Commentary

COVID-19 and diabetes: Can DPP4 inhibition play a role?

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In general, people with diabetes are at higher risk to develop complications when they are infected with a virus. Type 2 diabetes, the most common type of diabetes, is associated with a low grade chronic inflammation induced by the excessive visceral adipose tissue. This inflammatory status affects the homeostatic glucose regulation and peripheral insulin sensitivity. Chronic hyperglycemia and inflammation can cause an abnormal and ineffective immune response. This complex and multifactorial pathway includes a decreased mobilization of polymorphonuclear leukocytes, chemotaxis, and phagocytic activity, lower secretion of cytokines such as interleukin-1 (IL-1) and IL-6 in response to lipopolysaccharides, inhibition of Tumor Necrosis Alpha (TNFα) activity by T-cells and glycation of immunoglobulin.

The recent data from the coronavirus disease 2019 (COVID-19) caused by the 2019 novel coronavirus (2019-nCoV), confirm that diabetes, along with advanced age, is a major risk factor for an adverse outcome. Diabetes accounted for approximately 20% of the intensive care unit (ICU) admission according to an early analysis of a small cohort in Wuhan, China [1]. More recent data from Italy showed the more than two-thirds of those who died by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had diabetes [2].

The higher risk of mortality and complication among people with diabetes was similar in the two other recent coronavirus outbreaks, the SARS affecting more than 8000 people mainly in Asia at the beginning of 2002, and the Middle East respiratory syndrome (MERS) affecting more than 2000 persons, mainly in Saudi Arabia in 2012. The odds ratio of dying or developing severe complications following MERS coronavirus (MERS-CoV) infection when diabetes co-occurred ranged from 2.47 to 7.24. Diabetes was

unquestionably a major contributor to MERS-CoV disease severity and mortality [3].

Remarkably, human dipeptidyl peptidase 4 (DPP4) was identified as a functional receptor for the spike protein of the MERS-Co-V [4]. MERS-CoV binds to the receptor-binding domain and interacts with T cells and nuclear factors, such as NF-κB, highly involved in the pathogenesis of inflammatory disorders. Antibodies directed against DPP4 inhibited human coronavirus-Erasmus Medical Center (hCoV-EMC) infection of primary human bronchial epithelial cells and Huh-7 cells.

DPP4 enzyme is a type II transmembrane glycoprotein, expressed ubiquitously in many tissues, including the immune cells. Although its functions are not fully understood yet, DPP4 plays a major role in glucose and insulin metabolism. DPP4 degrades incretins such as glucagon like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide, ultimately leading to reduced insulin secretion and abnormal visceral adipose tissue metabolism. DPP4 regulates postprandial glucose via degradation of GLP-1. DPP4 expression is higher in visceral adipose tissue and directly correlates with adipocyte inflammation and insulin resistance. DPP4 plays also an important role in immune regulation by activating T cells and upregulating CD86 expression and NF-κB pathway. It can be summarized that DPP4 increases inflammation in type 2 diabetes via both catalytic and noncatalytic mechanisms. Of note, the enzymatic activity of DPP4 causes the cleavage and may affect the function of several cytokines, chemokines, and growth factors

To better understand the mechanism of the interaction between DPP4 and coronavirus, transgenic mouse models were developed. In one study, mice were made susceptible

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to MERS-CoV by expressing human DPP4 [5]. Type 2 diabetes was induced by administering a high-fat diet (HFD). Male DPP4 $^{H/M}$ mice fed a high-fat diet (HFD) for 12–17 weeks develop hyperglycemia, and hyperinsulinemia, resembling human type 2 diabetes. Upon infection with MERS-CoV, diabetic DPP4$^{H/M}$ mice developed weight loss, and had a prolonged phase of severe disease and delayed recovery. Interestingly, diabetic mice had fewer inflammatory monocyte/macrophages, CD4+ T cells, and lower expression of TNFα, IL-6 and Arg1.

Diabetic DPP4$^{H/M}$ mice had a delay in the initiation of inflammation in the lung characterized by reduced CD4$^+$ T cell recruitment. It was suggested that higher rate of mortality and complications in individuals with type 2 diabetes infected with MERS-CoV could be associated with a DPP4 mediated dysregulated immune response.

In another study, upon inoculation with MERS-CoV, human DPP4 knockin (KI) mice, with humanized exons 10–12 of the mouse *Dpp4* locus, supported virus replication in the lungs, but developed no illness [6,7].

Interestingly, mice lacking the gene encoding DPP4 (DP-IV-/-) are refractory to the development of obesity and insulin resistance [8].

It is tempting to translate these data in humans and explore how these findings may be of interest in the context of the COVID-19 outbreak.

Individuals with type 2 diabetes and obesity are commonly prescribed with DPP4 inhibitors and/or GLP-1 receptor analogs. DPP4 inhibitors can be divided in mimetics, sitagliptin, vildagliptin, saxagliptin and not peptide mimetics, alogliptin and linagliptin. DPP4 inhibitors target the enzymatic activity of DPP4 and consequently block the breakdown of GLP-1. This increases insulin secretion and decreases blood glucose levels in patients with type 2 diabetes. More recently, DPP4 inhibitors and mainly GLP-1 receptor analogs have shown to provide beneficial effects that go beyond their glucose lowering effects.

However, the effects of DPP4 inhibition on the immune response in patients with type 2 diabetes is controversial and not completely understood. A meta-analysis showed that upper respiratory tract infections does not increase significantly with DPP4 inhibitor treatment. When compared with placebo or active comparator treatment, risks of respiratory infection in for DPP4 inhibitors were all comparable [9]. Initiation of a DPP4 inhibitor was not associated with an increased risk of respiratory tract infections,

On the contrary, anti-inflammatory and anti-adipogenic, effects have been associated with the use of DPP4 inhibitors and GLP-1 receptor analogs [10]. Reduced macrophage infiltration directly via GLP-1 dependent signaling and reduced insulin resistance and inflammation by regulating M1/M2 macrophage polarization have been described with DPP4 inhibition and GLP-1 activation.

This brief overview wants to stimulate the discussion on the potential role of DPP4 in COVID-19- infected individuals with type 2 diabetes. It is unclear whether DPP4 inhibition or modulation should be the most appropriate strategy. However, DPP4 may represent a potential target for preventing and reducing the risk and the progression of the acute respiratory complications that type 2 diabetes may add to the COVID-19 infection.

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Declaration of Competing Interest

The author declares no conflict of interest.

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