

Diabetes and COVID-19 Pandemic: A Potential Mechanisms: A Review

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Abstract

Diabetes is the greatest public condition among patients with coronavirus disease and has been found to affect prognosis worldwide. It is revealed that hyperglycemia is one of the elements that elevates the risk of consequences in these persons. This study designed to analysis the overall features of the novel coronavirus and provide an understanding of the coronavirus disease in diabetic patients, and its treatment.

These patients are usually treated with various medications and this review clarify the role of metformin and dipeptidyl peptidase 4 inhibitors as helpful factors in these patients. Recommendations are made on the probable pathophysiological mechanisms of the association between coronavirus and diabetes, and its management. Additional study about this association and its clinical managing is necessary.

Keywords: Diabetes mellitus, Coronavirus disease, Severe acute respiratory syndrome-coronavirus-2, Metformin, Dipeptidyl peptidase 4 inhibitors.

Introduction

Diabetes mellitus (DM) is a main cause of morbidity and mortality through the world. It is related with various micro- and macrovascular complications, that eventually influence the general patient's endurance⁽¹⁾.

An association between infection and diabetes has long been clinically known⁽²⁾. Current epidemiological data of the Italian reported as the risk of mortality in coronavirus (COVID-19) patients progressively increases with the numbers of the comorbidities⁽³⁾.

Coronavirus belong to the Coronaviridae, the members of which infect a wide-ranging range of

hosts, generating symptoms and diseases ranging from a common cold to severe and eventually fatal diseases as severe acute respiratory syndrome (SARS), Middle-East Respiratory Syndrome (MERS), and as of present COVID-19 (Figure 1)⁽⁴⁾.

Differential Diagnosis of COVID-19:

The symptoms of the primary phases of the disease are non-specific. Differential diagnosis must contain the probability of a varied types of respiratory disorders.

- Influenza
- Parainfluenza
- Rhinovirus (common cold)
- Adenovirus
- Human metapneumovirus (HmPV)
- Respiratory syncytial virus (RSV)

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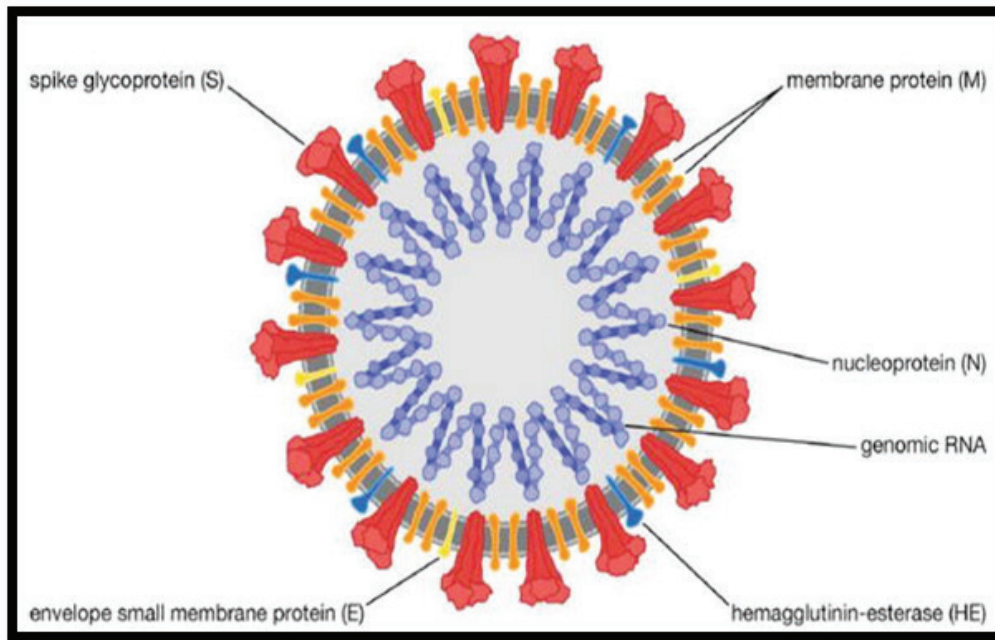


Figure 1. Structure of SARS-CoV2 (3)

Demography and Clinical Characteristics:

Although all age groups have been exaggerated by COVID-19, the middle age seems between 47–59 years, and commonly greater among severe cases and non-survivors. Signs and symptoms of COVID-19 are illustrated in table 1. It has been shown that males would be poorer exaggerated than females, with a male majority in recent researches. Less cases have been recognized among children and infants, while older COVID-19 cases were noticed to have a poor prognosis (5). Additionally, metabolic syndrome found to be related with a worse scenario in COVID-19 persons. Hypertension is related with worse consequences. These primary clinical explanations that cases with severe COVID-19 are: elderly persons, male, hypertensive, with higher blood glucose concentrations and abnormal liver blood examinations increase the prospect that insulin resistance (IR) might show a significant role in intermediating disease severity. Recent documents from China expected mortality rates near 10% in DM, from a model of 72,314 established cases (6).

Table 1. Signs and symptoms of COVID-19

Fever cough fatigue sputum production shortness of breath

Review has been documented a considerable correlation between DM and COVID-19 severity (OR 2.67, 95% CI 1.91–3.74). Diabetes and race both seem to be further risk elements emerging in the clinical consequences of the COVID-19 pandemic. Within the hospital population COVID-19, infected persons with DM is overrepresented. (7).

Criteria for Suspicion and Testing:

The diagnosis of COVID-19 is approved by microbiologic analysis. Patients who undergo coronavirus according to WHO criteria must be testing for SARS-CoV-2, also testing for additional respiratory pathogens (e.g., influenza, respiratory syncytial virus, etc) (8).

Glycemic Control and COVID-19:

Limited data are concerning glucose metabolism and progress of acute complications of DM in COVID-19

patients. Patients with infection of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) and DM probably initiate higher stress circumstances, with higher release of hyperglycemic hormones levels as catecholamines and glucocorticoids, leading to elevated blood glucose concentrations ⁽⁹⁾.

Glycated hemoglobin (HbA1c) is considered for estimating blood glucose concentration within 120 days before the test, and higher HbA1c value is associated with the complications risk among diabetics ⁽¹⁰⁾. Patients with COVID-19 who has higher HbA1c value may reveal moderately greater level of severity. Moreover, the infection may leading to a rise in HbA1c value ⁽¹¹⁾.

Inflammatory Markers and COVID-19:

It was reported that inflammatory markers such as C-reactive protein (CRP) level, serum ferritin level, erythrocyte sedimentation rate (ESR) and clotting factors were positively associated with HbA1c value

in cases of COVID-19. Previous data showed that DM not only leads to dysfunction of the epithelium in the pulmonary cilia and improves the permeability of the vascular system, but also donates dysregulated immune system function ^(12, 13).

The potential mechanisms of COVID-19 affecting glucose metabolism comprise β -cell damage and IR. Preceding data have documented that certain viruses can cause pancreatic β -cell damage directly ^(14, 15), and angiotensin converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor has greater expression in pancreatic endocrine tissues than in exocrine tissues ⁽¹⁶⁾.

Hyperglycemia and IR lead to improved synthesis of pro-inflammatory cytokines, oxidative stress (OS), and advanced glycation end products (AGEs) as well as stimulating the production of adhesion molecules, (Table 2) that mediate tissue inflammation ⁽¹⁷⁾.

Table 2. Factors that affecting on some process in human ⁽¹⁷⁾

Factors	Effects
- Hyperglycemia - IR	Pro-inflammatory cytokines AGEs OS Production of adhesion molecules

This inflammatory process may initiate the primary mechanism that leads to a greater tendency to infections, with poor consequences in diabetics. Autopsy revealed that though some of pancreatic cells were deteriorated in pancreatic tissue, whereas immunohistochemical examination and polymerase chain reaction (PCR) tests did not identify the occurrence of SARS-CoV-2 in pancreatic cells ⁽¹⁸⁾. COVID-19 patients frequently show on admission lymphocytopenia, and to a reduced extent thrombocytopenia and leukopenia, which are more noticeable in cases with severe disease ⁽¹⁹⁾.

A further mechanisms, independent of ACE2 expression, are possible to donate to the additional severe phenotype related with DM in COVID-19. A cytokine storm has been concerned in the multi-organ failure

related with COVID-19 and there is good indication from animal models of MERS that DM modifies the cytokine profile and augments a dysregulated immune response which aggravates lung pathology. Hence, higher levels of proinflammatory cytokines, including interleukin-6 (IL-6) and CRP, in addition to higher coagulation activity factor, (Figure 2) noticeable by elevated levels of d-dimer, were also related with severity ⁽²⁰⁾.

The concentrations of these elements can be diminished by lifestyle-related variations. There is rare documents on diabetic ketoacidosis (DKA) with COVID-19 infection. It has been reported cases of DKA precipitated by COVID-19 in a newly diagnosed patient with DM. The diabetic ketoacidosis occurs as

a consequence of insulin insufficiency and improved regulatory responses, which favor the production of ketones ⁽²¹⁾.

The relationship between SARS-CoV-2 and the reninangiotensin-aldosterone system (RAAS) might

reveal additional mechanism in the pathophysiology of DKA. Moreover, in T2DM an inequity between coagulation and fibrinolysis happens, with higher concentrations of clotting factors and inhibition of the fibrinolytic system. These irregularities favor the progress of a hypercoagulable pro-thrombotic state ⁽²²⁾.

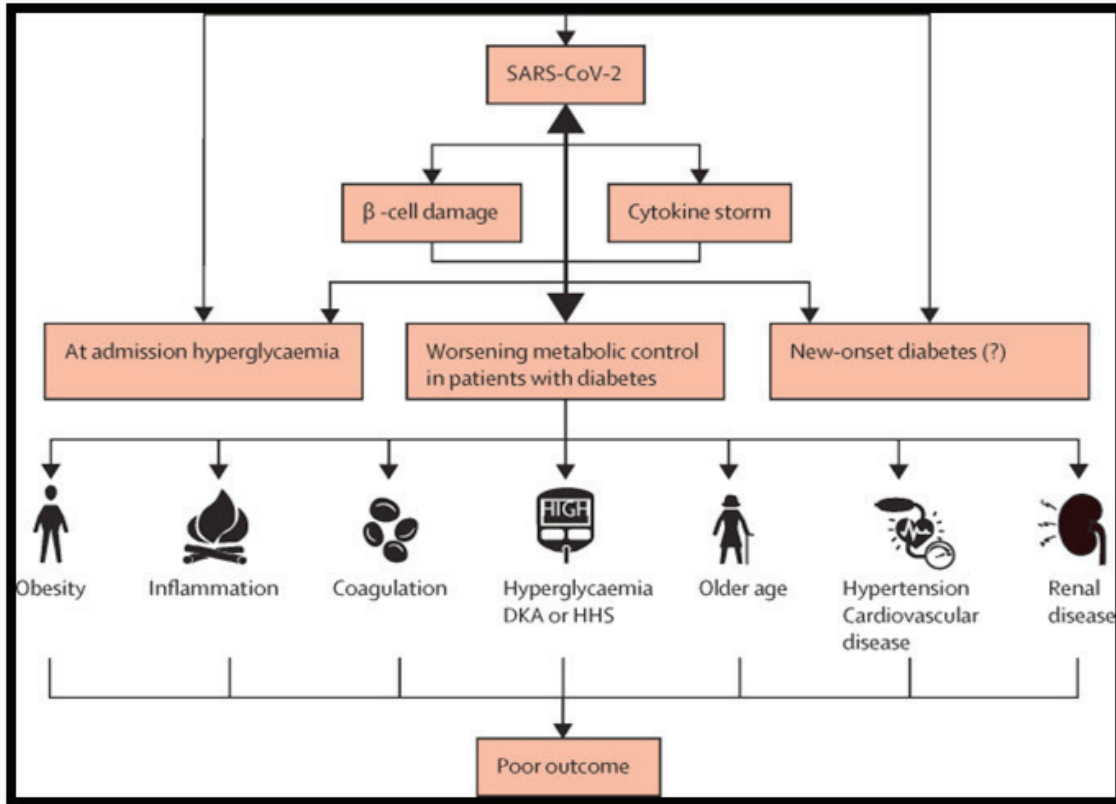


Figure 2. COVID-19 in diabetic patients ⁽²²⁾

It has been thought that the measure of clinical (skin tags, acanthosis nigricans, body weight, body mass index, waist/hip ratio) and biochemical (fasting glucose, insulin, leptin, adiponectin, leptin/adiponectin ratio) parameters related with IR, to conclude if they were related with COVID-19 severity. Consequently, large cohorts of prospectively genotyped cases might recognize genetic polymorphisms related with COVID-19 occurrence or severity that would improve the understanding of the mechanistic basis for the difference in severity of the infection.

The record current publication, encompassing 7336 patients, revealed the risk of fatal result from COVID-19 was up to 50% greater in diabetic patients. Additionally,

well regulated blood glucose was related with lesser hospital mortality than uncontrolled glucose (hazard ratio 0.14) ⁽²³⁾.

Renin Angiotensin System and COVID-19:

The ACE2 is a carboxypeptidase that is mainly located in the membrane. It is homologous to ACE ⁽²⁴⁾. The ACE2 down-regulates the RAAS and acts as an inhibitor of angiotensin II (AngII), an active peptide causing pro-inflammation action, vasoconstriction, pro-fibrosis, stimulating aldosterone secretion by binding to the AT1 receptor, converting it into Ang-(1-7), an active peptide with opposite possessions to AngII. It has been revealed that Ang-(1-7), by binding to the Mas

receptor, tempted vasodilatation and revealed anti-fibrosis and anti-inflammatory properties⁽²⁵⁾ (Figure 3). Also, AngII is inhibited by an aminopeptidase which converts AngII into AngIII, which prompts vasodilatation and elevates natriuresis. ACE2 then converts AngI into Ang-(1-9), which is also converted into Ang-(1-7) by ACE1⁽²⁶⁾.

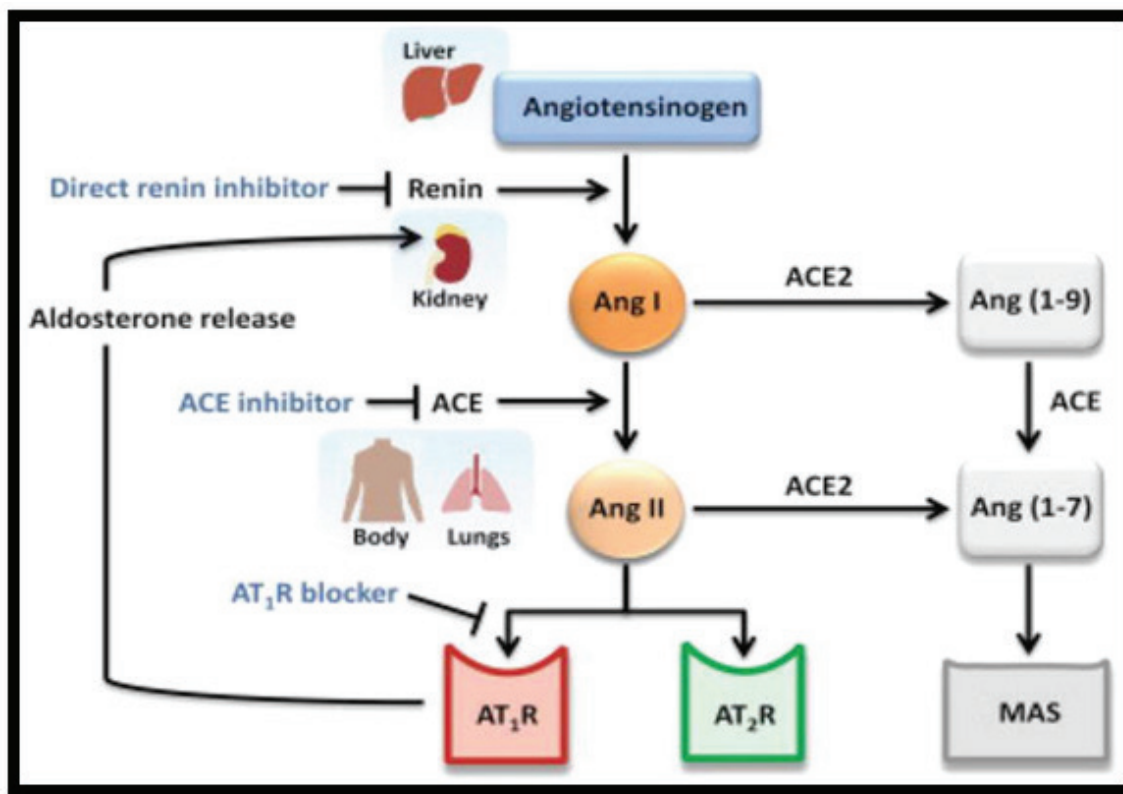


Figure 3. Renin angiotensin system⁽²⁶⁾

Additionally, SARS-CoV-2 binds to ACE2 which is largely expressed by the intestine, lung, and epithelial cells of blood vessels. The RAAS activity is elevated in the lung and is a major source of circulating AngII due to increased expression of ACE. Lung ACE2 regulates the RAAS activation balance by regulating the AngII / Ang1-7 ratio. AngII pulmonary exacerbates vascular permeability, initiating pulmonary edema⁽²⁷⁾.

Metformin in COVID-19: A Possible Role

Metformin is deliberated one of the safest oral hypoglycemic agents. It lessens IR, but does not promote insulin secretion from β -cells, and so it is not related with increased risk of hypoglycemia⁽²⁸⁾.

It has recommended that metformin be used as a medication to combat the virus. Also, women who are taking metformin may be at lesser risk for serious COVID-19. In 6,200 diabetic adults or obese who were

hospitalized with COVID-19, there were less deaths among women who had filled their 90-day metformin drugs than among those not taking it. This association was not shown in men. So, it is known that metformin has diverse influences between men and women⁽²⁹⁾. Metformin prompts AMP-activated protein kinase (AMPK) in hepatocytes by causing its phosphorylation.

This is the primary mechanism by which metformin is responsible for positive effects on glucose and lipid metabolism⁽³⁰⁾. Since metformin works by activating AMPK, which leads to ACE2 phosphorylation, it can be studied that this hypothetical addition of phosphate group would lead to conformational and functional alterations in the ACE2 receptor⁽³¹⁾. This may reduce the binding to the receptor binding domain (RBD) of the SARS-CoV-2 protein (SARS-CoV-2 RBD) due to inactivation by adding bulk PO₄-3 molecule. However, when it enters the virus, there is a decrease in the

regulation of ACE2 receptors. This leads to asymmetry of the RAAS which supports the harmful properties of its pro-inflammatory and anti-fibrotic arm., leading to potentially fatal cardiopulmonary consequences. By regulating ACE2, the defect in RAAS can be prevented. Therefore, metformin will not only block SARS-CoV-2 entry but also prevent harmful supplementation by activating ACE2 through AMPK signaling⁽³²⁾.

Conclusions

Present review illustrated that DM is related with severity of the disease and poorer short term consequences comprising death. Stronger individual strategies are advised for diabetics, and more serious investigation and management should be deliberated when they are infected with SARS-CoV-2. It is probable that SARS-CoV-2 may deteriorate pancreatic β -cell function and formation of DKA. High blood glucose and HbA1c level are related with inflammation and hypercoagulability. Though DPP4i have been described to be useful for the long term management in diabetic patients where in DPP4 enzyme is blocked, there is no actual data confirmed on the influence on the prognosis of COVID-19 infection.

Ethical Clearance: The Research Ethical Committee at scientific research by ethical approval of both MOH and MOHSER in Iraq

Conflict of Interest: None

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