Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Contents available at ScienceDirect

Diabetes Research and Clinical Practice

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

International Diabetes Federation

Letter to the Editor

Comment on "Should anti-diabetic medications be reconsidered amid COVID-19 pandemic?"

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ARTICLE INFO

Article history:
Received 21 April 2020
Accepted 24 April 2020
Available online 30 April 2020

Keywords:
COVID-19, T2DM
Diabetes mellitus
Angiotensin-converting enzyme 2
Dapagliflozin
Insulin
Metformin

Dear Sir,

We read with great interest the article by Pal R and Bhadada SK "Should anti-diabetic medications be reconsidered amid COVID-19 pandemic?" [1]. The study is interesting; however, we have some concerns and comments.

Novel coronavirus disease 2019 (COVID-19) penetrates to angiotensin-converting enzyme 2 (ACE2) at low pH, causing infection [2]. Insulin both lowers the ADAM17 activation and increases Na^+/H^+ exchanger (NHE) activation [1,3]. Decreased ADAM17 activation reduces ACE2 cleavage and ACE2 levels [1]. NHE activation increases intracellular pH. Both the reduced ACE2 and the increased intracellular pH decrease the possibility of the virus adhering ACE2 and infecting the cell. Insulin therapy seems to be the most appropriate treatment for diabetes patients with COVID-19. However, most of the time, blood sugar regulation cannot be achieved with a single agent.

Activation of NHE leads to increased blood pressure, insulin resistance, and alkali intracellular pH [3,4]. Increased intracellular pH cause decreased cell functions [3]. In COVID-19 infected patients with diabetes, cell signaling pathways will change completely. Lactate dehydrogenase (LDH) and creatine kinase increase in virus infection. These findings show that there is cell destruction. Elevated lactate levels as a result of cell destruction increase anaerobic glycolysis and hypoxia [5]. Thus, lactate production increases even more. Lactate levels are already high in diabetic patients [4]. The increased lactate, together with the H^+ ion, enters the cell

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https://doi.org/10.1016/j.diabres.2020.108184

through monocarboxylate transporters (MCT). As soon as the intracellular area becomes acidic, NHE is activated to compensate. Na^+ and Ca^{+2} pass into the cell and H^+ are pumped out of the cell. In this vicious circle, the cell swells and dies due to increased Na^+ and Ca^{+2} in the cell [6].

Metformin increases lactate production [7]. Lactate has already increased in COVID-19 infection. Therefore, metformin use may not be suitable. Not other SGLT2 inhibitors, dapagliflozin lowers the lactate level [5]. Dapagliflozin inhibits NHE [3]. Both the decreased lactate level and inhibition of NHE may protect intracellular pH. Dapagliflozin may increase ACE2 [1]. When dapagliflozin is combined with insulin treatment, insulin decreases ACE2 level by reducing ADAM17 activation and reduces viral load. Diabetic ketoacidosis may develop due to the increased need for insulin during infection. Insulin can prevent dapagliflozin from causing diabetic ketoacidosis by supplying the increased need for insulin in infection. Dapagliflozin regulates the activation of MCT and NHE by lowering the lactate level and can prevent cell ion balance degradation. Insulin plus dapagliflozin combination seems to be the best treatment option in patients with COVID-19 infection.

Funding

None

Declaration of Competing Interest

The authors declare that they have no conflicts of interest

Acknowledgement

None.

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