Potential pharmacological approach in the regulation of ACE-2 and DPP-IV in diabetic COVID-19 patient

Francesco Ferrara,¹ Antonio Vitiello²

¹Hospital Pharmacist Manager, Pharmaceutical Department, Usl Umbria 1; ²Clinical Pharmacologist, Pharmaceutical Department, Usl Umbria 1, Perugia, Italy

Correspondence: Francesco Ferrara, Hospital Pharmacist Manager, Pharmaceutical Department, Usl Umbria 1, via A. Migliorati, 06132 Perugia, Italy. E-mail: francesco.ferrara@uslumbria1.it

Key words: Diabetes; COVID-19; SARS-CoV-2; ACE-2; DPP-IV.

Acknowledgements: The authors have nothing to say about ethical standards, ethical approval and funding. This manuscript is not a clinical trial and does not violate ethical rules. No funding has been received for its preparation.

Contributions: AV, conceptualization, writing - original draft, methodology, writing - original draft; FF, writing - review and editing, supervision, validation. All authors contributed equally to the manuscript and had the opportunity to revise and approve the final text.

Conflicts of interest: None of the Authors have conflicts of interest to disclose.

Consent to Participate (Ethics): Not applicable

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the final one. Please cite this article as doi: 10.4081/itjm.2020.1435
Abstract

The global pandemic caused by COVID-19 has caused more than 1 million deaths worldwide. Some vaccines in clinical trials have reached stage 3. In the meantime, the understanding of the biological and pathophysiological mechanisms of Sars-CoV2 infection is still unclear, such as the role that ACE-2 and DPP-IV may play in patients with diabetes related to COVID-19. The individual with diabetes is a known COVID-19 risk patient. Probably the pharmacological regulation of the RAS system and of ACE-2 on the one hand, and of the incretin system and DPP-IV on the other, could represent a therapeutic route of fundamental importance to reduce the risk of Sars-CoV-2 infection or of serious complications caused by infection.

The COVID-19 global pandemic

Since March 2020, the world is facing a pandemic caused by a new Coronavirus (SARS-CoV-2) responsible for Coronavirus disease (COVID-19), a viral infection that can in some cases cause severe acute respiratory syndrome associated with multisystemic inflammation and tissue damage. To date, the virus has caused over 1 million deaths worldwide. (1) Effective vaccines are being tested. (2) Some risk factors for COVID-19 infection and mortality have been identified, including pulmonary diseases, cardiovascular system diseases, metabolic diseases such as diabetes. (3)

SARS-CoV-2 correlation with ACE-2 and DPP-IV

ACE-2 has a fundamental function in the angiotensin renin (RAS) system, as it metabolises Ang II into Ang-(1-7) and Ang I into Ang-(1-9) which in turn is metabolised as Ang-(1-7) by the angiotensin conversion enzyme (ACE). Ang-(1-7) from MASr opposes the effects induced by Ang II from AT1r. The effects of Ang-(1-7) are vasodilator, anti-inflammatory, antioxidant, antiproliferative and antithrombotic. (4) DPP4 is a serine exopeptidase that causes rapid cleavage of the active AQA-1 almost immediately after its secretion, with a half-life of 1-2min. The angiotensin-II conversion enzyme (ACE2) has been shown to be an entry receptor for SARS-CoV-2 cells. (5) However, it
appears that in cell adhesion and cell penetration other proteins are crucial for the entry action of the virus. Some experiments have suggested that SARS-CoV-2 could also use dipeptidil 4 peptidyl 4 (DPP-IV) as an entry receptor for cells. (6) It appears that the interaction between the SARS-CoV-2 glycoprotein peak and human DPP-IV is a key factor for hijacking and virulence. Changes in levels of soluble ACE-2 and DPP-IV are reported to be clinically relevant in a number of diseases, particularly diabetes (7). In addition, a change in ACE-2 has also been reported during COVID-19 infection, in particular a decrease in concentration in the most severe stages. (8) It will be important to investigate whether and how changes in ACE-2 and DPP-VI in patients with diabetes influence the risk of COVID-19 infection or mortality, also considering the protective role of ACE-2 against COVID-19 lung lesions. Patients with diabetes may be at increased risk for several reasons, such as a compromised immune system, dysregulated coagulation/fibrinolytic cascade, or due to the increased presence of ACE-2 and DPP-IV which may contribute to an increased presence of SARS-CoV-2 cell entry receptors. Probably the role of ACE-2 and DPP-IV is fundamental in the course of COVID-19 infection in patients with diabetes, and in this direction we can consider the enormous importance of the therapeutic potential of RAS modifying drugs and DPP-IV inhibitors.

**Therapeutic strategies acting on ACE-2 and DPP-IV**

Given the importance of ACE-2 and DPP-IV in COVID-19 pathophysiology, a potential pharmacological approach is represented by agents able to act on ACE-2 and DPP-IV. Considering the possible mechanisms of intracellular penetration of SARS-CoV-2 described above, the significant related risk factors, changes in ACE-2 concentration, increased expression of DPP-IV in patients with diabetes and COVID-19, modulation of RAS and ACE-2 and DPP-IV at certain stages of infection could be considered an important therapeutic strategy. In particular, the loss of ACE-2 function observed in the most severe stages of infection, and consequent non-activation of the Ace-2/Ang-(1-7) MASr axis and hyperstimulation of the Ace/Ang-2/ AT1r axis may be co-responsible for the pathophysiological mechanisms leading to tissue lesions. An increase in ACE-2 with RAS modifying
drugs such as ACEi or ARB could be a viable therapeutic option in the severe stages of infection. (9) An increase in DPP-IV appears to be related instead to a potential increased amount of cell entry receptor, and an increase in pro-inflammatory cytokines. Some evidence shows that DPP-IV could directly influence the kinetics of pulmonary inflammation and could itself act as a pro-inflammatory molecule. Inhibition of DPP-IV with gliptins could antagonise this mechanism. Inhibition of DPP-IV by gliptins could antagonise cell entry and virulence of SARS-CoV-2 and acute multi-organ damage by means of several additional effects such as cytokine reduction reduction of macrophage activity/function enhancement of GLP-1 anti-inflammatory activity especially in severe patients COVID-19 (10) (11) (12) (Figure 1).

**Risks**

The association of an ACEi and gliptins could represent a potential pharmacological synergy, however there are risks. ACE and DPP-IV are proteases with a metabolizing action of bradykinin and P substance. Excessive concentration of bradykinin could worsen through B2 receptors stimulating inflammation of the respiratory tract of the COVID-19 subject. (13)

**Conclusions and suggestions**

Patients with diabetes are more at risk of COVID-19 severity. While waiting for effective vaccines, it is urgent to identify the best therapeutic strategies for this category of patients. In patients with diabetes and COVID-19 infection there may be an alteration in the expression of RAS, ACE-2, DPP-IV. Pharmacological strategies aimed at regulating these mediators could represent a therapeutic potential. Well-structured clinical studies are necessary to generate evidence on this interesting topic.

**References**


Figure 1. DPP-IV inhibition leads to an increase in GLP-1 which causes a decrease in the activation of the proinflammatory transcription factor NF-kB.