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REVIEW ARTICLE

Type 2 Diabetes and its Impact on the Immune System

Afiat Berbudi[1,2,*], Nofri Rahmadika[2], Adi Imam Tjahjadi[2,3] and Rovina Ruslami[2,4]

[1]*Department of Biomedical Sciences, Parasitology Division, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia;* [2]*Infectious Disease Research Center, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia;* [3]*Department of Biomedical Sciences, Microbiology Division, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia;* [4]*Department of Biomedical Sciences, Pharmacology and Therapy Division, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia*

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Abstract: ***Introduction*:** Type 2 Diabetes (T2D) is a major health problem worldwide. This metabolic disease is indicated by high blood glucose levels due to insufficient insulin production by the pancreas. An inflammatory response occurs as a result of the immune response to high blood glucose levels as well as the presence of inflammatory mediators produced by adipocytes and macrophages in fat tissue. This low and chronic inflammation damages the pancreatic beta cells and leads to insufficient insulin production, which results in hyperglycemia.

Hyperglycemia in diabetes is thought to cause dysfunction of the immune response, which fails to control the spread of invading pathogens in diabetic subjects. Therefore, diabetic subjects are known to more susceptible to infections. The increased prevalence of T2D will increase the incidence of infectious diseases and related comorbidities.

***Objective*:** This review provides an overview of the immunological aspect of T2D and the possible mechanisms that result in increased infections in diabetics.

***Conclusion*:** A better understanding of how immune dysfunctions occur during hyperglycemia can lead to novel treatments and preventions for infectious diseases and T2D comorbidities, thus improving the outcome of infectious disease treatment in T2D patients.

Keywords: Type 2 diabetes, hyperglycemia, immune dysfunction, comorbidity, infection, treatment outcome.

1. INTRODUCTION

Diabetes is a tremendous health problem worldwide. It is caused by chronic high glucose levels in the blood as a result of the incapability of beta cells (β cells) in the pancreas to produce adequate insulin or ineffective insulin utilization by cells in the body [1]. In general, diabetes consists of two major types, type 1 diabetes (T1D) and type 2 diabetes (T2D).

As a chronic condition, diabetes tends to increase the risk of several other diseases caused by macrovascular and microvascular damage, and it has negative impacts on several organs, such as the brain, kidney, heart, and eyes [2]. In addition, diabetic patients are more susceptible to infection. Several studies have reported the increased risk of lower respiratory tract infections such as pulmonary tuberculosis [3-6] and pneumonia [7-10], urinary tract infections [11, 12], and skin and soft tissue infections [13-15] in people with diabetes. The outcome of infection treatment in patients who suffer from diabetes tends to be poor [11, 16-20]. Infection in patients with diabetes increases the economic burden on the patient due to the high cost of care, the length of treatment, and related complications [8, 10].

In 2016, the International Diabetes Federation reported around 425 million people living with diabetes worldwide [21]. This number is predicted to increase in both developed and developing countries. Without proper management and control, the number of diabetic patients is estimated to reach 629 million people by 2045. In 2017, around 5 million people died worldwide because of diabetes, and 850 million USD were spent on diabetic care [21]. The increasing number of diabetics in low and middle-income countries, especially those with tropical climates where the prevalence of the communicable disease is high, will naturally lead to an increase in the incidence of people with infectious diseases and related financial burdens.

2. TYPE 2 DIABETES

Almost 90% of all diabetes cases are T2D [22] due to both insufficient insulin action (insulin resistance) and im-

*Address correspondence to this author at the Department of Biomedical Sciences, Faculty of Medicine, Universitas Padjadjaran, Jl. Raya Bandung Sumedang Km. 21, 45363, West Java, Indonesia;
E-mail: a.berbudi@unpad.ac.id

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paired insulin production by islet β cells in the pancreas. This condition results in increased glucose levels in the blood. Insulin resistance in T2D is associated with obesity, physical inactivity, and ageing [1, 23]. The pancreatic islets increase their cell mass to produce more insulin to compensate for insulin resistance [24]. T2D is developed when this effort fails to compensate for insulin resistance [24]. More than half of T2D patients require insulin therapy due to the dysfunction of pancreatic β cells after 10 years of insulin resistance [25, 26]. Long term chronic insulin resistance in T2D leads to several consequences, including macrovascular complications such as atherosclerosis as well as microvascular complications such as nephropathy, neuropathy, and retinopathy [24].

3. INSULIN RESISTANCE AND HYPERGLYCEMIA

Increased blood glucose levels after eating induce insulin production and secretion by islet β cells into the blood. The binding of insulin and insulin receptors in cell membranes induces glucose transporter translocation to the cell membrane and increases glucose uptake by the cells, resulting in decreased glucose levels in the blood. Failure of the pancreas to produce sufficient insulin, improper insulin action, or both, results in hyperglycemia. This is associated with damage and failure of various organs and tissues in the long term.

Elevated levels of tumor necrosis factor (TNF)-α in adipose tissue of obese mice were shown to be associated with insulin resistance in those mice [27]. Furthermore, interleukin (IL)-6, C-reactive protein, plasminogen activator inhibitor, and other inflammation mediators were elevated in the plasma of obese mice [28, 29]. TNF-α, free fatty acids, diacylglyceride, ceramide, reactive oxygen species (ROS), hypoxia activate Iκβα kinase β (IKKβ), and c-Jun N-terminal kinase I (JNK1) in adipose tissue and the liver [30] induce insulin receptor substrate (IRS-1) inhibition [31-33] (Fig. **1**). Moreover, TNF-α also leads to insulin resistance *via* inhibition of peroxisome proliferator-activated receptor-gamma function [34, 35].

Insulin binds with its receptor, resulting in tyrosine phosphorylation at IRS-1 and -2. Insulin signaling inhibition occurs due to serine phosphorylation of IRS substrates by IKKβ and JNK1, which are the mediators for stress and inflammatory responses. Furthermore, JNK1 and IKKβ induce the transcriptional activation of various genes related to inflammatory response, resulting in insulin resistance. In addition, the influx of free fatty acids and glucose during obesity also activates JNK1 and IKKβ signaling pathways.

Activated IKKβ phosphorylates Iκβα, promotes ubiquitination and degradation of Iκβα in proteasome, and results in NFκβ translocation into the nucleus to induce transcription of various genes involved in inflammation and other

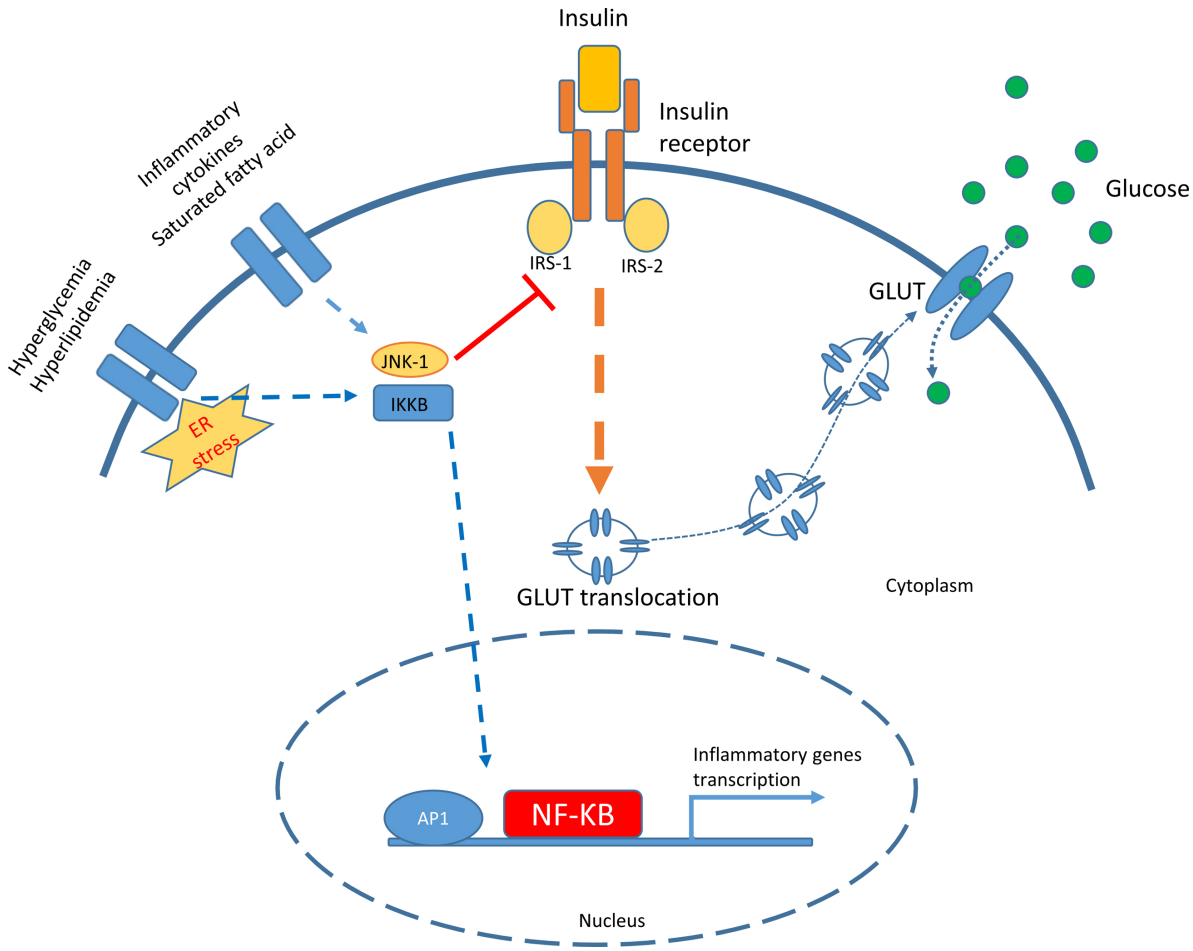

Fig. (1). Molecular mechanism of insulin resistance due to inflammation [73].

immune responses. IKKβ also inhibits insulin signaling pathways *via* phosphorylation of IRS-1 serine residues in adipocytes [32, 36]. JNK activation induced by TNF-α inhibits insulin signaling by phosphorylation of IRS-1 [33, 37] (Fig. **1**).

In addition, insulin signaling inhibition can be produced *via* the janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway. Tyrosine phosphorylation of STAT by JAK kinases induces dimerization and translocation of STAT to the nucleus [38] and results in IRS-1 phosphorylation at Ser636 and Ser307 [39]. This inhibition of insulin signaling eventually impairs the Glut-4 translocation to cell membranes and leads to hyperglycemia.

4. PANCREATIC B-CELL APOPTOSIS AND INSULIN DEFICIENCY

The inflammatory immune response due to adipocyte apoptosis and macrophage infiltration is further enhanced by the crosstalk between pathogenic CD4+ and CD8+ T cells and CD11c+ M1 macrophages in obese adipose tissue, which exacerbates adipose tissue inflammation and peripheral insulin resistance [40, 41]. Consequently, pancreatic β cells compensate for peripheral insulin resistance through increased insulin production, resulting in a hyperinsulinemia [40, 42]. However, in the long term, chronic progressive insulin resistance eventually causes β-cell exhaustion and insulin deficiency. In addition, the accumulation of free fatty acids, amyloids, and inflammatory cytokines induces β-cell apoptosis, leading to sustained hyperglycemia and T2D [24, 43, 44].

5. HYPERGLYCEMIA AND SUSCEPTIBILITY TO INFECTION

Normally, the human body uses amazing mechanisms to protect itself from invasion by millions of bacteria, viruses, fungi, toxins, and parasites. Under normal circumstances, it is difficult for pathogens to penetrate this defense system, but several conditions and defects lead to the immune system not working properly. For example, when there is an open wound, bacteria can easily enter and cause an infection, as seen by the presence of pus. While defending against pathogenic invasion, our defense systems are facilitated by natural barriers (for example, intact skin and mucosal surfaces) as well as the production of reactive oxygen species, cytokines, and chemokines.

Unfortunately, in diabetes, the host's immune response is disrupted. In addition to the risk of natural barrier damage due to neuropathy, T2D can also affect cellular immunity. This is caused by insulin deficiency and hyperglycemia [45]. According to the American Diabetes Association, infections are an important issue for individuals with diabetes due to the immune system's failure to fight off invading pathogens [46]. Numerous studies have been conducted to determine the diabetes-related mechanisms that impair the host's defense against pathogens. These mechanisms include suppression of cytokine production, defects in phagocytosis, dysfunction of immune cells, and failure to kill microbials.

5.1. Impairment of Cytokine Production

An *in vitro* study demonstrated that peripheral blood mononuclear cells (PBMCs) and isolated monocytes of individuals with T1D and T2D secreted less interleukin 1 beta (IL-1β) compared to controls after stimulation with lipopolysaccharides (LPS) [47]. In another study, monocytes isolated from PBMCs of T1D subjects secreted lower IL-1 and IL-6 compared to healthy donors [48]. PBMCs collected from non-diabetic subjects that were stimulated by anti-CD3 antibodies and exposed to high glucose levels showed suppression of cytokines IL-2, IL-6, and IL-10 production [49]. Since IL-6 is important for protection against pathogens and for adaptive immune response by inducing antibody production and effector T-cell development [50], these studies revealed that inhibition of those cytokines in hyperglycemia may suppress the immune response against invading pathogens [49]. Accordingly, Spindler *et al*. reported that PBMCs obtained from healthy subjects and induced with dextrose octreotide demonstrated reduced IL-6 and IL-17A expression, especially in CD14+ and CD16+ intermediate monocytes, indicating impaired immune responses due to high blood glucose levels [51]. Another study conducted by Price *et al*. reported that increased glycation leads to a loss of IL-10 secretion by myeloid cells [52]. Furthermore, they also demonstrated reduced production of interferon gamma (IFN-γ) and TNF-α by T cells. In addition, the IL-22 cytokine was observed to be lower in obese leptin-receptor-deficient (*db/db*) mice and high fat diet-induced hyperglycemic mice compared to normal mice [53]. A recent study by Hu *et al*. reported suppression of type 1 IFN production in PBMC cultured with a high glucose medium and stimulated by poly I:C [54]. A study by Tan *et al*. demonstrated lower production of IL-12 and IFNγ in PBMC cultures from diabetic subjects following *Burkholderia pseudomallei* infection compared to PBMCs from healthy donors [55]. Furthermore, intracellular bacterial load was higher in PBMCs of diabetic subjects compared to healthy controls, suggesting that hyperglycemia impairs the host's defense against invading bacteria. The addition of recombinant IL-12 and IFNγ significantly reduced bacterial load in PBMCs of diabetic subjects, indicating that low production of IL-12 and IFNγ in diabetes impairs immune cells' capacity to control bacterial growth during infection. Therefore, hyperglycemia in diabetics is thought to attenuate macrophage and other leukocyte activity in eliminating pathogens [45].

Unlike the effect of hyperglycemia on immune cell activity in T2D, the impact of insulin deficiency in T2D on macrophage activity against pathogens has not been widely studied. A study regarding the impact of insulin deficiency on immune response by Tessaro *et al*. demonstrated that the administration of insulin into bone marrow-derived macrophages isolated from diabetic mice significantly increased the production of TNF-α and IL-6 after LPS stimulation [45]. Another study using rats revealed that a lack of insulin resulted in a disruption in phagocytosis of alveolar macrophages as well as cytokine release, both of which were restored after insulin intervention [56]. Since TNF-α and IL-6 play a role in leukocyte function against pathogens, this result indicated that the administration of exogenous insulin in diabetes may enhance immune cell activity to protect against pathogens.

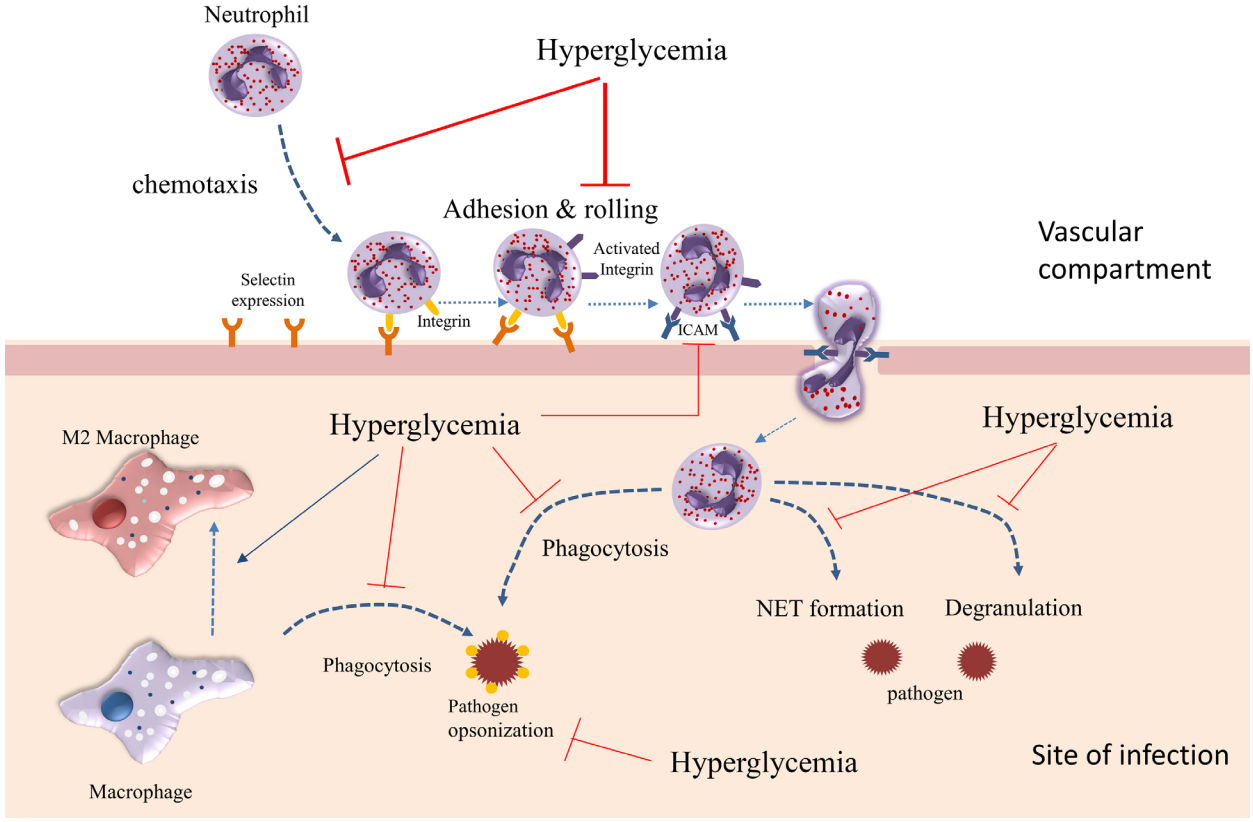

Fig. (2). Impairment in immune response mechanisms during hyperglycemia [74].

5.2. Leukocyte Recruitment Inhibition

Infiltration of CD45+ leukocytes and CD8+T cells was significantly reduced in the brains of *db/db* mice infected with West Nile virus-associated encephalitis [57]. This study revealed that the impairment of recruitment of CD45+ leukocytes and CD8+T cells was correlated with attenuated expression of cell adhesion molecules (CAMs) such as E-selectin and intracellular adhesion molecule (ICAM)-1 (Fig. **2**). This defect in leukocyte recruitment was also demonstrated by Martinez *et al*. in their *in vivo* study using streptozotocin-induced diabetic mice infected by *Klebsiella pneumoniae* [58]. Lower numbers of granulocytes were observed in the alveolar airspace of the diabetic mice. They also reported reduced cytokine production—such as CXCL1, CXCL2, IL-1β, and TNF-α—in lung tissue following lung exposure to *K. pneumoniae* LPS.

5.3. Defects in Pathogen Recognition

Martinez *et al*. also reported that expression of Toll-like receptor (TLR)-2 and Toll/IL-1R domain-containing adaptor protein (TIRAP), which play role in pathogen recognition, was reduced in diabetic mice [58]. However, several studies have shown increased expression of TLRs in neutrophils and monocytes isolated from people with diabetes [17, 59, 60]. An analysis by Gupta *et al*. revealed that TLR expression was lower in diabetic subjects with complications and poor glycemic control but elevated in patients with well-controlled hyperglycemia without complications [60]. Hence, the impact of hyperglycemia on TLR expression and related immunity in diabetic subjects remains unclear.

5.4. Neutrophil Dysfunction

ROS production of isolated neutrophils from T2D tuberculosis patients following phorbol 12-myristate 13-acetate stimulation was reduced. This defect in ROS production was associated with increased levels of resistin in T2D patients' serum [61]. In a comparable study, Perner *et al.* reported suppression of superoxide (O_2^-) in isolated neutrophils from healthy subjects when exposed to a high glucose concentration medium. This impairment occurred *via* glucose-6- phosphate dehydrogenase (G6PD) inhibition, which disturbed the formation of nicotinamide adenine dinucleotide phosphate [62].

Stegenga *et al.* induced hyperglycemia in the blood of healthy individuals and then challenged it with bacterial wall components; the blood showed a lower neutrophil degranulation [63]. Neutrophil dysfunction in phagoes *S. aureus* was also demonstrated due to C3-mediated complement inhibition caused by hyperglycemia [64]. In line with those studies, Joshi *et al.* reported that neutrophil action to produce neutrophil extracellular traps (NETs) was suppressed during hyperglycemia, leading to susceptibility to infections [65]. All of these studies revealed that hyperglycemia causes neutrophil dysfunction, including defects in ROS production [61], neutrophil degranulation impairment [63], inhibition of immunoglobulin-mediated opsonization [17], decreased phagocytosis, and NET formation defects [65] (Fig. **2**).

5.5. Macrophage Dysfunction

Hyperglycemia also alters the function of macrophages. Restrepo *et al.* demonstrated that chronic hyperglycemia was significantly associated with defects in complement receptors and Fcγ receptors on isolated monocytes, resulting in phagocytosis impairment [66]. An *in vitro* study using macrophages derived from mice bone marrow and treated with high glucose showed reduced antibacterial activity and phagocytosis [67]. In the same study, reduced phagocytosis was shown in peritoneal macrophages from diabetic mice. This could be related to the reduced glycolytic capacity and reserve of macrophages following long-term sensitization to high levels of glucose.

In another study using resident peritoneal macrophages (RPMs) isolated from mice, Liu *et al.* demonstrated significantly reduced phagocytosis and adhesion capacity in RPMs of *db/db* mice [68]. In addition, they reported increased macrophage polarization shifting to M2 macrophages in *db/db* mice compared to control mice. Similarly, macrophages derived from mice bone marrow and exposed to high glucose for a long period of time showed increased M2 macrophage markers, including Arginase 1 and IL-10 [67]. Given that M2 macrophages have poor microbicidal capacity, this shifting could weaken the immune response against bacterial infection.

5.6. Natural Killer Cell Dysfunction

Dysfunction of natural killer (NK) cells, which are important for controlling invading pathogens, was demonstrated by Berrou *et al.* [69]. In this study, isolated NK cells from T2D subjects demonstrated defects in NK cell-activating receptors NKG2D and NKp46, which were associated with functional defects in NK degranulation capacity.

5.7. Inhibition of Antibodies and Complement Effector

The dysfunction of complement activation was observed in an animal study in rats conducted by Clifford *et al*. [70]. They demonstrated that hyperglycemia was associated with decreased C4-fragment opsonization, which inhibits classical or lectin pathways of complement activation. The summary of possible mechanisms that cause infection susceptibility in people with diabetes is presented in Table **1** and Fig. (**2**).

Table 1. The immunological mechanism of susceptibility of diabetics to infections.

Impact on Immune System	Subjects	Possible Mechanism	References
Suppression of cytokine production	Isolated PBMCs from healthy subjects	Inhibition of mononuclear cell proliferation through the induction of cellular TGF-β production; TGF-β mediated suppression of IL-2, IL-6, and IL-10 production by PBMC	[49]
	Isolated PBMCs from healthy subjects	Decreased IL-6 expression in CD14+ and CD16+ intermediate monocytes; Reduced IL-17A resulting in impairment of immune responses	[51]
	db/db obese mice and high fat diet-induced hyperglycemic mice	Low level of IL-22 in blood plasma	[53]
	Isolated PBMCs from healthy subjects and THP-1 cell line	Impaired production of type 1 IFN	[54]
	Healthy donors and T2D subjects	Low production of IL-12 and IFγ correlated with deficiency of glutathione	[71]
Defect in leukocyte recruitment	Streptozotocin-treated mice (C57BL/6 background)	Reduction of cytokine production, such as CXCL1, CXCL2, IL-1β, and TNF-α	[58]
	C57BL/6 J (*db/db*) mice and C57BL/6 J (Wild Type)	Reduced migration of leukocytes, specifically cytotoxic CD8+ T cell, due to lower expression of CAM	[57]
Defect in pathogen recognition	Streptozotocin-treated mice (C57BL/6 background)	Downregulation of TLR and TIRAP expression	[58]
Neutrophil dysfunction	Isolated neutrophils of T2D subjects	Reduced production of ROS in neutrophils due to increased resistin	[61]
	Isolated neutrophils of healthy subjects	Impaired O_2^- production due to inhibition of G6PD production	[62]
	Isolated neutrophils of healthy subjects	Impaired neutrophil degranulation and coagulation	[63]
	Isolated neutrophils of healthy donors and T2D subjects	Impaired and delayed neutrophil NET formation	[72]
	Isolated neutrophils of healthy subjects	Dysfunction of neutrophils in *S. aureus* phagocytosis due to structural changes in C3b	[64]

(Table 1) Contd…

Impact on Immune System	Subjects	Possible Mechanism	References
Macrophage and monocyte dysfunction	Isolated resident peritoneal macrophages from *db/db* mice and littermate controls (C57BL/6J background)	Impaired chemotaxis and adhesion capacity of RPMs	[68]
		Increased proportion of anti-inflammatory M2 phenotype	[68]
	Bone marrow-derived macrophages from streptozotocin-treated mice (C57BL/6 J background)	Increased proportion of anti-inflammatory M2 phenotype	[67]
		Reduced glycolytic capacity and glycolytic reserve of macrophages after long-term sensitization to high glucose	[67]
	Isolated PBMCs from healthy donors and T2D subjects	Lower expression of Fc gamma receptors on DM2 monocytes	[66]
NK cell dysfunction	Isolated PBMC from T2D subjects	Susceptibility to infections and malignancies due to defects in NK cell-activating receptors NKG2D and NKp46	[69]
Inhibition of antibody and complement effector	Peritoneal cells of streptozotocin-treated Wistar rat	Reduced C4-fragment opsonization in hyperglycemic conditions and subsequent inhibition of complement activation *via* classical or lectin pathways	[70]

CONCLUSION

Diabetes is a metabolic disease that occurs due to inflammation in a complex immunological process. Insulin resistance due to insulin signaling inhibition results in a series of immune responses that exacerbate the inflammatory state, which leads to hyperglycemia. Both innate immune response defects (including dysfunction of neutrophils and macrophages) and dysfunction of the adaptive immune response (including T cells) are thought to be responsible for immune system weakness against invading pathogens in diabetic subjects. A better understanding of the mechanisms of hyperglycemia that impair host defense against pathogens is crucial for the development of novel strategies to treat infections in diabetic patients, thus improving treatment outcomes.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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