Diabetes mellitus in the context of COVID-19

La diabetes mellitus en el contexto de la COVID-19

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ABSTRACT

Introduction: a high prevalence of diabetes mellitus (DM) represents a challenge during the coronavirus disease 2019 (COVID-19) pandemic. DM represents an important risk factor for adverse outcomes in patients with COVID-19. **Objective:** to describe the clinical, epidemiological and molecular characteristics; including treatment options among patients with COVID-19 and diabetes mellitus. **Method:** a literature review was conducted in articles published by peer-reviewed journals up to June 2020. SciELO and PubMed databases were screened in search of articles. The search terms included diabetes mellitus, coronavirus infection, and its Spanish translation “diabetes mellitus”, “infección por coronavirus”. **Development:** COVID-19 and diabetic patients may be predisposed to immune dysfunction that results in severe late illness. Most patients with mild infection can continue with the usual antihyperglycemic medications. The result of the use of corticosteroids is not yet clear. There are safety concerns regarding treatment with chloroquine/hydroxychloroquine, due to its hypoglycemic role and adverse effects. **Conclusions:** the molecular and pathophysiological mechanisms between COVID-19 and diabetes mellitus are still not fully understood. The poor prognosis observed in these patients requires the creation of a novel treatment protocol.

Palabras clave: *Diabetes; Diabetes Mellitus; Infeción por Coronavirus; SARS-Cov-2.*

Keywords: *Diabetes; Mellitus diabetes; Coronavirus Infections; SARS-Cov-2*

RESUMEN

Introducción: una alta prevalencia de la diabetes mellitus representa un desafío durante la pandemia de la enfermedad por coronavirus 2019 o COVID-19. La diabetes mellitus constituye un importante factor de riesgo de complicaciones en pacientes con COVID-19. **Objetivo:** describir las características clínicas, epidemiológicas y moleculares; así como opciones de tratamiento en los pacientes con COVID-19 y diabetes mellitus. **Método:** se realizó una revisión bibliográfica en artículos publicados en revistas biomédicas revisadas por pares hasta junio de 2020. Se revisaron las bases de datos SciELO y PubMed. Los términos de búsqueda incluyeron *diabetes mellitus, coronavirus infection,* y su traducción al español «diabetes mellitus», «infección por coronavirus». **Desarrollo:** La COVID-19 y los pacientes diabéticos pueden estar predispuestos a una disfunción inmunológica que resulta en una enfermedad tardía severa. La mayoría de los pacientes con infección leve pueden continuar con los medicamentos anti-hiperglucémicos habituales. El resultado del uso de corticoesteroides aún no está claro. Existen preocupaciones de seguridad con respecto al tratamiento con cloroquina/hidroxicloroquina, en relación con su función hipoglucémica y demás efectos adversos. **Conclusiones:** los mecanismos moleculares fisiopatológicos entre la COVID-19 y la diabetes mellitus todavía no están del todo dilucidados. El mal pronóstico que se observa en pacientes con ambas enfermedades requiere la creación de nuevos

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INTRODUCTION

Since December 2019 China experienced an outbreak of pneumonia, caused by a novel coronavirus officially named as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), by the International Committee on Taxonomy of Viruses (ICTV)[1]. Coronaviruses (CoVs) are enveloped viruses with a single-stranded, positive-sense RNA genome and commonly linked to human respiratory infections. In most immunocompetent patients, CoVs infection leads to mild upper respiratory infection[2].

Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, converted to pandemic within a few months after the first reported case in Hubei province, China[3]. On June 21st, 2020, 185 countries affected with COVID-19 confirmed 8 796 469 cases and 464 294 deaths for a mortality rate of 5.28 %. In the Americas, a report of 4 374 446 confirmed cases reached 49.73 % of all cases worldwide, with 221 783 deaths and a mortality rate of 5.07 %. Cuba reported 2 315 positive cases, with an increased incidence of the male gender, and 85 confirmed deceased[4].

During COVID-19 pandemic, the high prevalence of metabolic diseases has become a challenge to achieve stability in infected patients. DM represents one of these diseases and the risk of severity of COVID-19 increases to the undiagnosed patients or with inadequate glycemic control. Although that the literature reports an increase in COVID-19 cases with comorbidities such as obesity, hypertension, and diabetes, the role of these comorbidities in patients infected with SARS-CoV-2 has not yet been explored[5].

Studying the behaviour of COVID-19, it has been observed that DM together with the elderly have become risk factors that lead to unfavourable prognoses of the disease. About 20% of admissions to intensive care units (ICU) are attributed to DM, according to reports from a small cohort study in Wuhan. Also, Italy has reported that two-thirds of those who died from the novel coronavirus had a past medical history of diabetes mellitus[6].

Middle East Respiratory Syndrome (MERS) outbreak that mainly affected Saudi Arabia in 2012, the relationship of complications of patients with diabetes and this disease can also be evidenced[7].

Several studies report the severity of COVID-19 in diabetic patients, although the reason for this severity and the effect of hyperglycemia in the course of the SARS-CoV-2 disease is still not well understood, even though that diabetics are at higher risk of respiratory infections because the immune system is compromised[8].

Increased awareness of the clinical features, pathophysiology, and potential mechanisms that increase the risk is needed to provide better care and spur new investigations, both basic and clinical, to better understand COVID-19 in patients with DM[2].

The objective of this review is to describe the clinical, epidemiological and molecular characteristics; including treatment options among patients with COVID-19 and diabetes mellitus.

METHOD

A literature review was conducted in articles published by peer reviewed journals up to June 21st, 2020. SciELO, Pubmed/Medline, The Lancet, and Nature Reviews Endocrinology were screened in search for articles. The search terms included diabetes mellitus, coronavirus infection, and its Spanish translation “diabetes mellitus”, “infección por coronavirus”. Twenty articles of interest were included in this research.

DEVELOPMENT

Most people with COVID-19 have a disease incubation period of 2 to 14 days and will experience cough, fever, shortness of breath or less commonly, nausea and diarrhoea. A late phase of sudden deterioration is observed in some patients after 7–10 days of fever, and deterioration in oxygen saturation[3].

Patients with diabetes develop similar symptoms, but less specific symptoms are also developed, fever may be less common, and deterioration could occur rapidly in later stages. A deteriorated glycemic control and hyperglycemic emergencies in those with type 1 diabetes may be the initial presentation of diabetic ketoacidosis (DKA)[3]. The available information does not indicate increased susceptibility to coronavirus infections in children or adults with type 1 diabetes (T1D)[8].

Alterations in laboratory markers and CT imaging

Zhang Y et al.[1] found that COVID-19 patients had a relatively high proportion (24%) of diabetes, and proved that diabetes was associated with alterations in laboratory markers, corresponding to a severer clinical subtype at

presentation, and poorer prognosis compared to those without diabetes after SARS-CoV-2 infection.

The diabetic COVID-19 patients had a higher median leucocytes number (6.34[IQR: 4.66, 8.15] vs. 5.45[IQR: 4.31, 7.19], P=0.039) and median neutrophils numbers (4.49[IQR: 3.12, 6.91] vs. 3.82[IQR: 2.81, 5.39], P=0.022) compared with non-diabetic patients. COVID-19 patients with diabetes had more leucocytes increase (20.6% vs. 6.7%) but less leucocytes decrease (4.8% vs. 10.3%, P=0.004) than those patients without DM. The neutrophil-to-lymphocytes ratio (NLR) was significantly higher in diabetic patients compared to those without diabetes (median: 4.56[IQR: 2.69, 9.51] vs. median: 3.8 [IQR: 2.25, 6.31], P=0.043)[1].

Elevated serum ferritin, lactate dehydrogenase, C-reactive protein (CRP), procalcitonin and erythrocyte sedimentation rate (ESR) predicted severe disease among patients with COVID-19 and DM; a possible explanation of secondary bacterial infection intensifying COVID-19. Increased serum ferritin, could predict a severe secondary bacterial infection among these patients[3].

Lymphopenia was also associated with severe conditions in patients with COVID-19. DM, it's related with a proinflammatory homeostatic immune response, skewed toward helper T cell 1 (Th1) and T17 cells and a decrease in regulatory T cells (Treg). Immune dysfunction of diabetes alone or following infection has been reported for a wide variety of immune cells, not just macrophages, monocytes and CD4+ T cells[1]. Raised D-dimer levels were observed in severe illness, suggesting a possible consumptive coagulopathy, while anticoagulation was linked to the decreased mortality rate in COVID-19 patients[3].

The COVID-19 in its severe forms is a state of severe inflammation and thrombotic tendency, and diabetic patients may be predisposed to an intense immune dysfunction as a cause of severe late illness. This is further supported by renal and cardiovascular comorbidities, which added to the proinflammatory state, increase the tendency to complications[3].

Elevated N-terminal pro-brain-type natriuretic peptide (NT-proBNP) and cardiac troponin I (cTnI), were significantly correlated with severe disease. The COVID-19 may lead to myocardial injury and impair cardiac function. In people with diabetes and preexisting ischemic heart disease, the limited cardiac reserve may increase morbidity and mortality risk[3].

Reports informed that intensive care unit (ICU) patients, non-ICU patients and recovery patients differ in computed tomography imaging results, which means CT results is an indicator to determine the severity of SARS-CoV-2 pneumonia. According to the quantifiable score (15 vs. 10 p=0.04), the diabetes group presented higher CT imaging score compared with the non-diabetes group, which means pneumonia in diabetic patients is more severe than non-diabetic patients[9].

Risk factors

Clinical medication determined that the increased insulin dose after infection by SARS-CoV-2 proved that the virus has an impact on the patient's glucose metabolism. Dysregulation of glucose metabolism aggravates DM and them affect the severity of pneumonia[9].

Two or more comorbidities in addition to age, it is common to find in diabetic patients, which increase the risk of SARS-CoV-2. However, a study in China of 1 590 patients with COVID-19 found that DM is an independent risk factor for the increase in admission of cases to ICU, with the need for mechanical ventilation and possible death (HR 1.59; 95% CI 1.03-2.45; p = 0.037). However, there are no publications that report on the severity in patients with type 1 diabetes, although experts comment that it maintains similar behaviours[3].

Aggravating molecular mechanisms

Increased susceptibility concerning COVID-19 in patients with DM is promoted by higher affinity cellular binding and efficient virus entry, decreased viral clearance, diminished T cell function, increased susceptibility to hyperinflammation including cytokine storm syndrome, and presence of cardiovascular diseases[2].

Kumar-Singh et al.[10] in a study of 161 patients with COVID-19 in Wuhan observed increased time for viral clearance to 25 days in patients with diabetes. Apart from the usual mechanisms of impaired neutrophil chemotaxis and phagocytosis predisposing to infections, there are several specific factors responsible for increased risk and severity of infection by SARS-CoV-2 among diabetes patients.

DM is associated with reduced expression of angiotensin-converting enzyme 2 (ACE-2). Under normal physiological conditions, ACE-2 degrades angiotensin-II

including a little extent angiotensin-I to smaller peptides. The pulmonary ACE-2/angiotensin system plays a potent anti-inflammatory and anti-oxidant role and ACE-2 is known to be protective against lethal avian influenza A H5N1 infection. Accordingly, low ACE-2 expression in DM might explain the increased incidence of severe lung injury and acute respiratory disease syndrome with COVID-19, in addition to other factors[11].

Increased expression of ACE-2-receptor in renal cortex, liver and pancreas have been found in diabetic mice, but not in lungs. A phenome-wide Mendelian randomization study found diabetes to be casually related to ACE-2 expression. Though the significance of these observations is not clear at present, increased ACE-2 expression might predispose patients with diabetes to infection with SARS-CoV-2[10].

The use of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin-receptor blockers (ARBs) is associated with increased expression of ACE-2-receptor as an adaptive response to counteract the elevated levels of angiotensin-II. Unfortunately, SARS-CoV-2 uses ACE-2-receptor to entry into the host pneumocytes, thus, ACE-2-receptor upregulation would facilitate entry and subsequent proliferation of the coronavirus[11].

DM is associated with an increase in furin, which is a type-1 membrane-bound protease, that belongs to the protein convertase subtilisin/Kexin family (PCSK). It is involved in coronaviruses entry into the cell and increased furin has been reported in diabetes, which might facilitate viral replication[10].

Effects in white blood cells

Alterations in CD4 lymphocytes have been reported in animal models with MERS. Lymphocytopenia is observed in patients with COVID-19 and also correlated with poor prognosis[10].

DM inhibits neutrophil chemotaxis, phagocytosis, and intracellular killing of microbes. Impairments in adaptive immunity characterized by an initial delay in the activation of Th1 cell-mediated immunity and a late hyperinflammatory response is often observed in patients with diabetes[2].

Several cytokines are increased in COVID-19 infection. Amongst these, IL-6 is increased in diabetes and may play a more deleterious role in COVID-19 infection. Testing monoclonal antibody against IL-6 receptor (tocilizumab) could represent a treatment option in COVID-19 patients[10].

ACE-2 receptors are expressed in pancreatic islets and infection with SARS-CoV it is linked to hyperglycemia in people without preexisting diabetes. Hyperglycemia persisted in some cases for 3 years after recovery from SARS indicating transient damage to beta cells. This effect still up to date, not reported in COVID-19, however, it is important to monitor blood glucose levels in the acute stage and during follow up of the disease[10].

A recent publish preprint established that non-structural proteins of SARS-CoV-2 attack the B1-chain of haemoglobin leading to dissociation of iron from porphyrin and impairing the ability of haemoglobin to transport oxygen. Although just a hypothesis, SARS-CoV-2 might have a higher affinity to glycated haemoglobin than non-glycated haemoglobin[11]. Future research should focus on describing the interaction of SARS-CoV-2 and glycated haemoglobin.

Dipeptidyl peptidase-4 (DPP4)

Dipeptidyl peptidase-4 (DPP4) is a tissue oligopeptide involved in multiple biological processes that include control of the activity of growth factors, chemokines and bioactive peptides included T-cell activation besides regulating glucose metabolism[10].

DPP4 serves as the receptor for MERS-CoV, in the same way as ACE-2 is the receptor for SARS-CoV and SARS-CoV-2. Experimental studies have suggested that certain changes in DPP-4 are associated with a reduced risk of MERS-CoV infection. This finding might explain the absence of MERS-CoV cases in Africa, despite the presence of the virus in camels, probably related to the frequent presence of protective polymorphisms of DPP-4 in Africans. Moreover, this has generated an immense interest whether to use DPP4 inhibitors (DPP4i) to reduce the viral entry of MERS-CoV. In one in vitro study, sitagliptin, vildagliptin and saxagliptin could not block the coronavirus entry into cells[10].

Though ACE-2 is recognized as the main receptor for SARS-CoV-2, a recent modelling study did not rule out its interaction with CD26 or DPP4. Moreover, a possible interaction of DPP4 and renin-angiotensin system (RAS) pathways seems to be plausible, although not completely studied. Interestingly, dipeptidyl amino-peptidase I-III

cleaves the Angiotensin II to Angiotensin III and IV which has cascading favourable effect through Angiotensin-4 (AT-4) receptors. Similarly, various endo- and oligo-peptidase cleaves Angiotensin I directly to Angiotensin which has a very favourable cascading effect. This suggests that a plausible interaction of non-specific DPP-4i with ACE-2 is theoretically possible, and therefore, this area needs future research[10].

Some of the studies found that co-administration of angiotensin-converting enzyme inhibitors (ACE-I) including DPP4 inhibitors led to an increased sympathetic tone and a consequent adverse hemodynamic effect. There has been an interaction observed between ACE-I and vildagliptin where a 4- to 5-folds increased risk of angioedema was noted, possibly due to the diminished degradation of bradykinin or substance P. In contrast, in the experimental study, sitagliptin was shown to inhibit ACE which could partially explain the purported beneficial cardiovascular effects[10].

DPP4 inhibitors are associated with an increased risk of upper respiratory infections, however, these agents did not show a lead to increased risk of pneumonia. There still insufficient evidence either for or against the use of DPP-4i in patients with diabetes and COVID-19[10].

Considerations of DM treatment in pandemic

At current times, treatment of diabetes has become a challenge because of the alterations in daily routine affect the dietary intake as well, regular walks and visits to the gym are limited, and the unpredictability of the disease increases mental stress too. Glucose dysregulation is caused by these factors and could predispose the patients to ketoacidosis, hyperosmolar coma, infections and even acute cardiac events [1,10].

Standardization of research protocols and identification of research priorities is essential to use time and resources productively. It is needed urgent steps to answer critical questions in the prevention and management of diabetic patients with COVID-19.

Insulin is extensively used to control glucose in critically ill hospitalized patients with diabetes, and the emerging use of continuous glucose monitoring may lower the rates of hypoglycemia associated with insulin use in the hospital, including in some patients with a critical illness[8, 10].

Amongst available agents for the treatment of acute illness complicated by diabetes, insulin is the most extensively used agent in human subjects with bacterial or viral infections and hospitalized critically ill patients. However, there is little information surrounding potential benefits or risks of insulin in the context of acute coronavirus infection[8,10].

Intravenous insulin infusion is requiring in patients on mechanical ventilation or with poor oral intake. The medical personnel are exposed to the virus with every visit to the patients to adjustment infusion rates, so is a need to make alternatives strategies of insulin administration. The use of subcutaneous short-acting insulin analogues is one of these strategies, but its safety in critically ill patients is less clear. A single dose of basal insulin has been an attempt in critically ill patients as in one study from Thailand[10].

In patients with type 1 diabetes with COVID-19 and hyperglycemia, it is important to monitor the blood glucose and ketone levels, maintain hydration and continue insulin therapy[8,10].

Most patients with mild infection and normal oral intake can continue the usual antihyperglycemic medication. Metformin should be used with caution in unstable hospitalized patients and should be discontinued in people with concomitant sepsis or severe impairment of hepatic and renal function. In severe COVID-19 infection, the hypoxia state may further increase the risk of lactic acidosis[3,8]. Further research is needed regarding the role of metformin as a host-directed treatment for severe COVID-19.

GLP-1R agonists have been explored as glucose-lowering agents in the perioperative period and the intensive care unit, and have generally been proven safe and effective for blood glucose management. However, the total number of subjects studied is small and the duration of therapy is limited. Although GLP-1 safely lowers blood glucose in short term studies of ventilated patients with a critical illness, there is insufficient experience with the safety and use of GLP-1R agonists in critically ill subjects to make therapeutic recommendations for use of these agents in the context of coronavirus infection and exenterate-based formulations should be stopped in subjects with deteriorating kidney function[8].

Sulfonylureas increase the risk of hypoglycemia and are best avoided in hospitalized subjects with severe medical illness. Although SGLT2 inhibitors are generally well-

tolerated in the outpatient setting, and cardioprotective most notably in the context of heart failure, SARS-CoV-2 infection may be associated with anorexia, dehydration, and rapid deterioration in clinical status. Hence, symptomatic individuals with T2D and active SARS-CoV-2 infection may be at heightened risk for volume depletion and euglycemic ketoacidosis. Accordingly, the available evidence suggests re-evaluation or discontinuation of these agents in very unwell ambulatory individuals, and the SGLT2 inhibitors should be routinely discontinued in unstable patients with severe SARS-CoV-2 infection upon admission to hospital[8].

To date, neither benefit nor harm has been shown in humans on DPP4 inhibitors during CoV infections. Therefore, DPP4 inhibitors could be continued, at least in mild cases of COVID-19, while potential benefit in treating CoV infection remains to be studied further. Similarly, GLP-1RAs are known to have anti-inflammatory effects and have shown potential for therapeutic benefit in acute lung injury. The available evidence is insufficient to determine the impact, if any, of sustained partial reduction of DPP4 activity, as achieved clinically in subjects with T2D treated with DPP4 inhibitors, on clinical outcomes in humans with active coronavirus infection[8].

Although glucocorticoids are used in the treatment of severe acute respiratory distress syndrome (ARDS), data for their use in ARDS caused by viral pneumonia are minimal and therefore they are not recommended for routine use in COVID-19. The place of glucocorticoids in the treatment of COVID-19 is being investigated. If they are used in patients with diabetes, hyperglycemia may worsen, necessitating escalation of insulin therapy[12].

The usage of cortisone had unexpectedly a negative effect on the process of viral clearance, although cortisone was commonly used in SARS patients. However, cortisone was targeted at particularly severe cases, which may have confounded the results. Compared to SARS, the outcome of using corticosteroids in COVID-19 patients is still unclear. Given that corticosteroids as immune-modulators that can decline circulating specific B- and T-cell subsets[12].

Treatment basis of COVID-19 patients with DM

Immunomodulators Cytokine release syndrome ('cytokine storm') is thought to be central to the pathogenesis of rapid deterioration and multi-organ dysfunction in patients with COVID-19. Therefore, immunomodulatory agents are postulated to be of benefit [13,14].

There are specific safety concerns for people with diabetes, as hypoglycemia is a known adverse effect of chloroquine / hydroxychloroquine treatment.

Suggested mechanisms are decreased intra-cellular insulin degradation, increased insulin-mediated glucose transport, increased insulin release and enhanced insulin sensitivity. Extra caution is required when is used with other glucose-lowering agents and dose reduction may become necessary [13,14,15].

It is very important to continue with an appropriate antihypertensive and lipid-lowering regime in these patients because most type 2 diabetic have other components of the metabolic syndrome such as hypertension and dyslipidaemia[15].

Statins reduce the expression of ACE-2-receptor induced by high lipids such as low-density lipoprotein or lipoprotein (a). The pleiotropic anti-inflammatory effects of statins have been attributed to the upregulation of ACE-2-receptor[16]. However, although it is believed that modulation of ACE-2 expression is associated with both infection and mortality rates in COVID-19, statins should not be discontinued because of the long-term benefits and the potential for tipping the balance towards a cytokine storm by rebound rises in interleukin(IL)-6 and IL-1B. Given the close links between diabetes and cardiovascular disease, the authors recommend control of lipid concentrations in all patients with COVID-19[17,18].

There is a hypothesis that increased ACE-2 expression could increase viral binding and entry into the cell, but there isn't clinical evidence to support this. Although, ACE inhibitor and ARBs increase the levels of ACE-2 by inhibiting the conversion of angiotensin1 to angiotensin2[18,19].

In patients with pneumonia, some articles have reported that calcium channel blockers (CCB) reduce the severity of disease and mortality. It seems safe to continue the administration of this drug in hypertensive patients, but the role of CCB in COVID-19 has not been studied[10].

Aspirin has anti-inflammatory properties, is advisable to discontinue in patients with sepsis and disseminated intravascular coagulation. However, in patients with underlying coronary artery disease, it needs to be continued as anticoagulant unless otherwise contraindicated[10,19,20].

CONCLUSIONS

The molecular and pathophysiological mechanisms between COVID-19 and diabetes mellitus are still not fully understood. Due to the poor prognosis that has been observed, the creation of treatment protocols for COVID-19 patients with a past medical history of diabetes mellitus is crucial, although it is for expert consideration depending on the characteristics and evolution of each patient. Diabetes prevention and control actions are a cornerstone to obtain better results when facing COVID-19.

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CONFLICT OF INTERESTS

The authors do not have conflicts of interests

AUTHORS CONTRIBUTIONS

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