SunKrist Publishing
Accelerate Scientific Knowledge in Open Access

SunKrist Endocrinology and Metabolism Research Journal

Research Note *Volume: 1, Issue: 1* *Scientific Knowledge*

Do DPP-4 Inhibitors Protect against COVID-19?

Nasser Mikhail MD*, Soma Wali MD, Laxmi Suthar MD

Endocrinology Division, Department of Medicine, Olive-View UCLA Hospital, David-Geffen-UCLA Medical School, CA, USA.

1. Abstract

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

Objective: To review the strength of evidence that supports possible protective role of sitagliptin in COVID-19.

Methods: PUBMED search until October 5, 2020. Search terms included COVID-19, sitagliptin, DPP-4, CD26, mortality, diabetes. Retrospective studies and pertinent animal and human studies are reviewed.

Results: One retrospective study (n=338) showed that sitagliptin use before hospitalization was associated with significant mortality reduction of approximately 60% in patients with type 2 diabetes and COVID-19. Pre-admission sitagliptin administration was associated with greater number of hospital discharge, 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. In addition, there was significant decrease in some pro-inflammatory markers in the sitagliptin group. Another 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.

Conclusions: Weak evidence from observational studies suggests possible beneficial effects of sitagliptin use before hospital admission in patients with type 2 diabetes and COVID-19. Randomized trials are urgently needed to clarify the efficacy and safety of in-hospital sitagliptin administration in patients with COVID-19 with and without type 2 diabetes.

2. Keywords: Diabetes; COVID-19; DPP-4 inhibitors; Sitagliptin; Mortality; CD26.

3. Introduction

Sitagliptin is an oral anti-diabetic agent approved by the Federal Drug Administration (FDA) in 2006 for treatment of type 2 diabetes [1]. This agent belongs to a class of drugs called DPP-4 inhibitors [2]. 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 [2]. It follows

***Corresponding author:** Nasser Mikhail MD, Endocrinology Division, Department of Medicine, Olive-View UCLA Hospital, David-Geffen-UCLA Medical School, CA, USA, E-mail: nmikhail@dhs.lacounty.gov

Received Date: October 05, 2020; **Accepted Date:** October 14, 2020; **Published Date:** October 16, 2020.

that inhibition of DPP-4 by sitagliptin decreases breakdown of these 2 incretins and prolongs the duration of their anti-hyperglycemic actions [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, particularly sitagliptin and COVID-19.

3.1. Effect of DPP-4 inhibitors on mortality in COVID-19

To the best of author's knowledge, only 2 retrospective studies, both from Italy, 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 [6,7]. The first study conducted by Solerte et al [6] was multi-center and 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) [8]. 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) [6]. 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 0.37 (95% CI, 0.23-0.62; P= 0.0001) [6]. 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 [6]. It should be emphasized that in the study of Solerte et al [6], 44% of patients in the sitagliptin group and 39% of patients in the control group were receiving metformin. Interestingly, pre-admission therapy with metformin did not have any effects on clinical outcomes [6]. The latter finding is in contrast with multiple retrospective studies showing significant mortality reduction in patients admitted with COVID-19 who were taking metformin. In fact, the most comprehensive data in this respect was derived from the recent meta-analysis conducted by Kow and Hassan [9]. 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 [9].

The second study was a much smaller investigation of 85 patients with type 2 diabetes and COVID-19 admitted to the hospital, 9 of whom were taking a DPP-4 inhibitor (specific name was not mentioned) prior to admission [7]. The authors found no significant differences in mortality rates between users of DPP-4 inhibitors and non-users, 11.1% and 13.9%, respectively; P=0.82 [7]. Corresponding rates of ICU admissions were also not significant, 19.2% and 33.3%, respectively; P=0.32 [7]. 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 [7]. In the meantime, the authors explored whether users of DPP-4 inhibitors might have low risk 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. Again, no significant difference was found between the 2 patient groups, 10.6% and 8.8%, respectively [7].

3.2. 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) [6]. 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) [6]. 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.

3.3. Effect of Sitagliptin on Biochemical Markers 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.

3.4. Limitations of the Available Studies

The main limitation of available sitagliptin studies in COVID-19 is their non-randomized retrospective design. The latter design can by no means 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 [6], 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 day 30 being 139 mg/dl and 170 mg/dl, respectively. 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 [10]. It was unclear why the authors did not statistically control for in-hospital blood glucose differences between the 2 study groups [6].

3.5. 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 [11]. However, Vankadari and Wilce [12] 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 [13,14]. Thus, sitagliptin administration results in inhibition of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and CRP [13,14]. 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 [13] 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.

4. 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 a relatively large retrospective study showing substantial reduction in mortality in patients with COVID-19 and type 2 diabetes taking sitagliptin prior to hospitalization [6]. This reduction in mortality was associated with significant improvement of clinical status and decrease in need for ICU transfer and mechanical ventilation [6]. However, another retrospective study failed to demonstrate such benefits in a limited number of 9 patients [7]. Nevertheless, there are plausible mechanisms whereby DPP-4 inhibitors could be useful therapeutic agents in 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 treatment of patients hospitalized for 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.

5. References

1. Januvia (sitagliptin) tablets. Prescribing information. Merk & CO., INC., Whitehouse Station, NJ 08889, USA. 2006.
2. Mikhail N. Safety of dipeptidyl peptidase 4 inhibitors for treatment of type 2 diabetes. Curr Drug Safety. 2011; 6: 304-309.
3. Dastan F, Abedini A, Shahabi S, Kiani A, Ali S, Zare A. Sitagliptin repositioning in SARS-CoV-2: Effects on ACE-2, CD-26, and inflammatory cytokine storms in the lungs. Iran J allergy Asthma Immunol. 2020; 19: 10-12.
4. Mozafari N, Azadi S, Mehdi-Alamdarlou S, et al. Inflammation: A bridge between diabetes and COVID-19, and possible management with sitagliptin. Med Hypotheses. 2020; 143: 110111.
5. Solerte SB, Di Sabatino A, Galli M, Fiorina P. Dipeptidyl peptidase-4 (DPP-4) inhibition in COVID-19. Acta Diabetol. 2020; 57: 779-783.
6. Solerte SB, D'Addio F, Trevisan R, et al. 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.
7. Fadini GP, Morieri ML, Longato E, Bonora BM, Pinelli S, Selmin E, et al. Exposure to dipeptidyl-peptidase-4 inhibitors and COVID-19 among people with type 2 diabetes: A case-control study. Diabetes Obes Metab. 2020.
8. American Diabetes Association. Diabetes care in the hospital: Standards of Medical Care in diabetes. 2020; 43: S193-S201.
9. Kow CS, Hasan SS. Mortality of COVID-19 with preadmission metformin use in patients with diabetes: a meta-analysis. J Med Virol. 2020.
10. Wu J, Huang J, Zhu G, et al. Elevation of blood glucose level predicts worse outcomes in hospitalized patients with COVID-19: a retrospective cohort study. BMJ Open Diabetes Research and Care. 2020; 8.
11. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020; 181: 271-280.
12. 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.

13. Satoh-Asahara N, Sasaki Y, Wada H, Tochiya M, Iguchi A, Reiko N, et al. A dipeptidyl peptidase-4 inhibitor, sitagliptin, exerts anti-inflammatory effects in type 2 diabetic patients. Metabolism. 2013; 62: 347-351.

14. Marques C, Mega C, Gonçalves A, et al. Sitagliptin prevents inflammation and apoptotic cell death in the kidney of type 2 diabetic animals. Mediators Inflamm. 2014.

Citation: Nasser Mikhail, Soma Wali and Laxmi Suthar MD. Do DPP-4 Inhibitors Protect against COVID-19? SunKrist Endocrinol and Metab Res J. 2020; 1: 1003.