COVID-19 and Diabetes

Vahid Asgharzadeh[1], Mir Reza Valiollahzadeh[2], Zahra Taghinejad[3], Mohammad Asgharzadeh[4], Jalil Rashedi[5], Behroz Mahdavi Poor[6], Hossein Jalaei Nobari[7], Ahmad Ali Khalili[8], Yousof Khairy[7], Amir Ali Mir Mazhari[6]

[1] Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran

[2] Medical Philosophies and History Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

[3] Hematology and Oncology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

[4] Biotechnology Research Center, Faculty of Paramedicine, Tabriz University of Medical Sciences, Tabriz, Iran

[5] Tuberculosis and Lung Disease Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

[6] Department of Laboratory Sciences, Faculty of Paramedicine, Tabriz University of Medical Sciences, Tabriz, Iran

[7] Department of Islamic Education, Faculty of Paramedicine, Tabriz University of Medical Sciences, Tabriz, Iran

[8] Cardiovascular Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.

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Abstract- Following the discovery of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in China, it has been transmitted to travelers through respiratory droplets and distributed worldwide. Viral, environmental, and host factors all play a role in getting infected with the virus and having severe forms of the disease named coronavirus disease 2019 (COVID-19). Diabetes is one of the most important host risk factors in the progression and severity of COVID-19. In diabetes, hyperglycemia and protein glycosylation increase pro-inflammatory cytokines levels and suppress innate and adaptive immune system by impairing the function of neutrophils, macrophages, and lymphocytes, especially regulatory T lymphocytes. The compromised immune system in diabetic patients makes them vulnerable to infectious diseases like COVID-19. Correspondingly, people with diabetes are usually treated with angiotensin-converting enzyme (ACE) inhibitors and angiotensin II Type-I receptor blockers (ARBs), which increase ACE2 expression as a receptor for SARS-CoV-2. Thus, diabetic patients are more likely to develop severe forms of COVID-19 and die due to chronic inflammation and impaired immune function.

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Keywords: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); Coronavirus disease 2019 (COVID-19); Host risk factors; Diabetes

Introduction

Because of the high morbidity and mortality caused by two coronavirus strains, severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002-2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, acute respiratory infections have become a global concern in the last two decades (1). Most recently, in December 2019, a new previously unknown viral pneumonia caused by SARS-CoV-2 was detected in China, raising a new threat for China and the entire world (2). The World Health Organization (WHO) declared COVID-19 as a pandemic after its rapid dissemination (3). SARS-CoV-2 is a zoonotic virus first transmitted to humans from a seafood and wet animal market in Wuhan (4) and spread rapidly to many countries (5). COVID-19 has a wide range of clinical manifestations in affected patients, and a combination of viral, environmental, and host factors affect its severity. Eighty percent of patients are asymptomatic or have only mild upper respiratory symptoms, and in 20% of cases, pneumonia is followed by fever, cough, shortness of breath, nausea, and even respiratory failure as well as multi-organ failure (6). Since SARS-CoV-2 infection can manifest itself in various forms, including asymptomatic to severe pneumonia, it's important to consider the risk factors that can contribute

Corresponding Author: J. Rashedi
Tuberculosis and Lung Disease Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
Tel: +98 4133392633, E-mail address: Rashedijalil@gmail.com

to negative clinical outcomes. The severity and progression of COVID-19 in symptomatic patients are linked to age and other comorbidities (7), such as hypertension, diabetes, and cardiovascular and renal disorders, putting patients at high risk of mortality. Because of the rising number of diabetic patients in the world, as well as their increased vulnerability to infections as a result of chronic inflammation, microcirculation disruption, and immune system dysfunction caused by high blood sugar (8), diabetes can be an important risk factor for a variety of infections, post-infection complications, and infection-related mortality (9). In COVID-19 pandemic, diabetic patients are at risk for severe complications such as acute respiratory syndrome and acute heart failure. Since diabetic patients infected with COVID-19 have a higher mortality risk than non-diabetic patients, they should use prevention strategies during the COVID-19 pandemic (10). In this article, we reviewed the causes of severe COVID-19 in diabetic patients for making preventive decisions and lowering COVID-19 mortality.

SARS-CoV-2

Coronaviruses are all enveloped viruses with single-stranded, positive-sense RNA genomes (7). Like the flu virus, coronaviruses circulate among different species of animals and are categorized into 4 subfamilies, including alpha- , beta- , gamma- and delta- coronaviruses. Gamma- and delta-coronaviruses originate from birds, while alpha- and beta-coronaviruses originate from mammals. Unlike alpha-coronaviruses, beta-coronaviruses have the potential to cause serious infections and even death in humans (11). SARS-CoV-2 is a beta-coronavirus with a crown-like appearance under the electron microscope owing to superficial glycoproteins. The crown-like appearance under the electron microscope is the basis for naming the virus corona. The genome of SARS-CoV-2 has 82% sequence homology with SARS-CoV, respectively (12). 229E and NL63 are alpha and OC43 and HKU1 are beta coronaviruses triggering colds in humans (13), whereas SARS-CoV-1, MERS-CoV, and SARS-CoV-2 are all extremely pathogenic. SARS- CoV-2's nucleic acid incorporates 5'- and 3'-untranslated regions, and two third of its length contains adjacent open reading frames (ORFs), ORF1a and ORF1b at the 5' end translating into two large polyproteins, polyprotein 1a (pp1a) and polyprotein 1ab(pp1ab), respectively (14). Spike (S), membrane (M), envelope (E) and nucleocapsid (N) are the four structural proteins encoded by the remaining third of the viral genome at the 3' end (N) of the viral genome (15). S1 and S2 are the two subunits of the spike protein. The S1 subunit helps SARS-CoV-2 bind to its receptor, angiotensin-converting enzyme 2 (ACE2), whereas the S2 subunit is responsible for membrane fusion (16). After attaching the virus to ACE2, the host cell facilitates virus processing and integrates it with the cell membrane through two serine proteases, furin and transmembrane proteases serine 2 (TMPRSS2) (17). ACE2 is mostly expressed in alveolar epithelial type II cells (AECII), but it is also found in the myocardium, kidney, lung, intestine, and vascular endothelium. High expression of ACE2 and genes associated with various viral processes, such as genes regulating viral processes, life cycle, assembling, and the genome replication (18) in AECII facilitate virus replication in these cells (19). Since diabetic patients get ACE inhibitors(ACEi) and ARBs which increase ACE2 expression as a treatment for blood glucose control, they are more susceptible to developing severe forms of COVID-19 (20).

Diabetes

Diabetes is the most important chronic metabolic disease in the world and is marked by high blood glucose levels causing serious complications to the heart, blood vessels, eyes, kidneys, and nerves in the long term. In diabetes, the body's ability to generate the insulin hormone is lost, or the body becomes insulin resistant means the released insulin is unable to act properly. A defect in insulin development due to the loss of beta cells in the pancreas is the major cause of type 1 diabetes. In type 2 diabetes, progressive insulin resistance in the body is the major problem and can ultimately lead to the destruction of pancreatic beta cells and a total loss of insulin production (21). Diabetes is one of the leading causes of a wide range of diseases around the world, and this trend is predicted to be continued in the coming decades (22). Due to the repression of the innate and adaptive immune systems (23), diabetic patients are more likely to contract a variety of infections with high morbidity and mortality (24). Since pneumonia is becoming a major cause of death in diabetic patients (25), diabetes may be considered as an early risk factor for serious pneumonia in viral infections caused by pandemic Influenza A 2009 (H1N1), SARS, and MERS (26,27). The probability of mortality from COVID-19 is greater in diabetic patients than in non-diabetic patients, according to epidemiological data from areas severely affected by the virus (28).

Diabetes and the immune system

Diabetes is not only a disorder of glucose metabolism

but also a chronic inflammatory disease that causes changes in carbohydrates, proteins, and lipids. In cells and tissues, glucose reacts with proteins, lipids, and carbohydrates and forms Madori products, which contribute to diabetic complications (29). Such an inflammatory process increases the synthesis of end products of glycosylation by increasing blood sugar. It also causes the production of reactive oxygen species (ROS), which ultimately leads to acute oxidative and inflammatory stress. Glycosylation causes the development of proinflammatory cytokines, which facilitates inflammation in the target tissue (30,31). Red blood cells in diabetes are damaged by lipid peroxidation and hemoglobin glycation (32), and the oxygen-carrying capacity of red blood cells is reduced (33). Hyperglycemia and insulin resistance cause surfactant D, a lung-derived innate immune protein, loss of function, leading to impaired lung innate immunity (34). Furthermore, hyperglycemia can reduce the airway's defense capacity against infections by loosening connections between airway cells and increasing trans-epithelial and glucose gradients of airway surface fluid (35). Uncontrolled diabetes reduces the lymphocyte count (36) and impairs the function of macrophages and neutrophils, which may affect the immune system's response to pathogens by reducing neutrophil chemotaxis, phagocytosis, superoxide formation and intracellular killing (22,37). Increased susceptibility to infection in diabetic patients with several immune deficiencies, including increased production of glycated end products, can inhibit T lymphocytes interferon-gamma production against viruses (38). This delayed activation of T lymphocytes expressing cluster of differentiation 4 (CD4), as well as delayed transform towards T helper 1 cells and reduction of regulatory T cells can be seen in diabetic patients and play a role in increasing inflammation and slowing down immune responses to viruses entering the body (37). High blood sugar inhibits the production of type 1 interferon (IFN-1), interleukin 22(IL-22) (39,40), interleukin 10(IL-10) and tumor necrosis factor–α (TNF–α) by T cells (41). Interferon type I has antiviral activity (42) IL-22 maintains the intestinal mucosal barrier and improves insulin sensitivity (43). Hyperglycemia also reduces the expression of the class I major histocompatibility complex (MHC) at the cell surface, which impairs the function of immune cells (44). Hyperglycemia also produces a rise in calcium in polymorphonuclears (PMNs), which is linked to the development of leukocytosis, especially in type 2 diabetic patients (45). Moreover high levels of cellular calcium prevent the synthesis of adenosine triphosphate (ATP), which is needed for phagocytosis (46). PMNs can migrate to the site of infection, destroy microorganisms and induce apoptosis. So elevated blood sugar has a detrimental impact on immune cells that make the body more susceptible to infections and their complications. Hyperglycemia also decreases cathelicidin production in macrophages and their antimicrobial effects (47).

Diabetes and COVID-19

Diabetes, along with hypertension, obesity, and coronary heart disease, is considered to be a risk factor for COVID-19 severity and mortality. Poor glycemic control disrupts various aspects of the innate and acquired immune systems in response to viral infections in the lungs (48). T cells, natural killer cells and complement system dysfunction also make it difficult to get rid of viral infections (49). Acute respiratory distress syndrome (ARDS) does not occur in patients with COVID-19 who have healthy immune systems, especially in their lungs, but it can exacerbate the cytokine storm in patients with pre-inflammatory conditions. In COVID-19 patients, existing chronic pre-inflammation can improve ARDS as well as other organ disorders (50). Despite having decreased number of lymphocytes, diabetic patients have higher levels of lactate dehydrogenase (LDH), c-reactive protein (CRP), ferritin, D dimer and pro-inflammatory cytokines like IL-1 and IL-6 (51,52). The level of D dimer, which is strongly linked to high mortality in COVID-19 patients, is significantly higher in diabetic patients (53), indicating a coagulation tendency (52). In addition, the level of IL-6 among different inflammatory markers is significantly increased in diabetic patients with COVID-19 compared to non-diabetic patients. Thus, interleukin 6 is a pleiotropic cytokine that increases significantly in acute phase inflammatory response as well as chronic inflammatory conditions such as metabolic disorders and cardiovascular diseases (50). IL-6 level is linked to disease severity and the coagulation process (54) and by increasing oxidative stress, it can damage proteins, lipids and DNA and disrupt the structure and function of the body. So this effect can lead to the rapid progression of COVID-19 in diabetic patients (55). In addition to IL-6, high levels of other pro-inflammatory cytokines, such as IL-18 and metalloproteinase 12, cause structural and functional changes in the cardiovascular system, as well as abnormal clot formation (56,57). As a result, in type 2 diabetes, there is an imbalance between fibrinolysis and coagulation, which is linked to higher levels of clotting factors, relative inhibition of the fibrinolytic system and

increased risk of COVID-19 severity.

Diabetes and ACE-2

ACE2 serves as a receptor for the SARS-CoV-2 virus, and is an essential component of the cardiovascular system cleaving angiotensin I (Ang-I) and angiotensin II (Ang-II) into Ang (1-9) and Ang (1-7) peptides, respectively. Ang (1-9) is then metabolized to Ang (1-7) (58). While Angiotensin 2 has a pro-inflammatory role that causes artery narrowing, Ang (1-7) has anti-inflammatory and antioxidant effects (59). ACE2 is a counter-regulatory enzyme of ACE1. ACE1 converts Ang-I to Ang-II, and Ang-II acts on Ang-II type-1 receptor (AT1R). ACE1 produces Ang-II, which increases blood pressure by constricting blood vessels and also increases oxidative stress leading to increased inflammation and fibrosis (60). Since patients with type 1 and type 2 diabetes who are treated with ACEi and ARBs have slightly higher ACE2 expression (20), and SARS-CoV-2 requires the attachment of S protein to ACE2 receptors on the cell surface of target cells for entry, elevated ACE2 expression could worsen COVID-19 disease. ACEis, such as captopril, increase ACE-2 expression by blocking the conversion of angiotensin 1 to Ang-II, and ARBs, such as losartan, increase ACE-2 expression by blocking the Ang-II receptor. Increased ACE2 expression level has been shown to improve viral binding and virus entry into cells (61). Reduced Ang-II as a result of ACE inhibition and increased Ang (1-7) as a result of increased ACE2 activity will lower cytosolic pH, making it more conducive to viral endocytosis (62). However, ACE -1 and ACE-2, both of which are strongly expressed in the lung, are implicated in the outcome of lung oxygenation and lung injury in ARDS (59,63). An experiment on SARS-CoV has shown that the interaction of S protein with ACE2 reduces ACE2's expression in the lungs, which in turn causes lung damage by increasing the Ang2 to Ang1-7 ratio (64). It appears that the ACE2 receptor plays an ambiguous function in SARS-CoV-2 pathophysiology. As increased ACE2 expression on cells facilitates virus entry into target cells and increases the viral load in the body, decreased ACE2 expression can cause significant lung damage after infection. Thus it appears that increasing ACE2 in body fluids with medication can compensate for the lung damage caused by decreased ACE2 expression (Figure 1).

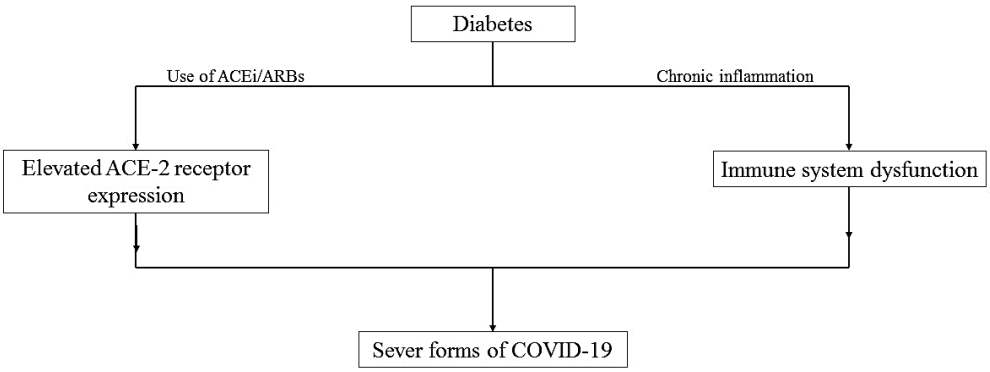

Figure 1. Diabetes and COVID-19 severity association

From this study, it can be concluded that diabetes is one of the host risk factors for infection with the SARS-CoV-2 because of the impaired immune response due to increased glycosylation of proteins. Despite the fact that elevated proinflammatory cytokines and chronic inflammation exacerbate ARDS and multiorgan disease and can even lead to death. Careful monitoring and taking care of diabetic patients' health can reduce their mortality rate during the COVID-19 pandemic.

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