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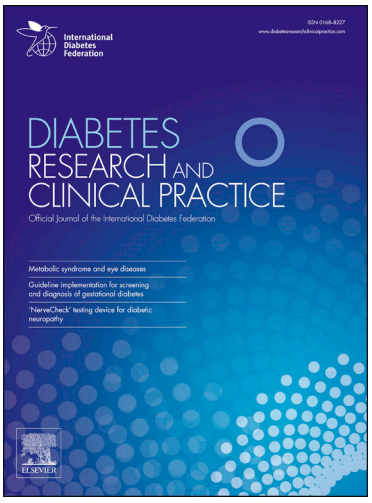

Letter to the Editor

COVID-19 and diabetes: Is this association driven by the DPP4 receptor? Potential clinical and therapeutic implications

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COVID-19 and diabetes: is this association driven by the DPP4 receptor? Potential clinical and therapeutic implications.

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Recently, Iacobellis (1) commented on the high prevalence of type 2 diabetes mellitus (T2DM) among individuals affected by the coronavirus disease COVID-19, especially in those with severe SARS-COV-2 infection needing intensive care for acute respiratory complications. The author reports observations that show that human dipeptidyl peptidase 4 (DPP4) was identified as a functional receptor for the spike protein of the MERS-Co-V [2]. MERS-CoV binds to the receptor-binding domain and interacts with T cells and nuclear factors, activating an inflammatory response. Antibodies directed against DPP4 inhibit human coronavirus-Erasmus Medical Center (hCoV-EMC) infection of primary human bronchial epithelial cells. Furthermore, transgenic mice were made susceptible to MERS-CoV by expressing human DPP4 [3], and these knock-in mice had a lethal form of lung disease, characterized by a strong inflammatory response [3-4].

Based on these observations, Iacobellis suggest that DPP4 may represent a potential target for DPP4 inhibitors for preventing and/or reducing the risk and progression of the acute respiratory complications that T2DM may add to the COVID-19 infection.

However, there are some points to consider carefully before claiming possible novel therapeutic approaches to COVID-19. The potential interaction between SARS-CoV-2 spike glycoproteins and DPP4 has been predicted by structural studies [5], but needs confirmation in human cells.

Moreover, Iacobellis does not take into account that the same authors that demonstrated human DPP4 as a functional receptor for the spike protein of the MERS-Co-V [2] showed that hCoV-EMC infection could not be blocked by the DPP4 inhibitors sitagliptin, vildagliptin and saxagliptin, probably because these inhibitors do not target the binding interface between the S1 domain of hCoV and the receptor. So, the potential role for DPP4 inhibition may not be as important as suggested.

There is, however, a point worth taking from Iacobellis' remarks. We have shown that higher plasma DPP4 is evident in obesity, metabolic syndrome and type 2 diabetes [6] and increases with aging [7],

all representing significant risk factors for unfavourable COVID-19 outcomes [8]. Thus, increased DPP4 may represent a driver for clinical severity in SARS-COV2 infection. On one side, the broad DPP4 distribution could contribute to explain the large number of SARS-COV2 target organs, which are more than those expressing ACE2 receptors, identified as the main SARS-COV2 receptor so far [8]. On the other, DPP4 levels may, at least in part, determine COVID-19 severity, reflecting the accessibility of SARS-COV2 to target cells, tissues and organs, and may explain the high incidence of mortality in severe COVID-19. Therefore, it may be warranted to further investigating the utility of DDP4 measurement. Plasma DPP4 measurement could represent an easy tool for risk stratification in SARS-COV2 infected patients, particularly in highly susceptible populations as those with Diabetes or other metabolic conditions, and a marker of disease progression and response to treatment in COVID-19.

Conflict of Interest
None

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None

References

1. Iacobellis G. COVID-19 and diabetes: Can DPP4 inhibition play a role? Diabetes Res Clin Pract. 2020 Mar 26;162:108125. doi: 10.1016/j.diabres.2020.108125. [Epub ahead of print]

2. Raj VS, Mou H, Smits SL, Dekkers DH, Mu¨ ller MA, Dijkman R, et al. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature 2013;495:251–4. doi: 10.1038/nature12005.

3. Li K, Wohlford-Lenane CL, Channappanavar R, Park JE, Earnest JT, Bair TB, Bates AM, Brogden KA, Flaherty HA, Gallagher T, Meyerholz DK, Perlman S, McCray PB Jr. Mouse-adapted MERS coronavirus causes lethal lung disease in human DPP4 knockin mice. Proc Natl Acad Sci U S A 2017;114. doi: 10.1073/pnas.1619109114.

4. Fan C, Wu X, Liu Q, Li Q, Liu S, Lu J, Yang Y, Cao Y, Huang W, Liang C, Ying T, Jiang S, Wang Y. l. A Human DPP4- Knockin Mouse's Susceptibility to Infection by Authentic and Pseudotyped MERS-CoV. Viruses 2018:10–9. doi: 10.3390/v10090448.

5. Qi F, Qian S, Zhang S, Zhang Z. Single cell RNA sequencing of 13 human tissues identify cell types and receptors of human coronaviruses. Biochem Biophys Res Commun. 2020 Mar 18. pii: S0006-291X(20)30523-4. doi: 10.1016/j.bbrc.2020.03.044. [Epub ahead of print].

6. Barchetta I, Ciccarelli G, Barone E, Cimini FA, Ceccarelli V, Bertoccini L, Sentinelli F, Tramutola A, Del Ben M, Angelico F, Baroni MG, Lenzi A, Cavallo MG. Greater circulating DPP4 activity is associated with impaired flow-mediated dilatation in adults with type 2 diabetes mellitus. Nutr Metab Cardiovasc Dis. 2019 Oct;29(10):1087-1094. doi: 10.1016/j.numecd.2019.07.010.

7. Zheng, T Gao Y, Baskota A, Chen T , Ran X, Tian H. Increased Plasma DPP4 Activity Is Predictive of Prediabetes and Type 2 Diabetes Onset in Chinese Over a Four-Year Period: Result From the China National Diabetes and Metabolic Disorders Study, The Journal of Clinical Endocrinology & Metabolism, Volume 99, Issue 11, 1 November 2014, Pages E2330–E2334, https://doi.org/10.1210/jc.2014-1480

8. Preliminary Estimates of the Prevalence of Selected Underlying Health Conditions Among Patients with Coronavirus Disease 2019 — United States, February 12–March 28, 2020; April 3, 2020 / 69(13);382–386, https://www.cdc.gov/mmwr/volumes/69/wr/mm6913e2.htm

9. Letko M, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. Nat Microbiol. 2020 Apr;5(4):562-569. doi: 10.1038/s41564-020-0688-y. Epub 2020 Feb 24.