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Sodium-Glucose Cotransporter 2 Inhibitors in the Era of COVID-19 Pandemic: Is the Benefit to Risk Ratio Still Favorable?

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We have learned that the introduction of sodium-glucose cotransporter 2 inhibitors (SGLT2i) into the therapeutic algorithm of type 2 diabetes (T2D) has led to a dramatic change in the landscape of the therapeutics of the disorder.

During the past few months, the humanity has been living under the shadow of the "Corona Virus Disease 2019 (COVID-19)" pandemic. At the time this paper is being written, approximately 4 000 000 of confirmed COVID-19 cases and 280 000 related deaths have been globally reported.[1] Furthermore, emerging evidence suggests that people living with both T2D and type 1 diabetes (T1D) are at increased risk for a rapid progression and bad prognosis of COVID-19.[2]

Latest guidelines for the management of T2D suggest the use of SGLT2i as second line treatment, following metformin.[3] For certain groups of people with T2D however, such as those with multiple risk factors for atherosclerotic disease or a history of cardiovascular (CV) event, recent recommendations suggest these agents as first line therapy, due to their potential to decrease CV risk, predominantly at the secondary prevention level.[4] Based on data showing the ability of SGLT2i to improve glucose levels and reduce body weight, insulin dose,[5] and glycemic variability[6] in T1D, dapagliflozin has been recently approved for administration to people with T1D and body mass index $\geq 27\,kg/m^2$, when insulin alone is unable to provide adequate control.

According to their mechanism of action, SGLT2i block the homonymous receptors expressed in the early portion of the proximal renal tube, leading to decreased renal glucose reabsorption and a reduction in plasma glucose levels.[7] At the same time, they lower insulin and raise glucagon concentrations, resulting in an increased glucagon-to-insulin ratio, which favors gluconeogenesis and stimulates lipolysis.[8] In this context, therapy with SGLT2i seems to promote a shift in energy substrate usage from carbohydrates to lipids,[9] in conjunction with reduced ketone body clearance from the kidneys.[10] The above mechanisms explain the increased rates of euglycemic diabetic ketoacidosis (DKA), observed in SLT2i users compared to nonusers, both in the community and during hospital admission.[11] The DKA risk among SGLT2i-treated patients might be even greater in the context of a severe infection, such as COVID-19. There are increasing reports in the literature describing cases of euglycemic DKA in people with diabetes receiving SGLT2i, in whom a moderate to severe infection triggered the presentation of DKA.[12] Apart from SGLT2i therapy, a number of infection-related conditions are believed to act as precipitating factors for the development of DKA, including reduced appetite, leading to decreased carbohydrate consumption, dehydration due to high fever or vomiting/diarrhea, and release of insulin-antagonistic hormones, such as catecholamines and cortisol.[13] On that basis, recently produced recommendations for the management of diabetes during the COVID-19 pandemic strongly suggest the cessation of therapy with SGLT2i in patients with suspicious symptoms, such as fever, dyspnea, and cough or in those admitted in the hospital.[14]

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However, there is a strong counter-argument to this; a number of preclinical studies have highlighted the potential of SGLT2i to ameliorate systemic and tissue-specific inflammation, tissue hypoxia, and oxidative stress, by downregulating the expression of adipokines and cytokines, including that of leptin and interleukin-6.[15] The latter has been recognized to play a crucial role in COVID-19 related cytokine release syndrome, which is known to be catastrophic in the majority of cases.[16] In this context, an ongoing trial (DARE-19)[17] aims to evaluate whether dapagliflozin, a SGLT2i, could reduce the risks of disease progression, clinical complications, and death due to COVID-19 in patients with at least one of the following: T2D, hypertension, CV disease, heart failure (HF), and/or mild-moderate renal dysfunction. It remains to be proved whether potential benefits can outweigh the risk of such an approach.

Prescribers might want to be cautious in initiating therapy with SGLT2i during the next few weeks and carefully weigh benefits against risks, putting patient safety, rather than heart and renal protection, as the top priority. Considering the large intercountry differences with respect to the disease's morbidity and mortality, this might be more applicable in areas of the world with a high COVID-19 burden. An exception may well be in those with diabetes and HF where the benefits of initiating SGLT2i may outweigh the risk and this will have to be assessed on a case by case basis.

There is no doubt that the contribution of SGLT2i to the modern management of diabetes has been critical. In the future, we predict that "cardiorenal concept" will continue to play a fundamental role in the way that physicians will treat people with both types of diabetes. However, "doing no harm" is a key pillar of medical management and it is perhaps best to hold back such treatment until more is learnt about COVID-19, with the exception of very high-risk groups, who are likely to experience immediate benefit from such therapy. According to Mark Twain's famous quote: "The right word may be effective, but no word was ever as effective as a rightly timed pause."

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