Ministry of Higher Education
and Scientific Research
Diyala University
College of medicine

Effect of diabetes mellitus in immune system

By

Yasser Gazhi salman

Supervised by

Lecturer Mustafa Abdulkareem Salman

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Abstract

Diabetes is a major health problem worldwide. This metabolic disease is indicated by high blood glucose levels due to ethier insufficient insulin production by the pancreas or destruction of beta cell . 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. Therefore, diabetic subjects are known to more susceptible to infections. The increased prevalence will increase the incidence of infectious diseases and related comorbidities.better understanding of how immune dysfunctions occur during hyperglycemia can lead to novel treatments and preventions for infectious diseases and co morbidities,

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) ,in addition to forther types for example diabetes in pregnancy.

As a chronic condition, diabetes increase the risk of several other diseases caused by macrovascular and microvascular harmful, 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.In 2016, the International Diabetes Federation reported around 425 million people living with diabetes worldwide [13]. 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 [13].
type 1 diabetes mellitus (T1DM) was believed to be a T cell-mediated autoimmune disease(14,15,16) This notion still holds, but several observations in the past few years point to a role of β-cells that goes beyond being a non-provoking victim of an autoimmune attack(17,18,19)
Almost 90% of all diabetes cases are T2D [20] due to both insufficient insulin action (insulin resistance) and impaired 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, 21]. The pancreatic islets increase their cell mass to produce more insulin to compensate for insulin resistance [22]. T2D is developed when this effort fails to compensate for insulin resistance [22]. More than half of T2D patients require insulin therapy due to the dysfunction of pancreatic β cells after 10 years of insulin resistance [23, 24]. 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 [22].

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. 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 [25]. 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 [26]. 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.

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) [27]. In another study, monocytes isolated from PBMCs of T1D subjects secreted lower IL-1 and IL-6 compared to healthy donors [28]. 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 [30]. Since IL-6 is important for protection against pathogens and for adaptive immune responseby inducing antibody production and effector T-cell development [29], these studies revealed that inhibition of those cytokines in hyperglycemia may suppress the immune response

against invading pathogens [30]. 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 [31]. Another study conducted by Price et al. reported that increased glycation leads to a loss of IL-10 secretion by myeloid cells [32]. 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 [33].A study by Tan et al. demonstrated lower production of IL-12 and IFNγ in PBMC cultures from diabetic subjectsfollowingBurkholderiapseudomallei infection compared to PBMCs from healthy donors [34].

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 [25].

Unlike the effect of hyperglycemia on immune cell activity in T2D, the impact of insulin deficiency in diabetes 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 [25]. 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 [35]. 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.

Abstract

Diabetes is associated with increased susceptibility to Klebsiellapneumoniae and poor prognosis with infection. We demonstrate accelerated mortality in mice with streptozotocin-induced diabetes following tracheal instillation of K. pneumoniae. Diabetic mice recruited fewer granulocytes to the alveolar airspace and had reduced early production of CXCL1, CXCL2, IL-1β and TNF-α following tracheal instillation of K.pneumoniae-lipopolysaccharide. Additionally, TLR2 and TIRAP expressionfollowing K. pneumoniae-lipopolysaccharide exposure was decreased in hyperglycemic mice.

Conclusion:
These findings indicate that impaired innate sensing and failure to rapidly recruit granulocytes to the site of infection is a mechanism for diabetic susceptibility to respiratory K. pneumoniae infection.

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 [36]. 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. This defect in leukocyte recruitment was also demonstrated by Martinez et al. in their in vivo study using streptozotocin-induced diabetic mice

infected by Klebsiellapneumoniae [37]. 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.

Abstract

Diabetes is a significant risk factor for developing West Nile virus (WNV)-associated encephalitis (WNVE) in humans, the leading cause of arboviral encephalitis in the United States. Using a diabetic mouse model (db/db), we recently demonstrated that diabetes enhanced WNV replication and the susceptibility of mice to WNVE. Herein,we have examined immunological events in the brain of wild type (WT) and db/db mice after WNV infection. We hypothesized that WNV-induced migration of protective leukocytes into the brain is attenuated in the presence of diabetes, leading to a high viral load in the brain and severe disease in diabetic mice. Results: We demonstrate that infiltration of CD45+ leukocytes and CD8+T cells was significantly reduced in the brains of db/db mice, which was correlated with attenuated expression of CAM such as E-selectin and ICAM-1. WNV infection in db/db mice was associated with an enhanced inflammatory response in the brain. mRNA and protein levels of key chemokines such as CXCL10, CXCL1, CCL2, CCL5, CCL3, and G-CSF, and cytokines such as IL-1β, TNF, IL-6, IFNγ, and IL-1α were significantly elevated in the brains of db/db mice compared to WT mice. Elevated levelsof cytokines also correlated with increased astrocytes activation and neuronal damage in the brains of db/db mice.

Conclusion: These data suggest that reduced leukocytes recruitment, in part, due to lower levels of CAM results in failure to clear WNV infection from the brain leading to increased production of inflammatory molecules, which mediates increased neuronal death

and mortality in db/db mice. This is the first study to elucidate the expression of CAM and their correlation with the migration of leukocytes, specifically cytotoxic CD8+ T cells, in increasing disease severity in the diabetic mouse model .

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 [37]. However, several studies have shown increased expression of TLRs in neutrophils and monocytes isolated from people with diabetes [38, 39, 40]. 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 [40]. Hence, the impact of hyperglycemia on TLR expression and related immunity in diabetic subjects remains unclear.

Abstruct: Hyperglycemia activates protein kinase C, and this inhibits neutrophil migration, phagocytosis, superoxide production and microbial killing. High glucose concentrations decrease the formation of neutrophil extracellular traps. Hyperglycemia can also induce Toll-like receptor expression and inhibit neutrophil function and apoptosis. High glucose concentrations decrease vascular dilation and increase permeability during the initial inflammatory responses, possibly through protein kinase C activation. Hyperglycemia can cause direct glycosylation of proteins and alter the tertiary structure of complement; these changes inhibit immunoglobulin-mediated opsonization of bacteria and complement fixation to bacteria and decreases phagocytosis. Hyperglycemia also stimulates the production and release of cytokines. Several trials have demonstrated that better glycemic control reduces nosocomial infections in critically ill patients and surgical site infections.

Conclusions: In summary, acute hyperglycemia can significantly alter innate immune responses to infection, and this potentially explains some of the poor outcomes in hospitalized patients who develop hyperglycemia.

Neutrophil Dysfunction

ROS production of isolated neutrophils from T2D tuberculosis patients following phorbol12-myristate 13-acetate stimulation was reduced. This defect in ROS production was associated with increased levels of resistin in T2D patients' serum [41]. In a comparable study, Perner et al. reported suppression of superoxide (O2-) in isolated neutrophils from healthy subjects when exposed to a high glucoseconcentration medium. This impairment occurred via glucose-6- phosphate dehydrogenase (G6PD) inhibition, which disturbed the formation of nicotinamide adenine dinucleotide phosphate [42].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 [43]. Neutrophil dysfunction in phagoes S. aureus was also demonstrated due to C3-mediated complement inhibition caused by hyperglycemia [44]. 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 [45]. All of these studies revealed that hyperglycemia causes neutrophil dysfunction, including defects in ROS production [41], neutrophil degranulation impairment [43], inhibition of immunoglobulin-mediated opsonization [38], decreased phagocytosis, and NET formation defects [45].

Abstract

Diabetic patients are at increased risk for bacterial infections; these studies provide new insight into the role of the host defense

complement system in controlling bacterial pathogens in hyperglycemic environments.

Conclusions: These results demonstrate that hyperglycemic conditions inhibit C3-mediated complement effectors important in the immunological control of S. aureus. Mass spectrometric analysis reveals that the glycation state of C3 is the same regardless of glucose concentration over a one-hour time period. However, in conditions of elevated glucose C3 appears to undergo structural changes.

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 [46]. An in vitro study using macrophages derived from mice bone marrow and treated with high glucose showed reduced antibacterial activity and phagocytosis [47]. 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 [48]. 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 glucosefor a long period of time showed increased M2 macrophage markers, including Arginase 1 and IL-10 [47]. Given that M2 macrophages have poor microbicidal capacity, this shifting could weaken the immune response against bacterial infection.

Abstruct

Macrophages are tissue resident immune cells important for host defence and homeostasis. During diabetes, macrophages and other innate immune cells are known to have a pro-inflammatory phenotype, which is believed to contribute to the pathogenesis of various diabetic complications. However, diabetic patients are highly susceptible to bacterial infections, and often have impaired wound healing.Recent evidence suggests that macrophage functions are governed by metabolic reprograming. Diabetes is a disorder that affects glucose metabolism; dysregulated macrophage function in diabetes may be related to alterations in their metabolic pathways. In this study, we seek to understand the effect of high glucose exposure on macrophage phenotype and functions.

Conclusion: Long-term high glucose sensitizes macrophages to cytokine stimulation and reduces phagocytosis and nitric oxide production, which may be related to impaired glycolytic capacity.

Natural Killer Cell Dysfunction

Dysfunction of natural killer (NK) cells, which are important for controlling invading pathogens, was demonstrated by Berrou et al. [49]. 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.

Abstract

Patients with Type 2 diabetes (T2D) are highly susceptible to infection and have an increased incidence of some tumors, possibly due to immune system dysfunction. In the innate cellular immune system, Natural Killer (NK) lymphocytes are important effectors responsible for controlling infections and combating tumor development.

We analyzed NK cell subsets in 51 patients with long-standing T2D. Decreased expression of these receptors was associated with functional defects, such as reduced NK degranulation capacity when challenged with the tumor target cell line. Thisdefect could be

restored in vitro by stimulating NK cells from T2D patients with IL-15. NKG2D expression was found to be negatively correlated with HBA1c level. suggesting that sustained hyperglycemia could directly influence NK cell defects. We demonstrated that endoplasmic reticulum (ER) stress, an important mediator in diabetes-associated complications, was inducible in vitro in normal NK cells and that tunicamycin treatment resulted in a significant decrease in NKG2D expression.

Furthermore, markers of the Unfolded Protein Response (UPR) BiP, PDI and sXBP1 mRNAs were significantly increased in NK cells from T2D patients, indicating that ER stress is activated in vivo through both PERK and IRE1 sensors.

Conclusion

These results demonstrate for the first time defects in NK cell-activating receptors NKG2D and NKp46 in T2D patients, and implicate the UPR pathway as a potential mechanism. These defects may contribute to susceptibility to infections and malignancies and could be targetted therapeutically.

Inhibition of Antibodies and Complement Effector

The dysfunction of complement activation was observed in an animal study in rats conducted by Clifford et al. [50]. They demonstrated that hyperglycemia was associated with decreased C4-fragment opsonization, which inhibits classical or lectin pathways of complement activation. Hyperglycemia from diabetes is associated with increased risk of infection from S. aureus and increased severity of illness. Previous work in our laboratory demonstrated that elevated glucose (>6 mM) dramatically inhibited S. aureus-initiated complement-mediated immune effectors. Here we report in vivo studies evaluating the extent to which a hyperglycemic environment alters complement-mediated control of S. aureus infection in a rat peritonitis model. Rats were treated with streptozocin to induce

diabetes or sham-treated and then inoculated i.p. with S. aureus. Rats were euthanized and had peritoneal lavage at 2 or 24 hours after infection to evaluate early and late complement-mediated effects. Hyperglycemia decreased the influx of IgG and complement components into the peritoneum in response to S. aureus infection and decreased anaphylatoxin generation. Hyperglycemia decreased C4-fragment and C3-fragment opsonization of S. aureus recovered in peritoneal fluids, compared with euglycemic or insulin-rescued rats. Hyperglycemic rats showed decreased phagocytosis efficiency compared with euglycemic rats, which correlated inversely with bacterial survival. These results suggest that hyperglycemia inhibited humoral effector recruitment, anaphylatoxin generation, and complement-mediated opsonization of S. aureus, suggesting that hyperglycemic inhibition of complement effectors may contribute to the increased risk and severity of S. aureus infections in diabetic patients.

Abstract

Hyperglycemia from diabetes is associated with increased risk of infection from S. aureus and increased severity of illness. Previous work in our laboratory demonstrated that elevated glucose (>6 mM) dramatically inhibited S. aureus-initiated complement-mediated immune effectors. Here we report in vivo studies evaluating the extent to which a hyperglycemic environment alters complement-mediated control of S. aureus infection in a rat peritonitis model. Rats were treated with streptozocin to induce diabetesor sham-treated and then inoculated i.p. with S. aureus. Rats were euthanized and had peritoneal lavage at 2 or 24 hours after infection to evaluate early and late complement-mediated effects. Hyperglycemia decreased the influx of IgG and complement components into the peritoneum in response to S. aureus infection and decreased anaphylatoxin generation. Hyperglycemia decreased C4-fragment and C3-fragment

opsonization of S. aureus recovered in peritoneal fluids, compared with euglycemic or insulin-rescued rats.

Conclusion

Hyperglycemic rats showed decreased phagocytosis efficiency compared with euglycemic rats, which correlated inversely with bacterial survival. These results suggest that hyperglycemia inhibited humoral effector recruitment, anaphylatoxin generation, and complement-mediated opsonization of S. aureus, suggesting that hyperglycemic inhibition of complement effectors may contribute to the increased risk and severity of S. aureus infections in diabetic patients.

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