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Commentary

Is DPP4 inhibition a comrade or adversary in COVID-19 infection

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ABSTRACT

Hypertension and Diabetes are the most common comorbid conditions in patients with COVID-19 and has been shown to adversely impact prognosis globally. It has been shown that hyperglycemia is one of the factors that increases the risk of poor outcomes in these patients. These patients are usually on multiple medications and recently a series of discussion on how Dipeptidyl peptidase 4 inhibitors (DPP4i) may be beneficial in these patients has been presented. This commentary presents a nuanced debate on why the DPP4i may not be beneficial in COVID-19 and that caution needs to be addressed in making any judgements until real world data is available.

Hypertension and Diabetes are the most common comorbid conditions in patients with COVID-19 and has been shown to adversely impact prognosis globally [1]. It has been shown that hyperglycemia is one of the factors that increases the risk of poor outcomes in these patients [2]. It is worthwhile considering that these patients are on multiple oral hypoglycemic agents and these medications may also affect the response to infection. A series of discussion has been initiated on the possible effects of dipeptidyl peptidase 4 inhibitors (DPP4i) in diabetes patients with COVID-19 infection.

Firstly, bioinformatic approaches combining human-virus protein interaction prediction and protein docking based on crystal structures have been performed and it has been shown that although the SARS CoV interacts with DPP4 enzyme as a coreceptor, its interaction is not as strong as its interaction with angiotensin converting enzyme 2 (ACE-2) [3]. Furthermore, in the experimental model of human coronavirus-EMC, DPP4i did not inhibit the viral entry and viral receptor interaction was independent of peptidase activity of DPP4 [4]. Hence DDP4i may not play a significant role in reducing the transmission of infection.

Secondly, DPP4i is known to modulate inflammation and is known to suppress T cell proliferation and production of pro-inflammatory cytokine and population-based studies done in patients with diabetes show 30% lower autoimmune diseases like rheumatoid arthritis [5]. However, we need to be cautious in the extrapolation of these findings of a risk of suppression of T cell immunity to acute COVID-19 infection. In COVID-19 infection, SARS Co-V has been shown to infect T cells through S protein-mediated membrane fusion although it's not clear whether the virus replicates inside the T cells or it leads to apoptosis [6]. Moreover, decreases in the counts of CD3 + T, CD4 + T, CD8 + T, NK cells, as well as increases in the CD4/CD8 ratio in COVID-19 patients compared to recovered

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patients have been reported. Lower levels have been reported to correlate with severity of infection. Regulatory T cells (Tregs) which have a very important role in autoimmune conditions did not have a significant role in COVID-19 [7]. It is possible that the baseline suppressed T cell immunity secondary to DPP4i may be a disadvantage in COVID-19 infection and lead to a more severe disease.

Thirdly, in a model of acute respiratory distress syndrome (ARDS), DPP4 inhibition by sitagliptin alleviated histological findings of lung injury by inhibiting proinflammatory cytokines IL-1β, TNFα, and IL-6 [8] and recently sitagliptin has been shown to have anti-fibroblastic activity in systemic sclerosis and to inhibit TGF-ß-induced lung fibroblasts activation in vitro study [9,10]. Moreover, DPP4 inhibition by vidagliptin has been shown to reduce lung cancer growths through induction of macrophage mediated natural killer cell activity in mouse models [11] Again, there is very sparse evidence of translation of these findings to the human lung. Conversely, according to the Japanese Adverse Drug Event Report database, 63 cases of vildagliptin-related Interstitial pneumonitis were reported between 2009 and 2018 [12]. Several case reports have been published of vildagliptin induced interstitial pneumonia and ground glass changes in lung postulated to mimic anti TNF-alpha treatment and is postulated to be secondary to reduced TNF-alpha. In one such case, these lesions had lymphocytosis with markedly increased CD4+/CD8+ ratio which is similar to what is seen in COVID-19 infection [13,14]. Hence, it is possible that baseline DPP-4 inhibition may increase the risk of fibrotic lesions in the lungs in COVID-19 infection wherein T cell immunity is affected.

Fourthly, experimental mouse model studies have shown that CD26/DPP-4 inhibition recruits regenerative stem cells via stromal cell-derived factor-1 and beneficially influences ischaemia-reperfusion injury in mouse lung transplantation [15]. On the contrary, after critical limb ischemia in DDP4 deficient mice, paradoxical impairment of angiogenesis, endothelial function and circulating number of EPCs has been reported [16]. Consistent with this reduced post-operative DPP4 activity has been associated with worse patient outcome after cardiac surgery due to similar mechanism invoked during tissue ischemia [17].

Fifthly, loss of DPP4 activity is associated with a prothrombotic state in myocardial microvessels and human umbilical vein endothelial cells due to the upregulation of the procoagulant tissue factor [18]. Increasingly, more reports of increased arterial and venous thrombosis have been reported in patients with COVID-19 infections although the exact cause is not clear at this time [19,20].

In summary, although DPP4 inhibitors have been reported to be beneficial and safe in the long term management of patients with diabetes wherein DPP4 enzyme is blocked at varying levels of 50–90%, there is no real world data published on the effect on the prognosis of COVID-19 infection. Until there is real world evidence and reports of observational evidence of impact of DPP4 inhibitors in patients with diabetes, no definite conclusions can be made with regards to the whether they are beneficial, neutral or harmful in the setting of COVID-19 infection.

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Declaration of Competing Interest

The author declares no competing interests.

REFERENCES

[1] Bornstein SR, Dalan R, Hopkins D, et al. Endocrine and metabolic link to coronavirus infection. Nat Rev Endocrinol 2020. https://doi.org/10.1038/s41574-020-0353-9.
[2] Bode B, Garrett V, Messler J, et al. Glycemic characteristics and clinical outcomes of COVID-19 patients hospitalized in the United States [published online April 12, 2020]. J Diabetes Sci Technol 2020. https://doi.org/10.1177/1932296820924469 [in press].
[3] Li, Yu and Zhang, Ziding and Yang, Li and Lian, Xianyi and Xie, Yan and Li, Shen and Xin, Shuyu and Cao, Pengfei and Lu, Jianhong, The MERS-CoV receptor DPP4 as a candidate binding target of the SARS-CoV-2 spike. ISCIENCE-D-20-00520. Available at SSRN: http://dx.doi.org/10.2139/ssrn.3570560.
[4] Raj VS, Mou H, Smits SL, Dekkers DH, Müller MA, Dijkman R, et al. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature 2013;495:251–4.
[5] Seong JM, Yee J, Gwak HS. Dipeptidyl peptidase-4 inhibitors lower the risk of autoimmune disease in patients with type 2 diabetes mellitus: a nationwide population-based cohort study. Br J Clin Pharmacol 2019;85:1719–27.
[6] Wang X, Xu W, Hu G, et al. SARS-CoV-2 infects T lymphocytes through its spike protein-mediated membrane fusion. Cell Mol Immunol 2020. https://doi.org/10.1038/s41423-020-0424-9.
[7] Jiang M, Guo Y, Luo Q, et al. T cell subset counts in peripheral blood can be used as discriminatory biomarkers for diagnosis and severity prediction of COVID-19. J Infect Dis, jiaa252.
[8] Kawasaki T, Chen W, Htwe YM, Tatsumi K, Dudek SM. DPP4 inhibition by sitagliptin attenuates LPS-induced lung injury in mice. Am J Physiol Lung Cell Mol Physiol 2018. 315L834-L845.
[9] Soare A, Györfi HA, Matei AE, et al. Dipeptidylpeptidase 4 as a marker of activated fibroblasts and a potential target for the treatment of fibrosis in systemic sclerosis. Arthrit Rheumatol 2020;72:137–49. https://doi.org/10.1002/art.41058.
[10] Liu X, Zhang T, Zhang C. Sitagliptin inhibits extracellular matrix accumulation and proliferation in lung fibroblasts. Med Sci Monit: Int Med J Exp Clin Res 2020;26:e922644. Available from: https://doi.org/10.12659/MSM.922644.
[11] Jang JH, Janker F, De Meester I, Arni S, Borgeaud N, Yamada Y, et al. The CD26/DPP4-inhibitor vildagliptin suppresses lung cancer growth via macrophage-mediated NK cell activity. Carcinogenesis 2019;29(40):324–34. https://doi.org/10.1093/carcin/bgz009.
[12] Pharmaceutical and Medical Device Agency. Japanese Adverse Drug Event Report database (since April, 1, 2004). Available from URL: https://www.pmda.go.jp/safety/info-services/drugs/adr-info/suspected-adr/0005.html [in Japanese].

[13] Sada KE, Wada J, Morinaga H, Tuchimochi S, Uka M, Makino H. Sarcoid-like lung granulomas in a hemodialysis patient treated with a dipeptidyl peptidase-4 inhibitor. Clin Kidney J 2014;7(182–185):22.
[14] Tanaka Y, Soda H, Fukuda Y, et al. Vildagliptin-induced ground-glass nodules mimicking lung metastases in a cancer patient receiving Lactobacillus probiotic supplementation. Thorac Cancer 2020;11:470–4.
[15] Jungraithmayr W, De Meester I, Matheeussen V. CD26/DPP-4 inhibition recruits regenerative stem cells via stromal cell-derived factor-1 and beneficially influences ischaemia-reperfusion injury in mouse lung transplantation. Eur J Cardiothorac Surg 2012;41:1166–73.
[16] Sun CK et al. Paradoxical impairment of angiogenesis, endothelial function and circulating number of endothelial progenitor cells in DPP4-deficient rat after critical limb ischemia. Stem Cell Res Ther 2013;4:31. https://doi.org/10.1186/scrt181.
[17] Noels H, Theelen W, Sternkopf M, Jankowski V, Moellmann J, Kraemer S, et al. Reduced post-operative DPP4 activity associated with worse patient outcome after cardiac surgery. Sci Rep 2018;8:11820. https://doi.org/10.1038/s41598-018-30235-w.
[18] Krijnen PA et al. Loss of DPP4 activity is related to a prothrombogenic status of endothelial cells: implications for the coronary microvasculature of myocardial infarction patients. Basic Res Cardiol 2012;107:233. https://doi.org/10.1007/s00395-011-0233-5.
[19] Dominguez-Erquicia P, Dobarro D, Raposeiras-Roubín S, et al. Multivessel coronary thrombosis in a patient with COVID-19 pneumonia. Eur Heart J. 2020 May 6. pii: ehaa393. doi: 10.1093/eurheartj/ehaa393. [Epub ahead of print].
[20] Wichmann D, Sperhake JP, Lütgehetmann M, et al. Autopsy findings and venous thromboembolism in patients with COVID-19: a prospective cohort study. Ann Intern Med 2020 May 6. https://doi.org/10.7326/M20-2003.