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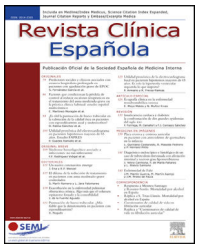

SPECIAL ARTICLE

Solving one of the pieces of the puzzle: COVID-19 and type 2 diabetes☆

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Abstract The emergence of the COVID-19 pandemic represents an enormous challenge. Given the considerable presence of type 2 diabetes mellitus in the current population, the pandemic is a health issue that requires an effort to provide better responses to our patients who are more vulnerable to the onset of infection and who are candidates for presenting more severe symptoms. This document attempts to address the relationship between COVID-19 infection and type 2 diabetes mellitus. To this end, we will briefly analyse whether the epidemiological data support this association and, subsequently, go in depth on the pathophysiological mechanisms that might connect the two diseases.

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Resolviendo una de las piezas del puzle: COVID-19 y diabetes tipo 2

Resumen La eclosión de la pandemia por COVID-19 supone un reto de enormes dimensiones y, dada la gran presencia de diabetes mellitus tipo2 en la población actual, hace que sea un problema de salud en el que centrar nuestros esfuerzos para dar la mejor respuesta a nuestros pacientes, que son más vulnerables al desarrollo de la infección y candidatos a presentar cuadros clínicos más graves. Este documento pretende abordar la relación entre la infección por COVID-19 y la DM2. Para ello analizaremos brevemente qué datos epidemiológicos sustentan esta asociación y, posteriormente, se profundizará en los mecanismos fisiopatológicos que podrían conectar ambas enfermedades.

The first data from observational studies, which were later corroborated both in systemic reviews and in several meta-analyses, show that hypertension, type 2 diabetes mellitus (DM2), obesity, and coronary disease are the main comorbidities in COVID-19 infection.[1–3] The prevalence of DM2 and the risk of complications vary widely depending on the region and series analyzed.

In the Chinese population, a recent meta-analysis that includes a large number of patients (n = 76,993) demonstrated a prevalence of DM2 of 7.87% (CI 95% 3.83–12.43)[2] whereas another with 1576 patients found a figure of 9.7% (CI 95% 7.2–12.2).[1]

In Italy, a randomized analysis of fatal cases of COVID-19 infection in elderly patients revealed a prevalence of DM2 of 35%[4] whereas in a retrospective study of 1591 patients hospitalized in intensive care units in the region of Lombardy (Italy), a prevalence of 17% was observed.[5]

In the data collected in the USA, (n = 7162), incidence of diabetes was 6% in patients who were not hospitalized, 24% in patients who were hospitalized, and 32% in patients admitted to intensive care units.[6] Along these lines, the data that we are now handling indicate that the risk of a fatal outcome due to COVID-19 is up to 50% higher in patients with DM2.[7]

There are various hypotheses that could explain why these patients have a higher incidence and severity of infection. It is well-known that a person with DM2 is at greater risk for infection *per se*, mainly due to a defect in innate immunity that affects phagocytosis, the chemotaxis of neutrophils, and cellular immunity, which make them especially vulnerable.[8] It is also true that the high frequency of DM2 in severe cases of COVID-19 could simply reflect the greater prevalence of DM2 in elderly people, which is in addition to the fact that these patients also have more comorbidities, including cardiovascular disease. Therefore, despite the fact that respiratory symptoms are predominant in COVID-19 infection, DM2 is of special interest in this disease: both risk of infection with the virus and its severity are increased in these patients.[9,10]

The next issue that arises is what mechanisms could link COVID-19 infection with disruption of the endocrine system. The virus penetrates the cell using angiotensin-converting enzyme 2 (ACE-2) as a receptor, an exopeptidase of the membrane mainly present in the kidneys, lungs, and heart but also in other organs, such as endothelial cells and the pancreas.[11]

The function of ACE-2 is the transformation of angiotensin I into angiotensin (1–9) and of angiotensin II into angiotensin (1–7). These final products have vasodilator, anti-inflammatory, and antifibrotic effects and in addition, they favor natriuresis. Therefore, they all antagonize angiotensin II action. ACE-2 has been linked to protection against hypertension, arteriosclerosis, and other vascular and pulmonary processes, including DM2.[12]

In animal models, it has been observed that absence of ACE-2 gives rise to greater lung damage in acute respiratory distress syndrome and that overexpression of ACE-2 protects against it.[13] In humans, it has been demonstrated that acute hyperglycemia regulates the increase in expression of the ACE-2 receptor, making it easier for the virus to penetrate the cell, whereas chronic hyperglycemia favors the cells losing their protective mechanism and being more vulnerable to the proinflammatory effect that the virus provokes. Although there has been great controversy surrounding use of ACE inhibitors and ARBs since the start of the pandemic, the most recent data confirm their safety in patients with COVID-19 infection.[14]

Likewise, it has been demonstrated that coronavirus infection affects both the endocrine and the exocrine pancreas.[15] Pancreaticells express ACE-2, which contributes to virus internalization and causes dysfunction in the ® cell. In this sense, preliminary data on the Italian population show that cytotoxicity cause by the virus is going to produce an insulin deficit, which could justify the presence of diabetic ketoacidosis observed in many patients upon their admission.[16]

Another interesting phenomenon in patients with COVID-19 infection lies in the tremendous requirement for insulin that they need during a severe course of the infection and which must be taken into account during hospitalization.

From a clinical perspective, it has been proposed that both fasting hyperglycemia and DM2 are independent predictors of morbidity and mortality in patients with acute respiratory distress syndrome.[17] In this context, a plausible hypothesis would be that the virus aggravates the char-

acteristic low-grade chronic inflammation in patients with DM2, triggering cytokine release syndrome with a systemic, uncontrolled hyperinflammatory response resulting in the release of large quantities of proinflammatory cytokines by immune effector cells, such as the macrophages activated by the infection. In the worst-case scenario, this cytokine storm could cause acute respiratory distress syndrome with multiple organ dysfunction syndrome and, finally, would lead to death in patients with severe cases of infection. This, in part, could justify the finding observed in hospitalized patients in which poor metabolic control in patients with DM2 increased the rate of mortality.

Today, there is great uncertainty about what type of antidiabetic drug would be more pathophysiologically appropriate in patients with DM2 and COVID-19 infection.[18] An initial mechanism that could explain the relationship between COVID-19 and DM2 involves dipeptidyl peptidase-4 (DPP-4), which acts by degrading the incretin hormones GLP-1 and GIP. In cellular studies, the DPP-4 enzyme was identified as a functional receptor for the coronavirus that causes Middle East respiratory syndrome. It has been demonstrated that antibodies that target DPP-4 inhibit infection by this virus at a cellular level.[19]

The DPP-4 enzyme is a type II transmembrane glycoprotein expressed ubiquitously that plays an important role in the metabolism of glucose and insulin and which favors inflammation in DM2. The issue that arises is whether this phenomenon observed in the Middle East respiratory syndrome coronavirus can be extrapolated to COVID-19 and, thus, if treatment with DPP-4 inhibitors in clinical practice could modify the course of the infection, reducing concentrations of DPP-4 and representing a good therapeutic tool for patients with COVID-19.[20]

As stated above, COVID-19 infection favors an imbalance in the renin-angiotensin-aldosterone axis which could be related to ACE-2 inhibition by the virus and due to presenting with elevated angiotensin II levels, which favors generation of secondary peptides with vasoconstrictor, proinflammatory, and sodium-retaining effects.

Although the evidence available is limited, one hypothesis points to the fact that incretin drugs can produce a beneficial effect through activation of the nonclassical renin-angiotensin system pathway. This boosts the ACE axis, with a consequent increase in angiotensin (1–7) that favors anti-inflammatory, antifibrotic, natriuretic, and antiproliferative phenomena.[21] Through this pathway, GLP-1 analogues could improve glucose and blood pressure control, reducing vascular damage. These drugs could compete with the virus itself for the ACE-2 receptor, exercising their beneficial effect through the combination of various mechanisms, including improvements in the metabolic, anti-inflammatory, and antiviral profile.

In the same manner, *in vitro* studies in human renal cells treated with type 2 sodium-glucose cotransporter inhibitors have demonstrated an increase in angiotensin (1–7), with important anti-inflammatory and antifibrotic effects.

A recent editorial in *Clinical Infectious Diseases* suggests that, by analogy, it is reasonable to suppose that these drugs independently activate the nonclassical pathway of the renin-angiotensin system in the lungs.[22]

Finally, another hypothesis that must be explored in the future and that is related to the endotheliitis phenomenon that is generated by COVID-19 infection is of note[23]: patients with DM2 could be more sensitive to experiencing deterioration in the systemic microcirculatory function in different beds.

On this point, with our current knowledge, we can pose some clinical questions that seem evident, although there are many more to which we still do not have a response. It is fundamental that people with DM2 maintain good metabolic control, which could help reduce risk of infection as well as its severity.[24] This includes adequate glucose control accompanied by tight blood pressure and lipid profile control. To this end, it is important raise awareness among patients of the importance, now more than ever, of self-control. This must be accompanied by physicians' proactive work on optimizing treatment as much as possible, considering the pros and cons of each drug, and paying particular attention to the potential interactions among antidiabetics, antihypertensives, and statins with the various treatments that are being used for COVID-19.

In case of infection that does not require hospitalization, appropriate monitoring of these patients *via* telemedicine and other similar methods must be evaluated, especially in frail and elderly patients. If patients require hospitalization due to the severity of the infection, a wide range of unanswered questions arise: Do they need frequent blood glucose monitoring? What is the importance of hyper- or hypoglycemia control in isolated hospitalized patients? Is stress hypoglycemia in critical patients associated with greater morbidity and mortality? Is this stress hyperglycemia of greater relevance than having prior DM2? What occurs with the use of high doses of glucocorticoids?

To respond to these and many other questions, the Spanish Internal Medicine Society has created an online registry, SEMI-COVID-19, with information (epidemiological, clinical, treatment, laboratory, and radiographic parameters) on an extensive number of patients hospitalized with SARS-CoV-2 infection confirmed by laboratories in Spanish hospitals.

To sum up, the emergence of the COVID-19 pandemic is an enormous challenge. The considerable prevalence of DM2 in the current population makes the pandemic a health issue that requires all our efforts in order to provide the best possible responses to our patients, who are more vulnerable to developing the infection and are more susceptible to presenting with more severe symptoms.[25] In this document, some of the mechanisms that support the association between COVID-19 and DM2 have been analyzed, with the limitations inherent to current evidence.

Lastly, we would like to highlight that the content of this document is based on the limited number of publications that there are on the issue to date and that, on many occasions, they are hypotheses in absence of any firm scientific evidence. Therefore, this information is susceptible to change as knowledge about COVID-19 infection evolves.

Conflicts of interest

The authors have no conflicts of interest with the content included in this material.

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