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Effect of COVID-19 Infection on the Immune System and Risk of Developing Diabetes Complications: A Review

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ABSTRACT

Coronavirus disease (COVID-19) is caused by SARS-COV2 and represents the causative agent of a potentially fatal disease that is of great global public health concern. The pandemic outbreak of COVID-19 is rapidly spreading all over the world. In this review, we try to summarize studies of the relationship between the alteration of immune system during COVID-19 infection and the risk of developing diabetes complications. The data were collected by searching Science Direct, Google Scholar, PubMed, Scopus, Springer and National Center for Biotechnology Information (NCBI). The Keywords used as search terms were "COVID-19", "SARS-COV2 induced inflammatory reaction", "ACE2 and COVID-19 infection", "Diabetes and Oxidative stress" and "COVID-19 induced Diabetes complication". The risk of COVID-19 infection in patients is due to the severity of the viral infection and also to the host's immune response. The risk of infection is one of the main complications of diabetics, as it has been suggested that diabetes inhibits the immune response which contributes to infection and progression to symptoms. Also, the evidence of generation of oxygen free radicals and oxidative stress is a key process in the onset of diabetes mellitus which participate in the development of the systemic inflammatory response syndrome. In addition, chronic hyperglycemia during COVID-19 infection may increase the release of inflammatory cytokines, a high ability to bind to the virus ACE2 glycosylated, worsen the ketoacidosis and vascular complications that may explain the severity of the SARS-CoV-2 infection in diabetic patients.

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Introduction

The sudden outbreak of the 2019 coronavirus (COVID-19) in Wuhan, China due to the SARS-CoV-2 virus, in just two months, after which the epidemic spread rapidly in the rest of the world (1). Coronaviruses target the human respiratory system, where previous coronavirus outbreaks (CoVs) include Middle East Respiratory Syndrome (MERS-CoV) and severe acute respiratory syndrome (SARS-CoV), which poses a major threat to public health (2).

The latest statistics for 2019 coronavirus (COVID-19) show that diabetes is a major risk factor for the development of the disease in patients with diabetes, which represents about 20% of those referred to the intensive care unit (ICU), where data showed that people with diabetes of both types represent that More than two-thirds of those who died from acute pneumonia syndrome 2 (SARS-CoV-2) (3). Diabetes mellitus is one of the leading causes of morbidity worldwide and is anticipated to rise substantially over the next decades (4). Diabetics are among the largest group of people with chronic diseases in terms of infection with viral infection and therefore they are most affected by the complications of this infection, which was what happened during the 2009 H1N1 influenza pandemic, where the disease with diabetes had the largest share in hospitalization (5). On the other hand, several studies confirm the strong relationship between diabetes and serious infection. Individuals with

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diabetes may be more susceptible to moderate or severe diseases associated with infection due to the immune system's altered with the consequences of diabetes. However, the mechanisms that link diabetes and immune suppression have not been well identified (6).

Many studies have suggested that the cause of progression of diabetes mellitus is reactive oxygen species and oxidative stress (7). Reactive oxygen species (ROS) are free radicals resulting from the metabolism of oxygen (8). The increased free radical production and antioxidant depletion in diabetes to be a causative factor in increasing the risk of infection and some investigators have reported increased lipid peroxidation and significant depletion in antioxidant capacity during the development of diabetes (9). On the other hand, chronic hyperglycemia is a cause of the Advanced Glycation End products (AGEs) production which play a role in the pathogenesis of diabetic complications including neuropathy, retinopathy and nephropathy (10). This review focuses on the relationship between the alteration of immune system during COVID-19 infection and the risk of developing diabetes complications.

Methods

The data were collected by searching Science Direct, Google Scholar, PubMed, Scopus, Springer and National Center for Biotechnology Information (NCBI). The Keywords used as search terms were "COVID-19", "SARS-COV2 induced inflammatory reaction", "ACE2 and COVID-19 infection", "Diabetes and Oxidative stress" and "COVID-19 induced Diabetes complication".

COVID-19 infection and immune system

Currently, very limited information about innate immunity activity is available on patients with SARS-CoV-2. In the latest reports in 99 cases in Wuhan, were observed increased overall neutrophils (38%), decreased total lymphocytes (35%), and increased serum IL-6 (52%) and increased protein reactivity (84%) (11). Viral infection in immune cells such as monocytes and macrophages can result in aberrant cytokine production, even if viral infection is not productive. The degree to which SARS-CoV-2 targets these cells remains poorly defined (12). Through numerous studies it has been determined that COVID-19 kills older adults with chronic diseases who have weak immune systems (13). As this disease appears as a new type of highly contagious disease in humans, the pathophysiology of unusually high diseases of COVID-19 has not been fully understood until now (14), but with the emergence of previous studies on other types of coronavirus it appears that the increased amounts of inflammatory cytokines in the serum was associated with extensive pneumonia and pneumonia in SARS and MERS-CoV, and more recently in COVID-19 (Table 1). However, little is known about subsets of lymphocytes and the immune response of patients with COVID-19 (15). The study of the pathophysiology of SARS-CoV-2 infection was found to be very similar to that of SARS-CoV infection, in terms of aggressive inflammatory reactions that were heavily involved in the damage caused in the airways (16). The increased severity pattern with age is also generally consistent with the epidemiology of SARS-CoV and MERS-CoV (17).

Table 1. Immune responses toward Coronavirus (18).

Virus	Cellular immune responses	Humoral immune responses
SARS-CoV	- Impaired circulating NK cells and T-cell subsets in mild and severe patients - Relatively higher frequency of CD81 than CD41 T cells in recovered patients - High type 2 cytokines present in sera of patients with severe diseases - Strong Memory T-cell responses correlating with high NAb serum levels	- Seroconversion few days after the disease onset and specific IgG detectable in most patients by 14 d - Long-lasting Specific IgG and NAbs reported 2 y after infection - NAbs specific for S, N, M epitopes, including the RBD domain - Delayed or weak antibody responses associated with severe outcome
MERS-CoV	- Early onset of CD81 T cells correlating with disease severity - Predominance of memory CD41 T cells with TH1or TH17 profiles in survived patients - Higher T-cell response in survived patients than in fatal cases	- Seroconversion within 2-3 wk. from disease onset still detectable until 13 mo. after infection. - Delayed or weak antibody responses associated with severe outcome
SARS-CoV-2	- Time of onset, phenotype, repertoire, functional profile, and amplitude of T-cell response still unknown - Reduction of circulating NK cells and T-cell subsets in relation to severity of disease - Few data on the recruitment of NK cells and T-cell subsets and their functions (scRNAseq) in the Broncho alveolar lavage fluid of patients with pneumonia	- IgM antibodies detectable 7-10 d after disease onset and serocoversion developed in most patients recovered - Infrequent antibody specificity for the RBD domain of S protein

Immune response in patients with COVID-19 is characterized by a cytokine storm (CS), which means excessive and uncontrolled release of pro-inflammatory cytokines (19). The incidence of SARS-CoV-2 leads to the destruction of the lung cells through the occurrence of a local immune response, the recruitment of macrophages and monocytes that respond to infection, and release cytokines and primary immune responses T and T cells (20). In most cases, this process is able to resolve the infection. However, in some cases, a defective immune response causes acute pulmonary diseases and even systemic diseases (21). Among the signs of COVID-19 is a lack of lymphocytes, which is one of the diagnostic criteria for it in China, and then both T cells and NK cells were reduced in patients with COVID-19 (22). The degree of reduction was even lower in severe cases where the latter had a greater number of leukocytes and a percentage of lymph neutrophils (NLR) as well. In other studies, a very significant decrease in NK cells, T-memory helper cells, and regulatory T cells is observed in some patients with serious diseases (23).

Diabetes and immune system

Chronic hyperglycemia and immune cell activity

Chronic hyperglycemic condition leads to severe diabetic condition by damaging the pancreatic β-cell and inducing insulin resistance (24). Glucose is also necessary for macrophage activity and stimulating lymphocytes to proliferation (25). But in high glucose in Diabetes has a significant negative effect on the body's immune system. Severe hyperglycemia decreases the activity of immune cells (26). These cells eventually become depleted and desensitized, which decreases their effectiveness against infection or other invading pathogens. Unbalanced diabetics are more prone to serious infections such as skin infections, pneumonia or urinary tract infections (27). One of the symptoms of diabetes is an increase in the production of ketoacidosis, which plays a major role in reducing the activity of the immune system (28). In people with diabetes, single-cell and single-celled cells secrete less interleukin-1 (IL-1) and IL-6 in response to stimulation by fatty lipopolysaccharides (29). However, other studies have reported that increased blood glucose can inhibit IL-10 production by marrow cells, as well as the production of interferon gamma (IFN-γ) and tumor necrosis factor (TNF) -α by T cells (30). High glucose will also reduce the expression of the Class I major histocompatibility complex (MHC) on the surface of myeloid cells, adversely affecting and weakening cell immunity (31). A complication of diabetes and increased blood glucose is non-enzymatic glycation for the biomolecules. Because immunoglobulin is rich in lysine residues, which makes it a potential target for glycation. Glycation of immunoglobulins occurs under physiological conditions and increases significantly during diabetes (32). High blood sugar causes an increase in cell calcium in polymorphic white blood cells (PMNs) which is inversely proportional to the occurrence of Leukocytosis in patients with type 2 diabetes (33). High levels of cellular calcium act to block the synthesis of adenosine triphosphate (ATP), which is necessary for phagocytosis (34). The ability of PMN leukocytes to move to the site of infection and stimulate apoptosis is also negatively affected. If the pathogen is able to invade the host without the aid of the innate immune system, then the risk of infection is expected to increase (35). With high blood sugar levels, the bacteria stimulate to thrive so that the immune response occurs to combat this infection (36).

Diabetes and free radical production

The evidence of oxidative stress is a key process in the onset of diabetes. Lipid peroxidation owing to free radical activity plays an important role in complications of diabetes (37). In fact, oxidative stress plays an important role in the development and progression of DM due to higher free radical production, damage to cell constituents, and impairment in the antioxidant defense enzymes, such as superoxide dismutase and catalase (38). The role of free radical generation in producing the hyperglycemia-dependent endothelial dysfunction is suggested by studies showing that in vitro and in vivo where acute effects of hyperglycemia are counterbalanced by antioxidants (39). The generation of oxygen free radicals participate in the development of the systemic inflammatory response syndrome while their actions as noxious mediators generated by inflammatory cells, these molecules play also a crucial role contributing to the onset and progression of inflammation where it activates of nuclear factors, as NFkB or AP1, that induce the synthesis of cytokines (40). So endothelial cells are activated due to the synergy between free radicals and cytokines, promoting the synthesis of inflammatory mediators and adhesion molecules. so free radicals exert their toxic effects at the site of inflammation by reacting with different cell components, inducing loss of function and cell death (41). Oxidative stress in diabetes results in stimulation of the polyol pathway, formation of advanced glycation end products (AGE), activation of protein kinase C (PKC) and subsequent formation of reactive oxygen radicals, Hyperglycemia is not only generating more reactive oxygen species (ROS), but also attenuates antioxidative mechanisms by scavenging enzymes and substances (42).

Chronic hyperglycemia and COVID-19 infection

It is unclear how, although there are several factors that

may be responsible for increasing diabetes mellitus severity of COVID-19 (Table 2). As uneven blood sugar levels weaken many aspects of the innate and adaptive immune response to viral and possible secondary bacterial infections in the lungs (43).

Table 2. Reasons of increased severity of COVID-19 in diabetes (44).

	Reasons
Established	Glycaemic instability: hyperglycaemia and possibly hypoglycaemia
	Immune defects especially impaired T-cell response
	Associated comorbidities like obesity, heart and kidney diseases
Postulated	
	Chronic subclinical inflammation, increased interleukin 6
	Increased plasmin
	Reduced ACE2
	Increased furin (involved in entry of virus into cell)

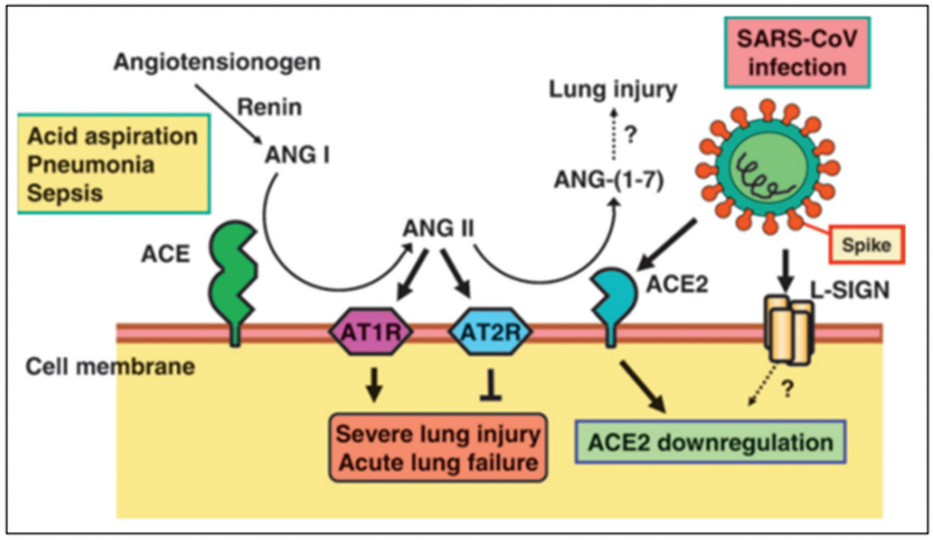
Glycosylation of the ACE2 and COVID-19 infection

The association between diabetes and COVID-19 is mainly represented by the role of angiotensin-converting enzyme (ACE2), a glycoprotein that is found in the membranes of epithelial cells of the lungs and is expressed in the kidneys and intestine as well as can be found at the level of blood vessels (45). The activity of this enzyme is to convert angiotensin 2 to angiotensin 1 and other small peptides (46) uncontrolled hyperglycemia can induced puissant changes in the glycosylation of the ACE2, and the glycosylation of the viral spike protein, which may alter the association between the viral spike protein and ACE2 and alter also the degree of the immune response to the COVID19 virus (47). Therefore, high glycosylated ACE2 in the tissue of diabetic patients could favor the cellular intrusion of SARS-CoV2, which may be leading to a higher propensity to COVID-19 infection and a higher disease severity (48). It is also likely that it is the amount of glycosylated ACE2 receptor, and not simply the amount of ACE2 alone, that is responsible for virus binding and fusion (49). On the other hand, diabetes is one of the most common co-morbidities of COVID 19. Inhibitors of angiotensin converting enzymes (ACE) are part of the treatments for this disease (50). COVID19 binds to epithelial cells in the lungs, blood vessels and intestines via the angiotensin 2 converting enzyme (ACE2) (51). Inhibition of the angiotensin II receptor leads to an increased expression of ACE2 in this group of diabetic patients, which explains the high infection with COVID-19 and the increased risk and severity of disease (52).

Diabetic Ketoacidosis and COVID-19 infection

In the case of Coronavirus infection, it may induce complication of diabetic ketoacidosis by the interaction between SARS-CoV-2 and renin angiotensin aldosterone system (RAAS) (53). Spike protein (S), one of the main structural proteins of SARS-CoV-2 that binds to the angiotensin-converting enzyme (ACE2) protein from the host cell membrane to fuse into the cell for nucleic acid replication (54). ACE2 is strongly expressed in the lungs and pancreas, it presents the entry point of SARS-CoV-2 in these tissues (55). After endocytosis of the viral complex, the expression of ACE2 is reduced, the entry of SARS-CoV-2 into the cells of the pancreatic islets can cause lesions in the beta cells which can impede the secretion of insulin and contribute at worsening of the state of ketoacidosis in diabetic patients (56). In addition, another complication of Diabetic Ketoacidosis can be seen through the interaction between SARS-CoV-2 and RAAS. Angiotensin II increases pulmonary vascular permeability and aggravates damage to the pulmonary parenchyma which causes excessive fluid resuscitation and therefore potentiate the acute respiratory distress syndrome (Figure 1) (57). In addition, a secretion of aldosterone is stimulated by angiotensin II which potentiates the risk of hypokalemia and increases ketoacidosis in diabetics (58).

Figure 1. proposed diagram of interaction between SARS infections and the RAS (59).



Vascular complications and COVID-19 infection

Hyperglycemia can promote local Ang II production in heart and kidney tissue (60). RAAS is also up-regulated in diabetes leading to activation of Ang II pathway and subsequently inflammation, increased oxidative stress, cell proliferation as well as apoptosis, and fibrosis (61). High blood pressure and nephropathy are considered one of the major complications of diabetes so that they have a strong relationship with macro-vascular and micro-vascular diseases (62), many mechanisms can contribute to understanding this relationship, including oxidative stress, inflammation and activation of the immune system (63). Also, the interaction between SARS-CoV-2 and RAAS is considered as a very important factor which contributes to high blood pressure and diabetes nephropathy complications in diabetic patients (64). Diabetic retinopathy is one of the most common complications of diabetes, which may increase with COVID19 infection (65). Where the abnormal activity of RAAS plays a key role in it, which reduces the expression of ACE2 and thus increases intraocular pressure and leads to retinopathy (66). SARS - CoV-2 infection can lead to higher stress situations in diabetic's patients, which leads to an increase in the secretion of cortisone and catecholamine hormones. These hormones increase blood glucose levels, which complicates the diabetes disease (67). Diabetics patients with COVID-19 also are characterized by low levels of lymphocytes, thrombocytes, and leukocytes with elevated levels of pro-inflammatory cytokines, including IL-6 and C-reactive protein (68), as well as increased coagulation activity with relative inhibition of the fibrous system. These anomalies favor developing a pro-clotting condition in diabetics (69).

Conclusion

The insufficiency of the immune response and the increase of oxidants associated with the rise of hyperglycemia in diabetes, which negatively affects the resistance of the COVID-19, leads to significant complications. Therefore, it is clear that a chronic hyperglycemia during COVID-19 infection may increase the release of inflammatory cytokines, a high ability to bind to the virus ACE2 glycosylated, worsen the ketoacidosis and vascular complications that may explain the severity of the SARS-CoV-2 infection in diabetics.

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