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Editorial – COVID-19 pandemic: is it time to learn about DPP-4/CD26?

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The rapid spread of SARS-CoV-2, a novel coronavirus that emerged in late 2019, and the resulting COVID-19 pandemic, has been labeled as a public health emergency of international concern by the World Health Organization. Individuals with diabetes mellitus are at high risk for severe manifestations of the disease, and COVID-19 mortality is increased in presence of major comorbidities, including diabetes[1]. The rate ratio of diabetes among patients who died with SARS-CoV-2 infection compared to the general population was 1.75[2]. DPP-4 inhibitors (saxagliptin, sitagliptin, vildagliptin, alogliptin and linagliptin) are used worldwide to treat type 2 diabetes. DPP-4 (dipeptidyl peptidase-4) is also known as CD26, a lymphocyte cell surface protein that plays an important role in T-cell immunity. Our group and others have shown that DPP-4 inhibitors have an immunosuppressive effect on T-lymphocyte differentiation and cytokine production[3-5].

Overall risk of infections (including respiratory infections) with DPP-4 inhibitors has not been confirmed in all studies[6-8]. However, increased incidence of upper airway infections appears to be the most common[6]. Of note, MERS-CoV uses DPP-4 as a specific receptor for cellular entry, while SARS-CoV and SARS-CoV-2 appear to use the entry receptor ACE2[9]. Liu et al[10] in a study of immunological characteristics of COVID-19, demonstrated that patients with severe disease had higher serum levels of IL-6, IL-10, IL-2, and IFN-γ and lower numbers of neutrophils and T cells (especially CD8+ T cells) than did patients with mild disease, suggesting that cytokine storm in general, and T cell-mediated dampening of exuberant immune responses in particular, participate in the pathophysiology of the severe disease. There appears to be an overactivation of T cells, manifested by increases in Th17 levels and high cytotoxicity of CD8+ T cells, partly accounting for the severe immune injury to lungs associated with COVID-19 infection[11].

DPP-4/CD26 is present and active in the lungs and is expressed constitutively by lung fibroblasts, where it exerts proliferative effects[12]. DPP-4/CD26 is also a marker of fibroblast migration and functional activation, including collagen synthesis and inflammatory cytokine secretion[12]. Inflammatory lung diseases are characterized by high expression levels of DPP-4/CD26, that could increase the inflammatory response and the severity of lung injury[13,14]. DPP-4 inhibitors could ameliorate the inflammatory response in the lung, as evidenced by animal and *in vitro* studies[15-18]. Nevertheless, some case reports showed lung inflammatory effects and/or interstitial pneumonia with the use of DPP-4 inhibitors[19-22]. Of note, all these patients were Asian, and they were using vildagliptin. We demonstrated an *in vitro* immunosuppressive effect of sitagliptin on Th1 and Th17 lymphocyte differentiation that leads to the generation of regulatory TGF-beta1-secreting cells with low CD26 gene expression that may beneficially modulate the inflammatory response[3]. Furthermore, type 2 diabetes patients treated with sitagliptin showed reduced levels of plasma markers of low-grade inflammation (C-reactive protein, IL-6, and TNF-α) and cell adhesion molecules (soluble intercellular adhesion molecule-1 and E-selectin); this effect was more pronounced in subjects with higher levels of inflammatory markers and cell adhesion molecules[23,24].

At this point, it is critical to observe the evolution of COVID-19 disease in patients with diabetes using DPP-4 inhibitors. DPP-4 inhibitors may worsen or in some cases ameliorate the evolution of lung injury in these patients. Thus, the exact impact of different DPP-4 inhibitors on COVID-19 clinical outcomes remains uncertain. Further investigation in this area is, therefore, warranted to better understand the exact role of these drugs in lung disease in the context of COVID-19 infection. Understanding this relationship could help to improve the management of COVID-19 infection in patients with diabetes mellitus using DPP-4 inhibitors.

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