Diabetes and COVID, a significant negative syndemic

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ABSTRACT

A syndemic is defined as the coexistence of 2 or more diseases that extend among the population by the interaction or synergy of biological and societal factors. Diabetes mellitus changes the progression and prognosis of COVID. Metformin has been shown to improve the prognosis of COVID-19. There are promising results with DPP4i and GLP-1RA.

They've promised that dreams can come true, but forgot to mention that nightmares are dreams, too.
Oscar Wilde

Over the past few months, we have experienced unique and unexpected times. The SARS-CoV-2 virus has shaken our world and forced us out of our comfort zone. We can no longer visit as we did before and, consequently, cannot care for patients with diabetes as before. This has forced us to come up with new options and to implement them… with uneven results.

We are facing a worldwide syndemic (the coexistence of 2 or more diseases that extend among the population due to the interaction or synergy of biological and societal factors), which we do not know how long will last, although we do know that individuals with diabetes are at greater risk… or are they?

THE EXTENSION OF THE TWO EPIDEMICS

For many years, we have known that the prevalence of diabetes mellitus (DM) is increasing spectacularly. According to the International Diabetes Federation,[1] there were 460 million adults with diabetes worldwide in 2019 (9.3% of the population), a figure that will increase to 700 million by 2045 (51% increase), although in some regions such as Africa the increase will be 143%. In 1 year, DM kills 4.2 million people and results in expenditures of $760 billion (USD).

On the other side, we have the unstoppable COVID epidemic. At the time this text was written (right in the third wave, in mid–April 2021), the pandemic has affected more than 136 million people and has caused more than 2.9 million deaths.

RISK OF COVID INFECTION IN INDIVIDUALS WITH DIABETES

We know that individuals with diabetes have greater susceptibility to infectious diseases. In general, they have delayed activation of immune mechanisms.[2]

The method for studying this risk has been to compare the prevalence of type 2 DM (DM2) in hospitalised patients with the prevalence of DM2 in the general population. Studies and meta-analyses in China,[3] Italy[4] and Spain[5] have found somewhat higher prevalence rates in hospitalised patients. In the case of Spain, with an estimated populational prevalence of DM2 of 13.8%,[6] we see that among the hospital admissions registered by the Spanish Society of Internal Medicine, the prevalence of DM was 19.4%.

In the United States, a review studied the prevalence of DM among COVID-19 patients who were not hospitalised (6%), those who were hospitalised (24%) and those admitted to intensive care units (32%).[7] In the US general population, the prevalence is 13.3%.[1]

In summary, these data seem to indicate that the risk of presenting COVID-19 infection is somewhat higher in individuals with diabetes; however, this fact might be due to the bias of age or the presence of other common comorbidities in individuals with DM2. More precise cohort and case-control studies are needed with real world data whose main objective should be to confirm this hypothesis.

DIABETES MELLITUS CHANGES THE PROGRESSION AND PROGNOSIS OF COVID

There is little doubt about this point. The prognosis of COVID-19 is determined in large part by the body's inflammatory response. All those clinical entities that involve chronic low-grade inflammation contribute to a poorer prognosis. Individuals with DM2 in reality are patients with chronic inflammation, poor resolution of oxidative stress, hypercoagulability, high insulin resistance and a frequent association with other comorbidities,[8] all of which contributes to worsening the prognosis of any infection, as confirmed by the clinical data.

In the case of COVID infection, it has also been observed that the prognosis especially worsens in those with marked hyperglycaemia at admission.[9,10] However, no clear relationship has been observed with deficient metabolic control previously measured by glycated haemoglobin (HbA_{1C}). A systematic review found a nonsignificant relationship between HbA_{1C} and COVID-19 infection severity,[11] which does not mean that it does not exist or that we should neglect HbA_{1C} control.

Virtually all systematic reviews and meta-analyses have shown that patients with DM who presented COVID infection have increased mortality (odds ratio [OR], 1.90), more ICU admissions, a greater likelihood of mechanical ventilation and longer hospital stays. This increased severity has an approximate combined OR of 2.75.[12-14] Obesity is also an important factor.[15]

CERTAIN DRUGS TAKEN REGULARLY BY PATIENTS WITH TYPE 2 DIABETES MELLITUS CAN CHANGE THE PROGRESSION AND PROGNOSIS OF COVID-19

At the start of the first wave of the pandemic, one of the potential pathophysiological mechanisms of SARS-CoV-2 toxicity was through the pathway of the angiotensin-converting enzyme 2 receptor. It was therefore feared that the drugs that blocked this pathway were associated with increased mortality. Subsequently, several meta-analyses ruled out this possibility and recommended maintaining their use.[16,17]

With regard to statins, a number of studies such as the one conducted in Spain by Lluis Massana et al.[18] observed lower COVID mortality among patients who took statins before their hospital admission, which led to raised hopes with this drug family. Subsequently, the CORONADO study not only was unable to confirm these results but also found higher mortality among statin users.[19]

In terms of antidiabetic drugs, there are a number of timely studies, but there is a lack of clear evidence. Metformin has been shown to improve the prognosis of COVID-19.[20] The role of sodium-glucose cotransporter-2 inhibitors[21] has also been studied, and it has been observed that they do not worsen the prognosis of COVID-19 but also do not improve it.

Currently, hopes are pinned on the family of incretins.[22] For dipeptidyl peptidase-4 inhibitors (DPP4i) in particular, the study by Solerte[23] was the first to show that patients who took sitagliptin before hospital admission had lower COVID-19 mortality (OR, 0.23) and better clinical progression, with fewer ICU admissions (OR, 0.51) and less mechanical ventilation (OR, 0.27). Proposed explanations for these results include the effect of DPP4i on cytokines by mainly preventing the pulmonary inflammatory storm. This beneficial effect has been observed in other studies[24] but not in all.[25]

It is possible that receptor agonists of the glucagon-like peptide-1 (GLP-1RA) also have a potential role in stabilising the barriers that prevent the action of proinflammatory mechanisms, slowing the progression of the virus and improving the clinical results.[26]

Pending the results of studies designed to provide a specific answer regarding the protective or harmful effects of various families of antidiabetic drugs, the most logical approach appears to be to continue with the same treatment philosophy for DM2 currently in use.

REPERCUSSIONS OF COVID-19 ON THE METABOLIC CONTROL OF DIABETES MELLITUS

One of the most significant problems caused by this COVID-19 epidemic is the lack of control of chronic diseases such as diabetes, most likely due to the lack of resources and time. A number of studies have remarked on the

diabetogenic role of the SARS–CoV–2 virus.[27] In our daily consultations, however, the problem has much simpler causes: an overload of people with COVID-19 infection requiring care has resulted in less care for individuals with chronic diseases such as DM2.

This fact has been demonstrated very recently in a study with data from actual practice on approximately 6 million patients of the Catalan health system, which analysed the impact of the COVID epidemic on the progression of 34 indicators of quality care.[28] In terms of DM2, the requests for HbA_{1C} measurements decreased 17% during the first wave (February to April 2020), and the percentage of patients with HbA_{1C} <8% decreased 2.5 points. The rates of diabetic foot screening (by 10 points), retinopathy (by 5 points) and oral health (by 1.3 points) also decreased.

CONCLUSIONS

The COVID-19/DM2 syndemic has presented severe repercussions and major issues. Individuals with DM2 very likely have a greater risk of infection (although it needs to be studied with a rigorous methodology). Patients with DM who experience SARS–CoV–2 infection definitely have a greater risk than the general population of COVID-19 progressing more poorly (more hospital admissions, longer ICU stays, greater need for mechanical ventilation and higher mortality).

We are unsure whether some of the antidiabetic drugs such as metformin, DPP4i and GLP-1RA have a protective role in COVID-19 infection, but we do know that unfortunately our patients' metabolic control worsens and is accompanied by an increased presence of diabetic complications.

The COVID-19 pandemic has undoubtedly changed our lives and that of our patients. We cannot have visits as we did before, and it is much more difficult to conduct preventive medicine for chronic non–COVID diseases. The patients are also disoriented. We do not know how long this situation will last nor how future consultations of health professionals in health centres will be conducted. Telemedicine and remote visits are being promoted, but will this philosophy become permanent?

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