

COVID-19 Versus Diabetes Mellitus: Whom Affect the Other?

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Abstract

Diabetes is considered as a precipitating factor for the poor outcomes of COVID-19. Patients with diabetes had a 2.5–3.9 times higher odds of being infected. Viral infection in diabetic patients could be harder to treat due to fluctuations in blood glucose levels. Their compromised immune system leads to a longer duration of recovery. Furthermore, poorly controlled diabetes impairs the immune response to viral infections. C-reactive protein, IL-6, and D-dimer are inflammatory biomarkers elevated among diabetic patients infected with COVID-19. Many scenarios could explain; how could COVID-19 induce Type 1 diabetes? and how COVID-19 brings out Type 2 diabetes? There is lack of data regarding pancreatic abnormalities and manifestation in COVID-19 patients. Hence, further investigations are required to stand on the consequences of COVID-19 in subjects with pre-diabetes and patients with diabetes. Losing at least 15 pounds, regular physical exercise, control diet and regular checkup are the most important measures for prevention of diabetes after COVID-19. Regular monitoring of blood sugar levels after COVID-19 illness and control of hyperglycemia as early as possible are essential to avoid development of severe complications and poor outcome. Appropriate management of comorbidities is of great significance in mitigating the COVID-19 pandemic. Diabetic patients must have priority for vaccination against COVID-19. CDC recommends that people with underlying medical conditions including diabetes should receive a third dose of COVID-19 Vaccine at least 3–6 months after completion of their second dose series.

Key words: Chronic diseases, comorbidities, COVID-19, diabetes, prognosis

INTRODUCTION AND BACKGROUND

Coronavirus disease 2019 (COVID-19) is a new and potentially serious coronavirus emerged disease. It is characterized by immense infectivity and high mortality. It was identified in Wuhan City, China in December 2019.^[1] There are many coronaviruses transmitted from animals to human; common cold, Severe Acute Respiratory Syndrome (SARS), and Middle East Respiratory Syndrome (MERS). SARS-CoV-2 belongs to the genus *Betacoronavirus*. It includes other pathogenic viruses like (SARS-CoV) and (MERS-CoV).^[2] SARS-CoV and SARS-CoV-2 that share nearly 80% sequence similarity, gain cellular entry through spike proteins binding to the angiotensin-converting enzyme-2

(ACE2).^[3] COVID-19 has rapid transmission rate among humans.^[4] It has higher binding affinity to ACE2. It could explain its exaggerated transmissibility.^[5] Coronaviruses can cause severe infection in the lungs (pneumonia), kidney failure, and even death.^[6] Chinese health authorities warned the World Health Organization (WHO) on December 31, 2019, about the novel coronavirus outbreak. Then, it declared the COVID-19 outbreak to be a public health emergency of international concern. The WHO on March 11, 2020 declared

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COVID-19 as a pandemic because of the rapid spread of infection and its enormous global impact.^[7]

MATERIALS AND METHODS

This study focused on COVID-19 patients and chronic diseases especially diabetes. Theories and hypotheses that explain mechanisms of occurrence of diabetes mellitus among COVID-19 patients were searched. The relevant literature published in English was searched in PubMed, Cochrane Library, Research Gait, and Google Scholar databases. The Boolean operators and keywords used in multiple electronic searches were COVID-19 and diabetes [All Fields] AND [mechanism of action] [All Fields] OR effect [All Fields]. The search strategy and the keywords were modified as appropriate according to the database search. Furthermore, the studies' listed references in included articles were manually searched. Articles retrieved were 197 which were reviewed by two independent assessors and finally both agreed to include 59 studies in this research [Figure 1].

RESULTS

Prevalence

Globally, the COVID-19 pandemic has had a profound impact on public health. As of 23 December 2021, there have been 276,436,619 confirmed cases of COVID-19, including 5,374,744 deaths, reported to the WHO. A total of 8,649,057,088 COVID-19 vaccine doses have been administered as of 22 December 2021.^[8] The Saudi Center for Disease Prevention and Control reported that “the total confirmed cases of COVID-19 in GCC as of one August 2021, was 1,869,971, and the total confirmed cases in Saudi Arabia was 525,730 cases”.

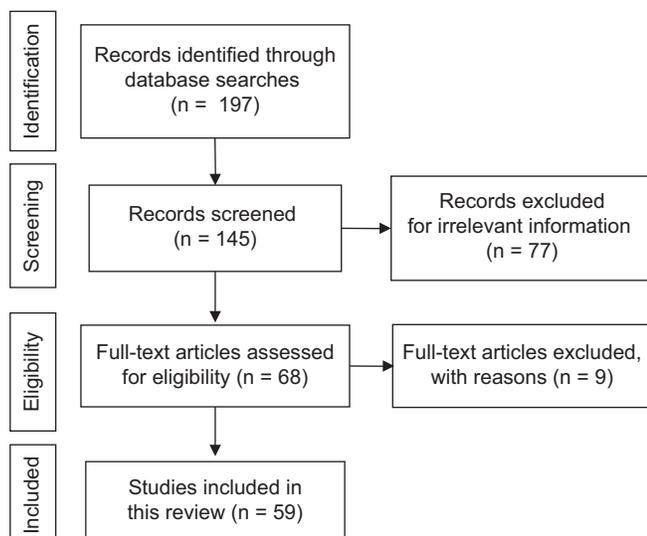


Figure 1: Prisma flow diagram

SYMPTOMS AND SIGNS

Common signs of COVID-19 are typical flu-like symptoms: a fever, cough, tiredness, muscle aches, fatigue, dyspnea, and bilateral lung infiltrates on imaging.^[9] Symptoms usually start within 3–7 days of infection, but in some cases, it has taken up to 14 days for symptoms to appear.^[10] It infects people of all ages and both sexes. Most of cases of COVID-19 is mild, with flu-like symptoms. Most of cases who have caught the virus have not needed to be hospitalized. However, in 10–15% of cases, COVID-19 has been severe and in around 5% of cases it has led to critical illness. The pathogenicity of the virus in some patients can lead to fatal complications, including organ failure, pulmonary edema, septic shock, severe pneumonia, and acute respiratory distress syndrome (ARDS).^[3,11] The vast majority of people infected to date have survived.^[6]

MODE OF TRANSMISSION

Like any other respiratory disease, COVID-19 spreads either by direct contact with an infected person or by air droplets that are dispersed when an infected person talks, coughs, or sneezes. The virus can survive from few hours up to few days depending on the environmental conditions.^[6]

COVID-19 AND COMORBIDITIES

The effect of associated comorbidities on COVID-19 has been studied widely. Comorbidities are observed in 20–30% of COVID-19 patients, while the proportion increases to 50–80% in patients with severe COVID-19.^[12-14] The most prevalent chronic diseases are hypertension, diabetes, cardiovascular diseases, obesity, chronic obstructive pulmonary disease (COPD), and cancer. The severity and death rate were several folds higher than that in the overall population.^[12,14] Diabetes is considered as a precipitating factor for the poor outcomes of COVID-19. Patients with diabetes or cardiovascular disease had a 2.5–3.9 times higher odds of being infected.^[15] The association between the presence of comorbidities and COVID-19 severity was clearly observed. A systematic review and meta-analysis conducted in China 2020,^[15] reported 20.8% were severe cases. Hypertension, diabetes, or chronic obstructive pulmonary disease (COPD) were the most associated comorbidities.^[15]

A descriptive study done in Riyadh, Saudi Arabia, that included a total of 439 patients, the most associated comorbidities were Vitamin D deficiency (74.7%), DM (68.3%), hypertension (42.6%), and obesity (42.2%). During hospitalization, 17.5% of cases were died. Diabetic patients have higher death rate (20.5%) as compared with 12.3% among non-diabetic ones; ($P = 0.04$). They also have lower survival time compared with non-diabetics ($P = 0.016$). This

study reported that other factors such as old age, congestive heart failure, β -blocker use, presence of bilateral lung infiltrates, elevated creatinine, smoking and severe Vitamin D deficiency, appear to be significant predictors of fatal outcome.^[16] Wang and his colleagues reported that 46.4% of COVID-19 patients had one or more underlying chronic condition.^[15] However, 26.1% of patients admitted to the emergency care unit, three-fourths of patients were stable without emergency care.^[15]

Nearly three-fourths (72.2%) of patients admitted to the emergency care had underlying chronic diseases. They were more likely to have dyspnea and anorexia, and many of them (47.2%) needed invasive ventilation. Findings indicate that older age and chronic diseases are considered as risk factors for poor COVID-19 outcomes. Another study from China describing the presence of comorbidities among COVID-19 deceased patients reported 48% of patients were hypertensive, 21.2% were diabetic and 14% having cardiovascular diseases.^[17] A study done in Italy on COVID-19 deceased patients reported that 77.8% having cardiovascular diseases, 70.6% of patients were hypertensive, and 31.7% were diabetic.^[18] Another study in the UK reported that 74% of patients were hypertensive, 44.7% having chronic kidney diseases, 41.8% were diabetic, and 36.1% having cardiovascular diseases.^[19]

Other study done in New York City (2020) included 5700 COVID-19 patients, the most common comorbidities reported were hypertension (56.6%), obesity with a body mass index (BMI) ≥ 30 (41.7%), and diabetes (33.8%). Other chronic conditions included coronary artery diseases, chronic respiratory diseases, chronic kidney diseases, congestive heart failure, and cancer in descending order.^[14] The findings of this study were consistent with preliminary U.S. data, including 7162 COVID-19 cases, that were reported to the Centers for Disease Control and Prevention (CDC) from 50 states.^[20] In this report, 37.6% of patients had one or more underlying health condition, with the most commonly described conditions being diabetes, chronic lung diseases, and cardiovascular diseases; (29.1%), (24.4%), and (24.0%) respectively.^[20] Among ICU admitted patients, 78% had at least one risk factor or pre-existing health problem.^[20] This report revealed that COVID-19 patients with pre-existing chronic diseases were at a higher risk for severe COVID-19 symptoms and associated with poor outcomes.^[20]

Mortality reports – although inaccurate - may explain COVID-19-related severe outcomes and the actual causes of death.^[21] Elderly patients aged 80 years and older had higher case-fatality rate (CFR) of COVID-19 in Italy and China compared to younger patients.^[21,22] Older patients are more likely to have pre-existing chronic diseases that increases the severity of COVID-19 and leads to poor prognosis.^[23] COVID-19 patients having comorbidities reported an elevated CFR; for cardiovascular diseases, diabetes, chronic respiratory diseases, and hypertension; (10.5%), (7.3%), (6.3%), and (6.0%), respectively.^[22]

LONG-TERM EFFECTS OF COVID-19

Unfortunately, COVID-19 could result in sudden onset of long-term organ damage in individuals that did not have preexisting chronic diseases. Some of these complications may include myocardial injury,^[24] acute or chronic diabetes,^[25] kidney injury,^[26] liver damage,^[27] and gastrointestinal (GI) complications.^[28]

CAUSES OF POOR OUTCOME

Patients with chronic illnesses could be affected by the COVID-19 pandemic either in a direct or an indirect manner. First, patients having chronic diseases follow regular and frequent visits to health-care facilities for review and follow-up with elevated risk of exposure to health-care-related infection. Second, the COVID-19 pandemic exhausts health-care resources, causing delayed medical care for patients with chronic diseases. Hence, health professionals should prioritize the treatment during pandemic. They should carefully weigh the risk of death and complications from COVID-19 against the benefits of intended therapies.^[29-31] Third, it affects the routine health services. It impacted both the quality and continuity of care for patients having chronic diseases.^[32] It provided a challenge to modern medical care, to control spread of infection in the community and shift toward the acute care for patients with severe COVID-19 in hospitals. Fourth, health-care resources at all levels have shifted away from chronic disease management during the outbreak. Reduced access to medical care, lack of hospitalizations of patients with non-COVID-19 pathology, and a decrease in referrals were the most.^[33] Fifth, patients having chronic illnesses postponed healthcare seeking fearing of getting infected with the coronavirus.^[34] Sixth, patients have less options for community-based care and support. This trigger alarm about the indirect health effects of COVID-19, especially on patients with chronic diseases with higher incidence of complications and poor outcome due to lack of accessibility to secondary health care and diminished follow-up at primary health care level.

At the same time, the increased severity of COVID-19 in patients with comorbid conditions may be attributed to excessive immune reaction to the virus, which is known as the “cytokine storm”.^[35,36] Furthermore, the higher expression of ACE2 in some organs such as the lungs, heart, islets of pancreas, kidneys, and small intestine^[11,37,38] could explain the severe presentation in a specific patient population because ACE2 is the functional receptor by which SARS-CoV-2 gains cellular entry.^[5]

Historically, during the outbreak of SARS-CoV and MERS-CoV, diabetic patients had reported severe and fatal forms of coronavirus pneumonia.^[39,40] During COVID-19 pandemic, diabetic patients have been identified at high risk for severe COVID-19 and poor outcome. Diabetes is one of the most

frequently reported comorbidities in ICU admitted and deceased COVID-19 patients.^[20,22,41] In a study conducted on 52 ICU admitted COVID-19 patients, 61.5% of patients had died 28 days post-admission. Diabetes and cerebrovascular diseases were the most common comorbidities in those patients (22%) each.^[23] Case fatality rate among 44,672 COVID-19 patients in China was 7.3% in patients with diabetes compared with 2.3% in patients without comorbidities.^[22]

Several factors may contribute to the poor prognosis of COVID-19 in diabetic patients.^[42] Viral infection in diabetic patients could be harder to treat due to fluctuations in blood glucose level. Their compromised immune system leads to a longer duration of recovery. Furthermore, poorly controlled diabetes impairs the immune response to viral infections.^[43] At the same time, the virus grows and replicated in an environment of elevated blood glucose. On the other hand, diabetic patients have elevated plasminogen levels.^[44] This particular protein cleaves the spike protein of SARS-CoV-2, enhancing cellular entry of the virus that increased virulence and infectivity of the virus.^[44] C-reactive protein, IL-6, and D-dimer are inflammatory biomarkers elevated among diabetic patients infected with COVID-19. This may be an indicator for poor prognosis of COVID-19.^[24] Furthermore, defective T-cell action impairs natural defense mechanisms, which reduces the capability of viral clearance.^[45] Attenuation of the innate immune response, pro-inflammatory state, possibly increased level of ACE2, as well as vascular dysfunction, probably contribute to higher susceptibility for COVID-19 infection and poor prognosis. Many diabetic patients receive ACE inhibitors for renal protection. ACE inhibitors increase the expression level of ACE2, which could enhance viral entry into the host cells.^[46] Treatment with glucocorticoids activates inflammation and islet damage induced by virus infection that could result in impaired glucose regulation with aggravation of the disease. Alternatively, diabetes associated with other chronic diseases such as hypertension, coronary artery disease, and chronic kidney disease have poorer COVID-19 prognosis.^[42] Therefore, glycemic control in patients with COVID-19, especially in those with severe illness, is of considerable importance. Collectively, diabetic patients are at a higher risk of developing severe illness due to COVID-19.

DOES COVID-19 INDUCE DIABETES?

Another point of view, a global analysis published in November 2020, reported that up to 14.4% of patients hospitalized with severe COVID-19 also developed diabetes. The question need to be answered is there an association between earlier appearance of diabetes and the viral infection or the COVID-19 illness? The response of these patients to insulin therapy does not suggest that there's an inherent property of this virus to directly impact pancreatic beta-cells responsible for producing insulin. It is well known that 90% of subjects with prediabetes don't know that they have prediabetes, even though this group is at high risk of developing

Type 2 diabetes. Furthermore, 25% of patients with diabetes are not yet diagnosed, according to data from the Centers for Disease Control and Prevention in 2018.^[47]

MECHANISMS THROUGH WHICH COVID-19 INDUCES DIABETES

It is well known that SARS-CoV causes damage in the islets of the pancreas leading to acute onset diabetes.^[23] A study done in China in 2010 reported that about 50% of healthy patients infected with SARS-CoV became diabetic during hospitalization.^[23] After 3-year follow-up, 10% of these patients had diabetes. Hence, they concluded that the damage to the islets of pancreas induced by SARS-CoV was transient.^[23] Rubino and his colleagues reported that "the presence of ACE2 in pancreatic beta cells and adipose tissues.^[25,37] provides a possible damaging effect of SARS-CoV-2 in these organs through altering glucose metabolism that may trigger new onset of diabetes or worsen preexisting one".^[25]

Length of hospital stay prolonged in diabetic patients with COVID-19 infection with higher health-care system expenses. COVID-19 induced ketoacidosis in healthy subjects and diabetic ketoacidosis in diabetic patients.^[37] that is directly related to the interaction with the renin-angiotensin-aldosterone system (RAAS).^[48] Entry of the virus through endocytosis is a result of binding of SARS-CoV-2 to ACE2, hence, ACE2 becomes downregulated, resulting in accumulation of angiotensin II (Ang II).^[49] Angiotensin II binds to Ang II type 1 receptor causing impairment of glucose-stimulated insulin secretion and hence preventing insulin biosynthesis.^[50,51] A study done in China recorded that six out of nine COVID-19 patients with pancreatic injury and abnormalities in amylase or lipase levels^[41] were found to have abnormal blood glucose levels. Another explanation could be the invasive immune response induced by COVID-19 causing pneumonia and respiratory failure, which contributes to damage of more than one organ.^[41] However, there is no prove of pancreatic abnormalities and manifestation in COVID-19 patients. Hence, further investigations are required to stand on the consequences of COVID-19 in patients with diabetes.^[41]

HOW COULD COVID-19 INDUCE TYPE 1 DIABETES?

The previous epidemiologic data revealed that Type 1 diabetes is most probably associated with an acute viral infection such as influenza. This infection enhances antibodies production, such as those directed toward the islet cells of the pancreas responsible for producing insulin. This response leads to sudden loss of beta cells, resulting in acute hyperglycemia. As the acute disease resolves, the immune system activation

subsides and the pancreas may resume function; hence, the patient experiences a “honeymoon phase” in which minimal doses of insulin are needed and glucose-regulation is deficient. This phase often remains for 1–10 years and, may, ends suddenly, with the need for daily doses of insulin.^[47]

HOW COULD COVID-19 BRING OUT TYPE 2 DIABETES?

Many scenarios could explain how COVID-19 brings out Type 2 diabetes. First, already diabetic patients but not diagnosed before COVID-19 infection. Second, the patient may be pre-diabetic, and become diabetic after COVID-19 infection. Third, treatment of pre-diabetic patient with steroid could induce diabetes. Forth, genetic predisposition associated with other stressors such as overweight and sedentary lifestyle could promote diabetes. Overall, insulin resistance due to acute infection and treatment of COVID-19 with steroids required extra insulin to control glucose level, meanwhile the pancreas cannot increase its output to the required level. However, many patients may still pre-diabetic 6 months to 5 years after infection, before being diagnosed with Type 2 diabetes.^[47]

PREVENTION OF DIABETES AFTER COVID-19

Losing at least 15 pounds

Losing 15 pounds at first is important, while losing more weight could help. In case of loss of weight during the illness, you have the opportunity to regain muscle weight instead of total weight lost. Body mass index (BMI) <25 is the optimal one.^[6]

Regular physical exercise

Regular daily walking help control body weight and maintain insulin sensitivity and hence slow the progression to Type 2 diabetes.^[6,52-56]

Control diet

Well-balanced diet helps control weight and enhance immunity. Replace sugared beverages with water or sugar-free beverages.^[6,52-56]

Regular checkup

Regular checkup for diabetes every 6 months after hospital discharge is recommended.^[6,52-56]

Seek medical help for diabetes

Uncontrolled hyperglycemia damages nerves and blood vessels throughout the body. This damage causes peripheral neuritis with loss of sensation in feet and can damage the heart, eyes, and kidneys. Furthermore, hyperglycemia leads to fatty liver disease and heart failure due to fat deposition in the liver and muscles. These complications of hyperglycemia may be the trigger for diagnosis of diabetes, in spite of such complications may take at least 5 years to develop. Hence, measuring blood sugar levels after COVID-19 illness is essential to avoid development of these complications. Control of hyperglycemia as early as possible can significantly delay such complications.^[6]

MANAGEMENT OF DIABETES IN COVID-19 PATIENTS

The first target concerning management of diabetic patients infected with COVID-19, is optimizing glycemic control to reduce the risk of complications.^[57] In addition to choosing the suitable hypoglycemic agents in patients with metabolic syndromes, we have to choose the suitable lipid-lowering and antihypertensive agents.^[57] Metformin and sodium-glucose-co-transporter 2 inhibitors have the risk of euglycemic ketoacidosis or lactic acidosis, so, these medications should be avoided in diabetic patients with severe manifestations of COVID-19 to decrease the incidence of acute metabolic decompensation.^[57,58] Renal function tests are essential during the disease to prevent the risk of acute kidney injury or chronic kidney disease.^[57] Dipeptidyl peptidase-4 inhibitors such as saxagliptin, linagliptin, and alogliptin are usually used but, insulin is the treatment of choice.^[57] Keep in mind that insulin lower plasma potassium concentrations in COVID-19 patients; hence, continuous monitoring of potassium levels is essential.^[59] Potassium balance should be maintained to prevent hypokalemia causing more disease severity.^[59] Fluid balance should be maintained to avoid accumulation of fluid causing pulmonary edema especially in severe inflamed lungs.^[52,56] In conclusion, insulin must be recommended to control acute glycemia. Further follow-up of the optimal management of COVID-19 in patients with diabetes is mandatory.

COVID-19 VACCINATION

Priority for vaccination against COVID-19 should be given for diabetic patients.^[6] CDC recommends that people with comorbidities including diabetes should receive third dose of COVID-19 Vaccine 3–6 months after second dose. Furthermore, people at any age with an underlying medical disease may receive a COVID-19 Vaccine booster.^[60]

WHAT SHOULD DIABETIC PATIENTS KNOW AND DO?

Diabetic patients should take precautions to avoid any viral infection whenever possible. Health precautions concerning prevention of COVID-19 that are being widely used by healthy people should be more strictly followed by diabetic patients.^[61,62]

- Thorough and regular hand washing and hand hygiene.
- Avoid touching face and eyes before washing and drying your hands.
- Regular cleaning and disinfecting surfaces and any objects that are frequently touched.
- Avoid shared towels, glasses, tools, food, etc.
- Cover your mouth and nose with a clean tissue or use the crook of left arm if you do not have a tissue when you cough or sneeze.
- Dispose of used tissue in appropriate clean receptacles.
- Avoid contact with people having symptoms of respiratory disease such as coughing.
- Avoid unnecessary travel.
- Avoid large gatherings.
- Avoid public transport.
- Regular checkup of glucose level help controls diabetes and prevent complications associated with hyperglycemia or hypoglycemia.
- Avoid contact with people If you have flu-like symptoms and immediately consult a healthcare professional.
- In case of any infection, you should take an equal amount of water.
- Maintain a regular supply of diabetes medications.
- Avoid stress and overwork.
- Have a good night's sleep.^[6]

CONCLUSION

Chronic illnesses are associated with complications and poor outcome of both COVID-19 and comorbid conditions. Switch and moving of health services toward COVID-19 without regular management and follow-up of chronic diseases lead to severe complications and death.

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CONFLICTS OF INTEREST

No any conflicts of interest.

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