Journal of Endocrinological Investigation
https://doi.org/10.1007/s40618-020-01307-4

LETTER

COVID-19 may affect the endocrine pancreas by activating Na^+/H^+ exchanger 2 and increasing lactate levels

E. Cure[1] · **M. Cumhur Cure**[2]

Received: 10 May 2020 / Accepted: 21 May 2020

Dear Editor,

We read with great interest the article by Pal R and Banerjee M "COVID-19 and the endocrine system: exploring the unexplored" [1], in which the authors also discuss the effects of COVID-19 on pancreatic tissue and glucose regulation. Novel coronavirus disease 2019 (COVID-19) binds to angiotensin-converting enzyme 2 (ACE2) at low intracellular pH. Since diabetes may be associated with lower intracellular pH, this could favor COVID-19 infection. We would like to also mention the effects that the virus could have on the endocrine pancreas and glucose regulation by affecting the Na^+/H^+ exchanger (NHE) and lactate pathways.

COVID-19 can infect all tissues expressing ACE2, such as the pancreas. ACE2 converts angiotensin II into angiotensin 1–7. When the virus blocks ACE2, angiotensin II degradation is reduced, and its levels increase. Conversely, angiotensin 1–7 level decreases. Angiotensin II increases insulin resistance and beta-cell damage; while, angiotensin 1–7 prevents insulin resistance. Also, the chymase pathway may play a role. When angiotensin II levels increase, this can activate NHE. NHE pumps 3 Na^+ ions inward the cell and 2 H^+ ions out of the cell. Simultaneously, Ca^{2+} transport into the cells is also affected [2]. The environment becomes hypoxic and acidic after pumping the H^+ ion out of the cell and increased hypoxia causes the production of reactive oxygen radicals. Endothelial damage and insulin resistance may occur due to increased oxidative stress. Accumulation of Ca^{2+} and Na^+ in the cell leads to cell damage and apoptosis [2]. NHE is present in all tissues and there is abundant NHE2 isoform in the pancreas [3]. NHE2 is directly related to insulin release. It is known that insulin secretion is decreased in case of NHE2 deficiency [3]. However, sustained NHE activation causes insulin resistance and beta-cell injury by increasing oxidative stress. NHE activity has been reported to be increased in patients with diabetes. Therefore, excessive and continuous NHE activation with COVID-19 infection can permanently damage the endocrine pancreatic tissue.

In patients with diabetes, lactate levels may be increased, also due to augmented release from adipose tissue in case of obesity. Increased lactate leads to pro-inflammatory cytokine release and stimulates direct insulin release from the pancreas. Hypoxia and cell lysis during COVID-19 infection cause increased lactate levels [2]. To reduce excessively increased lactate, monocarboxylate transporters transport lactate and H^+ ion inward the cell. This event further increases NHE activation [2]. On the other hand, since lactate rapidly enters the gluconeogenesis pathway in the liver, hepatic glucose output increases. This situation may become a vicious circle. If the COVID-19 infection is severe and prolonged, serious damage of the endocrine pancreas may, therefore, develop.

Author contributions EC is the primary author. MCC helped in literature search. Both EC and MCC approved the final version of the manuscript.

Compliance with ethical standards

Conflict of interest None to declare.

Ethical approval This letter article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of article, formal consent is not required.

✉ E. Cure
erkancure@yahoo.com

M. Cumhur Cure
medinecure@yahoo.com

[1] Department of Internal Medicine, Ota&Jinemed Hospital, Muradiye Mahallesi Nuzhetiye Cad, Deryadil Sokagi No: 1, Besiktas, 34357 Istanbul, Turkey

[2] Department of Biochemistry, Istanbul, Turkey

Published online: 28 May 2020

References

1. Pal R, Banerjee M (2020) COVID-19 and the endocrine system: exploring the unexplored. J Endocrinol Invest. https://doi.org/10.1007/s40618-020-01276-8
2. Cure E, Cumhur Cure M (2020) Can dapagliflozin have a protective effect against COVID-19 infection? A hypothesis. Diabetes Metab Syndr 14:405–406
3. Deisl C, Simonin A, Anderegg M, Albano G, Kovacs G, Ackermann D et al (2013) Sodium/hydrogen exchanger NHA2 is critical for insulin secretion in β-cells. Proc Natl Acad Sci U S A 110:10004–10009