PNAS LETTER

Reply to Firneisz: "Rebound increase in circulating dipeptidyl peptidase-4 (DPP4) enzyme activity after acute Covid-19"

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Dear Dr. Firneisz,

Thank you very much for your comments.

First, I would like to briefly summarize the association of coronavirus disease 2019 (COVID-19) with dipeptidyl peptidase 4 (DPP4). Zhu and colleagues provided clinical evidence correlating improved glycemic control with improved outcomes in patients with COVID-19 and preexisting type 2 diabetes (T2DM) (1). Notably, DPP4 inhibitors have been used as glucagon-like peptide-1 receptor agonists for anti-inflammatory effects, which may improve outcomes in COVID-19 patients (2–4). Another report indicates that clinical use of DPP4 inhibitors was not associated with adverse COVID-19–related outcomes among patients with T2DM (5). Nevertheless, the emerging evidence suggests that DPP4 inhibitors can be used safely in patients with diabetes mellitus and COVID-19 (6).

Second, it seems to be paradoxical that a recent report by your group suggests that the reduction of circulating DPP4 activity was associated with the worsening severity of acute COVID-19 disease and was one of the strongest prognostic biomarkers of mortality (7). Additionally, it was reported that those prescribed DPP4 inhibitors had a slightly higher risk of COVID-19–related mortality compared with those not prescribed these drugs in a nationwide observational study in England (8). Collectively, the obtained information indicates that the effects of DPP4 inhibitors on COVID-19 patients are still far from completely understood, calling for more randomized clinical trials for COVID-19 patients by using DPP4 inhibitors. Therefore, it is supposed that many factors including sex and age of COVID-19 patients, with or without T2DM, and variants of SARS-CoV-2 may impact the therapeutic effects of DPP4 inhibitors.

Notably, glycylproline (gly-pro) is a product of DPP4 and identified as a biomarker in COVID-19 convalescent patients with antibody or antibody fading. Interestingly, gly-pro can also function to regulate antibody levels after vaccination in our work (9). In this study, we found that DPP4 inhibitor sitagliptin may exert an immunologic effect for maintaining SARS-CoV-2 antibody levels rather than the use of sitagliptin in treatment of COVID-19 patients. I was excited when reading your data that the serum DPP4 from recovering COVID-19 patients had significantly higher enzyme activity than that from SARS-CoV-2–naive donors (7). This observation could provide positive support for our results that, during the convalescent phase, the plasma of COVID-19 convalescents, despite their various antibody levels, contained higher levels of gly-pro than that of healthy subjects [figure 3 of the original article ref. 9)].

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The authors declare no competing interest.

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