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Diabetes and coronavirus infections (SARS-CoV, MERS-CoV, and SARS-CoV-2)

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ABSTRACT

Diabetes, as the major cause of hyperglycemia, is a chronic metabolic disease. Immune system disorders caused by diabetes can increase the risk of respiratory diseases. Thus, diabetes is considered to be a major risk factor for viral respiratory infections such as coronavirus infections. Coronaviruses are members of the Coronaviridae, which has caused three outbreaks from 2003 to 2020. Patients with coronavirus infection in the lower and upper respiratory tract could show mild to severe symptoms. In this review, we focus on the relationship between diabetes and three coronaviruses: SARS-CoV, MERS-CoV, and SARS-CoV-2.

KEYWORDS: Diabetes; Coronavirus; SARS-CoV; MERS-CoV; SARS-CoV-2

1. Introduction

Diabetes is one of the most common metabolic diseases (a metabolic disorder) with a wide presence around the world[1]. According to new findings, a total of 463 million people worldwide are living with diabetes[2]. Diabetes, an aging-associate disease with a higher prevalence among people aged over 60 years, is considered to be the major cause of microvascular diseases such as retinopathy, nephropathy, and neuropathy[3,4]. Besides, it has been suggested that the immune system functions, including chemotaxis, phagocytosis, intracellular apoptosis, and respiratory burst can be negatively impacted by hyperglycemia that is the most prominent feature of diabetes[5]. Therefore, diabetic patients are more prone to infectious diseases[6]. As a result, these patients are more likely to develope respiratory infections, especially with more severe disease symptoms[5,6]. It is worthy to note that the incidence of influenza infection among diabetic patients is 6 times higher than the non-diabetic population. Similarly, the mortality rate of pneumonia or influenza is higher in diabetic patients[7]. In addition, diabetes is associated with an increased risk of viral respiratory diseases such as coronaviruses[8]. Hence, early detection would be an effective strategy in preventing severe complications in diabetic patients.

Coronaviruses are the members of the Coronaviridae. This family is composed of two subfamilies, including Coronavirinae and Torovirinae. The subfamily Coronavirine consists of four genera, known as alpha-coronavirus, beta-coronavirus, gamma-coronavirus, and delta-coronavirus[9]. SARS-CoV, MERS-CoV, and SARS-CoV-2 belong to the beta-coronavirus genus. Coronaviruses can cause illnesses ranging from the common cold to severer respiratory diseases such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), which are both zoonotic[10-12]. Researchers have found that MERS-CoV and SARS-CoV are transmitted from camels[13] and civet cats to humans, respectively[14].

SARS-CoV-2 is a member of Coronaviridae, which has caused coronavirus disease 2019 (COVID-19)[15]. COVID-19 was declared a worldwide pandemic by World Health Organization (WHO) on 11 March 2020[16]. Same with SARS-CoV and MERS-CoV,

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SARS-CoV-2 is a zoonotic virus, and it is transmitted from animals to humans[17]. According to the obtained evidence, the lower respiratory tract is the main target of SARS-CoV-2 infection[18], and it can also affect other organs[19]. Due to the the considerable worldwide concerns about the emergence of novel coronaviruses like SARS-CoV-2, and susceptibility of diabetic patients to viral infections, this review aims to explore the relationship between diabetes and three emerging coronaviruses including SARS-CoV, MERS-CoV, and SARS-CoV-2 .

2. SARS–CoV

SARS-CoV can cause a viral respiratory disease referred to as SARS[20]. SARS-CoV enters host cells through the binding of it's spike glycoprotein to angiotensin-converting enzyme 2 (ACE2)[21]. ACE2, as a cellular receptor of SARS-CoV, is highly expressed in a variety of cells including alveolar epithelial cells, small superficial enterocytes, and endothelial cells in the heart and kidneys[22]. Studies have indicated that the entry of SARS-CoV into pancreatic islets is mediated by ACE2 that can damage pancreatic beta cells and cause acute diabetes[23]. On the other hand, chronic hyperglycemia in diabetic patients can induce acidosis, which can restrain the phagocytic activity of immune cells. Thus diabetes can be a major cause of death in patients with SARS infection[24]. Furthermore, SARS-CoV infection has a crucial role in the onset of secondary hyperglycemia[25].

3. MERS–CoV

MERS-CoV was first identified in Saudi Arabia in June 2012[11]. According to surveys, the mortality rate of MERS was approximately 35%[26]. In the early stages, the common symptoms are shortness of breath and other respiratory problems, as well as severe respiratory difficulties, fever, coughing[27], gastrointestinal complications such as diarrhea occur[28]. Human dipeptidyl peptidase 4 (DDP4), which is also known as CD26, is the cell receptor of MERS-CoV. As a type 2 transmembrane protein, DDP4 enzyme is expressed on the surface of a variety of cells, including the immune cells. By affecting the function of the immune cells, DPP4 can modulate the immune system[29]. The expression of this multifunctional enzyme is dysregulated in numerous diseases such diabetes, and it can lead to inflammation in type 2 diabetes *via* various mechanisms. Therefore, DDP4 has key roles in coronavirus-infection in patients with type 2 diabetes[26,30]. Some studies showed that DPP4 inhibitors may increase the risk of pneumonia *via* the suppression of immune system, so the treatment of type 2 diabetes patients with DPP4 is controversial[27,28,31,32]. As mentioned above, MERS-CoV binds to DPP4, the cellular receptor, to enter the host cells through its surface spike (S) protein. The viral entry is subsequently followed by the membrane fusion of the virus and the host cell[33]. A study conducted on diabetic rats infected with MERS-CoV showed delayed and prolonged inflammatory response in their lungs[34]. It also indicated a decrease in inflammatory cytokines, macrophages, and T cells in diabetic mice[35]. Thus, it can be proposed that diabetes can cause the dysfunction of the immune system so that the immune system fails to respond to infections. This may explain why diabetic patients are susceptible to severe MERS-CoV infections and are more prone to severe influenza, pneumonia, and other respiratory infections. The increase in the severity of the disease in diabetic mice infected by MERS virus can be attributed to an unregulated immune response which leads to a more severe and prolonged lung pathology[34]. Overall, MERS-CoV has close association with diabetes.

4. SARS–CoV–2

SARS-CoV-2 induced COVID-19 is an ongoing pandemic, which has raised worldwide concern. SARS-CoV-2 is a new member of the Coronaviridae family and belongs to the genus beta-coronavirus[36,37]. Malaise, fever, dry cough, and shortness of breath are the main signs of COVID-19, but a runny nose, headache, diarrhea, and sore throat are less prevalent. Other complications of the COVID-19 include acute respiratory distress syndrome, acute heart damage, secondary infections, abnormal clotting, sepsis, damages to the liver, and kidneys[38].

SARS-CoV-2, like SARS-CoV, employs the same receptor to enter the target cell where the virus replicates and spreads into other cells in the respiratory tract[36]. SARS-CoV-2 and SARS-CoV share a sequence similarity of 76% in their S proteins. SARS-CoV-2 binds to ACE2 through S glycoprotein[39]. The spike glycoprotein of SARS-CoV-2 is a structural protein which consists of two subdomains:, including S1 and S2. The sequence of the S1 domain is variable and plays a role in binding to ACE2, and the S2 domain with a conserved sequence integrates the viral membrane into the cell membrane[39]. It has been shown that amino acid 493 in the receptor-binding domain of S glycoprotein plays an important role in ACE2 binding[40,41].

According to the available data from the WHO, the mortality rate of COVID-19 is estimated between 3%-4% and almost 80% of death cases aged over 60 years, and 75% of them had underlying health conditions such as diabetes[42]. In fact, diabetes down-regulates the immune system functions, and it is considered to be a risk factor for exacerbation of COVID-19 disease.

5. Association between diabetes, SARS, MERS, and COVID–19

It has been suggested that the cellular receptors are crucial factors in the association between diabetes mellitus (DM) and coronavirus infections including SARS, MERS, and COVID-19[43,44]. In addition, age is another risk factor for coronavirus diseases since age

affects the expression and distribution of ACE2[44]. The regulation of ACE2 is important considering the relationship between the expression of ACE2 and the development of coronavirus diseases in individuals with diabetes[45,46]. The expression of ACE2 is increased in the early phase of DM, however, it is down-regulated in the later phases of this disease[45,47].

With regard to the fixation and expression of the ACE2 receptor in the endocrine, such as the pancreas, SARS-CoV-1 penetrates islets *via* ACE2 receptor and devastates islets, which results in acute diabetes[26]. Studies showed that history of diabetes and hyperglycemia were associated with the mortality and morbidity rate of SARS-CoV patients. As a result, metabolic disorders checkup, such as diabetes, is recommended to be listed in the follow-up of SARS-CoV patients[48].

A meta-analysis suggested that diabetes is predominant in roughly 50% of the MERS-CoV patients[48]. Furthermore, diabetes can be related etiologically to the pathogenesis of MERS-CoV[49]. Diabetes, hyperglycemia, and insulinopenia can inhibit the synthesis of interferon-gamma and interleukins[50] and aggravates the MERS-CoV infection[34]. In addition, other studies proposed that the severity condition of MERS-CoV in the lung is associated with diabetes and dysregulation of the immune response[34].

According to surveys, prevalence of diabetes among COVID-19 patients is about 9.7%[51]. Results of studies confirmed that underlying diseases such as diabetes can influence the pathogenesis of COVID-19 due to the weakness in the innate immune response[50].

6. Conclusion

Diabetes is a common metabolic disease, which can down-regulate the immune system. It has been shown that age, an impaired immune status, and uncontrolled glycemia can affect the susceptibility and severity of coronaviruse infections among patients with diabetes. As mentioned above, coronaviruses such as SARS-CoV, MERS-CoV, and SARS-CoV-2 can cause damage to the pancreas, so coronavirus infections are more dangerous for patients with diabetes. As a consequence, diabetic patients ought to be included in vaccination proposals for flu and SARS-CoV-2.

Conflict of interest statement

The authors report no conflict of interest.

Authors' contributions

M.Z. designed the study; A.H.N., S.S. and M.M. collected all data; P.H. and S.N. drafted the manuscript; and all authors commented on the drafts of the manuscript and approved the final draft of the paper.

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