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Incretin-Based Therapies Role in COVID-19 Era: Evolving Insights

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Abstract

The current coronavirus disease 2019 (COVID-19) pandemic has led the scientific community to breach new frontiers in the understanding of human physiology and disease pathogenesis. It has been hypothesized that the human dipeptidyl peptidase 4 (DPP4) enzyme receptor may be a functional target for the spike proteins of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). Since DPP4-inhibitors are currently used for the treatment of patients with type-2 diabetes (T2DM), there is currently high interest in the possibility that these agents, or incretin-based therapies (IBTs) in general, may be of benefit against the new coronavirus infection. Diabetes is associated with increased COVID-19 severity and mortality, and accumulating evidence suggests that IBTs may favorably alter the clinical course of SARS-CoV-2 infection due to their inherent mechanisms of action. Further research into prognostic variables associated with various antidiabetic treatment regimens, and in particular the IBT, in patients with T2DM affected by the COVID-19 pandemic is therefore warranted.

Keywords

incretins, DPP4, GLP1, diabetes, COVID-19

The current coronavirus disease 2019 (COVID-19) pandemic has led the scientific community to breach new frontiers in the understanding of human physiology and disease pathogenesis. One of the hot topics is the identification of the receptors used by the new coronavirus severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) involved in its impact at the tissue level. This could potentially pave the way for specific therapeutic approaches by reducing and/or neutralizing receptor-mediated internalization of the virus in the human body.

It has been recently hypothesized that human dipeptidyl peptidase 4 (DPP4) enzyme may be a functional receptor for the spike protein of this new coronavirus.[1] In this context, the role of incretin-based therapies has gained increasing interest for possible benefit in patients with COVID-19. It is well-known that infectious processes tend to be more severe in patients with chronic illnesses such as cancers, diabetes, and cardiovascular, respiratory, liver, and kidney disease. However, available data from the COVID-19 pandemic does not support the assumption that patients with diabetes are at an increased risk of infection with SARS-CoV-2.

Preliminary statistics from China have shown that diabetes was present in a relatively low percentage (8%) among 46 248 infected people with COVID-19 with a mean age of 46 years, lower than the prevalence of diabetes in Chinese adults (10.9%).[2] Data from the Lombardy region of northern Italy, the most affected region in Europe so far, is consistent with this observation, where the prevalence of diabetes was 17% among 1591 patients with COVID-19 with a higher mean age of 63 years who were admitted to the intensive care unit.[3]

Patients with diabetes are prone to developing more severe symptoms and complications with viral infections, and the data available so far indeed suggests that the presence of diabetes is linked to higher mortality and also greater need of intensive care with COVID-19.[4] A retrospective study performed in Wuhan, China, where the disease was reported for the first

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time, revealed that the prevalence of diabetes was 14% in survivors of COVID-19. In comparison, it significantly increased to 31% in those who died.[5] Later findings from Italy, the first European country confronted with a large-scale pandemic, appeared to be similar: the prevalence of diabetes is 31.8% in 2351 patients with COVID-19 who succumbed to the virus.[6]

The dipeptidyl peptidase-4 enzyme receptor is expressed on the surface of the most cell (stem, stromal, immune, endothelial cell) and is associated with the immune regulation, signal transduction, and cell apoptosis. Ubiquitously, DPP4 enzyme receptor is also expressed in many tissues like kidney, gastrointestinal tract and liver, including the pulmonary tract, and some preclinical studies suggest that DPP4 may be a potential target of therapy to reduce the internalization and action of the new coronavirus.[7] Since DPP4-inhibitors are currently used for the treatment of patients with type-2 diabetes (T2DM), there is, of course, high interest to assess whether such therapies may also be beneficial against SARS-CoV-2. The mechanism of regulating the glucose homeostasis is through the enzymatic targeting of DPP4, blocking glucagon-like peptide 1 (GLP-1) degradation and prolonging the incretin effect. Indeed, it is worth noting that DPP4 inhibition is not only involved in the regulation of glycemic control in patients with diabetic but also a series of other biological processes.[7,8]

Besides its role of inactivating the incretin hormones, DPP4 also seems to be able to alter the immune function being present on certain cell surfaces.[8] Their immunomodulatory effect has been investigated particularly concerning the risk of developing infections; experimental data suggest that immune regulation of DPP4 is linked to T-cell activation and the overregulation of CD26 expression, mainly CD4(+) and CD(+8), and to the functions of the NF-κB line and the macrophage dendritic cells.[9] Interestingly, the newly discovered intracytosolic enzymes DPP8 and DPP9, which belong to the DPP4 family, also seem to be directly involved in the immune response; however, these aspects require further in vivo and in vitro studies.[10]

The enzymatic activity of DPP4 also affects the activity of chemokines, cytokines, and growth factors. It has been suggested that in patients with diabetic infected with Middle East respiratory syndrome coronavirus (MERS-CoV), the presence of postinfectious complications and mortality is dependent on the altered immune response, which is, in part, mediated by DPP4. Inoculation of human DPP4 knock-in mice with the MERS-CoV and viral replication in pulmonary tissue prevented the development of the infection[11]; this preclinical observation in animal models was somewhat confirmed by the results from systematic reviews and meta-analyses of clinical studies that pointed to an increased risk of urinary and nasopharyngeal infections in patients with diabetic compared to control groups.[12,13] A more recent meta-analysis comparing the currently available DPP4-inhibitors to other antidiabetic drugs (including metformin, sulfonylureas, thiazolidinediones, and alpha-glucosidase inhibitors) revealed no higher risk for infections with the former.[14]

Fadini et al[15] retrieved data on patients with T2DM hospitalized for COVID-19 between February and April 2020 at a university hospital located in northeast Italy, a region severely affected by COVID-19. Interestingly, their retrospective analysis revealed that exposure to DPP4 inhibitors in matched T2DM patients was similar in patients with (10.6%) and without (8.8%) COVID-19, in those attending the local outpatient clinic (15.4%) and in those hospitalized for other reasons (8.5%). The rate of DPP4 use was also similar in patients with T2DM hospitalized with COVID-19 pneumonia (11.3%) and with pneumonia of other etiology (10.3%). Since patients with T2DM with COVID-19 who were using DPP4 inhibitors had comparable outcomes to those who were not, the authors concluded that the data did not support the hypothesis that DPP4 inhibitors might be protective against COVID-19.

Dysregulation of the inflammatory response seems to play a key role in SARS-CoV-2 infection.[16] Incretin-based therapies, particularly GLP-1 receptor analogues (GLP1-RAs), have been demonstrated to exert significant anti-inflammatory effects.[17,18] It is well-known that other classes of drugs have much stronger anti-inflammatory effects, including corticosteroids, nonsteroidal anti-inflammatory drugs, aspirin, and some types of biological treatment; yet, their specific use in patients with COVID-19 has not been clearly indicated so far, most probably due to previous controversial findings of their benefit in pneumonia by coronavirus.[19,20]

In addition, the GLP1-RAs liraglutide and semaglutide have beneficial effects on obesity and inflammatory mediators, both of which associated more severity of COVID-19.[21-23] Moreover, there is increasing evidence that patients with cardiovascular disease have a worse prognosis during COVID-19 illness, and some GLP-1RAs have shown to have strong salutary effects on the cardiovascular systems.[24] It is still not known to which extent GLP-1RAs use can be beneficial in a time of this pandemic in reducing body weight, since patients with T2DM may be more motivated to lose weight due to prolonged lockdown periods with reduced physical activity and increased unbalanced nutritional states. Since it has been recently shown that the duration of lockdown is directly proportional to the worsening of glycemic control and diabetes-related complications,[25] the importance of GLP-1RAs use is also linked to the prevention of overweight/obesity, which is associated with short-term poor outcomes in many aspects as well as with longer-term fatal events.

In summary, diabetes is associated with increased mortality and severity of COVID-19[26] and accumulating evidence suggests that incretin-based therapies may be of benefit in the treatment of COVID-19 diabetic patients due to mechanisms associated with such therapies that may affect the course of coronavirus SARS-CoV-2 infection. Further research into prognostic variables with the use of various antidiabetic treatments in patients with T2DM affected by the COVID-19 pandemic, with particular regard to the incretin-based therapies, is therefore warranted.

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APS and MR have prepared the article and did the literature search. NP, MP and AAR have extensively reviewed the article and provided significant contribution to the discussion.

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