ImmunoTargets and Therapy

Dovepress
Taylor & Francis Group

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REVIEW

Interplay Between Insulin Resistance and Immune Dysregulation in Type 2 Diabetes Mellitus: Implications for Therapeutic Interventions

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Abstract: Type 2 Diabetes Mellitus (T2DM) is a rapidly growing global health issue characterized by insulin resistance and chronic inflammation. Beyond regulating glucose homeostasis, insulin plays a pivotal role in modulating immune cell function, linking metabolic dysregulation with immune responses. This review examines the intricate relationship between insulin resistance and immune dysfunction in T2DM, focusing on how impaired insulin signaling pathways, particularly PI3K/Akt and MAPK, contribute to immune cell activation, proliferation, and chronic inflammation. Insulin resistance impacts immune cells such as T cells, B cells, macrophages, and neutrophils, leading to an imbalance between pro-inflammatory and anti-inflammatory responses. Elevated pro-inflammatory cytokines (eg, TNF-α, IL-6) and adipokines (eg, leptin, resistin) exacerbate insulin resistance, promoting a vicious cycle of metabolic and immune dysregulation. This interplay contributes to the chronic low-grade inflammation that underlies T2DM pathogenesis, further impairing insulin signaling and glucose metabolism. Restoration of insulin sensitivity is, therefore, a critical step toward correcting immune imbalance in insulin-resistant states like T2DM. Therapeutic approaches that reduce inflammation could also support improvements in insulin sensitivity, addressing both metabolic and immune disturbances simultaneously. The review also explores therapeutic strategies, including insulin therapy, targeting insulin signaling pathways, and lifestyle interventions. Insulin therapy can reduce pro-inflammatory cytokine production and enhance anti-inflammatory responses, although challenges such as potential immune suppression and hyperinsulinemia remain. Targeting key signaling pathways and transcription factors offers promising avenues for modulating immune responses, while lifestyle interventions, such as dietary modifications, physical activity, and weight management, can improve insulin sensitivity and reduce inflammation. By understanding the dual role of insulin in regulating both metabolic and immune functions, this review underscores the importance of addressing immune dysfunction as part of comprehensive T2DM management. Targeting the interconnected pathways of insulin signaling and immune regulation could lead to more effective therapeutic approaches, ultimately improving patient outcomes and reducing disease complications.

Keywords: insulin resistance, type 2 diabetes mellitus, immune system dysregulation, inflammation, signal transduction, immunomodulation

Introduction

Type 2 Diabetes Mellitus (T2DM) has emerged as a major global health crisis, with its prevalence rising at an alarming rate worldwide. According to the World Health Organization (WHO) and the International Diabetes Federation (IDF), approximately 537 million individuals were affected by diabetes in 2021, with projections indicating that this figure could escalate to 783 million by 2045.[1,2] This dramatic surge is particularly evident in developing countries, where lifestyle shifts, including sedentary behaviors and poor dietary choices, have accelerated the spread of T2DM.[3,4] Consequently, T2DM has transitioned from being a disease of affluence to one of the most pressing public health challenges in low- and middle-income nations.

Received: 7 October 2024
Accepted: 20 February 2025
Published: 3 April 2025

The escalating prevalence of T2DM is closely linked to the rise in obesity rates, which serve as a major risk factor for insulin resistance and the subsequent development of diabetes.[5,6] As obesity reaches epidemic proportions worldwide, it contributes significantly to the burgeoning rates of T2DM. For instance, data indicate that the number of people living with T2DM increased dramatically from 382 million in 2013 to 592 million by 2035, highlighting the interplay between obesity and diabetes.[2,7] This correlation underscores the importance of addressing obesity through targeted public health interventions to mitigate the rising incidence of T2DM.

Compounding the complexity of T2DM are its associated complications, which include cardiovascular disease, kidney disease, and neuropathy, substantially worsening the disease's prognosis and increasing healthcare burdens.[8–10] The economic implications of T2DM are significant, with global diabetes-related healthcare expenditures estimated to have reached $376 billion in 2010 alone.[11] This financial burden emphasizes the necessity for comprehensive strategies focusing on both prevention and effective management of T2DM to curb its impact on healthcare systems.

Therefore, the rising prevalence of T2DM represents not only a clinical concern but also an urgent global public health challenge that demands a multifaceted response. Addressing this issue requires lifestyle interventions, public health policies, and increased awareness to effectively manage and reduce the risk factors and complications associated with T2DM.

Insulin plays a pivotal role in the regulation of glucose homeostasis, acting as a key hormone synthesized by pancreatic β-cells that facilitates glucose uptake by tissues such as skeletal muscle and adipose tissue.[12,13] In T2DM, however, insulin resistance impairs this regulatory mechanism, resulting in chronic hyperglycemia and further metabolic dysregulation. Beyond its classical role in glucose metabolism, insulin has been identified as a modulator of immune cell function, linking metabolic dysregulation with inflammation.[14] The intricate interplay between insulin signaling and immune cell activation suggests a bidirectional relationship between metabolic and immune pathways, which contributes to the pathogenesis of T2DM.

Recent studies have elucidated that insulin resistance is closely intertwined with immune dysfunction, which plays a significant role in the chronic low-grade inflammation observed in T2DM.[15] This inflammation is mediated by immune cells such as macrophages, which adopt a pro-inflammatory phenotype and secrete cytokines that further impair insulin signaling.[16,17] Additionally, insulin resistance in immune cells themselves perpetuates the inflammatory state, emphasizing the complex interactions between insulin action and immune responses in T2DM.[10,18]

The immune dysfunction associated with T2DM involves both innate and adaptive immune responses, with macrophages, T helper 17 (Th17) cells, and regulatory T cells (Tregs) playing prominent roles. Macrophages in adipose tissue contribute to insulin resistance by releasing pro-inflammatory cytokines, while the imbalance between pro-inflammatory Th17 cells and anti-inflammatory Tregs exacerbates chronic inflammation.[19] This suggests that targeting immune cell activity and their modulation by insulin could offer promising therapeutic strategies for T2DM.

Understanding the role of insulin in modulating immune cell function in T2DM is crucial for comprehending the multifaceted nature of this disease. This narrative review seeks to explore the interrelationship between insulin signaling and immune cell function in T2DM, focusing on how insulin resistance contributes to immune dysregulation and chronic inflammation. By elucidating these pathways, we aim to highlight potential therapeutic targets that could enhance the management of T2DM and its associated complications.

Inflammation, Insulin Resistance and Beta-Cell Failure

Excess adipose tissue in metabolically unhealthy obesity triggers chronic low-grade inflammation, leading to insulin resistance and beta-cell dysfunction. Visceral fat releases pro-inflammatory cytokines like TNF-α, IL-6, and MCP-1, fueling systemic inflammation that disrupts metabolic processes and impairs insulin signaling.[20] Specifically, TNF-α interferes with insulin receptor substrate (IRS) signaling, reducing glucose uptake, while elevated free fatty acids in obesity exacerbate inflammation and further impair insulin sensitivity.[20]

This persistent inflammation damages pancreatic beta cells, with inflammatory cytokines inducing apoptosis and reducing insulin secretion. Immune cell infiltration, particularly macrophages in the islets, elevates pro-inflammatory cytokine levels, aggravating beta-cell dysfunction and contributing to insulin resistance and hyperglycemia.[10]

Endoplasmic reticulum (ER) stress also plays a critical role. The increased demand for insulin in obesity strains the ER, initiating the unfolded protein response (UPR). Prolonged ER stress, when the UPR fails to adapt, leads to beta-cell apoptosis and progresses toward type 2 diabetes.[21] Additionally, oxidative stress in obesity exacerbates inflammation and insulin resistance, fueled by reactive oxygen species (ROS) and dysregulated adipokine secretion, creating a vicious cycle of cellular damage.[22,23]

Mechanisms of Insulin Signaling in Immune Cells

Insulin Receptor Expression on Immune Cells

Insulin receptors (IRs) are present on various immune cells, such as T cells, B cells, macrophages, and dendritic cells, and play a crucial role in modulating immune responses.[24] These receptors facilitate insulin signaling, impacting immune cell proliferation, differentiation, and cytokine production. For instance, T cells rely on insulin signaling for activation and glucose uptake, while macrophages enhance inflammatory responses via insulin receptor engagement.[25] Dendritic cells use insulin receptors to influence antigen presentation, underscoring insulin's role in immune homeostasis.

In T2DM, insulin receptor expression and functionality on immune cells are impaired, contributing to chronic inflammation and metabolic dysregulation.[26] This impairment is driven by factors such as elevated pro-inflammatory cytokines (eg, TNF-α, IL-6) that downregulate insulin receptor expression, promoting insulin resistance.[27] Consequently, immune cells, like macrophages, shift toward a pro-inflammatory M1 phenotype, perpetuating the inflammatory state typical of T2DM.[24]

Metabolic factors, including obesity and hyperglycemia, also impact insulin receptor levels. Excess fatty acids activate stress pathways (eg, JNK, IKKβ), impairing insulin receptor expression and signaling.[28] Conversely, insulin itself can upregulate its receptor on immune cells, suggesting adaptability to metabolic challenges.[29] Transcription factors, such as FOXO, further regulate insulin receptor expression, with activation leading to downregulation, contributing to insulin resistance.[30]

The expression of insulin receptors on immune cells is clearly shaped by various factors, including cytokines, metabolic signals, and transcriptional activity. Understanding these dynamics offers valuable insight into how immune dysfunction and insulin resistance interplay in T2DM.[10,26,31]

Insulin Signaling Pathways in Immune Cells

Insulin signaling plays a crucial role in immune cell activation, proliferation, and inflammation regulation, primarily through the PI3K/Akt and MAPK pathways[32] (Figure 1). In macrophages, insulin binding activates the IRS/PI3K/Akt pathway, which is essential for glucose uptake and inflammatory response modulation. This pathway promotes the anti-inflammatory M2 phenotype, but in T2DM, insulin resistance disrupts it, leading to an increase in the pro-inflammatory M1 macrophages, contributing to chronic inflammation.[33]

Similarly, insulin signaling is vital for T cell activation and proliferation, facilitating glucose uptake and glycolysis, which are essential for T cell function.[34] In T2DM, disrupted insulin signaling impairs T cell activation, contributing to immune dysfunction. For dendritic cells, insulin influences maturation and antigen presentation, impacting T cell activation and adaptive immune responses.[32]

The MAPK pathway, another insulin signaling route, regulates cytokine production and cell proliferation. In T2DM, insulin resistance impairs this pathway, leading to excessive inflammatory cytokine production, worsening insulin resistance and inflammation.[35]

Insulin signaling in immune cells differs from metabolic tissues, as it focuses more on inflammatory response regulation than glucose uptake. Immune cells have receptors like Toll-like receptor 4 (TLR4), which interact with insulin signaling pathways, linking immune activation with metabolic regulation, especially in obesity-induced insulin resistance.[36] Inflammatory cytokines such as TNF-α and IL-6, elevated in T2DM, can downregulate insulin receptor signaling, promoting a pro-inflammatory state and exacerbating insulin resistance[34] (Figure 1).

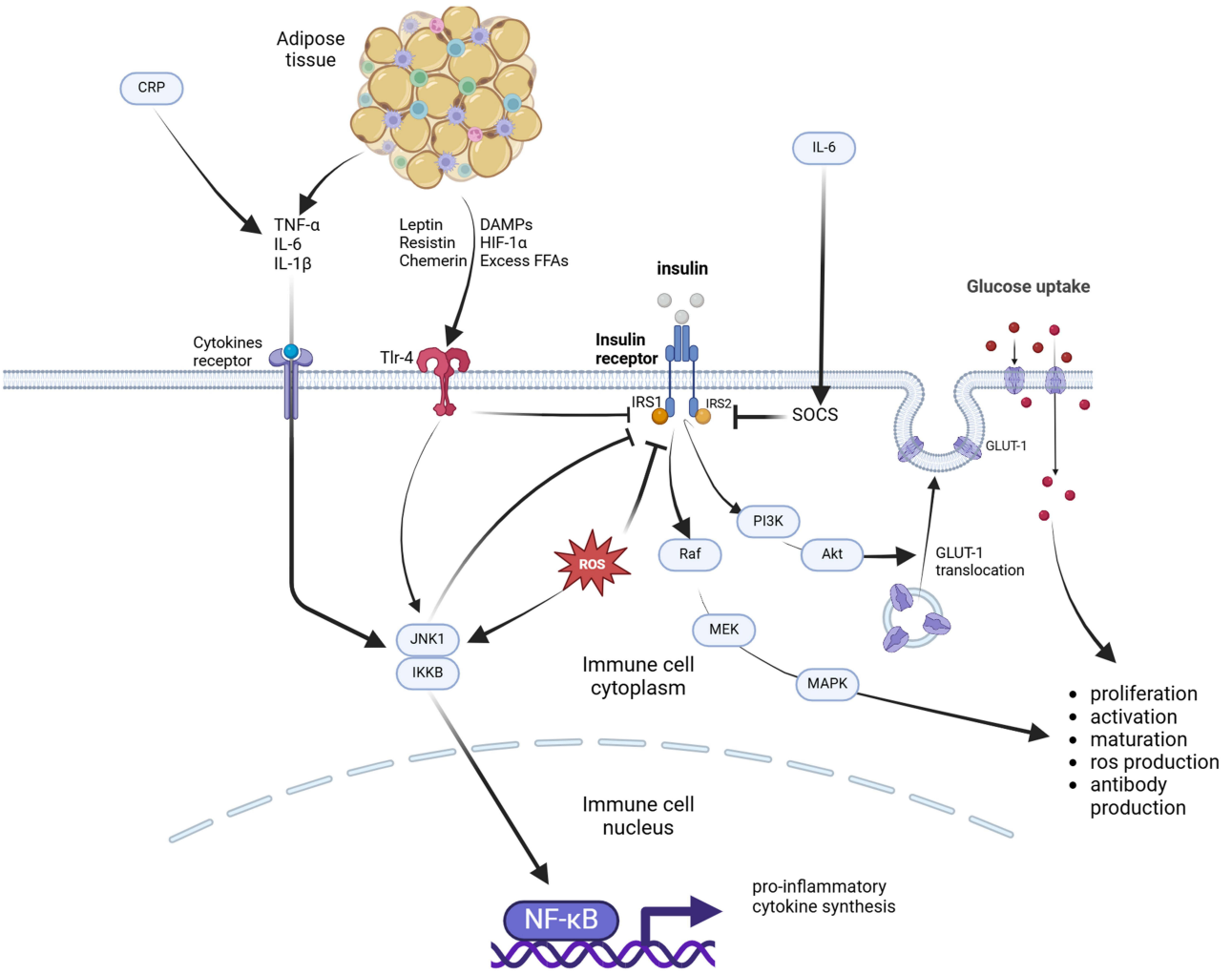

Figure 1 Mechanisms of Adipose Tissue Inflammation and Insulin Resistance Mediated by TLR4 Activation and Adipokines. Adipose tissue in obesity secretes pro-inflammatory cytokines (eg, TNF-α, IL-6, IL-1β) and adipokines (eg, leptin, resistin, chemerin), which activate Toll-like receptor 4 (TLR4) signaling. TLR4 is also activated by damage-associated molecular patterns (DAMPs), hypoxia-inducible factor 1α (HIF-1α), and excess free fatty acids (FFAs), leading to downstream activation of JNK1 and IκB kinase β (IKKβ). This signaling pathway activates nuclear factor kappa B (NF-κB) in immune cells, inducing pro-inflammatory cytokine synthesis. Simultaneously, reactive oxygen species (ROS) generated by these processes amplify the inflammatory response. Chronic inflammation interferes with insulin receptor signaling by suppressing IRS1/IRS2 via the induction of suppressor of cytokine signaling (SOCS) proteins. This disruption inhibits the PI3K/Akt pathway, impairing GLUT-1 translocation and glucose uptake. These processes collectively contribute to immune cell activation, proliferation, ROS production, and inflammation, exacerbating insulin resistance and metabolic dysfunction. *Created in BioRender. Berbudi, (A) (2024)* https://BioRender.com/p64z950.

It is evident that the PI3K/Akt and MAPK pathways are central to immune cell regulation, influencing processes like activation, proliferation, and cytokine production. This insight underscores the importance of these pathways in developing targeted therapies for T2DM.[32,35]

Insulin Resistance in Immune Cells

Insulin resistance in immune cells plays a vital role in the progression of Type 2 Diabetes Mellitus (T2DM), resulting from complex interactions between inflammatory signals, metabolic changes, and cellular adaptations.[37] Chronic low-grade inflammation, often associated with obesity, is a key driver. As obesity progresses, immune cells like macrophages and T cells infiltrate adipose tissue, releasing pro-inflammatory cytokines such as TNF-α and IL-6, which impair insulin signaling by disrupting insulin receptor substrates (IRS) phosphorylation, leading to insulin resistance[38] (Figure 1).

In macrophages, insulin resistance promotes a shift towards a pro-inflammatory M1 phenotype, increasing the production of cytokines and reactive oxygen species (ROS), further aggravating inflammation.[39] Elevated free fatty acids and lipopolysaccharides (LPS), common in obesity, activate Toll-like receptors (TLRs) on macrophages, initiating

inflammatory pathways like NF-κB, which further impair insulin signaling.[40] This process creates a cycle where inflammation and insulin resistance reinforce each other.

Metabolic reprogramming also plays a significant role, with immune cells undergoing increased glycolysis in response to inflammation, sustaining their pro-inflammatory activity and contributing to insulin resistance.[41] CD11c+ macrophages, which produce inflammatory mediators like TNF-α and IL-1β, are particularly influential in promoting insulin resistance in surrounding tissues, linking immune dysregulation to metabolic dysfunction.[42]

The chronic inflammatory state driven by insulin-resistant immune cells, particularly macrophages, significantly impacts adipose, liver, and muscle tissues, leading to impaired insulin signaling and systemic inflammation. In obesity, macrophages infiltrate adipose tissue, where they adopt a pro-inflammatory M1 phenotype, secreting cytokines such as TNF-α and IL-1β that disrupt insulin receptor signaling pathways.[43,44] This inflammatory milieu not only promotes insulin resistance in adipose tissue but also affects the liver and muscle, contributing to a systemic inflammatory response that exacerbates insulin resistance across these tissues.[45–47] In the liver, inflammatory cytokines from activated macrophages can enhance hepatic insulin resistance by promoting gluconeogenesis and lipid accumulation, further complicating metabolic control.[46,48] The interplay between adipose tissue inflammation and liver dysfunction creates a vicious cycle, where increased fatty acid release from adipose tissue exacerbates liver inflammation and insulin resistance.[43,45]

Macrophages also infiltrate pancreatic islets and secrete pro-inflammatory cytokines such as TNF-α and IL-1β, which impair insulin signaling pathways and promote β-cell apoptosis.[49] This inflammatory milieu not only disrupts the normal function of β-cells but also leads to a reduction in β-cell mass, further exacerbating insulin resistance and hyperglycemia.[50] Moreover, the accumulation of free fatty acids (FFAs) in the context of obesity contributes to oxidative stress and endoplasmic reticulum (ER) stress in β-cells, which are critical factors in the pathogenesis of β-cell dysfunction.[51,52] The interplay between chronic inflammation and metabolic dysregulation creates a vicious cycle where β-cell dysfunction leads to inadequate insulin secretion, worsening hyperglycemia and promoting further inflammation.[20] Thus, the chronic inflammatory response initiated by insulin-resistant macrophages is a central mechanism linking obesity to β-cell dysfunction and the progression of T2D.

Addressing insulin resistance in immune cells remains a key factor in understanding the inflammatory processes and metabolic dysregulation characteristic of T2DM. Interventions focusing on these mechanisms could be pivotal in managing the disease's progression.[53]

Insulin and Immune Cell Metabolism

Insulin is vital in regulating immune cell metabolism, impacting their energy utilization and function. It modulates glucose uptake, lipid metabolism, and amino acid transport, which are essential for immune cell activation, proliferation, and differentiation.[54] However, in Type 2 Diabetes Mellitus (T2DM), this regulation is disrupted, contributing to chronic inflammation and disease progression.

Insulin signaling activates the PI3K/Akt pathway in immune cells, facilitating glucose uptake via GLUT1 and enhancing glycolytic activity.[14] This process provides energy for immune cell activation. In macrophages, insulin signaling boosts glucose metabolism and promotes the production of pro-inflammatory cytokines like IL-1β. In T cells, insulin signaling supports activation, proliferation, and differentiation, linking energy availability to immune response.[15]

In T2DM, insulin resistance impairs glucose uptake in immune cells, such as macrophages and T cells, forcing them to rely on fatty acids as an energy source.[55] The shift from glucose to free fatty acids (FFAs) as a primary energy source in immune cells, particularly macrophages, promotes a pro-inflammatory state that exacerbates insulin resistance in peripheral tissues. When macrophages utilize FFAs, especially saturated fatty acids like palmitic acid, they undergo metabolic reprogramming that enhances the activation of inflammatory pathways, including the NLRP3 inflammasome. This activation leads to the production of pro-inflammatory cytokines such as IL-1β, which has been shown to inhibit insulin signaling in target tissues.[45]

Moreover, the accumulation of FFAs within macrophages can generate reactive oxygen species (ROS), further fueling inflammation and contributing to cellular stress responses.[56] This inflammatory environment not only impairs insulin signaling in adipose tissue, liver, and muscle but also promotes a cycle of chronic inflammation that perpetuates insulin

resistance.[57] Additionally, the metabolic byproducts of FFA oxidation can serve as signaling molecules that modulate immune responses, further entrenching the pro-inflammatory state.[58] Thus, the metabolic shift towards FFAs in immune cells is a critical mechanism linking obesity, chronic inflammation, and insulin resistance.

The imbalance of adipokines, like increased leptin and decreased adiponectin, also affects immune cell metabolism. Elevated leptin promotes pro-inflammatory responses, while reduced adiponectin impairs anti-inflammatory effects, contributing to immune dysfunction in T2DM.[59] Additionally, the activation of the NLRP3 inflammasome in immune cells, triggered by metabolic stress (eg, high glucose or fatty acids), leads to increased production of IL-1β, further worsening insulin resistance and inflammation.[60]

Metabolic changes in hepatocytes and myocytes, particularly the shift towards increased free fatty acid (FFA) utilization, significantly worsen insulin resistance through the promotion of an inflammatory state. In hepatocytes, elevated FFAs lead to the accumulation of diacylglycerols (DAGs), which activate protein kinase C (PKC) isoforms such as PKCε. This activation inhibits insulin receptor substrate (IRS) proteins, impairing insulin signaling and promoting hepatic insulin resistance.[61,62] Additionally, FFAs can induce endoplasmic reticulum (ER) stress and activate inflammatory pathways, further exacerbating insulin resistance in the liver.[63]

In skeletal muscle, the presence of FFAs similarly activates inflammatory signaling pathways, including the phosphorylation of STAT3, which is associated with insulin resistance.[64,65] The pro-inflammatory cytokines released from both adipose tissue and activated immune cells can also contribute to muscle insulin resistance by disrupting insulin signaling pathways.[64,66] This inflammatory response not only impairs glucose uptake in muscle cells but also perpetuates a cycle of metabolic dysfunction, as the inflammatory mediators can further stimulate lipid accumulation and inflammation in both liver and muscle tissues.[67,68]

The intricate relationship between insulin resistance and altered metabolic pathways in immune cells is a driving force in the chronic inflammation observed in T2DM. Targeting these metabolic shifts may offer a promising avenue for therapeutic strategies.[69]

The Impact of Insulin on Specific Immune Cell Types in T2DM

The immune system's complexity in T2DM is significantly influenced by insulin's regulatory role across various immune cell types. Insulin resistance disrupts normal immune cell signaling, leading to an altered immune landscape characterized by heightened inflammation. Each immune cell type—T lymphocytes, B lymphocytes, macrophages, and others—responds differently to insulin signaling, contributing uniquely to the progression of T2DM. This interplay between insulin signaling and immune responses not only exacerbates systemic inflammation but also perpetuates insulin resistance (Table 1). Understanding how insulin impacts specific immune cell types is crucial for developing targeted interventions that can break this cycle of chronic inflammation and insulin resistance, which are central to T2DM's pathogenesis.

T Lymphocytes

Insulin plays a crucial role in regulating T lymphocyte function, impacting their activation, differentiation, and cytokine production, which is particularly relevant in T2DM. T cells express insulin receptors, and insulin signaling via the PI3K/Akt pathway is essential for glucose uptake and glycolysis during T cell activation, providing energy for proliferation and effector functions.[70]

In T2DM, insulin resistance disrupts this pathway, leading to altered T cell metabolism and function. Insulin-resistant T cells shift from glucose metabolism to fatty acid oxidation, resulting in a pro-inflammatory state characterized by increased production of cytokines that exacerbate systemic inflammation and insulin resistance.[71,72] This shift impairs T cell activation and contributes to the chronic inflammation seen in T2DM.

Insulin also influences the balance of T cell subsets, such as Th1, Th2, Th17, and regulatory T cells (Tregs). In T2DM, there's a notable increase in pro-inflammatory Th1 and Th17 cells, which produce interferon-gamma (IFN-γ) and interleukin-17 (IL-17), respectively. These cytokines contribute to insulin resistance and tissue inflammation, worsening metabolic dysfunction.[73] Conversely, Tregs, which suppress inflammation and maintain immune tolerance, are reduced in T2DM due to insulin resistance, leading to an imbalance between pro-inflammatory and regulatory immune responses.[74]

Table 1 The Role of Insulin on Specific Immune Cell Types and Its Dysfunction Impacts in T2DM

Immune Cells	Insulin Roles	Impacts of Insulin dysfunction during T2DM	Reference
T Lymphocytes	• Regulate immune response through activation, differentiation, and cytokine production. • Supports glucose uptake via the PI3K/Akt pathway signaling. • Provides energy for proliferation and maintains balance between pro-inflammatory and anti-inflammatory subsets.	• Insulin resistance disrupts glucose metabolism in T cells. • Causes a shift to fatty acid oxidation, increasing pro-inflammatory TH1 and TH17 cells. • Reduces regulatory T cells (Tregs), leading to chronic inflammation and Insulin resistance.	[70–74]
B Lymphocytes	• Support B cells maturation and proliferation. • Ensures glucose uptake through the PI3K/Akt pathway. • Enables antibody production and energy supply for immune regulation.	• Insulin resistance impairs B cell glucose uptake. • Results in reduced antibody production and a shift towards pro-inflammatory cytokine production (IL-6, IL-8). • Promotes interactions with T cells that contribute to insulin resistance and pancreatic ß-cell dysfunction.	[75–79]
Macrophages	• Maintain balance between M1 (pro-inflammatory) and M2 (anti-inflammatory) phenotypes. • Promotes M2 macrophages that support tissue repair. • Enhances anti-inflammatory cytokine production like IL-10 through the PI3K/Akt pathway.	• Insulin resistance leads to a shift towards M1 macrophages. • M1 macrophages secrete pro-inflammatory cytokines (TNF-α, IL-6, IL-1ß). • Disrupts insulin signaling, contributing to chronic inflammation and affecting pancreatic ß-cell function.	[80–83]
Neutrophils & NK Cells	• Supports neutrophils to perform chemotaxis, phagocytosis, and ROS production for pathogen elimination. • Supports NK cells target infected or malignant cells. • Enhances neutrophil function and supports NK cell proliferation and cytotoxicity.	• Insulin resistance reduces neutrophil activity, impairing chemotaxis and phagocytosis. • Compromises NK cell cytotoxic function. • Results in heightened inflammation, increased infection susceptibility, and exacerbates T2DM progression.	[10,84–88]

This imbalance is further exacerbated by elevated levels of IL-6, which correlate with decreased Treg populations in T2DM patients, allowing for unchecked activity of pro-inflammatory Th1 and Th17 cells.[89] Additionally, increased expression of immune checkpoint molecules like PD-1 on T cells indicates T cell exhaustion, impairing their ability to regulate inflammation effectively.[90]

The influence of insulin on T cell function plays a crucial role in maintaining immune balance, with insulin resistance contributing significantly to the pro-inflammatory environment in T2DM. Expanding our comprehension of this relationship could lead to new therapeutic approaches.[73,84]

B Lymphocytes

Insulin significantly influences B lymphocyte development, function, and antibody production, playing a vital role in immune regulation and metabolic homeostasis. Insulin signaling through the PI3K/Akt pathway is crucial for B cell maturation, proliferation, and antibody production, as it facilitates glucose uptake needed for energy and antibody. However, in T2DM, insulin resistance impairs B cell responsiveness, leading to reduced glucose uptake and compromised antibody production, which contributes to overall immune dysfunction.[75]

In T2DM, B cells also exhibit a shift towards pro-inflammatory cytokine production, with increased levels of IL-6 and IL-8 and reduced anti-inflammatory cytokine IL-10.[76] This imbalance promotes chronic inflammation, exacerbating

insulin resistance and disrupting metabolic regulation. Pro-inflammatory cytokines not only impair insulin signaling but also recruit additional immune cells, intensifying inflammation in peripheral tissues.

B cells interact with T cells, influencing their differentiation and promoting pro-inflammatory subsets such as Th1 and Th17 cells, which produce cytokines like IFN-γ and IL-17, further impairing insulin signaling.[77] This interaction perpetuates a feedback loop of inflammation and insulin resistance. Additionally, in T2DM, B cells may lose tolerance, leading to autoantibody production that negatively affects pancreatic β-cells, contributing to dysfunction and apoptosis.[77]

The presence of activated B cells in adipose tissue, common in obesity and T2DM, contributes to the inflammatory environment, recruiting other immune cells like macrophages and further impairing insulin sensitivity.[78] This involvement of B cells in promoting inflammation and metabolic disruption underscores their role in T2DM progression.

The role of insulin in B cell function is vital, but its dysregulation in T2DM leads to significant immune disturbances. These findings highlight the potential of targeting B cell pathways to modulate inflammation and insulin resistance in diabetes management.[76,79]

Macrophages

Insulin plays a crucial role in regulating macrophage polarization between pro-inflammatory (M1) and anti-inflammatory (M2) phenotypes. In a healthy state, insulin promotes M2 macrophages, which support tissue repair and maintain metabolic balance through the PI3K/Akt pathway, enhancing anti-inflammatory cytokines like IL-10.[80,91] However, in T2DM, insulin resistance disrupts this balance, leading to a predominance of M1 macrophages that secrete pro-inflammatory cytokines like TNF-α and IL-6, worsening chronic inflammation and insulin resistance.[81]

This shift towards M1 macrophages creates a feedback loop that further impairs insulin signaling in macrophages and insulin-sensitive tissues, such as adipose tissue and liver. M1 macrophages infiltrate these tissues, releasing cytokines that interfere with insulin signaling, thus exacerbating insulin resistance.[82] Additionally, obesity-related free fatty acids and lipopolysaccharides (LPS) activate Toll-like receptors (TLRs) on macrophages, driving M1 polarization and inflammation.[92]

The influence of insulin on macrophages extends to the NLRP3 inflammasome, which, when activated in T2DM, produces interleukin-1β (IL-1β), further driving inflammation and insulin resistance.[83] Conversely, M2 macrophages, which are typically reduced in T2DM, limit anti-inflammatory cytokine production, like IL-10, resulting in unchecked inflammation.[93]

The imbalance between M1 and M2 macrophages contributes to adipose tissue inflammation, a key factor in T2DM.[72,94] The abundance of M1 macrophages secreting TNF-α, IL-6, and IL-1β creates a chronic inflammatory environment that disrupts insulin signaling in adipocytes, reducing glucose uptake and worsening hyperglycemia.[14] This process also contributes to pancreatic β-cell dysfunction, impairing insulin secretion.[95]

Moreover, M1 macrophages contribute to inflammation in other metabolic organs, such as the liver and muscle, reinforcing systemic inflammation and insulin resistance in T2DM. This chronic inflammation leads to progressive β-cell deterioration, accelerating T2DM progression.[96]

Insulin's regulatory impact on macrophage polarization directly affects the balance between inflammatory and anti-inflammatory states. Addressing this imbalance could be central to developing treatments that mitigate chronic inflammation in T2DM.[81,97]

Neutrophils, NK Cells, and Other Immune Cells

Neutrophils, natural killer (NK) cells, and other immune cells are crucial in maintaining immune homeostasis, but their functions are influenced by insulin, particularly in T2DM. In T2DM, chronic inflammation and insulin resistance significantly impair the activity and efficiency of these immune cells, contributing to immune dysfunction and disease progression.[94]

Insulin typically enhances neutrophil function by promoting chemotaxis, phagocytosis, and ROS production, which are essential for pathogen elimination.[84] However, in T2DM, insulin resistance reduces neutrophil activity, leading to a diminished capacity to fight infections. This dysfunction, along with the formation of neutrophil extracellular traps

(NETs), sustains chronic inflammation and tissue damage.[10] Impaired chemotaxis and phagocytosis in neutrophils increase susceptibility to infections in T2DM patients.[10,98]

NK cells, which target infected or malignant cells, are also affected by insulin signaling. In healthy conditions, insulin supports NK cell proliferation and cytotoxicity, but in T2DM, chronic inflammation impairs their cytotoxic function and alters cytokine production, contributing to immune imbalance.[85] The reduced activity of NK cells in T2DM hampers their ability to regulate other immune cells, aggravating inflammation and metabolic disruption.[86]

The impairment of neutrophil and NK cell functions due to insulin resistance sheds light on how immune dysregulation contributes to T2DM complications. Understanding these dynamics is crucial for developing comprehensive interventions.[87,88]

In a healthy state, insulin plays a regulatory role across diverse immune cell types, ensuring immune homeostasis and reducing inflammatory responses. Normal insulin signaling in T lymphocytes, for example, supports balanced cytokine production and differentiation, favoring a controlled immune response. Similarly, insulin enables B lymphocytes to maintain antibody production and supports macrophage polarization toward the anti-inflammatory M2 phenotype. Macrophages under insulin's influence help to limit inflammation, aiding tissue repair and metabolic balance. Insulin's regulatory influence extends to neutrophils and NK cells, enhancing chemotaxis, phagocytosis, and cytotoxic functions critical for pathogen clearance.

In contrast, insulin resistance in T2DM disrupts these regulatory pathways, resulting in immune dysregulation. T lymphocytes shift toward pro-inflammatory subsets (Th1, Th17), while B cells increase production of pro-inflammatory cytokines, contributing to systemic inflammation. Macrophages, under insulin resistance, predominantly polarize to the pro-inflammatory M1 phenotype, perpetuating chronic inflammation and exacerbating insulin resistance. Neutrophils and NK cells also lose functionality, diminishing their infection-fighting capabilities. This immune imbalance under insulin resistance fosters a self-perpetuating cycle of inflammation and metabolic dysfunction that drives T2DM progression. Understanding these contrasting roles of insulin in immune cell regulation could pave the way for targeted therapies to alleviate inflammation and improve metabolic outcomes in T2DM.

Inflammatory Mediators and Insulin Signaling in T2DM

Pro-Inflammatory Cytokines and Insulin Resistance

Chronic inflammation is closely linked to insulin resistance in T2DM, with pro-inflammatory cytokines like TNF-α, IL-6, and IL-1β playing a pivotal role. These cytokines interfere with insulin signaling, exacerbating metabolic dysfunction and promoting insulin resistance.

TNF-α is a well-studied cytokine that contributes to insulin resistance by promoting the serine phosphorylation of insulin receptor substrates (IRS), particularly IRS-1, which inhibits effective insulin signaling and reduces insulin sensitivity.[99] Elevated TNF-α levels, often produced by adipose tissue macrophages, are associated with increased insulin resistance and perpetuate the chronic inflammatory state in T2DM.[100]

IL-6 is another key cytokine involved in insulin resistance, secreted by adipocytes and macrophages. IL-6 induces the expression of suppressor of cytokine signaling (SOCS) proteins, which degrade IRS proteins, disrupting insulin signaling pathways.[101] Chronic elevation of IL-6 is linked to insulin resistance and increased inflammation in tissues such as the liver, muscle, and adipose tissue, contributing to glucose metabolism impairment.[102]

IL-1β, produced by activated macrophages, plays a significant role in the inflammatory response in T2DM. It promotes β-cell dysfunction, impairs insulin secretion, and induces apoptosis in pancreatic β-cells, exacerbating insulin resistance and hyperglycemia.[103] Specifically, IL-1β can inhibit insulin secretion by interfering with the signaling pathways essential for glucose-stimulated insulin release, primarily through the suppression of insulin receptor substrate-1 (IRS-1) signaling.[14,104] This inhibition not only reduces insulin output but also contributes to the overall decline in β-cell mass and function. Moreover, chronic exposure to IL-1β can induce β-cell apoptosis through mechanisms involving endoplasmic reticulum (ER) stress and the activation of pro-apoptotic pathways.[105,106] The sustained inflammatory environment created by IL-1β leads to the generation of reactive oxygen species (ROS), further exacerbating cellular stress and promoting cell death.[107] This cycle of inflammation and cell death not only diminishes the functional

β-cell mass but also contributes to systemic insulin resistance, as the loss of insulin-producing cells impairs the body's ability to regulate blood glucose levels effectively.[108,109]

C-reactive Protein (CRP), though not a cytokine, serves as a marker of systemic inflammation in T2DM. High CRP levels reflect chronic inflammation and correlate with insulin resistance, highlighting its role in metabolic dysfunction.[110] Similarly, IL-8 is elevated in T2DM and contributes to insulin resistance by promoting inflammation and altering insulin-sensitive tissue function.[101]

Pro-inflammatory cytokines like TNF-α, IL-6, and IL-1β impair insulin signaling by promoting serine phosphorylation of IRS proteins, reducing insulin receptor sensitivity and affecting glucose uptake in target tissues. Additionally, cytokine activity activates Toll-like receptors (TLRs), especially TLR4, which respond to inflammatory stimuli and further disrupt insulin signaling, reinforcing insulin resistance.[111]

Pro-inflammatory cytokines are key players in the progression of insulin resistance in T2DM. Targeting these inflammatory pathways offers a promising direction for therapeutic interventions aimed at improving insulin sensitivity.

Adipokines and Immune Modulation

Adipokines, bioactive molecules secreted by adipose tissue, significantly impact insulin signaling and immune cell function in T2DM, playing roles in both pro-inflammatory and anti-inflammatory responses (Table 2).

Adiponectin is an anti-inflammatory adipokine with insulin-sensitizing properties that enhances insulin signaling via the AMP-activated protein kinase (AMPK) pathway, improving glucose uptake and fatty acid oxidation.[112] Adiponectin exerts its effects primarily through adiponectin receptor 1 (AdipoR1) and adiponectin receptor 2 (AdipoR2), which activate AMPK as well as peroxisome proliferator-activated receptor alpha (PPAR-α), contributing to its metabolic benefits. In T2DM, adiponectin levels are often reduced, contributing to insulin resistance and inflammation, as its protective effects on insulin sensitivity diminish.[113,119,120]

In contrast, leptin is a pro-inflammatory adipokine that is elevated in obesity and T2DM. It promotes inflammatory cytokine secretion from immune cells, enhancing inflammation and contributing to insulin resistance.[114,115] This increase in leptin levels perpetuates the chronic low-grade inflammation typical of T2DM.

Resistin is another adipokine linked to insulin resistance and is often elevated in T2DM. Though its receptor is not fully elucidated, resistin is believed to interact with Toll-like receptor 4 (TLR4), promoting inflammation through the nuclear factor-kappa B (NF-κB) pathway, which increases the expression of cytokines like TNF-α and IL-6.[121] It promotes inflammation by increasing the expression of cytokines like TNF-α and IL-6, reinforcing the connection between adipose tissue inflammation and metabolic dysfunction.[116] Similarly, chemerin is associated with inflammation

Table 2 Roles of Adipokines in Modulating Insulin Resistance and Inflammation in Type 2 Diabetes

Adipokine	Role in Insulin Signaling	Impact on Immune Cells	Reference
Adiponectin	Enhances insulin sensitivity by activating the AMPK pathway; decreased levels in T2DM contribute to insulin resistance.	Improves insulin sensitivity and reduces inflammation.	[112,113]
Leptin	Elevated levels promote inflammation and insulin resistance; enhances secretion of inflammatory cytokines from immune cells.	Increases inflammation by activating pro-inflammatory pathways in immune cells.	[114,115]
Resistin	Implicated in promoting insulin resistance; elevated levels impair insulin signaling and promote pro-inflammatory cytokine expression.	Promotes inflammation and enhances pro-inflammatory cytokine expression.	[116]
Chemerin	Linked to insulin resistance and inflammation; elevated levels promote recruitment of macrophages and increase inflammation.	Influences immune cell activity and recruitment, promoting inflammation.	[117]
Fetuin-A	Contributes to insulin resistance by interfering with insulin signaling; elevated levels increase inflammatory responses.	Increases inflammatory responses in immune cells, impairing insulin action.	[113]
Adipsin	Involved in insulin secretion and sensitivity regulation; altered levels in T2DM contribute to inflammation and insulin resistance.	Alters immune cell function, contributing to the inflammatory environment.	[118]

and insulin resistance. It signals through the chemokine-like receptor 1 (CMKLR1), facilitating macrophage recruitment to adipose tissue, which contributes to the chronic inflammatory environment characteristic of T2DM. This receptor interaction links chemerin to the immune-modulatory pathways that exacerbate inflammation and insulin resistance in metabolic tissues.[117]

Fetuin A is implicated in insulin resistance through its effects on insulin signaling and inflammation. Fetuin A inhibits insulin receptor tyrosine kinase activity, disrupting insulin signaling pathways in tissues like the liver and skeletal muscle.[113] By serving as an adaptor protein for TLR4, fetuin A enhances lipid-induced insulin resistance, promoting inflammation within insulin-sensitive tissues.[122,123] Elevated fetuin A levels are linked to a higher risk of T2DM, exacerbating metabolic dysfunction by intensifying inflammatory responses in adipose and other insulin-sensitive tissues.

In contrast, adipsin has a complex and still-debated role in metabolic health. As an adipokine produced by adipose tissue, adipsin has been observed at lower circulating levels in individuals with T2DM, suggesting a potential protective role in β-cell function and insulin sensitivity.[118,124,125] Although some evidence indicates that adipsin may positively influence insulin secretion, its precise mechanisms of action and its interactions with other adipokines and inflammatory mediators remain insufficiently understood.[126,127] Further research is needed to clarify how adipsin interacts within the complex network of metabolic and inflammatory pathways to influence insulin sensitivity.

The dysregulation of these adipokines in T2DM promotes a pro-inflammatory environment, influencing immune cells such as macrophages and T cells. Elevated levels of leptin, resistin, and chemerin promote macrophage polarization towards the M1 pro-inflammatory phenotype, increasing the secretion of cytokines like TNF-α and IL-6, which further contribute to insulin resistance.[128] This pro-inflammatory state also affects T cells, shifting them towards a Th1-dominant immune response, perpetuating inflammation and metabolic dysfunction.[129]

The imbalance in adipokine levels contributes significantly to the inflammatory landscape of T2DM. Recognizing the impact of these molecules could guide the development of strategies to restore metabolic and immune equilibrium.

Myokines and Hepatokines in Insulin Sensitivity and Metabolic Health

Myokines and hepatokines play key roles in metabolic health, particularly in the regulation of insulin sensitivity and inflammation. Myokines like irisin and myonectin are released by skeletal muscles during exercise, enhancing insulin sensitivity, glucose uptake, and promoting the browning of white adipose tissue (WAT), which boosts energy expenditure.[130–132] Irisin specifically activates uncoupling protein 1 (UCP1) in adipocytes, facilitating thermogenesis and aiding in weight regulation.[133,134] Additionally, irisin has been shown to improve insulin receptor signaling in muscle and liver, enhance glucose metabolism, and protect pancreatic β-cells, essential for insulin secretion.[135–137] Its anti-inflammatory properties further contribute to metabolic stability, counteracting the chronic low-grade inflammation often associated with obesity and insulin resistance.[138,139]

In contrast, hepatokines such as fibroblast growth factor 21 (FGF21) and fetuin A, secreted by the liver, have complex effects on insulin sensitivity. FGF21 improves insulin sensitivity by modulating lipid metabolism and reducing inflammation in muscle and liver.[140] Conversely, fetuin A disrupts insulin receptor signaling and promotes inflammation, contributing to insulin resistance, especially in obesity.[141]

The interplay between myokines and hepatokines underscores the importance of muscle-liver communication in maintaining metabolic health. Dysregulation in these proteins can lead to insulin resistance, highlighting their potential as therapeutic targets for metabolic disorders.[130,131]

Insulin and Oxidative Stress in Immune Cells

Oxidative stress plays a multifaceted role in the immune system, influencing both immune responses and the overall health of immune cells. Under normal physiological conditions, reactive oxygen species (ROS) generated during metabolic processes serve as signaling molecules that help regulate immune functions, including the activation and proliferation of immune cells. For instance, ROS are crucial for the oxidative burst in phagocytes, which is essential for killing pathogens and initiating inflammatory responses.[142,143] This controlled production of ROS can enhance the immune response by promoting the expression of pro-inflammatory cytokines and facilitating communication between immune cells.[144]

However, excessive oxidative stress can lead to detrimental effects on immune function, particularly in states of chronic inflammation or disease. Elevated levels of ROS can cause cellular damage, impair immune cell function, and induce apoptosis, thereby diminishing the efficacy of the immune response.[145] For example, in conditions such as obesity and diabetes, oxidative stress contributes to the dysfunction of T cells and macrophages, promoting a pro-inflammatory state that exacerbates insulin resistance.[146]

One primary mechanism is the oxidative modification of insulin signaling proteins. ROS can oxidize key proteins, such as IRS-1, leading to its serine phosphorylation, which inhibits effective insulin signaling and disrupts pathways like PI3K/Akt.[147] This impairment is a critical factor in insulin resistance, as insulin signaling is essential for glucose uptake and metabolism in immune cells.

Oxidative stress also activates stress-sensitive kinases such as JNK and p38 MAPK, which further phosphorylate IRS proteins, exacerbating insulin resistance.[148] These kinases respond to increased inflammatory cytokines in T2DM, linking inflammation to impaired insulin signaling.

The alteration of the cellular redox state is another consequence, disrupting insulin signaling and promoting inflammatory responses.[149] This altered state affects glucose transporter GLUT4's expression and translocation, reducing glucose uptake and contributing to insulin resistance.[150]

Oxidative stress also impacts immune cell function, impairing neutrophil and macrophage activity, which promotes a pro-inflammatory state. It enhances cytokine production from macrophages, perpetuating inflammation and disrupting insulin signaling.[151] Additionally, mitochondrial dysfunction due to oxidative stress results in impaired ATP synthesis and increased ROS production, creating a feedback loop that worsens insulin resistance.[152]

Oxidative stress influences macrophage polarization towards the M1 phenotype, leading to increased secretion of inflammatory cytokines like TNF-α and IL-6, which further impair insulin signaling and β-cell function.[153] Elevated ROS levels also impair T cell function by inducing a pro-inflammatory state and promoting T cell exhaustion, contributing to immune dysregulation in T2DM.[154]

The impact of oxidative stress on insulin signaling and immune cell function is a critical factor in the development of insulin resistance in T2DM. Addressing this could help break the cycle of chronic inflammation and metabolic dysfunction.

Anti-Inflammatory Effects of Insulin

Insulin plays a critical role in modulating inflammation, with significant implications for managing T2DM. Its anti-inflammatory effects extend beyond glycemic control, influencing immune cell function and the overall inflammatory state.

One of the primary ways insulin exerts its anti-inflammatory effects is through the suppression of pro-inflammatory cytokines. Insulin administration decreases levels of cytokines like TNF-α, IL-1β, and IL-6, which are often elevated in T2DM.[155] Insulin inhibits nuclear factor kappa B (NF-κB) activation, a transcription factor that drives these cytokines' expression, thus reducing inflammation and mitigating insulin resistance.

Insulin also promotes the production of anti-inflammatory cytokines, particularly IL-10, which helps restore immune homeostasis and improve insulin sensitivity.[155] This shift from a pro-inflammatory to an anti-inflammatory state reduces the inflammatory burden in T2DM.

Another crucial effect of insulin is its role in macrophage polarization. Insulin promotes the shift of macrophages from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype, aiding in tissue repair and reducing inflammation.[156] This shift improves insulin sensitivity, counteracting one of the primary drivers of insulin resistance in T2DM.

However, insulin resistance can impair the insulin receptor's signaling efficacy, diminishing its ability to carry out anti-inflammatory actions, including suppressing pro-inflammatory cytokine production and encouraging anti-inflammatory responses. Consequently, immune cells in an insulin-resistant state may not fully experience insulin's anti-inflammatory benefits through exogenous insulin alone. To overcome this limitation, enhancing insulin sensitivity prior to or alongside insulin therapy is often necessary. Insulin sensitizers—such as physical activity, metformin, and thiazolidinediones (TZDs)—help improve insulin receptor functionality by reducing systemic inflammation, promoting

glucose uptake, and bolstering cellular insulin sensitivity. For instance, physical activity enhances glucose uptake in skeletal muscle, while metformin and TZDs regulate hepatic glucose production and improve overall cellular responsiveness to insulin. These mechanisms enable immune cells to effectively respond to insulin, allowing them to leverage its full metabolic and anti-inflammatory benefits.

In addition to modulating cytokine production, insulin enhances immune cell function by supporting glucose uptake and metabolism in T cells and NK cells, balancing immune responses (Xia et al, 2017). This is particularly relevant in T2DM, where immune cell dysfunction contributes to chronic inflammation and heightened susceptibility to infections. Insulin also reduces oxidative stress by lowering reactive oxygen species (ROS) levels, further aiding in the maintenance of normal insulin signaling in immune cells and helping to alleviate inflammation (Rehman & Akash, 2016).

The therapeutic implications of insulin's anti-inflammatory effects, especially when paired with insulin sensitizers, are substantial. By targeting both glucose regulation and inflammation, this dual approach offers a comprehensive treatment strategy for T2DM (L. Su et al, 2018). In summary, utilizing insulin sensitizers to restore insulin responsiveness may be essential for achieving the full range of insulin's metabolic and immune-modulating effects. This strategy could be more effective in managing both glycemic control and chronic inflammation in T2DM, as insulin exerts anti-inflammatory effects through the suppression of pro-inflammatory cytokines, promotion of anti-inflammatory cytokines, macrophage polarization, immune cell function enhancement, and reduction of oxidative stress.

Dual Roles of Insulin

The role of insulin in the immune response against pathogens can be conceptualized as a "double-edged sword", where it exerts both beneficial and detrimental effects depending on the context of its action. On one hand, insulin plays a crucial role in enhancing immune responses, while on the other hand, it can contribute to immune dysfunction, particularly in states of insulin resistance and metabolic disease.

Insulin's Role in Enhancing Immune Responses

Insulin is known to promote the proliferation and activation of immune cells, particularly T cells and macrophages, which are essential for mounting an effective immune response against pathogens. For instance, insulin signaling has been shown to enhance the differentiation of T cells into effector cells that produce cytokines such as IL-2 and IFN-γ, which are critical for fighting infections.[157] This enhancement of T cell function is particularly important in the context of acute infections, where a robust immune response is necessary for pathogen clearance.

Moreover, insulin facilitates glucose uptake in immune cells, providing the necessary energy for their activation and function. This metabolic support is vital during an immune response, as activated immune cells require increased energy to proliferate and produce cytokines.[158] Insulin also promotes the polarization of macrophages towards an M2 phenotype, which is associated with anti-inflammatory responses and tissue repair, further aiding in the resolution of inflammation following an infection.[159,160]

Insulin's Detrimental Effects in Immune Dysfunction

Conversely, in states of insulin resistance, which is commonly observed in obesity and type 2 diabetes, insulin can have detrimental effects on the immune system. Chronic hyperinsulinemia can lead to a state of immune dysfunction characterized by an overactive inflammatory response. For example, elevated insulin levels can promote the activation of pro-inflammatory pathways in macrophages, leading to increased production of cytokines such as TNF-α and IL-6, which are associated with chronic inflammation and insulin resistance[161,162]. This inflammatory milieu can impair the ability of immune cells to respond effectively to pathogens, thereby increasing susceptibility to infections.

Furthermore, the shift in macrophage polarization from M2 to M1 in the context of insulin resistance contributes to a chronic inflammatory state that exacerbates metabolic dysfunction.[84,163,164] This maladaptive immune response not only hinders the clearance of pathogens but also perpetuates a cycle of inflammation that can lead to further insulin resistance and metabolic disease.[163,164]

The Balance of Insulin's Effects

The dual role of insulin in the immune response underscores the importance of maintaining insulin sensitivity for optimal immune function. In healthy individuals, insulin promotes a balanced immune response that is capable of effectively combating pathogens while also resolving inflammation. However, in individuals with insulin resistance, the beneficial effects of insulin are overshadowed by its pro-inflammatory actions, leading to a compromised immune system.

Therapeutic strategies aimed at improving insulin sensitivity, such as lifestyle interventions, pharmacological agents, and dietary modifications, may help restore the beneficial effects of insulin on the immune system.[165,166] For instance, weight loss and physical activity have been shown to improve insulin sensitivity and reduce chronic inflammation, thereby enhancing immune function.[167,168] Additionally, medications that target insulin signaling pathways may also provide a means to modulate immune responses in individuals with metabolic disorders.

The dual nature of insulin in regulating immune responses emphasizes the delicate balance required for optimal immune function. Therapeutic strategies that enhance insulin sensitivity while managing inflammation could be transformative for T2DM care.

Therapeutic Implications and Interventions

Insulin Therapy and Immune Modulation in T2DM

Insulin therapy plays a crucial role in managing hyperglycemia in T2DM and has significant effects on immune cell function and inflammation. Beyond regulating glucose metabolism, insulin offers therapeutic benefits by modulating immune responses and reducing inflammation.

Insulin therapy reduces pro-inflammatory cytokine production by inhibiting NF-κB pathways, which decreases cytokines like TNF-α and IL-6, helping to alleviate chronic inflammation and improve insulin sensitivity.[54] Additionally, insulin promotes the secretion of anti-inflammatory cytokines, such as IL-10, contributing to a balanced immune response.[169]

Insulin also influences macrophage polarization, promoting a shift from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype, reducing inflammation and enhancing insulin sensitivity.[170] This shift aids tissue repair and inflammation resolution, contributing to insulin's anti-inflammatory effects.

The therapy impacts T cell function by promoting glucose uptake, which is essential for T cell activation and proliferation, leading to a more balanced immune response and reducing chronic inflammation in T2DM.[24] Moreover, insulin therapy helps reduce oxidative stress by lowering reactive oxygen species (ROS) levels, which restores normal insulin signaling pathways in immune cells, alleviating inflammation and improving insulin sensitivity.[171]

However, there are limitations and challenges associated with insulin therapy in T2DM. One concern is the potential for immune suppression, which can increase susceptibility to infections since insulin therapy might impair the overall immune response.[172] Additionally, insulin therapy may result in altered immune cell function, such as impaired bactericidal activity in neutrophils, potentially leading to a higher risk of infections.[173]

Hyperinsulinemia presents another challenge, as chronically high insulin levels can promote inflammatory pathways and shift macrophage polarization towards a pro-inflammatory M1 phenotype, exacerbating insulin resistance and inflammation.[172] This feedback loop presents a critical barrier to the long-term immunomodulatory effectiveness of insulin therapy in T2DM, underscoring the complexity of achieving sustained metabolic and immune benefits through insulin alone.

The onset of T2DM therapy typically involves insulin-sensitizing agents like metformin, which emphasizes the importance of improving insulin sensitivity as an initial therapeutic goal. This step is essential to restore physiological insulin responses, including within immune cells, to counter chronic inflammation. For patients with insulin resistance, initiating insulin therapy can aggravate hyperinsulinemia, contributing to adverse effects on immune cells.[172] Over time, the efficacy of insulin in modulating immune responses may diminish, as increased insulin resistance often necessitates higher insulin doses, complicating immune regulation and limiting long-term benefits.[172]

Overall, insulin therapy offers considerable anti-inflammatory benefits in T2DM management by reducing pro-inflammatory cytokines, supporting anti-inflammatory cytokine production, influencing macrophage polarization,

enhancing T-cell function, and mitigating oxidative stress. However, limitations such as immune suppression, increased infection risk, and hyperinsulinemia underscore the need for a more comprehensive approach. Integrating insulin therapy with lifestyle modifications, anti-inflammatory agents, and adjunctive therapies can more effectively address both the metabolic and immune challenges inherent to T2DM, fostering improved patient outcomes.

Targeting Insulin Signaling Pathways for Immune Modulation

Targeting insulin signaling pathways offers promising therapeutic options for modulating immune responses in T2DM. These pathways regulate insulin sensitivity and immune function, making them valuable targets for reducing inflammation and improving immune activity in T2DM (Table 3).

A key therapeutic target is the Insulin Receptor (IR). Enhancing the expression or sensitivity of IR on immune cells can improve insulin signaling, promoting glucose uptake and reducing inflammation.[54] Improving IR function could enhance immune cell activity and decrease inflammation in T2DM.

The PI3K/Akt pathway, a crucial component of insulin signaling, regulates glucose metabolism and immune function. Activation of this pathway plays a significant role in mediating anti-inflammatory responses, particularly in macrophages. Targeting the PI3K/Akt pathway could regulate immune responses and improve insulin sensitivity in T2DM.[174]

The mTOR pathway is another key regulator of immune cell metabolism and function. Insulin activates mTOR, influencing T cell and macrophage activity. Modulating mTOR could improve immune responses and insulin sensitivity, making it a valuable therapeutic target in T2DM.[175]

Suppressor of Cytokine Signaling (SOCS) proteins play a critical role in negatively regulating insulin signaling and contributing to insulin resistance in immune cells. Inhibiting SOCS expression enhances insulin signaling and reduces inflammation, offering a potential therapeutic strategy for improving insulin sensitivity in type 2 diabetes mellitus (T2DM).[176] Targeting cytokine receptors, particularly for pro-inflammatory cytokines like TNF-α and IL-6, has also been effective in reducing inflammation and improving insulin sensitivity, as demonstrated with TNF-α inhibition in adipose tissue.[177]

Table 3 Therapeutic Targets and Mechanisms for Modulating Insulin Signaling and Immune Responses in Type 2 Diabetes Mellitus

Target	Mechanism of Action	Reference
Insulin Receptor (IR)	Enhancing IR expression or sensitivity can improve insulin signaling, glucose uptake, and reduce inflammation in immune cells.	[15,54]
Phosphatidylinositol 3-Kinase (PI3K)/Akt Pathway	Targeting the PI3K/Akt pathway can enhance insulin signaling, improving metabolic responses and promoting anti-inflammatory actions in immune cells.	[174]
mTOR Pathway	Modulating mTOR activity can regulate immune responses, especially in T cells and macrophages, improving insulin sensitivity.	[175]
Suppressor of Cytokine Signaling (SOCS) Proteins	Inhibiting SOCS proteins can enhance insulin signaling and reduce inflammation, thus improving immune cell function.	[14,176]
Cytokine Receptors	Blocking pro-inflammatory cytokine receptors like TNF-Î± and IL-6 can improve insulin sensitivity and reduce inflammation.	[177]
Nuclear Factors (FoxO and NF-κB)	Modulating transcription factors FoxO and NF-κB can balance pro-inflammatory and anti-inflammatory responses in immune cells.	[121]
Adipokines	Enhancing beneficial adipokines (eg, adiponectin) or inhibiting detrimental ones can improve insulin sensitivity and reduce inflammation.	[119,120]
Endocannabinoid System	Targeting the cannabinoid receptors of the endocannabinoid system can regulate insulin signaling and inflammation, offering potential benefits.	[178,179]

https://doi.org/10.2147/ITT.S499605

Recent studies have highlighted the therapeutic potential of anti-inflammatory agents such as IL-1 receptor blockers (anakinra), IL-1β antagonists (canakinumab), TNF antagonists (etanercept), and salicylates in improving insulin sensitivity. Anakinra improves β-cell function and insulin sensitivity by inhibiting IL-1 and suppressing other pro-inflammatory cytokines.[180] Etanercept, targeting TNF-α, also reduces insulin resistance, and its combination with anakinra shows synergistic effects, restoring insulin sensitivity.[180,181] Salicylates act by inhibiting IκB kinase, reducing NF-κB activation and inflammatory cytokines, key contributors to insulin resistance.[182] These therapies demonstrate significant promise in mitigating inflammation and enhancing insulin action in T2DM.[183]

Transcription factors such as FoxO and NF-κB regulate insulin signaling and inflammatory responses in immune cells. Modulating their activity can influence the balance between pro- and anti-inflammatory responses, enhancing insulin sensitivity.[184]

The endocannabinoid system also regulates insulin sensitivity and immune responses. Activating cannabinoid receptors can influence insulin signaling and reduce inflammation, suggesting potential therapeutic benefits.[178,179]

Other promising molecules include Insulin-like Growth Factor-1 (IGF-1) and sphingosine 1-phosphate (S1P). IGF-1 stimulates regulatory T cells, reducing inflammation and improving insulin sensitivity, while S1P influences immune cell function, making it a potential target for enhancing insulin sensitivity in T2DM.[185]

Lastly, nutritional interventions, like omega-3 fatty acid intake, can modulate insulin signaling pathways and immune responses, impacting adipokine and cytokine production.[186]

Therapies that target insulin signaling pathways hold great potential in modulating immune responses in T2DM. Such interventions could redefine treatment paradigms by addressing both metabolic and immune dysfunctions.

Lifestyle Interventions and Insulin Sensitivity

Lifestyle interventions, including dietary modifications, physical activity, and weight management, play a fundamental role in enhancing insulin sensitivity and improving immune function in T2DM.

Dietary Modifications are crucial for managing insulin sensitivity. Diets low in saturated fats and high in fiber, whole grains, fruits, and vegetables can improve insulin sensitivity and reduce inflammation.[187] Such diets decrease pro-inflammatory cytokines and adipokines, which contribute to insulin resistance. Additionally, omega-3 fatty acids, antioxidants, and polyphenols promote anti-inflammatory responses and modulate immune function, further enhancing insulin sensitivity.

Physical Activity is a cornerstone of T2DM management. Regular exercise improves glucose uptake, insulin receptor sensitivity, and the translocation of glucose transporters (GLUT4) to cell membranes, enhancing glycemic control.[188] Moderate-intensity aerobic exercise, such as brisk walking for at least 150 minutes per week, significantly improves insulin sensitivity.[189] Exercise also reduces pro-inflammatory cytokines and promotes macrophage polarization towards the anti-inflammatory M2 phenotype, benefiting both metabolic control and immune modulation.[190]

Weight Management is another key factor. Modest weight loss (5–10% of body weight) leads to substantial improvements in insulin sensitivity and glycemic control by reducing adipose tissue mass.[191] This reduction lowers pro-inflammatory adipokine and cytokine secretion, alleviating the inflammatory burden and restoring normal insulin signaling.

Gut Microbiota Modulation can impact insulin sensitivity. Dietary changes, probiotics, and prebiotics positively influence gut microbiota composition, enhancing insulin sensitivity by modulating inflammatory responses and metabolic pathways.[192] A healthier gut microbiome increases the production of short-chain fatty acids (SCFAs) like butyrate, which have anti-inflammatory effects and improve glucose metabolism.

Behavioral Changes, such as self-monitoring of blood glucose, dietary intake, and physical activity, empower individuals to make healthier choices, leading to better insulin sensitivity.[193] Educational programs that promote these changes improve glycemic control and metabolic outcomes.

Pharmacotherapy Synergy enhances the benefits of lifestyle interventions. Combining medications like metformin with lifestyle changes improves insulin sensitivity and glycemic control more effectively than pharmacotherapy alone.[194] This combined approach addresses both metabolic and immune aspects of T2DM.

Lifestyle changes offer a foundational approach to improving insulin sensitivity and immune function in T2DM. These interventions serve as a cornerstone for reducing inflammation and enhancing overall metabolic health.

Future Perspectives and Challenges

Emerging therapies targeting insulin's role in immune modulation offer promising avenues for managing T2DM but also present significant challenges. Understanding the complex interactions between insulin signaling and immune function is crucial for developing effective treatments that address both metabolic and immune dysfunction in T2DM.

Targeting Insulin Resistance in immune cells is a major focus, as insulin resistance in these cells contributes to chronic inflammation in T2DM.[91] Restoring insulin sensitivity in immune cells could achieve desired anti-inflammatory effects, but this remains challenging, particularly as insulin resistance can worsen inflammation rather than reduce it.

Addressing Chronic Inflammation is another promising approach since elevated pro-inflammatory cytokines like TNF-α and IL-6 exacerbate insulin resistance. Therapies that reduce inflammation could improve insulin sensitivity; however, achieving this without causing immune suppression is a delicate balance.

Diverse Immune Cell Responses to Insulin present a challenge, as macrophages and T cells exhibit variable reactions based on the individual's inflammatory state. Insulin may reduce inflammation in some cells but exacerbate it in others, making it difficult to design targeted therapies that effectively modulate insulin signaling across all immune cell types.[195]

The Interaction with Competing Pathways is another hurdle. Pro-inflammatory cytokines activate pathways like NF-κB, which inhibit insulin signaling, creating a complex network that complicates therapeutic targeting.[196] Developing treatments that selectively target insulin-related pathways without disrupting others is a significant challenge.

Potential Side Effects are also a concern. While enhancing insulin sensitivity might improve metabolic outcomes, it could suppress immune responses and increase infection risk.[197] Balancing the anti-inflammatory effects of insulin with maintaining immune defenses is essential.

Individual Variability adds complexity, as T2DM patients have diverse genetic backgrounds, lifestyles, and comorbidities, making one-size-fits-all therapies impractical.[198] Personalized treatment approaches could be more effective but require extensive research.

The Long-term Efficacy of Insulin Therapy remains uncertain. Patients may develop tolerance over time, requiring higher doses and reducing effectiveness.[199] This underscores the need for sustainable treatment strategies.

For future research, mechanistic studies of insulin signaling in immune cells, focusing on pathways like PI3K/Akt and mTOR, can identify therapeutic targets.[54] Investigating the role of adipokines (eg, leptin, adiponectin, and resistin) in insulin signaling could further elucidate the link between obesity, metabolic dysfunction, and immune responses.[200]

The gut microbiota is another promising area for research, as the gut-immune axis plays a significant role in metabolic health. Understanding how lifestyle interventions alter gut microbiota could lead to innovative strategies for improving insulin sensitivity and immune function.[29]

Research on immune cell plasticity, especially macrophage and T cell polarization in response to insulin, could guide new approaches to managing chronic inflammation in T2DM.[10] Understanding how these cells transition between pro- and anti-inflammatory states could aid in developing therapies that promote immune balance.

Exploration of Novel Therapeutics targeting insulin signaling in immune cells, such as agents that enhance insulin sensitivity or modulate inflammatory pathways, shows potential for addressing both metabolic and immune dysfunctions in T2DM.[30] Long-term studies assessing these interventions would be valuable.

Lastly, the role of oxidative stress in modulating insulin signaling and immune responses warrants further investigation. Understanding its impact on immune cell function could reveal new therapeutic targets to reduce inflammation and improve metabolic health.[201]

In summary, while targeting insulin signaling pathways for immune modulation in T2DM offers promising opportunities, challenges related to insulin resistance, inflammation, immune variability, and potential side effects remain. Future research should focus on elucidating insulin-immune interactions, exploring novel treatments, and developing personalized strategies to manage T2DM's metabolic and immune dysfunctions effectively.

Concluding Remarks

Insulin is a key regulator of both glucose metabolism and immune function. In type 2 diabetes mellitus (T2DM), insulin resistance disrupts normal immune cell regulation, shifting T cells, B cells, macrophages, neutrophils, and natural killer (NK) cells toward a pro-inflammatory state. This chronic inflammation perpetuates a cycle of insulin resistance and β-cell dysfunction, exacerbating hyperglycemia and systemic inflammation. These interactions highlight T2DM as a disorder involving significant immune dysregulation in addition to metabolic dysfunction.

Insulin therapy offers substantial anti-inflammatory benefits, including suppression of pro-inflammatory cytokines, promotion of anti-inflammatory cytokines, macrophage polarization, improved T-cell function, and reduced oxidative stress. However, in insulin-resistant states, hyperinsulinemia may exacerbate systemic inflammation and impair immune responses. This underscores the importance of restoring insulin sensitivity as a foundational step. Insulin sensitizers, such as physical activity, metformin, and thiazolidinediones (TZDs), enhance insulin receptor functionality, reduce inflammation, and improve immune cell responses to insulin. When paired with insulin therapy, this dual strategy addresses both metabolic control and immune regulation, breaking the cycle of chronic inflammation and insulin resistance.

Future therapies should focus on the interplay between metabolic and immune pathways, integrating lifestyle interventions, anti-inflammatory agents, and adjunctive therapies. However, challenges such as individual variability, the long-term effects of insulin therapy, and the balance between immune modulation and insulin sensitivity must be addressed.

In conclusion, targeting immune dysfunction in T2DM is critical for comprehensive disease management. Insulin's dual role as a metabolic regulator and immune modulator provides unique therapeutic opportunities. By addressing the underlying immune and inflammatory mechanisms, we can improve insulin sensitivity, prevent complications, and enhance outcomes for individuals with T2DM.

Acknowledgment

We express our sincere gratitude to the Directorate General of Higher Education, Research and Technology the Ministry of Education, Culture, Research and Technology for their support in the completion of this article. We also extend our appreciation to the Research Center for Regional Development and Community Empowerment at Universitas Padjadjaran for their invaluable assistance throughout the literature review process.

Disclosure

The authors report no conflicts of interest in this work.

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