



Immunological Consequences of Hyperglycemia and Cellular Dysregulation

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Abstract

Hyperglycemia, whether chronic (as in type 1 and type 2 diabetes mellitus), intermittent (as in stress-induced hyperglycemia), or physiological (as during pregnancy), significantly impacts immunological homeostasis. High glucose levels interfere with both innate and adaptive immune responses by several mechanisms, including as oxidative stress, non-enzymatic glycation of proteins, epigenetic reprogramming, abnormal intracellular signalling, and changes in metabolic pathways. These immunometabolic alterations compromise host defence mechanisms, hinder wound healing, aggravate inflammatory consequences, and lead to unfavourable clinical outcomes in infectious and inflammatory illnesses, particularly COVID-19. This review integrates emerging evidence regarding the modulation of immune cell function by hyperglycemia, elucidates the underlying molecular and cellular mechanisms, and examines potential therapeutic strategies and future research avenues aimed at restoring immune competence in hyperglycaemic states.

Keywords: Immunological, Hyperglycemia, Cellular, Dysregulation.

Introduction

Hyperglycemia is a key sign of metabolic diseases like diabetes mellitus. It is becoming more and more clear that it has a big effect on immunological homeostasis as well as its metabolic effects. In addition to the traditional perspective of hyperglycemia as a metabolic disorder characterised by diminished insulin secretion or insulin resistance, contemporary studies highlight its extensive impact on immunological regulation, inflammation, and host defence mechanisms. Immune cells, such as neutrophils, macrophages, dendritic cells, lymphocytes, and natural killer (NK) cells, function in close association with their metabolic milieu, depending on glucose and other metabolites to drive their activation, differentiation, and effector activities. So, changes in how much glucose is available or how it is used can directly change how immune cells act and respond [1].

When glucose levels stay high for a long time, like in poorly controlled diabetes mellitus or during acute hyperglycaemic crises, a chain reaction of immunological problems happens. Elevated glucose levels cause oxidative stress, facilitate non-enzymatic glycation of proteins, and produce advanced glycation end-products (AGEs). These AGEs enhance inflammatory signalling via receptor-mediated pathways, including the receptor for advanced glycation end-products (RAGE) [2]. These metabolic changes affect cellular immunity in a number of ways. For example, they make neutrophil chemotaxis and phagocytosis less effective, lower the bactericidal ability of macrophages, and change cytokine production to a pro-inflammatory but ineffectual profile. Adaptive immune processes are also disrupted: T lymphocytes show changed activation thresholds and weaker responses to proliferation, and B cell antibody generation and class switching may not work as they should. These alterations make it easier for infections to get into the body and may make chronic inflammatory conditions worse, which makes metabolic control even worse [3].

The immunological effects of hyperglycemia are clinically manifested by the heightened vulnerability of diabetic individuals to infections such as tuberculosis, candidiasis, and urinary tract infections, alongside the increased morbidity associated with viral infections like influenza and COVID-19. Hyperglycemia not only hinders pathogen elimination but also aggravates tissue injury by sustaining chronic inflammation and endothelial dysfunction. Moreover, the continuous

activation of inflammatory pathways contributes to the development of diabetes-related comorbidities, including atherosclerosis, nephropathy, and retinopathy, linking metabolic imbalance to immune-mediated tissue harm [4].

Due to the worldwide rise in diabetes rates and the frequent emergence of complicating infections or immune challenges like those linked to SARS-CoV-2, dengue, and bacterial sepsis—grasping the immunological disturbances occurring within the hyperglycaemic environment has become an immediate imperative. Immunometabolism is the increasing link between immunology and metabolism. It gives us important information on how metabolic signals affect immune responses and disease outcomes [5]. For clinicians, immunologists, and biomedical researchers, elucidating these molecular and cellular pathways not only enhances our comprehension of hyperglycemia's systemic effects but also facilitates targeted therapeutic interventions designed to restore immune competence and ameliorate patient outcomes in diabetes and associated metabolic disorders.

Disruption of Natural Immunity

Function of Neutrophils

Neutrophils, as the earliest responders of innate immunity, are especially susceptible to the metabolic disruptions linked to hyperglycemia. These cells are the first line of defence against pathogens that invade the body. They do this by mechanisms such as chemotaxis, phagocytosis, degranulation, oxidative burst, and the development of neutrophil extracellular traps (NETs). But when blood sugar levels are too high, these important functions are severely affected, leading to a chain reaction of problems with the innate immune system that makes people more likely to get infections that come back and are very serious [6]. High levels of glucose have been proven to stop neutrophil chemotaxis, which is the mechanism by which these cells move towards chemical cues at locations of infection or inflammation. This deficit is partially attributable to modified intracellular signalling pathways and cytoskeletal dysfunction caused by glucose toxicity and oxidative stress. Consequently, neutrophils demonstrate delayed or insufficient migration to infection sites, permitting bacteria to grow uncontested in the initial phases of infection. The phagocytic capacity of neutrophils—their ability to engulf and internalise microbes—is markedly diminished in hyperglycaemic circumstances [7]. Studies indicate that this phenomenon may result from diminished expression or functionality of surface receptors, including Fcγ receptors and complement receptors, which are crucial for pathogen identification and binding.

In addition to chemotaxis and phagocytosis, neutrophils' ability to kill microbes is also weakened when there is a lot of glucose present. The oxidative burst, an important way to kill bacteria that depends on making reactive oxygen species (ROS) such as superoxide anion and hydrogen peroxide, doesn't work as well in high-sugar conditions. The decrease in ROS production is due to the reduced function of NADPH oxidase, the enzyme complex that makes ROS, and to an imbalance in redox levels inside cells caused by too much glucose being broken down through the polyol and hexosamine pathways. As a result, neutrophils in people with high blood sugar are not as good at destroying bacteria or fungi that they have eaten, which can lead to infections that last longer and wounds that take longer to heal [8]. Hyperglycemia also has an effect on another important part of neutrophil function: the creation of neutrophil extracellular traps (NETs). NETs are web-like structures made up of decondensed chromatin and antimicrobial proteins that catch and kill infections that are outside of cells. In hyperglycaemic conditions, both the amount and quality of NET production are compromised. Too much glucose messes up chromatin remodelling, slows down histone citrullination by peptidylarginine deiminase 4 (PAD4), and changes how neutrophils use energy, all of which lead to NETosis problems. Not being able to use NETs properly not only makes it harder to keep pathogens contained, but it can also lead to long-term inflammation and tissue damage since microbes aren't completely cleared out [9].

These several problems, which include problems with chemotaxis and phagocytosis, lower oxidative killing, and NET formation, all work together to make early immunological defence systems much weaker. The effects are clinically apparent in diabetic and hyperglycaemic individuals, who often exhibit recurrent cutaneous, urinary, and respiratory infections, protracted wound healing, and an elevated risk of sepsis. Moreover, the hindered resolution of inflammation in these individuals exacerbates chronic tissue damage and intensifies diabetes consequences. Comprehending these neutrophil-specific deficiencies highlights the need of glycaemic regulation for maintaining metabolic equilibrium and safeguarding innate immune functionality, hence mitigating infection-related morbidity in patients with diabetes mellitus [10].

Macrophages, Monocytes, and Trained Immunity

Monocytes and macrophages, essential elements of the innate immune system, are crucial in pathogen identification, antigen presentation, and the coordination of inflammatory responses. In hyperglycaemic conditions, these cells experience significant functional and phenotypic alterations that endure subsequent to the normalisation of blood glucose levels. This persistent modification, frequently referred to as “hyperglycemic memory” or “trained immunity,” signifies a transformative advancement in our comprehension of how metabolic anomalies can impose enduring effects on the immune system. In contrast to conventional immunological memory mediated by lymphocytes, trained immunity in

monocytes and macrophages entails epigenetic reprogramming and metabolic reconfiguration, rendering these cells susceptible to heightened inflammatory responses following subsequent exposure to stimuli [11].

Experimental evidence from both *in vitro* and *in vivo* models has elucidated the molecular foundations of this phenomena. Human monocytes grown in high-glucose media or mice induced to be hyperglycaemic via streptozotocin treatment demonstrate persistent modifications in gene expression, chromatin accessibility, and histone modification, even after reverting to euglycemic circumstances. These cells exhibit increased production of proinflammatory cytokines, including tumour necrosis factor- α (TNF- α), interleukin-1 beta (IL-1 β), and interleukin-6 (IL-6), following subsequent activation with microbial ligands such as lipopolysaccharide (LPS). This excessive response is facilitated by the sustained activation of transcription factors, including NF- κ B and HIF-1 α , alongside epigenetic modifications such as histone 3 lysine 4 trimethylation (H3K4me3) at the promoters of inflammatory genes [12]. Hyperglycemia significantly influences macrophage polarisation, a mechanism via which macrophages assume specific functional modes in reaction to environmental stimuli. Macrophages typically differentiate into two principal phenotypes: M1 (classically activated, proinflammatory) and M2 (alternatively activated, anti-inflammatory or reparative). When blood sugar levels are high, the balance swings strongly towards the M1 phenotype. M1 macrophages, stimulated by factors like IFN- γ and LPS, secrete elevated amounts of TNF- α , IL-1 β , IL-6, and inducible nitric oxide synthase (iNOS), hence sustaining inflammation and oxidative stress. On the other hand, the M2 phenotype, which is marked by the release of IL-10, the activity of arginase-1, and the encouragement of tissue repair, is inhibited in a high-glucose environment. This uneven polarisation causes chronic low-grade inflammation, problems with the endothelium, and slow wound healing, which are all signs of diabetes [13]. Additionally, metabolic alterations in macrophages contribute to this proinflammatory bias. Hyperglycemia increases glycolytic flow, mitochondrial ROS generation, and the polyol and hexosamine pathways, all of which make inflammatory signalling stronger. The oxidative stress that follows harms cellular parts and boosts the production of proinflammatory genes through redox-sensitive transcriptional pathways. Over time, this leads to a vicious cycle of metabolic and immunological dysregulation, where chronic inflammation makes insulin signalling even worse and hyperglycemia even worse. This is a key part of the pathogenesis of metaflammation in diabetes. These changes have important effects on health. The enduring presence of a trained, proinflammatory macrophage phenotype is implicated in various diabetes-associated problems, such as atherosclerosis, nephropathy, neuropathy, and compromised wound healing. In atherosclerosis, M1-polarized macrophages invade vascular plaques, release matrix-degrading enzymes, and enhance plaque instability. In diabetic wounds, inadequate M2 activity similarly prolongs the resolution of inflammation and the regeneration of tissue [14]. In conclusion, hyperglycemia alters the programming of monocytes and macrophages via metabolic and epigenetic pathways, resulting in a persistent proinflammatory condition that endures long after normal glucose levels are restored. This hyperglycaemic memory highlights the enduring effects of metabolic dysregulation on innate immunity and offers a persuasive rationale for the persistence of diabetic problems despite enhanced glycaemic control. Comprehending these pathways not only elucidates the immunopathology of diabetes but also underscores prospective treatment targets such as epigenetic modulators and metabolic regulators—to alleviate inflammation and re-establish immunological homeostasis in hyperglycaemic people.

The Complement System, Barrier Function, and Innate Immune Signalling

Hyperglycemia also weakens the complement cascade and the defences of the epithelial barrier. Non-enzymatic glycation of complement proteins disrupts opsonisation and the complement-mediated elimination of microorganisms. Furthermore, hyperglycemia increases the expression of pattern recognition receptors, especially Toll-like receptors (TLRs), which causes stronger inflammatory responses when pathogens are present. These cumulative effects disrupt the homeostasis of the innate immune system, rendering the host more susceptible to infections and inflammatory consequences [15].

Damage to Adaptive Immunity

T cells exhibit several dysfunctions in hyperglycemia. Long-term exposure to high glucose levels interferes with calcium signalling in T cells by reducing the calcium reserves in the endoplasmic reticulum (ER) through the downregulation of sarco/endoplasmic reticulum Ca²⁺-ATPase (SERCA) pumps. This leads to impaired T cell receptor (TCR)-mediated activation and signalling pathways. Moreover, hyperglycemia negatively impacts memory CD8⁺ T lymphocytes by diminishing their reactivity to viral antigens and hindering cytokine production—effects that seem to stem from glucose toxicity rather than insulin resistance. In infections like COVID-19, patients with poorly controlled type 2 diabetes often have lymphopenia, which is when their CD3⁺, CD4⁺, and CD8⁺ T cell counts go down and their natural killer (NK) cell function goes down. This is usually seen with higher levels of inflammatory markers like interleukin-6 (IL-6) and C-reactive protein (CRP).

B Cells and Antibody Responses [16]

Hyperglycemia, however less thoroughly examined, adversely affects B cell functionality and humoral immunity. Chronic elevated glucose levels may hinder antibody synthesis and diminish vaccination efficacy. In certain situations, hyperglycemia could facilitate the development of immune complexes, hence exacerbating pathogenic inflammation seen

in diabetic nephropathy and other related problems. The diminished efficacy of B cell-mediated immunity during hyperglycaemic stress partially elucidates the heightened susceptibility of diabetic individuals to infections and the inadequate effectiveness of specific vaccinations.[3]

Mechanisms that cause immune dysregulation

Oxidative Stress and Mitochondrial Dysfunction

Oxidative stress is a big reason why hyperglycemia weakens the immune system. Increased glucose levels boost the production of reactive oxygen species (ROS), which causes the mitochondrial membrane to become hyperpolarised and oxidative damage. Excessive ROS in immune cells interferes with intracellular signalling pathways, encourages apoptosis, and causes functional exhaustion. For instance, macrophages in high-glucose settings exhibit elevated intracellular ROS accumulation and reduced phagocytic activity. These redox abnormalities are fundamental to the pathogenesis of immune dysfunction and end-organ damage in diabetes [6].

Metabolic Reprogramming of Immune Cells

The metabolism of immune cells is closely connected to their activity. Hyperglycemia disrupts glycolytic and oxidative phosphorylation pathways, resulting in atypical metabolic reprogramming in macrophages, T cells, and NK cells. These changes in metabolism make it harder for cells to activate, grow, and release cytokines, which makes the immune system even less effective. The changed energy metabolism makes the immune system less effective and keeps inflammation going.

Changes in epigenetics and memory of high blood sugar [8]

Epigenetic pathways are crucial to the facilitation of chronic immunological dysfunction in hyperglycemia. High glucose levels cause long-lasting alterations in DNA methylation and histone modifications that keep the body in a proinflammatory state even after blood sugar levels return to normal. This "hyperglycaemic memory" explains why complications from diabetes and problems with the immune system often stay the same even after blood sugar levels are better controlled.

Stress in the endoplasmic reticulum and calcium balance

Hyperglycemia interferes with the function of the endoplasmic reticulum (ER), resulting in calcium dysregulation and the activation of the unfolded protein response (UPR). The resulting ER stress disrupts protein folding, signalling, and cytokine production in immune cells, ultimately culminating in death or functional exhaustion. These biological stressors establish a molecular connection between metabolic imbalance and immunological dysregulation [18].

Implications for Clinical Practice

People who have chronic or acute hyperglycemia are more likely to get infections from bacteria, viruses, and fungi. Impaired neutrophil and macrophage activity, along with lymphocyte dysfunction, leads to delayed pathogen clearance and exacerbated disease progression. The COVID-19 pandemic highlighted this correlation, as diabetes individuals with inadequate glycaemic management faced markedly increased morbidity and fatality rates. Bad Responses to Vaccines and Weak Immune Surveillance Impaired Memory T cell and B cell responses result in diminished vaccination effectiveness in hyperglycaemic patients. Moreover, hyperglycemia-induced immune suppression may hinder cancer immunosurveillance, as recent research indicates that increased glucose levels promote tumour immune evasion and attenuate anti-tumor immunity.

Long-term inflammation and problems that come with diabetes [18]

Chronic low-grade inflammation caused by immunological dysregulation makes diabetes consequences like atherosclerosis, nephropathy, neuropathy, and retinopathy worse. Notably, epigenetic reprogramming maintains inflammatory pathways even when glycaemic control is established, underscoring the enduring effects of hyperglycaemic immune activation.

Things to think about for treatment and management Consistent glycaemic management has been linked to better immune function and fewer infections [19]. In addition to glucose-lowering medication, interventions aimed at oxidative stress, endoplasmic reticulum stress, or metabolic reprogramming may have supplementary advantages. In critical illness, managing stress-induced hyperglycemia using insulin therapy has demonstrated efficacy in enhancing outcomes, in part by re-establishing immunological equilibrium. Even though there have been great steps forward, there are still crucial gaps in our understanding of the exact ways that hyperglycemia and immunological dysfunction are connected:

1. Need for Interventional Studies: The majority of human data are observational. Longitudinal clinical trials are necessary to ascertain the efficacy and extent to which the restoration of normoglycemia mitigates immunological deficiencies.
2. Patient Heterogeneity: Differences in age, length of illness, other health problems, and race make it harder to compare groups [19].

3. Standardisation of Immune Assays: It is not currently common for clinical practice to use reliable, reproducible tests to measure NETs, macrophage polarisation, and epigenetic or metabolic markers.
4. Thresholds of Glucose Toxicity: Additional research is necessary to delineate the doses, duration, and variations of glucose exposure needed to elicit particular immunological deficiencies.
5. Adjunctive Therapeutic Targets: In addition to glucose control, medicines designed to modulate oxidative stress, mitochondrial function, and epigenetic regulation signify promising avenues for alleviating hyperglycemia-induced immunological dysfunction.[20]

Conclusion

Hyperglycemia significantly disturbs immunological homeostasis by compromising both innate and adaptive immune responses via oxidative stress, metabolic reprogramming, epigenetic alterations, and endoplasmic reticulum dysfunction. These immunological abnormalities not only heighten vulnerability to infection but also sustain chronic inflammation and protract long-term diabetes consequences. Combining metabolic control with tailored immunomodulatory techniques is an important step towards better clinical care for people with diabetes and hyperglycemia. Ongoing investigation into the molecular and cellular foundations of hyperglycaemic immune dysregulation will be essential for the advancement of novel treatment strategies to address this escalating global health issue.

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