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# Antioxidant Defense Failure in Diabetic Immunopathy: Mechanistic Insights Into Oxidative Stress–Driven Immune Dysfunction

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## ABSTRACT

Diabetes mellitus, particularly type 2 diabetes mellitus (T2DM), is increasingly recognized as a state of chronic immunometabolic dysfunction driven in large part by oxidative stress and impaired antioxidant responses. Hyperglycaemia, dyslipidaemia, and adipose tissue inflammation collectively generate excessive reactive oxygen species (ROS), overwhelming endogenous antioxidant systems such as the Nrf2-Keap1 pathway, glutathione (GSH), thioredoxin, catalase, and superoxide dismutase. The resulting oxidative stress alters immune cell signalling, promotes inflammatory cytokine production, disrupts leukocyte recruitment, and impairs both innate and adaptive immune responses. This constellation of abnormalities-termed diabetic immunopathy-contributes to increased susceptibility to infections, impaired wound healing, suboptimal vaccine responses, and persistent low-grade inflammation that drives cardiometabolic complications. This review synthesizes mechanistic evidence on how antioxidant defense failure shapes immune dysregulation in diabetes, emphasizing the molecular pathways through which ROS modify immune receptors, disrupt cytokine signalling, promote post-translational modifications of proteins, and induce epigenetic reprogramming of immune cells. Additionally, it analyses the interplay between mitochondrial dysfunction, endoplasmic reticulum (ER) stress, ferroptosis, and immune cell exhaustion. Finally, emerging therapeutic strategies-including Nrf2 activators, mitochondrial-targeted antioxidants, dietary polyphenols, and metabolic modulators evaluated for their potential to restore redox balance and reverse immunopathy. Integrating immunology, redox biology, and metabolic disease, this article provides a comprehensive framework for understanding oxidative stress–driven immune dysfunction in diabetes and highlights potential precision interventions targeting redox–immune pathways.

**Keywords**: diabetic immunopathy, oxidative stress, Nrf2, immune dysfunction, antioxidant defense

## INTRODUCTION

Diabetes mellitus is increasingly recognized not only as a metabolic disorder but also as a condition marked by significant immune system dysfunction[1]. In particular, individuals with type 2 diabetes mellitus (T2DM) display a paradoxical immunological profile characterized by persistent low-grade inflammation coexisting with impaired innate and adaptive immunity. This dual pattern explains the wide range of immune-related complications observed clinically, including enhanced susceptibility to bacterial, viral, and fungal infections; impaired wound healing; suboptimal responses to vaccination; and increased morbidity from respiratory and systemic infections[2]. The immune abnormalities in diabetes extend beyond simple hyperglycaemia-related impairment and reflect a deeper disturbance in cellular signalling, redox homeostasis, and inflammatory regulation. A growing body of evidence identifies oxidative stress as the central driver of this dysregulated immune state[3]. Oxidative stress refers to the pathological accumulation of reactive oxygen species (ROS) when their production exceeds the capacity of antioxidant defense systems such as glutathione, superoxide dismutase, catalase, the thioredoxin system, and the Nrf2–Keap1 regulatory pathway. While physiological levels of ROS are essential for immune cell activation, pathogen killing, and intracellular signalling, the chronic metabolic disturbances in diabetes produce an overwhelming oxidative environment[4]. Hyperglycaemia, insulin resistance, dyslipidaemia, and adipose tissue inflammation converge to intensify mitochondrial ROS generation, activate NOX enzymes, and impair antioxidant systems. This persistent oxidative imbalance inflicts molecular injury on proteins, DNA, and lipids while simultaneously reprogramming immune cell function[5]. As a result, immune

cells in diabetic individuals often exhibit reduced chemotaxis, impaired phagocytosis, dysregulated cytokine secretion, diminished T-cell activation, and altered antigen presentation. The term diabetic immunopathy has therefore emerged to describe the cumulative immune dysfunction driven by metabolic stress and redox imbalance. It encapsulates the transformation of the immune system into a state of chronic activation yet functional insufficiency-a state that accelerates microvascular and macrovascular complications while compromising host defence[6]. Understanding the precise mechanisms through which oxidative stress shapes this immune dysfunction is essential for developing more targeted therapeutic strategies capable of restoring immune homeostasis, reducing infection risk, and improving clinical outcomes in diabetic patients[7].

## 2. Sources of Oxidative Stress in Diabetes

Oxidative stress in diabetes arises from multiple interconnected metabolic disturbances[8]. These pathways collectively generate excessive ROS and diminish antioxidant reserves, establishing a persistent oxidative burden that is particularly damaging to immune cells.

### 2.1 Hyperglycaemia-Induced ROS Production

Chronic elevation of blood glucose is one of the most potent triggers of intracellular ROS accumulation. Excess glucose drives mitochondrial electron transport chain overload, increasing electron leakage and superoxide formation[9]. Hyperglycaemia also enhances polyol pathway flux, diverting glucose into sorbitol production and consuming NADPH, which is required for glutathione regeneration. Simultaneously, the formation of advanced glycation end-products (AGEs) modifies proteins and activates RAGE receptors, stimulating further ROS production and promoting inflammatory signalling[10]. Activation of protein kinase C under hyperglycaemic conditions further enhances NOX enzyme activity, accelerating oxidative bursts within immune cells[11]. These processes combine to create a self-sustaining oxidative cycle that weakens antioxidant capacity and disrupts immune function at multiple levels.

### 2.2 Lipid Dysregulation and Lipotoxicity

T2DM is frequently accompanied by elevated circulating free fatty acids, which undergo increased β-oxidation in mitochondria, generating excess ROS. Lipid peroxidation further produces reactive aldehydes such as malondialdehyde and 4-hydroxynonenal, both of which modify proteins and impair immune cell function[12]. Fatty acids also activate TLR2 and TLR4, stimulating inflammatory signalling cascades that increase ROS production[13]. Lipotoxicity has particularly severe consequences for macrophages and T lymphocytes, which rely on tightly regulated redox environments to maintain functional competence.

### 2.3 Adipose Tissue Inflammation

Obesity-related expansion of adipose tissue promotes hypoxia, immune cell infiltration, and increased secretion of inflammatory cytokines such as TNF-α and IL-6[14]. These cytokines induce NOX activity and promote mitochondrial ROS formation. Macrophages accumulating within adipose tissue become major ROS producers, intensifying systemic oxidative stress and further propagating inflammatory signalling that affects immune cells throughout the body.

### 2.4 ER Stress and the Unfolded Protein Response

Chronic nutrient excess in diabetes places substantial stress on the endoplasmic reticulum, activating the unfolded protein response. Persistent ER stress activates PERK, IRE1, and CHOP pathways, each of which contributes to increased ROS generation and inflammation[15]. ER stress also disrupts immune cell signalling via JNK and NF-κB, linking metabolic overload directly to impaired immunity.

## 3. Antioxidant Defense Systems and Their Failure in Diabetes

Under normal physiological conditions, cellular antioxidant systems maintain redox balance by counteracting the continuous generation of reactive oxygen species (ROS)[16]. These systems, comprising enzymatic and non-enzymatic components, detoxify free radicals, repair oxidatively damaged macromolecules, and regulate redox-sensitive signalling pathways that support immune cell function. In diabetes, however, the antioxidant network becomes progressively overwhelmed due to chronic hyperglycaemia, inflammatory cytokine production, mitochondrial dysfunction, and metabolic overload[17]. This cumulative strain reduces antioxidant enzyme expression, depletes essential cofactors, and inhibits regulatory pathways, resulting in sustained oxidative pressure that contributes directly to immune dysfunction.

### 3.1 Nrf2–Keap1 Pathway Dysfunction

The Nrf2–Keap1 axis is central to the antioxidant defense system. Nrf2 controls the expression of numerous cytoprotective genes responsible for neutralising ROS, maintaining glutathione homeostasis, and facilitating detoxification[18]. In diabetes, persistent hyperglycaemia and pro-inflammatory cytokines suppress Nrf2 activation through multiple mechanisms. Overactivity of Keap1 enhances Nrf2 ubiquitination and degradation, while oxidative modifications of regulatory cysteine residues impair Nrf2 release from Keap1[19]. Consequently, reduced nuclear translocation of Nrf2 diminishes transcription of key antioxidant enzymes, including haem oxygenase-1 (HO-1), catalase, NAD(P)H quinone oxidoreductase 1, and enzymes responsible for glutathione

synthesis. Dysfunction of this pathway is considered one of the central failures that allows oxidative injury to accumulate throughout immune tissues.

### 3.2 Glutathione Depletion

Glutathione (GSH) represents the predominant intracellular antioxidant, essential for detoxifying ROS and maintaining redox homeostasis in immune cells. In diabetes, several metabolic disturbances converge to deplete GSH. Enhanced polyol pathway flux consumes NADPH, which is required to regenerate reduced GSH from its oxidised form[20]. Hyperglycaemia also accelerates GSH oxidation while impairing the activity of γ-glutamylcysteine synthetase, the rate-limiting enzyme in GSH synthesis. As GSH pools diminish, immune cells-particularly macrophages and neutrophils-lose the capacity to manage oxidative bursts, impairing phagocytosis and increasing susceptibility to oxidative injury.

### 3.3 Thioredoxin and Peroxiredoxin Impairment

The thioredoxin system plays a complementary role to glutathione in controlling oxidative stress. In diabetes, thioredoxin is frequently modified by glycation and lipid peroxidation products, diminishing its ability to donate reducing equivalents to peroxiredoxins and other antioxidant proteins[21]. Peroxiredoxins themselves undergo irreversible hyperoxidation under chronic oxidative pressure, leading to functional inactivation. Loss of the thioredoxin–peroxiredoxin axis disrupts redox-sensitive signalling, weakens immune cell adaptability to oxidative challenges, and contributes to increased inflammation.

### 3.4 Enzymatic Antioxidants: SOD, Catalase, and GPx

Key antioxidant enzymes-superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx)-are impaired in diabetes through reduced expression, oxidative inactivation, or insufficient availability of cofactors[22]. SOD, which dismutates superoxide into hydrogen peroxide, is vulnerable to glycoxidative modification, lowering its activity. Catalase, responsible for decomposing hydrogen peroxide into water and oxygen, exhibits decreased activity in diabetic tissues, thereby permitting accumulation of cytotoxic $H_2O_2$. GPx, which reduces peroxides using GSH, is compromised due to inadequate GSH availability[23]. Together, these impairments disable key detoxification pathways and contribute to the heightened oxidative burden that drives immune cell dysfunction.

## 4. Oxidative Stress–Driven Alterations in Innate Immunity

Innate immune malfunction is a defining feature of diabetic immunopathy, and oxidative stress plays a central mechanistic role in disrupting the structure and function of major innate immune cells[24]. Excess ROS directly damages cellular membranes and organelles, perturbs redox-sensitive signalling cascades, and interferes with metabolic pathways essential for immune activation, pathogen clearance, and tissue repair.

### 4.1 Macrophage Polarization and Dysfunction

Macrophages in the diabetic environment are exposed to chronic oxidative and inflammatory stimuli that skew their polarization toward the pro-inflammatory M1 phenotype. Activation of redox-sensitive transcription factors such as NF-κB and JNK enhances production of IL-1β, TNF-α, and other inflammatory mediators, sustaining systemic inflammation[25]. Meanwhile, mitochondrial damage and lipid peroxidation impair phagocytosis and antigen processing. As a result, macrophages contribute disproportionately to chronic inflammation while failing to efficiently clear pathogens or apoptotic cells[26].

### 4.2 Neutrophil Dysfunction

Neutrophils rely on controlled oxidative bursts to kill invading microbes. In diabetes, however, excessive basal ROS production exhausts this capacity, leaving neutrophils less able to mount effective antimicrobial responses[27]. Oxidative stress disrupts cytoskeletal dynamics, reducing chemotaxis and tissue infiltration. Dysregulated formation of neutrophil extracellular traps further exacerbates tissue injury or, in some cases, results in inadequate NET production, impairing pathogen entrapment[28]. This combination of defects contributes significantly to the heightened infection risk observed in diabetic individuals.

### 4.3 Dendritic Cell Impairment

Dendritic cells, which serve as crucial antigen-presenting cells, are highly sensitive to oxidative modifications. ROS accumulation impairs antigen uptake and processing by oxidising endosomal and lysosomal proteins[29]. Expression of costimulatory molecules required for T-cell activation is diminished, and secretion of IL-12 is reduced, weakening the initiation of adaptive immune responses. These defects compromise the interface between innate and adaptive immunity, contributing to the overall immune suppression characteristic of diabetes[30].

## 5. Molecular Mechanisms Linking Antioxidant Failure to Immune Dysregulation

Antioxidant collapse in diabetes initiates a cascade of molecular disturbances that directly reshape immune cell behaviour[31]. Persistent oxidative stress not only overwhelms classical antioxidant systems but also penetrates deeper regulatory layers of immune biology, altering signalling networks, receptor integrity, cell survival pathways, and epigenetic programming. These interconnected mechanisms collectively drive the chronic low-grade inflammation and impaired host defense characteristic of diabetic immunopathy.

### 5.1 Redox Modulation of Signalling Pathways

Excess ROS modulates major intracellular signalling pathways, skewing immune function toward pro-inflammatory dominance[32]. Activation of NF-κB is one of the earliest events, as ROS destabilize IκB proteins and promote transcription of genes encoding TNF-α, IL-6, IL-1β, and adhesion molecules. Simultaneously, JNK and p38 MAPK pathways-highly sensitive to redox fluctuations upregulated, reinforcing inflammatory gene expression and impairing insulin signalling in immune cells. Oxidative inhibition of the PI3K/Akt pathway further contributes to defective metabolic signalling and reduced cell survival[33]. Collectively, these redox-driven signalling disruptions foster a chronic inflammatory phenotype and impair coordinated immune responses.

### 5.2 Post-Translational Modifications

ROS inflict structural damage on proteins and lipids, generating post-translational modifications that compromise immune function. Protein carbonylation alters enzyme activity and receptor configuration, while lipid peroxidation products such as 4-HNE form adducts that impair membrane fluidity and receptor signalling[34]. Advanced glycation end-products (AGEs) modify immunoglobulins, cytokine receptors, and antigen-processing machinery, reducing antigen recognition fidelity and promoting inflammation via RAGE activation.

### 5.3 Ferroptosis and Immunocyte Death

Diabetes promotes intracellular iron accumulation and lipid peroxidation, triggering ferroptosis, a regulated form of cell death affecting macrophages, dendritic cells, and T lymphocytes[35]. Ferroptotic loss of immunocytes weakens pathogen clearance and contributes to persistent inflammatory activation by releasing danger-associated molecular patterns.

### 5.4 Epigenetic Reprogramming

Oxidative stress induces broad epigenetic changes, including altered DNA methylation, histone acetylation, and deregulated miRNA expression[36]. These modifications reprogram immune cell differentiation, reduce regulatory T-cell stability, and potentiate inflammatory macrophage profiles, cementing long-term immune dysfunction even when glycaemic levels fluctuate.

## CONCLUSION

Diabetic immunopathy arises from a complex interplay of chronic metabolic stress, excessive ROS production, and impaired antioxidant defenses. Oxidative stress not only damages immune cells but also reprograms immune signalling, disrupts cytokine balance, and impairs both innate and adaptive immunity. Understanding these mechanisms provides a robust foundation for therapeutic innovation. Targeting redox pathways-especially through Nrf2 activation, mitochondrial protection, and glutathione restoration-holds significant promise for restoring immune competence in individuals with diabetes. Continued research integrating clinical immunology, redox biology, and metabolic medicine will be essential to developing precision strategies capable of reversing oxidative stress–driven immune dysfunction.

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