Republic of Iraq
Ministry of higher education
and scientific research
University of Diyala
College of Medicine

The effect of COVID-19 on the blood glucose level

by
Osama Khalof Radif

Supervised by
Asst. Lec. Yasmine Sami Nassir

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Abstract

COVID-19 is a very serious and urgent infection disease. The incidence of diabetes is increasing year by year, and it more common in elderly. COVID-19 is associated with much chronic disease, especially diabetes. Patient with co-morbidities such as hypertension, cardiovascular disease, and diabetes mellitus (DM) seem to be more sever symptoms and appear to have a high mortality rate.

The worsened prognosis of COVID-19 patients with DM can be attributed to a facilitated viral uptake assisted by the hostels receptor angiotensin-converting enzyme 2 (ACE2). It can also be associated with a higher basal level of pro-inflammatory cytokine storm in response to the virus.

Effect of diabetes & COVID-19 infection on each other and the management of the COVID-19 patient with diabetes. Patients with diabetes are known to be at increased risk for infections including severe COVID-19. Elevated pre-infection blood glucose is a risk factor for severe COVID-19 even in non-diabetics. For patients with a diagnosis of diabetes both high as well as low pre-infection glucose levels are risk factors for severe COVID-19. Diabetes mellitus is associated with a significant risk of complication, extended hospital stays, and mortality in COVID-19 infection patients.

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has a wide spectrum of clinical manifestations ranging from asymptomatic infection to severe respiratory symptoms, and even death (1).

Diabetes mellitus (DM) is a complex chronic disease characterized by high blood glucose, absolute and relative insulin deficiency. It includes type1 diabetes, type 2 diabetes. Among them, the morbidity of type 2 diabetes was the highest (1). The analysis in China by Chinese Center for Disease Control and Prevention (CDC) shows that the mortality combined with diabetic patients is 7.3%, while the overall mortality is 2.3%. The National Institutes of health in Italy reported that the prevalence of diabetes in patients who died of SARS-CoV-2infection was 35.5% (2).

Diabetic patients are more likely to suffer from serious infection due to hyperglycemia, chronic inflammatory state, microcirculation damage and other factors. It was found that type 2 diabetes may increase the expression of Angiotensin Converting Enzyme 2 (ACE2) in the lung (4). Currently, several studies have been designed to focus on details of the clinical and virological course of SARS-CoV-2 infection. Subsequently, studies suggest that individuals with older age and comorbidities, such as diabetes and hypertension, are more likely to have COVID-19, as well as a higher risk of mortality (2, 3, 7).

Serious infections can damage insulin sensitivity, so infectious diseases lead to high mortality of diabetic patients. Many early studies have found that patients with chronic diseases such as diabetes are more severe and have worse prognosis, the duration, age, gender, race and blood glucose control of diabetes may have effect on the mortality of COVID-19 (5).

Pathophysiology of diabetes mellitus and COVID-19

Infection with SARS-CoV-2 in the setting of Diabetes mellitus (DM) initiates a flywheel of cascading effects that result in increased mortality. Infection with COVID-19 predisposes infected individuals to hyperglycemia, leading to hyper glycosylation of ACE2 and increased viral proliferation (Fig. 1) (8).

Worsening of hyperglycemia induces inflammation, endothelial dysfunction, and thrombosis via the generation of oxidative stress driving the dysregulation of glucose metabolism and hypercoagulability further (9).

Severe infection in the individuals predisposed to vasculopathy and impaired immunity may accentuate thrombotic and ischemic complications associated with multiorgan failure and increased mortality rates. It All the forms of DM can be characterized by abnormal signaling along pathways involved in glucose metabolism. DM is considered a vasculopathy equivalent as the progression of the disease is associated with both macrovascular and microvascular damage. Chronic

hyperglycemia and insulin resistance contribute to vasculopathy through various mechanisms (10).

In addition, metabolic abnormalities associated with oxidative damage causes changes in mitochondrial expression of superoxide in endothelial cells of both large and small vessels. Over time, increased superoxide production mediates a cascade of epigenetic alterations that result in persistent expression of proinflammatory pathways even after the normalization of blood glucose levels (11). Alterations in innate and adaptive immunity, including abnormal cytokine responses, inhibition of leukocyte recruitment, and neutrophil dysfunction, are also driven by states of chronic hyperglycemia (12).

The complications of chronic hyperglycemia are compounded during acute viral infections since activated immune responses can promote systemic insulin resistance and worsening of hyperglycemia (13).

Severe COVID-19 progression is significantly associated with increased blood glucose levels (14). In the setting of concomitant SARS-CoV-2 infection and DM, monitoring blood glucose levels to track worsening hyperglycemia has more prognostic value than hemoglobin A1c (HbA1c) in these patients. These findings suggest that worsening hyperglycemia occurs acutely and may drive rapid clinical deterioration in patients with pre-existing vasculopathy and endothelial dysfunction (13).

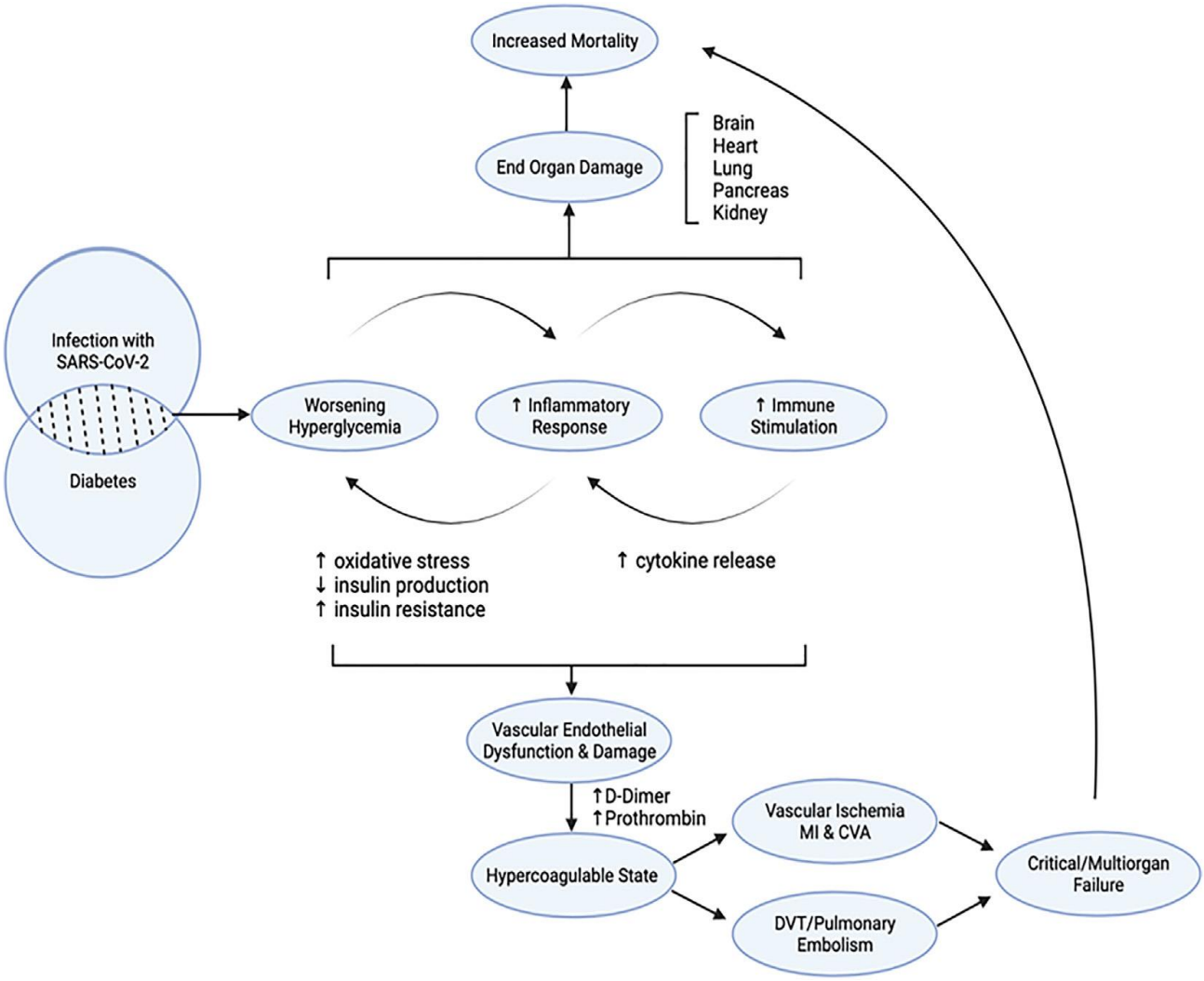

Figure 1. Pathophysiology of diabetes mellitus and COVID-19 (8).

Method of Transmission of Infection

Human coronaviruses are spread mostly though the air from an infectious person to a healthy person through sneezing and coughing (12). Close physical contact, such as rubbing or shaking hands and rubbing a virus-infected object or surface before brushing one's moth, nose or eyes before washing one's hands, seems to be spreading the virus (10).

Fecal exposure is an unusual way for these viruses to spread. Human coronavirus infections are most common in the fall and winter, although the virus will infect people at any time of year, and the weather dose not appear to affect transmission (11). Over his or her lifetime, someone may become infected with one or more human coronaviruses. Infection is also a possibility extends to kids (9).

COVID-19 and type 1 diabetes mellitus:

The prevalence of type 1 diabetes mellitus (T1DM) in COVID-19 patients ranges between 0.15% and 28.98% (14).

According to preliminary findings from a multicenter surveillance study in the United States that assessed clinical outcomes of COVID-19 in patients with T1DM, a total of 48.5% of patients had high blood glucose levels; 45.5%, elevated temperature; 39.4%, dry cough; 33.3%, excess fatigue, and vomiting; 30.3%, shortness of breath; 27.3%, nausea; and 21.2%, body/headaches (15).

Additionally, abdominal and chest pain, chills, loose stools, and loss of taste and smell were reported by <15% of patients (15).

Type 2 diabetes mellitus as a risk factor for COVID-19

Type 2 Diabetes Mellitus (T2DM) is considered a risk factor for a poor prognosis in COVID-19 (1). Many mechanisms have been described to explain the poorer prognosis of COVID-19 in diabetics, but these remain hypothetical at the time of this article. Some of these mechanisms include impaired neutrophil degranulation and complement activation, increased glucose concentration in airway secretion, which significantly increases viral replication, exaggerated proinflammatory cytokine response in diabetes, decreased viral clearance, and a more significant presence associated comorbidities (17).

One of the essential aspects of the relationship between COVID- 19 and T2DM is that the information on the condition of hyperglycemia at the time of hospital admission is more relevant for prognostic purposes than the HbA1c. It is thought that COVID-19 predisposes infected individuals to hyperglycemia, leading to hyper-glycosylation of the angiotensin-converting enzyme 2 (ACE2), the natural viral receptor on the host cell surface (16).

Clinical definitions

The severity of COVID-19 was defined according to the Guidance 7th edition. Patients were classified as ‘mild’ if there was no evidence of pneumonia on imaging nor any of the features for moderate or higher sever- ity; as ‘moderate’ if they had evidence of pneumonia on imaging but no features of severe or higher severity; as ‘severe’ if they meet any of the following criteria:

(1) Respiratory distress (≥30 breaths/min).

(2) Oxygen saturation≤93% at rest on room air.

(3) Arterial partial pressure of oxygen (PaO2) or fraction of inspired oxygen (FiO2) ≦300 mmHg (l mmHg=0.133 kPa); and as ‘critical’ if they required mechanical ventilation, had a septic shock or required admission to ICU (16).

Comorbidities were defined according to ICD10-CM code. Detailed definitions for clinical symptoms were provided in the supplemental materials. We considered a patient progressing to a severe or critical disease stage when the individual had none of the severe or critical stages at admission but developed these stages for the first-time during hospitalization (18).

Patients had to meet all the following criteria before being discharged:

(1) Body temperature returned to nor- mal (<37.5 °C) for three consecutive days.

(2) Respiratory symptoms improved substantially.

(3) Pulmonary imaging showed an obvious absorption of inflammation. (4) Two consecutive negative nuclei acid tests, each at least 24 h apart (19).

Effects of hyperglycemia on complications of COVID-19

Hyperglycemia is a well-known, established risk factor for mortality due to an increased susceptibility to infections, mainly due to pneumonia. COVID-19 is characterized by pneumonia that has led to the death of over 1.65 million individuals worldwide (25).

According to a retrospective, observational study involving adult patients with laboratory-confirmed COVID-19 and uncontrolled hyperglycemia (blood glucose [BG] >180 mg/dL within any 24 h), the mortality rate was 28.8% in patients without diabetes or hyperglycemia. Additionally, 41.7% of patients with uncontrolled hyperglycemia died versus 14.8% of patients with diabetes (26).

Furthermore, the median length of stay in patients with diabetes and/or uncontrolled hyperglycemia was more prolonged than in patients without diabetes or hyperglycemia (26).

A recent meta-analysis that assessed the outcomes of COVID-19 in patients with hyperglycemia reported death in 17%, 11% to have been admitted to the ICU, and 23% to have required mechanical or non-mechanical ventilation (27).

Drug therapy of DM among COVID-19 patients

Both oral and injectable non-insulin antidiabetics (summarized in Table 1) as well as insulin and their relation to COVID-19 management and outcomes.

Table 1. Antidiabetics and COVID-19 (21).

Anti-diabetic drug	**Potential benefit**
Metformin	It has been described as a potent drug to reduce mortality with its use in patients with type 2 diabetes and covid-19 infection.
Pioglitazone	Possible reduction in inflammatory markers.
Sulfonylureas	Potential reduction in disease severity.
DPP-4 inhibitors	It has been proposed that DPP-4 could be involved with the receptor binding domain of SARS-CoV-2. Furthermore, it could offer anti-inflammatory, anti-fibrotic and immunomodulatory effects. Several researchers have proposed its use as a repurposed agent for COVID-19.

Metformin:

The majority of the T2DM patients on oral hypoglycemics take Metformin, either alone or with other drugs. Metformin is the preferred initial drug to treat type 2 DM. Metformin therapy may be associated with lactic acidosis. This is rare in the absence of other factors

predisposing to lactic acidosis but could happen in patients suffering renal impairment, severe infections, or sepsis (27).

Pioglitazone:

Pioglitazone upregulates Angiotensin converting-2 enzyme (ACE-2) in rat tissues (22), leading to concerns that it may increase COVID-19 severity. Since ACE2 acts as a receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) enter cells (23).

Sulfonylureas:

Sulfonylureas may induce hypoglycemia, so in the patients with severe COVID-19 with inadequate oral intake, it is safer to restrict their usage. In addition, simultaneous use of hydroxychloroquine may increase the risk of hypoglycemia (24).

Dipeptidyl peptidase 4 (DPP-4) inhibitors:

DPP-4 inhibitors are well tolerated and can be continued safely in COVID-19 patients (16). They are associated with a low risk of hypoglycemia. DPP-4 may act as a receptor for some coronaviruses, and hence, DPP-4 inhibitors might inhibit such binding and mitigate COVID-19 infection (17).

Insulin:

Insulin therapy is preferred for hospitalized patients, including moderate to severe COVID-19 disease. For non-critical hospitalized patients, a basal plus bolus correction regimen is recommended with a target blood sugar range of 140e180 mg/dl (22).

Critically ill COVID-19 diabetic patients in ICU are managed by intravenous insulin infusion. Intensive insulin therapy was found to exert an anti-inflammatory effect in critically ill patients and reduce the levels of inflammatory markers {C-reactive protein (CRP) and mannose-binding lectin (MBL)} compared to conventional insulin therapy (19). Whether the anti-inflammatory effect of insulin is beneficial in COVID-19 patients or not needs further assessment and evaluation. A possible therapeutic regimen in non-critically ill COVID-19 diabetic patients is a combination of basal Insulin with GLP-1 agonist, given as a single injection. The rationale beyond this therapeutic strategy is giving a single daily injection minimizing exposure to COVID-19 patients. Also, both insulin and GLP-1 agonists have a glucose-lowering effect and a possible anti-inflammatory effect (20).

DKA and COVID-19

Hyperglycemic complications of diabetes mellitus include Diabetic Ketoacidosis (DKA), hyperosmolar hyperglycemic syndrome (HHS). DKA is the commonest of these complications, with the highest

hospitalizations rates that also increased in the last decade in developed countries, but positively, mortality decreased to less than 0.5% (28). Similar to a case of any severe infections, DKA can occur in diabetic patients with COVID-19. Severe Acute Respiratory Syndrome Coronavirus-1 (SARS-CoV-1) was found to bind to the ACE2 receptor in the pancreatic islets, which causes cellular damage leading to acute onset of diabetes DKA (29).

Many studies and case reports later reported new-onset diabetes with DKA as the presenting symptom in COVID-19 or DKA without respiratory symptoms, and even euglycemic DKA was reported (30). COVID-19 has also been linked to new-onset T1DM with DKA and pancreatic autoantibodies (31). A recent systematic review evaluated 110 cases of DKA with COVID-19, with the majority (91/110) presenting with DKA. Mortality reached 45%, and it was higher in the DKA group. This high mortality rate could be related to COVID-19 or combining both factors. A single study conducted at Jacobi center in New York had DKA mortality of 50% when patients had concomitant COVID- 19 (32). Management of DKA with COVID-19 follows the standard protocol, although it was noted that patients required higher than usual insulin doses (33).

Corticosteroids and COVID-19

Steroids show severe negative effects on diabetics. They are a part of many medicines used for both short-term and long-term treatment. Primarily they are used for their anti-inflammatory and immunosuppressive actions with subsequent undesirable side effects such as osteoporosis, hypertension, hyperglycemia, and steroid-induced diabetes (34).

Many factors contribute to the degree of hyperglycemia, including duration of treatment, dosage, relative potency, and associated infection. The higher the dose of steroid therapy, the higher the risk of developing steroid-induced diabetes. The use of steroids in diabetic patients increases the risk of hospitalization due to uncontrolled blood sugar (35). In the first few months of the pandemic, World Health Organization (WHO) recommended against corticosteroid treatment, based on historical evidence in clinical studies of Middle East Respiratory Syndrome-corona Virus (MERS-CoV) and SARS-CoV (36). That showed treatment complications such as delayed viral clearance, opportunistic infections, and hyperglycemia. Following the warning, many institutions-initiated observation all studies and randomized controlled trials (RCT) on steroid therapy for COVID-19, with the most extensive study in the UK, also known as The RECOVERY trial, which showed dexamethasone as opposed to usual care reduced 28-day mortality in patients requiring oxygen therapy or mechanical ventilation (37).

Conclusions:

Diabetes mellitus carries a significant risk of complications, extended hospital stays, and mortality in COVID-19 infected patients. Therefore, insulin is preferred to oral hypoglycemic medications in the management of hospitalized COVID-19 infected diabetic subjects. This cohort has recommended frequent blood sugar checks and prompt management of hypoglycemia, hyperglycemia, and DKA.

Presented stage-wise disease's first progression among COVID-19 patients. Identified that older age, elevated glucose level, together with other clinical indicators associated with systemic responses and multiple organ failures, predicted both the disease. Sever COVID- 19 is associated with increased blood glucose. Attention should be paid to monitor blood glucose status in patients with COVID-19 and better glycemic control may be an important supportive treatment.

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