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Interleukins' Function in the Pathophysiology of Diabetes

Ozoemena Chimaoge Covenant[1] and Nnodim Johnkennedy[2*]

[1]Department of Chemical pathology, Faculty of Medical Laboratory Science, Federal University Otuoke, Bayelsa State
[2]Department of Medical Laboratory science, Imo state university, Owerri, Nigeria

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Abstract

Chronic hyperglycemia is a defining characteristic of diabetes mellitus, a prolonged metabolic disorder resulting from inadequate insulin production, diminished insulin efficacy, or a combination of these factors. Increasing data indicates that inflammation strongly influences the aetiology of both Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM). Interleukins are pivotal inflammatory mediators in the disease process due to their regulation of immune responses, inflammation, and cellular metabolism. The article discusses the influence of interleukins on the development and progression of diabetes mellitus. Pro-inflammatory interleukins, including IL-1β, IL-6, and IL-17, facilitate the autoimmune destruction of pancreatic β-cells in type 1 diabetes via the activation of inflammatory pathways, oxidative stress, and immunological dysregulation. Moreover, the functionality of regulatory T cells is compromised by IL-2 depletion, which exacerbates autoimmunity. Chronic low-grade inflammation that obstructs insulin signalling and β-cell functionality in type 2 diabetes is associated with obesity and insulin resistance, mediated by cytokines such as IL-1β, IL-6, and IL-18. Conversely, the anti-inflammatory properties of interleukin-10 (IL-10) positively influence by diminishing inflammatory responses and enhancing insulin sensitivity. The progression of diabetes complications such as nephropathy, retinopathy, and cardiovascular issues is influenced by interleukins. The finding of molecular connections between interleukins and diabetes has facilitated the development of prospective treatment targets, including cytokine inhibitors and immunomodulatory approaches. Interleukins are significant biomarkers and therapeutic agents in the progression and management of diabetes mellitus.

***Corresponding author**: Nnodim Johnkennedy, Department of Medical Laboratory science, Imo state university, Owerri, Nigeria.

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Introduction

Diabetes mellitus is a chronic metabolic disorder marked by persistently elevated blood glucose levels due to impairments in insulin action, synthesis, or both. Owing to its increasing prevalence and related consequences, it ranks among the most prevalent endocrine disorders globally and constitutes a considerable public health issue. Diabetes manifests in two principal types. Type 1 and Type 2 Diabetes Mellitus The principal feature of type 1 diabetes is an autoimmune disorder that results in the destruction of pancreatic β-cells. Insulin resistance and heightened β-cell dysfunction are commonly linked to type 2 diabetes. Recent scientific research have demonstrated that inflammation plays a crucial role in the establishment and progression of diabetes.

Interleukins are among the several inflammatory mediators associated with the aetiology of the disease. Leukocytes and other immune cells are the primary makers of interleukins, a category of cytokines. They serve as signalling molecules that regulate tissue repair, immune response, inflammation, cell division, and proliferation. Some interleukins have anti-inflammatory properties and facilitate immune homeostasis, whereas others are pro-inflammatory, fostering immunological activation and tissue damage. The disparity between pro-inflammatory and anti-inflammatory interleukins significantly influences the aetiology, development, and consequences of diabetes mellitus.

In type 1 diabetes mellitus, interleukins contribute to the autoimmune obliteration of pancreatic β-cells. The immune system targets and eliminates β-cells as foreign entities, resulting in inadequate insulin production. Interleukin-1 beta (IL-1β) is a pivotal interleukin involvement. In pancreatic tissue, active macrophages and immune cells generate IL-1β, a powerful pro-inflammatory cytokine. It induces oxidative stress, facilitates pancreatic cell apoptosis, and activates inflammatory pathways, hence leading to the demise of β-cells. Nuclear factor kappa B (NF-κB), activated by IL-1β, promotes the expression of inducible nitric oxide synthase and inflammatory genes.

The generation of nitric oxide leads to cellular damage and mitochondrial malfunction, ultimately resulting in β-cell death. Interleukin-2 (IL-2), which modulates T-cell proliferation and immune tolerance, is a significant cytokine in Type 1 diabetes. The homeostasis of regulatory T-cells, which inhibit autoimmune responses, is contingent upon IL-2. Impaired immune regulation and the activation of autoreactive T-cells that attack pancreatic β-cells result from deficient or dysfunctional IL-2 signalling. The autoimmune processes underlying Type 1 diabetes are intensified by impaired IL-2 activity.

The aetiology of Type 1 diabetes also includes interleukin-6 (IL-6). IL-6 is a multifaceted cytokine involved in immune modulation and inflammatory processes. Individuals with newly diagnosed diabetes exhibit increased levels of IL-6. T helper 17 cells (Th17) are intricately linked to autoimmune inflammation and are differentiated by interleukin-6 (IL-6). IL-6 induces β-cell depletion and pancreatic inflammation by activating inflammatory pathways. Th17 cells secrete a significant quantity of interleukin-17 (IL-17), which is crucial for autoimmune tissue injury. In pancreatic tissues, IL-17 induces cytokine synthesis and recruits inflammatory cells. In Type 1 diabetes mellitus, heightened IL-17 levels correlate with augmented β-cell injury and autoimmune activity.

A significant pathogenic mechanism for type 2 diabetes mellitus is chronic low-grade inflammation. Macrophages and other immune cells that secrete inflammatory cytokines, such as interleukins, infiltrate adipose tissue due to obesity, a significant risk factor for type 2 diabetes. IL-6 is a cytokine that has been extensively researched. The persistent elevation of IL-6, which inhibits insulin receptor signalling, is associated with insulin resistance. Furthermore, IL-6 enhances hepatic lipolysis and glucose synthesis, resulting in hyperglycemia. Individuals with Type 2 diabetes, accompanied by obesity, insulin resistance, and cardiovascular complications, typically exhibit elevated serum IL-6 levels.

Interleukin-1 beta is another significant element in the pathophysiology of Type 2 diabetes mellitus. Chronic hyperglycemia induces the secretion of IL-1β by immune cells and pancreatic β-cells, which impedes insulin production and leads to β-cell apoptosis. This establishes a detrimental cycle in which inflammation exacerbates glycaemic control, while hyperglycemia induces inflammation. The function of β-cells progressively deteriorates when pancreatic tissues are subjected to IL-1β over time.

Interleukin-18 (IL-18) is an additional pro-inflammatory cytokine associated with type 2 diabetes. Obesity, insulin resistance, metabolic syndrome, and endothelial dysfunction are frequently correlated with increased IL-18 levels. IL-18 is implicated in the pathogenesis of cardiovascular illnesses and chronic inflammation, which are prevalent consequences of diabetes mellitus. Increased blood concentrations of IL-18 have been demonstrated to predict the future onset of Type 2 diabetes.

Unlike pro-inflammatory cytokines, interleukin-10 (IL-10) has the capacity to inhibit diabetes. The anti-inflammatory cytokine IL-10 diminishes inflammatory responses by inhibiting the synthesis of pro-inflammatory cytokines and reducing macrophage activation. Adequate IL-10 activity maintains immunological equilibrium and enhances insulin sensitivity. In individuals with diabetes, increased inflammation and metabolic irregularities are generally associated with diminished levels of IL-10.

The role of interleukins in the aetiology of diabetes can be elucidated through many molecular mechanisms. Nuclear factor kappa B (NF-κB), which governs

the expression of inflammatory genes and triggers oxidative stress, exemplifies this mechanism. Moreover, interleukins activate the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signalling pathway, leading to dysfunctional insulin signalling and glucose metabolism. Moreover, inflammatory cytokines elevate the synthesis of reactive oxygen species, resulting in oxidative damage to DNA, lipids, proteins, and pancreatic β-cells. The activation of the NLRP3 inflammasome is a significant mechanism, especially in obesity-related diabetes. Insulin resistance and chronic inflammation are intensified by the inflammasome's heightened production and secretion of IL-1β.

The pathophysiology of diabetes-related complications also encompasses interleukins. Elevated concentrations of IL-6, IL-1β, and IL-18 are associated with glomerular inflammation, fibrosis, and advancing renal impairment in diabetic nephropathy. In diabetic retinopathy, inflammatory cytokines induce aberrant neovascularisation, oxidative stress, and retinal vascular permeability. Moreover, interleukin-induced chronic inflammation accelerates endothelial dysfunction and atherosclerosis, increasing cardiovascular risk in diabetic individuals.

The expanding comprehension of interleukins in diabetes has substantial therapeutic implications. Medications that inhibit inflammatory cytokines are under investigation as potential therapies for diabetes and its associated problems. Anakinra and other IL-1 receptor antagonists have demonstrated potential effects on inflammation and insulin secretion. Research is being conducted on the efficacy of anti-IL-6 medicines in mitigating inflammation and insulin resistance. Lifestyle adjustments, such as exercise and weight loss, enhance metabolic control and reduce pro-inflammatory cytokine levels [1-13].

Conclusion

Interleukins significantly contribute to the development of both Type 1 and Type 2 diabetes. In Type 1 Diabetes (T1D), they facilitate the autoimmune death of pancreatic β-cells; however, in Type 2 Diabetes (T2D), they play a role in insulin resistance, chronic inflammation, and β-cell dysfunction. Although anti-inflammatory cytokines such as IL-10 have preventive advantages, pro-inflammatory interleukins include IL-1β, IL-6, IL-17, and IL-18 facilitate the onset and ramifications of disease. With a clearer understanding of the intricate role of interleukins in diabetes, enhanced diagnostic tools and targeted therapies for diabetes management may be devised.

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