Inventum Biologicum: *An International Journal of Biological Research*
2022, Vol. 2, Issue 2, pp. 87-93

Inventum Biologicum

Journal homepage: www.worldbiologica.com/ib

Review paper

SARS-CoV-2 and Diabetes Mellitus (DM): A Comprehensive Review

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ARTICLE INFO

Article history

Received 29 June 2022
Revised 22 July 2022
Accepted 25 July 2022
Published 27 July 2022

Keywords

SARS-CoV-2
Angiotensin-converting enzyme 2 (ACE2)
Endocrinological disorder
Immune system
Diabetes mellitus (DM)

ABSTRACT

Background and aims: Diabetes Mellitus with multi-systemic complications are allied with Covid-19. We conducted a comprehensive review in order to explore the interaction between diabetes Mellitus and Covid-19.

Methods: An extensive literature search was conducted for the relevant articles in PubMed, WHO and Google Scholar databases till April 16, 2020, with the keywords "SARS-CoV-2", "Angiotensin- converting enzyme 2 (ACE2)", "diabetes mellitus", and "management of diabetes mellitus".

Results: As of April 16, 2020, the number of confirmed Covid-19 cases had passed 1991562 and more than 130885 deaths globally.

Conclusion: Diabetes Mellitus is associated with risk of Covid-19. Our study suggests that clinicians should pay more attention to the monitoring and treatment of Covid-19 patients with DM.

1. Introduction

In the 21st century, 2 highly pathogenic HCoVs-severe acute respiratory syndrome coronavirus (SARS-CoV) and middle east respiratory syndrome coronavirus (MERS-CoV) emerged from animal reservoirs to cause global epidemics with alarming morbidity and mortality. The pathogenic human coronaviruses (HCoVs) called 2019-nCoV or Covid-19, began in Wuhan, China in late 2019. By early March 2020, the novel coronavirus was named as SARS-CoV-2 which had spread to 210 countries and territories around the world. The total global cases found were 2,056,055 out of which 511,019 cases have recovered

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DOI https://doi.org/10.5281/zenodo.6915243

and 134,178 have died as of April 16, 2020 (WHO, 2020).

The ultimate scope and effect of this outbreak is unclear at present as the situation is rapidly evolving and has been officially declared a global pandemic by WHO (WHO, 2020). The incubation period of Covid-19 is 2 to 14 days which means people can be exposed for spreading the virus in days or weeks before even developing any symptoms. The estimated mortality rate by the WHO is 3.4% as of March 3, 2020.

Coronaviruses are large, enveloped, positive strand RNA viruses that are divided into 4 genera: alpha, beta, gamma and delta, of which alpha and beta CoVs are known to infect humans (Wilde et al., 2018). SARS-CoV-2 is a positive-strand RNA virus that causes severe respiratory syndrome in humans. The genome of SARS-CoV-2 shares about 80% identities with that of SARS-CoV and is about 96% identical to the bat coronavirus BatCoV RaTG13 (Zhou et al., 2020). Four HCoVs (HCoV 229E, NL63, OC43, and HKU1) are endemic globally and usually cause mild to moderate upper-respiratory tract illnesses. Coronaviruses are ecologically diverse with the greatest variety seen in bats, suggesting that they are the reservoirs for many of these viruses (Wit et al., 2016). Peridomestic mammals may serve as intermediate hosts, facilitating recombination and mutation events with expansion of genetic diversity.

The novel coronaviruses, SARS-CoV-2 particles are spherical and have proteins called spikes protruding from their surface. These spikes latch onto human cells and undergo a structural change that allows the viral membrane to fuse with the cell membrane (Fig. 1). Spike protein mediates the fusion of host and viral cell membrane to begin infection and is the major target for neutralizing antibodies and vaccine development (Belouzard et al., 2012; Lee et al., 2006). Protein modeling suggests that there is a strong interaction between the spike protein receptor-binding domain and its host receptor angiotensin-converting enzyme 2 (ACE2), which regulates both the cross-species and human-to-human transmissions of Covid-19 (Wan et al., 2020). Therefore SARS-CoV-2 infection is caused by binding of the viral surface spike protein to the human angiotensin-converting enzyme 2 (ACE2) receptor following activation of the spike protein by transmembrane protease serine 2 (TMPRSS2) (Hoffmann et al., 2020). The spike protein is a large type I transmembrane protein containing two subunits, S1 (shown in red in Fig. 1) and S2 (shown in green in Fig. 1). S1 (red) contains a receptor-binding domain which is responsible for recognizing the cell surface receptor. S2 (green) contains the transmembrane domain which anchors the spike protein to the viral envelope and also has the elements needed for membrane fusion to initiate viral entry into the host cell. The viral genes enter the host cell to be copied, producing more viruses. Recent work shows that SARS-CoV-2 spikes bind to receptors on the human cell surface called angiotensin-converting enzyme 2 (ACE2).

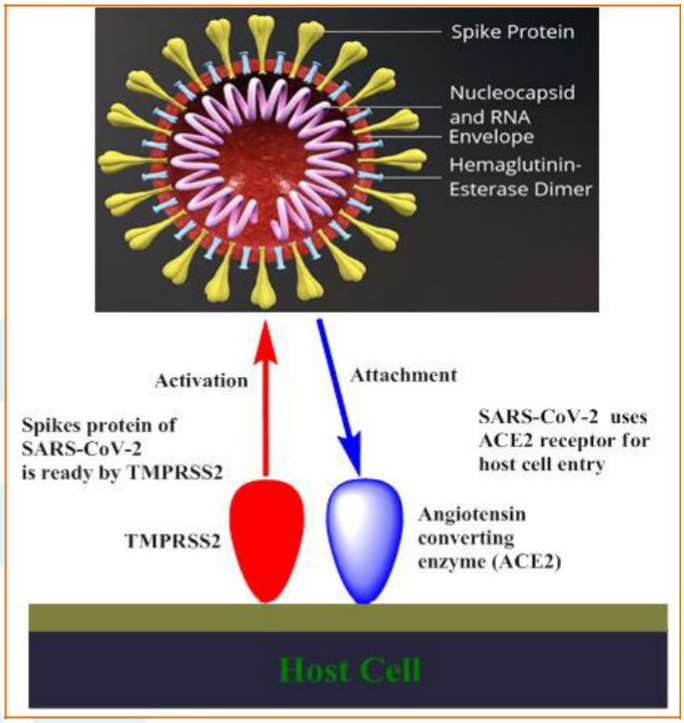

Fig. 1 Structure of novel coronavirus SARS-CoV-2 using Host cell

The angiotensin-converting enzyme (ACE2) reduces blood pressure and inflammation and acts like a "door" to the cell for the virus which causes Covid-19. When the virus attaches to ACE2 receptors and makes its way into cells, it hijacks the cells and makes copies of itself. When the virus enters the human body, it undergoes replications which kill the cells and spreads, causing fever, shortness of breath and other symptoms that can lead to severe illness or death. The SARS-CoV-2 spike is 10 to 20 times more likely to bind ACE2 on human cells than the spike from the SARS virus from 2002. This may enable SARS-CoV-2 to spread more easily from person to person than the earlier virus. Further the disease damages the lungs, both by killing cells and by prompting a response from the immune system. The immune system can overreact and cause damage

while trying to kill the virus. When infection affects the air sacs in the lungs which facilitate gas exchange, there will be fluid and pus that accumulate, which can cause pneumonia. The lungs become severely inflamed and injured, patients can develop acute respiratory distress syndrome, or ARDS. Fluid begins leaking into the lung, making it incredibly difficult for patients to breathe.

SARS-CoV-2 is spread predominantly via respiratory droplets when a person coughs or sneezes. It also spreads when someone touches a contaminated surface such as a door handle. Common symptoms of SARS include fever, cough, dyspnea, and occasionally watery diarrhea. These are associated with the common pneumonia, severe acute respiratory syndrome (SARS) and can also affect the gut. Transmission may occur from both symptomatic and asymptomatic patients, with secondary infection rates ranging from 0.5 to 5% (Zou et al., 2020; WHO, 2020). SARS-CoV-2 has been demonstrated to remain stable for up to 3 hours in the aerosolized form, up to 24 hours on cardboard, and as many as three days on plastic or stainless steel (Doremalen et al., 2020). For infected patients, 20% to 30% required mechanical ventilation, 10% died and higher fatality rates are seen in older patients and those with medical comorbidities. Covid-19 has higher prevalence of diabetic disease (7.3%), after the cardiovascular disease (10.5%) due to the weak immune system of the patient's body and thereby easily attacked by the virus.

A transmembrane protein, angiotensin-converting enzyme 2 (ACE2) is attached to the outer surface of the cells and serves as the entry point for coronavirus (NCBI, 2022). The binding of the spike S1 protein of SARS-CoV2 to the enzymatic domain of ACE2 on the surface of cells results in endocytosis and the enzyme into endosomes located within cells (Wang et al., 2008; Millet et al; 2018). The severe and critically ill patients with Covid-19 had higher occurrence of hypokalemia that resulted from renal potassium wasting. This can be explained by down regulation of ACE2 following viral intrusion resulting in decreased degradation of angiotensin-II, increased aldosterone secretion and subsequent increased urinary potassium loss. Thus, ACE2 over expression, while facilitating entry of SARS-CoV-2, is unable to protect against lung injury as the enzyme gets degraded by the virus. ACE2 expression is reduced in patients with DM due to glycosylation, which increased predisposition to severe lung injury and ARDS with Covid-19 (Tikellis & Thomas, 2012).

Diabetes mellitus is an endocrinological disorder with an increasing global occurrence and incidence. The person with diabetes is a host of other chronic diseases including cardiovascular diseases, kidney-related conditions, and others. Diabetes is a metabolic disorder that exposes to varied infections due to weakened immune system of the patient's body. The World Health Organization (WHO) warns that the most at-risk populations for Covid-19 are older persons and persons with pre-existing medical conditions as they are prone to develop more serious illness when they contract the virus. People with chronic conditions like diabetes are at greater risk of being hospitalized due to the coronavirus because glucose levels are fluctuating or elevated consistently. Diabetic ketoacidosis (DKA) is a serious acute metabolic complications of diabetes, and commonly precipitated by infection in 75% of the cases. The mortality rate of patients with an infection and ketoacidosis is high. The question then arises as to which pathogenetic mechanisms are responsible for this high infection rate in patients with DM. Possible causes include defects in immunity, an increased adherence of microorganisms to diabetic cells. In humans, the immune system protects the person from outside invaders (also known as pathogens), such as bacteria or viruses. The diabetes and the immune system are directly connected and patients with diabetes mellitus (DM) have infections more often than those without DM (Deresinski, 1995). One of the possible causes of this increased prevalence of infections is defects in immunity. When a healthy individual is invaded by foreign bacteria or a virus, the immune system will work on attacking that virus or bacteria and destroying it. With type-1 diabetes, the immune system will actually misdirect its signals to attack the bacteria and instead will attack the insulin-producing beta cells in the body and occurs in genetically predisposed individuals. Type-2 diabetes also results due to autoimmune disorder, therefore physical activity is recommended for type-2 diabetics to help keep blood sugar under control as well as keeping the immune system strong. Without insulin, glucose from the food cannot be utilized efficiently and the patients experience high blood glucose levels. High levels of blood glucose often experienced by diabetes patients have also been held responsible for the weak immune system. Besides, in diabetes, the

response of the immunity system towards bacteria and viruses also reduces to a great extent, causing infections and other diseases in diabetes patients. Thus hyperglycemia may be a cause of dysfunction of the immune response, which results in failure to control the spread of invading pathogens in diabetic subjects, making diabetics more susceptible to coronavirus infections.

Diabetes patients have a lower immune response, so risk of getting sicker is more. There have also underlying risk of exacerbated illness simply due to having diabetes even if glucose levels are in range. The American Diabetes Association (ADA) explains, in China, where most cases have occurred so far, people with diabetes had much higher rates of serious complications and deaths than people without diabetes. The higher case-fatality rate among those with preexisting conditions is 10.5% for cardiovascular disease, 7.3% for diabetes. 6.3% for chronic respiratory disease, 6.0% for hypertension and 5.6% for cancer (Hui et al., 2020). The Case Fatality Rate (CFR) number of deaths/number of those diagnosed varies by location and also depends on an individual's age. According to Chinese Center for Disease Control and Prevention (China CDC) weekly study, in Hubei Province of China, the epicenter of the outbreak, the death rate reached 2.9% in other provinces of China, the rate was just 0.4%. In addition, older adults have been hit the hardest. The death rate of 14.8% is seen in those who are older than 80 years. Among others the persons with age of 70 to 79, the Covid-19 death rate in China seems to be about 8%; 3.6% for ages between 60 to 69; 1.3% for 50 to 59; 0.4% for the age group 40 to 49; and just 0.2% for people aged between 10 to 39. No deaths in children under 9 have been reported. Based on the reported data from April 16th, 2020, the CFR varies significantly by country. According to early estimates by China's National Health Commission (NHC), about 80% of those who died were above the age of 60 and 75% of them had pre-existing health conditions who have a significantly increased CFR of 10.5% for cardiovascular disease (CVD); 7.3% for diabetes mellitus (DM); 6.3% for COPD; 6% for HTN; and 5.6% for cancer (Wu et al., 2020; Battegay et al., 2020). Coronavirus disease 2019 (Covid-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is of great concern.

2. Boosting Immunity in Diabetes Patients

As per the biochemical processes, beta-defensins are the compounds that help to build a strong immune system of the body. When glucose in the body is high, it breaks down into a molecule known as dicarbonyl. It is this compound that disrupts the smooth functioning of the beta-defensins. The dicarbonyls, namely methylglyoxal, and glyoxal weaken the ability of the beta-defensins to fight infections.

Following are the ways for boosting the immunity in diabetes:

- Try to manage weight effectively. Over weight affects the immune system.
- Never skip meals and eat small portions of food at one go.
- Eat plant foods like fibers which boost immunity system of the body.
- Regular exercise will boost the immunity and control body weight.
- Regularly monitor blood glucose and keep the same under check.
- Use probiotics to boost the immune system. Probiotics are the good bacteria that are required by the body. Apart from the probiotic supplements, there are a number of natural food items that are probiotic by their very nature.
- Some of important natural sources that helps boost immunity system include herbal tea, black tea as they are known to contain essential flavonoids, polyphenols that help in maintaining the levels of blood glucose.
- The most important reason for weakened immunity, as suggested by various experts is stress. The hormones are released when you are stressed out leading to loss of essential immunity in the body. Stress is reduced and even eliminated by practicing meditation, yoga and other physical and mental activities.
- Sleep well and soundly.
- Avoid smoking and alcohol drinking to a large amount to boost immunity.

Consequently, by applying the above-mentioned simple and easy steps, boosts the immunity system in diabetes and leads to fight any virus especially the Covid-19.

3. Preventive Measures of Diabetes Mellitus (DM) Patients from Coronavirus

Preventive measures are the best strategy for novel coronavirus (SARS-CoV-2) at this time. While vaccines and monoclonal antibodies against SARS-CoV-2 are in development, a number of other investigational therapies, using repurposed clinically approved drugs targeting SARS-CoV-2 cell invasion and replication, may be considered. Based on the information from health authorities including Centers for Disease Control and Prevention (CDC) agency resources, World Health Organization (WHO), and credentialed medical professionals within and beyond the diabetes space. The diabetic patients protecting against Covid-19 include social distancing of at least six feet, use of face masks, washing hands often with soap or sanitizer and water for at least 20 seconds, and making sure you are up to date with vaccinations like the flu and pneumonia shot. Further keep hands away from the eyes, nose, and mouth, because that allows germs that cause respiratory infections to enter the body. Keep distance or just try to be very cautious about physical contact with people who have signs of respiratory illnesses who are coughing, sneezing, etc. A humid environment is also beneficial. If the house is dry, especially in the wintertime, use a humidifier. Patients of diabetes mellitus (DM) must have plethora of water, as that will keep their mucous membranes moist which can further lower the chances of cold and flu. Further use of plenty of water, minerals like magnesium and zinc, micronutrients, herbs, food rich in vitamins C, D and E, and better life style one can promote the health and can overcome this infection. Various studies showed that a powerful antioxidant glutathione and a bioflavonoid quercetin may prevent various infections including Covid-19. The first place where germs can penetrate into the body is the nasal passages and if they dry out due to dry air, keep opening the door and marshaling germs into your system. The most important issue is managing the glucose, which becomes more challenging, but even more important, because when glucose levels are elevated, you are sort of help and assisting the infection of virus (Covid-19), which can easily enter the body. Further for high blood sugar patients, the recovery time is extended and cause varied symptoms that is much worse for the whole body. The most important precautionary measures for diabetic patients are self-quarantining. However using insulin needs at least the advanced and prior supply and one must know how to adjust your insulin doses to maintain healthy blood sugar levels. Further make sure you have enough medication available to manage your diabetes. In general, it is good idea to have a friend, family member, or trusted neighbor so that they can bring you groceries or call your doctor in case you are not well. There should be someone who understands your history of diabetes and can help you during the pandemic situations.

Hydroxychloroquine is a good anti-diabetic medication in the present scenario as the drug has also been shown to inhibit SARS-CoV-2 infection in-vitro as well as reduce the viral load in Covid-19 patients. The drug has also been approved for prophylaxis against Covid-19 in many countries (Singh et al., 2020). Tocilizumab is known to improve insulin resistance and reduces HbA1c in patients with rheumatoid arthritis and diabetes mellitus (Otsuka et al., 2018). A large number of medicinal plants are believed to possess anti-diabetic activities and have been utilized to control diabetes. One of the medicinal plants that is emerging as a possible therapeutic agent for the management of DM is cinnamon (*Cinnamomum verum*). Several studies have been conducted to confirm the effect of cinnamon on decreasing the blood glucose of diabetic patients (Gupta et al., 2017; Gheibi et al., 2005).

4. Conclusion

Covid-19, caused by SARS-CoV-2, is a global pandemic declared by WHO. The ultimate scope and effect of this outbreak is unclear at present as the situation is rapidly evolving. Emergency efforts are underway to find optimum medical products to prevent infection and diagnose and treat patients during the coronavirus disease 2019 (Covid-19) pandemic, but none with proven clinical efficacy till date. Production and supply chains for Covid-19 drugs and for many other essential medical products are being impaired by this crisis. Supply chains for vital drugs for other diseases (such as cardiovascular disease, diabetes mellitus, cancer, systemic lupus erythematosus etc) are being disrupted because they are being repurposed to use against Covid-19 without adequate supporting evidence. For diabetes mellitus, self-quarantine and social distancing is the best option to prevent from alarming Covid-19 disease. Use of soap or sanitizers for hand washing can minimize the chances of infection. The plant-based foods play a vital role to enhance the immunity of people to

control Covid-19 infection. Thus prevention is the best option to fight against Covid-19.

Funding Information

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Conflict

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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