SARS-CoV-2 and diabetes: A potential therapeutic effect of dipeptidyl peptidase 4 inhibitors in diabetic patients diagnosed with COVID-19

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ABSTRACT

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 and has become an urgent economic and health challenge. Dipeptidyl peptidase 4 (DPP4), also mentioned as a cluster of differentiation 26 (CD26) is a serine exopeptidase found in two arrangements: a soluble form (sDPP-4) and a plasma membrane-bound form. Because other coronaviruses enter the cells by binding to DPP-4, it has been speculated that DPP-4 inhibitors may exert activity against COVID-19. Therefore, this review aimed to summarize the potential therapeutic effect of dipeptidyl peptidase 4 inhibitors in diabetic patients diagnosed with COVID-19. To include different studies, publications related to Dipeptidyl peptidase-4 inhibitor use and clinical outcomes from COVID-19 were searched from the databases such as Web of Science, PubMed, Medline, Elsevier, Google Scholar, and SCOPUS, via English key terms. A direct engrossment of DPP4 in COVID-19 needs to be elucidated, there is also evidence confirming that DPP4 inhibitors exert anti-fibrotic and modulate inflammation activity. Thus, the use of DPP-4 inhibitors could reduce mortality due to COVID-19 or improve the progression of COVID-19; this evidence may support the management of diabetic patients diagnosed with COVID-19; however more well-designed investigation is urgently required.

1. Introduction

The coronavirus disease 2019 (COVID-19) caused by the novel coronavirus SARS-CoV-2 represents a global health threat [1]. It has spread worldwide, as of September 2021, more than 220,655,863 patients are infected and about 4,567,602 deaths were reported due to COVID-19 [2]. Male gender and older age are the two features that have been linked to worse outcomes [3,4]. Although diabetes mellitus (DM) may not be linked to increased risk of infection, it may conversely increase the risk for progression and mortality [5,6]. Nearly 2/3 of severely ill patients have at least one comorbidity, usually cardiometabolic diseases, with DM covering 17% of cases [4].

Diabetic patients have a higher risk of acute respiratory distress syndrome, mortality from the COVID19, intensive care unit admission, and severe disease [7,8]. Potential pathogenic associations between COVID-19 and DM comprise the hyperglycemia-mediated dysregulated immune system, viral proliferation, and altered renin-angiotensin-aldosterone system [7–9]. Moreover, patients with DM are at high risk of severe COVID-19 due to elevated expression of Dipeptidyl Peptidase-4 and angiotensin II converting enzyme-2 mediating infection [10]. Similarly, Patients with DM are thought to have raised pro-inflammatory cytokine levels including tumor necrosis factor-α, interleukin-6, and interleukin-1 [11].

Metformin can constrain the inflammatory response that may contribute to mortality via a mechanism like vascular damage and cytokine storm [12]. In addition to metformin, one of the anti-diabetic medications which are frequently used by diabetic patients is the dipeptidyl peptidase-4 inhibitor. This medication has been suggested to benefit in decreasing the mortality and severity from SARS-CoV-2 infection due to its capability to block the host CD26 receptor and modulate the DPP4/CD26 activity, consequently restricting SARS-CoV-2 way to enter T cells [13].

Dipeptidyl peptidase-4 inhibitor is also supposed to have an activity on the enhancement of Glucagon-Like Peptide-1 anti-inflammatory activity, downregulation of macrophages activity/function, and reduction of cytokines overproduction, thus can progress the poor outcomes patients with COVID-19 [10,13]. This review aimed to summarize the potential therapeutic effect of dipeptidyl peptidase 4 inhibitors in...
diabetic patients diagnosed with COVID-19.

2. Diabetes as a promoter of mortality and severity in COVID-19

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 and has become an urgent economic and health challenge because of its pandemic magnitudes [14,15]. In the last two decades other two beta coronaviruses busted, namely MERS-CoV and SARS-CoV, yet without such epidemic influence. Likewise, to former influenza infections, there is rising evidence that DM is a vital risk factor for the mortality and severity of COVID-19 [3,16,17].

A study revealed that diabetes mellitus and cardiovascular disease are the most dominant cardiometabolic comorbidities in hospitalized COVID-19 infected patients [18]. A cohort study conducted in Europe showed that arterial hypertension, chronic heart disease, and DM are the most common comorbidities in hospitalized patients with COVID-19. Whereas hypertension, obesity, and DM were the most frequent comorbidities in the intensive care unit [19,20]. Moreover, findings revealed that obesity may be associated with increased COVID19 severity [21,22], even in younger patients [23]. Being cardiovascular diseases the main cause of morbidity and mortality in patients with DM, it is not amazing that besides being comorbidities, DM, obesity, and cardiovascular diseases have been reported as risk factors for severity in COVID-19 in numerous studies [24,25].

A study conducted previously revealed that previous cardiovascular comorbidities displayed five-fold greater mortality risk [26]. As the epidemiological study showed that COVID-19 particularly affecting elderly patients where diabetes, cardiovascular diseases, obesity, and DM are common comorbidities, it is under argument whether these comorbidities, particularly DM can increase the risk of infection or only the severity [27,28].

3. Cardiovascular effects of sDPP4 upregulation

DPP4/CD26 is a serine protease cleaving an extensive range of substrates such as the gastric inhibitory peptide, cytokines, growth factors, and incretin hormones glucagon-like peptide 1, [29]. DPP4 is existed as a soluble form (sDPP4) or as a membrane-bound form that sustains its enzymatic activity [29]. In the context of diabetes mellitus and obesity, both liver and AT have been suggested as pertinent sources of sDPP4 in humans, though the key source remains under discussion. sDPP4 was identified as a novel adipose-derived factor [30], whose circulating levels are enriched in visceral fat from insulin-resistant and obese patients and relate with BMI [31]. While sDPP4 levels and plasma activity have been linked to fibrosis, NAFLD, fat content, and liver apoptosis [32,33].

DPP4 can endorse systemic and local inflammation by its immunomodulatory effect. Therefore, DPP4 activates cytokine production, T cell activation, and proliferation [34], or through the interaction with immune partners on antigen-presenting cells as manose-6 phosphate receptor, caveolin-1, CD45, or adenosine deaminase [29,35]. DPP4 expression is greater on blood T lymphocytes from DM patients and related to glycated hemoglobin and insulin resistance [36]. sDPP4 treatment enhanced IL-6 secretion and LPS-induced tumor necrosis factor-a in activated monocytes. In addition to its upregulation in obesity and DM, DPP4 expression is higher in senescent cells [37].

A study conducted in vivo model revealed that exogenous administration of sDPP4 rise monocyte migration. Fascinatingly, upregulation of DPP4 in diabetic animals and obese have shown immune responses dysregulation [29,33]. DPP4 substrates with cardiovascular impact are upregulated in DM and/or obesity as well as in COVID-19 such as BNP and CXCL5/RANTES [38,39]. Indeed, high BNP levels were positively associated with the occurrence of cardiovascular mortality and events in HIV/AIDS patients and were proposed as a pointer of patient’s condition deterioration from mild to severe progression [40].

DPP4 is known to interact with extracellular matrix proteins, contributing to both tissue remodeling and cell migration. Through binding to fibronectin, DPP4 can endorse T cell helper accumulation and migration in areas with rising extracellular matrix proteins like damaged blood vessels [41]. DPP4 also interrelates with fibroblast activation protein-a/seprase resulting in invasion and migration of endothelial cells into collagen matrices [42]. Furthermore, stromal cell-derived factor-alpha is also a substrate of DPP4, and inhibition of DPP4 has been detected to rise stromal cell-derived factor-alpha/CXCR4-induced mobilization of endothelial cells [41]. Through its communication with ADA, DPP4 activates plasminogen-2 resulting in increased plasmin levels which pay to the activation of matrix metalloproteinase-4 and degradation of extracellular matrix proteins, which enables diapedesis and immune cells migration [29,43]. Currently, plasmin among other proteases may cleave a new furin site in the spike protein of COVID-19, leading to an increase in severity and infectivity. This high plasmin may pay to the hyperfibrinolysis leading to increased D-dimer in critically ill patients [44]. Notably, in addition to its immunomodulatory activities, sDPP4 can have a direct injurious effect on the vascular wall. sDPP4 directly increased inflammation and human smooth muscle cell proliferation through NF-kB activation leading to upregulation of pro-inflammatory cytokines like IL-6 and IL-8, and monocyte chemo-attractant protein-1, via a novel mechanism facilitated by the activation of the protease activated receptor-2 [45]. Moreover, protease activated receptor-2 stimulation persuaded by sDPP4 activated endothelial dysfunction in mesenteric micro vessels via thromboxane A2 release facilitated by the thromboreux A2 receptor and cyclooxygenase activation [46].

Therefore, DPP4 expression may contribute to the diabetes mellitus-related severity of COVID-19. Moreover, because of its vascular effects, DPP4 arises as a likely contributor to associated acute respiratory distress syndrome severity via inducing bronchoconstriction and inflammation.

4. Dipeptidyl peptidase-4, dipeptidyl peptidase-4 inhibitors, and COVID-19

DPP-4 also mentioned as a cluster of differentiation 26 (CD26) is a serine exopeptidase found in two arrangements: a soluble form (sDPP-4) and a plasma membrane-bound form (mDPP-4, containing a type two transmembrane homodimeric glycoprotein). The soluble form preserves its peptidase (enzymatic) activity and is supposed to be out from the membrane into the circulation. DPP-4/CD26 is expressed unanimously in numerous tissues and cells such as intestine, endothelia, lung, liver, immune cells (activated B cells, myeloid cells, activated natural killer cells, and T cells), and kidney [47].

DPP-4 has been recognized as an efficient receptor for the spike protein of the MERS-CoV facilitating the virus entry into the host cells [48]. DPP-4 inhibitors like gliptins have been extensively used as anti-diabetic agents for the management of type II DM and have been confirmed in improving blood glucose levels through suppressing glucagon secretion and enhancing endogenous insulin secretion and preventing the DPP-4-mediated inactivation and cleavage of incretin hormones [49]. DPP-4 inhibitors include saxagliptin, linagliptin, alogliptin, vildagliptin, and sitagliptin [50]. Both SARS-CoV-2 and SARS-CoV use ACE2 as the main receptor for viral entry into host cells [51]. Though, bioinformatics methods joining protein-docking based on crystal structures, computational model-based selective docking, and human-virus protein interaction prediction suggest DPP-4 as a potential candidate binding target of the receptor-binding S1domain of the COVID-19 spike glycoprotein. Moreover, the crucial binding residues of DPP-4 are similar to those that are bound to the spike protein of MERS-CoV [52,53].

As DPP-4 inhibitors are expressed ubiquitously in numerous tissues and cells other than the respiratory tract and lung, they may consequently contribute to direct COVID-19-mediated damage of such cells and tissues. Therefore, DPP-4 inhibition may play a key role to counter
the DPP-4-mediated COVID-19 virulence and hijacking and to progress clinical outcomes of SARS-CoV-2 by affecting the interaction between target host cells and SARS-CoV-2 [13,54,55]. Though, the main glucose-independent mechanism which is responsible for beneficial activities of DPP-4 inhibition in COVID-19 includes the antifibrotic, anti-inflammatory, and immunomodulatory properties exerted by this class of medications, which may denote an effective therapeutic tool to halt or prevent the progression toward the cytokine storm and hyperinflammatory state related to the most severe COVID-19 cases [1,56].

Several findings revealed that DPP-4/CD26 modifies both adaptive and innate immune responses [47,57]. DPP-4/CD26 is highly upregulated upon T-cell activation, while it is expressed only on a fraction of resting T-cells [47]. DPP-4/CD26 on T-cell surface persuades co-stimulatory activities on T-cell stimulation, leading to the promoted inflammatory state related to the most severe COVID-19 cases [1,56].

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Numerous studies revealed that sitagliptin have anti-inflammatory activity in diabetic patients, leading to the rise of the expression of an anti-inflammatory cytokine (IL-10) and reduced expression of various markers of pro-inflammatory cytokines, cell adhesion molecules, and low-grade inflammation, such as E-selectin IL-6, serum amyloid A-low-density lipoprotein complex, IL-18, secreted phospholipase-A2, TNF-α, soluble intercellular adhesion molecule-1, and C-reactive protein [67-69]. A Phase II clinical trial revealed that the combination of sitagliptin and a standard immunosuppressive regimen of sirolimus and tacrolimus caused a low occurrence of acute graft-versus-host disease [70]. Therefore, the immunomodulatory and anti-inflammatory activities of DPP-4 inhibitors may have an advantage in the management or prevention of cytokine storm in patients with COVID-19. The protective activity of DPP-4 inhibitors against COVID-19 may relies on the hypothesis of inhibition of DPP-4, which may result in a significant increment in circulating levels of the soluble form of DPP-4 [71,72]. The consequent abundance of soluble form of DPP-4 can provide a binding sites for COVID-19, therefore limiting or preventing the attachment of the virus to the membrane-bound DPP-4 on target host cells, such as endothelial cells, pneumocytes, or other cells pertinent for viral replication and spread [71].

5. Dipeptidyl peptidase-4 as a therapeutic target in diabetic patients with COVID-19

5.1. Glitpins

DPP4 inhibitors (glitpins) are antidiabetic medications that control glucose homeostasis via inhibition of dipeptidyl peptidase-4 enzymatic activity. Dipeptidyl peptidase-4 inactivates and cleaves the incretin hormones GIP and GLP-1, which are responsible for the release of postprandial insulin (60-70%); hence, DPP4 inhibitors extend the half-life of incretins. In addition, its effect on incretins, DPP4 inhibitors (glitpins) has been suggested to provide other off-target activities such as cardiovascular effects. There is a continuing argument concerning dipeptidyl peptidase-4 inhibition as a potential therapeutic approach to prevent and manage cardiovascular diseases in DM and/or obese patients. Prominently, glitpins are favored as add-on therapy in patients with DM streaming with previous cardiovascular or chronic kidney disease [73].

Cardiovascular safety of glitpins has been reported in numerous cardiovascular outcome trials (NCT00790205; NCT01107886; EXAMINE, TECOS, CARMELINA, NCT00968708; NCT01897532; SAVOR TIMI 53). Glitpins have shown a significant decrement of glycosylated hemoglobin levels, neutral influence on body weight, and no risk of hypoglycemic episodes, which are vital factors related to reduced cardiovascular mortality and risk [74]. Furthermore, DPP4 inhibitors have shown positive activities over surrogate vascular endpoints, such as lipemia, blood pressure, and endothelial function [75]. It has been revealed that a combination of glitin and metformin can significantly reduced the risk of nonfatal cardiovascular events, cardiovascular mortality, and all-cause mortality when compared with other antidiabetic medications like sulfonylureas [76].

The indirect cardioprotective activities of glitpins are improved by increased bioavailability of substrates of DPP4 (GLP-1). Diabetic patients managed with sitagliptin exhibited high SDF-1a plasma levels leading to augmented endothelial progenitor cells, which have a significant role in vascular repair [77]. In vitro study revealed that SDF-1a was capable of increasing blood flow in a model of peripheral artery disease [78]. Similarly, an increase in BNP improved the regulation of the vasodilatory responses and natriuresis [79]. Ex vivo endothelial dysfunction, as well as hVSMC inflammation and proliferation exerted by SDF4, were equally prevented by the clinically and experimental available linagliptin and DPP4i K579, respectively [45,46]. This suggests that these medications could have cardiovascular benefit in addition to controlling glucose homeostasis.

In the in-vivo model, glitpins have shown protective activities. Streptozotocin-induced diabetic rats treated with vildagliptin were showed decreased oxidative stress and expression of plasminogen activator inhibitor type-1 and ICAM-1 [80]. In db/db mice linagliptin...
enhanced cardiovascular dysfunction by decreasing the upregulation of collagen-1 and collagen-3 and reducing the stimulation of the Nlrp3/ASC inflammasome [81]. Likewise, sitagliptin also enhanced cardiovascular function in mice [82]. Anti-oxidant activity of DPP4 inhibitors has been also revealed under acute inflammation in the in-vivo model of LPS persued sepsis.

In diabetic patients, treatment with sitagliptin decreased the molecular markers of inflammation as IL-6 and CRP in mononuclear cells [67], as well as circulating levels of IL-1β, IL-6, TNF-a, CRP, and intra-cellular adhesion molecules [69]. Sitagliptin also enhanced the flow-mediated vasodilation effect in adult diabetic patients [63]. Prominently, sitagliptin has shown a cardio protective effect in chronic kidney disease diabetic patients [84]. Gliptins improve endothelial function through their anti-oxidant, potentially protective effects on the vascular system, and anti-inflammatory [85], which are important in fighting SARS-CoV-2. Furthermore, a randomized clinical trial revealed that treatment with glititin didn’t raise the risk of infections in diabetic patients [86]. In addition to providing potential cardiovascular protection, gliptins also play a key role to confine COVID-19 binding to the host cells. Vildagliptin, saxagliptin, or Sitagliptin can inhibit MERS-CoV entrees to Vero cells [87].

All DPP4 inhibitors (gliptins) are competitive reversible inhibitors of dipeptidyl peptidase-4 enzymatic activity [88]. According to the sub-sites within the DPP4 molecule they occupy, gliptins can be grouped into three categories. Class one includes peptidomimetic DPP4 inhibitor with the greatest basic binding to DPP4 like saxagliptin and vildagliptin; class two inhibitors include linagliptin and alogliptin; and class three inhibitors include teneiliglptin and sitagliptin exhibit an increased interacting point. The higher the interacting points the more the inhibitory activity [89]. Fascinatingly, class one and two gliptins (alogliptin, saxagliptin, and linagliptin) can bind near to a residue (Tyr547) in a zone acting point. The higher the interacting points the more the inhibitory activity [89]. Fascinatingly, class one and two gliptins (alogliptin, saxagliptin, and linagliptin) can bind near to a residue (Tyr547) in a zone acting point. The higher the interacting points the more the inhibitory activity [89].

Table 1
Summarized effects of sDPP4-targeted agents reported in preclinical and clinical research.

| Agents          | Preclinical data                                                                 | Animal models                                                                 | Previous clinical trials                                                                 | COVID-19                                                                 |
|-----------------|----------------------------------------------------------------------------------|--------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| GLP1            | Increased GLP-1 in type 1 and type 2 diabetic mice [104,105].                    |                                                                             | Decreased risk of non-fatal CV events and CV mortality [76].                             | SIDIACO Sitagliptin (NCT04365517)                                       |
| Anti-DPP4 vaccine | Blockade of MERS-CoV infection [107].                                             |                                                                             | block MERS-CoV infection in Vero cells [87].                                            | Linagliptin: NCT04371978, NCT04341935                                    |
| All DPP4 inhibitors (gliptins) | Prevention of sDPP4-induced endothelial dysfunction in mice [46]. | Prevention of sDPP4-induced endothelial dysfunction in mice [46]. | Prevention of sDPP4-induced endothelial dysfunction in mice [46]. | Anti-inflammatory effects in type 1 and type 2 diabetic patients [86]. |
| GLP1            | Endothelial dysfunction in murine mesenteric microvessels [46].                  |                                                                             | Increased cardio and vasculoprotective substrates [28, 78,79].                          | Anti-inflammatory effects in type 1 and type 2 diabetic patients [86]. |
| GLP1            | Increased monocyte migration in LDLR−/− mice [112].                             |                                                                             | Anti-inflammatory effects in type 1 and type 2 diabetic patients [86].                   | Anti-inflammatory effects in type 1 and type 2 diabetic patients [86]. |
| SKD4            | Blockage of MERS-CoV infection [107].                                             |                                                                             | Prevents sDPP4-induced endothelial dysfunction in mice [46].                         | Anti-inflammatory effects in type 1 and type 2 diabetic patients [86]. |
| SKD4            | Blockage of MERS-CoV infection [107].                                             |                                                                             | Prevents sDPP4-induced endothelial dysfunction in mice [46].                         | Anti-inflammatory effects in type 1 and type 2 diabetic patients [86]. |
| SKD4            | Blockage of MERS-CoV infection [107].                                             |                                                                             | Prevents sDPP4-induced endothelial dysfunction in mice [46].                         | Anti-inflammatory effects in type 1 and type 2 diabetic patients [86]. |

Furthermore, linagliptin and vildaglptin have been prophesied to bind ACE2 with similar or even higher binding capacity than they have for dipeptidyl peptidase-4 [90]. The pharmacodynamic and pharmacokinetic profiles of DPP4 inhibitors allow that dipeptidyl peptidase-4 enzymatic activity in circulation and tissues is not completely blocked [91]. Both genetic deletion of DPP4 and DPP4 inhibition with des-fluro sitagliptin in mice didn’t alter T-cell-dependent immune responses [92]. Saxagliptin, vildaglptin, and sitagliptin didn’t change the innate immune response triggered by Toll-like receptor activation in terms of co-stimulation, secretion, and T cell migration and proliferation both in mice in vivo and human cells in vitro [93].

A previous study revealed that DPP4 inhibitors are not linked with increased risk for respiratory infections they may raise the risk of nasopharyngitis and urinary tract infection [94]. A similar study showed that long-term use of sitagliptin in diabetic patients has not increased the risk of infection [95]. Another finding also reported that there was no association between the risk of respiratory tract infections and glucose-lowering therapies among diabetic patients [96]. But, the potential induction of cough in asthma [97], angioedema [98] or leucopenia [99] by DPP4 inhibitors epitomizes potential drawbacks to their use as a therapeutic agent in patients with COVID-19 [100]. However, further investigation will help to know if DPP4 inhibitors can affect immune homeostasis, T cell development, and infection risk in diabetic patients (Table 1) [47].

5.2. sDPP4 as soluble decoy factor

A study conducted in VERO cells showed that exogenous administration of sDPP4 repressed MERS-CoV infection [87]. Thus, SARS-CoV-2 can bind to DPP4, administration of exogenous sDPP4 as a decoy factor will compute with the virus to bind with an endogenous DPP4. sDPP4 load benefit may depend on the blockade of detrimental pathways worsening/afflicting immune responses and on virus trapping and prominently, to prevent SARS-CoV-2 effects on the vasculature. Hence, exogenous administration of sDPP4 via in-vitro model was shown a
preventive effect on the formation of endogenous DPP4/CD26-ADA complex in human macrophages/dendritic cells leading to inhibited proliferation and activation of T-cells [101]. Disruption of CCL5-CCR5/RANTES axis with the anti-CCR5 antibody lenimerilab decreased plasma viral load and IL-6 plasma levels in patients diagnosed with COVID-19 [102]. It has been suggested that sDPP4 can directly shorten RANTES/CCL5 obstructing its union to CCR5 [103], thus sDPP4 can show the same activity as lenimerilab management, resulting in a reduced cytokine storm and an improved immune response. In patients with diabetes mellitus, it was reported that the plasma concentration of sDPP4 is significantly increased [31], therefore, the possible risk-benefit of exogenous administration of sDPP4 as decoy factor should be judiciously explored (Table 1).

5.3. Anti-DPP4 vaccine

Anti-DPP4 vaccination is another therapeutic modality confirmed to control plasma DPP4 activity through the in-vivo model. The anti-DPP4 vaccine didn’t cause any side effect on the immune-mediated attack towards DPP4 expressing cells nor immune cell activation. Moreover, it showed comparable activity to glipizide treatment regarding GLP-1 plasma levels and glycemia control in animal models of both type I and type II DM [104,105]. In a study conducted on in-vitro on human CD26-positive lymphocytes, a humanized IgG1 monoclonal antibody with high affinity for CD26 was assessed, which showed no effect on cytokine production and T-cell proliferation [106]. Fascinatingly, humanized IgG1 monoclonal antibodies also expressed MERS-CoV infection [107]. Though, it has been argued that in-vivo administration of anti-DPP4 antibodies can counteract plasma sDPP4 prior to impede virus entry and coate cellular DPP4. In this condition, intranasal administration of anti-DPP4 antibodies or sDPP4 has been a reasonable solution to overwhelming such effects (Xia et al., 2014). In contrast, CD26/DPP4-related signaling was effectively obstructed via the soluble fusion protein Caveolin-1g, which confirmed extra immune-suppressive activity [108]. Tissue factor pathway inhibitor is a biological inhibitor of DPP4. Furthermore, because of its anticoagulant activity (Mast, 2016), tissue-factor pathway blocker may be seen as a positive feature in the situation of COVID-19 management (Table 1) [109].

6. Conclusion

DPP-4 inhibitors are a class of oral antidiabetic agents extensively used for the management of Type II diabetes mellitus; and have been proposed as a potential binding target of the receptor-binding S1 domain of the COVID-19 spike glycoprotein. DPP-4 inhibition could have the potential to block the interaction between target host cells and SARS-CoV-2; and current findings suggest that DPP-4 inhibitors display anti-fibrotic properties, anti-inflammatory, and immunomodulatory in addition to their confirmed antidiabetic activity. The use of DPP-4 inhibitors could reduce mortality due to COVID-19 or improve the progression of COVID-19; this evidence may support the management of diabetic patients diagnosed with COVID-19; however more well-designed investigation is promptly required.

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Declaration of competing interest

The authors declares that they have no competing interests.

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