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**Dipeptidyl peptidase 4 inhibitors in COVID-19: Beyond glycemic control**

Narayanan N *et al*. DPP-4 inhibitors and COVID-19

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**Abstract**

Coronavirus disease 2019 (COVID-19) is associated with a high risk of mortality and complications in patients with diabetes mellitus. Achieving good glycemic control is very important in diabetic patients to reduce complications and mortality due to COVID-19. Recent studies have shown the mortality benefit and anti-inflammatory effects of Dipeptidyl-peptidase‑4 inhibitors (DPP-4i) in diabetic patients with COVID-19. DPP-4i may have a beneficial role in halting the severity of infection primarily by three routes, namely viral entry inhibition, anti-inflammatory and anti-fibrotic effects and glycemic control. This has raised the promising hypothesis that DPP-4i might be an optimal strategy for treating COVID-19 in patients with diabetes. This review aims to summarise the possible therapeutic non-glycemic effects of DPP-4i in diabetic patients diagnosed with COVID-19 in the light of available evidence.

**Key Words:** Dipeptidyl -peptidase‑4; Diabetes mellitus; COVID-19; Mortality

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**Core Tip:** Patients with pre-existing comorbidities, particularly diabetes mellitus (DM), are at increased risk of complications from coronavirus disease 2019 (COVID-19). Beyond their glycemic effects, Dipeptidyl-peptidase‑4 inhibitors (DPP-4i) have proven effective in COVID-19 individuals with DM. Available observational studies and trials have shown a significant mortality reduction in COVID-19 patients with DM when DPP-4i were continued during the course of illness. As a result, COVID-19 individuals with DM may choose DPP-4i as the preferred anti-diabetic medication if it is not contraindicated.

**INTRODUCTION**

The current coronavirus disease 2019 (COVID-19) pandemic is caused by a novel beta coronavirus known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which is similar to SARS-CoV-1 and Middle East Respiratory Syndrome Coronavirus (MERS-CoV)[1]. Since late 2019, the disease has spread rapidly worldwide, posing a significant threat to public health. To date more than 539 million patients have been infected across the globe leading to over 6.32 million deaths[2]. The overall mortality rate for COVID-19 ranges from 0.7% to 10.8%[3]. Nearly two-thirds of severely affected individuals have comorbidities, most commonly cardiometabolic disorders, with diabetes mellitus (DM) accounting for 17% of cases[4].

Although DM is not associated with an increased risk of COVID-19, it confers a high risk of rapid progression in the severity of the infection and hence a poor prognosis. Specifically, people with DM are more prone to invasive mechanical ventilation, intensive care unit (ICU) admission, and the development of organ dysfunction, as compared with patients without diabetes[5,6]. A recent meta-analysis of 83 eligible studies with 78874 COVID-19 hospitalized patients found that people with pre-existing DM had a doubling of the risk for severe or critical COVID-19 illness (odds ratio [OR] 2.10, 95% confidence interval [95%CI] 1.71-2.57) and a tripling of the risk for in-hospital mortality (OR 2.68, 95%CI 2.09-3.44)[7]. Putative pathogenic processes linking COVID-19 and DM include hyperglycemia-mediated immune dysregulation, inflammation, and activation of the renin-angiotensin-aldosterone pathway[8].

The increasing spread of the SAR-CoV-2 infection and the high morbidity necessitates rapid identification of an effective therapy. While developing novel therapies (such as antivirals and vaccines) is a priority, repurposing "old" medications or reconsidering previously well-characterized targets with an emerging function in COVID-19 is the need of the hour. Dipeptidyl-peptidase-4 (DPP-4), also known as cluster of differentiation 26 (CD26), has recently been suggested as a potential target receptor for SAR-CoV-2[8,9]. MERS-CoV, a beta coronavirus similar to SARS-CoV-2, uses DPP-4 as an entrance receptor. Due to its similarity with the MERS-CoV, it has also been proposed that DPP-4 may aid SARS-CoV-2 entry into the target cells[10]. In this context, DPP-4i have gained increasing interest as a therapeutic target in patients with COVID-19.

DPP-4 is a 110 kDa glycoprotein, a membrane-bound endopeptidase that cleaves many peptide hormones such as cytokines, growth factors, and incretin hormones like glucagon-like peptide 1 (GLP-1) and gastric inhibitory peptide (GIP)[11]. Also, DPP-4 interacts with cellular proteins such as adenosine deaminase and caveolin-1 to regulate immune responses[12]. DPP-4 exists in two forms in the body, a membrane-bound form or as a soluble form (sDPP-4)[13]. The extracellular portion of DPP-4 is cleaved from cell membranes to form the 727 amino acid soluble moiety sDPP-4, which circulates in the plasma with retained enzyme activity. The DPP-4 receptor is found on the surface of nearly every cell and plays a role in immune regulation, signaling, and cell apoptosis. It is widely expressed in many tissues such as the kidney, gastrointestinal tract, and lungs. The primary role of DPP-4 is to regulate glucose and insulin metabolism by degradation of incretin hormones such as GLP-1 and GIP. Visceral adipose tissue has greater expression of DPP-4 and it has been linked to adipocyte inflammation and insulin resistance. DPP-4 promotes inflammation in subjects with type 2 diabetes through both catalytic and noncatalytic pathways. DPP-4 directly regulates the immune system by activating T cells and upregulating CD86 expression and the nuclear factor kappa B (NF-kB) pathway[14].

**Dipeptidyl- peptidase-4 inhibitors**

DPP-4i are oral anti-diabetic drugs that affect glucose homeostasis by inhibiting the enzyme DPP-4. DPP-4i prolong the half-life of incretins by deactivating DPP-4, which cleaves and inactivates them. Incretin hormones, GLP-1 and GIP are responsible for the regulation of postprandial insulin[15]. DPP-4i have been suggested to have cardiovascular benefits. Hence, these medications are commonly used in diabetic patients with a history of cardiovascular or chronic renal disease[16]. They achieve reasonable glycemic control with no significant effect on body weight, no risk of hypoglycemic events, and a safe cardiovascular profile. They have also shown a favorable effect on surrogate vascular markers, such as lipid profile, blood pressure, and endothelial function[13].

**Proposed mechanisms of DPP-4i in COVID-19**

DPP-4i can effectively control blood glucose levels with a favorable safety profile. Good glycemic control can improve the prognosis and outcome of COVID-19[17]. Hence, DPP-4i can influence the clinical outcome in COVID-19 patients through their glycemic effects. The mechanisms by which DPP-4i influence the clinical outcomes in COVID-19 patients with DM beyond their glycemic effect are still under speculation and are detailed below (Figures 1 and 2).

**DPP-4 and SARS-CoV-2 interaction**

***Role as an alternate co-receptor***

SARS-CoV-2 binds to specific host receptors on the target cell to facilitate entry into the host cell. The SARS-CoV-2 enters the cell *via* binding of the viral spike (S) protein to the angiotensin-converting enzyme 2 (ACE-2) receptor on the surface of the host cell membrane. The binding of the S-protein causes a conformational change in the receptor, which is essential for its activation. This critical step known as priming comprises the cleaving of the spike protein by cellular serine proteases. This step enables viral fusion with the cellular membrane and promotes viral entry into the target cell[18]. Studies have shown a wide distribution of ACE-2 across human tissues, including the lung, gastrointestinal tract, and kidney. However, the expression of ACE-2 on alveolar type 2 cells, which is supposed to be the primary target cell of SARS-CoV-2, is markedly low. This has created interest in a possible role for other co-receptors for viral entry[19].

In-silico modelling of the SARS-CoV-2 spike protein, predicted a potential interaction with the DPP-4 in addition to ACE-2[20]. These models suggest that DPP-4 may be a co-receptor for SARS-CoV-2 viral entry. As DPP-4 is widely expressed in cells and tissues other than the respiratory tract, it may facilitate the spread of SARS-CoV-2 infection to a wider range of tissues[10]. DPP-4 is the receptor for the MERS-CoV spike protein, which mediates viral entrance into host cells[21]. Due to the high homology between SARS-CoV-2 and MERS-CoV, DPP-4 may also be an accessory entry receptor for SARS-CoV-2[22]. The presumed role of DPP-4 as a co-receptor for SARS-CoV-2 is still under study[14].

***Cross-talk between DPP-4 and ACE-2 receptor***

DPP-4 interacts with several essential proteins for viral processing, including ACE-2, implying a possible cross-talk between the two proteins[23]. *In vivo* studies have shown that the DPP-4i sitagliptin inhibits ACE activity and reduces angiotensin II levels in rats[24]. This cross-talk could interfere with viral surface binding and fusion, thereby affecting spread of the infection.

***Role of soluble DPP-4***

The fact that DPP-4 exists in two forms, a soluble form (sDPP-4) and membrane-bound form, adds to the intricacy of the role of DPP-4i in COVID-19. Previous research has shown that sDPP-4 acts as a decoy receptor for MERS-CoV, preventing viral replication[12]. The same may be applicable to SARS-CoV-2. sDPP-4 may bind SARS-CoV-2, preventing the virus from attaching to membrane-bound DPP-4 in the host cell, thereby hindering viral spread. A German study showed a reduced circulating level of sDPP-4 in patients with severe COVID-19[25]. A similar scenario was reported in MERS-CoV infected patients[26]. Previous studies have shown that sDPP-4 was significantly lower in older individuals than younger individuals[27]. Serum levels of sDPP-4 are also altered in various clinical diseases, such as DM, obesity, and metabolic syndrome, and are linked to insulin resistance[27,28]. This may contribute to the severe presentation of SARS-CoV-2 infection in diabetic, obese, and elderly individuals. In this regard, a recent study has shown a 50%-100% rise in the levels of sDPP-4 in mice after exposure to DPP-4i[29]. Hence, DPP-4i, in addition to interfering with viral entrance, may enhance viral particle sequestration in the circulation by increasing sDPP-4 levels, limiting viral growth in humans.

***Immunomodulatory role of DPP-4i***

Dysregulated inflammation accounts for the severity of COVID-19. The severe presentation is linked to a hyperinflammatory state, characterized by an abnormal increase in circulating levels of pro-inflammatory cytokines such as Interleukin (IL)-1, IL-2, IL-6, Interferon-γ and tumor necrosis factor (TNF), leading to acute respiratory distress syndrome, disseminated intravascular coagulation, multi-organ failure, and death. There is significant activation of CD4+ and CD8+ T cells in COVID-19 patients and a skewing of T-cells toward the T-helper 17 functional phenotype[30]. DPP-4 is found in various cell lines involved in immune control, such as Th17 T helper cells, natural killer cells, activated B cells, macrophages, and myeloid cells[31]. DPP-4 promotes T cell proliferation, NF-kB activation, CD86 expression, and excessive production of inflammatory cytokines, all of which contribute to inflammation. Additionally, GLP-1, which DPP-4 degrades, also possesses anti-inflammatory properties[32].

DPP-4i reduce pro-inflammatory cytokines and mediators such as IL-1, IL-6, C-reactive protein (CRP), and TNF-alpha and thereby mitigate the severity of COVID-19. Many studies have shown that sitagliptin has anti-inflammatory effects in diabetic patients, which leads to an increase in the anti-inflammatory cytokine IL-10 and a decrease in several pro-inflammatory cytokines, such as TNF-alpha[13]. Therefore, the immunomodulatory effects of DPP-4i may prevent dysregulated inflammation and cytokine storms in COVID-19 patients, thereby reducing the severity of the disease.

***Pleiotropic effects of DPP-4i***

DPP-4i confer multiple vasculoprotective effects, which reduce the risk of comorbidities associated with DM, including hypertension, cardiovascular disease (CVD), and kidney disease. Insulin resistance, oxidative stress, dyslipidemia, adipose tissue dysfunction, and immune dysfunction may all contribute to endothelial dysfunction and arterial stiffness in DM. Beyond glycemic control, DPP-4i regulate these pathogenic mechanisms through GLP-1-dependent and independent pathways for CVD protection[33]. DPP-4i have been proven in numerous trials to prevent atherosclerosis, improve endothelial function, and promote wound healing possibly by modulating monocyte/macrophage-mediated responses, reducing oxidative stress, and decreasing neutrophil recruitment and activity[33]. As a result, Du *et al*[34] recently proposed DPP-4i as a potential therapy for preventing or treating CVD produced either directly or indirectly by the COVID-19-induced cytokine storm. Through their immune-modulatory action, DPP-4i have also been useful in obesity-related inflammation, hepatic fibrosis, myocarditis, diabetic nephropathy, and chemotherapy-induced kidney injury in animal research trials[31].

DPP-4 inhibition directly reduces lipopolysaccharide-induced lung damage in mice and human lung epithelial cells[35]. Soare *et* *al*[36] recently discovered that DPP-4 enhances fibroblast activation by increasing transforming growth factor β, a harbinger of tissue fibrosis. Hence, the inactivation of DPP-4 has significant anti-fibrotic effects, validated in numerous experimental models of pulmonary and skin fibrosis. Sadikot *et al*[37] have recently claimed that GLP-1 could be a new treatment for acute respiratory distress syndrome, demonstrating that human GLP-1 reduces NF-kB activation in cultured macrophages and a mouse model of acute lung damage. All these studies point to a possible anti-fibrotic role for DPP-4i.

**Observational studies**

With the above hypothesis, several observational studies have been performed to investigate the impact of DPP-4i on clinical outcomes in type 2 diabetes mellitus (T2DM) patients hospitalized for COVID-19 (Table 1).

In a cohort study conducted at the university hospital of Padova, amongst 403 patients hospitalized for COVID-19, 85 had DM, and nine were on DPP-4i. DPP-4i users and comparators had no significant difference in ICU admission or death rate[38]. In a retrospective observational study of 120 patients with diabetes, Chen *et al*[39] found that DPP-4i users and non-users had identical clinical outcomes. Users of DPP-4i had a non-significant higher rate of in-hospital death than non-users (OR 1.48, 95%CI 0.4-5.53). Similarly, after propensity score matching, Pérez-Belmonte *et al*[40] found that DPP-4i users were not at higher risk for adverse outcomes such as ICU admission, mechanical ventilation, multi-organ dysfunction, or long-term hospital admissions. In a few other observational studies there was no link between DPP-4i therapy and COVID-19-related mortality[41-46] and severity[44,47].

On the contrary, few observational studies have revealed that DPP-4i have favourable effects on COVID-19-related outcomes. In a case series encompassing 387 patients admitted to a research hospital in Lombardy (Northern Italy) with COVID-19, 90 patients were diabetic and 12.2% were on DPP-4i. After adjusting for confounders, DPP-4i use was associated with a decreased death risk (adjusted hazard ratio (HR) 0.13; 95%CI 0.02–0.92). Furthermore, DPP-4i users required less non-invasive mechanical ventilation, implying that their pneumonia was less severe[48].

In a multicentric retrospective observational study conducted in Northern Italy, 169 age and gender-matched subjects treated with sitagliptin plus insulin were compared with a similar number of subjects treated with insulin therapy. Primary outcomes assessed were hospital discharge and death, and secondary outcomes analyzed were ICU admission, the need for mechanical ventilation, and extracorporeal membrane oxygenation. The sitagliptin users had significantly lower mortality (18% *vs* 37%, *P* < 0.001) even after adjusting for confounders like age, gender, comorbidities, and ongoing treatment (HR 0.44; 95%CI 0.29-0.66). On day 30, a larger number of patients treated with sitagliptin were discharged from the hospital than those on conventional therapy (71% *vs* 59%, *P* < 0.01). Compared to usual treatment, sitagliptin was associated with a lower probability of needing mechanical ventilation and ICU admission. At follow-up, patients treated with sitagliptin had significantly lower inflammatory markers such as procalcitonin and CRP and lower mean blood glucose levels during hospitalization[49].

Similarly, a Korean database-based retrospective study found that DPP-4i treatment was significantly associated with better clinical outcomes even after adjusting for age, gender, comorbidities, and medications (adjusted OR 0.362, 95%CI 0.135-0.971). The study included 832 subjects with DM, of whom 263 were on DPP-4i[50]. Similarly, DPP-4i usage was related to a shorter ICU stay in 67 patients with DM admitted with COVID-19 pneumonia in a single centre in Iraq (OR 0.3, 95%CI 0.2-3)[51].

In the coronavirus disease and diabetes outcome (CORONADO) study, a multicentric prospective observational trial conducted in France, 2796 patients hospitalized for SARS-CoV-2 with DM were assessed. Around 21.6% of the participants were on DPP-4i. The primary outcome as assessed by the need for mechanical ventilation and/or death within seven days was similar in DPP-4i users compared to nonusers (OR 0.83; 95%CI 0.67-1.03)[52]. Wong *et al*[53] retrospectively analyzed 1214 T2DM patients with confirmed COVID-19 admitted to public hospitals in Hong Kong. They found a lower risk for clinical deterioration (OR = 0.71, 95%CI 0.54-0.93), hyperinflammatory syndrome (OR = 0.56, 95%CI 0.45-0.69) and invasive mechanical ventilation (OR = 0.30, 95%CI 0.21-0.42) in DPP-4i users. However, DPP-4i users had no significant in-hospital mortality reduction.

A retrospective review of 717 COVID-19 patients admitted to a health care centre in Singapore found contradictory results. Patients on DPP-4i (*n* = 27) showed greater odds of ICU admission than those on other glucose-lowering medicines (adjusted relative risk [RR] 5.14, 95%CI 1.5-17.7). Also, patients on DPP-4i were more likely to require mechanical ventilation; however, no data on mortality were provided[54]. Similarly, Khunti *et al*[55] in their nationwide observational cohort study in the UK analysed the HR of COVID-19-related mortality in people prescribed DPP-4i. DPP-4i users had a HR of 1.07 (95%CI 1.01-1.13) for COVID-19-related mortality.

The evidence available from observational studies on the link between DPP-4i and DM and COVID-19 outcomes suggests some heterogeneity. These outcomes were extensively evaluated in multiple meta-analyses[56-62]. Bonora *et al*[56] analyzed seven studies that reported data on mortality. There was no significant difference in death rate between patients treated with DPP-4i and other anti-diabetic medications (RR 0.74, 95%CI 0.47–1.16). Han *et al*[57] also showed similar results with a statistically non-significant lower mortality (OR 0.95, 95%CI 0.72-1.26) or poor composite outcomes (OR 1.27, 95%CI 0.91–1.77) in diabetic COVID-19 patients. Similarly, Pal *et al*[58] included nine observational studies of high quality consisting of 7008 COVID-19 patients with DM. A pooled analysis of unadjusted and adjusted data revealed no significant link between DPP-4i usage and mortality. However, subgroup analysis discovered that DPP-4i use in the hospital (rather than before admission) was related to lower mortality (adjusted OR 0.27, 95%CI 0.13-0.55). Contrary to the above studies, Nguyen *et al*[59] in their recent meta-analysis linked DPP-4i to a higher mortality risk (OR 1.23, 95%CI 1.07-1.42).

DPP-4i appear to have a neutral action in COVID-19, but the available studies are still insufficient to draw definitive conclusions. It is worth noting that all the data are from retrospective observational studies and that most of them were not specifically designed to study the effects of DPP-4i. The discrepancies reported for the connection between DPP-4i and COVID-19 outcomes could be explained by variations in methodology, baseline characteristics, and sample size.

**Randomized controlLED trials**

Two randomized controlled trials (RCTs) have evaluated DPP-4i in patients with diabetes and COVID-19 (Table 2).

Abuhasira *et al*[63] investigated 64 patients who were randomized to receive linagliptin 5 mg once daily or standard of care medication in an open-label, prospective, multicentre RCT (32 in each group). The time to clinical improvement within 28 days of randomization was the primary outcome measured. Treatment with linagliptin in addition to standard therapy did not enhance time to resolution of symptoms (HR 1.22, 95%CI, 0.70-2.15) or death on day 28 (OR 0.56, 95%CI 0.16-1.93). Furthermore, no differences in any of the secondary outcomes, such as the proportion of patients admitted to an ICU, mechanical ventilation rates, length of hospitalization, or supplemental oxygen use, were observed between the study groups. However, due to containment of the COVID-19 epidemic in Israel, the experiment was prematurely terminated, leaving the study underpowered to identify possible differences in the primary results and mortality.

In a parallel, double-blind RCT, Guardado-Mendoza *et al*[64] evaluated the efficacy of the combination of linagliptin and insulin on metabolic control and prognosis in hospitalized patients with COVID-19 and DM. A total of 73 patients were randomly assigned to either 5 mg linagliptin plus insulin (LI group, *n* = 35) or insulin alone (I group, *n* = 38). The need for assisted mechanical ventilation and mortality were the two primary outcomes. Secondary outcomes were glucose levels and insulin requirements during the first 5-10 days in the hospital, pulmonary parameters, and clinical progression of COVID-19. Both groups had similar average hospital stays (12 ± 1 *vs* 10 ± 1 d, *P* = 0.343). Three patients in the LI group and twelve in the I group needed assisted mechanical ventilation (HR 0.258, 95%CI 0.092-0.719), and two patients in the LI group and six in the I group died after a 30-d follow-up period (*P* = 0.139). The inclusion of linagliptin reduced the relative risk of assisted mechanical ventilation by 74% and improved pre- and postprandial glucose levels, requiring less insulin and posing no increased risk of hypoglycemia.

**CONCLUSION**

Beyond their well-known glycemic role, DPP-4i have anti-inflammatory, immunomodulatory, and anti-fibrotic properties. They are among the non-insulin glucose-lowering medications that are safe and effective in treating T2DM, even in the presence of COVID-19, without increasing the risk of significant side effects such as hypoglycemia. As a result, practical recommendations for the management of diabetes in patients with COVID-19 do not propose stopping DPP-4i. Even though results from observational studies and a few RCTs have been inconsistent, the existing evidence suggests that DPP-4i are safe for patients with T2DM and COVID-19. Studies showed a trend towards reducing mortality in COVID-19 patients with DM, especially with continued in-hospital use of DPP-4i. As a result, it is appropriate to start or continue DPP-4i in COVID-19 individuals with DM unless contraindicated.

**REFERENCES**

1 **Zhu N**, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W; China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* 2020; **382**: 727-733 [PMID: 31978945 DOI: 10.1056/NEJMoa2001017]

2 COVID Live - Coronavirus Statistics - Worldometer. Available from: https://www.worldometers.info/coronavirus/?%3D%3D

3 **Omer SB**, Malani P, Del Rio C. The COVID-19 Pandemic in the US: A Clinical Update. *JAMA* 2020; **323**: 1767-1768 [PMID: 32250388 DOI: 10.1001/jama.2020.5788]

4 **Grasselli G**, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, Cereda D, Coluccello A, Foti G, Fumagalli R, Iotti G, Latronico N, Lorini L, Merler S, Natalini G, Piatti A, Ranieri MV, Scandroglio AM, Storti E, Cecconi M, Pesenti A; COVID-19 Lombardy ICU Network. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *JAMA* 2020; **323**: 1574-1581 [PMID: 32250385 DOI: 10.1001/jama.2020.5394]

5 **Fadini GP**, Morieri ML, Longato E, Avogaro A. Prevalence and impact of diabetes among people infected with SARS-CoV-2. *J Endocrinol Invest* 2020; **43**: 867-869 [PMID: 32222956 DOI: 10.1007/s40618-020-01236-2]

6 **Pal R**, Bhadada SK. COVID-19 and diabetes mellitus: An unholy interaction of two pandemics. *Diabetes Metab Syndr* 2020; **14**: 513-517 [PMID: 32388331 DOI: 10.1016/j.dsx.2020.04.049]

7 **Mantovani A**, Byrne CD, Zheng MH, Targher G. Diabetes as a risk factor for greater COVID-19 severity and in-hospital death: A meta-analysis of observational studies. *Nutr Metab Cardiovasc Dis* 2020; **30**: 1236-1248 [PMID: 32571616 DOI: 10.1016/j.numecd.2020.05.014]

8 **Lim S**, Bae JH, Kwon HS, Nauck MA. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. *Nat Rev Endocrinol* 2021; **17**: 11-30 [PMID: 33188364 DOI: 10.1038/s41574-020-00435-4]

9 **Iacobellis G**. COVID-19 and diabetes: Can DPP4 inhibition play a role? *Diabetes Res Clin Pract* 2020; **162**: 108125 [PMID: 32224164 DOI: 10.1016/j.diabres.2020.108125]

10 **Li Y**, Zhang Z, Yang L, Lian X, Xie Y, Li S, Xin S, Cao P, Lu J. The MERS-CoV Receptor DPP4 as a Candidate Binding Target of the SARS-CoV-2 Spike. *iScience* 2020; **23**: 101160 [PMID: 32405622 DOI: 10.1016/j.isci.2020.101160]

11 **Lambeir AM**, Durinx C, Scharpé S, De Meester I. Dipeptidyl-peptidase IV from bench to bedside: an update on structural properties, functions, and clinical aspects of the enzyme DPP IV. *Crit Rev Clin Lab Sci* 2003; **40**: 209-294 [PMID: 12892317 DOI: 10.1080/713609354]

12 **Krejner-Bienias A**, Grzela K, Grzela T. DPP4 Inhibitors and COVID-19-Holy Grail or Another Dead End? *Arch Immunol Ther Exp (Warsz)* 2021; **69**: 1 [PMID: 33527308 DOI: 10.1007/s00005-020-00602-5]

13 **Kifle ZD**, Woldeyohanin AE, Demeke CA. SARS-CoV-2 and diabetes: A potential therapeutic effect of dipeptidyl peptidase 4 inhibitors in diabetic patients diagnosed with COVID-19. *Metabol Open* 2021; **12**: 100134 [PMID: 34661092 DOI: 10.1016/j.metop.2021.100134]

14 **Bassendine MF**, Bridge SH, McCaughan GW, Gorrell MD. COVID-19 and comorbidities: A role for dipeptidyl peptidase 4 (DPP4) in disease severity? *J Diabetes* 2020; **12**: 649-658 [PMID: 32394639 DOI: 10.1111/1753-0407.13052]

15 **Nauck MA**, Meier JJ. Incretin hormones: Their role in health and disease. *Diabetes Obes Metab* 2018; **20 Suppl 1**: 5-21 [PMID: 29364588 DOI: 10.1111/dom.13129]

16 **Hanssen NM**, Jandeleit-Dahm KA. Dipeptidyl peptidase-4 inhibitors and cardiovascular and renal disease in type 2 diabetes: What have we learned from the CARMELINA trial? *Diab Vasc Dis Res* 2019; **16**: 303-309 [PMID: 31018682 DOI: 10.1177/1479164119842339]

17 **Apicella M**, Campopiano MC, Mantuano M, Mazoni L, Coppelli A, Del Prato S. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. *Lancet Diabetes Endocrinol* 2020; **8**: 782-792 [PMID: 32687793 DOI: 10.1016/S2213-8587(20)30238-2]

18 **Lu R**, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, Song H, Huang B, Zhu N, Bi Y, Ma X, Zhan F, Wang L, Hu T, Zhou H, Hu Z, Zhou W, Zhao L, Chen J, Meng Y, Wang J, Lin Y, Yuan J, Xie Z, Ma J, Liu WJ, Wang D, Xu W, Holmes EC, Gao GF, Wu G, Chen W, Shi W, Tan W. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* 2020; **395**: 565-574 [PMID: 32007145 DOI: 10.1016/S0140-6736(20)30251-8]

19 **Qi F**, Qian S, Zhang S, Zhang Z. Single cell RNA sequencing of 13 human tissues identify cell types and receptors of human coronaviruses. *Biochem Biophys Res Commun* 2020; **526**: 135-140 [PMID: 32199615 DOI: 10.1016/j.bbrc.2020.03.044]

20 **Vankadari N**, Wilce JA. Emerging WuHan (COVID-19) coronavirus: glycan shield and structure prediction of spike glycoprotein and its interaction with human CD26. *Emerg Microbes Infect* 2020; **9**: 601-604 [PMID: 32178593 DOI: 10.1080/22221751.2020.1739565]

21 **Lu G**, Hu Y, Wang Q, Qi J, Gao F, Li Y, Zhang Y, Zhang W, Yuan Y, Bao J, Zhang B, Shi Y, Yan J, Gao GF. Molecular basis of binding between novel human coronavirus MERS-CoV and its receptor CD26. *Nature* 2013; **500**: 227-231 [PMID: 23831647 DOI: 10.1038/nature12328]

22 **Eleftheriou P**, Amanatidou D, Petrou A, Geronikaki A. In Silico Evaluation of the Effectivity of Approved Protease Inhibitors against the Main Protease of the Novel SARS-CoV-2 Virus. *Molecules* 2020; **25** [PMID: 32485894 DOI: 10.3390/molecules25112529]

23 **Dastan F**, Abedini A, Shahabi S, Kiani A, Saffaei A, Zare A. Sitagliptin Repositioning in SARS-CoV-2: Effects on ACE-2, CD-26, and Inflammatory Cytokine Storms in the Lung. *Iran J Allergy Asthma Immunol* 2020; **19**: 10-12 [PMID: 32534505 DOI: 10.18502/ijaai.v19i(s1.r1).2849]

24 **Beraldo JI**, Benetti A, Borges-Júnior FA, Arruda-Junior DF, Martins FL, Jensen L, Dariolli R, Shimizu MH, Seguro AC, Luchi WM, Girardi ACC. Cardioprotection Conferred by Sitagliptin Is Associated with Reduced Cardiac Angiotensin II/Angiotensin-(1-7) Balance in Experimental Chronic Kidney Disease. *Int J Mol Sci* 2019; **20** [PMID: 31010001 DOI: 10.3390/ijms20081940]

25 **Schlicht K**, Rohmann N, Geisler C, Hollstein T, Knappe C, Hartmann K, Schwarz J, Tran F, Schunk D, Junker R, Bahmer T, Rosenstiel P, Schulte D, Türk K, Franke A, Schreiber S, Laudes M. Circulating levels of soluble Dipeptidylpeptidase-4 are reduced in human subjects hospitalized for severe COVID-19 infections. *Int J Obes (Lond)* 2020; **44:** 2335-2338 [PMID: 32958905 DOI: 10.1038/s41366-020-00689-y]

26 **Inn KS**, Kim Y, Aigerim A, Park U, Hwang ES, Choi MS, Kim YS, Cho NH. Reduction of soluble dipeptidyl peptidase 4 Levels in plasma of patients infected with Middle East respiratory syndrome coronavirus. *Virology* 2018; **518**: 324-327 [PMID: 29587190 DOI: 10.1016/j.virol.2018.03.015]

27 **Lamers D**, Famulla S, Wronkowitz N, Hartwig S, Lehr S, Ouwens DM, Eckardt K, Kaufman JM, Ryden M, Müller S, Hanisch FG, Ruige J, Arner P, Sell H, Eckel J. Dipeptidyl peptidase 4 is a novel adipokine potentially linking obesity to the metabolic syndrome. *Diabetes* 2011; **60**: 1917-1925 [PMID: 21593202 DOI: 10.2337/db10-1707]

28 **Röhrborn D**, Wronkowitz N, Eckel J. DPP4 in Diabetes. *Front Immunol* 2015; **6**: 386 [PMID: 26284071 DOI: 10.3389/fimmu.2015.00386]

29 **Varin EM**, Mulvihill EE, Beaudry JL, Pujadas G, Fuchs S, Tanti JF, Fazio S, Kaur K, Cao X, Baggio LL, Matthews D, Campbell JE, Drucker DJ. Circulating Levels of Soluble Dipeptidyl Peptidase-4 Are Dissociated from Inflammation and Induced by Enzymatic DPP4 Inhibition. *Cell Metab* 2019; **29**: 320-334.e5 [PMID: 30393019 DOI: 10.1016/j.cmet.2018.10.001]

30 **Pinheiro MM**, Fabbri A, Infante M. Cytokine storm modulation in COVID-19: a proposed role for vitamin D and DPP-4 inhibitor combination therapy (VIDPP-4i). *Immunotherapy* 2021; **13**: 753-765 [PMID: 33906375 DOI: 10.2217/imt-2020-0349]

31 **Pantanetti P**, Cangelosi G, Ambrosio G. Potential role of incretins in diabetes and COVID-19 infection: a hypothesis worth exploring. *Intern Emerg Med* 2020; **15**: 779-782 [PMID: 32592113 DOI: 10.1007/s11739-020-02389-x]

32 **Klemann C**, Wagner L, Stephan M, von Hörsten S. Cut to the chase: a review of CD26/dipeptidyl peptidase-4's (DPP4) entanglement in the immune system. *Clin Exp Immunol* 2016; **185**: 1-21 [PMID: 26919392 DOI: 10.1111/cei.12781]

33 **Aroor AR**, Sowers JR, Jia G, DeMarco VG. Pleiotropic effects of the dipeptidylpeptidase-4 inhibitors on the cardiovascular system. *Am J Physiol Heart Circ Physiol* 2014; **307**: H477-H492 [PMID: 24929856 DOI: 10.1152/ajpheart.00209.2014]

34 **Du H**, Wang DW, Chen C. The potential effects of DPP-4 inhibitors on cardiovascular system in COVID-19 patients. *J Cell Mol Med* 2020; **24**: 10274-10278 [PMID: 32713161 DOI: 10.1111/jcmm.15674]

35 **Kawasaki T**, Chen W, Htwe YM, Tatsumi K, Dudek SM. DPP4 inhibition by sitagliptin attenuates LPS-induced lung injury in mice. *Am J Physiol Lung Cell Mol Physiol* 2018; **315**: L834-L845 [PMID: 30188745 DOI: 10.1152/ajplung.00031.2018]

36 **Soare A**, Györfi HA, Matei AE, Dees C, Rauber S, Wohlfahrt T, Chen CW, Ludolph I, Horch RE, Bäuerle T, von Hörsten S, Mihai C, Distler O, Ramming A, Schett G, Distler JHW. Dipeptidylpeptidase 4 as a Marker of Activated Fibroblasts and a Potential Target for the Treatment of Fibrosis in Systemic Sclerosis. *Arthritis Rheumatol* 2020; **72**: 137-149 [PMID: 31350829 DOI: 10.1002/art.41058]

37 **Sadikot RT**, Rubinstein I. Long-acting, multi-targeted nanomedicine: addressing unmet medical need in acute lung injury. *J Biomed Nanotechnol* 2009; **5**: 614-619 [PMID: 20201223 DOI: 10.1166/jbn.2009.1078]

38 **Fadini GP**, Morieri ML, Longato E, Bonora BM, Pinelli S, Selmin E, Voltan G, Falaguasta D, Tresso S, Costantini G, Sparacino G, Di Camillo B, Tramontan L, Cattelan AM, Vianello A, Fioretto P, Vettor R, Avogaro A. Exposure to dipeptidyl-peptidase-4 inhibitors and COVID-19 among people with type 2 diabetes: A case-control study. *Diabetes Obes Metab* 2020; **22**: 1946-1950 [PMID: 32463179 DOI: 10.1111/dom.14097]

39 **Chen Y**, Yang D, Cheng B, Chen J, Peng A, Yang C, Liu C, Xiong M, Deng A, Zhang Y, Zheng L, Huang K. Clinical Characteristics and Outcomes of Patients With Diabetes and COVID-19 in Association With Glucose-Lowering Medication. *Diabetes Care* 2020; **43**: 1399-1407 [PMID: 32409498 DOI: 10.2337/dc20-0660]

40 **Pérez-Belmonte LM**, Torres-Peña JD, López-Carmona MD, Ayala-Gutiérrez MM, Fuentes-Jiménez F, Huerta LJ, Muñoz JA, Rubio-Rivas M, Madrazo M, Garcia MG, Montes BV, Sola JF, Ena J, Ferrer RG, Pérez CM, Ripper CJ, Lecumberri JJN, Acedo IEA, Canteli SP, Cosío SF, Martínez FA, Rodríguez BC, Pérez-Martínez P, Ramos-Rincón JM, Gómez-Huelgas R; SEMI-COVID-19 Network. Mortality and other adverse outcomes in patients with type 2 diabetes mellitus admitted for COVID-19 in association with glucose-lowering drugs: a nationwide cohort study. *BMC Med* 2020; **18**: 359 [PMID: 33190637 DOI: 10.1186/s12916-020-01832-2]

41 **Silverii GA**, Monami M, Cernigliaro A, Vigneri E, Guarnotta V, Scondotto S, Allotta VA, Conti M, Giordano C, Mannucci E. Are diabetes and its medications risk factors for the development of COVID-19? Data from a population-based study in Sicily. *Nutr Metab Cardiovasc Dis* 2021; **31**: 396-398 [PMID: 33223405 DOI: 10.1016/j.numecd.2020.09.028]

42 **Kim MK**, Jeon JH, Kim SW, Moon JS, Cho NH, Han E, You JH, Lee JY, Hyun M, Park JS, Kwon YS, Choi YK, Kwon KT, Lee SY, Jeon EJ, Kim JW, Hong HL, Kwon HH, Jung CY, Lee YY, Ha E, Chung SM, Hur J, Ahn JH, Kim NY, Kim SW, Chang HH, Lee YH, Lee J, Park KG, Kim HA, Lee JH. The Clinical Characteristics and Outcomes of Patients with Moderate-to-Severe Coronavirus Disease 2019 Infection and Diabetes in Daegu, South Korea. *Diabetes Metab J* 2020; **44**: 602-613 [PMID: 32794386 DOI: 10.4093/dmj.2020.0146]

43 **Noh Y**, Oh IS, Jeong HE, Filion KB, Yu OHY, Shin JY. Association Between DPP-4 Inhibitors and COVID-19-Related Outcomes Among Patients With Type 2 Diabetes. *Diabetes Care* 2021; **44**: e64-e66 [PMID: 33547204 DOI: 10.2337/dc20-1824]

44 **Zhou JH**, Wu B, Wang WX, Lei F, Cheng X, Qin JJ, Cai JJ, Zhang XJ, Zhou F, Liu YM, Li HM, Zhu LH, She ZG, Zhang X, Yang J, Li HL. No significant association between dipeptidyl peptidase-4 inhibitors and adverse outcomes of COVID-19. *World J Clin Cases* 2020; **8**: 5576-5588 [PMID: 33344548 DOI: 10.12998/wjcc.v8.i22.5576]

45 **Izzi-Engbeaya C**, Distaso W, Amin A, Yang W, Idowu O, Kenkre JS, Shah RJ, Woin E, Shi C, Alavi N, Bedri H, Brady N, Blackburn S, Leczycka M, Patel S, Sokol E, Toke-Bjolgerud E, Qayum A, Abdel-Malek M, Hope DCD, Oliver NS, Bravis V, Misra S, Tan TM, Hill NE, Salem V. Adverse outcomes in COVID-19 and diabetes: a retrospective cohort study from three London teaching hospitals. *BMJ Open Diabetes Res Care* 2021; **9** [PMID: 33408084 DOI: 10.1136/bmjdrc-2020-001858]

46 **Israelsen SB**, Pottegård A, Sandholdt H, Madsbad S, Thomsen RW, Benfield T. Comparable COVID-19 outcomes with current use of GLP-1 receptor agonists, DPP-4 inhibitors or SGLT-2 inhibitors among patients with diabetes who tested positive for SARS-CoV-2. *Diabetes Obes Metab* 2021; **23**: 1397-1401 [PMID: 33502076 DOI: 10.1111/dom.14329]

47 **Yan H**, Valdes AM, Vijay A, Wang S, Liang L, Yang S, Wang H, Tan X, Du J, Jin S, Huang K, Jiang F, Zhang S, Zheng N, Hu Y, Cai T, Aithal GP. Role of Drugs Used for Chronic Disease Management on Susceptibility and Severity of COVID-19: A Large Case-Control Study. *Clin Pharmacol Ther* 2020; **108**: 1185-1194 [PMID: 32910830 DOI: 10.1002/cpt.2047]

48 **Mirani M**, Favacchio G, Carrone F, Betella N, Biamonte E, Morenghi E, Mazziotti G, Lania AG. Impact of Comorbidities and Glycemia at Admission and Dipeptidyl Peptidase 4 Inhibitors in Patients With Type 2 Diabetes With COVID-19: A Case Series From an Academic Hospital in Lombardy, Italy. *Diabetes Care* 2020; **43**: 3042-3049 [PMID: 33023989 DOI: 10.2337/dc20-1340]

49 **Solerte SB**, D'Addio F, Trevisan R, Lovati E, Rossi A, Pastore I, Dell'Acqua M, Ippolito E, Scaranna C, Bellante R, Galliani S, Dodesini AR, Lepore G, Geni F, Fiorina RM, Catena E, Corsico A, Colombo R, Mirani M, De Riva C, Oleandri SE, Abdi R, Bonventre JV, Rusconi S, Folli F, Di Sabatino A, Zuccotti G, Galli M, Fiorina P. Sitagliptin Treatment at the Time of Hospitalization Was Associated With Reduced Mortality in Patients With Type 2 Diabetes and COVID-19: A Multicenter, Case-Control, Retrospective, Observational Study. *Diabetes Care* 2020; **43**: 2999-3006 [PMID: 32994187 DOI: 10.2337/dc20-1521]

50 **Rhee SY**, Lee J, Nam H, Kyoung DS, Shin DW, Kim DJ. Effects of a DPP-4 Inhibitor and RAS Blockade on Clinical Outcomes of Patients with Diabetes and COVID-19. *Diabetes Metab J* 2021; **45**: 251-259 [PMID: 33752274 DOI: 10.4093/dmj.2020.0206]

51 **Nafakhi H**, Alareedh M, Al-Buthabhak K, Shaghee F, Nafakhi A, Kasim S. Predictors of adverse in-hospital outcome and recovery in patients with diabetes mellitus and COVID-19 pneumonia in Iraq. *Diabetes Metab Syndr* 2021; **15**: 33-38 [PMID: 33296788 DOI: 10.1016/j.dsx.2020.12.014]

52 **Wargny M**, Potier L, Gourdy P, Pichelin M, Amadou C, Benhamou PY, Bonnet JB, Bordier L, Bourron O, Chaumeil C, Chevalier N, Darmon P, Delenne B, Demarsy D, Dumas M, Dupuy O, Flaus-Furmaniuk A, Gautier JF, Guedj AM, Jeandidier N, Larger E, Le Berre JP, Lungo M, Montanier N, Moulin P, Plat F, Rigalleau V, Robert R, Seret-Bégué D, Sérusclat P, Smati S, Thébaut JF, Tramunt B, Vatier C, Velayoudom FL, Vergès B, Winiszewski P, Zabulon A, Gourraud PA, Roussel R, Cariou B, Hadjadj S; CORONADO investigators. Predictors of hospital discharge and mortality in patients with diabetes and COVID-19: updated results from the nationwide CORONADO study. *Diabetologia* 2021; **64**: 778-794 [PMID: 33599800 DOI: 10.1007/s00125-020-05351-w]

53 **Wong CKH**, Lui DTW, Lui AYC, Kwok ACY, Low MCH, Lau KTK, Au ICH, Xiong X, Chung MSH, Lau EHY, Cowling BJ. Use of DPP4i reduced odds of clinical deterioration and hyperinflammatory syndrome in COVID-19 patients with type 2 diabetes: Propensity score analysis of a territory-wide cohort in Hong Kong. *Diabetes Metab* 2022; **48**: 101307 [PMID: 34863934 DOI: 10.1016/j.diabet.2021.101307]

54 **Dalan R**, Ang LW, Tan WYT, Fong SW, Tay WC, Chan YH, Renia L, Ng LFP, Lye DC, Chew DEK, Young BE. The association of hypertension and diabetes pharmacotherapy with COVID-19 severity and immune signatures: an observational study. *Eur Heart J Cardiovasc Pharmacother* 2021; **7**: e48-e51 [PMID: 32766831 DOI: 10.1093/ehjcvp/pvaa098]

55 **Khunti K**, Knighton P, Zaccardi F, Bakhai C, Barron E, Holman N, Kar P, Meace C, Sattar N, Sharp S, Wareham NJ, Weaver A, Woch E, Young B, Valabhji J. Prescription of glucose-lowering therapies and risk of COVID-19 mortality in people with type 2 diabetes: a nationwide observational study in England. *Lancet Diabetes Endocrinol* 2021; **9**: 293-303 [PMID: 33798464 DOI: 10.1016/S2213-8587(21)00050-4]

56 **Bonora BM**, Avogaro A, Fadini GP. Disentangling conflicting evidence on DPP-4 inhibitors and outcomes of COVID-19: narrative review and meta-analysis. *J Endocrinol Invest* 2021; **44**: 1379-1386 [PMID: 33512688 DOI: 10.1007/s40618-021-01515-6]

57 **Han T**, Ma S, Sun C, Zhang H, Qu G, Chen Y, Cheng C, Chen EL, Ayaz Ahmed M, Kim KY, Manem R, Chen M, Guo Z, Yang H, Yan Y, Zhou Q. Association Between Anti-diabetic Agents and Clinical Outcomes of COVID-19 in Patients with Diabetes: A Systematic Review and Meta-Analysis. *Arch Med Res* 2022; **53**: 186-195 [PMID: 34412904 DOI: 10.1016/j.arcmed.2021.08.002]

58 **Pal R**, Banerjee M, Mukherjee S, Bhogal RS, Kaur A, Bhadada SK. Dipeptidyl peptidase-4 inhibitor use and mortality in COVID-19 patients with diabetes mellitus: an updated systematic review and meta-analysis. *Ther Adv Endocrinol Metab* 2021; **12**: 2042018821996482 [PMID: 33680425 DOI: 10.1177/2042018821996482]

59 **Nguyen NN**, Ho DS, Nguyen HS, Ho DKN, Li HY, Lin CY, Chiu HY, Chen YC. Preadmission use of antidiabetic medications and mortality among patients with COVID-19 having type 2 diabetes: A meta-analysis. *Metabolism* 2022; **131**: 155196 [PMID: 35367460 DOI: 10.1016/j.metabol.2022.155196]

60 **Rakhmat II**, Kusmala YY, Handayani DR, Juliastuti H, Nawangsih EN, Wibowo A, Lim MA, Pranata R. Dipeptidyl peptidase-4 (DPP-4) inhibitor and mortality in coronavirus disease 2019 (COVID-19) - A systematic review, meta-analysis, and meta-regression. *Diabetes Metab Syndr* 2021; **15**: 777-782 [PMID: 33838614 DOI: 10.1016/j.dsx.2021.03.027]

61 **Zein AFMZ**, Raffaello WM. Dipeptidyl peptidase-4 (DPP-IV) inhibitor was associated with mortality reduction in COVID-19 - A systematic review and meta-analysis. *Prim Care Diabetes* 2022; **16**: 162-167 [PMID: 34952805 DOI: 10.1016/j.pcd.2021.12.008]

62 **Patoulias D**, Doumas M. Dipeptidyl Peptidase-4 Inhibitors and COVID-19-Related Deaths among Patients with Type 2 Diabetes Mellitus: A Meta-Analysis of Observational Studies. *Endocrinol Metab (Seoul)* 2021; **36**: 904-908 [PMID: 34311543 DOI: 10.3803/EnM.2021.1048]

63 **Abuhasira R**, Ayalon-Dangur I, Zaslavsky N, Koren R, Keller M, Dicker D, Grossman A. A Randomized Clinical Trial of Linagliptin vs. Standard of Care in Patients Hospitalized With Diabetes and COVID-19. *Front Endocrinol (Lausanne)* 2021; **12**: 794382 [PMID: 35002970 DOI: 10.3389/fendo.2021.794382]

64 **Guardado-Mendoza R**, Garcia-Magaña MA, Martínez-Navarro LJ, Macías-Cervantes HE, Aguilar-Guerrero R, Suárez-Pérez EL, Aguilar-García A. Effect of linagliptin plus insulin in comparison to insulin alone on metabolic control and prognosis in hospitalized patients with SARS-CoV-2 infection. *Sci Rep* 2022; **12**: 536 [PMID: 35017617 DOI: 10.1038/s41598-021-04511-1]

**Footnotes**

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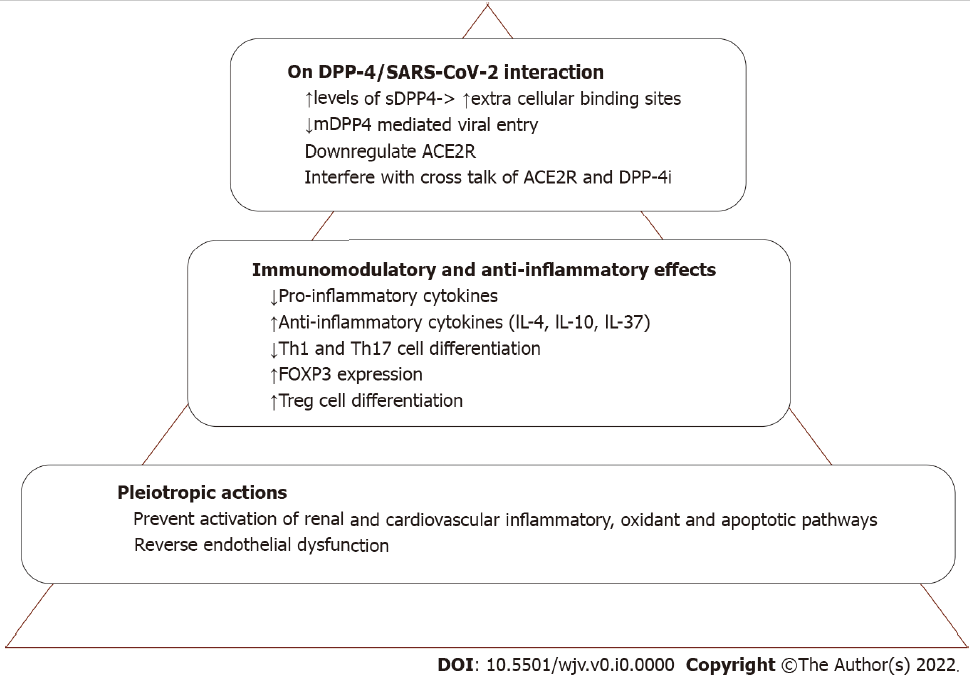
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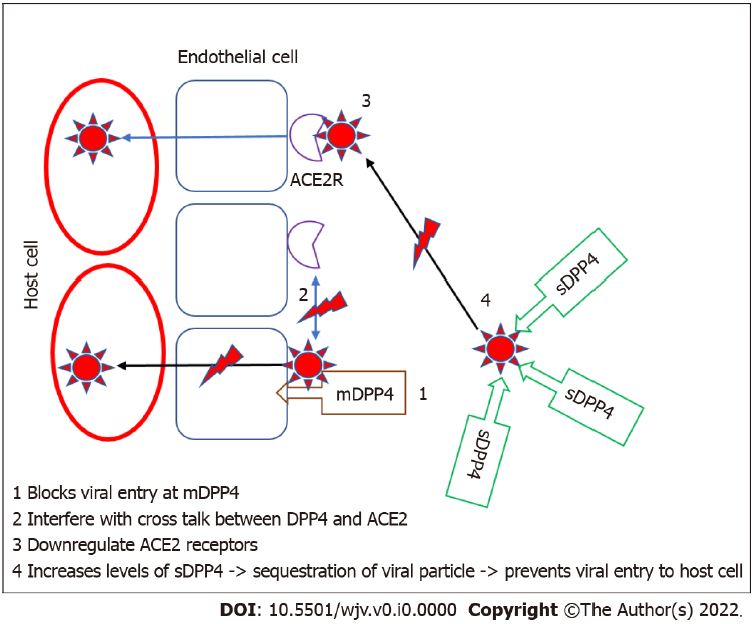
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**Figure Legends**



**Figure 1 Proposed mechanisms of dipeptidyl peptidase-4 inhibitors in coronavirus disease 2019 infection.** ACE2R: Angiotensin converting enzyme 2 receptor; COVID-19: Coronavirus disease 2019; DPP-4: Dipeptidyl peptidase-4; FOXP3: Forkhead box P3; IL: Interleukin; mDPP4: Membrane bound DPP4; sDPP4: Soluble DPP4; TGF-β: Transforming growth factor beta.



**Figure 2 Hypothetical interactions between dipeptidyl peptidase-4 and severe acute respiratory syndrome coronavirus 2 virus.** ACE-2: Angiotensin-converting enzyme 2; ACE2R: Angiotensin converting enzyme 2 receptor; DPP-4: Dipeptidyl peptidase-4; mDPP4: Membrane bound DPP4; sDPP4: Soluble DPP4.

**Table 1 Observation studies assessing** **coronavirus disease 2019 outcomes and dipeptidyl peptidase-4 inhibitors therapy**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Sl no** | **Ref.** | **Design, Location** | **Population** | **Findings** |
| **Studies with neutral outcomes with the use of DPP-4i** | | | | |
| 1 | Fadini *et al*[38], 2020 | RO, Italy | Registry based DM patients with and without COVID-19. Subgroup analysis of proportion of DPP-4i users | Diabetic COVID-19 patients who were on DPP-4i had a similar disease outcome as those who were not |
| 2 | Chen *et al*[39], 2020 | RO, China | Single centre hospitalised COVID-19 patients with DM; DPP-4i users (*n* = 20) compared with nonusers (*n* = 100) | Mortality OR 1.48, 95%CI 0.4-5.53, *P* = 0. 56 |
| 3 | Pérez-Belmonte *et al*[40], 2020 | RO, Spain | Registry based COVID-19 patients with DM. DPP-4i users (*n* = 105) compared with nonusers (*n* = 105) | Composite outcome of ICU admission, mechanical ventilation, or in-hospital death: OR 1.12, 95%CI 0.65-1.95, *P* = 0.675 |
| 4 | Silverii *et al*[41], 2021 | RO, Italy | Registry based all deaths due to COVID-19 infection; Subgroup analysis of DPP-4i users (*n* = 13) *vs* nonusers (*n* = 146) in DM patients | Mortality risk in COVID-19 infection. HR 1.0, 95%CI 0.5-2.1, *P* = 0.56 |
| 5 | Kim *et al*[42], 2020 | RO, Korea | Single centre hospitalised COVID-19 patients with and without DM; Subgroup analysis of DM patients using DPP-4i (*n* = 85) and others (*n* = 235) | Mortality OR 1.47, 95%CI 0.45-4.78, *P* = 0.52; Severe disease OR 1.05, 95%CI 0.44-2.49, *P* = 0.92. |
| 6 | Noh *et al*[43], 2021 | PO, South Korea | Registry based COVID-19 patients with DM; Mortality in DPP-4i users (*n* = 453) compared with nonusers (*n* = 133) | All-cause mortality: HR 0.74, 95%CI 0.43-1.26; Severe disease HR 0.83, 95%CI 0.45-1.53 |
| 7 | Zhou *et al*[44], 2020 | RO, China | Multi-centre, hospitalised COVID-19 patients with DM; Subgroup analysis of DPP-4i users (*n* = 142) *vs* nonusers (*n* = 1257) | 28-d mortality: aHR = 0.44, 95%CI: 0.09-2.11, *P* = 0.31); Secondary outcomes such as septic shock, acute respiratory distress syndrome, organ (kidney, liver, and cardiac) injuries, were also comparable between the two groups |
| 8 | Yan *et al*[47], 2020 | RO, China | Hospitalised COVID-19 patients; Subgroup analysis of DPP-4i use in patients with severe illness | No significant association between use of DPP-4i and COVID-19 severity after adjustment for age, sex, and BMI (OR 0.32, 95%CI 0.02-2.18, *P* = 0.31) |
| 9 | Izzi-Engbeaya *et al*[45], 2021 | RO, United Kingdom | Registry based COVID-19 patients with DM admitted to 3 hospitals (*n* = 337); DPP-4i users (*n* = 93) | Admission to ICU or death OR 1.27 (0.79-2.05) |
| 10 | Israelsen *et al*[46], 2021 | RO, Denmark | Registry based COVID-19 patients with DM; DPP-4i users (*n* = 284) compared with SGLT2i users (*n* = 342) | DPP-4i users- 30-d mortality aRR 2.42 (95%CI 0.99-5.89) when compared with SGLT-2i users. DPP-4i use was not associated with decreased risk of hospital admission |
| **Studies with positive outcomes with the use of DPP-4i** | | | | |
| 1 | Mirani *et al*[48], 2020 | RO, Italy | Single centre hospitalised COVID-19 patients with DM; DPP-4i users (*n*=11) compared with nonusers (*n*=79) | DPP-4i users had lower risk of mortality (aHR 0.13, 95%CI 0.02-0.92; *P* = 0.042) |
| 2 | Solerte *et al*[49], 2020 | RO case control, Italy | Hospitalised COVID-19 patients with DM; Case sitagliptin + standard care (*n* = 169) Controls – age sex matched patients with standard care (*n* = 338) | Mortality: HR 0.44, 95%CI 0.29–0.66, *P* = 0.0001); Admission to ICU: HR: 0.51, 95%CI 0.27-0.95, *P* = 0.03; Mechanical ventilation HR: 0.27, 95% CI 0.11-0.62, *P* = 0.03; Hospital discharges 120 *vs* 89, *P* < 0.01 |
| 3 | Rhee *et al*[50], 2021 | RO, South Korea | Registry based COVID-19 patients with DM; DPP-4i users (*n* = 263) *vs* non users (*n* = 832); Assessed for severity of disease | OR for severe disease was 0.303 (95%CI 0.135-0.682) among DPP-4i users |
| 4 | Nafakhi *et al*[51], 2020 | RO, Iraq | Newly diagnosed COVID-19 pneumonia; Subgroup analysis to assess predictors for adverse outcomes | DPP-4i users had decreased length of ICU stay. (OR 0.3, 95%CI 0.2-3, *P* = 0.04) |
| 5 | Wargny *et al*[52], 2021 | PO, France | Registry based COVID-19 patients with DM. Subgroup analysis of DPP-4i use in patients succumbing to death within 28 days | The need for mechanical ventilation and death within seven days were similar in DPP-4i users compared to nonusers. (OR 0.83, 95%CI 0.65-1.05, *P* = 0.12). Discharge at day 28: OR 1.22, 95%CI 1.02-1.47, *P* = 0.03). |
| 6 | Wong *et al*[53], 2021 | RO, China | Registry based COVID-19 patients with DM (*n* = 1214); DPP-4i users (*n* = 107) compared with others (*n* = 1107) | DPP4i users were associated with lower odds of clinical deterioration (OR 0.71, 95%CI 0.54-0.93, *P* = 0.013), hyperinflammatory syndrome (OR = 0.56, 95%CI 0.45-0.69, *P* < 0.001), invasive mechanical ventilation (OR = 0.30, 95%CI 0.21-0.42, *P* < 0.001), reduced length of hospitalization (-4.82 days, 95%CI-6.80 to -2.84, *P* < 0.001). No difference seen in mortality |
| **Studies with negative outcomes with the use of DPP-4i** | | | | |
| 1 | Dalan *et al*[54], 2021 | RO, Singapore | Single centre hospitalised COVID-19 patients with and without DM; Subgroup analysis of DM patients using DPP-4i (*n* = 27) and others (*n* = 49) | DPP-4i were at higher risk of ICU admission (aRR 4.07, 95%CI 1.42-11.66) and mechanical ventilation (aRR 2.54, 95%CI 0.43-14.99) |
| 2 | Khunti *et al*[55], 2021 | RO, United Kingdom | Registry based Nationwide cohort data; HR of COVID-19-related mortality assessed in patients with diabetes on DPP-4i | HR 1·07 (1·01-1·13) |

COVID-19: Coronavirus disease 2019; DPP-4i: Dipeptidyl peptidase-4 inhibitors; CI: Confidence interval; HR: Hazard ratio; ICU: Intensive care unit; n: Number of patients on DPP-4i; N: Number of patients with diabetes; OR: Odds ratio; PO: Prospective observational; RO: Retrospective observational; RR: Relative risk;

**Table 2 Randomized controlled trials assessing coronavirus disease 2019 outcomes and dipeptidyl peptidase-4 inhibitors therapy**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Sl no** | **Ref.** | **Design, location** | **Comparators** | **Age (mean ± SD)** | **% male** | **Primary outcomes** | **Secondary outcomes** | **Results** |
| 1 | Abuhasira *et al*[63] | Open-label, prospective, multi-centre trial, Germany | Linagliptin 5 mg + standard therapy (*n*=32); Standard therapy (*n* = 32) | 65.5 ± 16; 68.4 ± 11.5 | 65.6%; 53.1% | Time to clinical improvement | Proportion of patients with 2- point clinical improvement at 28 days, mortality at 28 days, length of hospitalization, ICU admissions, and MV | Time to clinical improvement (HR 1.22; 95%CI, 0.70-2.15; *P* = 0.49); In-hospital mortality; (OR 0.56; 95%CI, 0.16-1.93). No difference in secondary outcomes |
| 2 | Guardado-Mendoza *et al*[64] | Parallel double  ‑blind single centre trial, Mexico | LI group (*n* = 35) I group (*n* = 38) | 57 ± 2; 60 ± 2 | 51%; 76% | Need for assisted MV and mortality | Glucose levels and insulin requirements, pulmonary parameters and clinical progression | Reduced risk of assisted MV; (HR 0.258, 95%CI 0.1-0.7, *P* = 0.009), improved blood glucose levels, lower insulin requirements in LI group |

HR: Hazard risk, I: Insulin, LI: Linaglitin plus insulin, MV: Mechanical ventilation, OR: Odds ratio, RR: Relative risk, SD: Standard deviation.