Increased infection risk in diabetes mellitus: the interplay of hyperglycaemia and immune system Impairment

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[Received: October 2024 / Revised: November 2024 / Accepted: November 2024]

Abstract: People with diabetes, particularly those with poorly controlled blood glucose levels, exhibit a 1.5 to 4-fold increased susceptibility to bacterial infections. This heightened vulnerability is primarily attributed to immune system dysfunctions exacerbated by hyperglycaemia. Impaired neutrophil and macrophage function, altered T-cell responses, and compromised skin and mucosal barriers all contribute to an impaired immune defence, increasing both the frequency and severity of infections. Hyperglycaemia directly affects neutrophil functions such as migration, phagocytosis, and apoptosis, while also promoting excessive neutrophil extracellular trap (NET) formation. Macrophages in diabetes tend to favour a pro-inflammatory M1 phenotype, impairing their ability to effectively clear pathogens. Additionally, T-cell dysfunction and altered antibody responses hinder adaptive immunity. Furthermore, the hyperglycaemic environment supports bacterial growth and enhances the virulence of pathogens such as *Staphylococcus aureus* and Group B *Streptococcus*, which thrive in this altered metabolic state. These bacteria produce various virulence factors that contribute to chronic infections and worsened outcomes. Collectively, the interplay of immune dysfunction and hyperglycaemia leads to an increased risk of persistent and severe infections in individuals with diabetes, necessitating a deeper understanding of the underlying mechanisms to improve clinical outcomes.

Keywords: diabetes mellitus, infection, hyperglycaemia

1. Introduction

People with diabetes, particularly those with poorly controlled blood glucose levels, have a 1.5 to 4-fold increased susceptibility to bacterial infections due to several immunological and physiological factors. Not only that the infections in people with diabetes are more frequent, but they tend to last longer and have worse outcomes (Singh *et al.* 2020). However simplistic, the paradigm of too-much-sugar-not-enough-blood-flow can be considered the underlying principle explaining much of this phenomenon. This, however, may not necessarily be related to diabetes as such, but also to co-morbidities and long-term complications of this complex disease (Akinosoglou *et al.* 2021). Still, extensive research body shows that diabetes adversely affects both innate and adaptive immunity (Donath *et al.* 2019). In the following sections, we will describe the main elements of immune system affected by diabetes (or, more specifically, hyperglycaemia), as well as the interaction with the offending pathogens that may make them more harmful than in otherwise healthy people.

2. Impaired neutrophil function

Neutrophils are essential for the body's first line of defence against infections (Liew & Kubes, 2019), initially (trans)migrating to the site of infection/inflammation, performing phagocytosis, releasing the content of their granules and initiating the synthesis of reactive oxygen species (ROS). After performing those functions, they die and their remnants are cleared from infection site

(Tu *et al.* 2024). In people with diabetes, there are impairments of neutrophil function at each of these steps. Considering that neutrophils solely rely on glucose metabolism (DeBerardinis *et al.* 2007), the effects of hyperglycaemia can be ascribed to the generation of advanced glycation end products (AGE) (Tian *et al.* 2016) by non-enzymatic glycation of proteins (Chen *et al.* 2024).

2.1. Reduced transendothelial migration and chemotaxis

In people with diabetes, neutrophils have a reduced ability to migrate through the endothelial membrane and reach the extracellular space. This is attributable to the activation of RAGE on neutrophils, on one hand (Collison *et al.* 2002), as well as blunted up-regulation of vascular cell adhesion molecule 1 and intercellular adhesion molecule 1, factors necessary for leucocyte transmigration into surrounding extracellular space (Andreasen *et al.* 2010), on the other. Further, after initial contradictory findings in the early research on neutrophil migration in diabetic patients, it is considered that neutrophils in people with diabetes also exhibit impaired chemotaxis, meaning they are less able to migrate toward infection sites (Mowat & Baum, 1971). This reduced migration can result in slower responses to bacterial infections (Delamaire *et al.* 1997).

2.2. Decreased phagocytosis and killing

The ability of neutrophils to engulf and kill bacteria is diminished in people with diabetes, particularly due to reduced C3-mediated opsonisation (Hair *et al.* 2012) and defects in oxidative burst and enzyme function (Davidson *et al.* 1984). Hyperglycemia impairs these functions of neutrophils, leading to suboptimal pathogen clearance (Lin *et al.* 2006; Yano *et al.* 2012).

2.3. Reduced apoptosis

Among various modalities of neutrophil cell death (the others being NETosis, pyroptosis, necroptosis and ferroptosis), apoptosis normally predominates and, in doing so, serves to produce immunosuppressive signals to restrict further inflammation and tissue damage (Tu *et al.* 2024). Reduced apoptosis in people with diabetes was associated with impaired clearance of neutrophils by macrophages, both *in vitro* and *in vivo*, prolonged production of the proinflammatory cytokine tumour necrosis factor alpha by neutrophils from diabetic mice (Hanses *et al.* 2011), as well as down-regulation of caspases 3 and 9, as the key enzymes involved (Manosudprasit *et al.* 2017). These findings suggest that defects in neutrophil apoptosis may play a role in the chronic inflammation and the inability to eliminate pathogens in diabetic patients (Hanses *et al.* 2011; Javid *et al.* 2016).

2.4. Increased NETosis

Strictly speaking, NETosis does not necessarily need to lead to actual cell death, i.e. it can be lytic/suicidal and non-lytic/vital (H. Wang *et al.* 2024). Formed by expulsion of decondensed neutrophil nuclear chromatin from activated neutrophils, these extracellular filamentous structures have positive roles in restricting infection that go beyond the mechanistic ones (i.e. trapping pathogens, as the name implies), occurring via altering pathogen morphology, modifying virulence factors and disrupting bacterial biofilms. The neutrophils in diabetic patients are primed for increased NETosis (Wong *et al.* 2015) via the binding of AGEs to their receptor (RAGE) and increased expression of neutrophil peptidyl arginine deiminase 4 (PAD4). RAGE is a transmembrane pattern recognition receptor, having various ligands, including AGEs. Activation of RAGE leads to downstream signalling mechanisms that induce neutrophil activation and promote the formation of NETs. In forming NETs, the loss of dense chromatin structure is induced by PAD4 (Zhu *et al.* 2023). PAD4 is a calcium-specific enzyme which mediates histone hypercitrullination and consequent chromatin depolymerisation (Thiam *et al.* 2020). PAD4 expression is increased in neutrophils of patients with both T1D and T2D, making them more susceptible to NET activation (Giovenzana *et al.* 2022). The detrimental effects of this process may not be directly associated with reduced ability to combat infection, but to protracted wound healing, providing access to pathogens via disturbed tissue barrier.

3. Impaired macrophage function

Macrophages play a key role in immune defence, having three main functions: phagocytosis, exogenous antigen presentation and immune regulation (Luo *et al.* 2024). However, their functions are also compromised in diabetes.

Mimicking a Th1/Th2 duality in T helper lymphocytes, macrophages can be divided into M1 ("classically activated") and M2 ("alternatively activated") phenotypes (Luo *et al.* 2024). The caveat here is that, in reality, macrophages exist on a spectrum, with M1/M2 dichotomy being a useful simplification. Either way, interferon-α (INF-α), IL-12 and IL-23 polarise resting macrophages (M0) into M1-like macrophages (M1), whereas IL-4 and IL-10 stimulate the development of M2-like phenotype. The former are believed to have pro-inflammatory, whereas the latter are believed to have wound-healing ability. In diabetes, the macrophages tend to polarise toward M1 phenotype (Sun *et al.* 2024), which, in principle, should increase the ability of macrophages in diabetic patients to protect them against bacteria. However, similar to neutrophil

dysfunction, hyperglycaemia disrupts macrophage phagocytic (Q. Wang *et al.* 2017), bactericidal (Pavlou *et al.* 2018), as well as antigen-presenting function (Nie *et al.* 2021). With regards to reduced phagocytic function, its initiation is compromised by reduced function and/or expression of complement receptor 3 (CR3) and Fc-gamma receptor (FcγRs) (Restrepo *et al.* 2014). Whether this is attributable to intrinsic reprogramming of cells or the noxious effects of the local hyperglycaemic environment remains a paradox that is still to be resolved.

4. Altered T-cell function

T cells, which are essential for adaptive immunity, also exhibit dysfunction in people with diabetes. The mechanisms by which this occurs are, to a certain extent, similar to those impeding the function of innate immunity. Namely, reduced expression of adhesion molecules such as intercellular adhesion molecules (ICAM) and E selectin on endothelial cells impairs the recruitment of cytotoxic CD8+ T lymphocytes to infection sites (Kumar *et al.* 2014) Further, reduced phagocytosis and cytokine secretion by innate immunity cells and delayed recruitment of antigen-presenting cells (APCs) lead to delayed activation of adaptive immunity, allowing the replication of pathogens to continue (Pari *et al.* 2023). Again, the effect seems to be mediated by hyperglycaemia, as exemplified by the reduced function of memory CD8+ T-cells upon viral re-challenge (Kavazović *et al.* 2022). Activation of cellular immunity is supported and amplified by CD8+ T cells, which produce cytokines that attract other component of adaptive immune system. With regards to adaptive immunity, glycation negatively affects the function of antibodies themselves, further contributing to the state of immunodeficiency in people with diabetes (Fournet *et al.* 2018)

5. Impaired skin and mucosal barriers

Diabetes can compromise the integrity of the skin and mucosal barriers, further increasing infection risk. The main factors contributing to the development of diabetic foot ulcers are peripheral arterial disease, peripheral neuropathy, bacterial infection, and immune cell dysfunction (Deng *et al.* 2023). Of those, peripheral angiopathy, manifested by accelerated atherosclerosis of distal arteries in lower limbs are the primary culprit. It is nevertheless associated with the loss of protective positioning and unawareness of pain associated with it, combined with skin dryness occurring as a result of sensory and autonomic neuropathy, respectively. Once initiated, the process is aggravated by the consequences of immune system dysfunction described above, which results in restricted ability to restrain the infection and impaired wound healing.

6. Hyperglycaemia-mediated increase in bacterial growth and virulence

Switching to the other side, hyperglycaemia is literally a fertile ground for bacteria typical of infections in people with diabetes – the worse the glycaemic control is, the more frequent are the bacterial infection in various sites (Hine *et al.* 2017), e.g. bronchitis, pneumonia, skin and soft tissue infections, urinary tract infections, and genital and perineal infections. Both humans and bacteria utilise glucose, metabolising it via different pathways (O'Connor *et al.* 2024).

A remarkable adaptability of *Staphylococcus aureus* to various environments within human body makes it one of the most important pathogens for both surface (skin and soft tissue infections – SSTIs) and confined infections (e.g. osteomyelitis) in people with diabetes. It thrives in hyperglycaemic environment, which not only provides abundant source of energy, but also stimulates the production of its various virulence factors. In relation to that, production of reactive oxygen species (ROS) is one of the defence mechanisms utilised by immune system. However, hyperglycaemia stimulates the expression of *S. aureus* superoxide dismutase which allows it to detoxify its environment, allowing it to survive (Butrico *et al.* 2023).

Another *S. aureus* virulence factor increased in hyperglycaemic environment is caseinolytic protease (Clp), a family of bacterial proteases involved in the proteolytic elimination of misfolded or aggregated proteins (Aljghami *et al.* 2022), the expression of which contributes to worse outcomes of *S. aureus* infections (Jacquet *et al.* 2019; Kim *et al.* 2020).

Another important concept in understanding the defence mechanisms against bacteria is nutritional immunity – the ability of a host to sequester and starve invading pathogens of trace minerals and nutrients (Hennigar & McClung, 2016). The opposite occurs in diabetes, with hyperglycaemia providing a source of energy, which, when combined with metabolic adaptations to better utilise it (e.g. via expression of glucose transporters (Vitko *et al.* 2016)) and the reduced utilisation of glucose by immune cells described above, creates favourable conditions for bacterial growth.

Biofilms are aggregates of microorganisms in which cells are frequently embedded in a self-produced matrix of extracellular polymeric substances (EPS) that are adherent to each other and/or a surface (Flemming *et al.* 2016), allowing for social and physical interactions, conferring antibiotic and immunologic resistance. Aureolysin (Aur) is one of the major virulence factor in *S. aureus*, as it is crucial for its biofilm

formation and its expression is increased in hyperglycaemic environment (Wei *et al.* 2022).

To regulate collective behaviour in transitioning from individual life to a highly organised three-dimensional structure of a biofilm, bacteria utilise quorum sensing, a mode of communication activated upon reaching a certain cell density, which allows coordinated gene expression in bacteria (Mitra, 2024). In *S. aureus*, the process is controlled by *agr* locus, which is a quorum-sensing regulator. Importantly, hyperglycaemia stimulates its activity, facilitating the formation of a biofilm-like aggregate that is able to disseminate to peripheral organs (Thurlow *et al.* 2020).

People with diabetes are particularly prone to UTIs and Group B Streptococcus is a prominent causative agent (Geerlings *et al.* 2014). In healthy people, lack of nutrients, high concentration of urea, acidification and induction of antimicrobial peptide production if infection occurs serve as protective factors. Glycosuria, however, is shown to facilitate GBS infection via increased GBS adherence to human bladder epithelial cell line, expression of corresponding *PI2a* fimbrial gene, antimicrobial peptide LL-37 resistance, GBS haemolytic ability and expression of genes encoding pore-forming toxins (John *et al.* 2021).

7. Conclusion

People with diabetes are at increased risk of bacterial infections due to a combination of factors, including impaired neutrophil and macrophage function, altered T-cell responses, the effects of hyperglycaemia on immune cells, and defects in skin and mucosal barriers. Together, these factors hinder the immune system's ability to fight off infections. In addition, hyperglycaemic environment itself is conducive to growth and reproduction of bacteria, as well as to the increase of their virulence.

Funding: Not applicable.
Informed Consent Statement: Not applicable.
Data Availability Statement: Not applicable.
Conflicts of Interest: The authors declare no conflicts of interest.

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