

Review Article,

COVID-19 and Diabetes: Relationship and Factors of Severity

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Abstract:

The first case of pneumonia caused by a SARS-CoV-like coronavirus was diagnosed in December 2019 in Wuhan, in Hubei Province of China. World Health Organization (WHO) declared this pneumonia outbreak as a public health emergency of international concern and officially named it "coronavirus disease 2019 (COVID-19)" on 11th February 2020. COVID-19 has spread unexpectedly and very rapidly around the world, leading to the 2019-2020 pandemic. According to recent data from September 24th, 2021, more than 230 million cases of COVID-19 have been confirmed worldwide and more than 4.72 million deaths reported since December 31st, 2019. Diabetes and COVID-19 have in common acute and chronic inflammation, insulin resistance and kidney damage. Both diseases can influence each other in terms of clinical course and outcome, and a fusion between these inflammatory states can increase the damage induced by the inflammations. Diabetes mellitus, epidemiologically, is the second most common comorbidity of COVID-19. Studies have shown that 12 to 16% of patients with a complication were diabetic, with mortality approximately 3-fold higher in diabetics. The roles of angiotensin-converting-enzyme-2 and dipeptidyl peptidase-4 in COVID-19 infection and diabetes, as well as the side effects of some drugs used in the management of diabetic patients infected by COVID-19, are the major factors of severity in COVID-19 infection, thus increasing mortality in these patients. To date, there is no established treatment regimen for diabetic patients infected with COVID-19. The best alternative for diabetic patients remains prevention and then, in the event of infection, the use of evidence-based therapy.

Keywords: Diabetes mellitus; COVID-19; Relationship; Factors of severity.

Introduction:

The first case of pneumonia caused by a SARS-CoV-like coronavirus was diagnosed in December 2019 in Wuhan, in Hubei Province of China, and, was initially, named the novel coronavirus (2019-nCov). The novel coronavirus 2019 (2019-nCov), has spread in China's Hubei province and has reached other provinces in China and all parts of the world. On 30th January 2020, the World Health Organization (WHO) declared this pneumonia outbreak as a public health emergency of international concern and officially named it "coronavirus disease 2019 (COVID-19)" on 11th February 2020. COVID-19 has spread

unexpectedly and very rapidly around the world, leading to the 2019-2020 pandemic, declared by the WHO and the Public Health Emergency of International Concern (PHEIC). [1-3] According to recent data from September 24th 2021, more than 230 million cases of COVID-19 have been confirmed worldwide and more than 4.72 million deaths reported since December 31st, 2019 according to counts by Johns Hopkins University and The European Center for Disease Prevention and Control. [4] Fever or chills cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose,

nausea or vomiting, and diarrhea are the minor symptoms characteristic of COVID-19, however, several studies, have shown that severe cases can be complicated by acute respiratory distress syndrome (ARDS), septic shock, and multi-organ dysfunction syndrome (MODS). Similarly, elderly people or have associated medical tares, such as diabetes mellitus, hypertension, cardiovascular disease, and acute kidney injury, have a higher risk of presenting more severe cases, with higher mortality risk. [5-8]

Diabetes mellitus is a metabolic disease characterized by chronic hyperglycemia and other related metabolic disturbances. It is caused either to a defect in insulin secretion or to a defect in the action of insulin or both, responsible in the long term for severe and debilitating complications such as retinopathy, nephropathy, peripheral neuropathy, cardiovascular disorders, and other organ or systems disturbances. Patients with diabetes have a higher risk of infection as a result of multiple disruptions in innate immunity. [8-11] the prevalence of diabetes worldwide could exceed 700 million people by 2025, or more than 10% of the global population. [12]

Diabetes and COVID-19 have in common acute and chronic inflammation, insulin resistance and kidney damage. Both diseases can influence each other in terms of clinical course and outcome, and a fusion between these inflammatory states can increase the damage induced by the inflammations. [13] Diabetes mellitus, epidemiologically, is the second most common comorbidity of COVID-19. Type 2 diabetics are more susceptible to COVID-19 infection. ARDS, which is the main cause of death in patients with COVID-19, is more frequent in diabetics with COVID-19. Studies have shown that 12 to 16% of patients with a complication were diabetic, with mortality approximately 3-fold higher in diabetics. [7, 14-16]

The purpose of this study is to review the different studies on the effects of these two diseases on each other, clarifying the close relationship between diabetes and COVID-19, the factors worsening the prognosis of diabetic patients infected with COVID-19, as well as the therapeutic considerations of COVID-19 associated with diabetes.

Pathophysiology of COVID-19:

Being classified in the genus Betacoronavirus, SARS-CoV-2 which is the causative agent of

COVID-19 is a single-stranded positive RNA virus. The SARS-CoV-2 genome is composed of non-structural protein genes encoded in the 5' end and structural protein genes encoded in the 3' end. During the asymptomatic phase, SARS-CoV-2 binds to nasal epithelial cells of the upper respiratory tract after being received via respiratory aerosols, with ACE-2 as the primary host receptor for pathogen entry into nasal cells. During this phase, which lasts only a few days, SARS-CoV-2 replicates and spreads locally, leading to infection of the hair cells in the respiratory tract and a limited immune response. At this point, although the viral load is low, patients are highly infectious, and the virus is detectable by a nasal swab test. SARS-CoV-2 then invades the nasal epithelium into the upper respiratory tract through the conducting airways. This is followed by disease symptoms of fever, dry cough and malaise, with the release of interferons (IFN- β and IFN- λ), C-X-C pattern chemokines and C-X-C pattern chemokine ligand 10 (CXCL-10) from the virus-infected cells. In most cases, the disease is limited to this phase because patients have a sufficient immune response to limit the spread of the infection. [17-20]

Viral transmission: COVID-19 infection is primarily person-to-person through respiratory droplets, through close contact with a person who is actively coughing or sneezing. This is related to exposure of the host's mucosal surfaces, namely the nose, eyes and mouth, to infectious respiratory droplets. Transmission of COVID-19 can also occur through contact with objects used by or on the infected person such as kitchen utensils, bed sheets, blankets, stethoscopes and thermometers. Airborne transmission for COVID-19 is possible in some specific circumstances, such as bronchoscopy, endotracheal intubation, open suctioning, balloon and mask ventilation prior to intubation, nebulization with oxygen bronchodilators or steroids, cardiopulmonary resuscitation and tracheostomy. [8, 21-26]

Pathophysiology of diabetes:

Diabetes mellitus is caused either by relative/absolute insulin deficiency (insufficient insulin secretion), cellular resistance to insulin action, or both. It can be classified into two categories: type 1 diabetes, which consists of a destruction of the beta cells of the pancreas,

resulting in insulin deficiency, and type 2 diabetes, which consists of a combination of decreased insulin secretion and decreased insulin sensitivity. Long-term diabetes can progress to acute complications such as diabetic ketoacidosis (DKA), hyperosmolar hyperglycemic states, and hypoglycemia (mainly seen with the use of insulin or sulfonylureas). Infection is the main trigger for ketoacidosis and hyperosmolar hyperglycemic states, as it increases the body's need for insulin, resulting in uncontrollable hyperglycemia. Chronic hyperglycemia promotes infections, and infections, in turn, worsen hyperglycemia, creating a vicious cycle. C-reactive protein, plasminogen activator inhibitor-1, IL-6, tumor necrosis factor- α , adiponectin, and leptin are the inflammatory markers associating with diabetes and inflammation. [13, 27-29]

Close relationship between diabetes and COVID-19:

Diabetes represents one of the leading causes of morbidity and mortality in the world. Its evolution can be marked by severe and disabling macro and microvascular complications. A relationship between diabetes and infection has been clinically known. Diabetes mellitus is a multisystemic disease characterized by a chronic inflammatory state, many metabolic and vascular abnormalities that can affect the response to pathogens. Hyperglycemia and insulin resistance lead to increased synthesis of pro-inflammatory cytokines and final glycosylation products (AGEs). It is linked to oxidative stress and stimulates the production of adhesion molecules, thus mediating tissue inflammation. This inflammatory state may be the underlying mechanism leading to greater susceptibility to infections, with poor prognosis in diabetics. It is also important to remember that diabetes and uncontrolled blood glucose states have already been reported as important predictors of severity and mortality in patients infected with pandemic influenza A (H1N1), SARS-CoV, and MERS-CoV. Several studies in China and elsewhere in the world conducted in COVID-19 patients have shown that elderly patients with chronic diseases, namely diabetes, had a higher risk of severity and mortality. [30-37]

Glucagon-like peptides and gastric inhibitory peptides improve insulin secretion in type 2 diabetics. However, in the intestinal tract, these peptides (glucagon-like peptide and gastric

inhibitory peptide) can be degraded by dipeptidyl peptidase-4 (DPP4), thus reducing their activity. With a molecular weight of 220 kDa, DPP4 is a transmembrane glycoprotein that exists as a dimer in its active state. DPP4 inhibitors such as vildagliptin, saxagliptin, sitagliptin, linagliptin, teneligliptin, and trelagliptin, inhibit the degradative activity of DPP4, thus increasing the capacity of these peptides in insulin secretion. This enzyme (DPP4), originally named CD26, has also been implicated as a component of an entry receptor for human coronavirus-Erasmus Medical Center and MERS-CoV. However, the bronchial tree represents the site of DPP4 in coronavirus pathogenesis. Human Erasmus Medical Center coronavirus has a genetic similarity to other coronaviruses. Data from a retrospective study have shown that DPP4 inhibitors may possibly be useful in reducing the risk of severity of COVID-19. Nevertheless, this evidence remains miniscule at this time to confidently conclude that DPP-4i could substantially alter the outcome in diabetic with COVID-19.

The ACE2 (Angiotensin-Converting Enzyme) receptor is highly expressed by epithelial cells of the lung, kidney, intestine and vessels, and is also very important for the entry of SARS-CoV-2 into the cells. ACE2 is also elevated in diabetic patients, especially those treated with angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme (ACEi) inhibitors. SARS-CoV-2 virus infectivity is related to the rate of ACE2 shedding. ACE inhibitors and ARBs are antihypertensive drugs known to increase cardiac ACE2. Despite the role of ACE2 in the pathogenesis of COVID-19 and the theoretical knowledge of increased ACE2 with ACE inhibitors or ARBs, studies have shown that there was no significant difference in clinical outcomes between COVID-19-positive patients with diabetes and coexisting hypertension using an ACE inhibitor or angiotensin II receptor blocker and those not using these drugs. [13, 38-42]

Potential mechanisms involved in the severity of COVID-19 in diabetics:

Understanding the interaction between diabetes and COVID-19 may provide access to therapeutic measures, but to date, there are little data on this issue. Although some studies have claimed that diabetes is one of the factors that increase the severity of COVID-19, on the contrary, data from

a study on MERS and diabetes mentioned that the replication and clearance of the MERS-CoV virus are not influenced by diabetes.[9,43,44] Diabetes mellitus is known to be associated with a pro-inflammatory state, limitation of the innate immune response, and increased susceptibility to infections (particularly influenza and pneumonia), leading to adverse outcomes associated with these infections. Metabolic disorders secondary to diabetes mellitus can lead to impaired macrophage and lymphocyte function, resulting in decreased immune function, which predisposes patients to severe forms of the disease. [45,46] An animal study conducted on transgenic mouse models, which were made susceptible to MERS-CoV by expressing DPP4. Type 2 diabetes was induced in these same mice by a high-fat diet. These diabetic mice, infected with MERS-CoV, showed a severe viral infection with weight loss independent of viral titers, and impaired immune responses, which were manifested by decreased and delayed recruitment of CD4+ T cells, inflammatory macrophages and monocytes in the lungs. These MERS-CoV-infected diabetic mice also had elevated levels of IL-17a, suggesting that an altered cytokine profile may be partly related to increased disease severity. We can infer from this experience that it would be possible that diabetes has similar effects on viral infections, since MERS-CoV and SARS-CoV-2 belong to the same subfamily of Coronavirinae. [47] Recently, a clinical study that compared diabetic patients with COVID-19 and non-diabetic patients infected with COVID-19 reported that patients with diabetes had an activated inflammatory response manifested by elevated levels of neutrophils, C-reactive protein, sedimentation rate, erythrocytes, IL-6, and serum ferritin, with suppressed immunity (manifested by markedly decreased lymphocyte counts). Cytokine is also considered to be the main factor promoting the progression of COVID-19, as increased cytokine levels have been observed in critical cases of COVID-19. [48] We can deduce from these 2 studies that diabetic patients infected with COVID-19 will be more susceptible to overactivated inflammation and imbalanced immune response, which are risk factors involved in the rapid deterioration of COVID-19.

Hyper or hypoglycemic states would also be a poor prognostic factor in diabetic patients infected with COVID-19. In COVID-19-infected diabetics,

the cytokine storm process, endothelial dysfunction, and multiple organ damage, all of which are secondary to hyperglycemia, worsen the course of COVID-19. This same hyperglycemia leads to rapid deterioration in spirometric function, particularly the decline in forced expiratory volume in one second and forced vital capacity in the lungs (the primary target of COVID-19). Studies have suggested that severe hypoglycemia may increase overall mortality, particularly cardiovascular mortality, by increasing pro-inflammatory (monocyte) activity, thereby increasing platelet aggregation. [13,49,50] The stress induced by COVID-19 infection in diabetic patients results in the release of catecholamines and glucocorticoids into the blood, leading to a glycemic disorder, which increases the formation of glycation end products in many organs and thus worsens the vital prognosis of patients. Data from some studies have suggested the possibility of invasion of the pancreas by SARS-CoV-2, confirmed by the presence of elevated ACE2 levels in islet beta cells, leading to unexplained increases in blood glucose levels in diabetic patients with COVID-19, requiring the use of high doses of insulin. SARS-CoV-2 replication would have a direct cytopathic effect on the pancreas, as well as the detrimental immune response induced by SARS-CoV-2 infection and the systemic response to respiratory failure; appear to be the likely mechanisms related to pancreatic injury in diabetic patients infected with COVID-19. [51-55]

Therapeutical considerations:

Chloroquine or (Hydroxychloroquine) and Antiviral agents:

In several studies, the treatment of diabetic patients infected with COVID-19, the use of chloroquine or hydroxychloroquine combined with zinc, antibiotics (such as meropenem or linezolid) and antiviral agents (such as ganciclovir or oseltamivir) is suggested. But chloroquine or hydroxychloroquine seems to cause hypoglycemia, precisely in patients on insulin or sulfonylureas, because of its effect on insulin secretion, degradation and even action. [56-58] some antivirals are also reported to have side effects such as hyperglycemia, liver and muscle toxicity (special caution should be taken in patients with hepatic steatosis and taking statins).

Notions of drug interactions with antidiabetics are also reported, causing under- or overexposure to either antidiabetics and/or antivirals. [59, 60]

Glucocorticoids:

Glucocorticoids such as hydrocortisone and methylprednisone have been used in COVID-19 patients to suppress inflammation and control the cytokine storm (in severe ARDS). However, some studies have stated that the evidence has not shown benefit. These glucocorticoids can exacerbate insulin resistance, sustain gluconeogenesis and also by interfering with the effects of GLP-1 and increasing glucagon production, thus cause severe hyperglycemia in 80% of diabetic patients with COVID-19 (which may increase mortality in these patients). They also inhibit immunity and pathogen clearance. In cases of extreme need for glucocorticoids, careful blood glucose monitoring is required to maintain normal blood glucose levels to ensure optimal pulmonary and immunologic function. [60-63]

Metformin:

In T2DM patients, metformin has an anti-inflammatory effect that reduces circulating biomarkers of inflammation. It also activates adenosine monophosphate kinase to phosphorylate the ACE2 receptor, resulting in the reduction of its binding capacity due to steric hindrance by the incorporation of the PO₄-3 molecule. Although there are little data on its immunomodulatory actions in the context of COVID-19 infection. Despite all the beneficial effects of metformin in diabetic patients infected with COVID-19, other more serious side effects have been reported by several studies, namely the risk of lactic acidosis (in case of respiratory distress which can occur in diabetic patients); the risk of acute renal failure and heart failure and a drug interaction with lopinavir has been reported. For the clinical management of diabetic patients infected with COVID-19, metformin is not recommended. [60, 64-66]

Sulfonylureas:

The use of sulfonylureas is not recommended, in diabetic patients infected by COVID-19, due to hypoglycemia induced by low caloric intake during acute infections. [46] In some studies, a drug interaction with hydroxychloroquine, lopinavir and ritonavir has been reported. [60]

Insulin:

Insulin therapy remains the best alternative treatment for infectious complications in diabetic patients. Its beneficial effect in diabetic patients infected with COVID-19 is thought to be related to its anti-inflammatory action, acting by reducing pro-inflammatory cytokines and increasing immune mediators. Its major side effect is hypoglycemia, requiring strict glycemic control. A study suggests that insulin may have a drug interaction with hydroxychloroquine. In diabetic patients infected with COVID-19 treated in hospitals, insulin therapy is mandatory. [60,67]

GLP-1 receptor agonists:

In type 2 diabetes and obesity, GLP-1R agonists act by reducing biomarkers of systemic inflammation. Studies have also reported beneficial effects related to GLP-1R agonists in patients infected with COVID-19, such as:

- ✓ Attenuate pulmonary inflammation;
- ✓ Reduce cytokine production (especially in ARDS);
- ✓ Preserve pulmonary function by stimulating pulmonary vasodilators (atrial natriuretic peptide and surfactant protein A).

From these beneficial effects, we can deduce that they are fundamental elements in the treatment of patients infected with COVID-19 patients with or without diabetes. Despite all these beneficial effects, the safety of GLP-1R agonists in diabetic patients infected with covid 19 is still unclear. Gastrointestinal side effects and a drug interaction with Atazanavir have been reported in some studies. [60, 68-71]

SGLT2-inhibitors:

In addition to their anti-diabetic effects, sodium-glucose cotransporter-2 (SGLT2i) also have additional cardiovascular and renal effects. Studies have shown that the combination of SGLT2i and ACEI/ARB increases intrarenal expression of ACE2, secondary to improved cardiac and renal function. Studies have reported that in diabetic patients infected with COVID-19, SGLT2i prevent acute respiratory distress syndrome (ARDS), promote massive production of angiotensin 17 (vasodilator, anti-fibrotic and anti-oxidant), and reduce cytokine storm and oxidative stress (thus improving cardio-renal dysfunction).

Although it should be remembered that in patients infected with COVID-19, the increase in ACE2 can be detrimental, flooding the cells through the ACE2 entry receptor.

In addition, using SGLT2i in diabetic patients infected with COVID-19 may have a drug interaction with lopinavir/ritonavir, and some side effects have been mentioned, such as:

- ✓ Increase the risk of acute kidney injury (related to their natriuretic effect);
- ✓ Affect hemodynamic stability (hypovolemia, electrolyte imbalances) related to infection;
- ✓ Inhibit the release of IL-6;
- ✓ Euglycemic ketoacidosis. [60,72-76]

Artemisinin:

The natural antimalarial drug, commonly known as artemisinin, is believed to have other pharmacological effects against inflammation and viral infections that may positively affect innate immunity. Data from some clinical studies have reported that artemisinin could be used in the treatment of diabetic patients infected with COVID-19 by shortening the duration of COVID-19 treatment and improving the vital prognosis. [7]

Conclusion:

Diabetes and COVID-19 may influence each other in terms of clinical course and outcome. The roles of ACE2 and DPP4 in COVID-19 infection and diabetes, as well as the side effects of some drugs used in the management of diabetic patients infected by COVID-19, are the major factors of severity in COVID-19 infection, thus increasing mortality in these patients. To date, there is no established treatment regimen for diabetic patients infected with COVID-19. The best alternative for diabetic patients remains prevention and then, in the event of infection, the use of evidence-based therapy. Further experimental studies may lead to more effective treatments against COVID-19 for patients with diabetes.

Conflict of interest

The authors have no conflict of interest to declare that are relevant to the content of this article.

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