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# Journal Pre-proofs

Commentary

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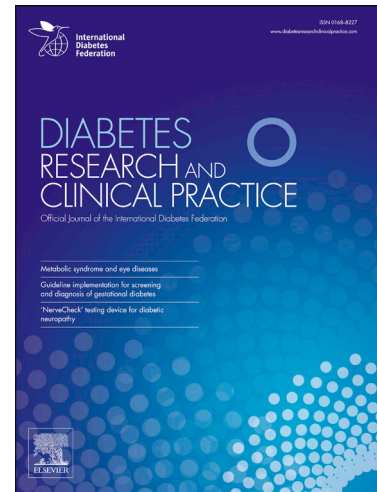
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## **SARS-CoV-2 and DPP4 inhibition: is it time to pray for Janus Bifrons?**

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Diabetes could be a risk factor for severity and mortality in patients with coronavirus disease 2019 Covid-19.

It has been hypothesized that DPP4 inhibition, a therapy currently available for type 2 diabetes, might represent a target for decreasing the risk of the acute respiratory complications of the COVID-19 infection but 1) lack of demonstration of SARS-CoV2 binding to DPP4 2) possible protective role of sDPP4 in Middle East respiratory Syndrome (MERS-CoV 3) demonstrated inhibition and downregulation of DPP4 by HIV1 and MERS-CoV and 4) not exclusive role of the receptor binding in tropism of the Coronavirus family, support that DPP4 inhibition at present doesn't represent a plausible approach to mitigate Covid-19.

The rapid spread of the coronavirus disease 2019 (Covid-19), caused by a zoonotic beta-coronavirus entitled SARS-CoV2, has become a global threat. According to a meta-analysis of 76993 patients presented in 10 articles, the prevalence of diabetes among people who were infected with SARS-CoV2 was estimated to be 7,9%<sup>1</sup>. Diabetes could be a risk factor for severity and mortality in patients with Covid-19. A study, which included 72.314 cases of Covid-19, demonstrated that diabetic subjects had a threefold higher mortality rate than did those without diabetes (7.3% vs 2.3 %)<sup>2</sup>.

A recent commentary on Diabetes Research and Clinical Practice described the interplay between the Middle East Respiratory Syndrome (MERS-CoV), another coronavirus responsible for an outbreak of acute respiratory syndrome, and human dipeptidyl peptidase 4 (DPP4) identified as a functional receptor for virus spike protein<sup>3</sup>. It has been interestingly hypothesized that DPP4 inhibition, a therapy currently available for type 2 diabetes, might represent a target for decreasing

the risk of the acute respiratory complications of the COVID-19, but, unfortunately, this hypothesis is on the basis of another hypothesis. To the best of our knowledge, no one has yet shown that DPP4 is a possible receptor for SARS-CoV2. On the contrary most recent data exclude this possibility, confirming that human angiotensin-converting enzyme 2 (ACE2) is the receptor for SARS-CoV2, in analogy to SARS-CoV<sup>4</sup>.

DPP4, like the ancient roman god Janus Bifrons (Two-Faced), is a dual and multifunctional molecule: it exists as soluble form (sDPP4) in the circulation<sup>5</sup>, but also as a type II transmembrane glycoprotein located on endothelial, epithelial cells and immune cells (CD26)<sup>6</sup>. DPP4 in the bloodstream and at surface membrane rapidly inactivates biologically active molecules as gastrointestinal hormones, neuropeptides and chemokines, but in some cases shifts their receptor preference and thus modifies their functional activity. In addition to enzymatic cleavage, CD26 executes other multiple physiological mechanisms, as adhesion to extracellular matrix proteins, and it plays a co-stimulatory role in T-cell maturation, activation and interaction with antigen-presenting cells. Thus, DPP4 inhibition is associated with some degree of immune suppression and may be useful in some autoimmune diseases<sup>7</sup>. However, in most patients long-term immune suppression, albeit mild, could represent an undesirable side effect<sup>8</sup>. We described a case of a type 2 diabetes subject with a severe leucopenia as a consequence of DPP4 inhibitor Sitagliptin therapy<sup>9</sup>. In diabetic subjects treated with DPP4 inhibitors there is no increase in respiratory tract infections<sup>10</sup>, but we want to highlight that they could produce respiratory side effects as angioedema<sup>11</sup>, rhinorrhea<sup>12</sup>, cough and dyspnea<sup>13</sup>, as consequences of reduced degradation of bradykinin and substance P.

MERS is another example of DPP4 ambivalence. As expected, human DPP4 transgenic mice following MERS-CoV infection develop an acute inflammatory response of the lung with progressive pulmonary fibrosis<sup>14</sup>. However hDPP4+/+ mice were more resistant than hDPP4+/- mice to MERS-CoV infection, as judged from increased LD50, reduced lung viral infection, attenuated morbidity and mortality, and reduced histopathology<sup>15</sup>. A possible explanation of this paradoxical protective effect of DPP4 against MERS-CoV is that the soluble DPP4 can act as a "buffer" competitively inhibiting virus entry into host cells. In fact, in human patients affected by MERS there is a reduction in circulating levels of sDPP4 with an inverse relationship with IL-10 level. In support of an antiviral effect of sDPP4, the authors demonstrated that viral infection was inhibited by 50% in the presence of more than 8000 ng/ml of sDPP4<sup>16</sup>. Another aspect to consider is the possibility that MERS-CoV downregulates its receptor after the binding: dromedaries with experimental MERS show reduction of the cell surface receptor dipeptidyl peptidase<sup>17</sup>. Likewise, downregulation of ACE2 receptor has

been already demonstrated for SARS-CoV and SARS-CoV2<sup>18</sup>. Furthermore, the Human Deficiency Virus 1 (HIV1) uses DPP4 as a receptor; HIV-infected cells produce TAT proteins that inhibit DPP4 activity inducing a decrease of responsiveness of human peripheral T cells<sup>19</sup>.

Finally, virus tropism is a complex phenomenon. In the case of the Coronavirus family, while understanding the expression pattern of the receptor can define which cells can be infected, it does not mean all cells that express the receptor or even the cells with the highest expression are the major targets. In the case of ACE2 the human lung is the 22<sup>th</sup> tissue for the amount of receptors<sup>20</sup>. Probably is not only the spike protein that impacts on tissue tropism; other “background genes,” including nucleocapsid, replicase and accessory genes, are also important determinants of tropism. In conclusion, 1) lack of demonstration of SARS-CoV2 binding to DPP4 2) possible protective role of sDPP4 in MERS 3) demonstrated inhibition and downregulation of DPP4 by HIV1 and MERS-CoV and 4) not exclusive role of the receptor binding in tropism of the Coronavirus family, support that DPP4 inhibition does not represent a plausible approach to mitigate Covid-19.

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