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LETTER TO THE EDITOR

Use of DPP-4 inhibitors in patients with COVID-19

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We read with interest the discussion by Solerte et al. [1] on the various physiological processes on the immune system where dipeptidyl peptidase-4 (DPP-4) is involved. Besides, as hypothesized by the authors, the presence of DPP-4 in the respiratory tract may facilitate the entry of severe acute respiratory syndrome (SARS-CoV-2), the causative pathogen for coronavirus disease 2019 (COVID-19). Therefore, at first sight, it seems logical for the authors to propose that the use of DPP-4 inhibitors may be benficial in patients with COVID-19.

However, as the pathophysiology of COVID-19 being unraveled, we have now acknowledged the potential for a substantial number of patients with COVID-19 to be complicated by the development of venous thromboembolism, especially those admitted into intensive care units. To illustrate, despite the initiation of pharmacological thromboprophylaxis, 31% of patients with COVID-19 admitted into intensive care units still developed venous thromboembolic events [2]. Indeed, COVID-19 has now been recognized as a hypercoagulable state where the elevation of several circulating prothrombotic factors had been reported [3].

Therefore, we should be very careful to call on for DPP-4 inhibitors to be repurposed as one of the treatment options for patients with COVID-19 since DPP-4 inhibitors have the potential to induce a prothrombic state. Other than their actions on glucose homeostasis and immune homeostasis, DPP-4 also acts on the vascular system where it possesses anti-thrombotic properties and may act as an immobilized anticoagulant on endothelial cells. This is owing to their ability to inhibit fibrin polymerization and clot formation.

In vivo model has demonstrated a reduction in the expression and activity of DPP-4 within the infarction area of patients with acute myocardial infarction, which corresponded to an increase in pro-coagulant Tissue Factor expression, suggesting a shift toward a prothrombogenic status [4]. Furthermore, when human umbilical vein endothelial cells were treated with diprotin A which inhibits the activity of DPP-4, increased adherence of non-stimulated platelets under flow conditions was observed, corresponding to a sign of thrombogenicity [4].

Real-world data have also indicated a safety signal with DPP-4 inhibitors due to the increased reporting of venous thromboembolism events. A recent pharmacovigilance study [5] observed excess of reporting of venous thromboembolism events with DPP-4 inhibitors compared with other antidiabetic agents except for insulin, with a proportional reporting ratio of 2·0 (95% confidence interval 1.7–2.3). In the post hoc subgroup analysis considering separately sitagliptin and other DPP-4 inhibitors, sitagliptin was associated with a significantly higher probability of reporting of venous thromboembolism events, with a proportional reporting ratio of 3.2 (95% confidence interval 2.8–3.7).

Although no definite conclusion could be made to the effect of DPP-4 inhibitors in COVID-19 patients, it may be unwise to repurpose DPP-4 inhibitors for the treatment of COVID-19 which is associated with a hypercoagulability state. In addition, in the aforementioned pharmacovigilance study [5], almost 50% of venous thromboembolism events associated with DPP-4 inhibitors were co-reported with an infection, which demanded cautious use of DPP-4 inhibitors, especially sitagliptin, during an active infection such as COVID-19.

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References

1. Solerte SB, Di Sabatino A, Galli M, Fiorina P (2020) Dipeptidyl peptidase-4 (DPP4) inhibition in COVID-19 Acta Diabetol 57:779–783.
2. Hasan SS, Radford S, Kow CS, Zaidi STR (2020) Venous thromboembolism in critically ill COVID-19 patients receiving prophylactic or therapeutic anticoagulation: a systematic review and meta-analysis [published online ahead of print, 2020 Aug 3]. J Thromb Thrombolysis 1–8.
3. Maier CL, Truong AD, Auld SC, Polly DM, Tanksley CL, Duncan A (2020) COVID-19-associated hyperviscosity: a link between inflammation and thrombophilia? Lancet 395:1758–1759
4. Krijnen PA, Hahn NE, Kholová I et al (2012) 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 107:233
5. Gouverneur A, Lair A, Arnaud M et al (2020) DPP-4 inhibitors and venous thromboembolism: an analysis of the WHO spontaneous reporting database. Lancet Diabetes Endocrinol 8:365–367