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# Chronic Inflammation in Diabetes: Mechanisms Linking Hyperglycaemia to Immune Dysregulation

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## ABSTRACT

Chronic inflammation is a hallmark of diabetes mellitus and a key driver of its long-term complications. Hyperglycaemia triggers a cascade of molecular and cellular events that disrupt immune homeostasis, promote persistent low-grade inflammation, and impair resolution pathways. This review synthesizes current understanding of the mechanisms linking elevated glucose levels to immune dysregulation, including advanced glycation end product (AGE) formation, oxidative stress, metabolic reprogramming of immune cells, inflammasome activation, and dysregulated cytokine networks. We discuss how these processes converge to sustain chronic inflammation, contribute to insulin resistance, endothelial dysfunction, and tissue damage in organs such as the vasculature, kidneys, liver, nerves, and retina. We also examine emerging biomarkers of inflammatory activity in diabetes and evaluate therapeutic strategies targeting inflammatory pathways, including glycaemic control, anti-inflammatory agents, immune modulators, and lifestyle interventions. A clearer understanding of how hyperglycaemia orchestrates immune dysfunction will enhance prevention and treatment of diabetic complications and inform precision medicine approaches.

**Keywords:** chronic inflammation, diabetes mellitus, hyperglycaemia, immune dysregulation, advanced glycation end products

## INTRODUCTION

Diabetes mellitus is a chronic metabolic disease characterized by elevated blood glucose levels resulting from insufficient insulin secretion, impaired insulin action, or both [1-5]. While hyperglycaemia is the central metabolic aberration, it also functions as a potent pro-inflammatory stimulus. Chronic, low-grade inflammation accompanies both type 1 and type 2 diabetes, contributes to insulin resistance, β-cell dysfunction, and promotes the development of microvascular and macrovascular complications [6-9]. Despite advances in glycaemic management, inflammation remains an underappreciated therapeutic target in diabetes care. Inflammation in diabetes is not an acute, self-limiting process but a maladaptive, persistent state involving cross-talk between metabolic and immune pathways [10-14]. Elevated glucose and metabolic by-products disrupt innate and adaptive immune responses, creating an environment of sustained activation and impaired resolution [15-20]. The intricacies of this immune-metabolic cross-talk are complex and multifactorial, involving soluble mediators, cellular reprogramming, and alterations in tissue microenvironments. Recognizing chronic inflammation as an integral component of diabetes pathobiology reframes our understanding of disease progression and opens avenues for novel diagnostic and therapeutic strategies [21-24]. This review provides a comprehensive examination of the biological mechanisms that link hyperglycaemia to immune dysregulation, with an emphasis on molecular pathways, cellular responses, organ-specific effects, biomarkers, and therapeutic implications [25-30].

**2. Hyperglycaemia as a Pro-Inflammatory Stimulus**

*2.1 Glucose Toxicity and Cellular Stress*

Persistent hyperglycaemia exerts profound cytotoxic effects through multiple interconnected mechanisms that disturb cellular homeostasis [31-34]. Excess intracellular glucose is shunted into alternative metabolic pathways, including the polyol, hexosamine, and protein kinase C pathways, generating metabolites that disrupt normal cell function. In the polyol pathway, glucose is reduced to sorbitol by aldose reductase, consuming NADPH and depleting antioxidant reserves such as glutathione [35-39]. This reduction in antioxidant capacity predisposes cells to oxidative stress, which damages macromolecules and impairs cellular signalling. The hexosamine pathway generates UDP-N-acetylglucosamine, which modifies transcription factors and proteins through O-linked glycosylation, altering gene expression and promoting pro-inflammatory phenotypes [40-43]. Furthermore, hyperglycaemia impairs mitochondrial function, causing electron transport chain inefficiency and increased production of reactive oxygen species, which act as both damaging agents and signalling molecules, perpetuating inflammatory pathways [44-48].



*2.2 Advanced Glycation End Products*

Non-enzymatic glycation of proteins, lipids, and nucleic acids leads to the formation of advanced glycation end products, which accumulate in tissues over time [49-53]. AGEs interact with receptors for advanced glycation end products (RAGE) on endothelial cells, immune cells, and vascular smooth muscle cells, triggering intracellular signalling cascades [54-60]. Activation of nuclear factor kappa B, a master transcription factor for inflammatory genes, drives production of pro-inflammatory cytokines, including interleukin-1β, interleukin-6, and tumour necrosis factor α [61-63]. AGE-RAGE engagement also enhances oxidative stress and induces a positive feedback loop, sustaining chronic inflammation within vascular and metabolic tissues[64-66].

*2.3 Oxidative Stress and Reactive Oxygen Species*

Hyperglycaemia increases mitochondrial and cytosolic production of reactive oxygen species, which overwhelm antioxidant defences and induce oxidative stress [67]. ROS directly activate redox-sensitive transcription factors such as NF-κB and activator protein-1, amplifying the expression of inflammatory mediators. Oxidative damage to lipids, proteins, and DNA generates damage-associated molecular patterns that stimulate innate immune receptors, further propagating inflammatory signalling[68]. Together, glucose toxicity, AGE accumulation, and oxidative stress form an interconnected network that positions hyperglycaemia as a central driver of chronic inflammation and immune dysregulation in diabetes [68].

**3. Innate Immune Activation in Diabetes**

*3.1. Pattern Recognition Receptors*

The innate immune system detects danger signals via pattern recognition receptors (PRRs), including toll-like receptors (TLRs) and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs)[18]. In diabetes, elevated glucose and metabolic by-products serve as endogenous ligands for PRRs. For example, TLR4 on macrophages and dendritic cells is activated by saturated fatty acids and AGEs, initiating pro-inflammatory signalling through MyD88-dependent pathways that culminate in NF-κB activation and cytokine release. NLR family members, particularly NLRP3, assemble into inflammasomes multiprotein complexes that activate caspase-1 and process IL-1β and IL-18 into their active forms[19]. Hyperglycaemia, ROS, and AGEs promote NLRP3 inflammasome activation, linking metabolic stress to potent inflammatory cytokine production.

*3.2. Macrophage Polarization*

Macrophages exhibit functional plasticity, broadly classified into pro-inflammatory (M1-like) and anti-inflammatory (M2-like) phenotypes [20]. In diabetes, metabolic cues skew macrophage polarization toward a pro-inflammatory state. Elevated glucose and lipid metabolites enhance glycolytic metabolism favoured by M1 macrophages—and suppress oxidative phosphorylation associated with anti-inflammatory phenotypes [21]. These pro-inflammatory macrophages secrete TNF-α, IL-1β, and other mediators that exacerbate insulin resistance and drive tissue inflammation.

*3.3. Neutrophil Dysfunction and NETosis*

Neutrophils are early responders in the innate immune system. In diabetic conditions, neutrophils display impaired chemotaxis yet increased propensity for NETosis a form of cell death characterized by release of neutrophil extracellular traps (NETs)[22]. NETs contain DNA, histones, and proteases that trap pathogens but also promote local inflammation and tissue damage. High glucose enhances NET formation, contributing to vascular inflammation and delayed wound healing common in diabetes [23].

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**4. Adaptive Immune Dysregulation in Diabetes**

*4.1. T Lymphocyte Imbalance*

Adaptive immunity also undergoes significant alterations in diabetes. T lymphocytes play diverse roles; subsets such as Th1 and Th17 are associated with pro-inflammatory responses, whereas regulatory T cells (Tregs) exert immune-suppressive functions [24]. In diabetes, there is an increase in pro-inflammatory Th1/Th17 cells and a relative deficiency or dysfunction of Tregs. Hyperglycaemia and AGEs impair Treg survival and function, shifting the immune balance toward chronic inflammation and autoimmune tendencies [25].

*4.2. B Cell Activation and Autoantibodies*

B cells contribute to inflammation by producing antibodies, presenting antigens, and secreting cytokines. In type 1 diabetes, autoreactive B cells participate in autoimmune β-cell destruction. In type 2 diabetes, B cells exhibit enhanced production of pro-inflammatory cytokines and contribute to adipose tissue inflammation [26]. Autoantibodies, including those recognizing oxidized lipid epitopes and modified proteins, further perpetuate immune activation and complement engagement.

*4.3. Immune Metabolic Reprogramming*

Immune cells dynamically adjust their metabolic pathways in response to environmental cues. Activated T cells and macrophages increase glycolysis to support rapid proliferation and effector functions [27]. In diabetes, persistent hyperglycaemia reinforces glycolytic metabolism in immune cells and supplies abundant metabolic intermediates, supporting pro-inflammatory phenotypes. Disruption of fatty acid oxidation and mitochondrial metabolism further skews immune cells away from quiescent or anti-inflammatory states.

**5. Inflammatory Mediators and Cytokine Networks**

*5.1. Pro-Inflammatory Cytokines*

Chronic inflammation in diabetes is characterised by elevated levels of pro-inflammatory cytokines that influence systemic metabolism [28]. TNF-α interferes with insulin signalling by promoting serine phosphorylation of insulin receptor substrate proteins. IL-6 contributes to hepatic insulin resistance and stimulates acute-phase responses. IL-1β impairs β-cell function and survival, linking inflammation to progressive insulin deficiency.

*5.2. Chemokines and Immune Cell Recruitment*

Chemokines such as monocyte chemoattractant protein-1 (MCP-1) orchestrate the recruitment of monocytes and other immune cells into tissues. In diabetic adipose tissue and vascular walls, increased chemokine expression leads to macrophage infiltration, sustaining local inflammation [29]. This recruitment is self-reinforcing as macrophages produce additional chemokines and cytokines.

*5.3. Adipokines and Metabolic Inflammation*

Adipose tissue is an active endocrine organ producing adipokines cytokines derived from adipocytes [30]. In obesity-associated type 2 diabetes, adipose tissue hypertrophy and hypoxia enhance the secretion of pro-inflammatory adipokines such as resistin and leptin, while anti-inflammatory adiponectin is reduced. These alterations promote systemic inflammation and insulin resistance.

**6. Tissue-Specific Consequences of Inflammatory Dysregulation**

*6.1. Endothelial Dysfunction and Atherosclerosis*

Endothelium exposed to hyperglycaemia and inflammatory mediators exhibits reduced nitric oxide bioavailability, increased oxidative stress, and upregulated adhesion molecules [31]. These changes facilitate leukocyte adhesion and transmigration, driving atherosclerotic plaque initiation. Inflamed plaques are prone to instability and rupture, contributing to cardiovascular events.

*6.2. Diabetic Nephropathy*

In the kidney, chronic inflammation drives glomerular and tubular injury. Macrophage infiltration and inflammasome activation contribute to fibrosis and declining glomerular filtration [32]. Cytokines such as TNF-α and IL-1β promote mesangial expansion and extracellular matrix deposition.

*6.3. Neuropathy and Neuroinflammation*

Persistent inflammation affects peripheral nerves through microvascular compromise and direct cytokine-mediated neuronal injury [33]. ROS and pro-inflammatory cytokines disrupt axonal transport and Schwann cell function, leading to sensory and motor deficits.

*6.4. Retinopathy*

In the retina, inflammation drives microvascular leakage, capillary dropout, and neovascularisation[34]. Elevated VEGF and inflammatory mediators increase vascular permeability, contributing to vision loss.

**7. Therapeutic Strategies Targeting Chronic Inflammation**

Effective management of chronic inflammation in diabetes requires an integrated approach addressing both metabolic and immune dysregulation [35]. Maintaining optimal glycaemic control is foundational, as sustained hyperglycaemia drives AGE formation, oxidative stress, and persistent inflammatory signalling. Pharmacologic agents such as metformin improve glucose homeostasis while activating AMP-activated protein kinase, which enhances antioxidant responses and suppresses pro-inflammatory pathways [36]. In addition to glucose-lowering effects, glucagon-like peptide-1 receptor agonists and SGLT2 inhibitors provide anti-inflammatory and cardiovascular benefits. Direct modulation of immune pathways represents a complementary strategy [37]. Therapies targeting pro-inflammatory cytokines, including IL-1 antagonists and TNF inhibitors, have demonstrated reductions in systemic inflammation and modest improvements in glycaemic control. Experimental approaches focus on inhibiting inflammasome assembly and pattern recognition receptor signalling to dampen metabolic inflammation at its source. Adjunctive antioxidant therapies aim to counteract ROS-mediated damage [38]. Nrf2 activators and small molecule ROS scavengers enhance endogenous antioxidant defences and reduce oxidative injury in vascular and metabolic tissues. Lifestyle interventions remain essential. Structured exercise, caloric restriction, and diets rich in anti-inflammatory nutrients such as omega-3 fatty acids, polyphenols, and fiber improve insulin sensitivity, reduce adipose tissue inflammation, and lower circulating cytokine levels. Combining pharmacologic and lifestyle approaches provides a multifaceted strategy to attenuate chronic inflammation, preserve organ function, and slow progression of diabetic complications.



## CONCLUSION

Chronic inflammation in diabetes arises from intricate interactions between hyperglycaemia, metabolic stress, and immune dysregulation. Persistent inflammatory signalling underlies insulin resistance, β-cell dysfunction, and the development of microvascular and macrovascular complications. Targeting inflammatory pathways alongside metabolic control offers a promising strategy to improve outcomes and prevent long-term sequelae of diabetes. Understanding these complex mechanisms is essential for advancing therapeutic innovation and precision medicine in diabetes care.

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