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*MINIREVIEWS*

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

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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

**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.

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## 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.

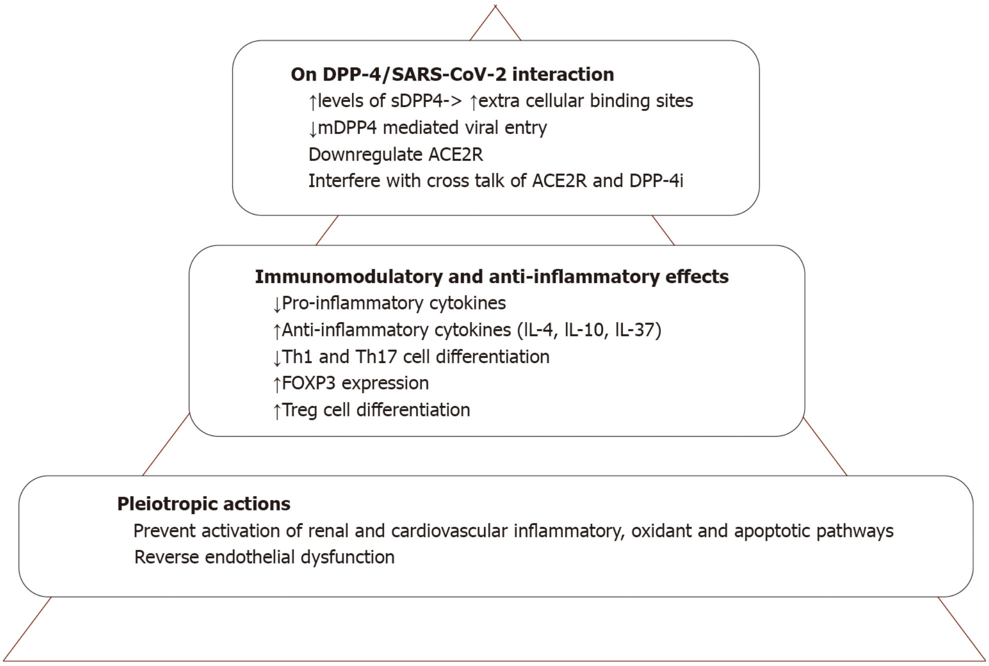

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**Figure 1 Proposed mechanisms of dipeptidyl peptidase-4 inhibitors in coronavirus disease 2019 infection.** ACE2R: Angiotensin converting enzyme 2 receptor; COVID-19: Coronavirus disease 2019; DPP-4: Dipeptidyl peptidase-4; FOXP3: Forkhead box P3;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

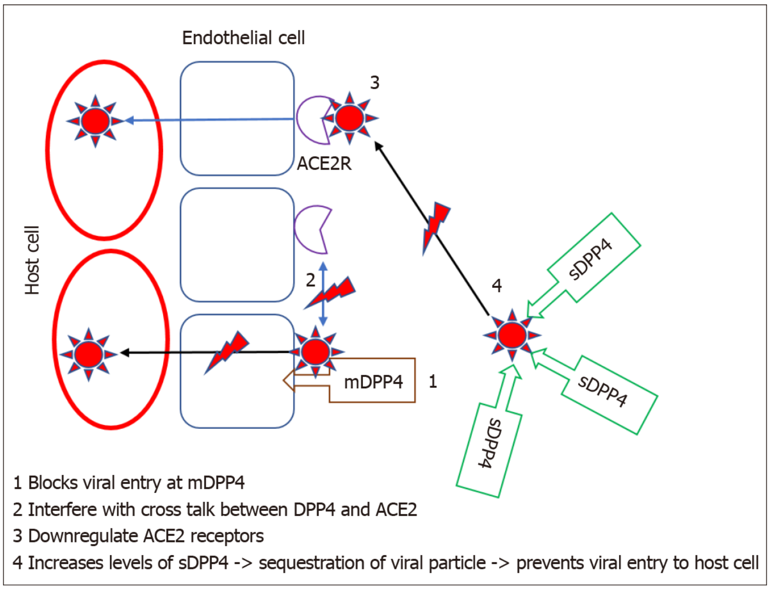

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**Figure 2 Hypothetical interactions between dipeptidyl peptidase-4 and severe acute respiratory syndrome coronavirus 2 virus.** ACE-2: Angiotensin-converting enzyme 2; ACE2R: Angiotensin converting enzyme 2 receptor; DPP-4: Dipeptidyl peptidase-4;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

### *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

**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 d | 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;

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).

**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 d, mortality at 28 d, 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.

The time to clinical improvement within 28 d 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.

## FOOTNOTES

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