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Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Letter to the Editor

Reply to comment on "Should anti-diabetic medications be reconsidered amid COVID-19 pandemic?"

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Dear Editor

We went through the comment by Cure *et al.* in rebuttal to our article entitled "Should anti-diabetic medications be reconsidered amid COVID-19 pandemic?" [1] Although it is interesting, certain clarifications are needed.

Firstly, the authors do agree with us on the fact that insulin reduces the activity of ADAM-17, metalloproteinase that cleaves ACE2 [2,3]. This should, in turn, increase the expression of ACE2. On the contrary, Cure *et al.* state that ACE2 levels are reduced with insulin. This disparity needs clarification.

Secondly, we agree with the authors that activation of NHE by insulin can lead to intracellular alkalization and inhibit binding and entry of SARS-CoV-2. However, NHE1 activity of erythrocytes has been found to be insulin-resistant in obese subjects [4]. Interestingly, NHE1 is also predominantly expressed in lungs and might be resistant to the action of insulin in people with T2DM. Moreover, activation of NHE1 in the pulmonary arterial has been implicated in the pathogenesis of pulmonary arterial hypertension [5]. This would be undesirable in a patient with COVID-19 and acute respiratory distress syndrome.

Thirdly, the original commentary by us was intended towards people with diabetes mellitus (DM) at risk for developing COVID-19 and not towards those already diagnosed with COVID-19. However, much of the comments put forward by Cure *et al.* cater to people with DM already having COVID-19. As in any patient with severe infection/sepsis/hypoxia, use of metformin in COVID-19 does theoretically increase the risk of lactic acidosis [6]. Notwithstanding this fact, metformin use in patients with severe septic shock has been found to significantly lower in-hospital mortality as compared to non-users [7].

Finally, the discussion on dapagliflozin is also controversial. By inhibiting NHE, dapagliflozin should theoretically result in intracellular acidosis. Thus, activation of NHE by insulin and subsequent rise in intracellular pH will be counteracted by inhibition of NHE by dapagliflozin when both drugs are used in combination. Moreover, patients on dapagliflozin will be at a higher risk of dehydration and acute kidney injury amid the already increased insensible water loss precipitated by fever and tachypnea [8]. Lastly, acute illness happens to be the most common precipitating factor for euglycemic diabetic ketoacidosis (DKA) in patients on SGLT2 inhibitors [9]. Moreover, SARS-CoV-2, *per se* may aggravate pancreatic β-cell damage and precipitate DKA [10].

Thus, in the absence of robust data, we would be highly skeptical and advice against the use of dapagliflozin in diabetic patients with COVID-19. Insulin however remains a good choice for in-hospital patients; however, in the absence of in-clinic visits, it might be difficult to counsel diabetic patients in the community about insulin usage amid the ongoing pandemic.

Funding

None.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

Acknowledgement

None.

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https://doi.org/10.1016/j.diabres.2020.108192
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