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Therapeutic Role of Dipeptidyl Peptidase-4 Inhibitors in COVID-19

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ABSTRACT

Background: Limited retrospective data suggest that dipeptidyl peptidase-4 (DPP-4) inhibitors such as sitagliptin may decrease mortality in patients with type 2 diabetes hospitalized with coronavirus disease 2019 (COVID-19).

Objective: To review the strength of evidence that supports possible therapeutic role of DPP-4 inhibitors in COVID-19.

Methods: PUBMED search until October 10, 2020. Search terms included COVID-19, DPP-4 inhibitors, sitagliptin, CD26, mortality, diabetes. Retrospective studies, pertinent animal investigations and pre-print studies are reviewed.

Results: Three retrospective studies have shown that use of DPP-4 inhibitors was associated with significant mortality reduction of approximately 56-87% in patients with diabetes admitted with COVID-19. In addition, in one of these studies, the use of sitagliptin before hospitalization was associated with greater number of hospital discharges, improvement of clinical status, reduced risk of transfer to intensive care unit (ICU) and need for mechanical ventilation compared with patients who were not receiving sitagliptin. Moreover, there was significant decrease in some pro-inflammatory markers in the sitagliptin group. A small retrospective study of 9 patients who were taking a DPP-4 inhibitor prior to admission did not find any significant effect of DPP-4 inhibitors on mortality and clinical outcomes after hospitalization. Results of another small study suggested increase susceptibility to COVID-19, but not to its severity, in patients taking DPP-4 inhibitors.

Conclusions: Weak evidence derived from observational studies suggests possible beneficial effects of DPP-4 inhibitors use in patients with type 2 diabetes and COVID-19. Randomized trials are urgently needed to clarify the efficacy and safety of DPP-4 inhibitors in patients with COVID-19 with and without type 2 diabetes.

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Introduction

Dipeptidyl peptidase-4 (DPP-4) inhibitors such as sitagliptin are oral anti-diabetic agents approved by the Federal Drug Administration (FDA) for treatment of type 2 diabetes. DPP-4, also called CD26, is the enzyme causing breakdown of the incretin hormones glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP). These 2 incretins normally lower blood glucose levels after meals by stimulation of insulin secretion, inhibition of glucagon production, slowing of gastric emptying, and promotion of early satiety. It follows that inhibition of DPP-4 by DPP-4 inhibitors decreases breakdown of these 2 incretins and prolongs the duration of their anti-hyperglycemic actions [1,2]. Many authors believe that DPP-4 inhibitors could be useful therapeutic agents in patients with COVID-19 with and without type 2 diabetes [3-5]. The purpose of this manuscript is to review available studies related to the relationship between DPP-4 inhibitors and COVID-19.

Effect of DPP-4 Inhibitors on Mortality in COVID-19

To the best of authors' knowledge, only 4 observational studies examined the effects of pre-admission administration of DPP-4 inhibitors on mortality and clinical outcomes in patients with type 2 diabetes and COVID-19. In addition, one study addressed the relationship of use of DPP-4 inhibitors with development of COVID-19 [6,10]. Overview and main findings of these studies are summarized in table 1. The first study conducted by Solerte et al specifically evaluated the effects of sitagliptin on mortality, as primary outcome. This investigation included 338 consecutive patients of whom 169 subjects were taking sitagliptin as part of their anti-diabetic therapy (sitagliptin group) and an equal group of 169 subjects were receiving other diabetes therapy (the control group) [6]. After admission, all oral anti-diabetic agents, including sitagliptin, were discontinued and patients were switched to insulin therapy as per recommendations of American Diabetes Association (ADA) [11]. The use of sitagliptin at the time of hospitalization was associated with significant reduction in mortality; 18% and 37% in the sitagliptin group and control group, respectively (P= 0.0001). Thus, after adjustment for clinically relevant factors (age, sex, comorbidities, and ongoing treatments), pre-admission treatment with sitagliptin was associated with a decreased odds-ratio (OR) for in-hospital death; OR 0.44 (95% CI, 0.29-0.66; P=0.0001). The beneficial effect of pre-admission sitagliptin therapy did not

significantly change as a function of age, gender, body mass index, and hemoglobin A1c levels. In another Italian study, Mirani et al found that use of DPP-4 inhibitors was independently associated with reduction in mortality in hospitalized patients with type 2 diabetes and COVID-19. The hazard ratio (HR), adjusted for age and sex, among users of DPP-4 inhibitors was 0.13 (95% CI, 0.02-0.92). Interestingly, the latter study was the only available investigation in which administration of DPP-4 inhibitors was continued after hospital admission. Using national claims data related to COVID-19 in Korea, Rhee et al reported that use of DPP-4 inhibitors was associated with significant reduction in intensive care or death among patients with diabetes and COVID-19, adjusted OR 0.36 (95% CI, 0.13-0.97). Meanwhile, in a small Italian retrospective study, Fadini et al reported on 85 patients with type 2 diabetes and COVID-19 admitted to the hospital, 9 of whom were taking a DPP-4 inhibitor prior to admission. The authors found no significant differences in mortality rates between users and non-users of DPP-4 inhibitors, 11.1% and 13.9%, respectively; P=0.82. Corresponding rates of ICU admissions were also not significant, 19.2% and 33.3%, respectively; P=0.32. Clearly, it is difficult to draw any conclusion from these results due to the small number of users of DPP-4 inhibitors in this study [6-9].

Effect of Sitagliptin on Other Clinical Outcomes of COVID-19
Other primary end points in the study of Solerte et al [6] included the number of discharged patients and overall amelioration in clinical status. Thus, a greater number of patients were discharged at 30 days in the sitagliptin group than in the control group, 120 and 89 patients, respectively (P=0.008). Moreover, greater proportions of patients in the sitagliptin group than in the control group had overall improvement of clinical score, 60% and 38%, respectively; P=0.0001). Furthermore, the study of Solerte et al [6] showed that pre-admission sitagliptin intake was associated with decreased risk of mechanical ventilation; hazard ratio (HR) 0.27 (95% CI, 0.11-0.65; P= 0.003), and ICU admission; HR 0.51 (95% CI, 0.27-0.95; P= 0.03), compared with the control group. In a small retrospective Chinese study, Yan et al [10] found that use of DPP-4 inhibitors was not associated with clinical severity of COVID-19.

Effect of Sitagliptin on Other Clinical Outcomes of COVID-19
Solerte et al [6] observed that patients who were receiving sitagliptin prior to admission had significant reduction in serum markers of inflammation such as C-reactive protein (CRP) and procalcitonin as well as significant increase in lymphocytic count compared to the control group.

Effect of DPP-4 Inhibitors on Risk to COVID-19
Fadini et al [9] explored whether users of DPP-4 inhibitors might have low risk of COVID-19 infection by comparing the frequency of users of DPP-4 inhibitors in COVID-19 patients with type 2 diabetes versus age- and sex-matched patients with type 2 diabetes without diagnosis of COVID-19. They found no significant difference between the 2 patient groups, 10.6% and 8.8%, respectively. On the contrary, in a Chinese case-control retrospective study, Yan et al [10] reported that use of DPP-4 inhibitors was associated with increased risk of COVID-19 infection; OR being 6.02 (95% CI, 2.3-15.5), but not with increased clinical severity of COVID-19. These data, however, should be interpreted with caution as the number of patients who were using DPP-4 inhibitors was only 6 patients.

Limitations of the Available Studies
The main limitation of available studies of DPP-4 inhibitors in COVID-19 is their non-randomized retrospective design. The latter

design cannot prove a causative role of sitagliptin in mortality reduction, i.e. association does not mean causation. In addition, retrospective studies are frequently limited by imbalance between the study groups at baseline in many confounding factors that may affect outcomes. For instance, in the study of Solerte et al, glycemic control was significantly better in the sitagliptin group than in the control group during hospitalization, as well as at follow-up at day 30, with means blood glucose concentrations at 30 days: 139 and 170 mg/dl, respectively [6]. Since poor glycemic control during hospital stay was shown to be independently associated with poor prognosis in COVID-19 patients, this difference in blood glucose values might partly explain the favorable prognosis observed in the sitagliptin group [12].

Mechanisms of the possible protective effects of DPP-4 inhibitors in COVID-19
The rationale of using DPP-4 inhibitors as treatment for COVID-19 is based on 2 hypotheses. First, COVID-19 is caused by a coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) that uses the angiotensin converting enzyme 2 (ACE2) as receptor and the transmembrane protease serine 2 (TMPRSS2) as co-receptor for host cell binding and penetration. However, Vankadari and Wilce have shown that CD26 could be also involved in binding of SARS-Cov-2 to its target cells. Therefore, inhibition of CD26 by DPP-4 inhibitors could virtually inhibit viral penetration into host cells. Second, both animal and human studies have shown that sitagliptin might exert anti-inflammatory actions. Thus, sitagliptin administration results in inhibition of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and CRP [14-16]. Accordingly, sitagliptin could virtually inhibit the severe inflammatory reaction and cytokine storm that occur in COVID-19 and represent a major cause of death. This hypothesis is in agreement with the findings Solerte et al [6] who observed that patients who were receiving sitagliptin prior to admission had significant reduction in serum markers of inflammation such as CRP and procalcitonin. In addition, in patients with type 2 diabetes, Satoh-Asahara et al [15] have shown that sitagliptin therapy was associated with significant increase in expression of the anti-inflammatory cytokine interleukin-10 (IL-10), a finding that further supports the inflammation-suppressive effects of sitagliptin.

Metformin and COVID-19 Related Mortality
Multiple retrospective studies have shown significant mortality reduction in patients admitted with COVID-19 who were taking metformin, possibly due to its anti-inflammatory effects. The most comprehensive data in this respect was derived from the recent meta-analysis conducted by Kow and Hassan [18]. In the latter study, the authors analyzed data (up to August 8, 2020) of 5 studies including 8,121 patients with diabetes and COVID-19 who were using metformin prior to hospital admission. Pooled analysis revealed a significantly reduced risk for mortality with the use of metformin prior to admission, pooled odds ratio (OR) being 0.62 (95% CI, 0.43-0.89) compared to patients with diabetes who were not using metformin [17,18]. Interestingly, this mortality benefit of metformin was not demonstrated in the studies of DPP-4 inhibitors mentioned above. Thus, in the study of Solerte et al [6], pre-admission therapy with metformin did not have any effects on clinical outcomes. Meanwhile, in the study of Mirani et al [7], there was a trend towards mortality reduction among COVID-19 patients who were taking metformin prior to hospitalization. Yet, this trend did not reach statistical significance; adjusted OR 0.55, 95% CI (0.27-1.11). Nevertheless, further data are needed as studies of both DPP-4 inhibitors and metformin suffer from similar limitations with respect to their non-randomized designs.

Conclusions and Current Directions

It is tempting to speculate that DPP-4 inhibitors such as sitagliptin may have protective effects in COVID-19. This concept is based on results of 3 retrospective investigations showing substantial reduction in mortality in patients with COVID-19 and type 2 diabetes taking DPP-4 inhibitors prior to hospitalization. The decrease in mortality was associated with significant improvement of clinical status and decrease in need for ICU transfer and mechanical ventilation. Moreover, in one study, the DPP-4 inhibitor was continued during hospitalization. Indeed, the latter study reported the highest reduction in mortality in association with the use of in-hospital DPP-4 inhibitors, approximately 87% reduction (table 1). However, another retrospective study failed to demonstrate such benefits in a limited number of 9 patients [6-9]. Nevertheless, there are plausible mechanisms whereby DPP-4 inhibitors could be useful agents for treatment of COVID-19 including their anti-inflammatory actions, and possibly interference with SARS-Cov-2 penetration into host cells through CD26 inhibition. Randomized trials are urgently needed to clarify the therapeutic role of DPP-4 inhibitors in hospitalized patients with COVID-19. It is worthwhile to evaluate patients with and without type 2 diabetes in these trials to see to what extent the beneficial actions of DPP-4 inhibitors are related to their anti-diabetic effects.

Table 1: Retrospective Studies of DPP-4 Inhibitors in COVID-19

Reference	Solerte et al [6]	Mirani et al [7]	Rhee et al [8]	Fadini et al [9]	Yan et al [10]
Country	Italy	Italy	South Korea	Italy	China
Design	Case-control, multicenter	Case series, single center	Claims of COVID-19 in National Review and Assessment Service data base	Retrospective	Case control analysis
Patients	338 hospitalized patients with type 2 diabetes, 169 on sitagliptin	90 hospitalized patients with diabetes including 11 patients on DPP-4 inhibitors	263 patients on DPP-4 inhibitors vs 569 patients on no DPP-4 inhibitors	9 hospitalized patients on DPP-4 inhibitors vs 76 patients on no DPP-4 inhibitors	6 patients on DPP-4 inhibitors and 52 diabetic patients on no DPP-4 inhibitors, and 48,667 control subjects
Effect of DPP-4 inhibitors on mortality	18% mortality sitagliptin vs 37% other patients, HR 0.44 (95% CI, 0.29-0.66; P=0.0001)	Reduction in mortality with DPP-4 inhibitors HR 0.13 (95% CI, 0.02-0.92, P=0.042).	Reduction in risk of death or ICU admission, OR 0.36 (95% CI, 0.13-0.97).	No significant difference in mortality: DPP-4 inhibitors 11.1% vs no DPP-4 inhibitors 13.9% (P=0.82).	Not reported
Effect of DPP-4 inhibitors on other clinical outcomes	Improvement in clinical outcomes 60% sitagliptin vs 38% other patients (P=0.0001) & number of hospital discharges sitagliptin 120 vs other patients 89 discharges (P=0.0008).	Not reported	Not reported	No difference in ICU admissions: DPP-4 inhibitors 33.3% vs no DPP-4inhibitors 19.2% (P=0.32)	No significant association of use of DPP-4 inhibitors and severity of COVID-19
Comments	Reduction in procalcitonin and C-reactive protein in sitagliptin group	Only study in which use of DPP-4 inhibitors were continued after admission	This database is representative of the Korean population		PPP-4 inhibitors associated with Increased risk of COVID-19. OR 6.02 (95% CI, 2.3-15.5)

Abbreviations: HR: hazard ratio, OR: odds ratio, ICU: intensive care unit

Conflicts of interest

The authors have no conflict of interest to declare.

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