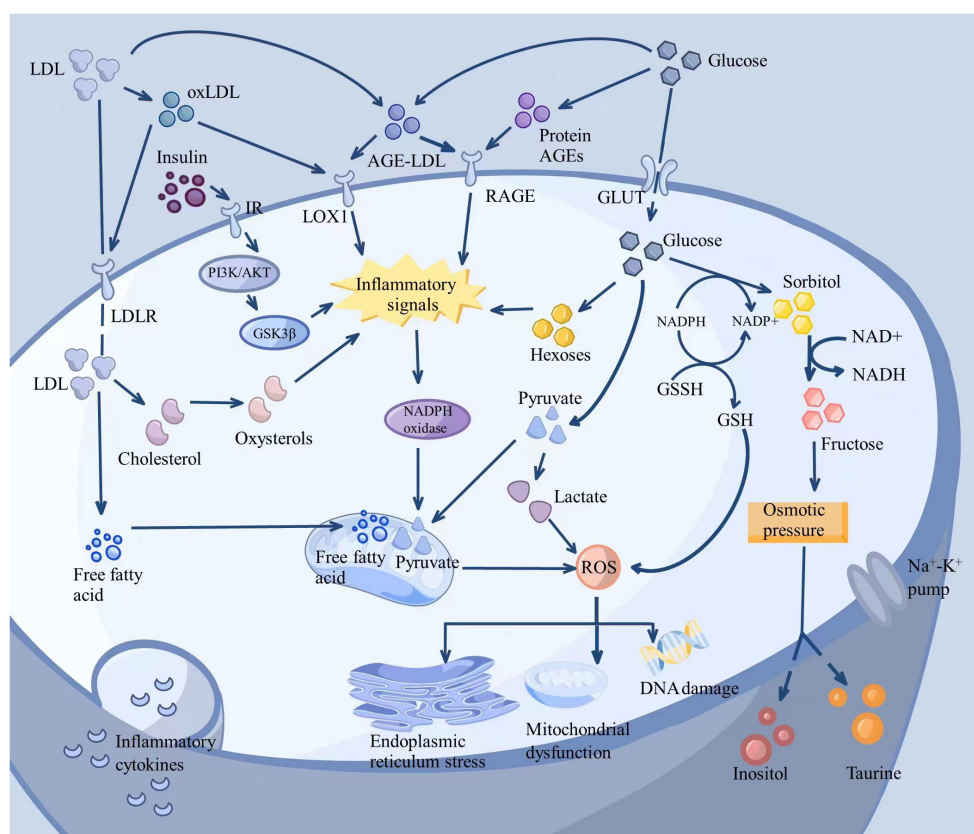


FIGURE 1 The pathogenesis of diabetic neuropathy. Hyperglycemia, dyslipidemia, and insulin resistance cause oxidative stress and inflammatory response, induce pathological alterations including DNA damage, endoplasmic reticulum stress, and mitochondrial dysfunction, and ultimately lead to diabetic neuropathy.

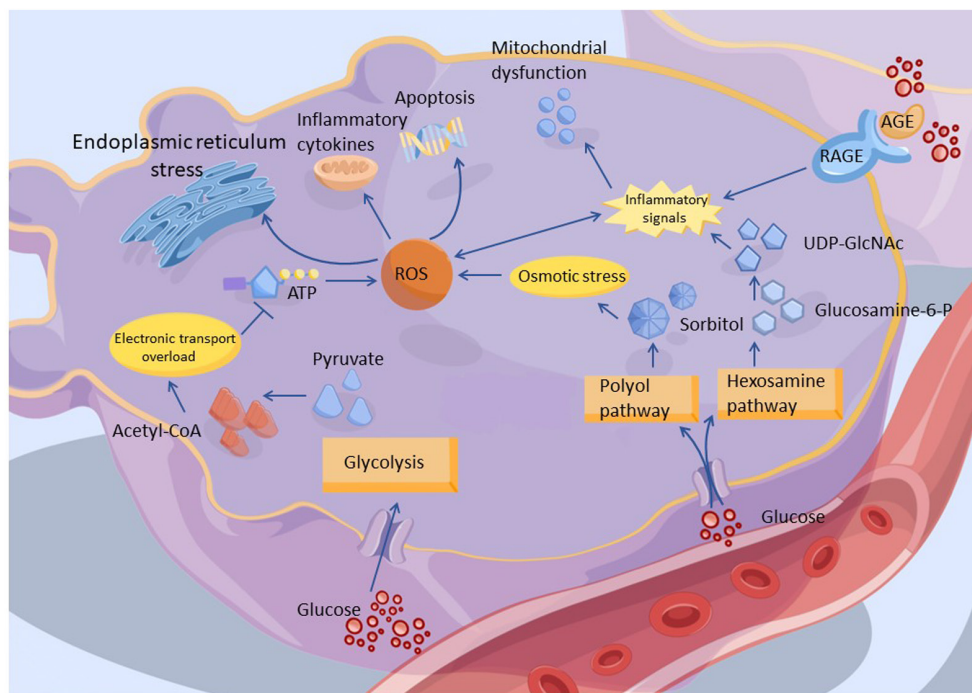


FIGURE 2 Hyperglycemia initiated injury mechanisms in neurons. Intracellular glucose is metabolized through the process of glycolysis principally. Besides, excess glucose activates advanced glycation end products (AGEs) formation and the polyol and hexosamine pathways. They cause an imbalance in the mitochondrial redox state, lead to excess formation of reactive oxygen species (ROS), and promote inflammatory response that result in neuronal injury.

of lactate and pyruvate.^{13,14} This accumulation causes oxidative stress and mitochondrial damage due to an increased voltage gradient on the mitochondrial membrane.^{15,16} Second, the polyol pathway, triggered by high blood sugar, results in an excessive buildup of sorbitol and fructose, activating the intracellular osmotic stress pathway. This pathway disrupts neuron function and its response to oxidative stress through an imbalance in myoinositol efflux and excessive consumption of NADPH.^{17–19} Third, excessive glucose can activate the hexosamine pathway, resulting in gene expression changes through the conversion of fructose-6-phosphate into uridine diphosphate N-acetylglucosamine (UDP-GlcNAc) and its subsequent binding to transcription factors.^{20–22} Finally, chronic hyperglycemia facilitates the formation of advanced glycation end products (AGEs) which alter protein structure and function. The binding of AGEs to their receptors in neurons and Schwann cells triggers an inflammatory response and additional oxidative stress.^{23–25}

Studies have shown that dyslipidemia accelerates the progression of neuropathy, even in patients in the early stages of diabetes.^{26,27} Dyslipidemia, especially triglycerides, and cholesterol are considered neurotoxic. Neuronal damage caused by dyslipidemia is associated with free fatty acids (FFA) and oxidized low-density lipoprotein (ox-LDL).^{27,28} Ox-LDL and glycated LDL bind to neuronal receptors, typically LDL receptor 1 (LOX1) and Toll-like receptor 4, triggering inflammatory signals and increasing oxidative stress responses.^{29,30} High levels of FFA lead to insulin resistance and hyperglycemia and enhance the complications of diabetes. FFA also induces mitochondrial dysfunction and accumulation of reactive

oxygen species through β -oxidation and lipid toxicity.³¹ Studies also show that high-density lipoprotein cholesterol is associated with the later development of diabetic neuropathy.³² It is also the only negative predictor of risk for diabetic foot ulcers.³³ In addition, higher levels of sphingolipids DSLs, associated with diabetic neuropathy, were found in patients with type 2 diabetes mellitus (T2DM), highlighting the intricate connection between lipid metabolism and diabetic neuropathy.³⁴

Insulin resistance (IR) plays a crucial role in the pathogenesis of diabetic neuropathy, and IR has a more significant role in T2DM neuropathy.³⁵ Low vitamin D levels appear to be associated with insulin-resistant diseases, such as T1DM, T2DM, and diabetic neuropathy.³⁶ IR cross-influences inflammatory responses, oxidative stress, and ectopic lipid accumulation in the liver and skeletal muscles.^{37–39} At the cellular level, insulin resistance affects diabetic neuropathy by damaging insulin signaling in postganglionic neurons and disrupting lipid metabolism in Schwann cells through the PI3K / AKT / mTOR pathway.⁴⁰

3 | ROLE OF THE INFLAMMATORY RESPONSE IN DIABETIC NEUROPATHY

Inflammation is an adaptive response triggered by noxious stimuli and conditions.⁴¹ Tissue stress or malfunction may induce mild chronic inflammatory activity by activating the innate immune system.⁴² Evidence shows that long-term mild inflammation has a

significant negative impact on the pathogenesis of diabetic neuropathy (Figure 3).^{43,44} Generally, glucose, lipoproteins, and oxidized and glycated proteins bind with various receptors on neurons. These receptors include transporters that internalize glucose and lipids, which increase the accumulation of glucose and lipids in cells and disrupt mitochondrial metabolic pathways. These receptors also initiate inflammatory signals.^{6,18,45} Immune cells, cytokines, chemokines, soluble adhesion molecules, and inflammation-related biomarkers are increased in peripheral nerve or cerebrospinal fluid samples from patients with diabetic neuropathy.^{46–52} Understanding the role of key inflammatory pathways and molecules in diabetic neuropathy will help discover anti-inflammatory approaches that could potentially inhibit the development of neuropathy. This section summarizes the inflammatory cells, molecules (including inflammatory cytokines, chemokines, and adhesion molecules), and critical inflammatory pathways (the NF- κ B pathway and the MAPK pathway) involved in developing diabetic neuropathy.

3.1 | Immune cells in DPN

In T1DM individuals with pain compared to those without, a proportional increase in CD4+ central memory T cells and an absolute increase in classical and nonclassical monocytes is observed among peripheral blood immunophenotypes.⁵³ Calcitonin gene-related

peptide (CGRP)-specific CD4 T cells may be a potential marker for T1DM. Given the widespread presence of CGRP in the nervous system and its critical role in developing peripheral neuropathic pain, CGRP is likely to play an important role in diabetic neuropathy.⁵⁴ In the early and late stages of disease in STZ-induced T1DM model animals, significant neutrophil infiltration was found in the dorsal root ganglia (DRG). T-cell infiltration in the DRG was prominent in the late phase.⁵⁵ Sciatic nerve samples from T2DM patients showed macrophage and T-cell infiltration and increased expression of clusters of cells expressing CD40, a critical, crucial molecule in the upregulation of HIF-1 α and PTEN underlying microangiopathy in diabetic nerve pathology.⁵⁶

The innate immune system utilizes distinct classes of pattern recognition receptors (PRRs), which recognize danger-associated molecular patterns (DAMPs) to initiate downstream inflammatory cascades (Figure 4).⁵⁷ Toll-like receptors (TLRs) are PRRs.⁵⁸ Emerging evidence shows TLR-mediated inflammatory cascades contribute to diabetic neuropathy.⁵⁹ TLR4 is highly expressed in endoneurial vessels of sciatic nerves in leptin-deficient ob/ob mice.⁶⁰ TLR4 downregulation ameliorated hyperalgesia and mechanical allodynia in an experimental diabetic neuropathy model.^{61,62} TLR2 is an important regulator that promotes the polarization of inflammatory macrophages, and TLR2 inhibitors were found to suppress inflammation and promote M2 phenotype macrophages in sciatic nerves from T2DM mice.⁶³

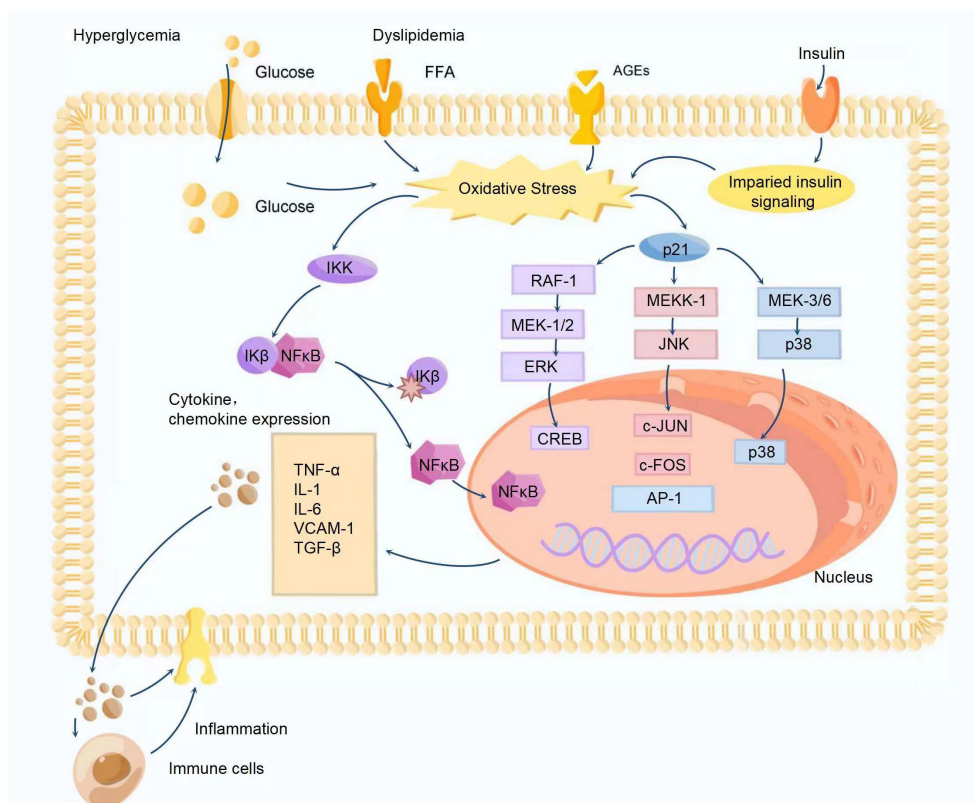


FIGURE 3 The role of DAMPs in inflammation-mediated diabetic neuropathy. Chronic exposure to hyperglycemia damages neurons, resulting in the release of intracellular damage-associated molecular patterns (DAMPs) into the extracellular space. DAMPs are recognized by PRRs such as Toll-like receptors. Activation of these receptors leads to inflammatory responses and progressive nerve injury.

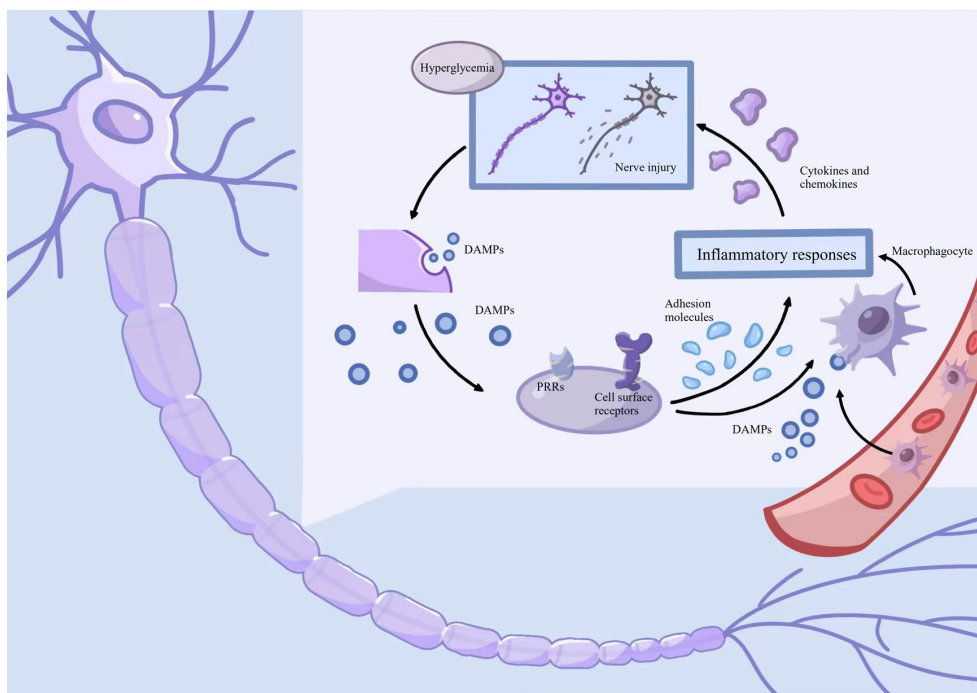


FIGURE 4 Inflammatory response implicated in the pathophysiology of diabetic neuropathy. Hyperglycemia and dyslipidemia together with insulin resistance result in the activation of stress and inflammatory pathways (NF- κ B and MAPK) leading to widespread changes in gene expression and upregulation of cytokines/chemokines, and soluble adhesion molecules, which further leads to the recruitment of immune cells, augmenting the inflammatory response.

Among innate immune cells, macrophages have been primarily investigated in diabetic neuropathy. A growing body of evidence has shown that macrophage polarization, according to their microenvironment, plays an essential role in the development of diabetes. M1 phenotype macrophages that promote inflammation favor glycolysis, produce lactate instead of metabolizing pyruvate to acetyl-CoA, and have a tricarboxylic acid cycle interrupted at two points. M2 phenotype macrophages that downregulate inflammation use the beta-oxidation of fatty acids and oxidative phosphorylation to create energy-rich molecules.⁶⁴ The recruitment of blood monocyte-derived macrophages in the spinal cord was found to promote the development of painful diabetic neuropathy in diabetes.⁶⁵

3.2 | Role of inflammatory cytokines in diabetic neuropathy

Cytokines are low-molecular-weight glycoproteins that are secreted mainly, but not exclusively, by immunological cells such as T cells, macrophages, and neutrophils. Other cells that secrete cytokines include Schwann cells and glial cells of the central nervous system. Proinflammatory cytokines, such as TNF- α , IL-1, IL-6, IL-8, monocyte chemoattractant protein-1, and C-reactive protein, are mainly produced by activated immune cells. Proinflammatory cytokines were reported to play a critical essential role in developing diabetic neuropathy. Table 1 lists clinical studies assessing the relationship between markers of inflammation and diabetic neuropathy (Table 1).^{44,50,51,66–68}

3.2.1 | Tumor necrosis factor- α (TNF- α)

TNF- α is a mighty potent proinflammatory cytokine mainly secreted by macrophages that can regulate the inflammatory response and immune cells.⁶⁹ Plasma concentrations of soluble fractions of TNF- α receptors 1 and 2 (sTNFR1 and sTNFR2, respectively) were found to be increased in diabetic neuropathy patients with T1DM.⁵⁰ In the Cooperative Health Research in the Region of Augsburg F4/FF4 cohort prospective study, it was reported that increased plasma levels of TNF- α predicted both the onset and progression of DPN.⁷⁰ Compared with nondiabetic mice, TNF- $\alpha^{+/+}$ diabetic mice have displayed significant impairments in motor and sensory nerve conduction velocities, tail-flick test, and intraepidermal nerve fiber density, as well as increased expression of NF- κ B p65 and cleaved caspase-3 in their DRG. Diabetic TNF- $\alpha^{-/-}$ mice showed no evidence of abnormal nerve function compared to nondiabetic TNF- $\alpha^{-/-}$ mice.⁷¹ Increased levels of TNF- α plasma protein were found in diabetic neuropathic patients and were closely related to neuropathic pain.⁷² Nerve biopsy in patients with painful neuropathy showed high expression levels of TNF- α .⁷³ TNF- α induces COX-2 overexpression, which, in turn, generates causes inflammatory changes that lead to DPN.⁷⁴ Membrane K⁺-ion conductivity can also be enhanced in a non-voltage-gated manner, resulting in the overexcitation of the whole neuron, resulting in TNF- α enhancing the tetrodotoxin-resistant (TTX-R) Na⁺ current in cultured DRG cells from wild-type animals compared to those from neuropathic pain model animals.⁷⁵ TNF- α automatically stimulates its production through G-protein-coupled

TABLE 1 Studies assessing the relationship between markers of inflammation and diabetic neuropathy.

Study	Protocol	Biomarkers	Main finding	Ref.
González Clemente 2005	120 patients with T1DM in Spain, 36 had diabetic neuropathy and 84 did not.	sTNFR1, sTNFR2	Higher sTNFR1 and sTNFR2 in diabetic neuropathy compared to T1DM without diabetic neuropathy.	50
Doupis 2009	212 individuals aged 21–80 years, 55 healthy control subjects, 77 diabetes patients with DPN, and 80 diabetes patients without DPN. The neuropathic group was subsequently subdivided into patients with and without neuropathic pain.	CRP, TNF α , fibrinogen, RANKL, OPG, IP-10/CXCL10, RANTES/CCL5, and leptin	Higher CRP, TNF α , fibrinogen, OPG, and leptin in diabetes patients with DPN compared to diabetes patients without DPN. Higher sICAM-1 and CRP in patients with painful neuropathy compared to painless neuropathy.	51
Zheng 2021	315 T2DM patients in China, with 6.5 years follow-up, evaluate the predictive effect of cytokines on incidence of DPN.	IL-6, TNF- α , VEGF, ICAM-1	Increased TNF- α and ICAM-1, predicted the incidence of DPN over 5 years in Chinese diabetes patients.	88
KORA F4 Study 2013	Determine serum concentrations of mediators of subclinical inflammation among 1047 participants 61–82 years of age in the German KORA F4 survey.	CRP, IL-6, IL-18, TNF α , IL-1RA, adiponectin	Higher IL-1RA in DPN patients; positive association of IL-6 and IL-1RA with MNSI score.	89
KORA F4 Study 2015	measured circulating levels of seven immune mediators and assessed their associations with the presence of painful DSPN in individuals with painless ($n=337$) and painful DPN ($n=54$) from participants aged 61–82 years ($n=1047$) in the German KORA F4 survey.	CRP, IL-6, IL-18, TNF α , IL-1RA, adiponectin	Higher IL-6 in painful compared to painless DPN.	90
KORA F4/FF4 Study 2017	530 participants in Germany aged 62–81 years with 6.5 years follow-up; evaluate the predictive effect of cytokines on incidence of DPN and DPN progression.	CRP, TNF α , IL-6, IL-1RA, IL-18, sICAM-1, adiponectin, omentin	Higher IL-6 and TNF- α associated with incident DSPN; sICAM-1 and IL-1RA were positively associated with progression of DPN	70
The German Diabetes Study	Motor and sensory NCV was assessed in 352 individuals with T2DM and 161 individuals with T1DM	CRP, IL-6, IL-18, total adiponectin, HMW adiponectin, HMW/total adiponectin	High-serum IL-6, HMW adiponectin, total adiponectin, and their ratio were associated with the presence of DPN and reduced motor NCV in T2DM. In T1DM, only HMW and total adiponectin showed positive associations with motor NCV.	91

receptors and TNF- α invertase, induces the expression of miR-146a, inhibits the expression of TRAK1 and TRAF6, and reduces the expression of Toll-like receptors,³⁰ which results in a series of reactions that lead to the production of IL-1, IL-6, NO, and ATP, all of which activate neurons involved in pathological pain.⁷⁵

3.2.2 | Interleukin 1 (IL-1)

IL-1 is a critical molecule in the immune system, mediating the inflammatory response to various stimuli. IL-1 produces multiple cytokines and chemokines by activating nuclear factors.⁷⁶ Compared with a control group and type 2 diabetes mellitus (T2DM) group, DPN rats expressed a higher level of IL-1 β .⁷⁷ In activated macrophages, lipopolysaccharide (LPS) activates the pentose phosphate pathway, the serine synthesis pathway, and one-carbon metabolism, the synergism of which drives epigenetic reprogramming for IL-1 β expression, which operates the proinflammatory phenotype.⁷⁸ IL-1 β plays a vital role in neuropathic pain. Liao YH et al. found that the expression of IL-1 β could be significantly enhanced by activated

astrocytes in the spinal cord, which may induce the phosphorylation of N-methyl-D-aspartate receptor (NMDAR) in spinal dorsal horn neurons and improve pain transmission in *db/db* mice.⁷⁹ However, the injection of IL-1 β alone does not induce a nociceptive effect.⁸⁰

3.2.3 | Interleukin 6 (IL-6)

IL-6 is not only a proinflammatory cytokine but also a pleiotropic cytokine that plays diverse physiological roles, including the regulation of immunity,^{81,82} metabolism,⁸³ endothelial function,⁸⁴ and neuronal activity.^{85,86} IL-6 is a sensitive marker for predicting the progression and severity of type 1 diabetic nephropathy.⁸⁷ Plasma levels of IL-6 predicted the incidence of neuropathy over 5 years in Chinese diabetes patients.⁸⁸ The KORA F4 study showed increased IL-6 with MNSI and painful DPN.^{89,90} Another study from Germany revealed that IL-6 was associated with DSPN and reduced motor NCV.⁹¹ It is unclear whether IL-6 is beneficial in developing diabetic neuropathy. IL-6 mediates pathological pain related to peripheral nerve injury,⁹² and IL-6 treatment caused marked improvements in

several measures of somatic sensory and motor nerve function of conduction velocities, tactile allodynia, and thermal hyperalgesia in experimental diabetes.^{93,94} In contrast, liraglutide treatment reduced the level of IL-6 in type 1 diabetic patients but did not improve the function of neurons.⁹⁵ IL-6 may have dual effects under different conditions.⁹⁶

3.2.4 | Interferon (IFN)- γ

IFN- γ is a lymphokine with diverse but mainly proinflammatory effects on immunocytes and target tissue.⁹⁷ IFN- γ plays an essential role in the development of neuropathy in nonobese diabetic (NOD) mice, and T-cell infiltration in the peripheral nervous system of NOD-B7-2KO mice is significantly reduced or even blocked due to a lack of IFN- γ .⁹⁸

3.3 | Role of chemokines in diabetic neuropathy

Chemokines are a large family of small chemokines that stimulate the migration of cells, especially leukocytes, by signaling through cell surface G-protein-coupled heptahelical chemokine receptors.⁹⁹ They are released locally at sites of inflammation and act as signaling molecules in the inflammatory response, which can activate various proinflammatory mediators and induce various inflammatory factors.^{80,100} Regarding the CXC family of chemokines, the expression of CXCL13 in human inflammatory demyelinating nerves is increased.¹⁰¹ In B7-2-deficient NOD mice that have developed spontaneous autoimmune polyneuropathy, CXCL10 mRNA levels are increased in the sciatic nerve.¹⁰² According to the results of a meta-analysis, CCL1, CCL2, CCL4, CCL5, CCL11, CXCL8, CXCL10, and CXCL13 chemokines were significantly higher in patients with T2DM than in controls.¹⁰³ Genetic mapping and gene-phenotype studies have revealed the genetic architecture of T1DM, suggesting that chemokine signaling is also the main pathogen of T1DM.¹⁰⁴

3.4 | Role of adhesion molecules in diabetic neuropathy

Diabetes always results in the activation of the endothelium and increases the expression of the adhesion molecules E-selectin, intercellular adhesion molecule (ICAM-1), and vascular cell adhesion molecule (VCAM-1).^{105,106} These adhesion molecules can induce leukocyte recruitment and infiltration into diabetic tissues.¹⁰⁴ Dekaban and colleagues provided extensive, ample evidence that the upregulation of selectins and cell adhesion molecules on endothelial cells after injury may potentiate destructive neuroinflammation.¹⁰⁷ Adhesion molecules can be activated by the NF- κ B pathway.^{108,109} Serum VCAM-1 can reflect inflammatory activity.^{110,111} Studies have shown that connecting adhesion molecule-A (JAM-A) plays a nonredundant and novel role in controlling inflammation by regulating the integrity

and permeability of the epithelial barrier.¹¹² Poorly controlled type 2 diabetes patients have higher sE-selectin and soluble VCAM-1 levels.¹¹³ Diabetic patients with chronic infection have higher levels of VCAM-1 and tumor necrosis factor receptor 1.¹¹¹

3.5 | Inflammation-related signaling pathways

3.5.1 | Activation of the NF- κ B pathway

NF- κ B was first identified as a protein that binds to a specific, conserved DNA sequence in the nuclei of activated B lymphocytes, so we named it nuclear factor binding near the κ light-chain gene in B cells, or NF- κ B.¹¹⁴ It is triggered by genotoxic, oxidative, and inflammatory stress and regulates cytokines, growth factors, and genes that regulate apoptosis, cell cycle progression, cell senescence, and inflammation.¹¹⁵⁻¹¹⁷

Numerous studies have shown the critical role of the NF- κ B pathway in the pathogenesis of diabetic neuropathy. Activated NF- κ B was observed in the perineurium, epineural vessels, and endoneurium in sural nerve biopsy samples from patients with impaired glucose tolerance and diabetes and model mice.^{118,119} Furthermore, elevated levels of NF- κ B were also observed in Schwann cells cultured in high-glucose medium compared to those cultured in low-glucose medium.¹²⁰ NF- κ B is a significant intracellular target of hyperglycemia and oxidative stress.¹²¹ In hyperglycemia, excessive ROS, iNOS activation, and AGEs can activate the classic NF- κ B pathway.¹²² It was found that the effects of hyperglycemia on ROS formation and NF- κ B activation preceded the stimulation of other systems, which indicated that the activation of NF- κ B was an initial signaling event.¹²³ The activation of the NF- κ B signal cascade in experimental diabetic neuropathy increases the expression of NF- κ B, I κ B- α , and phosphorylated I κ B- α and the nuclear translocation of the p65/p50 subunit, promoting the production of proinflammatory cytokines such as IL-6, TNF- α , cox-2, and iNOS, which then initiates the neuroinflammatory response.^{124,125} The neuroinflammatory response causes the proliferation of related inflammatory cells, further enhancing the release of proinflammatory mediators and forming a vicious inflammatory response cycle. Thus, reducing the activity of the NF- κ B pathway may be therapeutically beneficial.

3.5.2 | Activation of the MAPK pathway

Mitogen-activated protein kinases (MAPKs) are a group of intracellular messenger proteins that mainly consist of extracellular signal-regulated protein kinases (ERKs), p38 kinases, and c-Jun NH2-terminal kinases (JNK).¹²⁶⁻¹²⁸ They may be activated in injured nerves via different mechanisms, which are considered essential media in cell differentiation, apoptosis, and the development of diabetic complications.¹²⁷⁻¹³⁰ MAPKs may be involved in the cellular response to diabetes and activated by hyperglycemia-induced oxidative stress in the DRGs of rats with streptozotocin (STZ)-induced diabetes.¹³¹

Studies have demonstrated that MAPKs significantly contribute to the development of neuropathic pain, and the inhibition of the MAPK pathway can rescue inflammation or relieve pain.^{132,133} The activation of ERKs and p38 is involved in developing the mechanical allodynia observed in the early stages of disease in db/db mice.¹³⁴ Glucagon-like peptide-1 receptor (GLP-1R) agonists were found to prevent nerve dysfunction in the sciatic nerves of diabetic rats via p38 MAPK/NF- κ B signaling pathways independent of glycemic control.¹³⁵ Low-dose insulin therapy suppresses MAPK signaling and ameliorates peripheral sensory nerve dysfunction in rats with STZ-induced diabetes.¹³⁶ The AGE/RAGE interaction triggers ERK/MAPK and JNK and activates transcription factors such as CREB and AP-1, which results in oxidative stress and inflammation.¹³⁷ JNK and p38 pathways promote M1 macrophage polarization, M2 to M1 macrophage transformation, and inflammation. IL-35 promotes inflammatory progression in DPN rats by inhibiting JNK signal transduction.¹³⁸

3.6 | The inflammation exacerbates ischemia of nerve cells

Studies have revealed that diabetic peripheral neuropathy is associated with pathological microvascular changes, such as endothelial cell proliferation, basement membrane thickening, and pericyte degeneration. These vascular alterations are closely linked to clinical defects and neuropathology. Researchers have observed reduced neural blood flow and increased resistance of endothelial cells in both human and animal models, leading to an ischemia-hypoxia state of nerve cells. Additionally, compelling evidence suggests hypoxia causes nerve fiber degeneration and damage in diabetic peripheral neuropathy.¹³⁹ In addition, studies have shown that inflammation can worsen ischemia, which is also the case in diabetic peripheral neuropathy. Inflammation causes vascular swelling and constriction, reducing blood flow and increasing hypoxia in nerve cells. This can further harm Schwann cells, essential for nerve cells and myelin sheaths that encase nerve fibers.^{140,141}

3.7 | Proinflammatory changes in bone marrow

Diabetes affects the production of mesenchymal stem cells (MSCs), essential for tissue maintenance and repair. In type 2 diabetes patients, particularly those with osteogenic potential, one study found a reduction in the number of MSCs derived from bone marrow.¹⁴² Additionally, diabetes can cause proinflammatory changes in the bone marrow that may affect the production and function of various immune cells. One way this occurs is by enhancing the production of proinflammatory cytokines such as TNF- α , IL-1 β , and IL-6 in the bone marrow. Proinflammatory cytokines can impact hematopoietic stem cell quiescence, proliferation, and differentiation. For example, TNF- α induces apoptosis of hematopoietic stem cells and progenitor cells while affecting their self-renewal/differentiation balance.¹⁴³

Similarly, IL-1 β and IL-6 regulate survival, proliferation, and differentiation processes within hematopoietic stem cells/progenitors. A study showed that STZ-induced diabetic mice had significantly increased levels of IL-1 β in their bone marrow, thus suggesting its involvement in regulating hematopoiesis under diabetic conditions. The same study also found a significant correlation between STZ-induced diabetes and elevated levels of pro-sexual gene expression within progenitor cells.¹⁴⁴ Furthermore, oxidative stress caused by diabetes leads to DNA damage/cell death exacerbating inflammatory responses within the bone marrow. These proinflammatory changes may disrupt immune homeostasis by affecting both the bone marrow microenvironment/immune cell production leading to DPN development potentially.

4 | THERAPEUTIC POTENTIAL OF TARGETING THE INFLAMMATORY RESPONSE IN THE TREATMENT OF DIABETIC NEUROPATHY

Due to the lack of therapies that target underlying nerve damage, there are no effective therapeutic strategies for diabetic neuropathy. Although early and intensive glucose control can reduce the incidence of neuropathy in patients with T1DM,^{145,146} it has little effect in patients with T2DM.¹⁴⁷ In addition, pain is the most severe consequence of neuropathy. The American Diabetes Association recommends tricyclic antidepressants, anticonvulsants, and opioids, such as tapentadol or oxycodone.¹² However, only one-third of patients report at least a 50% reduction in pain after treatment.¹⁴⁸

As mentioned above, the inflammatory response plays an indispensable role in the pathogenesis of diabetic neuropathy. Therefore, inhibiting inflammation is the new hope for treating or preventing diabetic neuropathy (Table 2).

4.1 | NF- κ B inhibitors

In STZ-induced diabetic neuropathy model animals, BAY 11-7082, an I κ B phosphorylation inhibitor, ameliorated abnormal sensory responses and deficits in nerve functions, reduced the expression of NF- κ B, I κ B, and p-I κ B, and decreased the levels of IL-6, TNF- α , COX-2, and iNOS in the sciatic nerve.¹⁴⁹ In addition, JSH-23, an NF- κ B inhibitor, reversed the nerve conduction and nerve blood flow deficits in diabetic animals and reduced the elevated IL-6, TNF- α , COX-2, and iNOS levels.¹²⁵ Furthermore, melatonin ameliorated the functional deficits and improved pain by modulating neuroinflammation by decreasing the NF- κ B activation cascade and increasing Nrf2 expression.^{124,150} α -Lipoic acid inhibited the activation of NF- κ B and subsequently increased monocyte adhesion to endothelial cells, improving vascular dysfunction and diabetic peripheral neuropathy in rodent models of diabetes.^{108,151,152}

TABLE 2 Anti-inflammatory agents for diabetic neuropathy.

Drug	Target	Protocol	Effects	Ref.
BAY 11-7082	NF- κ B inhibitor	Rats (1 and 3 mg/kg/day, 2 weeks, p.o.)	Ameliorated abnormal sensory responses and deficits in nerve functions, reduced the expression of NF- κ B, I κ B, and p-I κ B, and curbed down the levels of IL-6, TNF- α , COX-2, and iNOS in the sciatic nerve	149
JSH-23	NF- κ B inhibitor	Rats (1 and 3 mg/kg/day, 2 weeks, p.o.)	Reversed the nerve conduction and nerve blood flow deficits in diabetic animals, and reduced the elevated IL-6, TNF- α , COX-2, and iNOS levels	125
Melatonin	NF- κ B inhibitor	Rats (3 and 10 mg/kg/day, 2 weeks, p.o.)	Ameliorated the function deficits along with improvement in pain by modulating neuroinflammation via decreasing NF- κ B activation cascade and increasing Nrf2 expression	150,124
Meloxicam	Selective COX-2 inhibitor	Rats (1 mg/kg/day, 4 weeks, p.o.)	Prevents diabetes-induced motor nerve conduction slowing and endoneurial blood flow deficits	153
SD-282	MAPK inhibitor	Rats (15 and 45 mg/kg/day, 1 week, i.p.)	Correction of mechanical allodynia and attenuated flinching behavior during the quiescent period and the second phase of the formalin response in STZ-diabetic rats	155
Naringin	Flavonoids	Rats (40 and 80 mg/kg/day, 4 weeks, p.o.)	Attenuates decreases in nociceptive thresholds; is an endogenous antioxidant and membrane-bound inorganic phosphate enzyme; dose dependently decreases elevations in oxidative-nitrosative stress, inflammatory mediators, and apoptosis in neural cells.	158
Baicalein	Flavonoids	Mice (30 mg/kg/day, 4 weeks, i.p.)	Alleviates nerve conduction deficits and small sensory nerve fiber dysfunction; counteracts diabetes-associated p38 MAPK phosphorylation, oxidative-nitrosative stress, and 12/15-lipoxygenase overexpression and activation.	159
Genistein	Flavonoids	Rats (3 and 6 mg/kg/day, 4 weeks, s.c.)	Reverts neuropathic pain symptoms and the overexpression of IL-1 β and IL-6; reverts increases in proinflammation cytokine levels in the sciatic nerve.	157

4.2 | COX-2 inhibitors

Selective inhibition of the proinflammatory enzyme COX-2 by meloxicam prevented diabetes-induced motor nerve conduction slowing and endoneurial blood flow deficits in experimental diabetic neuropathy.^{74,153,154}

4.3 | MAPK inhibitors

The p38 MAPK pathway is a signaling pathway within cells crucial in transmitting hyperglycemia-induced biochemical and metabolic changes. This pathway has been linked to conditions such as diabetic neuropathy. SD-282, an inhibitor of this pathway, has demonstrated promising results in managing pain associated with diabetic neuropathy.

SD-282 is a selective inhibitor of p38 α MAPK, which belongs to the indole-5-carboxamide class. It is 14.3 times more potent against p38 α than p38 β . Notably, SD-282 does not affect other closely related kinases, such as jun-N-terminal kinase, p38 δ , and p38 γ , even at concentrations up to 50 mM in human PBMCs. This indicates that the effects of SD-282 are likely due to its specific inhibition of the p38 α MAPK isoform.¹⁵⁵

In a study examining the effect of SD-282 on streptozotocin-induced diabetic rats, it was found that the inhibitor was effective in managing symptoms of diabetic neuropathy. The rats had exhibited symptoms of mechanical allodynia, decreased mechanical thresholds, and C- and A δ -fiber-mediated thermal hyperalgesia, all significantly reduced with the administration of SD-282. This suggests that the p38 α MAPK inhibitor can effectively reduce inflammation and pain in diabetic neuropathy, providing a promising therapeutic avenue for this challenging condition.¹⁵⁵

4.4 | Flavonoids

Flavonoids are a ubiquitous group of naturally occurring polyphenolic compounds characterized by the flavan nucleus and represent one of the most prevalent classes of compounds in fruits, vegetables, and plant-derived beverages. Flavonoids are considered health-promoting and disease-preventing dietary supplements with antibacterial, antioxidant, and anti-inflammatory effects. Flavonoids, such as genistein, baicalein, and naringin, were found to alleviate diabetes-induced neuropathic pain by inhibiting the anti-inflammatory response.¹⁵⁶⁻¹⁵⁹

Although animal experiments have achieved exciting results, most clinical trials have produced disappointing results.¹⁶⁰ On the

one hand, the failures of new drugs may result from multiple mechanisms that contribute to neuronal injury in diabetes. On the other hand, these trials have often been confounded by high improvement rates in the placebo group or other unanticipated effects.

4.5 | Using a small molecule to regulate Hsp70 and Hsp90 may improve DPN

Diabetes significantly increases inflammatory pathways, promoting the development and progression of DPN. Molecular research highlights the critical role of molecular chaperones, particularly heat shock proteins (HSP), in regulating these pathways and influencing neuro-pathological defects. Two novel biorexin analogs, KU-32 and KU-596, have shown significant therapeutic potential in this context.^{141,161,162}

The drug KU-32 can regulate Hsp90 and Hsp70, making it a promising candidate for treating various defects associated with DPN in animal models of type 1 and type 2 diabetes. These defects include psychological perception, electrophysiology, morphology, and bioenergy. Notably, treatment with KU-32 improved mitochondrial bioenergy—a crucial factor in nerve health—closely linked to DPN reduction. It is worth noting that this improvement relies on Hsp70 because the drug does not work in mice with type 2 diabetes who lack this molecular chaperone. This underscores the significance of Hsp70 in the pathology and treatment of DPN.¹⁶¹

Another novel Biogen analog, KU-596, has been found to exhibit neuroprotective activity and improve diabetes-induced hypoalgesia and sensory neuronal bioenergetic defects in a dose-dependent manner. However, it is essential to note that the drug does not improve these neuropathological defects in type 2 diabetic Hsp70 knockout mice, which further emphasizes the critical role of Hsp70. The anti-inflammatory effect of KU-596 appears to be independent of Hsp70, while its impact on reducing regulated reactive oxygen species gene expression depends more on Hsp70. These findings suggest that although targeting molecular chaperones with monologues may be a practical approach to correct neural dysfunction in DPN, normalizing inflammatory pathways through monologues alone may not be sufficient to reverse sensory deficits associated with losing sensation in DPN.¹⁶²

The “heat shock response” (HSR) has become an attractive therapeutic target due to its protective effect against abnormal physiological conditions, stress, and carcinogenesis. Hsp90 is the main regulatory factor of HSR. It represents a promising treatment method that can be used to combat peripheral and central nervous system lesions when regulated by small-molecule drugs.¹⁶³

Inflammation's interaction with DPN provides a potential pathway for therapeutic intervention. Although existing treatment strategies mainly focus on controlling disease progression and managing symptoms, recent research on molecular chaperones, heat shock proteins, and bioenergetic regulation brings hope for more targeted

and effective treatment options. However, further exploration in relevant fields is necessary to translate these findings into clinical applications.

4.6 | Alleviating Immune Cells to Improve DPN

Glial cells, specifically astrocytes and microglia, work together to promote and maintain neuronal health. They play a crucial role in regulating brain neuronal network activity. Neuroinflammation activates microglia, which promotes the development of pain signal transmission through p38 MAPK activation or P2X4 receptor expression in microglia. Astrocytes are susceptible to hypoxia under acidic conditions caused by diabetes. The spinal cords of diabetic rats consistently report increased activation of microglia.

A study demonstrated that cilostazol administration at both low (10 mg/kg) and high doses (100 mg/kg) could alleviate the dysfunction of spinal cord glial cells induced by streptozotocin. Low doses were sufficient to weaken activated microglia immunoreactivity and restore reduced astrocyte immunoreactivity induced by DM. Cilostazol's potential for regulating essential immune cell function in the central nervous system provides a promising approach for treating inflammation caused by diabetic peripheral neuropathy.¹⁶⁴

Cilostazol may improve pathological changes related to diabetes in the central nervous system by alleviating functional impairment and activation of microglia and astrocytes. Although these initial findings are encouraging, further research is necessary to clarify cilostazol's mechanism on glial cells and confirm its therapeutic potential for managing diabetic peripheral neuropathy.

5 | CONCLUSION

The pathogenesis of diabetic neuropathy involves the accumulation or interaction of multiple factors. The presence of “metabolic memory” indicates that obtaining reasonable blood glucose control is insufficient.

Metabolic disorders are more critical than hyperglycemia in the pathogenesis of neuropathy due to T2DM. Despite the evidence that the pathogenesis of DPN may differ between the types of diabetes, only very few studies have investigated potential differences between T1DM and T2DM. In addition, most studies evaluating structural nerve injury are based on T1DM model animals, and only a few studies have used T2DM model animals. Moreover, most studies on neuropathic pain were conducted using nondiabetic animals. This may be why drugs are effective in animal experiments but ineffective in clinical trials. Stronger collaborations among neurologists, endocrinologists, and basic scientists are necessary to solve these problems.

Several lines of evidence link inflammation with the development of diabetic neuropathies. The inhibition of the inflammatory

response is effective in treating diabetic neuropathy. Mechanisms of inflammation in diabetic neuropathy include activating the NF- κ B and MAPK/JNK pathways, cytokine and chemokine release, and the recruitment of immune cells. Inflammatory factors have diverse biological effects activating other receptors and pathways that induce nerve injury. Therefore, it is essential to understand the inflammatory cascade changes and select candidate drugs targeting several DPN therapy mechanisms.

AUTHOR CONTRIBUTIONS

Yifan Cheng, Yinuo Chen, and Kezheng Li contributed equally to this work. Yifan Cheng, Jiali Xie, and Shuwei Liu wrote the manuscript, Yinuo Cheng and Kezheng Li drew the figures and tables, Wenjing LV, Chunyang Pang, and Lingfei Cao reviewed and edited the article, and Binbin Deng is the guarantor of this work and takes responsibility for this review. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests;

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in PubMed at <https://pubmed.ncbi.nlm.nih.gov>.

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REFERENCES

- Jensen TS, Karlsson P, Gylfadottir SS, et al. Painful and non-painful diabetic neuropathy, diagnostic challenges and implications for future management. *Brain*. 2021;144:1632-1645.
- Feldman EL, Callaghan BC, Pop-Busui R, et al. Diabetic neuropathy. *Nat Rev Dis Primers*. 2019;5:42.
- Sloan G, Selvarajah D, Tesfaye S. Pathogenesis, diagnosis and clinical management of diabetic sensorimotor peripheral neuropathy. *Nat Rev Endocrinol*. 2021;17:400-420.
- Cole JB, Florez JC. Genetics of diabetes mellitus and diabetes complications. *Nat Rev Nephrol*. 2020;16:377-390.
- Cernea S, Raz I. Management of diabetic neuropathy. *Metabolism*. 2021;123:154867.
- Baum P, Toyka KV, Blüher M, Kosacka J, Nowicki M. Inflammatory mechanisms in the pathophysiology of diabetic peripheral neuropathy (DN)-new aspects. *Int J Mol Sci*. 2021;22:10835.
- Stino AM, Rumora AE, Kim B, Feldman EL. Evolving concepts on the role of dyslipidemia, bioenergetics, and inflammation in the pathogenesis and treatment of diabetic peripheral neuropathy. *J Peripher Nerv Syst*. 2020;25:76-84.
- Powers AC. Type 1 diabetes mellitus: much progress, many opportunities. *J Clin Invest*. 2021;131:e142242.
- Demir S, Nawroth PP, Herzig S, Ekim ÜB. Emerging targets in type 2 diabetes and diabetic complications. *Adv Sci (Weinh)*. 2021;8:e2100275.
- Thomas MC, Woodward M, Neal B, et al. Relationship between levels of advanced glycation end products and their soluble receptor and adverse outcomes in adults with type 2 diabetes. *Diabetes Care*. 2015;38:1891-1897.
- Khalid M, Petroianu G, Adem A. Advanced glycation end products and diabetes mellitus: mechanisms and perspectives. *Biomol Ther*. 2022;12:542.
- Pop-Busui R, Boulton AJM, Feldman EL, et al. Diabetic neuropathy: a position statement by the American Diabetes Association. *Diabetes Care*. 2016;40:136-154.
- Lund J, Ouwens DM, Wettergreen M, Bakke SS, Thoresen GH, Aas V. Increased glycolysis and higher lactate production in hyperglycemic myotubes. *Cell*. 2019;8:8.
- Fuller GG, Kim JK. Compartmentalization and metabolic regulation of glycolysis. *J Cell Sci*. 2021;134:jcs258469.
- Meldgaard T, Olesen SS, Farmer AD, et al. Diabetic enteropathy: from molecule to mechanism-based treatment. *J Diabetes Res*. 2018;2018:3827301.
- Yako H, Niimi N, Kato A, et al. Role of pyruvate in maintaining cell viability and energy production under high-glucose conditions. *Sci Rep*. 2021;11:18910.
- Greene DA, Lattimer SA, Sima AA. Sorbitol, phosphoinositides, and sodium-potassium-ATPase in the pathogenesis of diabetic complications. *N Engl J Med*. 1987;316:599-606.
- Feldman EL, Nave KA, Jensen TS, Bennett DLH. New horizons in diabetic neuropathy: mechanisms, bioenergetics, and pain. *Neuron*. 2017;93:1296-1313.
- Thakur S, Gupta SK, Ali V, Singh P, Verma M. Aldose reductase: a cause and a potential target for the treatment of diabetic complications. *Arch Pharm Res*. 2021;44:655-667.
- Thornalley PJ. The potential role of thiamine (vitamin B1) in diabetic complications. *Curr Diabetes Rev*. 2005;1:287-298.
- Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature*. 2001;414:813-820.
- Zhang Q, Hu Y, Hu JE, et al. Sp1-mediated upregulation of Prdx6 expression prevents podocyte injury in diabetic nephropathy via mitigation of oxidative stress and ferroptosis. *Life Sci*. 2021;278:119529.
- Wang X, Li Q, Han X, Gong M, Yu Z, Xu B. Electroacupuncture alleviates diabetic peripheral neuropathy by regulating glycolipid-related GLO/AGEs/RAGE axis. *Front Endocrinol*. 2021;12:655591.
- Juranek JK, Aleshin A, Rattigan EM, et al. Morphological changes and immunohistochemical expression of RAGE and its ligands in the sciatic nerve of hyperglycemic pig (Sus Scrofa). *Biochemistry Insights*. 2010;2010:47-59.
- Thornalley PJ. Glycation in diabetic neuropathy: characteristics, consequences, causes, and therapeutic options. *Int Rev Neurobiol*. 2002;50:37-57.
- Iqbal Z, Bashir B, Ferdousi M, et al. Lipids and peripheral neuropathy. *Curr Opin Lipidol*. 2021;32:249-257.
- Vincent AM, Hayes JM, McLean LL, Vivekanandan-Giri A, Pennathur S, Feldman EL. Dyslipidemia-induced neuropathy in mice: the role of oxLDL/LOX-1. *Diabetes*. 2009;58:2376-2385.
- Wu S, Cao X, He R, Xiong K. Detrimental impact of hyperlipidemia on the peripheral nervous system: a novel target of medical epidemiological and fundamental research study. *Neural Regen Res*. 2012;7:392-399.
- Ishiyama J, Taguchi R, Yamamoto A, Murakami K. Palmitic acid enhances lectin-like oxidized LDL receptor (LOX-1) expression and promotes uptake of oxidized LDL in macrophage cells. *Atherosclerosis*. 2010;209:118-124.
- Nowicki M, Müller K, Serke H, et al. Oxidized low-density lipoprotein (oxLDL)-induced cell death in dorsal root ganglion cell cultures

- depends not on the lectin-like oxLDL receptor-1 but on the toll-like receptor-4. *J Neurosci Res.* 2010;88:403-412.
31. Padilla A, Descorbeth M, Almeyda AL, Payne K, De Leon M. Hyperglycemia magnifies Schwann cell dysfunction and cell death triggered by PA-induced lipotoxicity. *Brain Res.* 2011;1370:64-79.
 32. Cho YN, Lee KO, Jeong J, et al. The role of insulin resistance in diabetic neuropathy in Koreans with type 2 diabetes mellitus: a 6-year follow-up study. *Yonsei Med J.* 2014;55:700-708.
 33. Ahmadi SAY, Shirzadegan R, Mousavi N, Farokhi E, Soleimaninejad M, Jafarzadeh M. Designing a logistic regression model for a dataset to predict diabetic foot ulcer in diabetic patients: high-density lipoprotein (HDL) cholesterol was the negative predictor. *J Diabetes Res.* 2021;2021:5521493.
 34. Semler A, Hammad S, Lopes-Virella MF, Klein RL, Huang Y. Deoxysphingolipids upregulate MMP-1, downregulate TIMP-1, and induce cytotoxicity in human Schwann cells. *NeuroMolecular Med.* 2022;24:352-362.
 35. Yip J, Mattock MB, Morocutti A, Sethi M, Trevisan R, Viberti G. Insulin resistance in insulin-dependent diabetic patients with microalbuminuria. *Lancet.* 1993;342:883-887.
 36. Yorek M. Treatment for diabetic peripheral neuropathy: what have we learned from animal models? *Curr Diabetes Rev.* 2022;18:e040521193121.
 37. Alam U, Petropoulos IN, Ponirakis G, et al. Vitamin D deficiency is associated with painful diabetic neuropathy. *Diabetes Metab Res Rev.* 2021;37:e3361.
 38. Putz Z, Tordai D, Hajdú N, et al. Vitamin D in the prevention and treatment of diabetic neuropathy. *Clin Ther.* 2022;44:813-823.
 39. Contreras-Bolívar V, García-Fontana B, García-Fontana C, Muñoz-Torres M. Mechanisms involved in the relationship between vitamin D and insulin resistance: impact on clinical practice. *Nutrients.* 2021;13:3491.
 40. Hackett AR, Strickland A, Milbrandt J. Disrupting insulin signaling in Schwann cells impairs myelination and induces a sensory neuropathy. *Glia.* 2020;68:963-978.
 41. Barton GM. A calculated response: control of inflammation by the innate immune system. *J Clin Invest.* 2008;118:413-420.
 42. Medzhitov R. Origin and physiological roles of inflammation. *Nature.* 2008;454:428-435.
 43. Magrinelli F, Briani C, Romano M, et al. The association between serum cytokines and damage to large and small nerve fibers in diabetic peripheral neuropathy. *J Diabetes Res.* 2015;2015:547834.
 44. Jin HY, Park TS. Role of inflammatory biomarkers in diabetic peripheral neuropathy. *J Diabetes Investig.* 2018;9:1016-1018.
 45. Rumora AE, Lentz SI, Hinder LM, et al. Dyslipidemia impairs mitochondrial trafficking and function in sensory neurons. *FASEB J.* 2018;32:195-207.
 46. Cornblath DR, Griffin DE, Welch D, Griffin JW, McArthur JC. Quantitative analysis of endoneurial T-cells in human sural nerve biopsies. *J Neuroimmunol.* 1990;26:113-118.
 47. Schröder HD, Olsson T, Solders G, Kristensson K, Link H. HLA-DR-expressing cells and T-lymphocytes in sural nerve biopsies. *Muscle Nerve.* 1988;11:864-870.
 48. Younger DS, Rosoklija G, Hays AP. Peripheral nerve immunohistochemistry in diabetic neuropathy. *Semin Neurol.* 1996;16:139-142.
 49. Strom A, Kaul K, Brüggemann J, et al. Lower serum extracellular superoxide dismutase levels are associated with polyneuropathy in recent-onset diabetes. *Exp Mol Med.* 2017;49:e394.
 50. González-Clemente JM, Mauricio D, Richart C, et al. Diabetic neuropathy is associated with activation of the TNF-alpha system in subjects with type 1 diabetes mellitus. *Clin Endocrinol.* 2005;63:525-529.
 51. Doupis J, Lyons TE, Wu S, Gnardellis C, Dinh T, Veves A. Microvascular reactivity and inflammatory cytokines in painful and painless peripheral diabetic neuropathy. *J Clin Endocrinol Metab.* 2009;94:2157-2163.
 52. Kallestrup M, Møller HJ, Tankisi H, Andersen H. Soluble CD163 levels are elevated in cerebrospinal fluid and serum in people with Type 2 diabetes mellitus and are associated with impaired peripheral nerve function. *Diabet Med.* 2015;32:54-61.
 53. O'Brien JA, McGuire HM, Shinko D, et al. T lymphocyte and monocyte subsets are dysregulated in type 1 diabetes patients with peripheral neuropathic pain. *Brain Behav Immun Health.* 2021;15:100283.
 54. Li W, Li R, Wang Y, Zhang Y, Tomar MS, Dai S. Calcitonin gene-related peptide is a potential autoantigen for CD4 T cells in type 1 diabetes. *Front Immunol.* 2022;13:951281.
 55. Agarwal N, Helmstädter J, Rojas DR, Bali KK, Gangadharan V, Kuner R. Evoked hypoalgesia is accompanied by tonic pain and immune cell infiltration in the dorsal root ganglia at late stages of diabetic neuropathy in mice. *Mol Pain.* 2018;14:1744806918817975.
 56. Kan HW, Hsieh JH, Chien HF, et al. CD40-mediated HIF-1 α expression underlying microangiopathy in diabetic nerve pathology. *Dis Model Mech.* 2018;11:dmm033647.
 57. Wada J, Makino H. Innate immunity in diabetes and diabetic neuropathy. *Nat Rev Nephrol.* 2016;12:13-26.
 58. Thaiss CA, Levy M, Itav S, Elinav E. Integration of innate immune signaling. *Trends Immunol.* 2016;37:84-101.
 59. Aghamiri SH, Komlakh K, Ghaffari M. Toll-Like Receptors (TLRs) and their potential therapeutic applications in diabetic neuropathy. *Int Immunopharmacol.* 2022;102:108398.
 60. Nowicki M, Kosacka J, Serke H, Blüher M, Spanel-Borowski K. Altered sciatic nerve fiber morphology and endoneurial microvessels in mouse models relevant for obesity, peripheral diabetic polyneuropathy, and the metabolic syndrome. *J Neurosci Res.* 2012;90:122-131.
 61. Yan JE, Yuan W, Lou X, Zhu T. Streptozotocin-induced diabetic hyperalgesia in rats is associated with upregulation of toll-like receptor 4 expression. *Neurosci Lett.* 2012;526:54-58.
 62. Zhou DM, Zhuang Y, Chen WJ, Li W, Miao B. Effects of duloxetine on the toll-like receptor 4 signaling pathway in spinal dorsal horn in a rat model of diabetic neuropathic pain. *Pain Medicine (Malden, Mass).* 2018;19:580-588.
 63. Tian J, Song T, Wang H, Wang W, Ma X, Hu Y. Toll-like receptor 2 antagonist ameliorates type 2 diabetes mellitus associated neuropathic pain by repolarizing pro-inflammatory macrophages. *Neurochem Res.* 2021;46:2276-2284.
 64. Russo S, Kwiatkowski M, Govorukhina N, Bischoff R, Melgert BN. Meta-inflammation and metabolic reprogramming of macrophages in diabetes and obesity: the importance of metabolites. *Front Immunol.* 2021;12:746151.
 65. Sun JJ, Tang L, Zhao XP, Xu JM, Xiao Y, Li H. Infiltration of blood-derived macrophages contributes to the development of diabetic neuropathy. *J Immunol Res.* 2019;2019:7597382.
 66. Vincent AM, Feldman EL. New insights into the mechanisms of diabetic neuropathy. *Rev Endocr Metab Disord.* 2004;5:227-236.
 67. Chanda D, Ray S, Chakraborti D, Sen S, Mitra A. Interleukin-6 levels in patients with diabetic polyneuropathy. *Cureus.* 2022;14:e21952.
 68. King GL. The role of inflammatory cytokines in diabetes and its complications. *J Periodontol.* 2008;79:1527-1534.
 69. Kriegler M, Perez C, DeFay K, Albert I, Lu SD. A novel form of TNF/cachectin is a cell surface cytotoxic transmembrane protein: ramifications for the complex physiology of TNF. *Cell.* 1988;53:45-53.
 70. Herder C, Kannenberg JM, Huth C, et al. Proinflammatory cytokines predict the incidence and progression of distal sensorimotor polyneuropathy: KORA F4/FF4 study. *Diabetes Care.* 2017;40:569-576.

71. Yamakawa I, Kojima H, Terashima T, et al. Inactivation of TNF- α ameliorates diabetic neuropathy in mice. *Am J Physiol Endocrinol Metab*. 2011;301:E844-E852.
72. Purwata TE. High TNF- α plasma levels and macrophages iNOS and TNF- α expression as risk factors for painful diabetic neuropathy. *J Pain Res*. 2011;4:169-175.
73. Chao G, Tian X, Zhang W, Ou X, Cong F, Song T. Blocking Smad2 signalling with loganin attenuates SW10 cell cycle arrest induced by TNF- α . *PLoS One*. 2017;12:e0176965.
74. Kellogg AP, Wiggin TD, Larkin DD, Hayes JM, Stevens MJ, Pop-Busui R. Protective effects of cyclooxygenase-2 gene inactivation against peripheral nerve dysfunction and intraepidermal nerve fiber loss in experimental diabetes. *Diabetes*. 2007;56:2997-3005.
75. Leung L, Cahill CM. TNF- α and neuropathic pain—a review. *J Neuroinflammation*. 2010;7:27.
76. Mizukami H, Osonoi S. Pathogenesis and molecular treatment strategies of diabetic neuropathy collateral glucose-utilizing pathways in diabetic polyneuropathy. *Int J Mol Sci*. 2020;22:22.
77. Feng Y, Chen L, Luo Q, Wu M, Chen Y, Shi X. Involvement of microRNA-146a in diabetic peripheral neuropathy through the regulation of inflammation. *Drug Des Devel Ther*. 2018;12:171-177.
78. Yu W, Wang Z, Zhang K, et al. One-carbon metabolism supports S-adenosylmethionine and histone methylation to drive inflammatory macrophages. *Mol Cell*. 2019;75:1147-1160.e5.
79. Liao YH, Zhang GH, Jia D, et al. Spinal astrocytic activation contributes to mechanical allodynia in a mouse model of type 2 diabetes. *Brain Res*. 2011;1368:324-335.
80. Abbadié C. Chemokines, chemokine receptors and pain. *Trends Immunol*. 2005;26:529-534.
81. Kang S, Narazaki M, Metwally H, Kishimoto T. Historical overview of the interleukin-6 family cytokine. *J Exp Med*. 2020;217:e20190347.
82. Rose-John S. Interleukin-6 signalling in health and disease. *F1000Res*. 2020;9:9.
83. Wallenius V, Wallenius K, Åhrén B, et al. Interleukin-6-deficient mice develop mature-onset obesity. *Nat Med*. 2002;8:75-79.
84. Villar-Fincheira P, Sanhueza-Olivares F, Norambuena-Soto I, et al. Role of Interleukin-6 in vascular health and disease. *Front Mol Biosci*. 2021;8:641734.
85. Rothaug M, Becker-Paully C, Rose-John S. The role of interleukin-6 signaling in nervous tissue. *Biochim Biophys Acta*. 2016;1863:1218-1227.
86. Kummer KK, Zeidler M, Kalpachidou T, Kress M. Role of IL-6 in the regulation of neuronal development, survival and function. *Cytokine*. 2021;144:155582.
87. Shalbaya S, Amer H, Seddik S, et al. Study of the role of interleukin-6 and highly sensitive C-reactive protein in diabetic neuropathy in type 1 diabetic patients. *Eur Rev Med Pharmacol Sci*. 2012;16:176-182.
88. Zheng H, Sun W, Zhang Q, et al. Proinflammatory cytokines predict the incidence of diabetic peripheral neuropathy over 5 years in Chinese type 2 diabetes patients: a prospective cohort study. *EClinicalMedicine*. 2021;31:100649.
89. Herder C, Bongaerts BW, Rathmann W, et al. Association of subclinical inflammation with polyneuropathy in the older population: KORA F4 study. *Diabetes Care*. 2013;36:3663-3670.
90. Herder C, Bongaerts BW, Rathmann W, et al. Differential association between biomarkers of subclinical inflammation and painful polyneuropathy: results from the KORA F4 study. *Diabetes Care*. 2015;38:91-96.
91. Schamarek I, Herder C, Nowotny B, et al. Adiponectin, markers of subclinical inflammation and nerve conduction in individuals with recently diagnosed type 1 and type 2 diabetes. *Eur J Endocrinol*. 2016;174:433-443.
92. Zhou YQ, Liu Z, Liu ZH, et al. Interleukin-6: an emerging regulator of pathological pain. *J Neuroinflammation*. 2016;13:141.
93. Cotter MA, Gibson TM, Nangle MR, Cameron NE. Effects of interleukin-6 treatment on neurovascular function, nerve perfusion and vascular endothelium in diabetic rats. *Diabetes Obes Metab*. 2010;12:689-699.
94. Cox AA, Sagot Y, Hedou G, et al. Low-dose pulsatile interleukin-6 as a treatment option for diabetic peripheral neuropathy. *Front Endocrinol*. 2017;8:89.
95. Brock C, Hansen CS, Karmisholt J, et al. Liraglutide treatment reduced interleukin-6 in adults with type 1 diabetes but did not improve established autonomic or polyneuropathy. *Br J Clin Pharmacol*. 2019;85:2512-2523.
96. Skundric DS, Lisak RP. Role of neuropoietic cytokines in development and progression of diabetic polyneuropathy: from glucose metabolism to neurodegeneration. *Exp Diabetes Res*. 2003;4:303-312.
97. Bhat P, Leggatt G, Waterhouse N, Frazer IH. Interferon- γ derived from cytotoxic lymphocytes directly enhances their motility and cytotoxicity. *Cell Death Dis*. 2017;8:e2836.
98. Bour-Jordan H, Thompson HL, Bluestone JA. Distinct effector mechanisms in the development of autoimmune neuropathy versus diabetes in nonobese diabetic mice. *J Immunol*. 2005;175:5649-5655.
99. Hughes CE, Nibbs RJB. A guide to chemokines and their receptors. *FEBS J*. 2018;285:2944-2971.
100. Neuroscience MG. The dark side of glia. *Science (New York, NY)*. 2005;308:778-781.
101. Kim YH, Jang SY, Shin YK, et al. Serum CXCL13 reflects local B-cell mediated inflammatory demyelinating peripheral neuropathy. *Sci Rep*. 2019;9:16535.
102. Kim HJ, Jung CG, Jensen MA, Dukala D, Soliven B. Targeting of myelin protein zero in a spontaneous autoimmune polyneuropathy. *J Immunol*. 2008;181:8753-8760.
103. Pan X, Kaminga AC, Wen SW, Liu A. Chemokines in prediabetes and type 2 diabetes: a meta-analysis. *Front Immunol*. 2021;12:622438.
104. Todd JA. Etiology of type 1 diabetes. *Immunity*. 2010;32:457-467.
105. Siddiqui K, George TP, Nawaz SS, Joy SS. VCAM-1, ICAM-1 and selectins in gestational diabetes mellitus and the risk for vascular disorders. *Futur Cardiol*. 2019;15:339-346.
106. Goligorsky MS. Vascular endothelium in diabetes. *Am J Physiol Renal Physiol*. 2017;312:F266-F275.
107. Orr MB, Gensel JC. Spinal cord injury scarring and inflammation: therapies targeting glial and inflammatory responses. *Neurotherapeutics*. 2018;15:541-553.
108. Yorek MA, Dunlap JA. Effect of increased concentration of D-glucose or L-fucose on monocyte adhesion to endothelial cell monolayers and activation of nuclear factor-kappaB. *Metab Clin Exp*. 2002;51:225-234.
109. Zhang Q, Lenardo MJ, Baltimore D. 30 years of NF- κ B: a blossoming of relevance to human pathobiology. *Cell*. 2017;168:37-57.
110. Takami S, Yamashita S, Kihara S, Kameda-Takemura K, Matsuzawa Y. High concentration of glucose induces the expression of intercellular adhesion molecule-1 in human umbilical vein endothelial cells. *Atherosclerosis*. 1998;138:35-41.
111. Ng YT, Phang SCW, Tan GCJ, et al. The effects of tocotrienol-rich vitamin E (Tocovid) on diabetic neuropathy: a phase II randomized controlled trial. *Nutrients*. 2020;12:12.
112. Vetrano S, Rescigno M, Cera MR, et al. Unique role of junctional adhesion molecule-a in maintaining mucosal homeostasis in inflammatory bowel disease. *Gastroenterology*. 2008;135:173-184.
113. Zhou J, Zhou S. Inflammation: therapeutic targets for diabetic neuropathy. *Mol Neurobiol*. 2014;49:536-546.

114. Fang F, Wang J, Wang YF, Peng YD. Microangiopathy in diabetic polyneuropathy revisited. *Eur Rev Med Pharmacol Sci*. 2018;22:6456-6462.
115. Barnabei L, Laplantine E, Mbongo W, Rieux-Laucat F, Weil R. NF- κ B: at the borders of autoimmunity and inflammation. *Front Immunol*. 2021;12:716469.
116. Zhang T, Ma C, Zhang Z, Zhang H, Hu H. NF- κ B signaling in inflammation and cancer. *MedComm*. 2021;2:618-653.
117. Tilstra JS, Clauson CL, Niedernhofer LJ, Robbins PD. NF- κ B in aging and disease. *Aging Dis*. 2011;2:449-465.
118. Bierhaus A, Haslbeck KM, Humpert PM, et al. Loss of pain perception in diabetes is dependent on a receptor of the immunoglobulin superfamily. *J Clin Invest*. 2004;114:1741-1751.
119. Haslbeck KM, Schleicher E, Bierhaus A, et al. The AGE/RAGE/NF-(kappa)B pathway may contribute to the pathogenesis of polyneuropathy in impaired glucose tolerance (IGT). *Exp Clin Endocrinol Diabetes*. 2005;113:288-291.
120. Suzuki T, Sekido H, Kato N, Nakayama Y, Yabe-Nishimura C. Neurotrophin-3-induced production of nerve growth factor is suppressed in Schwann cells exposed to high glucose: involvement of the polyol pathway. *J Neurochem*. 2004;91:1430-1438.
121. Matulewicz N, Karczewska-Kupczewska M. Insulin resistance and chronic inflammation. *Postepy Hig Med Dosw (Online)*. 2016;70:1245-1258.
122. Rojas DR, Tegeder I, Kuner R, Agarwal N. Hypoxia-inducible factor 1 α protects peripheral sensory neurons from diabetic peripheral neuropathy by suppressing accumulation of reactive oxygen species. *J Mol Med (Berl)*. 2018;96:1395-1405.
123. Impellizzeri D, Peritore AF, Cordaro M, et al. The neuroprotective effects of micronized PEA (PEA-m) formulation on diabetic peripheral neuropathy in mice. *FASEB J*. 2019;33:11364-11380.
124. Negi G, Kumar A, Sharma SS. Melatonin modulates neuroinflammation and oxidative stress in experimental diabetic neuropathy: effects on NF- κ B and Nrf2 cascades. *J Pineal Res*. 2011;50:124-131.
125. Kumar A, Negi G, Sharma SS. JSH-23 targets nuclear factor-kappa B and reverses various deficits in experimental diabetic neuropathy: effect on neuroinflammation and antioxidant defence. *Diabetes Obes Metab*. 2011;13:750-758.
126. Ding M, Zhao J, Bowman L, Lu Y, Shi X. Inhibition of AP-1 and MAPK signaling and activation of Nrf2/ARE pathway by quercitrin. *Int J Oncol*. 2010;36:59-67.
127. Johnson GL, Lapadat R. Mitogen-activated protein kinase pathways mediated by ERK, JNK, and p38 protein kinases. *Science (New York, NY)*. 2002;298:1911-1912.
128. Kumar A, Mittal R. Nrf2: a potential therapeutic target for diabetic neuropathy. *Inflammopharmacology*. 2017;25:393-402.
129. Xia P, Kramer RM, King GL. Identification of the mechanism for the inhibition of Na⁺, K(+)adenosine triphosphatase by hyperglycemia involving activation of protein kinase C and cytosolic phospholipase A2. *J Clin Invest*. 1995;96:733-740.
130. Xia Z, Dickens M, Raingeaud J, Davis RJ, Greenberg ME. Opposing effects of ERK and JNK-p38 MAP kinases on apoptosis. *Science (New York, NY)*. 1995;270:1326-1331.
131. Daulhac L, Mallet C, Courteix C, et al. Diabetes-induced mechanical hyperalgesia involves spinal mitogen-activated protein kinase activation in neurons and microglia via N-methyl-D-aspartate-dependent mechanisms. *Mol Pharmacol*. 2006;70:1246-1254.
132. Peng G, Han M, Du Y, et al. SIP30 is regulated by ERK in peripheral nerve injury-induced neuropathic pain. *J Biol Chem*. 2009;284:30138-30147.
133. Wei TH, Hsieh CL. Effect of acupuncture on the p38 signaling pathway in several nervous system diseases: a systematic review. *Int J Mol Sci*. 2020;21:21.
134. McDonnell C, Leáñez S, Pol O. The induction of the transcription factor Nrf2 enhances the antinociceptive effects of delta-opioid receptors in diabetic mice. *PLoS One*. 2017;12:e0180998.
135. Ma J, Shi M, Zhang X, et al. GLP-1R agonists ameliorate peripheral nerve dysfunction and inflammation via p38 MAPK/NF- κ B signaling pathways in streptozotocin-induced diabetic rats. *Int J Mol Med*. 2018;41:2977-2985.
136. Sugimoto K, Baba M, Suzuki S, Yagihashi S. The impact of low-dose insulin on peripheral nerve insulin receptor signaling in streptozotocin-induced diabetic rats. *PLoS One*. 2013;8:e74247.
137. Yan SF, Ramasamy R, Naka Y, Schmidt AM. Glycation, inflammation, and RAGE: a scaffold for the macrovascular complications of diabetes and beyond. *Circ Res*. 2003;93:1159-1169.
138. Jiang Y, Wang J, Li H, Xia L. IL-35 promotes microglial M2 polarization in a rat model of diabetic neuropathic pain. *Arch Biochem Biophys*. 2020;685:108330.
139. Nukada H. Ischemia and diabetic neuropathy. *Handb Clin Neurol*. 2014;126:469-487.
140. Jin R, Liu L, Zhang S, Nanda A, Li G. Role of inflammation and its mediators in acute ischemic stroke. *J Cardiovasc Transl Res*. 2013;6:834-851.
141. Xue T, Zhang X, Xing Y, et al. Advances about immunoinflammatory pathogenesis and treatment in diabetic peripheral neuropathy. *Front Pharmacol*. 2021;12:748193.
142. Cassidy FC, Shortiss C, Murphy CG, et al. Impact of type 2 diabetes mellitus on human bone marrow stromal cell number and phenotypic characteristics. *Int J Mol Sci*. 2020;21:2476.
143. Yamashita M, Passequé E. TNF- α coordinates hematopoietic stem cell survival and myeloid regeneration. *Cell Stem Cell*. 2019;25:357-372.e7.
144. Dominguez JM 2nd, Yorek MA, Grant MB. Combination therapies prevent the neuropathic, proinflammatory characteristics of bone marrow in streptozotocin-induced diabetic rats. *Diabetes*. 2015;64:643-653.
145. Martin CL, Albers J, Herman WH, et al. Neuropathy among the diabetes control and complications trial cohort 8 years after trial completion. *Diabetes Care*. 2006;29:340-344.
146. Albers JW, Herman WH, Pop-Busui R, et al. Effect of prior intensive insulin treatment during the diabetes control and complications trial (DCCT) on peripheral neuropathy in type 1 diabetes during the epidemiology of diabetes interventions and complications (EDIC) study. *Diabetes Care*. 2010;33:1090-1096.
147. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet (London, England)*. 1998;352:837-853.
148. Jensen TS, Backonja MM, Hernández Jiménez S, Tesfaye S, Valensi P, Ziegler D. New perspectives on the management of diabetic peripheral neuropathic pain. *Diab Vasc Dis Res*. 2006;3:108-119.
149. Kumar A, Negi G, Sharma SS. Suppression of NF- κ B and NF- κ B regulated oxidative stress and neuroinflammation by BAY 11-7082 (I κ B phosphorylation inhibitor) in experimental diabetic neuropathy. *Biochimie*. 2012;94:1158-1165.
150. Negi G, Kumar A, Kaundal RK, Gulati A, Sharma SS. Functional and biochemical evidence indicating beneficial effect of melatonin and nicotinamide alone and in combination in experimental diabetic neuropathy. *Neuropharmacology*. 2010;58:585-592.
151. Yorek MA, Coppey LJ, Gellett JS, Davidson EP, Lund DD. Effect of fidarestat and alpha-lipoic acid on diabetes-induced epineurial arteriole vascular dysfunction. *Exp Diabetes Res*. 2004;5:123-135.
152. Oltman CL, Davidson EP, Coppey LJ, et al. Vascular and neural dysfunction in Zucker diabetic fatty rats: a difficult condition to reverse. *Diabetes Obes Metab*. 2008;10:64-74.

153. Pop-Busui R, Marinescu V, Van Huysen C, et al. Dissection of metabolic, vascular, and nerve conduction interrelationships in experimental diabetic neuropathy by cyclooxygenase inhibition and acetyl-L-carnitine administration. *Diabetes*. 2002;51:2619-2628.
154. Kellogg AP, Pop-Busui R. Peripheral nerve dysfunction in experimental diabetes is mediated by cyclooxygenase-2 and oxidative stress. *Antioxid Redox Signal*. 2005;7:1521-1529.
155. Sweitzer SM, Medicherla S, Almirez R, et al. Antinociceptive action of a p38alpha MAPK inhibitor, SD-282, in a diabetic neuropathy model. *Pain*. 2004;109:409-419.
156. Valsecchi AE, Franchi S, Panerai AE, Sacerdote P, Trovato AE, Colleoni M. Genistein, a natural phytoestrogen from soy, relieves neuropathic pain following chronic constriction sciatic nerve injury in mice: anti-inflammatory and antioxidant activity. *J Neurochem*. 2008;107:230-240.
157. Valsecchi AE, Franchi S, Panerai AE, Rossi A, Sacerdote P, Colleoni M. The soy isoflavone genistein reverses oxidative and inflammatory state, neuropathic pain, neurotrophic and vasculature deficits in diabetes mouse model. *Eur J Pharmacol*. 2011;650:694-702.
158. Kandhare AD, Raygude KS, Ghosh P, Ghule AE, Bodhankar SL. Neuroprotective effect of naringin by modulation of endogenous biomarkers in streptozotocin induced painful diabetic neuropathy. *Fitoterapia*. 2012;83:650-659.
159. Stavniichuk R, Drel VR, Shevalye H, et al. Baicalein alleviates diabetic peripheral neuropathy through inhibition of oxidative-nitrosative stress and p38 MAPK activation. *Exp Neurol*. 2011;230:106-113.
160. Tesfaye S, Tandan R, Bastyr EJ 3rd, Kles KA, Skljarevski V, Price KL. Factors that impact symptomatic diabetic peripheral neuropathy in placebo-administered patients from two 1-year clinical trials. *Diabetes Care*. 2007;30:2626-2632.
161. Ma J, Farmer KL, Pan P, et al. Heat shock protein 70 is necessary to improve mitochondrial bioenergetics and reverse diabetic sensory neuropathy following KU-32 therapy. *J Pharmacol Exp Ther*. 2014;348:281-292.
162. Ma J, Pan P, Anyika M, Blagg BS, Dobrowsky RT. Modulating molecular chaperones improves mitochondrial bioenergetics and decreases the inflammatory transcriptome in diabetic sensory neurons. *ACS Chem Neurosci*. 2015;6:1637-1648.
163. Chaudhury S, Keegan BM, Blagg BSJ. The role and therapeutic potential of Hsp90, Hsp70, and smaller heat shock proteins in peripheral and central neuropathies. *Med Res Rev*. 2021;41:202-222.
164. Cheng KI, Wang HC, Tseng KY, et al. Cilostazol ameliorates peripheral neuropathic pain in streptozotocin-induced type I diabetic rats. *Front Pharmacol*. 2021;12:771271.

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