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REVIEW

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Inflammation in diabetes complications: molecular mechanisms and therapeutic interventions

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Abstract

At present, diabetes mellitus (DM) has been one of the most endangering healthy diseases. Current therapies contain controlling high blood sugar, reducing risk factors like obesity, hypertension, and so on; however, DM patients inevitably and eventually progress into different types of diabetes complications, resulting in poor quality of life. Unfortunately, the clear etiology and pathogenesis of diabetes complications have not been elucidated owing to intricate whole-body systems. The immune system was responsible to regulate homeostasis by triggering or resolving inflammatory response, indicating it may be necessary to diabetes complications. In fact, previous studies have been shown inflammation plays multifunctional roles in the pathogenesis of diabetes complications and is attracting attention to be the meaningful therapeutic strategy. To this end, this review systematically concluded the current studies over the relationships of susceptible diabetes complications (e.g., diabetic cardiomyopathy, diabetic retinopathy, diabetic peripheral neuropathy, and diabetic nephropathy) and inflammation, ranging from immune cell response, cytokines interaction to pathomechanism of organ injury. Besides, we also summarized various therapeutic strategies to improve diabetes complications by target inflammation from special remedies to conventional lifestyle changes. This review will offer a panoramic insight into the mechanisms of diabetes complications from an inflammatory perspective and also discuss contemporary clinical interventions.

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KEYWORDS
diabetes complications, inflammation, molecular mechanisms, therapeutic interventions

1 | INTRODUCTION

Diabetes mellitus (DM), a metabolic disease characterized by hyperglycemia, can injury multiple organs and tissues. The international diabetes federation estimated the diabetic patients with age 20–79 years were over 536.6 million in 2021 and would rise to 783.2 million in 2045, as much as about 10% of adult population.[1] Diabetes contains type 1 diabetes (T1DM) and type 2 diabetes (T2DM), and the former is a chronic autoimmune disease caused by innate insulin deficiency,[2] while the latter is due to dysfunction of insulin secretion, thereby inflicting insulin resistance (IR).[3] DM threatens the life span and quality to patients by directly or indirectly pathways. Owing to long-term high glucose environment, both macrovessels and microvessels are impaired and will eventually inflict a series of complications, like diabetic cardiomyopathy (DCM), diabetic nephropathy (DN), diabetic retinopathy (DR), diabetic peripheral neuropathy (DPN), diabetic foot ulcer, and so on. Of note, most of patients with DM burden more than one complication at the early stage of DM, which indicates that there may be some related inducement between the complications.

It has been reported that plenty of factors were involved in diabetes complications including but not limited oxidative stress, metabolic disorders, immune inflammation, and so on.[4] Among which, inflammation was deemed to play a pivotal role in the pathogenesis of diabetes complications. Slight inflammation was the main characteristic of DM, by mediating IR, vascular injury, and other related pathological processes.[5] In addition, inflammation was used as a biomarker to predict the occurrences of diabetes complications including DCM,[6] DN,[7] DR,[8] and DPN.[9] Inflammatory cytokines such as tumor necrosis factor-α (TNF-α),[8] transforming growth factor-β (TGF-β),[10] interleukins (ILs),[11] adhesion molecules,[12,13] and other genes related to macrophage could be used as biomarkers.[14] Due to the complex roles of inflammation in the occurrence and development of diabetes complications, their relationship has not been fully clarified.

In this paper, we introduced the molecular mechanisms of inflammation and how it interfered diabetes complications, ranging from immune cell response, cytokines interaction to pathomechanism of organ injury. Furthermore, the representative drugs based on target inflammation to improve diabetes complications were discussed in the paper to support for follow-up clinical research.

2 | MOLECULAR MECHANISMS OF INFLAMMATION IN DIABETES COMPLICATIONS

Immune cells play critical roles in the inflammatory response. During the long-term stimulation with high blood sugar, immune cells are activated and triggered a series of responses. For instance, when macrophages are activated, they initiate a series of downstream signaling pathways in the high glucose environment and release inflammatory cytokines. The TNF-α, IL-1β, IL-6, or other inflammatory factors being released will activate various inflammatory signaling pathways, such as nuclear factor kappa-B (NF-κB), signal transducer, activator of transcription 3 (STAT3), and so on, resulting in organ damage.

2.1 | Activation of immune cells

Monocytes and macrophages are important first line defenders in immune system of body. Once inflammation occurs, monocytes and macrophages will quickly gather to lesion area, and monocytes will differentiate into macrophage to destroy pathogens or cell fragments through phagocytosis and so on. Previous data showed the polarization of infiltrating macrophage was affected by the tissue microenvironment and external stimulation. For instance, macrophage could differentiate into M1 macrophages coming up abundant interferon-γ (IFN-γ) and TNF-α microenvironment in situ.[15] If some anti-inflammatory cytokines such as IL-4 and IL-13 were present, M2 macrophage would be increased.[16]

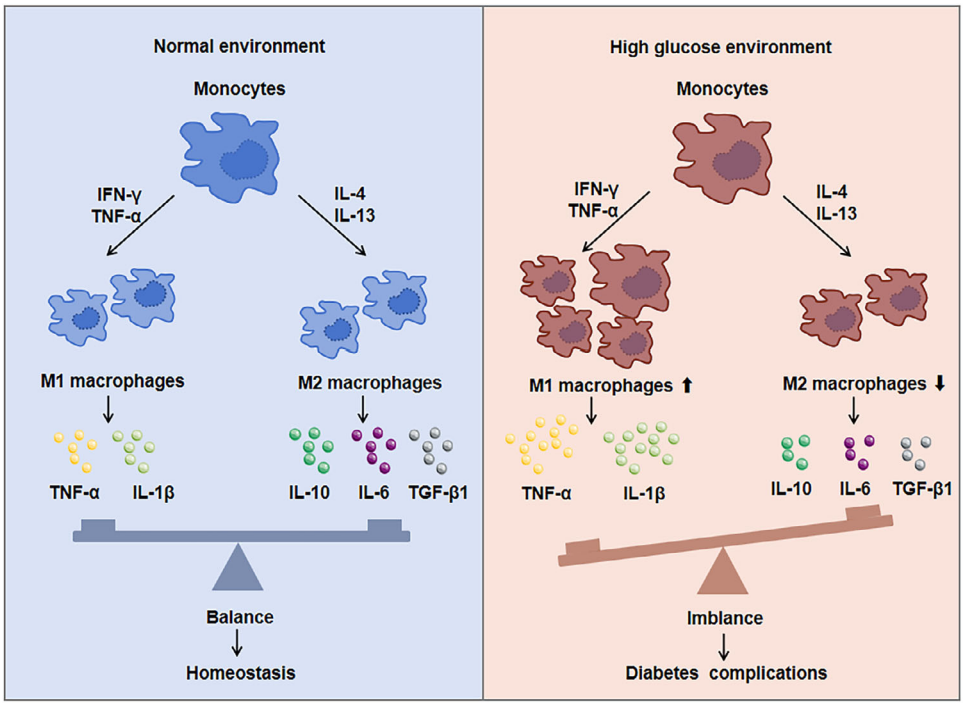

FIGURE 1 Activation of monocytes and macrophages in diabetes complications. Under normal environment, the ratio of M1/M2 macrophages is balanced, while the balance is disrupted under high glucose environment, the ratio of M1/M2 macrophages increases and produces a large number of proinflammatory cytokines, which aggravates the development of diabetic complications.

Studies have found that when diabetes complications occurred, monocytes were activated and recruited to the lesion area. Cytokines or chemokines secreted by monocytes also promoted much more monocytes recruitment and macrophage activation.[17] Moreover, the ratio of M1/M2 macrophages increased and efferocytosis of macrophages gradually decreased to aggravate the DM (Figure 1). M1 macrophages secreted a large number of proinflammatory cytokines, resulting in IR, while M2 macrophages secreted anti-inflammatory cytokines to enhance tissue repair and regeneration. For example, compared with healthy individuals, the number of infiltrating inflammatory monocytes and M1 macrophages in DCM patients were significantly increased.[18] M1 macrophages secreted large amounts of proinflammatory cytokines, causing IR as well as accelerating the development of DCM.[19] M2 macrophages secreted IL-10 and slowed down the development of myocardial fibrosis,[20] which could protect the heart in the early stages of DM. Therefore, transforming M1 macrophages into M2 phenotype and rebalancing the ratio of M1/M2 to inhibit myocardial fibrosis is a drug therapy strategy.[21] As abundant immune cells infiltrated in patients with DN, the accumulation of macrophages indicated the renal dysfunction. Glucose promoted the transformation of M1 macrophages and podocytes apoptosis in DN rats and while activating M2 macrophages could protect podocytes from injury.[22] On the one hand, proinflammatory M1 could change the integrity of podocytes. On the other hand, podocytes significantly promoted the migration of macrophages stimulated by high glucose medium.[23] Also, macrophage-depleted DM mice could reduce proteinuria and alter glomerular histology.[23] Furthermore, the polarization of macrophages from M1 to M2 could reduce the inflammatory injury of kidney.[24] At early stage of DR, both M1 and M2 microglia/macrophages were activated, but the numbers of M2 macrophages decreased with disease progress, and eventually resulted in retinal dysfunction. Previous data showed M2 macrophages-related genes, such as *COL5A2* and *CALD1*, were highly expressed in immune cells in the retinal fibrovascular membrane and could be used as potential biomarkers for proliferative DR.[14] It has been reported that asiatic acid reduced M1 polarization through TLR4/MyD88/NF-κB p65 pathway and increased M2 polarization to prevent early DR.[25] Histone demethylase Kdm6a could affect the gene transcription of macrophages, thereby affecting retinal thickness, visual acuity, and aggravating the development of DR.[26] Macrophages can affect the neurovascular function of peripheral nerve tissue and regulate the occurrence of neuroinflammation. By analyzing the sciatic nerve of DPN mice, it was found that the markers of M1 macrophages such as TNF-α and IL-1β increased, and the markers of M2 macrophages such as IL-10 and TGF-β decreased,[27] while after treatment,

macrophages expressed lower levels of proinflammatory genes and higher levels of anti-inflammatory genes.[27] Therefore, interfering with macrophages to M2 polarization has positive effect to attenuate diabetes complications. In addition, the active macrophages could be regulated by T cell immunoglobulin domain and mucin domain-3 (Tim-3) and aggravated diabetic kidney damage, and the deletion of *Tim-3* gene ameliorated podocyte injury and foot process disappearance in DN mice.[28] Therefore, it can improve diabetes complications by reducing the recruitment of macrophages or affecting its activation and polarization in future.

2.2 | Cytokines and chemokines interaction

As a small molecular protein with a wide range of biological activities, cytokines and chemokines can not only interact with each other but also participate in cellular pathological process, which eventually lead to diabetes complications.

2.2.1 | TNF-α

TNF-α expression was significantly increased in patients with DM, which could be used as a potential biomarker to predict the severity of the disease.[29] In DCM, TNF-α was overexpression in the heart and caused myocardial fibrosis, myocardial hypertrophy, and IR.[30] TNF-α was also as a biomarker for acute myocardial injury[29] and enabled to increase itself expression as well as other inflammatory cytokines, which might lead to a vicious circle.[31] Cardiovascular function would be improved in diabetic rats when TNF-α expression was suppressed.[32] Inhibition of TNF-α resulted in suppression of P38 mitogen-activated protein kinase (MAPK) and its downstream inflammatory mediators.[33] PI3K/AKT signaling could be activated by TNF-α as well, thereby inducing cardiomyocyte apoptosis and accelerating disease development.[34] In DN, the level of TNF-α in the urine was related to the presence and severity of microalbuminuria.[35] TNF-α/TIM-3 deficiency macrophages could eliminate the podocyte injury.[28] TNF-α ablation of macrophages could improve various physiological indexes, such as albuminuria, plasma creatinine, renal macrophage recruitment, and so on.[36] TNF-α also enhanced the secretion of matrix metalloproteinases and promoted glomerular basement membrane deposition and fibrosis.[37] In DR, TNF-α increased the permeability of endothelial cells and in turn released adhesion molecules, while inhibiting TNF-α expression could reverse the destruction of the blood–retinal barrier in DM mice and maintain the integrity of retinal tissue.[38] Besides, its receptor TNFR1 could prevent retinal cell death induced by high glucose.[39] Its receptor superfamily member CD40 was upregulated in the retina of diabetic mice, while CD40-deficient mice affected nitration of retinal proteins and prevented retinal vascular degeneration.[40] In DPN, TNF-α expression was positively correlated with diabetic neuropathy symptoms and nerve conduction velocity, which was suggested that TNF-α could catalyze DPN and be used as a biomarker of DPN.[41–43] When TNF-α was inhibited, the related symptoms of DPN could be improved, such as nerve conduction velocity increased, lamellar and axonal structure returning to normal, and so on.[44] Downregulate TNF-α expression and its receptors could also reduce the neuropathic pain of DM.[45] Besides, TNF-α stimulated IL-6 production, in turn affecting the peripheral nerve axons and accelerating the development of DPN.[46] Therefore, as an important proinflammatory cytokine, TNF-α not only affected other cytokines or immune cells directly, but also mediated various pathological processes by affecting islet cells or IR.[47]

2.2.2 | Interleukin

ILs played an important role in diabetes complications. The level of IL-6 was found to be increased in patients with DCM, which were involved in affecting myocardial fibrosis, cardiac hypertrophy, and glucose homeostasis during the development of DCM.[48–50] When pyroptosis occurred, inflammatory substances such as IL-1β and IL-18 were released and involved in the pathogenesis of DCM.[51] Accumulation of IL-18 in the body could cause cardiomyocyte hypertrophy and myocardial fibrosis,[52] and myocardial dysfunction was improved after using IL-18 neutralizing antibodies.[53] In DN, the serum IL-18 and IL-1β levels are positively correlated with DN stage. IL-18 directly accelerated glomerular injury and its content was related to urinary albumin excretion rate.[54–57] IL-6 was independently correlated with the risk of DN, overexpression of IL-6 could induce podocyte apoptosis and growth arrest in high glucose environment,[11] and it was also related to podocyte hypertrophy.[58] IL-17A was not only related to the decrease of glomerular filtration rate,[59] but also mediated glomerular injury and interstitial fibrosis by mediating autophagy.[60] In DR, IL-6 participated in cell recruitment of microglia and the integrity of blood–retinal barrier.[61] IL-17A could induce retinal neurons and retinal endothelial cells apoptosis, activate retina Müller cells and disrupt its function, and deform the capillaries.[62–64] IL-8 was also considered to be the risk of proliferative DR.[65] The polymorphism of IL-10 gene was associated with the occurrence and development of DR.[66] IL-1β and IL-18 mediated

the scorched death of retinal cells, pericyte apoptosis, endothelial cell permeability, and retinal angiogenesis.[67,68] In DPN, IL-6 could improve the neurovascular function, promote nerve regeneration, and protect Schwann cells injury from high glucose.[69–72] IL-1β expression was increased in DPN rats and the ultrastructure of myelin and the axon of DPN rats treated with IL-1β receptor antagonist got more highly protective effect than normal rats.[73] Therefore, ILs can be used as a biomarker for the prevention and detection of diabetes complications.

2.2.3 | TGF-β1

TGF-β1 was one of the strongest cytokines to induce fibrosis in organisms.[74] TGF-β1 could activate its downstream protein Smads to induce myocardial fibrosis,[75] renal fibrosis,[76] and retinal fibrosis.[10] In DCM, TGF-β1 could promote myocardial fibrosis as well as induce DCM progress through TGF-β1/Smads pathway.[75] The decreased content of TGF-β1, Smad2, and Smad3 protein improved heart function and prevented DCM devolopment.[77] Smad3 deficiency had been reported to inhibit myocardial fibrosis and cardiac inflammation in db/db mice.[78] In DN, TGF-β1 contributed to the repair process of renal injury and was a key regulator of renal inflammation.[79] It could exert its anti-inflammatory effect by inhibiting glomerular cell mitosis and cytokine response[80] and mediate the transformation of renal tubular epithelial cells into myofibroblasts to induce renal fibrosis through epithelial–mesenchymal transition (EMT). Specific Smad3 inhibition could improve the progression of disease by inhibiting TGF-β1/Smads signal.[81] Moreover, TGF-β1 could decrease nephrin and lead to albumin permeability, suggesting that TGF-β1 played a crucial role in hyperalbuminuria production.[82] Studies have proved that TGF-β1 was not only a biomarker and pharmacological target for DR,[10] but also an inhibitory factor for retinal neovascularization in proliferative retinopathy.[83] TGF-β1 could affect vascular maturation and endothelial cell proliferation.[84] Previous study has been shown that TGF-β1 at low concentration promoted endothelial cell proliferation and migration, while inhibited these effects at high concentration.[85] In addition, TGF-β1 was involved in retinal fibrosis and its activation played an additive role in promoting the overexpression of extracellular matrix proteins in Muller cell.[86] In DPN, there was a positive correlation between TGF-β1 and nerve conduction velocity, suggesting that it might be used as a biomarker of DPN.[9] Also, inhibition of TGF-β1 could inhibit neuronal apoptosis and regulate extracellular matrix and neuronal demyelination.[87,88] Therefore, TGF-β can be used as a therapeutic target for complications of diabetes.

2.2.4 | Chemokines

Chemokines can be roughly divided into four subfamilies CC, C, CXC, and CX3C families. Monocyte chemotactic protein-1 (MCP-1) protein was extensive expressed in myocardial tissue and involved in the pathogenesis of DCM[89]; it activated mononuclear macrophages to enhance the inflammatory response and finally promote fibrous tissue deposition.[90] Downregulation of MCP-1 levels with drugs treatment slowed the development of DCM.[91] Inhibition CCR5 could reduce the proportion of M1 macrophages in rat heart tissue as well as block M2 macrophages due to nuclear receptor subfamily 4 group A member 2 induction in vitro.[92] CXCR4 antagonists could reduce diabetes-induced cardiac fibrosis.[93] CCR2 was upregulated in diabetic heart; knockdown of CCR2 could reverse cardiac fibrosis, improve cardiac function, and reduce M1 macrophage infiltration.[94] CCL2 and its receptor CCR2 could mediate VCAM-1 to injury glomerular endothelial cells in DN.[95] CXCL9 was found to be increased in serum and urine of DN patients; it regulated the numbers of podocytes by Janus kinase-signal transducer and activators of transcription pathway (JAK/STST3) pathway.[96] CXCR4 had a protective effect on the kidney to promote renal tubular cell survival but it could be affected by ligand-inactivation gendopeptidases.[97] CXCL10 was involved in occurrence of renal fibrosis after high glucose stimulating in DN and restoring the abundance of CXCL10 could reduce the occurrence of fibrosis.[98] CXCL13 might play a role in the recruitment of T-follicular helper (Tfh) cells in different stages of DR.[99] CXCL1 could change the blood–optic retina barrier of DR through neutrophil recruitment, thus becoming a potential new therapeutic target.[100] CCR2/CCR5 inhibitors could reduce the content of stromal cell-derived factor-1 (SDF-1), intercellular cell adhesion molecule-1 (ICAM-1) and retinal vascular permeability in DM animals.[101] CCR2 knockout microglia inhibited TNF-α expression in retinal neurons, significantly.[102] CXCL2 regulated sciatic nerve and schwann cells apoptosis through NOD-like receptor thermal protein domain-associated protein 3 (NLRP3) pathway.[103] SDF-1 and its receptor CXCR4 mediate calcium influx and excitability of dorsal root neurons, and using its inhibitors could relieve neuropathic pain.[104] CXCL12/CXCR4 and CCR4 were also found to be one of the targets for the treatment of diabetic neuropathic pain.[105,106] CXCL1, CXCL5, CXCL9, CXCL10, CXCL11, and CXCL12 were important in nociceptive transmission and promoted the recruitment and penetration of CD8+ T cells in DPN.[107,108] Therefore, chemokines could attract and activate inflammatory cells to move toward the inflammatory site, participate in the regulation of inflammatory response, and be involved in tissue

injury repair and the occurrence of vascular lesions in DM.

Taken together, immune cell activation and cytokines interaction were necessary in the progress of diabetes complications, which deserved to further explore the specific role of macrophage subsets and studied how specific subsets play a role in diabetes complications. At the same time, the relationship between macrophages and other cells, such as endothelial cells and fibrous cells, should be attended. Furthermore, exploring efficient inhibitors of cytokines provide valuable insights into understanding their transmission within cells. This could potentially lead to discovering novel targets for treating diabetic complications.

3 | IR AND INFLAMMATION

As one of the pathological factors of diabetes, IR was the cell abnormal response to insulin stimulation, which caused the body to produce much more insulin, compensatively.[109] Previous studies showed that inflammation was closely related to IR; the relevant inflammatory signaling pathways and inflammatory mediators were worth exploring.[110]

3.1 | Impaired insulin signaling pathways

Several studies have shown that activation of phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) and MAPK signaling pathways could promote the occurrence of hyperglycemia and IR.[111,112] C-Jun N-terminal kinase (JNK),[113] JAK/STAT,[114] and NF-κB[115] were closely related to IR. The activity of JNK and insulin receptor substrate 1 (IRS-1) serine phosphorylation inhibited the occurrence of IR.[116] JAK/STAT could affect the secretion of proinflammatory cytokines, such as TNF-α and IL-6, thus mediating IR.[114,117] IKK/NF-κB signal pathway was involved in IR in DM.[115,118] In DCM, activating PI3K/AKT signal pathway or inhibiting NF-κB signal pathway could reduce the occurrence of IR,[119,120] and AKT2 deficiency resulted in severe glucose intolerance, myocardial contractile dysfunction, cardiomyocyte apoptosis, and impaired cardiac function.[121,122] IRS1/PI3K/AKT pathway was the main signal regulation pathway of podocyte IR, and blocking this pathway would induce EMT and glomerulosclerosis in DN podocytes.[123] Further study found that AKT2 deficiency induced obvious podocyte damage including foot process fusion and podocyte apoptosis.[124] In addition, inhibition of adenosine 5′-monophosphate (AMP)-activated protein kinase α (AMPKα) activity could result in podocyte damage and albuminuria.[125] In DR, mammalian target of rapamycin (mTOR) activation could reverse the occurrence of IR in retinal pigment epithelial cells.[126] JNK/S6K1-induced IR was linked with retina injury as well.[127] In DPN, diabetic neuropathy was affected by previous IR even though blood glucose was controlled at normal levels.[128] Activated JNK could induce IRS-1 serine phosphorylation, inhibit AKT and GSK3β serine phosphorylation, and promote the occurrence of IR in diabetic neuropathy.[129] In addition, increase of serine phosphorylation of IRS2 changed insulin support in neurons and promotes peripheral nerve dysfunction.[130] Therefore, the new strategy to attenuate IR would have positive significance for the improvement of diabetes therapy.

3.2 | Inflammatory mediators disrupting glucose homeostasis

The abnormal level of various inflammatory mediators caused intracellular inflammatory response and blocked insulin signal transmission. As one of the most important proinflammatory mediators, TNF-α expression increased at the early inflammatory stage and insulin signal transduction was damaged and leaded to IR by IRS-1 and JNK1/2.[131,132] In high glucose environment, the levels of IL-6 and IL-1β were significantly increased, which were closely related to IR.[117,133] Among them, IL-1β could not only inhibit insulin signal transduction in macrophages to cause abnormal insulin secretion,[133] but also attracted proinflammatory cells to migrate to islets and damage it.[134] IL-6 could trigger the JAK/STAT and PI3K signal pathway to induce IR.[135] Moreover, IL-6 could improve glucose tolerance, reduce gluconeogenesis genes expression in the liver, and increase the phosphorylation of AKT, thus maintaining insulin homeostasis.[136] IL-17-deficient mice showed higher glucose tolerance and insulin sensitivity, which was suggested that IL-17 was a negative regulator of glucose metabolism.[137] IL-33 produced by islet mesenchymal cells could promote β-cell function through islet-resident group 2 innate lymphoid cells, and they interacted with each other to promote insulin secretion.[138] On the contrary, some anti-inflammatory cytokines, such as IL-4 and IL-5, could increase insulin sensitivity and slow down the occurrence of IR.[139] Leukocyte cell-derived chemotaxin 2 (LECT 2), as a hepatocyte factor, caused IR in skeletal muscle through JNK signal pathway.[140] The MCP-1 increased in adipose tissue contributed to macrophage infiltration and induced IR.[141] NLRP3 inflammasome cooperating with ROS-liberated TXNIP derived pancreatic islets to secrete IL-1β and delayed pancreatic islets function damage in the response of chronic elevated glucose.[142] C-reaction protein (CRP) could directly regulate the central role of leptin and hypothalamic signal

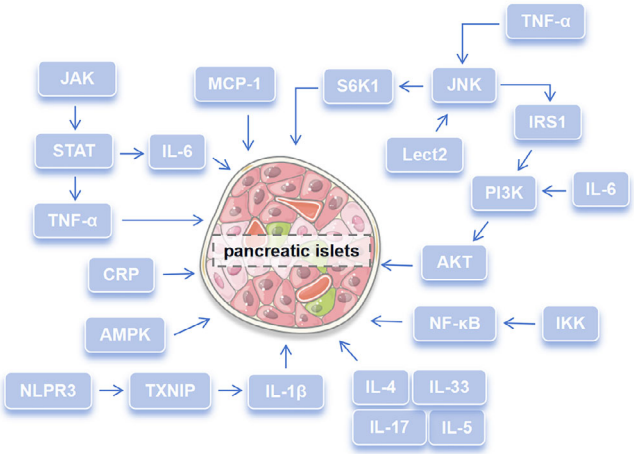

FIGURE 2 Signaling pathways and inflammatory mediators are involved in insulin resistance. Plenty of signaling pathways such as IKK/NF-κB, IRS1/PI3K/AKT, JNK/S6K1, AMPK, JAK/STAT, and so on can mediate insulin resistance, while related inflammatory mediators including TNF-α, IL-4, IL-5, IL-33, IL-17, IL-6, IL-1β, CRP, Lect2, NLRP3 inflammasome, and so on affect the occurrence of insulin resistance.

to affect insulin sensitivity and glucose homeostasis.[143] Enhanced IκB kinase beta activity could improve insulin sensitivity and consequently had a beneficial role in glucose homeostasis.[144] Therefore, inflammatory mediators may affect the homeostasis of glucose and mediate the occurrence and development of diabetes by inhibiting insulin secretion and affecting insulin sensitivity. Signaling pathways and inflammatory mediators involved in diabetes complications were summarized in Figure 2 and new strategy targeting IR would have positive significance for the improvement of diabetes therapy.

Taken together, inflammatory mediators and various inflammatory signal pathways interact with each other, in turn affecting glucose homeostasis and mediating the complications of diabetes. In the future, it can deeply study the gene regulation mechanism of inflammatory mediators, including the role of transcription factors, DNA methylation, and so on. At the same time, it can also analyze different types of cells to further reveal the similarities and differences of the regulation mechanism of inflammatory mediators on glucose homeostasis in different cells. Further it is essential to understand the relationship between cytokines and insulin signaling pathway, which can provide new ideas for the treatment of DM in future.

4 | INFLAMMATION-MEDIATED COMPLICATIONS IN DIABETES

According to the different pathological mechanism, diabetes complications could be divided into microvascular complications and macrovascular complications. The former includes DN, DR, and DPN, while the latter includes cardiovascular disease, cerebrovascular disease, peripheral arterial disease, and so on.[145] In patients with DM, long-term hyperglycemia activated a variety of inflammatory signal pathways and inflammatory mediators, resulted in aggravating the development of diabetes complications, and eventually led to damage of various organs.[146] Inflammation could participate in the many pathological processes such as apoptosis, vascular endothelial damage, plaque formation, tissue fibrosis, and so on.[147] The common complications in DM patients, with the purpose of clarifying the relationship between inflammation and cardiovascular disease, nephropathy, retinopathy, and neuropathy, are discussed as follow.

4.1 | Cardiovascular system

When the body is subjected to a prolonged high-glucose environment, it can result in vascular damage, which in turn can lead to a variety of cardiovascular conditions, including DCM, coronary heart disease, and atherosclerosis (AS). Individuals with DM have a significantly higher incidence of these cardiovascular diseases compared with those without diabetes.

4.1.1 | AS and inflammation

AS was caused by vascular endothelial injury that led to cholesterol and platelets deposited in the blood vessel wall and formed plaques, then finally resulted in vascular obstruction or stenosis. Under long-term stimulation of inflammation in a high glucose environment, arterial endothelial cells were dysfunctional and released adhesion molecules, resulting in adhesion between white blood cells and small blood vessels. Meantime, because of increase of vascular endothelial permeability, low-density lipoprotein (LDL) was accumulated and was oxidized and influenced monocytes.[148] Oxidized LDL could induce macrophages to express scavenger CD36 and make self-antigen presentation disappear, then transforming into foam cells. With the accumulation of these foam cells and other inflammatory cells, AS plaques were eventually formed. In addition, while the inflammatory response persisted, it would induce various inflammatory cytokines expression, stimulate macrophages activation, trigger a series of cascade reactions, and accelerate AS.[149] Therefore, AS was closely related to the activation of macrophage and the secretion of adhesion molecules or inflammatory cytokines. As one of the common triggered of DM and AS, the dynamic changes of inflammation level

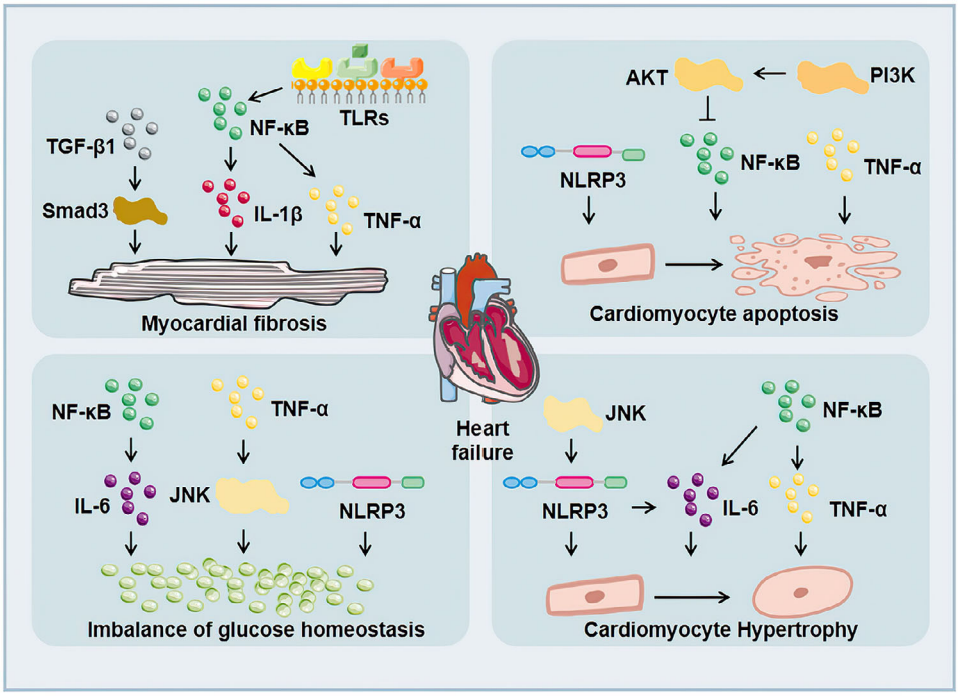

FIGURE 3 Cytokines that regulate cardiac pathological processes. TNF-α causes cardiomyocyte apoptosis, cardiomyocyte hypertrophy, myocardial fibrosis, and impaired glucose homeostasis. IL-6 promotes cardiomyocyte hypertrophy and impaired glucose homeostasis. TGF-β1 participates in myocardial fibrosis. NLRP3 inflammasome engages in the process of glucose homeostasis, cell apoptosis, cardiomyocyte hypertrophy and impaired glucose homeostasis.

were closely related to the occurrence of AS in patients with diabetes.[150] Intervention of inflammatory levels in patients with DM could delay the occurrence of AS.[151]

4.1.2 | Cytokines impact on heart function

Under the influence of long-term chronic hyperglycemia, the heart of DM patients was seriously damaged, resulting in myocardial hypertrophy, myocardial fibrosis, myocardial ischemia, myocardial infarction, and might eventually lead to heart failure, which was threaten to the health of DM patients. The incidence rate of heart failure in DM patients was two to four times higher than that in non-DM patients.[152] Cytokines and inflammasomes accelerated the injury of cardiac function (Figure 3). TNF-α in the heart caused cell apoptosis, myocardial hypertrophy, and myocardial fibrosis.[30] IL-6 promoted cardiac hypertrophy, proliferation of cardiac fibroblasts, and collagen production in diabetic rats.[48,49] TGF-β1 activated its target protein Smads and promoted myocardial fibrosis in DCM.[75] NLRP3 inflammasome activation participated in the process of glucose homeostasis,[142] cardiomyocyte apoptosis,[153] cardiomyocyte hypertrophy,[154] and myocardial fibrosis.[155] ICAM-1 was related to Ang II-induced cardiac remodeling.[156] Related signal pathways also affected inflammatory cytokines expression, thus affecting the function of the heart. For example, Toll-like receptors (TLRs) might accelerate many inflammatory cytokines expression, such as IL-6, IL-1β, TGF-β, and so on.[157] Upregulation of TLR4 could activate NF-κB in cardiomyocytes and promote the production of inflammatory cytokines, such as TNF-α and IL-1β, causing myocardial inflammation and myocardial fibrosis in DCM.[158,159] *TLR* gene knockout could reduce the level of NF-κB phosphorylation, adhesion molecules, and proinflammatory cytokines.[160,161] NF-κB affected the release of related inflammatory cytokines, such as TNF-α, IL-6, and IL-1β, which mediated cardiac hypertrophy, myocardial fibrosis, cardiomyocyte apoptosis, and so on.[162,163] The P38 pathway could regulate a variety of genes including TNF-α and TGF-β. At the same time, its activity could also be enhanced by proinflammatory cytokines such as TNF-α and IL-6, thereby exacerbating the inflammatory response.[164] JNK was a key upstream molecule of NF-κB[165] and it could be activated by inflammatory cytokines such as TNF-α, which induced IR.[166] TGF-β1/JNK was related to myocardial fibrosis in DCM.[167] In addition, JNK was involved in regulating NLRP3 inflammasome activation in macrophages.[168] IL-1β, IL-6, and TNF-α could stimulate JAK/STAT after binding to the receptor, thereby initiating the expression of downstream inflammation-related target genes.[169] The activation of JAK/STAT further stimulated cytokines, aggravated the inflammatory response,[170]

and participated in myocardial fibrosis.[171] Besides, activation of the PI3K/AKT pathway could also inhibit NF-κB expression to alleviate high glucose-induced cardiomyocytes damage.[172] Therefore, inflammation accelerates the damage of cardiac structure and function in patients with DM, and eventually lead to heart failure.

4.2 | Nephropathy

DN is the renal damage caused by diabetic microangiopathy, characterized by persistent proteinuria. It was the most common chronic kidney disease at present, more than 50% of DM patients would develop DN.[173] Inflammation participates in variety of pathological process of DN including renal tubular fibrosis, inflammatory cell infiltration, extracellular matrix accumulation, podocyte autophagy, and so on.

4.2.1 | Inflammation damage to renal structures

In the pathological process of DN, the aggravation of inflammation damage the structure of the kidney, thus leading to the deterioration of the disease. In the early stage of DN, tubular injury, glomerular hypertrophy, and glomerular basement membrane thickening occur by the effect of inflammatory cytokines and immune cells. Glomerulosclerosis, tubulointerstitial fibrosis, and other symptoms emerged at the late stage of DN.[174] The glomerular filtration membrane consisted of endothelial cells, glomerular basement membrane, and podocytes from the inside to the outside. TNF-α and IL-6 reduced the capillary space between endothelial cells, resulting in impaired vasodilation function. At the same time, inflammation increased the adhesion of leukocytes to endothelial cells and promoted the folding of red blood cells, which reduced NO production and promoted the occurrence of EMT, and then finally led to renal fibrosis.[175] In a high glucose environment, accompanied by thickening of the glomerular basement membrane, podocytes appeared hypertrophy, EMT, apoptosis, and exfoliation, which interfered with the normal structure and function of glomeruli, ultimately leading to abnormal glomerular filtration and the occurrence of proteinuria.[176] A variety of inflammatory reactions could affect the structure and function of kidney. TNF-α could mediate podocyte injury[28] and affect various physiological indexes, such as albuminuria, plasma creatinine, and renal macrophage recruitment.[36] IL-18 could directly accelerate glomerular injury[56] and IL-6 could induce podocyte apoptosis and growth arrest in high glucose environment.[11] IL-6 also played a role in podocyte hypertrophy induced by high glucose through JAK2/STAT3 pathway.[58] IL-17A could affect the expression of CD40 and TGF-β1[59] and participate in the process of podocyte injury and renal interstitial fibrosis.[60] TGF-β1 could mediate the transformation of renal tubular epithelial cells into myofibroblasts to induce renal fibrosis through EMT.[76] NLRP3 silencing could improve podocyte autophagy, reduce podocyte injury, and inhibit renal fibrosis.[177,178] Inhibition of TXNIP/NLRP3 pathway could inhibit apoptosis.[179] CXCR4 could mediate the death of renal tubular epithelial cells[97] and CXCL9 was related to podocyte injury.[96] Inhibiting the activation of NF-κB pathway could reduce renal inflammation and improve renal fibrosis.[180] APMK/Sirt1/NF-κB pathway could affect inflammation in DN,[181] and NF-κB/TNF-α pathway mediated podocyte injury in DM rats.[28] The lack of *TLR4* gene or inhibition of TLR4 expression improved urinary protein, glomerular hypertrophy, and renal tubular injury.[182,183] Also, the activation of TLR under high glucose could activate NF-κB and the subsequent inflammatory and fibrotic reactions.[183] JNK inhibitor reduced the activity of NF-κB, adhesion molecules expression, and the infiltration of inflammatory cells in DN mice.[184] The activation of P38/JNK signal pathway could promote podocyte apoptosis and aggravate renal injury in DN mice.[185] JAK/STAT3 participated in podocyte damage,[96] renal interstitial fibrosis,[186] and podocyte hypertrophy.[58] PI3K/AKT signal was involved in renal tubulointerstitial fibrosis, tubulointerstitial cell injury, and glomerulosclerosis.[123,187] Therefore, various inflammatory reactions will aggravate the damage of renal structure in DN patients and eventually lead to renal dysfunction (Figure 4).

4.2.2 | Altered filtration and kidney function

The decrease of proteinuria and glomerular filtration was a typical manifestation of DN, and it could be influenced by inflammation. Under the condition of high glucose, inflammatory cells such as macrophages infiltrated the glomeruli and released related inflammatory cytokines.[188] Inflammatory cytokines such as IL-6 and TNF-α caused extracellular matrix proliferation, glomerular fibrosis, filtration barrier destruction, and albuminuria.[189] During the process of DN, mesangial cell hypertrophy, podocyte rearrangement, and podocyte decrease appeared in glomeruli, changing the permeability of glomerular capillaries, and eventually led to glomerular filtration barrier damage and albuminuria.[190] Podocytes are an important part of glomerular filtration barrier; its related inflammatory signaling pathways, such as NF-κB, TLRs, JAK/STAT and PI3K/AKT, mediate glomerular filtration of podocytes. NF-κB inhibitor reversed HG-treated macrophage-mediated

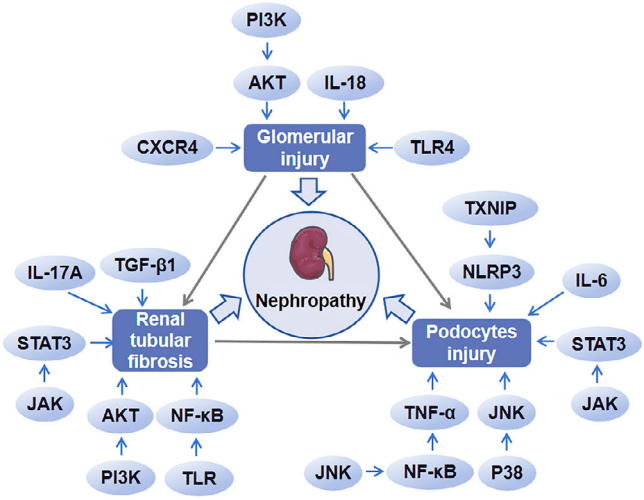

FIGURE 4 Inflammation damage to the kidneys. Multiple inflammatory reactions can play a role in aggravating the development of DN. PI3K/AKT, IL-18, CXCR4, and TLR4 aggravate glomerular injury. TXNIP/NLRP3, JAK/STAT3, P38/JNK, TNF-α, and IL-6 participate in podocytes apoptosis. PI3K/AKT, TLR/NF-κB, JAK/STAT3, TGF-β1, and IL-17A influence renal tubular fibrosis.

podocyte injury.[28] TLR4 inhibition increased the number of podocytes and played a role in improving renal inflammation and renal fibrosis.[182,183] JAK2/STAT3 was associated with podocyte hypertrophy.[96] IRS1/PI3K/AKT signaling pathway was involved in glomerular podocyte EMT and glomerulosclerosis.[123] Activating PI3K/AKT pathway could inhibit the Hippo pathway and led to nuclear YAP accumulation, thus accelerated glomerular mesangial cell proliferation in DN.[191] Therefore, inflammation will lead to damage of the glomerular filtration barrier, thus resulting in glomerulosclerosis and proteinuria, which seriously affect the function of the kidney.

4.3 | Retinopathy

DR encompasses a spectrum of eye conditions that arise from microvascular damage to the retina due to diabetes. It is a chronic and progressive disease that can compromise vision and, in severe cases, lead to blindness. The precise mechanisms underlying DR remain incompletely understood, although a considerable body of research suggests a strong association with inflammation exacerbated by prolonged hyperglycemia.

4.3.1 | Inflammatory damage to retinal structures

Inflammation seriously affects the structural changes of the retina. Excessive inflammatory response changes vascular permeability, capillary occlusion, and angiogenesis, resulting in damage to the blood–retinal barrier and retinal fibrosis. Based on the progress of disease, DR is divided into nonproliferative and proliferative. The loss of pericytes in capillaries was one of the early pathological changes of DR.[192] Due to loss of pericytes and the migration of endothelial cells, nonfunctional blood vessels appeared in the retina, and formed an ischemic and anoxic retinal environment, which promoted the formation of neovascularization and eventually developed into proliferative DR.[193] In the condition of high glucose, IL-1β induced apoptosis of pericyte cells and increased vascular permeability through NF-κB signal pathway, and it could also stimulates TLR4 through AGE to increase angiogenic factor Galectin-1 expression of macrophages and microglia.[194] TNF-α could affect the integrity of blood–retinal barrier in DM mice[38] and this process was regulated by IL-6.[61] IL-17A could damage retinal microvessels, retinal Müller cells, and ganglion cells.[63] TGF-β1 exerted a certain role in endothelial cell interaction and vascular remodeling.[195] Adhesion molecule Ninjurin1 played an important role in maintaining vascular integrity mediated by macrophages.[196] NLRP3 participated in the immune response of the retina and the pathological neovascularization in the late stage of DR.[197] NLRP3-caspase-1-GSDMD-mediated pyrolysis might be the factor for the partial loss of retinal pericytes upon high glucose environment.[198] CXCL1 could change the blood–optic retina barrier of DR through neutrophil recruitment.[100] The activation of NF-κB/STAT3 signal pathway could stimulate the polarization of M1 phenotypic microglia/macrophages and upregulated IL-1β, IL-6, and TNF-α expression to demolish the retinal structure.[199] The inhibition of JNK mitigated the pathological damage of retina and reduced apoptosis, thus improving DR.[200] PI3K/AKT/STAT3/NF-κB signal pathway could inactivate microglia and maintain the integrity of the blood–retinal barrier.[201] Therefore, a variety of inflammatory cytokines, chemokines, inflammasome, and related inflammatory signaling pathway are involved in the structural changes of the retina especially blood–retinal barrier.

4.3.2 | Visual impairment and risk of blindness

During the progression of the disease, patients with DR would deteriorate from limited field of vision to blindness due to gradual destruction of the blood retina barrier and the increase of neovascularization.[202] With sustained high glucose stimulation, the capillaries were destructed and their permeability was altered, and macular edema was formed subsequently, which lead to blurred or impaired vision. In addition, neovascularization in ischemic retina was prone to rupture, allowing blood to enter the eye,

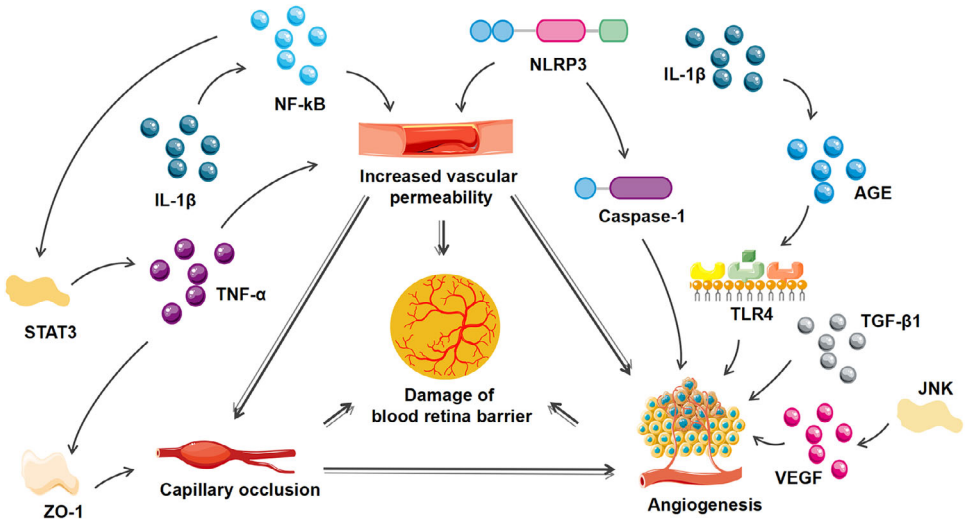

FIGURE 5 Inflammation damage to blood retina barrier. NLRP3 affects angiogenesis and capillary permeability by secreting proinflammatory cytokines. JNK activation can increase retinal VEGF expression and then speed up pathological retinal neovascularization. STAT3 activation increases TNF-α expression and promotes ZO-1 disintegration to damage blood–retinal barrier. IL-1β increases vascular permeability through NF-κB signal pathway, and it can also stimulate TLR4 through AGE to regulate angiogenesis.

and further exacerbating the sudden loss of vision. Various inflammatory responses and signaling pathways were involved in vascular permeability and angiogenesis of DR. NF-κB promoted the permeability of endothelial cell.[67] O-GlcNAcylation of NF-κB increased the death of retinal ganglion cells in DR.[203] TLR4/AGE pathway was activated by IL-1β and then increased angiogenic factor Galectin-1 of macrophages or microglia to promote angiogenesis in retina.[194] JNK activation could increase retinal VEGF expression and then speed up pathological retinal neovascularization.[204] STAT3 activation increased TNF-α expression and promoted ZO-1 disintegration to injure blood–retinal barrier.[61] The activation of PI3K/AKT could mediate endothelial cells autophagy,[205] slow down vascular endothelial cell–mesenchymal transformation,[206] and improve visual impairment in DR. Therefore, inflammation aggravates the damage of blood–retinal barrier in DR patients and increases the risk of visual impairment and blindness (Figure 5).

4.4 | Neuropathy

Diabetic neuropathy is among the most prevalent chronic complications of diabetes, affecting both the central and peripheral nervous systems. DPN is the most prevalent form of diabetic neuropathy, characterized by symptoms such as symmetrical pain and sensory disturbances that arise due to peripheral nerve dysfunction. This condition is known to be modulated by inflammation present in patients with DM.

4.4.1 | Inflammatory damage to nerve tissue

Inflammatory cytokines, immune cells and inflammasome participated in regulation of nerve conduction velocity, nerve regeneration function, neuronal apoptosis, neurovascular function and hyperalgesia (Figure 6). TNF-α slowed down the nerve conduction velocity and disrupted the lamellar and axonal structures.[41–43] IL-1β and its receptor damaged the ultrastructure and axon of myelin in DPN.[73] TGF-β triggered neuronal apoptosis by inducing inflammation.[87] NLRP3 was activated by excessive ROS and led to pyroptosis of Schwann cells.[207] Adhesion molecules might slow down the motor nerve conduction velocity in DPN.[208] Related inflammatory signal pathways also affected the structure and function of nerve tissue. Activation of NF-κB by targeting genes of miR-146 was related with inflammation, peripheral tissue blood perfusion, and thrombosis in DPN.[209] Ciliary neurotrophic factor could promote axons regeneration and protect the peripheral nerve by activating NF-κB.[210] TLRs could stimulate the secretion of cytokines and chemokines,[211,212] affect the early neuropathy of sensory neurons through immunomodulation or recruitment,[211] and regulate axonal growth and apoptosis of dorsal root ganglion neurons under hyperglycemia.[213] TLR4/MyD88/NF-κB signal pathway exerted a neuroprotective effect,[214] while JNK,[215] JAK/STAT3, and PI3K/AKT/mTOR pathway[216,217] were involved in the apoptosis, autophagy, and proliferation of Schwann cells. Therefore, inflammation can damage nerve tissue through various pathways and aggravate the progress of DPN.

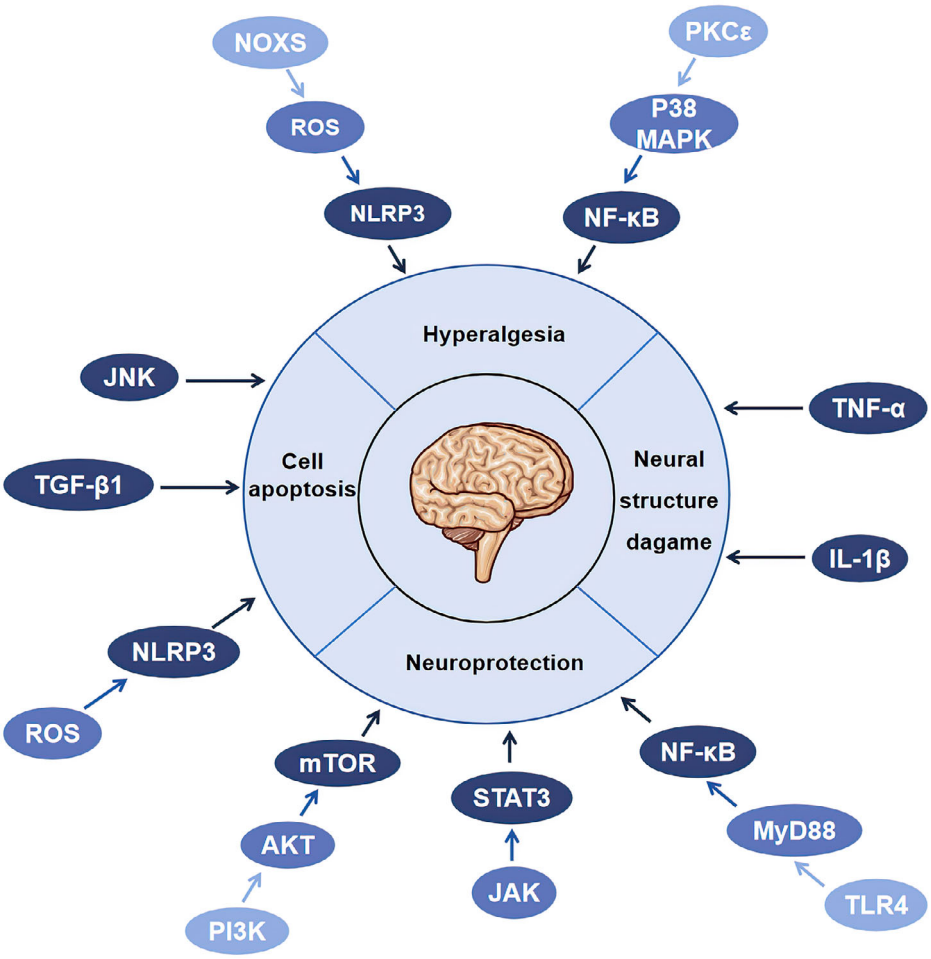

FIGURE 6 Inflammation damage to nerve tissue. Inflammatory reaction promotes the development of DPN, accompanied by cell apoptosis, neural structure damage, neuroprotection, and hyperalgesia. JNK, TGF-β, and NLRP3 promote cell apoptosis. TNF-α and IL-1β damage nerve structure. TLR4/MyD88/NF-κB, JAK/STAT3, and PI3K/AKT/mTOR exert a neuroprotective effect. PKCε/P38MAPK/NF-κB and NOXS/ROS/NLRP3 aggravate hyperalgesia.

4.4.2 | Sensory and motor nerve dysfunction

Loss of sensory function was one of the early manifestations of diabetic neuropathy, which was characterized by the acquisition or loss of sensory function.[218] In the late stage of the disease, patients with DN appeared neuromuscular damage, resulting in motor disorders, and impacted on daily life.[219] Similar to neuropathic pain-like symptoms, the loss of sensory function was related by inflammatory. NLRP3 was activated in dorsal root ganglion, which could increase mechanical hyperalgesia in DPN.[220] Moreover, activating NLRP3 in the peripheral nerve caused paclitaxel-induced neuropathic pain.[221] PKCε/P38MAPK/NF-κB and NOXS/ROS/NLRP3 were involved in inflammatory of hyperalgesia.[222,223] The chemokine SDF-1 and its receptor CXCR4 could mediate calcium influx and excitability of dorsal root neurons, which lead to neuropathic pain.[104] Additionally, inhibition of T cell infiltration was of positive significance in improving peripheral neuropathic pain in DPN.[224] Therefore, all kinds of inflammatory reactions will aggravate the sensory and motor dysfunction in patients with DN.

Considered collectively, excessive inflammation can intensify the progression of diabetes-related complications, resulting in organ damage, including the heart, kidneys, brain, and eyes. A comprehensive investigation into the potential targets within the inflammatory process may represent one of the strategic approaches for the treatment and prevention of these diabetes-related complications.

5 | THERAPEUTIC INTERVENTIONS TARGETING INFLAMMATION IN DIABETES

As inflammation exists throughout the pathological process of DM, it has become one of the important targets for

the treatment of DM. At present, anti-inflammatory drugs and lifestyle improvement are commonly used in clinical treatment of DM.

5.1 | Anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids and immunosuppressive agents are anti-inflammatory drugs commonly used in the treatment of DM. NSAIDs could regulate blood glucose and improve insulin sensitivity by anti-inflammatory effect.[225] It reduced the incidence of cardiovascular events in patients with DM, while might increase the risk of bleeding to some extent.[226] For example, salsalate, one of NSAIDs, could reduce inflammatory parameters such as CRP, free fatty acid in obese individuals at high risk of DM.[225] Anti-inflammatory effect of salsalate could improve blood glucose parameters and insulin sensitivity.[227] However, it might be not beneficial to cardiac and renal function.[228] Indomethacin could not only stimulate the production of endogenous glucose in T2DM patients by inhibiting insulin secretion,[229] but also reduced the increase of albumin excretion rate in T1DM patients with microalbuminuria by inhibiting renal prostaglandin synthesis.[230] Additionally, indomethacin could also improve the cerebrovascular reactivity in patients with DM.[231] Celecoxib, as a cyclo-oxygenase-2 inhibitor, had a certain efficacy in the treatment of early DR and it could play an anti-inflammatory role in reducing fluorescein leakage.[232] It was worth noting that indomethacin and celecoxib might damage renal function.[231,232] Diclofenac could inhibit postoperative inflammation and control intraocular pressure in patients with diabetic macular edema, but its inhibitory effect decreased with the extension of operation time.[233] At the same time, studies found that diclofenac could be used as an effective analgesic before treatment, reducing the pain during surgical treatment of DR,[234] and preventing early macular thickening after cataract surgery in patients with nonproliferative and mild nonproliferative DR.[235] Diclofenac should be used with caution in the treatment of DM patients with heart disease because it will aggravate cardiovascular disease.[234] Curcumin could reduce the average concentration of high-sensitivity CRP in DM patients, suggesting it reduced the risk of diabetes complications by reducing inflammatory reaction.[236] Further research found that in patients who met the criteria for prediabetes and were treated with curcumin, the levels of the anti-inflammatory cytokine adiponectin gradually increased, which could effectively prevent DM in prediabetic people.[237] In addition, during the 9-month treatment period, there were no significant adverse reactions in the curcumin treatment group, and only some subjects experienced mild symptoms such as itching, constipation, and dizziness.[237]

Corticosteroids and immunosuppressive agents regulated the number and activity of immune cells[238,239] as well as inhibited the activation and secretion of inflammatory cytokines and inflammasome.[240] It was reported that rituximab could temporarily stabilize β-cell function, trigger increases in T cell genes and decreases in B cell genes by analyzing the blood of patients with T1DM after rituximab treatment.[241] It was suggested that the combination of rituximab and other drugs with the function of blocking T cell activity had a more longstanding clinical effect. However, a study of rituximab in the treatment of T1DM found that although rituximab delayed the progression of the disease, it increased the frequency of asymptomatic viremias caused by polyomavirus.[242] The level of fibroblast growth factor-21 (FGF 21) was closely related to inflammation and IR.[243] Studies have found that FGF 21 levels in patients with DM decreased after treatment with dexamethasone, but the effect of its persistence needed more in-depth study.[244] What is more, dexamethasone could improve vision loss caused by macular edema.[245] However, it caused a mild increase in glucose levels.[246] Betamethasone could not only improve peripheral insulin sensitivity, but also inhibit systemic inflammation and control intraocular pressure in patients with diabetic macular edema,[233,247] while it might have a negative effect on bone formation.[247] Azathioprine could improve β-cell function, decrease glycosylated hemoglobin level and patients' dependence on insulin therapy, and inhibit T-cell proliferation, though it might cause vomiting and mild hair loss.[248,249] Abatacept improved immune cell subsets and insulin secretion in patients with T1DM, including reducing the frequency of inducible T-cell costimulatory (ICOS)+ PD1+ Tfh cells, naive CD4+ T cells, and the frequency of CD4+ regulatory T cells (Tregs) upregualtion.[250,251] However, abatacept might induce skin and connective tissue disease in patients with DM.[250] A random clinical trial of otelixizumab in the treatment of T1DM reported that the reactivation rate of Epstein–Barr virus (EBV) was associated with increased productive T cell clonality. It was found that otelixizumab could temporarily damage immune activity and allow EBV to be replenished in a dose-dependence.[238] In addition, otelixizumab was a chimeric CD3 antibody whose structure limited the ability to bind complement or Fc receptors, thereby reducing the risk of adverse clinical reactions caused by cytokine release.[239] However, in clinical trials, participants taking otelixizumab got more than one adverse event due to cytokine dysfunction and the frequency and severity of adverse events were dose dependent.[238] Teplizumab, an FcR non-binding anti-CD3 mAb, has also effective in the clinical treatment of diabetes. The study found that compared with the control

group, immune activation-related genes decreased, while genes expressions related to T cell differentiation and regulation increased in DM patients after treated with Teplizumab.[252] Other study found Teplizumab reduced the circulating pool of CD3-expressing lymphocytes, increased the proportion of CD8+ central memory T cells, effector cells, and programmed cell death protein 1+ (PD-1+) cells, and regulated CD127 expression in circulating CD8 T cell subsets.[252,253] Teplizumab was also reported to preserve the function of β-cells, but it might lead to adverse events such as headache, gastrointestinal symptoms, rash, lymphopenia, and mild cytokine release syndrome.[254] Cilostazol could inhibit the activation of NLRP3 inflammasome in endothelial cells, thereby inhibiting the production of IL-1β and IL-18, suggesting it could reduce adverse vascular reactions and treat endothelial dysfunction in DM patients.[240] While a case report showed that cilostazol could cause nephrotoxicity at any time after ingestion.[255] Rapamycin affected DM patients directly by refitting the suppressive activity of CD4+ Tregs, though it did not directly alter effector T cell function.[256] In a clinical trial, it was found that although rapamycin treatment of T1DM patients increased Tregs in the first month, it could also lead to transient β-cell dysfunction.[257] The common clinical drugs of anti-inflammatory for DM were listed in Table 1.

5.2 | Lifestyle modifications

5.2.1 | Healthy diet and exercise

It has been reported that exercise could control blood sugar, increase insulin sensitivity, lose weight, reduce cardiovascular risk factors, and improve life well-being in diabetes.[261,262] Sedentariness should be interrupted every 30 min, which was benefit to adults with T2DM. Besides, regular physical exercise was of great benefit to patients with DM, because it in part could downregulate pro-inflammatory cytokines, inhibit inflammasome, and upregulate anti-inflammatory cytokines. The study found that high sensitivity CRP and IL-18 decreased and IL-10 increased in DM patients in the exercise group compared with the control group.[263] 12 weeks of Tai chi training[264] or 6 months of exercise[265] could decrease the activity of NLRP3 inflammasome and related inflammatory cytokines like IL-1β and IL-18 in prediabetic patients to alleviate systemic inflammation, reduce blood glucose, and improve IR. A single dose of high-intensity interval training (HIIT) had obvious anti-inflammatory effects on patients with T2DM, which was characterized by the decrease of TNF-α and TLR2 surface protein.[266] Except for HIIT, moderate continuous training (MCT) also played a positive role in patients with DM. It was found that both HIIT and MCT owned favorable adaptability to IL-6, but only HIIT group could improve the blood lipid status of DM patients.[267] Previous data showed endurance training significantly decreased the gene expression of NLRP3, P38MAPK, TNF-α, and IL-1β in the spinal cord of DM rats.[268] Therefore, exercise played a pivotal role in improving the level of NLRP3 inflammasome and its related inflammatory factors. In future, it is worth to study the effects of exercise type, intensity and duration on DM patients. At the same time, it is necessary to make comprehensive use of exercise, drug therapy, and diet management to find out a better individual treatment plan.

Studies have shown that about 70% of global T2DM was caused by poor diet due to insufficient intake of whole grains and excessive intake of refined grains and processed meat.[269] Therefore, a healthy and regular diet was particularly crucial for patients with DM. In a short-term study, vitamin C was found to improve blood glucose control and blood pressure in patients with T2DM.[270] Supplementation of vitamin D in patients with abnormal glucose homeostasis could reduce the expression of related inflammatory cytokines, such as CRP, TNF-α, and IL-6.[271] A healthy diet could improve inflammation in overweight or obese people and reduce risk of developing DM.[272] As compared with traditional low-fat diet, traditional low-carbohydrate diet could regulate blood glucose and downregulate inflammatory cytokines, suggesting low-carbohydrate diet could improve the subclinical inflammatory state of T2DM patients.[273] Whole-grain diet could reduce body weight, serum inflammatory markers, IL-6, CRP, to improve low-grade systemic inflammation, even though it did not change insulin sensitivity.[274] As compared with the control group, almonds decreased the level of IL-6, CRP, and TNF-α in T2DM patients.[275] Other study also found that nut intake was negatively correlated with inflammation and markers of blood glucose/insulin homeostasis.[276] Therefore, it is helpful to reduce the intake of harmful dietary diseases and eat protective diets appropriately, such as, yogurt, fruits, whole grains, nonstarchy vegetables, nuts, and seeds.

5.2.2 | Weight management and inflammation reduction

The inflammatory reaction could induce abnormal insulin secretion of β cells, which was one of the characteristics of T2DM.[277] Studies have found that obesity was a strong driving force for the occurrence and development of DM, might affect the early β-cell function and cell fate.[278,279] Meanwhile, when DM patients were overweight or obese, excessive adipose tissue would release

TABLE 1 The anti-inflammatory drugs used in diabetes.

Classification	Drugs	Function	Pharmacological mechanism	Side effect	References
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Aspirin	Anti-inflammation Antiplatelet aggregation	Inhibiting cyclooxygenase activity	Bleeding risk increase	226,258–260
	Salsalate	Regulating blood sugar Improving insulin sensitivity Anti-inflammation Reducing the risk of cardiovascular disease	Inhibiting the level of glycosylated hemoglobin and C-reaction protein Decreasing the number of leukocytes, neutrophils and lymphocytes	Injury of cardiac and renal function	225,228
	Indomethacin	Regulating blood sugar Improving cerebrovascular reactivity Reducing proteinuria	Inhibiting insulin secretion Stimulating endogenous glucose production Reducing cyclooxygenase production and renal prostaglandin synthesis	Renal function damage	229–231
	Celecoxib	Anti-inflammation Inhibition fluorescein leakage	Inhibiting cyclooxygenase activity Reducing VEGF expression	Renal function damage	232
	Diclofenac	Preventing intraocular pressure and cystoid macular edema Analgesia Anti-inflammation	Inhibiting COX expression Blocking prostaglandin synthesis	Cardiovascular risk	233–235
	Curcumin	Anti-inflammation Improving overall function of β-cells	Reducing C-reaction proteins Increasing anti-inflammatory cytokines	Itching Constipation Vertigo	236,237
Corticosteroids and immunosuppressive agents	Rituximab	Anti-inflammation Regulating blood sugar Stabilize β-cell function	Increasing heterogeneous T cell population Inhibiting B cell activity	Increasing the frequency of asymptomatic viremias	241,242
	Dexamethasone	Protecting against cystoid macular edema Anti-inflammation	Decreasing fibroblast growth factor	Mild increase in glucose	244–246
	Betamethasone	Regulating blood sugar Anti-inflammation	Reducing endogenous glucose production Regulating cyclooxygenase expression	Affecting bone formation	233,247
	Azathioprine	Regulating blood sugar Improving insulin resistance	Decreasing glycosylated hemoglobin level Affecting T-cell proliferation	Vomiting Mild hair loss	248,249

(Continues)

TABLE 1 (Continued)

Classification	Drugs	Function	Pharmacological mechanism	Side effect	References
	Abatacept	Regulating immune cell subsets Affecting insulin secretion	Reducing CD4 central memory T-cell and CD4+ regulatory T cells Increasing naive CD4+ T cells	Inducing skin and connective tissue disorders	250,251
	Otelixizumab	Regulating immune cell subsets Anti-inflammation	Inhibiting T cells Reducing cytokines level	Headache Nausea Vomiting Rash	238,239
	Teplizumab	Regulating immune cell subsets Anti-inflammation	Increasing proportions of CD8+ central memory T cells, effector memory and PD-1+ cells Reducing CD4+ effector memory T cells	Headache Gastrointestinal symptoms Rash Lymphopenia Mild cytokine release syndrome	252–254
	Cilostazol	Anti-inflammation Reducing endothelial dysfunction	Reducing the activity of NLRP3 inflammasome, IL-1β and IL-18 Increasing sirtuin 1	Inducing nephrotoxicity	240,255
	Rapamycin	Anti-inflammation Reducing insulin requirement	Refitting CD4+ regulatory T-cells function	Inducing transient β-cell dysfunction	256,257

related inflammatory mediators to facilitate the development of DM. Multiple inflammatory signaling pathways were closely related to the occurrence of obesity, such as MAPK, PI3K, JAK/STAT, JNK, which were also essential to DM.[280]

Taken together, anti-inflammatory drugs and good living habits had positive significance for DM patients. However, the current clinical use of drugs targeting inflammation might cause a series of side effects in patients, and its development still needs a large number of in-depth clinical trials. Moreover, not all patients with diabetes can use anti-inflammatory drugs, and the appropriate treatment plan needs to be chosen according to the specific situation in clinical use. Of note, it also needs to pay attention to individual differences over the relationship between inflammation and diabetes to achieve more accurate and effective treatment strategies.

6 | CONCLUSION AND FUTURE DIRECTIONS

This review concentrates on the molecular mechanisms underpinning inflammation in diabetes complications, encompassing the activation of immune cells, interactions between cytokines and the signaling pathways involving IR and inflammation, and the consequences of inflammation on diabetes-related complications. Furthermore, the article summarizes existing interventions that aim to mitigate diabetes complications through the modulation of inflammation.

Inflammation plays a pivotal role in the development and progression of complications in diabetes, a chronic condition. Targeting inflammation has emerged as a promising therapeutic approach for managing diabetes complications. For instance, the development of inhibitors that can regulate or control the activity of proinflammatory cytokines may help slow down the advancement of the disease. Similarly, designing drugs that can specifically modulate the balance of immune cell populations or prompt a shift in cell state could potentially lead to the recovery or improvement of diabetes-related conditions.

However, the current researches on the relationship between inflammation and diabetes complications are not enough. Due to the complex inflammatory process in the pathogenesis of diabetes, there are still much more problems to be explored. For instance, it is not yet known whether inflammatory signaling pathways will change in line with the diabetes progress or whether the treatment of some inflammatory drugs will lead to new complications

of diabetes, or if there are clear inflammatory markers to reflect the inflammatory progression of DM patients. Also, it is worth noting that there is no clear inflammation model that can simulate clinical diabetes, and a large number of clinical samples are still needed to determine the exact significance of inflammation indicators and the relationship between inflammation and diabetes. Although there are still many treatments of diabetes complications, unique drugs targeting inflammation and with fewer adverse reactions are still ready to be designed. Therefore, there needs to be more in-depth study on the inflammatory process in diabetes complications by the combination of basic research and clinical practice. Of note, inflammation treatment strategies should be combined with other treatment methods, such as drug therapy, diet management, and exercise, to get better effects in future.

AUTHOR CONTRIBUTIONS

Writing—original draft: Lu Zhao. *Visualization*: Haoran Hu. *Literature search*: Lin Zhang, Zheting Liu, Yunchao Huang, and Qian Liu. *Writing—reviewing*: Liang Jin. *Editing and supervision*: Meifei Zhu. *Conceptualization, writing—reviewing, editing and supervision*: Ling Zhang. All the authors have read and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

All authors have declared that no conflict of interest exists.

DATA AVAILABILITY STATEMENT

Not applicable.

ETHICS STATEMENT

Not applicable.

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REFERENCES

1. Sun H, Saeedi P, Karuranga S, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract*. 2022;183:109119.
2. DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. *Lancet*. 2018;391(10138):2449-2462.
3. Galicia-Garcia U, Benito-Vicente A, Jebari S, et al. Pathophysiology of Type 2 diabetes mellitus. *Int J Mol Sci*. 2020;21(17):6275.
4. Lotfy M, Adeghate J, Kalasz H, Singh J, Adeghate E. Chronic complications of diabetes mellitus: a mini review. *Curr Diabetes Rev*. 2017;13(1):3-10.
5. Pop-Busui R, Ang L, Holmes C, Gallagher K, Feldman EL. Inflammation as a therapeutic target for diabetic neuropathies. *Curr Diab Rep*. 2016;16(3):29.
6. Guo Q, Zhu Q, Zhang T, et al. Integrated bioinformatic analysis reveals immune molecular markers and potential drugs for diabetic cardiomyopathy. *Front Endocrinol (Lausanne)*. 2022;13:933635.
7. Mou X, Zhou DY, Zhou DY, et al. Serum TGF-β1 as a biomarker for type 2 diabetic nephropathy: a meta-analysis of randomized controlled trials. *PLoS One*. 2016;11(2):e0149513.
8. Khaloo P, Qahremani R, Rabizadeh S, et al. Nitric oxide and TNF-α are correlates of diabetic retinopathy independent of hs-CRP and HbA1c. *Endocrine*. 2020;69(3):536-541.
9. Hussain G, Rizvi SA, Singhal S, Zubair M, Ahmad J. Serum levels of TGF-β1 in patients of diabetic peripheral neuropathy and its correlation with nerve conduction velocity in type 2 diabetes mellitus. *Diabetes Metab Syndr*. 2016;10(1 Suppl 1):S135-S139.
10. Bonfiglio V, Platania CBM, Lazzara F, et al. TGF-β serum levels in diabetic retinopathy patients and the role of anti-VEGF therapy. *Int J Mol Sci*. 2020;21(24):9558.
11. Kim DI, Park SH. Sequential signaling cascade of IL-6 and PGC-1α is involved in high glucose-induced podocyte loss and growth arrest. *Biochem Biophys Res Commun*. 2013;435(4):702-707.
12. Blum A, Pastukh N, Socea D, Jabaly H. Levels of adhesion molecules in peripheral blood correlat with stages of diabetic retinopathy and may serve as bio markers for microvascular complications. *Cytokine*. 2018;106:76-79.
13. Xu Y, Hou H, Zhao L. The role of VCAM-1 in diabetic retinopathy: a systematic review and meta-analysis. *J Diabetes Complications*. 2023;37(1):108380.
14. Meng Z, Chen Y, Wu W, et al. Exploring the immune infiltration landscape and M2 macrophage-related biomarkers of proliferative diabetic retinopathy. *Front Endocrinol (Lausanne)*. 2022;13:841813.
15. Lampiasi N, Russo R, Zito F. The alternative faces of macrophage generate osteoclasts. *Biomed Res Int*. 2016;2016:9089610.
16. Sica A, Mantovani A. Macrophage plasticity and polarization: in vivo veritas. *J Clin Invest*. 2012;122(3):787-795.
17. Randolph GJ. Mechanisms that regulate macrophage burden in atherosclerosis. *Circ Res*. 2014;114(11):1757-1771.

18. Elmadbouh I, Singla DK. BMP-7 attenuates inflammation-induced pyroptosis and improves cardiac repair in diabetic cardiomyopathy. *Cells*. 2021;10(10):2640.
19. Bugger H, Abel ED. Molecular mechanisms of diabetic cardiomyopathy. *Diabetologia*. 2014;57(4):660-671.
20. Bene NC, Alcaide P, Wortis HH, Jaffe IZ. Mineralocorticoid receptors in immune cells: emerging role in cardiovascular disease. *Steroids*. 2014;91:38-45.
21. Widiapradja A, Kasparian AO, McCaffrey SL, et al. Replacement of lost substance P reduces fibrosis in the diabetic heart by preventing adverse fibroblast and macrophage phenotype changes. *Cells*. 2021;10(10):2659.
22. Ji L, Chen Y, Wang H, et al. Overexpression of Sirt6 promotes M2 macrophage transformation, alleviating renal injury in diabetic nephropathy. *Int J Oncol*. 2019;55(1):103-115.
23. You H, Gao T, Cooper TK, Brian Reeves W, Awad AS. Macrophages directly mediate diabetic renal injury. *Am J Physiol Renal Physiol*. 2013;305(12):F1719-F1727.
24. Liu J, Zhang Y, Sheng H, et al. Hyperoside suppresses renal inflammation by regulating macrophage polarization in mice with type 2 diabetes mellitus. *Front Immunol*. 2021;12:733808.
25. Fang M, Wan W, Li Q, et al. Asiatic acid attenuates diabetic retinopathy through TLR4/MyD88/NF-κB p65 mediated modulation of microglia polarization. *Life Sci*. 2021;277:119567.
26. Wen Y, Chen X, Feng H, et al. Kdm6a deficiency in microglia/macrophages epigenetically silences Lcn2 expression and reduces photoreceptor dysfunction in diabetic retinopathy. *Metabolism*. 2022;136:155293.
27. Fan B, Li C, Szalad A, et al. Mesenchymal stromal cell-derived exosomes ameliorate peripheral neuropathy in a mouse model of diabetes. *Diabetologia*. 2020;63(2):431-443.
28. Yang H, Xie T, Li D, et al. Tim-3 aggravates podocyte injury in diabetic nephropathy by promoting macrophage activation via the NF-κB/TNF-α pathway. *Mol Metab*. 2019;23:24-36.
29. van Loo G, Bertrand MJM. Death by TNF: a road to inflammation. *Nat Rev Immunol*. 2023;23(5):289-303.
30. Saklani R, Gupta SK, Mohanty IR, Kumar B, Srivastava S, Mathur R. Cardioprotective effects of rutin via alteration in TNF-α, CRP, and BNP levels coupled with antioxidant effect in STZ-induced diabetic rats. *Mol Cell Biochem*. 2016;420(1-2):65-72.
31. Nelson A, Cunha C, Nishimura MI, Iwashima M. Activated human Foxp3(+) regulatory T cells produce membrane-bound TNF. *Cytokine*. 2018;111:454-459.
32. Costa GC, Montagnoli TL, Da Silva JS, et al. New benzofuran N-acylhydrazone reduces cardiovascular dysfunction in obese rats by blocking TNF-alpha synthesis. *Drug Des Devel Ther*. 2020;14:3337-3350.
33. Lu CH, Ou HC, Day CH, et al. Deep sea minerals ameliorate diabetic-induced inflammation via inhibition of TNFα signaling pathways. *Environ Toxicol*. 2020;35(4):468-477.
34. Yang B, Yan P, Gong H, et al. TWEAK protects cardiomyocyte against apoptosis in a PI3K/AKT pathway dependent manner. *Am J Transl Res*. 2016;8(9):3848-3860.
35. Lampropoulou IT, Stangou M, Papagianni A, Didangelos T, Iliadis F, Efstratiadis G. TNF-α and microalbuminuria in patients with type 2 diabetes mellitus. *J Diabetes Res*. 2014;2014:394206.
36. Awad AS, You H, Gao T, et al. Macrophage-derived tumor necrosis factor-α mediates diabetic renal injury. *Kidney Int*. 2015;88(4):722-733.
37. Nee LE, McMorrow T, Campbell E, Slattery C, Ryan MP. TNF-alpha and IL-1beta-mediated regulation of MMP-9 and TIMP-1 in renal proximal tubular cells. *Kidney Int*. 2004;66(4):1376-1386.
38. Liu Y, Li L, Pan N, et al. TNF-α released from retinal Müller cells aggravates retinal pigment epithelium cell apoptosis by upregulating mitophagy during diabetic retinopathy. *Biochem Biophys Res Commun*. 2021;561:143-150.
39. Costa GN, Vindeirinho J, Cavadas C, Ambrósio AF, Santos PF. Contribution of TNF receptor 1 to retinal neural cell death induced by elevated glucose. *Mol Cell Neurosci*. 2012;50(1):113-123.
40. Portillo JA, Greene JA, Okenka G, et al. CD40 promotes the development of early diabetic retinopathy in mice. *Diabetologia*. 2014;57(10):2222-2231.
41. Xu H, Wang Q, Wang Q, et al. Clinical significance of apelin in the treatment of type 2 diabetic peripheral neuropathy. *Medicine (Baltimore)*. 2021;100(17):e25710.
42. Ristikj-Stomnaroska D, Risteska-Nejashmikj V, Papazova M. Role of inflammation in the pathogenesis of diabetic peripheral neuropathy. *Open Access Maced J Med Sci*. 2019;7(14):2267-2270.
43. Hussain G, Rizvi SA, Singhal S, Zubair M, Ahmad J. Serum levels of TNF-α in peripheral neuropathy patients and its correlation with nerve conduction velocity in type 2 diabetes mellitus. *Diabetes Metab Syndr*. 2013;7(4):238-242.
44. Shi X, Chen Y, Nadeem L, Xu G. Beneficial effect of TNF-α inhibition on diabetic peripheral neuropathy. *J Neuroinflammation*. 2013;10:69.
45. Li Y, Zhang Y, Liu DB, Liu HY, Hou WG, Dong YS. Curcumin attenuates diabetic neuropathic pain by downregulating TNF-α in a rat model. *Int J Med Sci*. 2013;10(4):377-381.
46. 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.
47. Roca-Rivada A, Marín-Cañas S, Colli ML, et al. Inhibition of the type 1 diabetes candidate gene PTPN2 aggravates TNF-α-induced human beta cell dysfunction and death. *Diabetologia*. 2023;66(8):1544-1556.
48. Zhang Y, Wang JH, Zhang YY, et al. Deletion of interleukin-6 alleviated interstitial fibrosis in streptozotocin-induced diabetic cardiomyopathy of mice through affecting TGFβ1 and miR-29 pathways. *Sci Rep*. 2016;6:23010.
49. Chiang CJ, Chao YP, Ali A, et al. Probiotic Escherichia coli Nissle inhibits IL-6 and MAPK-mediated cardiac hypertrophy during STZ-induced diabetes in rats. *Benef Microbes*. 2021;12(3):283-293.
50. Lehrskov LL, Christensen RH. The role of interleukin-6 in glucose homeostasis and lipid metabolism. *Semin Immunopathol*. 2019;41(4):491-499.
51. Jia C, Chen H, Zhang J, et al. Role of pyroptosis in cardiovascular diseases. *Int Immunopharmacol*. 2019;67:311-318.
52. Peiró C, Lorenzo Ó, Carraro R, Sánchez-Ferrer CF. IL-1β inhibition in cardiovascular complications associated to diabetes mellitus. *Front Pharmacol*. 2017;8:363.

53. O'Brien LC, Mezzaroma E, Van Tassell BW, et al. Interleukin-18 as a therapeutic target in acute myocardial infarction and heart failure. *Mol Med*. 2014;20(1):221-229.
54. Elneam AI, Mansour NM, Zaki NA, Taher MA. Serum interleukin-18 and its gene haplotypes profile as predictors in patients with diabetic nephropathy. *Open Access Maced J Med Sci*. 2016;4(3):324-328.
55. Yuan Y, Li L, Wang X, Zhang P, Wang J, Xiao Y. Correlation between plasma NLRP3, IL-1β, and IL-18 and diabetic nephropathy in patients with type 2 diabetes. *Altern Ther Health Med*. 2023;29(4):52-56.
56. Fujita T, Ogihara N, Kamura Y, et al. Interleukin-18 contributes more closely to the progression of diabetic nephropathy than other diabetic complications. *Acta Diabetol*. 2012;49(2):111-117.
57. Yaribeygi H, Atkin SL, Sahebkar A. Interleukin-18 and diabetic nephropathy: a review. *J Cell Physiol*. 2019;234(5):5674-5682.
58. Jo HA, Kim JY, Yang SH, et al. The role of local IL6/JAK2/STAT3 signaling in high glucose-induced podocyte hypertrophy. *Kidney Res Clin Pract*. 2016;35(4):212-218.
59. Kuo HL, Huang CC, Lin TY, Lin CY. IL-17 and CD40 ligand synergistically stimulate the chronicity of diabetic nephropathy. *Nephrol Dial Transplant*. 2018;33(2):248-256.
60. Kim KH, Hong GL, Jung DY, Karunasagara S, Jeong WI, Jung JY. IL-17 deficiency aggravates the streptozotocin-induced diabetic nephropathy through the reduction of autophagosome formation in mice. *Mol Med*. 2021;27(1):25.
61. Jo DH, Yun JH, Cho CS, Kim JH, Kim JH, Cho CH. Interaction between microglia and retinal pigment epithelial cells determines the integrity of outer blood-retinal barrier in diabetic retinopathy. *Glia*. 2019;67(2):321-331.
62. Qiu AW, Bian Z, Mao PA, Liu QH. IL-17A exacerbates diabetic retinopathy by impairing Müller cell function via Act1 signaling. *Exp Mol Med*. 2016;48(12):e280.
63. Qiu AW, Huang DR, Li B, Fang Y, Zhang WW, Liu QH. IL-17A injury to retinal ganglion cells is mediated by retinal Müller cells in diabetic retinopathy. *Cell Death Dis*. 2021;12(11):1057.
64. Lindstrom SI, Sigurdardottir S, Zapadka TE, et al. Diabetes induces IL-17A-Act1-FADD-dependent retinal endothelial cell death and capillary degeneration. *J Diabetes Complications*. 2019;33(9):668-674.
65. Shi Q, Wang Q, Wang Z, Lu J, Wang R. Systemic inflammatory regulators and proliferative diabetic retinopathy: a bidirectional Mendelian randomization study. *Front Immunol*. 2023;14:1088778.
66. Shi YL, Shi MY, Yin LZ, Shang JM, Zhuang JY. IL-10 gene polymorphism in diabetic retinopathy. *Eur Rev Med Pharmacol Sci*. 2019;23(12):5059-5064.
67. Yun JH. Interleukin-1β induces pericyte apoptosis via the NF-κB pathway in diabetic retinopathy. *Biochem Biophys Res Commun*. 2021;546:46-53.
68. Song Z, Sun M, Zhou F, Huang F, Qu J, Chen D. Increased intravitreous interleukin-18 correlated to vascular endothelial growth factor in patients with active proliferative diabetic retinopathy. *Graefes Arch Clin Exp Ophthalmol*. 2014;252(8):1229-1234.
69. 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(8):689-699.
70. Yang P, Qin Y, Bian C, Zhao Y, Zhang W. Intrathecal delivery of IL-6 reactivates the intrinsic growth capacity of pyramidal cells in the sensorimotor cortex after spinal cord injury. *PLoS One*. 2015;10(5):e0127772.
71. Skundric DS, Dai R, Mataverde P. IL-6 modulates hyperglycemia-induced changes of Na+ channel Beta-3 subunit expression by Schwann cells. *Ann N Y Acad Sci*. 2003;1005:233-236.
72. Lehmann HC, Höke A. Schwann cells as a therapeutic target for peripheral neuropathies. *CNS Neurol Disord Drug Targets*. 2010;9(6):801-806.
73. Hangping Z, Ling H, Lijin J, et al. The preventive effect of IL-1beta antagonist on diabetic peripheral neuropathy. *Endocr Metab Immune Disord Drug Targets*. 2020;20(5):753-759.
74. Diao J, Chen X, Jiang L, Mou P, Wei R. Transforming growth factor-β1 suppress pentraxin-3 in human orbital fibroblasts. *Endocrine*. 2020;70(1):78-84.
75. Meng S, Yang F, Wang Y, et al. Silymarin ameliorates diabetic cardiomyopathy via inhibiting TGF-β1/Smad signaling. *Cell Biol Int*. 2019;43(1):65-72.
76. Huang XR, Chung AC, Zhou L, Wang XJ, Lan HY. Latent TGF-beta1 protects against crescentic glomerulonephritis. *J Am Soc Nephrol*. 2008;19(2):233-242.
77. Dugbartey GJ, Wonje QL, Alornyo KK, et al. Combination therapy of alpha-lipoic acid, gliclazide and ramipril protects against development of diabetic cardiomyopathy via inhibition of TGF-β/Smad pathway. *Front Pharmacol*. 2022;13:850542.
78. Dong L, Li JC, Hu ZJ, et al. Deletion of Smad3 protects against diabetic myocardiopathy in db/db mice. *J Cell Mol Med*. 2021;25(10):4860-4869.
79. Ruiz-Ortega M, Rayego-Mateos S, Lamas S, Ortiz A, Rodrigues-Diez RR. Targeting the progression of chronic kidney disease. *Nat Rev Nephrol*. 2020;16(5):269-288.
80. Meng XM, Nikolic-Paterson DJ, Lan HY. TGF-β: the master regulator of fibrosis. *Nat Rev Nephrol*. 2016;12(6):325-338.
81. Chen L, Yang T, Lu DW, et al. Central role of dysregulation of TGF-β/Smad in CKD progression and potential targets of its treatment. *Biomed Pharmacother*. 2018;101:670-681.
82. Nadarajah R, Milagres R, Dilauro M, et al. Podocyte-specific overexpression of human angiotensin-converting enzyme 2 attenuates diabetic nephropathy in mice. *Kidney Int*. 2012;82(3):292-303.
83. Shih SC, Ju M, Liu N, Mo JR, Ney JJ, Smith LE. Transforming growth factor beta1 induction of vascular endothelial growth factor receptor 1: mechanism of pericyte-induced vascular survival in vivo. *Proc Natl Acad Sci USA*. 2003;100(26):15859-15864.
84. Fràter-Schröder M, Müller G, Birchmeier W, Böhlen P. Transforming growth factor-beta inhibits endothelial cell proliferation. *Biochem Biophys Res Commun*. 1986;137(1):295-302.
85. Serratì S, Margheri F, Pucci M, et al. TGFbeta1 antagonistic peptides inhibit TGFbeta1-dependent angiogenesis. *Biochem Pharmacol*. 2009;77(5):813-825.
86. Fan J, Shen W, Lee SR, et al. Targeting the Notch and TGF-β signaling pathways to prevent retinal fibrosis in vitro and in vivo. *Theranostics*. 2020;10(18):7956-7973.
87. Patel RK, Prasad N, Kuwar R, Haldar D, Abdul-Muneer PM. Transforming growth factor-beta 1 signaling regulates neuroinflammation and apoptosis in mild traumatic brain injury. *Brain Behav Immun*. 2017;64:244-258.

88. Suryavanshi SV, Barve K, Addepalli V, Utpat SV, Kulkarni YA. Triphala Churna—a traditional formulation in ayurveda mitigates diabetic neuropathy in rats. *Front Pharmacol*. 2021;12:662000.
89. Yin MS, Zhang YC, Xu SH, et al. Puerarin prevents diabetic cardiomyopathy in vivo and in vitro by inhibition of inflammation. *J Asian Nat Prod Res*. 2019;21(5):476-493.
90. Haller H, Bertram A, Nadrowitz F, Menne J. Monocyte chemoattractant protein-1 and the kidney. *Curr Opin Nephrol Hypertens*. 2016;25(1):42-49.
91. Suryavanshi SV, Kulkarni YA. Abrogation of cardiomyopathy in diabetic rats by escin - possible role of NF-$\kappa\beta$ and MCP-1. *Arch Physiol Biochem*. 2024;130(1):49-55.
92. Miao H, Li X, Zhou C, Liang Y, Li D, Ji Q. NR4A2 alleviates cardiomyocyte loss and myocardial injury in rats by transcriptionally suppressing CCR5 and inducing M2 polarization of macrophages. *Microvasc Res*. 2022;140:104279.
93. Chu PY, Walder K, Horlock D, et al. CXCR4 antagonism attenuates the development of diabetic cardiac fibrosis. *PLoS One*. 2015;10(7):e0133616.
94. Tan X, Hu L, Shu Z, et al. Role of CCR2 in the development of streptozotocin-treated diabetic cardiomyopathy. *Diabetes*. 2019;68(11):2063-2073.
95. Alghamdi TA, Batchu SN, Hadden MJ, et al. Histone H3 serine 10 phosphorylation facilitates endothelial activation in diabetic kidney disease. *Diabetes*. 2018;67(12):2668-2681.
96. Yu J, Wu H, Liu ZY, Zhu Q, Shan C, Zhang KQ. Advanced glycation end products induce the apoptosis of and inflammation in mouse podocytes through CXCL9-mediated JAK2/STAT3 pathway activation. *Int J Mol Med*. 2017;40(4):1185-1193.
97. Siddiqi FS, Chen LH, Advani SL, et al. CXCR4 promotes renal tubular cell survival in male diabetic rats: implications for ligand inactivation in the human kidney. *Endocrinology*. 2015;156(3):1121-1132.
98. Zhang Y, Thai K, Kepecs DM, Winer D, Gilbert RE. Reversing CXCL10 deficiency ameliorates kidney disease in diabetic mice. *Am J Pathol*. 2018;188(12):2763-2773.
99. Liu Y, Yang Z, Lai P, et al. Bcl-6-directed follicular helper T cells promote vascular inflammatory injury in diabetic retinopathy. *Theranostics*. 2020;10(9):4250-4264.
100. Monickaraj F, Acosta G, Cabrera AP, Das A. Transcriptomic profiling reveals chemokine CXCL1 as a mediator for neutrophil recruitment associated with blood-retinal barrier alteration in diabetic retinopathy. *Diabetes*. 2023;72(6):781-794.
101. Monickaraj F, Oruganti SR, McGuire P, Das A. A potential novel therapeutic target in diabetic retinopathy: a chemokine receptor (CCR2/CCR5) inhibitor reduces retinal vascular leakage in an animal model. *Graefes Arch Clin Exp Ophthalmol*. 2021;259(1):93-100.
102. Dong N, Chang L, Wang B, Chu L. Retinal neuronal MCP-1 induced by AGEs stimulates TNF-α expression in rat microglia via p38, ERK, and NF-κB pathways. *Mol Vis*. 2014;20:616-628.
103. Zhang Y, Li C, Wang Z, Wang T, Zhou Y, Zheng L. Blocking CXC motif chemokine ligand 2 ameliorates diabetic peripheral neuropathy via inhibiting apoptosis and NLRP3 inflammasome activation. *Biol Pharm Bull*. 2023;46(5):672-683.
104. Menichella DM, Abdelhak B, Ren D, Shum A, Frietag C, Miller RJ. CXCR4 chemokine receptor signaling mediates pain in diabetic neuropathy. *Mol Pain*. 2014;10:42.
105. Song ZH, Song XJ, Yang CL, et al. Up-regulation of microglial chemokine CXCL12 in anterior cingulate cortex mediates neuropathic pain in diabetic mice. *Acta Pharmacol Sin*. 2023;44(7):1337-1349.
106. Bogacka J, Ciapała K, Pawlik K, Dobrogowski J, Przeklasa-Muszynska A, Mika J. Blockade of CCR4 diminishes hypersensitivity and enhances opioid analgesia - evidence from a mouse model of diabetic neuropathy. *Neuroscience*. 2020;441:77-92.
107. Tang W, Lv Q, Chen XF, Zou JJ, Liu ZM, Shi YQ. CD8(+) T cell-mediated cytotoxicity toward Schwann cells promotes diabetic peripheral neuropathy. *Cell Physiol Biochem*. 2013;32(4):827-837.
108. Zychowska M, Rojewska E, Pilat D, Mika J. The role of some chemokines from the CXC subfamily in a mouse model of diabetic neuropathy. *J Diabetes Res*. 2015;2015:750182.
109. Lebovitz HE. Insulin resistance: definition and consequences. *Exp Clin Endocrinol Diabetes*. 2001;109(Suppl 2):S135-S148.
110. Matulewicz N, Karczewska-Kupczewska M. Insulin resistance and chronic inflammation. *Postepy Hig Med Dosw (Online)*. 2016;70(0):1245-1258.
111. Wang C, Chen Z, Li S, et al. Hepatic overexpression of ATP synthase β subunit activates PI3K/Akt pathway to ameliorate hyperglycemia of diabetic mice. *Diabetes*. 2014;63(3):947-959.
112. Zhao Y, Tang Z, Zhu X, et al. TAB3 involves in hepatic insulin resistance through activation of MAPK pathway. *Gen Comp Endocrinol*. 2015;224:228-234.
113. Sun B, Zhou J, Gao Y, et al. Fas-associated factor 1 promotes hepatic insulin resistance via JNK signaling pathway. *Oxid Med Cell Longev*. 2021;2021:3756925.
114. Heo YJ, Choi SE, Jeon JY, et al. Visfatin induces inflammation and insulin resistance via the NF-κB and STAT3 signaling pathways in hepatocytes. *J Diabetes Res*. 2019;2019:4021623.
115. Li A, Lin C, Xie F, Jin M, Lin F. Berberine ameliorates insulin resistance by inhibiting IKK/NF-κB, JNK, and IRS-1/AKT signaling pathway in liver of gestational diabetes mellitus rats. *Metab Syndr Relat Disord*. 2022;20(8):480-488.
116. Li P, Oh DY, Bandyopadhyay G, et al. LTB4 promotes insulin resistance in obese mice by acting on macrophages, hepatocytes and myocytes. *Nat Med*. 2015;21(3):239-247.
117. Bako HY, Ibrahim MA, Isah MS, Ibrahim S. Inhibition of JAK-STAT and NF-κB signalling systems could be a novel therapeutic target against insulin resistance and type 2 diabetes. *Life Sci*. 2019;239:117045.
118. Luo C, Yang H, Tang C, et al. Kaempferol alleviates insulin resistance via hepatic IKK/NF-κB signal in type 2 diabetic rats. *Int Immunopharmacol*. 2015;28(1):744-750.
119. Song R, Zhao X, Cao R, Liang Y, Zhang DQ, Wang R. Irisin improves insulin resistance by inhibiting autophagy through the PI3K/Akt pathway in H9c2 cells. *Gene*. 2021;769:145209.
120. Gao Z, Ti Y, Lu B, et al. STAMP2 attenuates cardiac dysfunction and insulin resistance in diabetic cardiomyopathy via NMRAL1-mediated NF-κB inhibition in Type 2 diabetic rats. *Diabetes Metab Syndr Obes*. 2022;15:3219-3229.
121. Hu N, Dong M, Ren J. Hydrogen sulfide alleviates cardiac contractile dysfunction in an Akt2-knockout murine model of insulin resistance: role of mitochondrial injury and apoptosis. *Am J Physiol Regul Integr Comp Physiol*. 2014;306(10):R761-R771.

122. Wang Q, Ren J. mTOR-Independent autophagy inducer trehalose rescues against insulin resistance-induced myocardial contractile anomalies: Role of p38 MAPK and Foxo1. *Pharmacol Res*. 2016;111:357-373.
123. Wang Y, Cao DW, Wan YG, et al. Effects and mechanisms of total flavones of Abelmoschus manihot in improving insulin resistance and podocyte epithelial-mesenchymal transition in diabetic kidney disease based on IRS1/PI3K/Akt pathway. *Zhongguo Zhong Yao Za Zhi*. 2023;48(10):2646-2656.
124. Canaud G, Bienaimé F, Viau A, et al. AKT2 is essential to maintain podocyte viability and function during chronic kidney disease. *Nat Med*. 2013;19(10):1288-1296.
125. Lu J, Chen PP, Zhang JX, et al. GPR43 deficiency protects against podocyte insulin resistance in diabetic nephropathy through the restoration of AMPKα activity. *Theranostics*. 2021;11(10):4728-4742.
126. Leontieva OV, Demidenko ZN, Blagosklonny MV. Rapamycin reverses insulin resistance (IR) in high-glucose medium without causing IR in normoglycemic medium. *Cell Death Dis*. 2014;5(5):e1214.
127. Miller WP, Ravi S, Martin TD, Kimball SR, Dennis MD. Activation of the stress response kinase JNK (c-Jun N-terminal Kinase) attenuates insulin action in retina through a p70S6K1-dependent mechanism. *J Biol Chem*. 2017;292(5):1591-1602.
128. 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(3):700-708.
129. Cheng YC, Chiu YM, Dai ZK, Wu BN. Loganin ameliorates painful diabetic neuropathy by modulating oxidative stress, inflammation and insulin sensitivity in streptozotocin-nicotinamide-induced diabetic rats. *Cells*. 2021;10(10):2688.
130. Grote CW, Morris JK, Ryals JM, Geiger PC, Wright DE. Insulin receptor substrate 2 expression and involvement in neuronal insulin resistance in diabetic neuropathy. *Exp Diabetes Res*. 2011;2011:212571.
131. Akash MSH, Rehman K, Liaqat A. Tumor necrosis factor-alpha: role in development of insulin resistance and pathogenesis of type 2 diabetes mellitus. *J Cell Biochem*. 2018;119(1):105-110.
132. Fernández-Veledo S, Vila-Bedmar R, Nieto-Vazquez I, Lorenzo M. c-Jun N-terminal kinase 1/2 activation by tumor necrosis factor-alpha induces insulin resistance in human visceral but not subcutaneous adipocytes: reversal by liver X receptor agonists. *J Clin Endocrinol Metab*. 2009;94(9):3583-3593.
133. Grant RW, Dixit VD. Mechanisms of disease: inflammasome activation and the development of type 2 diabetes. *Front Immunol*. 2013;4:50.
134. Youm YH, Adijiang A, Vandanmagsar B, Burk D, Ravussin A, Dixit VD. Elimination of the NLRP3-ASC inflammasome protects against chronic obesity-induced pancreatic damage. *Endocrinology*. 2011;152(11):4039-4045.
135. Moshapa FT, Riches-Suman K, Palmer TM. Therapeutic targeting of the proinflammatory IL-6-JAK/STAT signalling pathways responsible for vascular restenosis in type 2 diabetes mellitus. *Cardiol Res Pract*. 2019;2019:9846312.
136. Peppler WT, Townsend LK, Meers GM, et al. Acute administration of IL-6 improves indices of hepatic glucose and insulin homeostasis in lean and obese mice. *Am J Physiol Gastrointest Liver Physiol*. 2019;316(1):G166-G178.
137. Zúñiga LA, Shen WJ, Joyce-Shaikh B, et al. IL-17 regulates adipogenesis, glucose homeostasis, and obesity. *J Immunol*. 2010;185(11):6947-6959.
138. Dalmas E, Lehmann FM, Dror E, et al. Interleukin-33-activated islet-resident innate lymphoid cells promote insulin secretion through myeloid cell retinoic acid production. *Immunity*. 2017;47(5):928-942.e7.
139. Yang CP, Shiau MY, Lai YR, et al. Interleukin-4 boosts insulin-induced energy deposits by enhancing glucose uptake and lipogenesis in hepatocytes. *Oxid Med Cell Longev*. 2018;2018:6923187.
140. Hwang HJ, Jung TW, Kim BH, et al. A dipeptidyl peptidase-IV inhibitor improves hepatic steatosis and insulin resistance by AMPK-dependent and JNK-dependent inhibition of LECT2 expression. *Biochem Pharmacol*. 2015;98(1):157-166.
141. Kanda H, Tateya S, Tamori Y, et al. MCP-1 contributes to macrophage infiltration into adipose tissue, insulin resistance, and hepatic steatosis in obesity. *J Clin Invest*. 2006;116(6):1494-1505.
142. Luo B, Li B, Wang W, et al. NLRP3 gene silencing ameliorates diabetic cardiomyopathy in a type 2 diabetes rat model. *PLoS One*. 2014;9(8):e104771.
143. Yang M, Qiu S, He Y, et al. Genetic ablation of C-reactive protein gene confers resistance to obesity and insulin resistance in rats. *Diabetologia*. 2021;64(5):1169-1183.
144. Liu J, Ibi D, Taniguchi K, et al. Inflammation improves glucose homeostasis through IKKβ-XBP1s interaction. *Cell*. 2016;167(4):1052-1066.e18.
145. Lu Y, Wang W, Liu J, Xie M, Liu Q, Li S. Vascular complications of diabetes: a narrative review. *Medicine (Baltimore)*. 2023;102(40):e35285.
146. Khan RMM, Chua ZJY, Tan JC, Yang Y, Liao Z, Zhao Y. From pre-diabetes to diabetes: diagnosis, treatments and translational research. *Medicina (Kaunas)*. 2019;55(9):546.
147. Lontchi-Yimagou E, Sobngwi E, Matsha TE, Kengne AP. Diabetes mellitus and inflammation. *Curr Diab Rep*. 2013;13(3):435-444.
148. Mollace V, Gliozzi M, Musolino V, et al. Oxidized LDL attenuates protective autophagy and induces apoptotic cell death of endothelial cells: Role of oxidative stress and LOX-1 receptor expression. *Int J Cardiol*. 2015;184:152-158.
149. Migdalski A, Jawien A. New insight into biology, molecular diagnostics and treatment options of unstable carotid atherosclerotic plaque: a narrative review. *Ann Transl Med*. 2021;9(14):1207.
150. Gao X, Song J, Watase H, et al. Differences in carotid plaques between symptomatic patients with and without diabetes mellitus. *Arterioscler Thromb Vasc Biol*. 2019;39(6):1234-1239.
151. Karstoft K, Pedersen BK. Exercise and type 2 diabetes: focus on metabolism and inflammation. *Immunol Cell Biol*. 2016;94(2):146-150.
152. Park JJ. Epidemiology, pathophysiology, diagnosis and treatment of heart failure in diabetes. *Diabetes Metab J*. 2021;45(2):146-157.
153. Zhang L, Ai C, Bai M, Niu J, Zhang Z. NLRP3 inflammasome/pyroptosis: a key driving force in diabetic cardiomyopathy. *Int J Mol Sci*. 2022;23(18):10632.

154. Lim S, Lee ME, Jeong J, et al. sRAGE attenuates angiotensin II-induced cardiomyocyte hypertrophy by inhibiting RAGE-NFκB-NLRP3 activation. *Inflamm Res*. 2018;67(8):691-701.
155. Zhang X, Fu Y, Li H, et al. H3 relaxin inhibits the collagen synthesis via ROS- and P2×7R-mediated NLRP3 inflammasome activation in cardiac fibroblasts under high glucose. *J Cell Mol Med*. 2018;22(3):1816-1825.
156. Lin QY, Lang PP, Zhang YL, et al. Pharmacological blockage of ICAM-1 improves angiotensin II-induced cardiac remodeling by inhibiting adhesion of LFA-1(+) monocytes. *Am J Physiol Heart Circ Physiol*. 2019;317(6):H1301-H1311.
157. Wang Y, Cui Y, Cao F, Qin Y, Li W, Zhang J. Ganglioside GD1a suppresses LPS-induced pro-inflammatory cytokines in RAW264.7 macrophages by reducing MAPKs and NF-κB signaling pathways through TLR4. *Int Immunopharmacol*. 2015;28(1):136-145.
158. Ali TM, Abo-Salem OM, El Esawy BH, El Askary A. The potential protective effects of diosmin on streptozotocin-induced diabetic cardiomyopathy in rats. *Am J Med Sci*. 2020;359(1):32-41.
159. Li J, Xie C, Zhuang J, et al. Resveratrol attenuates inflammation in the rat heart subjected to ischemia-reperfusion: role of the TLR4/NF-κB signaling pathway. *Mol Med Rep*. 2015;11(2):1120-1126.
160. Zhang Y, Li Y, Huang X, et al. Systemic delivery of siRNA specific for silencing TLR4 gene expression reduces diabetic cardiomyopathy in a mouse model of streptozotocin-induced type 1 diabetes. *Diabetes Ther*. 2020;11(5):1161-1173.
161. Zhang Y, Zhang Y. Toll-like receptor-6 (TLR6) deficient mice are protected from myocardial fibrosis induced by high fructose feeding through anti-oxidant and inflammatory signaling pathway. *Biochem Biophys Res Commun*. 2016;473(2):388-395.
162. Li L, Luo W, Qian Y, et al. Luteolin protects against diabetic cardiomyopathy by inhibiting NF-κB-mediated inflammation and activating the Nrf2-mediated antioxidant responses. *Phytomedicine*. 2019;59:152774.
163. Yu H, Zhen J, Yang Y, Gu J, Wu S, Liu Q. Ginsenoside Rg1 ameliorates diabetic cardiomyopathy by inhibiting endoplasmic reticulum stress-induced apoptosis in a streptozotocin-induced diabetes rat model. *J Cell Mol Med*. 2016;20(4):623-631.
164. Song H, Wohltmann M, Tan M, Bao S, Ladenson JH, Turk J. Group VIA PLA2 (iPLA2β) is activated upstream of p38 mitogen-activated protein kinase (MAPK) in pancreatic islet β-cell signaling. *J Biol Chem*. 2012;287(8):5528-5541.
165. Pan Y, Wang Y, Zhao Y, et al. Inhibition of JNK phosphorylation by a novel curcumin analog prevents high glucose-induced inflammation and apoptosis in cardiomyocytes and the development of diabetic cardiomyopathy. *Diabetes*. 2014;63(10):3497-3511.
166. Zhuang J, Song Y, Ye Y, et al. PYCR1 interference inhibits cell growth and survival via c-Jun N-terminal kinase/insulin receptor substrate 1 (JNK/IRS1) pathway in hepatocellular cancer. *J Transl Med*. 2019;17(1):343.
167. Gui L, Wang F, Hu X, et al. Epigallocatechin gallate protects diabetes mellitus rats complicated with cardiomyopathy through TGF-β1/JNK signaling pathway. *Curr Pharm Des*. 2022;28(33):2758-2770.
168. Hara H, Tsuchiya K, Kawamura I, et al. Phosphorylation of the adaptor ASC acts as a molecular switch that controls the formation of speck-like aggregates and inflammasome activity. *Nat Immunol*. 2013;14(12):1247-1255.
169. Kim BK, Tran HY, Shin EJ, et al. IL-6 attenuates trimethyltin-induced cognitive dysfunction via activation of JAK2/STAT3, M1 mAChR and ERK signaling network. *Cell Signal*. 2013;25(6):1348-1360.
170. Abdelsamia EM, Khaleel SA, Balah A, Abdel Baky NA. Curcumin augments the cardioprotective effect of metformin in an experimental model of type I diabetes mellitus; Impact of Nrf2/HO-1 and JAK/STAT pathways. *Biomed Pharmacother*. 2019;109:2136-2144.
171. Wang L, Li J, Li D. Losartan reduces myocardial interstitial fibrosis in diabetic cardiomyopathy rats by inhibiting JAK/STAT signaling pathway. *Int J Clin Exp Pathol*. 2015;8(1):466-473.
172. Luan Y, Sun C, Wang J, et al. Baicalin attenuates myocardial ischemia-reperfusion injury through Akt/NF-κB pathway. *J Cell Biochem*. 2019;120(3):3212-3219.
173. Selby NM, Taal MW. An updated overview of diabetic nephropathy: Diagnosis, prognosis, treatment goals and latest guidelines. *Diabetes Obes Metab*. 2020;22(Suppl 1):3-15.
174. Alicic RZ, Rooney MT, Tuttle KR. Diabetic kidney disease: challenges, progress, and possibilities. *Clin J Am Soc Nephrol*. 2017;12(12):2032-2045.
175. Basile DP, Collett JA, Yoder MC. Endothelial colony-forming cells and pro-angiogenic cells: clarifying definitions and their potential role in mitigating acute kidney injury. *Acta Physiol (Oxf)*. 2018;222(2).
176. Li X, Zhang Y, Xing X, et al. Podocyte injury of diabetic nephropathy: novel mechanism discovery and therapeutic prospects. *Biomed Pharmacother*. 2023;168:115670.
177. Wu M, Han W, Song S, et al. NLRP3 deficiency ameliorates renal inflammation and fibrosis in diabetic mice. *Mol Cell Endocrinol*. 2018;478:115-125.
178. Hou Y, Lin S, Qiu J, et al. NLRP3 inflammasome negatively regulates podocyte autophagy in diabetic nephropathy. *Biochem Biophys Res Commun*. 2020;521(3):791-798.
179. An X, Zhang Y, Cao Y, Chen J, Qin H, Yang L. Punicalagin protects diabetic nephropathy by inhibiting pyroptosis based on TXNIP/NLRP3 pathway. *Nutrients*. 2020;12(5):1516.
180. Xiao H, Sun X, Liu R, et al. Gentiopicroside activates the bile acid receptor Gpbar1 (TGR5) to repress NF-kappaB pathway and ameliorate diabetic nephropathy. *Pharmacol Res*. 2020;151:104559.
181. Li F, Chen Y, Li Y, Huang M, Zhao W. Geniposide alleviates diabetic nephropathy of mice through AMPK/SIRT1/NF-κB pathway. *Eur J Pharmacol*. 2020;886:173449.
182. Jialal I, Major AM, Devaraj S. Global Toll-like receptor 4 knockout results in decreased renal inflammation, fibrosis and podocytopathy. *J Diabetes Complications*. 2014;28(6):755-761.
183. Ma J, Chadban SJ, Zhao CY, et al. TLR4 activation promotes podocyte injury and interstitial fibrosis in diabetic nephropathy. *PLoS One*. 2014;9(5):e97985.
184. Pan Y, Zhang X, Wang Y, et al. Targeting JNK by a new curcumin analog to inhibit NF-kB-mediated expression of cell adhesion molecules attenuates renal macrophage infiltration and injury in diabetic mice. *PLoS One*. 2013;8(11):e79084.
185. Lian H, Cheng Y, Wu X. TMEM16A exacerbates renal injury by activating P38/JNK signaling pathway to promote podocyte

apoptosis in diabetic nephropathy mice. *Biochem Biophys Res Commun*. 2017;487(2):201-208.
186. Sun MY, Wang SJ, Li XQ, et al. CXCL6 promotes renal interstitial fibrosis in diabetic nephropathy by activating JAK/STAT3 signaling pathway. *Front Pharmacol*. 2019;10:224.
187. Lei L, Zhao J, Liu XQ, et al. Wogonin alleviates kidney tubular epithelial injury in diabetic nephropathy by inhibiting PI3K/Akt/NF-κB signaling pathways. *Drug Des Devel Ther*. 2021;15:3131-3150.
188. Taniguchi K, Xia L, Goldberg HJ, et al. Inhibition of Src kinase blocks high glucose-induced EGFR transactivation and collagen synthesis in mesangial cells and prevents diabetic nephropathy in mice. *Diabetes*. 2013;62(11):3874-3886.
189. Liu Y. Cellular and molecular mechanisms of renal fibrosis. *Nat Rev Nephrol*. 2011;7(12):684-696.
190. Fu H, Liu S, Bastacky SI, Wang X, Tian XJ, Zhou D. Diabetic kidney diseases revisited: a new perspective for a new era. *Mol Metab*. 2019;30:250-263.
191. Qian X, He L, Hao M, et al. YAP mediates the interaction between the Hippo and PI3K/Akt pathways in mesangial cell proliferation in diabetic nephropathy. *Acta Diabetol*. 2021;58(1):47-62.
192. Seo EJ, Choi JA, Koh JY, Yoon YH. Aflibercept ameliorates retinal pericyte loss and restores perfusion in streptozotocin-induced diabetic mice. *BMJ Open Diabetes Res Care*. 2020;8(1):e001278.
193. Omae T, Nagaoka T, Yoshida A. Relationship between retinal blood flow and serum adiponectin concentrations in patients with type 2 diabetes mellitus. *Invest Ophthalmol Vis Sci*. 2015;56(6):4143-4149.
194. Kanda A, Dong Y, Noda K, Saito W, Ishida S. Advanced glycation endproducts link inflammatory cues to upregulation of galectin-1 in diabetic retinopathy. *Sci Rep*. 2017;7(1):16168.
195. Kim KS, Park JM, Kong T, et al. Retinal angiogenesis effects of TGF-β1 and paracrine factors secreted from human placental stem cells in response to a pathological environment. *Cell Transplant*. 2016;25(6):1145-1157.
196. Hwang SJ, Ahn BJ, Shin MW, et al. miR-125a-5p attenuates macrophage-mediated vascular dysfunction by targeting Ninjurin1. *Cell Death Differ*. 2022;29(6):1199-1210.
197. Chaurasia SS, Lim RR, Parikh BH, et al. The NLRP3 inflammasome may contribute to pathologic neovascularization in the advanced stages of diabetic retinopathy. *Sci Rep*. 2018;8(1):2847.
198. Gan J, Huang M, Lan G, Liu L, Xu F. High glucose induces the loss of retinal pericytes partly via NLRP3-caspase-1-GSDMD-mediated pyroptosis. *Biomed Res Int*. 2020;2020:4510628.
199. Li J, Yu S, Lu X, et al. The phase changes of M1/M2 phenotype of microglia/macrophage following oxygen-induced retinopathy in mice. *Inflamm Res*. 2021;70(2):183-192.
200. Zhu YN, Zuo GJ, Wang Q, Chen XM, Cheng JK, Zhang S. The involvement of the mGluR5-mediated JNK signaling pathway in rats with diabetic retinopathy. *Int Ophthalmol*. 2019;39(10):2223-2235.
201. Tang L, Zhang C, Lu L, et al. Melatonin maintains inner blood-retinal barrier by regulating microglia via inhibition of PI3K/Akt/Stat3/NF-κB signaling pathways in experimental diabetic retinopathy. *Front Immunol*. 2022;13:831660.
202. Bora K, Kushwah N, Maurya M, Pavlovich MC, Wang Z, Chen J. Assessment of inner blood-retinal barrier: animal models and methods. *Cells*. 2023;12(20):2443.
203. Kim SJ, Yoo WS, Choi M, Chung I, Yoo JM, Choi WS. Increased O-GlcNAcylation of NF-κB enhances retinal ganglion cell death in streptozotocin-induced diabetic retinopathy. *Curr Eye Res*. 2016;41(2):249-257.
204. Guma M, Rius J, Duong-Polk KX, Haddad GG, Lindsey JD, Karin M. Genetic and pharmacological inhibition of JNK ameliorates hypoxia-induced retinopathy through interference with VEGF expression. *Proc Natl Acad Sci USA*. 2009;106(21):8760-8765.
205. Fang Y, Shi K, Lu H, Lu L, Qiu B. Mingmu xiaomeng tablets restore autophagy and alleviate diabetic retinopathy by inhibiting PI3K/Akt/mTOR signaling. *Front Pharmacol*. 2021;12:632040.
206. He Y, Dan Y, Gao X, Huang L, Lv H, Chen J. DNMT1-mediated lncRNA MEG3 methylation accelerates endothelial-mesenchymal transition in diabetic retinopathy through the PI3K/Akt/mTOR signaling pathway. *Am J Physiol Endocrinol Metab*. 2021;320(3):E598-E608.
207. Cheng YC, Chu LW, Chen JY, et al. Loganin attenuates high glucose-induced schwann cells pyroptosis by inhibiting ROS generation and NLRP3 inflammasome activation. *Cells*. 2020;9(9):1948.
208. Kanazawa Y, Takahashi-Fujigasaki J, Ishizawa S, et al. The Rho-kinase inhibitor fasudil restores normal motor nerve conduction velocity in diabetic rats by assuring the proper localization of adhesion-related molecules in myelinating Schwann cells. *Exp Neurol*. 2013;247:438-446.
209. Liu XS, Fan B, Szalad A, et al. MicroRNA-146a mimics reduce the peripheral neuropathy in Type 2 diabetic mice. *Diabetes*. 2017;66(12):3111-3121.
210. Saleh A, Roy Chowdhury SK, Smith DR, et al. Ciliary neurotrophic factor activates NF-κB to enhance mitochondrial bioenergetics and prevent neuropathy in sensory neurons of streptozotocin-induced diabetic rodents. *Neuropharmacology*. 2013;65:65-73.
211. Elzinga S, Murdock BJ, Guo K, et al. Toll-like receptors and inflammation in metabolic neuropathy; a role in early versus late disease? *Exp Neurol*. 2019;320:112967.
212. Dasu MR, Ramirez S, Isseroff RR. Toll-like receptors and diabetes: a therapeutic perspective. *Clin Sci (Lond)*. 2012;122(5):203-214.
213. Jia L, Wang L, Chopp M, Zhang Y, Szalad A, Zhang ZG. MicroRNA 146a locally mediates distal axonal growth of dorsal root ganglia neurons under high glucose and sildenafil conditions. *Neuroscience*. 2016;329:43-53.
214. Zhao B, Zhang Q, Liang X, Xie J, Sun Q. Quercetin reduces inflammation in a rat model of diabetic peripheral neuropathy by regulating the TLR4/MyD88/NF-κB signalling pathway. *Eur J Pharmacol*. 2021;912:174607.
215. Wang QQ, Zhai C, Wahafu A, Zhu YT, Liu YH, Sun LQ. Salvianolic acid B inhibits the development of diabetic peripheral neuropathy by suppressing autophagy and apoptosis. *J Pharm Pharmacol*. 2019;71(3):417-428.
216. Li R, Li Y, Wu Y, et al. Heparin-poloxamer thermosensitive hydrogel loaded with bFGF and NGF enhances peripheral

nerve regeneration in diabetic rats. *Biomaterials*. 2018;168:24-37.
217. Zhang X, Liang Z, Zhou Y, et al. Artesunate inhibits apoptosis and promotes survival in schwann cells via the PI3K/AKT/mTOR axis in diabetic peripheral neuropathy. *Biol Pharm Bull*. 2023;46(6):764-772.
218. Zhu GC, Chen YW, Tsai KL, Wang JJ, Hung CH, Schmid AB. Effects of neural mobilization on sensory dysfunction and peripheral nerve degeneration in rats with painful diabetic neuropathy. *Phys Ther*. 2022;102(10):pzac104.
219. Orlando G, Balducci S, Boulton AJM, Degens H, Reeves ND. Neuromuscular dysfunction and exercise training in people with diabetic peripheral neuropathy: A narrative review. *Diabetes Res Clin Pract*. 2022;183:109183.
220. Chen W, Wang X, Sun Q, et al. The upregulation of NLRP3 inflammasome in dorsal root ganglion by ten-eleven translocation methylcytosine dioxygenase 2 (TET2) contributed to diabetic neuropathic pain in mice. *J Neuroinflammation*. 2022;19(1):302.
221. Sun Q, Wang C, Yan B, et al. Jinmaitong ameliorates diabetic peripheral neuropathy through suppressing TXNIP/NLRP3 inflammasome activation in the streptozotocin-induced diabetic rat model. *Diabetes Metab Syndr Obes*. 2019;12:2145-2155.
222. Chen L, Wang H, Xing J, et al. Silencing P2×7R alleviates diabetic neuropathic pain involving TRPV1 via PKCε/P38MAPK/NF-κB signaling pathway in rats. *Int J Mol Sci*. 2022;23(22):14141.
223. Wang B, Yao J, Yao X, et al. Swertiamarin alleviates diabetic peripheral neuropathy in rats by suppressing NOXS/ROS/NLRP3 signal pathway. *Nan Fang Yi Ke Da Xue Xue Bao*. 2021;41(6):937-941.
224. Wu Y, Gu Y, Shi B. miR-590-3p Alleviates diabetic peripheral neuropathic pain by targeting RAP1A and suppressing infiltration by the T cells. *Acta Biochim Pol*. 2020;67(4):587-593.
225. Fleischman A, Shoelson SE, Bernier R, Goldfine AB. Salsalate improves glycemia and inflammatory parameters in obese young adults. *Diabetes Care*. 2008;31(2):289-294.
226. Bowman L, Mafham M, Wallendszus K, et al. Effects of aspirin for primary prevention in persons with diabetes mellitus. *N Engl J Med*. 2018;379(16):1529-1539.
227. Tripathy D, Mohanty P, Dhindsa S, et al. Elevation of free fatty acids induces inflammation and impairs vascular reactivity in healthy subjects. *Diabetes*. 2003;52(12):2882-2887.
228. Goldfine AB, Fonseca V, Jablonski KA, et al. Salicylate (salsalate) in patients with type 2 diabetes: a randomized trial. *Ann Intern Med*. 2013;159(1):1-12.
229. Pereira Arias AM, Bisschop PH, Ackermans MT, Endert E, Romijn JA, Sauerwein HP. Indomethacin does not affect endogenous glucose production in type 2 diabetes mellitus. *Horm Metab Res*. 2001;33(11):659-663.
230. Rudberg S, Sätterström G, Dahlqvist R, Dahlquist G. Indomethacin but not metoprolol reduces exercise-induced albumin excretion rate in type 1 diabetic patients with microalbuminuria. *Diabet Med*. 1993;10(5):460-464.
231. Vuletic V, Drenjancevic I, Rahelic D, Demarin V. Effect of indomethacin on cerebrovascular reactivity in patients with type 2 diabetes mellitus. *Diabetes Res Clin Pract*. 2013;101(1):81-87.
232. Chew EY, Kim J, Coleman HR, et al. Preliminary assessment of celecoxib and microdiode pulse laser treatment of diabetic macular edema. *Retina*. 2010;30(3):459-467.
233. Yasuda K, Motohashi R, Kotake O, Nakagawa H, Noma H, Shimura M. Comparative effects of topical diclofenac and betamethasone on inflammation after vitrectomy and cataract surgery in various vitreoretinal diseases. *J Ocul Pharmacol Ther*. 2016;32(10):677-684.
234. Zakrzewski PA, O'Donnell HL, Lam WC. Oral versus topical diclofenac for pain prevention during panretinal photocoagulation. *Ophthalmology*. 2009;116(6):1168-1174.
235. Shimura M, Nakazawa T, Yasuda K, Nishida K. Diclofenac prevents an early event of macular thickening after cataract surgery in patients with diabetes. *J Ocul Pharmacol Ther*. 2007;23(3):284-291.
236. Adibian M, Hodaei H, Nikpayam O, Sohrab G, Hekmatdoost A, Hedayati M. The effects of curcumin supplementation on high-sensitivity C-reactive protein, serum adiponectin, and lipid profile in patients with type 2 diabetes: A randomized, double-blind, placebo-controlled trial. *Phytother Res*. 2019;33(5):1374-1383.
237. Chuengsamarn S, Rattanamongkolgul S, Luechapudiporn R, Phisalaphong C, Jirawatnotai S. Curcumin extract for prevention of type 2 diabetes. *Diabetes Care*. 2012;35(11):2121-2127.
238. Keymeulen B, van Maurik A, Inman D, et al. A randomised, single-blind, placebo-controlled, dose-finding safety and tolerability study of the anti-CD3 monoclonal antibody otelixizumab in new-onset type 1 diabetes. *Diabetologia*. 2021;64(2):313-324.
239. Hale G, Rebello P, Al Bakir I, et al. Pharmacokinetics and antibody responses to the CD3 antibody otelixizumab used in the treatment of type 1 diabetes. *J Clin Pharmacol*. 2010;50(11):1238-1248.
240. Wang X, Huang H, Su C, Zhong Q, Wu G. Cilostazol ameliorates high free fatty acid (FFA)-induced activation of NLRP3 inflammasome in human vascular endothelial cells. *Artif Cells Nanomed Biotechnol*. 2019;47(1):3704-3710.
241. Linsley PS, Greenbaum CJ, Rosasco M, Presnell S, Herold KC, Dufort MJ. Elevated T cell levels in peripheral blood predict poor clinical response following rituximab treatment in new-onset type 1 diabetes. *Genes Immun*. 2019;20(4):293-307.
242. Kroll JL, Beam C, Li S, et al. Reactivation of latent viruses in individuals receiving rituximab for new onset type 1 diabetes. *J Clin Virol*. 2013;57(2):115-119.
243. Kim KH, Jeong YT, Oh H, et al. Autophagy deficiency leads to protection from obesity and insulin resistance by inducing Fgf21 as a mitokine. *Nat Med*. 2013;19(1):83-92.
244. Ebrahimi F, Urwyler SA, Betz MJ, et al. Effects of interleukin-1 antagonism and corticosteroids on fibroblast growth factor-21 in patients with metabolic syndrome. *Sci Rep*. 2021;11(1):7911.
245. Cunha RB, Siqueira RC, Messias A, et al. Safety and feasibility of a novel 25-gauge biodegradable implant of dexamethasone for treatment of macular edema associated with retinal vein occlusion: a phase i clinical trial. *Retin Cases Brief Rep*. 2018;12(1):50-58.
246. Polderman JA, Farhang-Razi V, Van Dieren S, et al. Adverse side effects of dexamethasone in surgical patients. *Cochrane Database Syst Rev*. 2018;11(11):Cd011940.

247. Gether L, Storgaard H, Kezic S, et al. Effects of topical corticosteroid versus tacrolimus on insulin sensitivity and bone homeostasis in adults with atopic dermatitis-A randomized controlled study. *Allergy*. 2023;78(7):1964-1979.
248. Silverstein J, Maclaren N, Riley W, Spillar R, Radjenovic D, Johnson S. Immunosuppression with azathioprine and prednisone in recent-onset insulin-dependent diabetes mellitus. *N Engl J Med*. 1988;319(10):599-604.
249. Falta MT, Atkinson MA, Allegretta M, Vacek PM, Albertini RJ. Azathioprine associated T-cell mutations in insulin-dependent diabetes mellitus. *Scand J Immunol*. 2000;51(6):626-633.
250. Russell WE, Bundy BN, Anderson MS, et al. Abatacept for delay of type 1 diabetes progression in stage 1 relatives at risk: a randomized, double-masked, controlled trial. *Diabetes Care*. 2023;46(5):1005-1013.
251. Orban T, Beam CA, Xu P, et al. Reduction in CD4 central memory T-cell subset in costimulation modulator abatacept-treated patients with recent-onset type 1 diabetes is associated with slower C-peptide decline. *Diabetes*. 2014;63(10):3449-3457.
252. Tooley JE, Vudattu N, Choi J, et al. Changes in T-cell subsets identify responders to FcR-nonbinding anti-CD3 mAb (teplizumab) in patients with type 1 diabetes. *Eur J Immunol*. 2016;46(1):230-241.
253. Long SA, Thorpe J, Herold KC, et al. Remodeling T cell compartments during anti-CD3 immunotherapy of type 1 diabetes. *Cell Immunol*. 2017;319:3-9.
254. Ramos EL, Dayan CM, Chatenoud L, et al. Teplizumab and β-cell function in newly diagnosed type 1 diabetes. *N Engl J Med*. 2023;389(23):2151-2161.
255. Shahidi S, Kabiri Naeini E, Mazaheri-Tehrani S. Cilostazol-induced acute kidney injury in a patient with diabetic foot ulcer: a case report and review of literature. *Iran J Kidney Dis*. 2022;16(5):311-314.
256. Monti P, Scirpoli M, Maffi P, et al. Rapamycin monotherapy in patients with type 1 diabetes modifies CD4+CD25+FOXP3+ regulatory T-cells. *Diabetes*. 2008;57(9):2341-2347.
257. Long SA, Rieck M, Sanda S, et al. Rapamycin/IL-2 combination therapy in patients with type 1 diabetes augments Tregs yet transiently impairs β-cell function. *Diabetes*. 2012;61(9):2340-2348.
258. Sagar RC, Naseem KM, Ajjan RA. Antiplatelet therapies in diabetes. *Diabet Med*. 2020;37(5):726-734.
259. Bell DS. Aspirin in the prevention of cardiovascular events in patients with diabetes. *Postgrad Med*. 2016;128(2):180-190.
260. Lopez LR, Guyer KE, Torre IG, Pitts KR, Matsuura E, Ames PR. Platelet thromboxane (11-dehydro-Thromboxane B2) and aspirin response in patients with diabetes and coronary artery disease. *World J Diabetes*. 2014;5(2):115-127.
261. Wronka M, Krzemińska J, Młynarska E, Rysz J, Franczyk B. The influence of lifestyle and treatment on oxidative stress and inflammation in diabetes. *Int J Mol Sci*. 2022;23(24):15743.
262. 5. Lifestyle management: standards of medical care in diabetes-2019. *Diabetes Care*. 2019;42(Suppl 1):S46-S60.
263. Kadoglou NP, Iliadis F, Angelopoulou N, et al. The anti-inflammatory effects of exercise training in patients with type 2 diabetes mellitus. *Eur J Cardiovasc Prev Rehabil*. 2007;14(6):837-843.
264. Hu S, Hu Y, Long P, Li P, Chen P, Wang X. The effect of tai chi intervention on NLRP3 and its related antiviral inflammatory factors in the serum of patients with pre-diabetes. *Front Immunol*. 2022;13:1026509.
265. Zhang T, Tian J, Fan J, Liu X, Wang R. Exercise training-attenuated insulin resistance and liver injury in elderly pre-diabetic patients correlates with NLRP3 inflammasome. *Front Immunol*. 2023;14:1082050.
266. Durrer C, Francois M, Neudorf H, Little JP. Acute high-intensity interval exercise reduces human monocyte Toll-like receptor 2 expression in type 2 diabetes. *Am J Physiol Regul Integr Comp Physiol*. 2017;312(4):R529-R538.
267. Magalhães JP, Santos DA, Correia IR, et al. Impact of combined training with different exercise intensities on inflammatory and lipid markers in type 2 diabetes: a secondary analysis from a 1-year randomized controlled trial. *Cardiovasc Diabetol*. 2020;19(1):169.
268. Habibi A, Taheri A, Habibi S. Attenuation of some inflammatory markers by endurance training in the spinal cord of rats with diabetic neuropathic pain. *Contrast Media Mol Imaging*. 2022;2022:6551358.
269. O'Hearn M, Lara-Castor L, Cudhea F, et al. Incident type 2 diabetes attributable to suboptimal diet in 184 countries. *Nat Med*. 2023;29(4):982-995.
270. Mason SA, Keske MA, Wadley GD. Effects of vitamin C supplementation on glycemic control and cardiovascular risk factors in people with type 2 diabetes: a GRADE-assessed systematic review and meta-analysis of randomized controlled trials. *Diabetes Care*. 2021;44(2):618-630.
271. Dashti F, Mousavi SM, Larijani B, Esmaillzadeh A. The effects of vitamin D supplementation on inflammatory biomarkers in patients with abnormal glucose homeostasis: A systematic review and meta-analysis of randomized controlled trials. *Pharmacol Res*. 2021;170:105727.
272. de Mello VD, Schwab U, Kolehmainen M, et al. A diet high in fatty fish, bilberries and wholegrain products improves markers of endothelial function and inflammation in individuals with impaired glucose metabolism in a randomised controlled trial: the Sysdimet study. *Diabetologia*. 2011;54(11):2755-2767.
273. Jonasson L, Guldbrand H, Lundberg AK, Nystrom FH. Advice to follow a low-carbohydrate diet has a favourable impact on low-grade inflammation in type 2 diabetes compared with advice to follow a low-fat diet. *Ann Med*. 2014;46(3):182-187.
274. Roager HM, Vogt JK, Kristensen M, et al. Whole grain-rich diet reduces body weight and systemic low-grade inflammation without inducing major changes of the gut microbiome: a randomised cross-over trial. *Gut*. 2019;68(1):83-93.
275. Liu JF, Liu YH, Chen CM, Chang WH, Chen CY. The effect of almonds on inflammation and oxidative stress in Chinese patients with type 2 diabetes mellitus: a randomized crossover controlled feeding trial. *Eur J Nutr*. 2013;52(3):927-935.
276. Mazidi M, Vatanparast H, Katsiki N, Banach M. The impact of nuts consumption on glucose/insulin homeostasis and inflammation markers mediated by adiposity factors among American adults. *Oncotarget*. 2018;9(58):31173-31186.
277. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2019. *Diabetes Care*. 2019;42(Suppl 1):S13-S28.
278. Eizirik DL, Pasquali L, Cnop M. Pancreatic β-cells in type 1 and type 2 diabetes mellitus: different pathways to failure. *Nat Rev Endocrinol*. 2020;16(7):349-362.

279. Ruze R, Liu T, Zou X, et al. Obesity and type 2 diabetes mellitus: connections in epidemiology, pathogenesis, and treatments. *Front Endocrinol (Lausanne)*. 2023;14:1161521.
280. Wen X, Zhang B, Wu B, et al. Signaling pathways in obesity: mechanisms and therapeutic interventions. *Signal Transduct Target Ther*. 2022;7(1):298.

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