Received: 17 May 2020 | Accepted: 22 May 2020

DOI: 10.1111/1753-0407.13069

LETTER TO THE EDITOR

Journal of Diabetes WILEY

Comment on "Is the type of diabetes treatment relevant to outcome of COVID-19?"

Dear Editor:

We read with interest the editorial entitled "Is the type of diabetes treatment relevant to outcome of COVID-19?"[1] The concept of harnessing the pleiotropic anti-inflammatory properties of antidiabetic medications in the management of early/advanced coronavirus disease 2019 (COVID-19) in people with diabetes mellitus (DM) is intriguing. However, translation into clinical practice requires more justifications.

Thiazolidinediones reduce cardiovascular events in terms of recurrent myocardial infarction/stroke in people with type 2 DM (T2DM).[2,3] However, pioglitazone use is also associated with an increased risk of heart failure (HF) in patients with and without pre-existing cardiovascular disease.[4-6] Increased plasma volume secondary to fluid retention is attributed as the cause of HF.[7] A significant number of COVID-19 patients develop cardiac complications with the cause of death attributed to cardiac failure/arrest in 25% of cases.[8,9] Isolated cardiac involvement has also been reported.[10] It is believed that COVID-19 induces a state of classic HF with preserved ejection fraction in early stages that later culminates into acute systolic HF amid a state of cytokine storm, biochemically manifesting as elevated troponin and natriuretic peptides.[9] HF is likely to be exacerbated with use of pioglitazone; in fact, the drug has been associated with significant elevation in natriuretic peptides.[11] Moreover, pioglitazone has been shown to upregulate angiotensin-converting enzyme 2 (ACE2).[12-14] Upregulation of ACE2 may be counterproductive as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) uses ACE2 as a receptor for entry into host cells. Although pioglitazone does have anti-inflammatory properties independent of its glucose-lowering effect, it is debatable whether it would be of any benefit in COVID-19. Even corticosteroids, potent anti-inflammatory drugs, have not been found to be beneficial in COVID-19.[15]

Hydroxychloroquine/chloroquine is being used against COVID-19 although available studies have not shown any mortality benefit.[16,17] In addition, many patients developed QT prolongation.[18-20] It is not universally accepted as an antidiabetic agent either and is not Food and Drug Administration (FDA) approved for this purpose. Moreover, robust double-blinded, randomized controlled trials demonstrating its glucose-lowering efficacy are very limited,[21,22] most being either open-label/real-world/observational studies. Besides, it has primarily been evaluated as a third-line antidiabetic drug in patients with poor glycemic control; in the present scenario, insulin would be a better choice in such patients.[14] Thus, in absence of robust clinical data favoring its use in either COVID-19 or T2DM, advocating hydroxychloroquine for its anti-inflammatory effects is certainly not wise.

Sodium glucose cotransporter 2 inhibitors (SGLT2i) are also known for their anti-inflammatory properties, both at systemic and tissue level.[23-25] However, it is always advisable to withhold SGLT2i in the presence of any active infection as it increases the chances of euglycemic diabetic ketoacidosis. Moreover, patients on SGLT2i are at a higher risk of dehydration and acute kidney injury amid the already increased insensible water loss precipitated by fever and tachypnea.[26,27]

Thus, while choosing an antidiabetic drug in patients with COVID-19, a physician should take into account the therapeutic efficacy and potential adverse effects of the drug, rather than its anti-inflammatory properties. Most often, insulin happens to be the best option in hospitalized patients with COVID-19 and DM.

ACKNOWLEDGEMENTS

None.

CONFLICT OF INTEREST

None.

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