COVID-19 and Diabetes: A Narrative Review

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Abstract
The pandemic of the novel human coronavirus disease 2019 (COVID-19) has become an evolving global health issue due to the high morbidity and mortality rate. Patients who have comorbidities (e.g., diabetes, hypertension, obesity, cancer, and cardiovascular disease) are significantly at increased risk for admission into the intensive care unit, and this situation could affect the survival of the infected patients. Among the various comorbidities in this review, we focused on the diabetic patients who were highly affected because of increased viral entry into the cell via angiotensin-converting enzyme 2 (ACE2) in the respiratory system, leading to decreased immunity. Furthermore, several studies have been conducted on the beneficial effects of metformin in diabetic patients with COVID-19, but other studies have demonstrated the severe course of COVID-19 disease. Hence, further comprehensive studies are necessary in this regard. For these reasons, the prevention and management of COVID-19 in diabetic patients are essential and play a key role in reducing the fatality rate.

Background
Coronavirus is one of Nidovirales phylum members. This is a positive-sense virus with single-stranded RNA, and capsule.1-3 Fundamentally, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is similar to SARS-associated coronavirus (SARS-CoV) and the Middle East respiratory syndrome (MERS), which caused the pandemic in 2003 and 2012, respectively.4-6 The first report of the novel coronavirus 2019 (COVID-19) was from Wuhan, China, in December 2019.6 The virus which was reported as a pandemic was spread to many countries in March 2020. According to the studies, the mortality rate is 2.3%, and it rises with the age of the patients.7 Therefore, the death toll among the patients within the age range of 70 to 79 and patients over 80 was reported to be up to 8% and 14.8%, respectively.6 This virus has a high dissemination rate, even during its incubation period. The patients suffer from chronic lower respiratory disease and acute respiratory distress syndrome.8,9 Clinical symptoms of this disease are progressive asthma and hypoxia. Finally, half of the infected people by SARS-CoV-2 who need aggressive mechanical ventilation pass away in hospitals. Many underlying factors affect the virus death toll.10-12 This study aimed at evaluating the clinical features of COVID-19 and the relationship between underlying diseases with a greater emphasis on diabetes due to the severity of the disease as well as the mortality rate due to COVID-19 infection. We also looked more closely at diabetes in infections, especially the relationship between diabetes and COVID-19 in terms of disease severity and epidemiology. We conducted the study using PubMed and Google Scholar databases. In addition, we used keywords such as 'COVID-19', '2019-NCOV', 'SARS-CoV2', '2019 novel coronavirus', and 'comorbidity'.

General Characteristics of COVID-19
COVID-19 is a severe respiratory disease leading to pneumonia, and it can affect some different organs. The incubation period of the virus is mainly 5-6 days (the period from exposure to the virus to the time when you are affected). However, it can take up to 14 days.14 According to numerous reports, the main symptoms
are fever, dry cough, dyspnea, myalgia, tiredness, and headaches. Other symptoms are less common such as diarrhea, vomiting, nervous symptoms, skin manifestation (petechiae, purpura, rash, and urticaria), renal dysfunction, insomnia, conjunctivitis, and olfactory disorders.\textsuperscript{15-20} It should be noted that the clinical symptoms of novel coronavirus are not specific to this virus, and they are similar to other infections such as influenza. For this reason, it may not be timely and well diagnosed (Figure 1). In thoracic computed tomography of patients, some abnormalities emerged in lungs such as ground-glass opacity, bilateral patchy shadowing, multiple cerebral infarction, and infectious lesions. This evidence was consistent with viral pneumonia.\textsuperscript{21-23} Moreover, different images of patients' chests were observed at different stages of the disease, which may be related to the mechanism of this pathogen. As reported by some research, most of the patients' images were taken to 1-5 days after the early demonstration of the disease. In the severe and advanced cases of the disease, an increase was observed in inflammatory cytokines (e.g., IL2, IL6, IL7, IL10, TNF-α, GCSF, IP10, MCP1, and MIP1A) compared to mild cases, indicating that the release of inflammatory cytokines is important in the progression of COVID-19. This means that the inflammatory spreading cytokines are crucial in COVID-19 progression, and they can be
measured. The increased HLA-DR expression has been reported in CD4+ and CD8+ cells, and a significant increase was also observed in the expression of perforin and granulysin in CD8+ cells. Laboratory findings of most affected patients by COVID-19 indicated increased d-dimer, lactate dehydrogenase, and lymphopenia as well as decreased albumin and hemoglobin. These findings were more noticeable among patients with severe disease because laboratory tests helped with the rapid diagnosis and timely management of many infections; accordingly, the primary diagnosis of patients with SARS-CoV-2 can significantly control the disease transmission and prevalence in society. This is important because some affected people have no symptoms or only mild symptoms.

**Diabetes**

Diabetes is a chronic inflammatory disease, diagnosed by some metabolic disorders that can affect the patient’s responses to the pathogens. Based on the world health organization report in 2014, nearly 422 million adults had diabetes, while it was about 108 million people in 1980. Some factors such as weight gain and obesity are the reasons for this increase. It was reported that the mortality rate caused by diabetes was 1.5 million people in 2012. The main reason for casualties was glucotoxicity, leading to disorders. The relationship between diabetes and the susceptibility to some infections (e.g., pulmonary system infection, urinary system, and soft tissue infections) was approved long time ago. Numerous scientists found that diabetic patients exhibit the susceptibility to some pathogens, including *Mycobacterium tuberculosis*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Legionella*. They are possible causes of immune system failure. For instance, a study indicated that diabetic patients possess *Staphylococcus aureus* in their nasopharynx three times more than people with no diabetes. Abnormal delayed hypersensitivity reactions and complement activation disorders have been observed in diabetic patients. These patients had pathogenesis failure, bactericidal activity rate, chemo toxic neutrophils, and cell-mediated inherited immunity disorders. Fortunately, some immune deficiencies can be corrected with proper glucose control. The relationship between diabetes and infections has been clinically studied for a long time. It has been observed that patients with diabetes are more vulnerable to periodontal disease, and immune system failure can be reported as an important factor for these cases. Diabetes may make the patient susceptible to intestine pathogens and cause gastrointestinal dysmotility. As digestive system movements are one of the main defenses against the infections in the host, huge numbers of pathogens such as *Salmonella enteritis*, *Campylobacter*, and *Listeria monocytogenes* were reported in diabetic patients. Research evidenced that the lung is another target organ in diabetic people. Diabetes is one of the factors contributing to the severity of the disease and the mortality of patients infected with influenza A (H1N1), SARS-CoV, and MERS-CoV viruses. Numerous research characterized the fundamental and physiological disorders in diabetic patients’ lungs. A diabetic person is at a high risk of being affected by asthma, respiratory infections, pulmonary injury, pneumonia, pulmonary tuberculosis, and sleep-related breathing disturbance. Diabetes causes damage to the respiratory system due to lung damage caused by microangiopathy. In diabetic people, the lung capacity decreases possibly due to the increased collagen and elastin accumulation in the connective tissue of the chest wall and lung parenchyma compared to the healthy individuals. Five possible biochemical factors that have been considered as the main pneumological reasons for diabetes progression include NADPH oxidase which inverts oxidative stress damages, non-enzymatic glycosylation, polypol pathway that is the main source for producing ROS in diabetes, NF-KB pathway, and protein kinase C pathway activation. For this reason, diabetic patients are in danger of being afflicted by a virus infection and lots of regular infections. Hence, it may be a disaster for them; as such, diabetic patients should have their blood sugar under control.

**Association Between COVID-19 and Diabetes**

Diabetes is a common metabolic disorder that affects the whole body, so it is one of the main reasons for mortality worldwide. This disease accompanies somemicrovascular complications (i.e., nephropathy, retinopathy, and neuropathy) and macrovascular complications such as coronary artery disease. COVID-19 infection is affected by diabetes, creating a more stressful condition that accompanies hyperglycemia. Secretion of indicator hormones such as catecholamines and glucocorticoids can increase blood sugar. Based on research, hypoglycemia regulates pre-inflammatory monocytes and increases the platelet numbers. These conditions are related to cardiovascular mortality in diabetic patients. Furthermore, it is not obvious how immune responses and inflammation occur in diabetic people. Can low or high blood sugar alter the virulence of the virus or does it interfere with the insulin secretion or glucose control? In addition, the outcomes of diabetes treatment drugs on this virus are not totally clear. Since metformin is used as a hypoglycemic agent in the treatment of type II diabetes, its synergistic function with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may increase angiotensin-converting enzyme 2 (ACE2) in the respiratory system, therefore leading to the entry and consequent infection of COVID-19. Various studies have shown that metformin is associated with a reduction in mortality rate in COVID-19. Therefore, the association between metformin and clinical outcomes among patients...
with type 2 diabetes mellitus and COVID-19 has not been established yet.\textsuperscript{59,61} Moreover, few studies have been conducted on the association between glucose metabolism and the progression of diabetic acute complications such as ketoacidosis.\textsuperscript{52-64} Diabetes incidence in patients afflicted by COVID-19 is different depending on their age and their geographical region.\textsuperscript{88} Further, it has been found that diabetic people affected by COVID-19 have a severe condition and higher mortality rate than non-diabetic patients. Those who are affected by the novel coronavirus need more confinement in intensive care unit.\textsuperscript{66,67} A center for disease control and prevention in China reported the mortality rate of 44,672 affected individuals. Interestingly, the rate in cases with no background disease and in people with diabetes was 0.9% and 7.3%, respectively.\textsuperscript{64} How diabetes causes disease severity in COVID-19 is a controversial topic. Several factors may play a role. Regarding COVID-19 pandemic, some studies from different countries suggested that elderly patients with chronic diseases (e.g., diabetes) are at a higher risk for more serious disease and mortality.\textsuperscript{66,69-72} In a study conducted on 1561 patients suffering from COVID-19, 9.8% had diabetes with average age of 64.\textsuperscript{74} Based on the results, of a total of 52 patients, 17% of them had diabetes, and from all of the COVID-19 afflicted patients, 32 cases passed away, and 22% of them had diabetes.\textsuperscript{75} Nowadays, it is not clear why this kind of condition occurs more severely in patients with COVID-19, but a possible reason could be attributed to ACE2. This enzyme neutralizes the angiotensin 2 effects and elevates vasodilation during angiotensin 2 to angiotensin 1 conversion.\textsuperscript{59} Because of the similarity of SARS-CoV-1 and SARS-CoV-2 amino acid sequences, it can be acknowledged that both of them have a similar mechanism which uses ACE2 on the surfaces of epithelial cells to bind and enter the host’s cells.\textsuperscript{73} Results have indicated that ACE2 expression is more frequent in male lung cells; therefore, it could be justified as a proof for the higher rate of male affliction.\textsuperscript{74} Furthermore, another investigation indicated a relationship between ACE2 expression and age, different tissue, Asian race, and sexuality.\textsuperscript{75} Currently, the expression of ACE2 is not genetically clear among different societies; therefore, the epidemiological examination and genetic analysis of COVID-19 are crucial among other societies.

**COVID-19 and Comorbidities**

Based on the research results, we can mention some risk factors associated with the severity of pathogenicity and COVID-19 death tolls including diabetes, old age, hypertension, cardiovascular diseases, obesity, and cancer.\textsuperscript{12-24} It needs to be noted that people of different age groups can be afflicted by SARS-CoV-2 severe respiratory infection. It is more common in adults during their middle ages and elder ones. Additionally, older age is accompanied by the higher rates of mortality.\textsuperscript{79,80} Cardiac disorders including heart failure, arrhythmia, and myocardial infarction are common in patients with pneumonia. Important factors in the development of cardiac disorders after pneumonia include the severity of pneumonia, old age, and cardiovascular disease.\textsuperscript{81,82} The prevalence of obesity in adults has increased from 2017 to 2018 (42%) compared to 2009 to 2010 (9%).\textsuperscript{83} Obesity may play a crucial role in disease transmission in respiratory infections. According to the results of a study, obesity caused 42% more deaths compared with people without obesity during the prevalence of H1N1 influenza, and this was considered a risk factor for afflicted patient’s confinement and death.\textsuperscript{84,85} Therefore, the importance of obesity in the novel coronavirus pandemic should not be overlooked and needs to be considered as a risk factor related to SARS-CoV-2 fatality.\textsuperscript{86,87} The coronavirus has access to the host cell through ACE2.\textsuperscript{88} ACE2 expression varies in different tissues including lung, heart, and kidney in SARS-CoV-2 patients compared to healthy individuals. The important point is that ACE2 expression in adipose tissue is higher than in the lung (the COVID-19 target organ). This is important because obese people have more adipose and therefore higher ACE2 expression; hence, the virus is more likely to attach to this receptor.\textsuperscript{89,90} Furthermore, curing the patients with antihypertensive medications (i.e., angiotensin-converting enzyme inhibitors and angiotensin receptor blockers) cause an increase in ACE2 expression;\textsuperscript{91} consequently, more receptors are expressed for the virus to enter and be replicated. As a result, people with high blood pressure are 2.5 times more likely to develop SARS-CoV-2.\textsuperscript{92} Another main risk factor that should be considered is patients with cancer. In the COVID-19 incidence, the most dangerous risk is for patients with cancer who do not receive medical services due to the incidence and the probability of being affected by this virus. In majority of cases, measuring their clinical tests is postponed.\textsuperscript{93} According to a study, the incidence of cancer was 1% among 1590 novel coronavirus-affected cases,\textsuperscript{94} which is higher than the overall prevalence of cancer in the Chinese population (0.29%).\textsuperscript{95} According to another similar study conducted on 1099 COVID-19 patients, 23.7% of the total population suffered from an additional disease such as hypertension, diabetes, chronic obstructive pulmonary disease, coronary artery diseases, and cancer; further, 58.1% of patients were men.\textsuperscript{1} In another study in the United States, 393 patients were affected by COVID-19, their average age was 62, 60.6% of them were men, and 37.4% of the afflicted cases were of the white race. In addition, the most common diseases among the patients were hypertension, diabetes, obesity, coronary artery disease, asthma, and chronic obstructive pulmonary disease.\textsuperscript{96} The results obtained from a meta-analysis study that was performed on 42648 patients with COVID-19 revealed that most comorbidities were...
hypertension, diabetes, and cardiovascular coronary disease. Numerous studies have been carried out on the effect of comorbidity on the severity of COVID-19 as well as on the mortality rate. Therefore, it is important to investigate this relationship in patients.

### Conclusion

Due to the rapid global prevalence of COVID-19 and its huge mortality rate, the importance of virus pathogenesis and different clinical aspects can be a great help to accurately and rapidly diagnose the patients. Moreover, examining some disease severity predisposing factors is substantial in patients with COVID-19. Research conducted on comorbidity and COVID-19 demonstrated that people with diabetes are at a higher risk of being affected by the virus and have a higher mortality rate.

Patients with diabetes are more likely to have serious complications. One reason is that hyperglycemia weakens the immune system and makes it less capable of fighting against viral infections. Various investigations have indicated the positive effect of metformin in patients suffering from COVID-19, while some investigations have reported the higher risk of disease severity in COVID-19 patients using metformin. Thus, further research is required in this regard.

Clinicians need to diagnose and cure COVID-19 patients with diabetes. Indeed, proper management of glucose levels in diabetic patients and immune system improvement in susceptible ones may be effective in novel coronavirus patients because they can suppress the COVID-19 severity in the patients.

### Authors’ Contributions

MD and FS designed the study. BH, MG, SHS, and NN conducted the search strategy. MJN and AK wrote and edited the manuscript. MD and FS assumed the overall responsibility for the accuracy and integrity of the manuscript.

### Conflict of Interest Disclosures

The authors declare no conflict of interests.

### Ethical Approval

Not required.

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