International Journal of Science and Research Archive
eISSN: 2582-8185
Cross Ref DOI: 10.30574/ijsra
Journal homepage: https://ijsra.net/

(REVIEW ARTICLE)

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Inflammation in Type 2 diabetes mellitus and its complications

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International Journal of Science and Research Archive, 2026, 18(03), 795-807

Publication history: Received on 04 February 2026; revised on 10 March 2026; accepted on 12 March 2026

Article DOI: https://doi.org/10.30574/ijsra.2026.18.3.0517

Abstract

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance, β-cell dysfunction, and persistent hyperglycemia. Growing evidence indicates that chronic low-grade inflammation plays a central role in the development and progression of T2DM and its associated complications. This review examines the inflammatory mechanisms underlying T2DM, focusing on cytokine signaling, immune cell activation, and inflammasome pathways that contribute to metabolic dysfunction. Obesity-associated adipose tissue inflammation promotes the release of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β), which disrupt insulin signaling and impair glucose homeostasis. Activation of the NLRP3 inflammasome further amplifies inflammatory responses, leading to β-cell dysfunction and reduced insulin secretion. Inflammatory processes also contribute to the development of major diabetic complications, including diabetic nephropathy, retinopathy, neuropathy, and atherosclerotic cardiovascular disease. Elevated inflammatory biomarkers such as C-reactive protein (CRP), TNF-α, and IL-6 are consistently associated with disease progression and increased cardiovascular risk. While current pharmacological treatments primarily focus on glycemic control, increasing attention has been directed toward therapies that target inflammatory pathways. Anti-inflammatory strategies, including cytokine inhibition and inflammasome modulation, have shown potential in improving metabolic outcomes and reducing cardiovascular risk. Targeting inflammation therefore represents a promising complementary approach in the management of T2DM and its complications.

Keywords: Type 2 Diabetes Mellitus; Inflammation; Loxoprofen Sodium; NLRP3 Inflammasome; Diabetic Complications; Anti-inflammatory Therapy

1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic, progressive metabolic disorder characterized by insulin resistance, impaired insulin secretion, and chronic hyperglycemia. It is one of the most prevalent non-communicable diseases worldwide, with over 537 million adults affected globally [1]. The World Health Organization (WHO) projects a continued rise in T2DM prevalence due to population aging, urbanization, sedentary lifestyles, and dietary transitions [2, 3].Low-grade inflammation is now recognized as a central pathophysiological feature in the development and progression of T2DM and its complications [4]. Inflammatory cytokines, immune cell infiltration, and oxidative stress contribute to both metabolic dysregulation and vascular damage, linking obesity, insulin resistance, and cardiovascular disease (CVD). The management of T2DM typically involves lifestyle modifications, oral hypoglycemic agents, and insulin therapy to achieve glycemic control and prevent complications [5-7]. However, emerging evidence has highlighted the central role of chronic low-grade inflammation in the pathogenesis and progression of T2DM and its

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complications, including cardiovascular disease, nephropathy, and atherosclerosis [8-11]. This has spurred interest in anti-inflammatory strategies as adjunctive therapies in diabetes care. Non-steroidal anti-inflammatory drugs (NSAIDs) have demonstrated pleiotropic effects beyond their analgesic and antipyretic properties, including modulating inflammatory pathways implicated in insulin resistance and vascular complications [12]. Among these, loxoprofen sodium, a widely used NSAID in East Asia, has shown promising anti-inflammatory and anti-atherosclerotic properties in experimental models of diabetes [13].This literature review comprehensively examines the potential therapeutic role of loxoprofen sodium in T2DM management. It evaluates the mechanistic rationale, preclinical and clinical evidence, and future prospects of integrating loxoprofen into diabetes treatment regimens.

1.1. Pathophysiology of Type 2 Diabetes Mellitus

T2DM develops from a complex interplay of genetic, epigenetic, and environmental factors leading to insulin resistance and β-cell dysfunction [14-16]. Insulin resistance, the diminished ability of cells to respond to insulin, primarily affects skeletal muscle, adipose tissue, and the liver. Compensatory hyperinsulinemia occurs initially, followed by progressive β-cell failure, resulting in chronic hyperglycemia[17].Key pathophysiological mechanisms include, impaired insulin receptor signaling, dysregulated adipokine secretion, ectopic lipid accumulation, oxidative stress and chronic low-grade inflammation [10].Inflammation plays a pivotal role in perpetuating insulin resistance and promoting vascular complications by activating pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP) [11]. These cytokines disrupt insulin signaling via serine phosphorylation of insulin receptor substrate (IRS) proteins and enhance hepatic gluconeogenesis [12].Moreover, T2DM is closely associated with endothelial dysfunction, increased oxidative stress, and a pro-coagulant state, contributing to its high cardiovascular morbidity and mortality [13].

1.1.1. Obesity-Induced Inflammation

Obesity induces adipose tissue expansion and hypertrophy leading to hypoxia, cellular stress, and adipocyte dysfunction, which in turn drive the release of danger-associated molecular patterns (DAMPs), pro-inflammatory adipokines (including TNF-α, IL-6, MCP-1) and reduction of insulin-sensitizing adiponectin, creating a chronic low-grade inflammatory state that impairs insulin signaling [18, 19]. Adipocyte death further recruits macrophages forming crown-like structures, with adipose tissue macrophages becoming major sources of TNF-α, iNOS, IL-6 and other inflammatory mediators, and the extent of macrophage infiltration correlates strongly with adiposity and insulin resistance[19]. Chemokines such as MCP-1 (CCL2) produced by enlarged adipocytes promote monocyte recruitment and differentiation to inflammatory M1 macrophages, which secrete TNF-α, IL-6 and further MCP-1, perpetuating inflammation and insulin resistance in liver and muscle[20].TNF-α itself disrupts insulin receptor signaling by serine phosphorylation of insulin receptor substrate-1 (IRS-1), undermining glucose uptake and promoting systemic insulin resistance[21].Components of the innate immune system, especially the NLRP3 inflammasome expressed primarily in adipose tissue macrophages (and possibly adipocytes), sense obesity-related DAMPs including ceramides, saturated fatty acids, ROS, ATP and mediate caspase-1 activation with subsequent maturation and release of IL-1β and IL-18, exacerbating adipose tissue inflammation and impairing insulin signaling. Studies show that the genetic ablation of NLRP3, ASC, or caspase-1 in mice protected against high-fat-diet-induce inflammation, improves insulin sensitivity, lowers IL-1β/IL-18 levels, and alters T-cell subsets within adipose depots (decreasing effector memory and increasing naïve T cells)[21-23]; in humans, weight loss through calorie restriction or exercise reduces adipose NLRP3 and IL-1β expression and improves insulin sensitivity[22].Adipose tissue expansion in obesity triggers a state of chronic low-grade inflammation. Hypertrophic adipocytes release chemokines like monocyte chemoattractant protein-1 (MCP-1), which recruit pro-inflammatory macrophages to adipose tissue [18]. These macrophages shift from an anti-inflammatory M2 phenotype to a pro-inflammatory M1 phenotype, releasing cytokines such as TNF-α, IL-6, and IL-1β [24].

1.1.2. Cytokines and Insulin Resistance

Inflammatory cytokines which interfere with insulin signaling include TNF-α which impairs insulin receptor substrate (IRS) phosphorylation through activation of JNK and IKK-β pathways [25].IL-6 promotes hepatic insulin resistance and dyslipidemia**,** IL-1β impairs insulin secretion and induces β-cell apoptosis[26].Obesity-associated and other chronic inflammatory states drive production of proinflammatory cytokines that directly disrupt insulin signaling and glucose homeostasis; early seminal work showed increased adipose TNF-α expression in rodent obesity and that neutralizing TNF-α improves insulin-stimulated glucose uptake, establishing a mechanistic link between cytokines and insulin

resistance[27, 28].TNF-α promotes serine phosphorylation of insulin receptor substrate-1 (IRS-1), reducing its tyrosine phosphorylation and downstream PI3K–Akt signaling required for GLUT4 translocation, and TNF-α also activates stress and inflammatory kinases (JNK, IKKβ) that further impair insulin action; the IKKβ–NF-κB axis has been implicated as a central node linking nutrient excess, cytokine signaling, and insulin resistance[29]. Interleukin-6 (IL-6), produced by adipocytes and infiltrating immune cells, correlates with adiposity and local adipose IL-6 content predicts reduced insulin-stimulated glucose uptake in human studies; IL-6 can induce hepatic insulin resistance by promoting SOCS3 expression which inhibits insulin receptor signaling and promotes IRS degradation[30].Interleukin-1β (IL-1β), produced upon inflammasome activation in adipose and islet resident immune cells, contributes to β-cell dysfunction and systemic metabolic inflammation; blocking IL-1 signaling with IL-1 receptor antagonist or IL-1β antibodies ameliorates hyperglycemia, reduces inflammation, and improves insulin secretion and sensitivity in preclinical and clinical studies, highlighting IL-1β as a pathogenic cytokine in metabolic disease[31, 32].Chemokines such as MCP-1 (CCL2) recruit monocytes to expanding adipose depots where they differentiate into proinflammatory M1 macrophages that secrete TNF-α, IL-6 and IL-1β, forming a self-amplifying loop of local inflammation that spills over to liver and muscle and promotes systemic insulin resistance[33]. Chronic low-grade inflammation associated with obesity is therefore not merely correlative: genetic or pharmacologic inhibition of key cytokines or their upstream activators (for example NLRP3 inflammasome components, IKKβ, or IL-1 signaling) protects against diet-induced insulin resistance in animals and, in some cases, improves glycaemic control in humans, supporting causality[29, 31].Anti-inflammatory adipokines, most notably adiponectin are decreased in obesity, removing a counter-regulatory, insulin-sensitizing influence and thereby sensitizing tissues to the deleterious effects of proinflammatory cytokines; reduced adiponectin is associated with insulin resistance and vascular inflammation in multiple studies[34]. Systemic markers of inflammation (CRP, fibrinogen) correlate with insulin resistance and predict incident diabetes in cohort studies, providing epidemiological support for cytokine-mediated pathogenesis; mechanistically, cytokine signaling in hepatocytes, myocytes and adipocytes converges on common nodes (IRS proteins, PI3K–Akt, GLUT4 trafficking) to lower insulin responsiveness while also altering lipid metabolism and promoting ectopic lipid deposition that further aggravates insulin signaling[33]. A body of experimental, clinical and epidemiologic research identifies TNF-α, IL-6, IL-1β and chemokines as key cytokine mediators of insulin resistance, acting via serine phosphorylation of IRS, induction of SOCS proteins, activation of NF-κB/JNK pathways and inflammasome-driven IL-1β production; therapeutic targeting of these inflammatory pathways yields metabolic benefit in many preclinical models and selective human trials, underscoring the role of cytokine-driven inflammation in the pathogenesis of insulin resistance.

1.1.3. Inflammation and β-cell Dysfunction

The NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome is a critical sensor of metabolic stress. Activated by glucose, lipids, and ROS, it triggers the maturation of IL-1β and IL-18, promoting systemic inflammation and β-cell dysfunction[35].Inflammatory mediators from adipose tissue, such as IL-1β and TNF-α, reach pancreatic islets via circulation. Chronic exposure suppresses insulin gene expression, induces β-cell apoptosis through nitric oxide and ROS, impairs insulin secretion[36].Chronic, low-grade inflammation within pancreatic islets is increasingly recognized as a central contributor to β-cell dysfunction in type 2 diabetes. Multiple lines of evidence indicate that metabolic stressors glucotoxicity, lipotoxicity, islet amyloid polypeptide (hIAPP) deposition, and saturated fatty acids induce β-cell and islet-resident cell production of chemokines and cytokines (notably IL-1β) that recruit and polarize macrophages toward a proinflammatory M1-like phenotype, establishing a local cytokine milieu that suppresses insulin secretion and promotes β-cell stress and death[32, 37].High glucose stimulates human β cells to produce IL-1β in an autocrine/paracrine loop that activates NF-κB, upregulates death receptors (eg, Fas), impairs glucose-stimulated insulin secretion and increases DNA fragmentation. Blockade of IL-1 signaling with IL-1 receptor antagonist protects human islets from glucose-induced dysfunction in vitro, demonstrating a direct mechanistic link between islet-derived cytokines and glucotoxicity[38].In vivo and translational studies support causality, pharmacologic IL-1 blockade with anakinra improved glycemic control and β-cell secretory function and lowered systemic inflammatory markers in patients with type 2 diabetes, indicating that interrupting IL-1 signaling can restore β-cell performance in humans[39].The inflammasome, particularly NLRP3, is a key upstream activator of IL-1β maturation in islets and is activated by obesity-related signals including ceramides, reactive oxygen species and metabolic danger signals; genetic or pharmacologic disruption of NLRP3/ASC/caspase-1 reduces IL-1β processing, limits islet fibrosis, preserves islet architecture and protects β cells from high-fat-diet-induced exhaustion in animal models[40, 41].Islet macrophages amplify β-cell dysfunction by secreting IL-1β, TNF-α and IL-6 and by promoting chemokine expression in β cells, creating a feed-forward loop of immune cell recruitment and cytokine production; experimental depletion or modulation of macrophages in rodent models improves glucose-stimulated insulin secretion and glycemic control,

underscoring the pathogenic role of innate immune cells within islets[42].Mechanistically, cytokines impair β-cell function through several convergent pathways: NF-κB–dependent transcriptional programs that suppress insulin gene expression, induction of endoplasmic reticulum stress and unfolded protein responses, activation of apoptotic cascades (including Fas signaling), and promotion of β-cell dedifferentiation with loss of mature β-cell markers, processes that collectively diminish functional β-cell mass and responsiveness[37, 38, 40, 42]. Importantly, islet inflammation is heterogeneous among patients, some individuals show pronounced insulitis and macrophage infiltration while others do not, suggesting that inflammatory β-cell failure is one of several mechanisms driving disease progression and that biomarkers of islet inflammation may help identify patients most likely to benefit from targeted anti-inflammatory interventions[42, 43].Together, experimental, clinical and histopathologic data support a model in which metabolic stressors initiate β-cell cytokine production and innate immune activation within islets, the resultant IL-1β/NLRP3-driven inflammatory cascade and macrophage polarization impair insulin secretion and promote β-cell death or dedifferentiation, and therapeutic interruption of these inflammatory nodes can partially restore β-cell function, highlighting inflammation as both a mechanism and a target in β-cell-centered strategies for treating type 2 diabetes[38, 42].

1.2. Inflammatory Biomarkers in T2DM

Elevated levels of systemic inflammatory markers observed in T2DM are C-reactive protein (CRP), Tumor necrosis factor-alpha (TNF-α)**,** Interleukin-6 (IL-6) and Fibrinogen. These biomarkers predict the onset and progression of T2DM and cardiovascular events[44].Elevated systemic inflammatory biomarkers are a consistent feature in people with type 2 diabetes mellitus (T2DM) and its antecedent states, reflecting chronic low-grade inflammation driven by adipose tissue dysregulation, immune cell infiltration, metabolic stress and inflammasome activation; among the most reproducible findings are increased circulating C-reactive protein (CRP) and interleukin-6 (IL-6), which have been shown to predict incident T2DM in prospective cohorts and to track with worsening insulin resistance[44].Multiple meta-analyses and systematic reviews confirm that pro-inflammatory cytokines especially IL-6, tumor necrosis factor-α (TNF-α), IL-1β and IL-18 are elevated in people who develop or who have established T2DM, while the insulin-sensitizing adipokine adiponectin is reduced, producing a net shift toward a pro-inflammatory, pro-atherogenic milieu[45]. Mechanistically, hypertrophied adipocytes and infiltrating macrophages secrete TNF-α and IL-6, which promote hepatic acute-phase responses (raising CRP) and impair insulin signaling via serine phosphorylation of insulin receptor substrates. This adipose-driven cytokine production links obesity to systemic inflammation and metabolic dysfunction[46].The NLRP3 inflammasome has emerged as a central intracellular sensor coupling metabolic danger signals (high glucose, free fatty acids, islet amyloid) to caspase-1 activation and release of mature IL-1β and IL-18; NLRP3 activation contributes to β-cell dysfunction, insulin resistance and vascular complications in T2DM, and is an attractive target for translational interventions[47]. From a biomarker perspective, high-sensitivity CRP (hs-CRP), IL-6 and selected chemokines (eg, MCP-1) are useful as epidemiologic markers of risk and as pharmacodynamic readouts in trials, whereas panels that combine proinflammatory cytokines with adipokines (low adiponectin) and measures of inflammasome activity may better capture pathogenic processes and predict complications than single analytes alone[45, 48]. Clinical trials that modulate inflammation provide proof-of-concept that inflammatory biomarkers are biologically meaningful.IL-1 pathway blockade and anti-inflammatory agents reduce CRP and sometimes improve insulin secretion or glycaemia, although large outcome trials have shown mixed effects on diabetes incidence and cardiovascular endpoints, underscoring that lowering biomarkers does not always translate to durable clinical benefit and that patient selection, timing and pathway specificity matter[44, 46].Finally, integrating inflammatory biomarkers into clinical care requires attention to assay standardization, confounding by obesity/infection/medication, and longitudinal sampling, nonetheless, inflammation-focused biomarkers clarify pathophysiology, help stratify risk, and support novel therapeutic strategies (for example, targeting NLRP3–IL-1β signaling or raising adiponectin activity) that aim to interrupt the inflammatory drivers of insulin resistance and diabetes complications[47, 48].

1.3. Inflammation and T2DM Complications

1.3.1. Diabetic Nephropathy

Inflammation plays a major role in diabetic kidney disease (DKD) through infiltration of macrophages and T cells in renal tissue, elevated MCP-1 and TNF-α levels in urine and kidney biopsies, as well as activation of NF-κB signaling pathway [49].It is also a central driver of diabetic nephropathy (DN) in type 2 diabetes, where metabolic stress, hemodynamic changes and dysregulated innate immunity converge to produce glomerular and tubulointerstitial injury; key inflammatory mediators implicated in DN include cytokines (IL-1β, IL-6, TNF-α), chemokines (monocyte

chemoattractant protein-1 [MCP-1/CCL2]), acute-phase reactants (C-reactive protein), and innate immune complexes such as the NLRP3 inflammasome, each of which contributes to cellular dysfunction, extracellular matrix expansion and progressive loss of renal function[50].The NLRP3 inflammasome has been repeatedly linked to podocyte injury, tubular inflammation and renal fibrosis in experimental and human DKD. Activation of NLRP3 and downstream caspase-1 drives maturation and release of IL-1β and IL-18, promotes pyroptotic death of glomerular cells, and amplifies interstitial inflammation that accelerates albuminuria and GFR decline[51, 52].Chemokine signaling particularly MCP-1 produced by injured tubular epithelial cells and resident glomerular cells recruits monocytes/macrophages into the kidney, where these immune cells secrete profibrotic factors (eg, TGF-β) and matrix-remodeling enzymes that foster mesangial expansion and interstitial fibrosis; urinary and serum MCP-1 levels correlate with albuminuria and progressive DN and have prognostic value for renal decline[53-55]. Systemic markers such as high-sensitivity CRP and circulating IL-6 are associated with presence and severity of nephropathy and may reflect the systemic inflammatory milieu that potentiates intrarenal injury, although their predictive performance is influenced by obesity, infection, and cardiovascular disease[56, 57].Experimental studies have also shown mechanistic links whereby CRP and other systemic inflammatory mediators can activate intra-renal Smad/NF-κB and NLRP3 pathways, thereby directly promoting fibrogenesis[58].Temporal and spatial heterogeneity of inflammation in DKD argues for multi-analytic approaches: combining urinary tubular markers (eg, epidermal growth factor), urinary MCP-1, albuminuria and inflammasome-related signatures improves risk stratification beyond albuminuria or eGFR alone in several cohorts[53, 59].Interventional data provide proof of principle that targeting inflammation can modify renal outcomes, blockade of IL-1 signaling, inhibition of NLRP3 activation, and therapies that modulate macrophage recruitment or polarization reduce albuminuria and histologic injury in preclinical models and small clinical studies, although large-scale randomized trials demonstrating sustained preservation of GFR in T2DM through anti-inflammatory strategies remain limited[51, 58, 60].Challenges to clinical translation include standardization of biomarker assays, determining which patients most benefit (eg, early inflammatory phenotype vs advanced fibrotic disease), and disentangling systemic versus intra-renal inflammatory drivers. Moving forward, integrating molecular inflammatory biomarkers (chemokines, inflammasome activity, cytokine panels) with clinical measures and emerging omic signatures offers the best path toward precision risk prediction and targeted anti-inflammatory therapy to slow or prevent progression of diabetic nephropathy[50, 53, 54].

1.3.2. Diabetic Retinopathy

Inflammation is a fundamental driver of retinal injury in diabetic retinopathy (DR), where chronic hyperglycaemia, oxidative stress and metabolic dysregulation activate resident glia and innate immune pathways leading to breakdown of the blood–retinal barrier (BRB), vascular leakage, neurodegeneration and pathologic neovascularization activation [61, 62].Microglial activation is an early event in DR. Microglia adopt pro inflammatory phenotypes, migrate to sites of vascular damage and release IL-1β, TNF-α, IL-6 and reactive oxygen species that promote neuronal apoptosis and impair retinal homeostasis[63]. Müller glia and retinal endothelial cells amplify this response by producing chemokines (MCP-1/CCL2), adhesion molecules (ICAM-1, VCAM-1) and matrix metalloproteinases, which together drive endothelial injury and increased vascular permeability that manifest clinically as diabetic macular edema (DME)[64]. Endothelial dysfunction and up-regulation of adhesion molecules under the influence of cytokines and VEGF facilitate leukocyte adhesion and capillary occlusion, fueling ischemia and subsequent pro-angiogenic signaling[65].The NLRP3 inflammasome has emerged as a central intracellular hub linking metabolic danger signals (advanced glycation end products, elevated free fatty acids, mitochondrial damage) to caspase-1 activation and release of mature IL-1β and IL-18; NLRP3 activation contributes to pyroptotic death of retinal cells and is implicated in progression from non-proliferative to proliferative DR[66, 67]. Complement activation and inflammasome dependent pathways converge with toll-like receptor signaling to sustain a chronic, self-propagating inflammatory milieu in the vitreous and retina, reflected in elevated levels of VEGF, IL-1β, IL-6, IL-8, TNF-α, MCP-1 and complement fragments in ocular fluids of affected patients. Biomarker studies show that vitreous and aqueous cytokine profiles correlate with disease stage and treatment response: higher intraocular IL-6, MCP-1 and VEGF often associate with DME and proliferative disease, and serial sampling can reveal pharmacodynamic effects of anti-VEGF agents, corticosteroids and other interventions[68, 69].Preclinical and translational work demonstrates that pharmacologic inhibition of key inflammatory nodes—NLRP3 inflammasome blockers, IL-1 pathway antagonists, modulators of microglial activation and inhibitors of leukocyte adhesion—reduces retinal inflammation, vascular leakage and neovascularization in experimental models, supporting inflammation as a therapeutic target alongside VEGF blockade[66, 70].Clinically, intravitreal corticosteroids and systemic/ocular anti-inflammatory strategies (including NSAIDs and steroid implants) reduce DME and inflammation markers, but systemic immunomodulation requires careful risk–benefit assessment; moreover, anti-VEGF therapy can

indirectly reduce inflammatory mediators but does not fully address neuroinflammation or inflammasome activity in all patients, which helps explain variable treatment responses[69, 71].Outstanding challenges include heterogeneity of inflammatory phenotypes (neuroinflammatory vs predominantly vasculopathic), limited standardization of ocular biomarker assays, and the need to identify which patients will benefit from specific anti-inflammatory approaches and at which disease stage; advancing precision medicine in DR will therefore require integrated panels that combine vitreous/aqueous cytokines, imaging biomarkers of neurodegeneration and molecular readouts of inflammasome activation to guide therapy and predict outcomes[66, 68, 70].

1.3.3. Diabetic Neuropathy

Inflammation contributes to peripheral nerve damage through cytokine-mediated oxidative stress, endothelial dysfunction and ischemia, and activation of glial cells in peripheral nerves[72]. It is a central driver of diabetic peripheral neuropathy (DPN), linking chronic hyperglycaemia, metabolic stress and immune signaling to demyelination, axonal degeneration and nociceptor sensitization. Chronic hyperglycaemia and advanced glycation end-products (AGEs) activate innate immune pathways (notably NF-κB) and increase production of pro inflammatory cytokines such as TNF-α, IL-1β and IL-6, which sensitize sensory neurons, impair nerve conduction and promote structural nerve injury[73, 74]. Mitochondrial dysfunction and excess reactive oxygen species (ROS) produced by neurons and Schwann cells further amplify inflammatory signalling and foster activation of the NLRP3 inflammasome, a key intracellular sensor that drives maturation and release of IL-1β/IL-18 and pyroptotic cell death pathways implicated in nerve loss[47, 75]. Schwann cells, besides their trophic/myelinating roles, adopt a pro inflammatory phenotype in diabetes: they upregulate chemokines and cytokines, display endoplasmic reticulum stress and mitochondrial injury, and contribute to demyelination and failed axon support changes strongly associated with reduced nerve conduction velocity and small-fibre loss[74] . Resident and infiltrating macrophages in the peripheral nerve microenvironment are pivotal mediators that can either aid repair or, when skewed to a pro inflammatory phenotype, secrete TNF-α, IL-1β, CCL2 and other mediators that perpetuate axonal degeneration and painful neuropathic signaling[76, 77]. Neuroinflammation also alters vascular support to peripheral nerves: endothelial dysfunction, microvessel rarefaction and increased vascular permeability reduce nerve blood flow and oxygenation, which compounds metabolic stress and inflammation and accelerates nerve fiber loss[73]. At the receptor and signaling level, inflammatory mediators sensitize ion channels (e.g., TRP channels) and kinases in nociceptors, producing hyper-excitability and chronic pain even before overt structural loss is evident[78]. Clinical and translational studies correlate higher circulating and local levels of TNF-α and IL-1β with worse nerve conduction studies and neuropathic symptoms, supporting inflammation as both marker and mechanism of progression in DPN[60, 77] . Therapeutically, targeting inflammatory nodal points NF-κB signalling, NLRP3 activation, cytokine action or macrophage phenotype—has shown promise in preclinical models (reduced demyelination, preserved axons, less pain behaviours), and several small-molecule and natural compounds that inhibit inflammasome activation or downstream cytokine signaling are under active investigation for DPN[75, 79]. Taken together, a modern model of diabetic neuropathy places sustained, dysregulated inflammation at the heart of peripheral nerve injury: metabolic stress and mitochondrial ROS initiate and maintain innate immune activation, Schwann cells and macrophages amplify the response, microvascular dysfunction deprives nerves of metabolic support, and cytokine/ion-channel interactions produce pain and functional loss interventions that reduce neuroinflammation therefore offer rational routes to prevent or slow DPN progression[47, 73, 77, 79].

1.3.4. Atherosclerosis and Cardiovascular Disease

T2DM-associated inflammation accelerates atherosclerosis as inflammatory cytokines promote endothelial dysfunction, macrophage infiltration in plaques,NLRP3 activation and IL-1β promote plaque instability[80].Inflammation is a pivotal mechanism in the development of atherosclerosis and cardiovascular disease in type 2 diabetes mellitus (T2DM), linking metabolic dysfunction with vascular injury and plaque progression. Hyperglycaemia, dyslipidaemia, and insulin resistance synergistically induce endothelial dysfunction, oxidative stress, and activation of innate immune pathways such as NF-κB, leading to increased expression of adhesion molecules and recruitment of monocytes into the vascular intima[81, 82] . Monocytes differentiate into macrophages and ingest modified lipoproteins to form foam cells, a hallmark of atherosclerotic plaques, while secreting pro inflammatory cytokines including TNF-α, IL-1β, and IL-6 that perpetuate vascular inflammation and plaque growth[83]. The NLRP3 inflammasome has emerged as a central mediator, activated by excess glucose, oxidized LDL, and mitochondrial dysfunction, resulting in IL-1β/IL-18 release and promotion of vascular smooth muscle cell proliferation and migration, which destabilize plaques and increase rupture risk[84, 85]. Endothelial cells in T2DM exhibit impaired nitric oxide

bioavailability and heightened oxidative stress, exacerbating leukocyte adhesion and vascular stiffness, processes tightly coupled with systemic inflammation[86]. Additionally, adipose tissue in T2DM serves as a reservoir of inflammatory mediators such as MCP-1 and resistin, further amplifying systemic low-grade inflammation and accelerating atherosclerotic burden[87]. Clinical studies demonstrate that patients with T2DM display elevated circulating inflammatory markers, including C-reactive protein (CRP) and IL-6, which correlate with coronary artery calcification, carotid intima-media thickness, and increased incidence of myocardial infarction and stroke [88, 89]. Chronic vascular inflammation also promotes endothelial-to-mesenchymal transition and neointimal hyperplasia, aggravating arterial stiffness and hypertension that further increase cardiovascular risk[90]. Therapeutic interventions targeting inflammatory pathways, such as IL-1β inhibition with canakinumab or modulation of the NLRP3 inflammasome, have shown significant promise in reducing cardiovascular events, highlighting the pathogenic role of inflammation in T2DM-associated atherosclerosis[91, 92]. Collectively, T2DM-associated inflammation orchestrates endothelial dysfunction, lipid accumulation, innate immune activation, and plaque destabilization, accelerating the progression of atherosclerosis and driving heightened cardiovascular morbidity and mortality [81, 83, 86, 89, 92].

1.4. Therapeutic Targeting of Inflammation in T2DM

Several anti-inflammatory approaches have shown promise in clinical trials. These include IL-1β inhibitors (e.g., Canakinumab) which reduced CVD events in the CANTOS trial, salicylates (e.g., salsalate) which improve glycemia and reduce inflammation and PPAR-γ agonists which reduce cytokine expression and improve insulin sensitivity[91].Inflammation is now recognised as a therapeutic axis in type 2 diabetes mellitus (T2DM) because chronic metabolic stress drives innate and adaptive immune pathways that promote insulin resistance, β-cell dysfunction and macrovascular complications; several anti-inflammatory strategies have therefore been tested to reduce cardiovascular risk and improve metabolic outcomes. Targeting interleukin-1 (IL-1) signalling produced some of the earliest translational signals: blockade with the IL-1 receptor antagonist anakinra improved glycaemia, β-cell secretory function and reduced systemic inflammatory markers in randomized studies, supporting cytokine neutralisation as a disease-modifying approach[39] . Downstream of IL-1, the large CANTOS trial tested canakinumab (a monoclonal antibody to IL-1β) in patients with prior myocardial infarction and elevated hsCRP and showed a significant reduction in recurrent cardiovascular events independent of lipid lowering, proving that specific anti-cytokine therapy can reduce clinical CV outcomes[91]. By contrast, broad immunomodulation with low-dose methotrexate failed to lower IL-1β, IL-6 or hsCRP and did not reduce cardiovascular events in the CIRT trial, illustrating that non-selective anti-inflammatory approaches may be ineffective if they do not target the key pathogenic pathways [93]. More pragmatic, inexpensive agents have also been studied: low-dose colchicine reduced ischemic cardiovascular events after myocardial infarction in COLCOT and subsequent trials, probably via inhibition of microtubule-dependent inflammatory signaling and inflammasome activity, and is now an attractive repurposed therapy for secondary prevention[94]. Small-molecule and oral agents that directly or indirectly reduce inflammasome activation have shown promise in early studies: salicylates (salsalate) improved glycaemia and lowered inflammatory mediators in T2DM pilot trials, though long-term safety and cardiorenal outcomes require clarification [95]. At the level of the NLRP3 inflammasome, powerful preclinical data (eg, MCC950 and related inhibitors) demonstrate reductions in vascular inflammation, plaque burden and diabetes-augmented atherosclerosis in animal models, motivating the translation of selective NLRP3 inhibitors into early-phase human trials[96, 97] . Interest in IL-6 pathway modulation has grown because IL-6 sits downstream of inflammasome/IL-1 signalling and genetic and pharmacologic data suggest cardiovascular benefit from IL-6R inhibition; trials and Mendelian-randomisation studies are actively exploring this axis [98]. Beyond direct cytokine blockade, several glucose-lowering agents with pleiotropic anti-inflammatory effects (including GLP-1 receptor agonists and SGLT2 inhibitors) have reduced cardiovascular events in large outcome trials, and some of their benefit may be mediated by reducing vascular and systemic inflammation—this supports a combined metabolic plus immunomodulatory therapeutic strategy[99]. Safety, cost and patient selection remain central issues: canakinumab reduced events but increased infection risk and is costly, methotrexate was ineffective, colchicine carries risks of gastrointestinal and haematologic adverse effects, and the long-term consequences of inflammasome inhibition in humans are not yet established. Precision targeting—matching the anti-inflammatory mechanism to the dominant pathogenic pathway in an individual (eg, IL-1/NLRP3-driven inflammation versus IL-6 dominated profiles), using biomarkers such as hsCRP/IL-1β/IL-6 or genetic instruments, and combining anti-inflammatory therapy with proven cardiometabolic drugs—represents the most rational path forward. In summary, clinical trials to date show that selective cytokine inhibition (IL-1β) and some repurposed anti-inflammatory agents (colchicine, salsalate) can modulate inflammation and produce meaningful metabolic or cardiovascular effects, whereas non-specific immunosuppression (eg, low-dose methotrexate) may not; ongoing development of NLRP3 and IL-6 pathway inhibitors, better biomarker-driven patient

selection, and integration with modern glucose-lowering therapies are likely to define the next wave of anti-inflammatory treatments for T2DM and its cardiovascular complications[39, 91, 93-99].

2. Current Pharmacological Treatments for Type 2 Diabetes Mellitus

Current pharmacological management of T2DM is multifaceted and aimed at achieving optimal glycaemic control, reducing insulin resistance, preserving β-cell function, and minimizing long-term complications. Metformin remains the first-line therapy and acts primarily by reducing hepatic gluconeogenesis, improving peripheral insulin sensitivity, and exerting modest anti-inflammatory and cardioprotective effects [100, 101]. Sulfonylureas such as glibenclamide and glimepiride stimulate insulin secretion from pancreatic β-cells but are associated with risks of hypoglycaemia and weight gain, limiting long-term safety compared to newer agents[102]. Thiazolidinediones (TZDs), including pioglitazone, target peroxisome proliferator-activated receptor-γ (PPAR-γ) to enhance insulin sensitivity in adipose tissue and muscle, while also exerting beneficial effects on lipid metabolism and vascular inflammation, though concerns remain regarding fluid retention, heart failure risk, and bone fractures [103, 104]. Dipeptidyl peptidase-4 (DPP-4) inhibitors such as sitagliptin and linagliptin prolong endogenous incretin activity, increasing glucose-dependent insulin release and reducing glucagon secretion with a neutral weight profile and low hypoglycaemia risk, although cardiovascular benefit beyond glycaemic control has been limited[105]. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) including liraglutide and semaglutide provide robust glycaemic control, promote weight loss, and have demonstrated significant reductions in major adverse cardiovascular events in large outcome trials, making them a preferred option in patients with T2DM and cardiovascular disease[106, 107] . Sodium-glucose cotransporter-2 (SGLT2) inhibitors such as empagliflozin, dapagliflozin, and canagliflozin lower plasma glucose by promoting renal glucose excretion and have demonstrated significant reductions in cardiovascular mortality, heart failure hospitalization, and progression of diabetic kidney disease, highlighting their role as organ-protective therapies [108, 109]. Insulin therapy remains essential for patients with advanced T2DM or severe hyperglycaemia, with basal-bolus regimens tailored to patient needs, though weight gain and hypoglycaemia remain challenges[17]. Emerging pharmacotherapies include dual GLP-1/GIP receptor agonists such as tirzepatide, which have shown superior glycaemic and weight reduction effects compared to established agents, representing a new era of incretin-based therapy [110]. Overall, pharmacological treatment of T2DM has evolved from glucose-centric to complication-centric approaches, with emphasis on agents that not only achieve glycaemic control but also reduce cardiovascular and renal risks[101, 107, 109, 110].

3. Conclusion

Inflammation is a core mechanism in the pathogenesis and progression of T2DM and its complications. It bridges the gap between metabolic dysfunction and organ damage, particularly in the presence of obesity and insulin resistance. Targeting inflammation presents a viable strategy to delay the onset of diabetes and reduce the risk of long-term complications, especially cardiovascular disease.

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