International Journal of Medical Science and Clinical Research Studies

ISSN(print): 2767-8326, ISSN(online): 2767-8342

Volume 02 Issue 01 January 2022

Page No: 40-44

DOI: https://doi.org/10.47191/ijmscrs/v2-i1-07, Impact Factor: 5.276

COVID-19 and Diabetes Mellitus: The Mechanisms of Potentially Fatal Comorbidity

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ABSTRACT

It's known that Diabetes Mellitus (DM) can be a risky disease, full of complications if it's not controlled properly. These complications, along with the coronavirus disease 2019 (COVID-19) can be lethal due to suppression of innate and humoral immune functions, the hyperglycemic state increases the virulence of pathogens and reduces the production of interleukin in response to infections, which could result in an aggravation of pneumonia. Elevated blood glucose levels can directly elevate airway glucose concentrations, resulting in a higher viral load and these become more viral load and become riskier, it is also important to highlight the importance of ACE2 pulmonary disease because it causes cellular damage and rapid disease progression. It's because of these mechanisms that DM is related to obesity, coagulopathies, thrombotic events, diabetic ketoacidosis, among others. It is necessary to have proper control of both diseases to improve the patient's quality of life and avoid a poor prognosis. It is necessary to have proper control of both diseases to improve life quality and avoid a poor prognosis. The patient can rely on good nutritional education, diet, exercise, and adequate glucose to keep control of the disease.

KEYWORDS: Diabetes Mellitus, COVID-19, Comorbidities, Complications, Pandemic.

ARTICLE DETAILS

Published On:
19 January 2022

Available on:
https://ijmscr.org

INTRODUCTION

COVID-19 disease has been a challenging public health crisis in modern history. Since its discovery in late 2019, COVID-19 has rapidly spread to more than 200 countries worldwide. Despite the low mortality rate of COVID-19, older adult patients, or those with comorbidities such as hypertension, cardiovascular disease, and DM seem to be prone to more severe symptoms and a higher mortality rate than others. (1, 2)

DM is one of the most important risk factors because patients are more vulnerable to infections due to hyperglycemia, impaired immune functionality, vascular complications, and other comorbidities such as hypertension, dyslipidemias, and cardiovascular pathologies. (3)

DM is associated with complications, because it's a metabolic disorder characterized by hyperglycemia, has been reported to down-regulate immune response and increase inflammation, and increases the risk of morbidity and mortality during infections. (1, 4)

There is increasing evidence highlighting DM as comorbidity associated with acute respiratory distress syndrome (ARDS) and increased subsequent mortality. (2) As of March 28, 2020, out of a total of 122,653 laboratory-confirmed cases of COVID-19, DM (784, 10.9%) was the most frequently reported condition among 7162 cases with data where underlying health conditions were available. (3)

In past pandemics evidence of the impact that diabetes has had as comorbidity, for example: In 2002 to 2003 SARS-CoV-1 and diabetes were considered a risk factor regardless of was considered an independent risk factor for complications and death during the SARS-CoV-1. In 2009 influenza A (H1N1) where once again the presence of diabetes tripled the risk of hospitalization and quadrupled the

risk of being admitted to the intensive care unit (ICU) during the outbreak. (4)

METHODS

To obtain a favorable result in our research, the following review article was carried out using different bibliographies obtained from different databases such as the New England Journal of Medicine, Endocrinology and Metabolic and Endocrinology of the COVID-19 pandemic, Journal of Diabetes and Its Complications, among others.

To carry out this work, a total of 13 bibliographies were reviewed, of which 10 articles were used; there were looked for scientific articles with the following inclusion criteria, to be published from the year 2020, to be original articles, and to be written in English; also, talk about the new coronavirus and its relationship with diabetes. Any article that did not include the SASR-CoV 2 virus was excluded. The rest of the bibliographies were book reviews.

Having the opportunity to perform a complete systematic comparison of the results of our research, it was fundamental for the writing of this article to use words or phrases with key concepts such as diabetes in patients with COVID, diabetes and COVID 19, management of the diabetic patient with COVID 19, DM and the SARS-CoV-2 virus, chronic diseases and COVID.

RESULTS

In COVID-19 disease, both DM type 1 and type 2 can increase the risk of morbidity and mortality by 50% during acute infections due to suppression of innate and humoral immune functions, including complications associated with this comorbidity. (1 , 5) Glycosylated hemoglobin (HbA1c) levels >9% have been associated with a 60 % increased risk of hospitalizations, making DM an independent predictor of admissions to the intensive care unit (5) and related to the severity of pneumonia (4), on the other hand, it has been reported that people with glucose intolerance or DM have a 50 to 60 % higher risk of pulmonary infection of any type, this is due to the glycemic status and the immune system, as they are compromised. Immune systems, which are compromised as the first line of defense against any infection. (6)

In daily life without COVID 19, patients with DM are at increased risk for community-acquired pneumonia and have to be hospitalized, especially when there is uncontrolled glycemia. (7) The hyperglycemic state of the individual increases the virulence of pathogens, reduces the production of interleukins in response to infections, and reduces the phagocytic and polymorphonuclear activity of leukocytes (6). The first line of defense against SARS-CoV-2 is compromised in patients with uncontrolled DM and those diabetic patients have an impaired immune response to infection both about cytokines and cytokine-mediated by changes in immune responses, including activation of T cells and macrophages. (5) Poor blood glucose control affects several aspects of the immune response, as it has been shown that elevated blood glucose levels can directly increase glucose concentrations in airway secretion, which leads to an altered antiviral immune response. As a consequence, patients with diabetes often have a higher viral load and a much more severe disease when infected with respiratory viruses (8), easily culminating in viral infection and also possible secondary bacterial infection in the lungs (3).

Patients with DM appear to have an altered adaptive immune response characterized by an initial delay in Th1 cell-mediated immunity and a delayed hyperinflammatory response. In the absence of an immunostimulant, DM is associated with an increased proinflammatory cytokine response marked by increased secretion of IL-1, IL-6, IL-8, and TNF-α. Elevated basal cytokine levels can also be attributed to advanced glycation end products (AGEs), consisting of glucose and lysine/arginine residues. Prolonged occurrence of AGEs was observed to occur in patients with poorly regulated DM (4,2). SARS CoV-2 has ACE-2 as a cell entry receptor, ACE-2, causes a conformational change in the S-glycoprotein, allowing proteolytic digestion by host cell protease such as TMPRSS2 and Furin, ACE-2 is expressed not only in type I and II alveolar epithelial cells of the lungs and upper respiratory tract but also in other places such as the heart, renal tubular endothelium, intestinal epithelium, and pancreas. (4)

Specific factors responsible for increased risk and severity of SARS CoV2 infection in DM: This increase may predispose patients with DM to infection with SARS-CoV2 (4), this low ACE2 expression in the lung in DM could explain the higher incidence of severe lung injury and ARDS with COVID-19. The role of ACE2 in the crosstalk between COVID-19 and DM is still a matter of debate. Some studies recognized decreased levels of ACE2 in diabetes, perhaps secondary to glycosylation (2). Hypertension is a comorbidity of DM2, in addition to the fact that a SARS-CoV-2 2 DM, in addition to which COVID 19 infection can lead to dysregulation of blood pressure with increased susceptibility to blood pressure dysregulation with increased susceptibility to heart disease. (6)

COVID-19 is often associated with hypokalemia; this has been attributed to down-regulation of pulmonary ACE2, reduced angiotensin II degradations, and subsequently increased aldosterone secretion (5). Coronavirus through angiotensin-converting enzyme 2 (ACE2) receptors may result in cell damage and rapid disease progression (1). One possible mechanism of SARS-CoV-2- mediated inflammatory responses involves down-regulation and elimination of ACE2, a terminal carboxypeptidase that degrades angiotensin II to angiotensin (4,9), thus acting as a negative regulator of renin concentration whereas ACE, which converts angiotensin I to angiotensin II and induces pulmonary edema and promotes lung injury. ACE 2 appears to protect the lungs from an acute injury (2,10).

The entry of the virus triggers an inflammatory response with the recruitment of T-helper cells, which produce interferon-gamma. This leads to the recruitment of other inflammatory cells leading to a cytokine storm that could lead to multi-organ failure and rapid deterioration seen in severe disease **(5),** which in turn appears to be directly related to the severity of COVID-19 pneumonia cases, resulting in death **(2).** The cytokine IL-37, which cancan suppresssuppress both innate and acquired immune responses and to inhibit inflammation by acting on the IL-18Rα receptor, has also been shown to suppress IL-1β and IL-6 production by modulating the mTOR pathway and increasing adenosine monophosphate kinase (AMPK). IL-38 is another cytokine inhibitory to IL-1β and other members of the proinflammatory IL family. It was suggested that both IL-38 and IL-37 serve as potential therapeutic cytokines 4 by inhibiting inflammation caused by COVID-19, providing a new relevant approach to treat the disease (9,10).

It has been observed in patients with DM and COVID-19 that their serum levels of interleukin-6 (IL-6), C-reactive protein, and ferritin were significantly higher than in patients without DM. In people with DM2 and DM1 (especially those who are obese and have some component of insulin resistance in addition to absolute insulin deficiency), even mild COVID-19 can induce a pro-inflammatory environment, as evidenced by high amounts of IL-6, IL-1 b, tumor necrosis factor-a (TNF-a), monocyte chemoattractant protein-1 (MCP-1), and inducible protein-10 that can lead to decreased insulin sensitivity. (4 , 5)

DM is associated with an increase in furin, which is a type I membrane-bound protease that could facilitate viral replication and belongs to the pro-protein convertase subtilisin/Kexin (PCSK) family involved in the entry of coronaviruses into the cell (4). The increase in D-dimer perhaps signifies an over-activation of the static heme system. Overactivation of the coagulation cascade in COVID-19 may lead to fatal thromboembolic complications thus increasing mortality (5) Vitamin D is recognized to have some suppress antioxidant and immunomodulatory properties so that in a fatal disease of COVID-19 infection, this vitamin offers. (7)

It has been observed that vitamin D has an important role in the innate immune response to eliminate pathogens, has an endocrine action on the activation of antigen-presenting cells such as monocytes and on the motility of neutrophils further contributing to their antibacterial activity (7) However, low vitamin D is known to exist in human diseases such as DM, so it may offer a worse prognosis. (8)

We found a global vitamin D deficiency due to a lack of vitamin D supply in dietary supplements **(1).** Hypovitaminosis D has been considered a risk factor for insulin resistance. Therefore, it may lead to a worsening of the glucose profile in patients infected with COVID-19 **(5)**. Vitamin D deficiency, (below 10 mg/ml) is related to a high cytokine response in infection **(7),** therefore it is recommended that diabetic patients have adequate levels of vitamin D, because, through its paracrine and autocrine action, it regulates dendritic cells and inhibits the proliferation of helper T cells (Th1), biasing the production of cytokines towards T-helper 2 (Th2) cells. Treatment with high-dose vitamin D on the order of 250,000 to 500,000 IU was generally safe in critically ill mechanically ventilated patients and was associated with a decreased hospital stay (7,6).

Similarly, the control of the diabetic patient is fundamental, to have adequate glycemic control, since it has been shown that patients with poor glycemic control have a lower. It is also recommended to discontinue the SGLT-2 inhibitor due to the risk of dehydration and diabetic ketoacidosis, and if the patient is being treated with metformin, it is recommended that the patient be managed directly with insulin. An adequate diet and physical activity are essential. (4,11)

COVID-19 can cause worsening of glycemic control in persons with pre-existing DM above normal caused by the stress of critical illness (i.e., hyperglycemic stress) (5). This stress response to infection in the body worsens hyperglycemia by antagonizing insulin action or inhibiting insulin secretion by beta cells **(1)**. Such uncontrolled glucose levels precede secondary infections as well as increased mortality risks, and the use of antidiabetic GLP1 agonists acting on ACE2 has been suggested **(6)**. Controlled (glycemic variability within 3.9-10 mmol/L) had less severity and lower mortality than patients with poorly controlled hyperglycemia (glycemic variability greater than 10 mmol/L) **(3).** Another complication seen is diabetic ketoacidosis which coexists with COVID-19 and is particularly dangerous to treat, due to the risk of pulmonary fluid accumulation **(8)**, likewise diabetic ketoacidosis is precipitated by respiratory tract infection. (6)

Another important factor is obesity, which is common comorbidity affecting people with DM. In people with DM, adiposity affects both the adaptive immune system and the innate development of the adaptive immune system and the innate development of chronic systemic inflammation, and the presence of elevated levels of IL-6 and CRP. (6)

The high impact of COVID-19 in patients with obesity and severe obesity is probably related to the deleterious effects of obesity on pulmonary function. Obesity is associated with decreased expiratory reserve volume, functional capacity, and respiratory system compliance. (8) Obesity has also been linked to coagulopathy and thrombosis, as well as by COVID 19; patients with DM and COVID 19 have elevated dopamine levels of COVID 19 have higher D-dimer levels than those without DM Therefore, there are more possible thrombotic events such as strokes (6). Obesity is related to low-grade inflammation that is associated with adipocyte hypoxia and dysfunction. This results in an exuberant secretion of pro-inflammatory cytokines such as tumor necrosis factor α (TNF- α), interleukin (IL) 1β and interleukin 6 and adipokines that lead to the recruitment of immune cells macrophage, T

cell, and B-cells, creating an auto-regenerating inflammation loop (8 , 12).

DISCUSSION

According to the accumulated data, patients with DM have a higher risk of complications in COVID-19 infection, showing a risk of complications in COVID-19 infection, showing higher rates of hospital admission rates because they develop severe pneumonia and have a higher mortality rate. (9) Hence the importance of the subject, currently we are experiencing a global health emergency and coupled with the high incidence of DM in the population, special attention should be paid because this is a comorbidity that worsens the prognosis of patients. During this literature review, different pathophysiological mechanisms were mentioned. (1,12).

ACE-2 is used by SARS-CoV-2 as a cell entry receptor. Where the S-glycoprotein on the surface of SARS-CoV2 binds to ACE-2, allowing entry of the virus triggers an inflammatory response this leads to the recruitment of other inflammatory cells leading to a cytokine storm that could lead to organ or multi-organ failure seen in severe disease. (4 , 5)

It is further mentioned that COVID-19 is often associated with hypokalemia; this has been attributed to down-regulation of pulmonary ACE2, reduced degradation of angiotensin II and subsequently increased aldosterone secretion. (1,13)

The journal Endocrine and Metabolic Disorders, it mentions that the increase of Furin found in DM intervenes in the entry of coronavirus into the cell and facilitates viral replication. (4)

In people with DM2 and T1DM (especially those who are obese and have some component of insulin resistance in addition to absolute insulin deficiency), even mild COVID-19 can induce a pro-inflammatory environment, among these, IL-6 is increased in DM and may play a more deleterious role in Covid-19. Therefore, a monoclonal antibody against the IL-6 receptor (tocilizumab) is being tested in a trial in COVID-19. (9, 10) For these reasons, patients with DM should pay special care and attention, since different mechanisms significantly worsen the prognosis of these patients. (2,13)

CONCLUSION

In conclusion, the complex interaction between these diseases places patients at alarmingly high risk. Patients with DM should be more cautious and ensure strict adherence to the indications given by the health authorities. Knowing these mechanisms helps us to determine better treatment and control measures for these patients. Patients should maintain a healthy, balanced diet and not vary in caloric intake to maintain good glycemic control, and they should be educated about the need to visit the hospital urgently in emergencies such as vomiting, drowsiness, shortness of breath, chest pain, weakness of the limbs of the extremities.

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