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Efficacy and Safety of Sitagliptin in the Treatment of COVID-19

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Abstract

Background: Coronavirus disease 2019 (COVID-19) is associated with a high risk of mortality especially among diabetes mellitus (DM) patients. Effective treatments against COVID-19 can complement the vaccination effort worldwide. Many review articles studied the effects of the dipeptidyl peptidase 4 (DPP-4) inhibitors among COVID-19 patients and found conflicting results. This heterogeneity may be due to different systemic pleiotropic effects of different DPP-4 inhibitors. Sitagliptin appears to be one of the good DPP-4 inhibitors that have antiinflammatory and antithrombotic effect. Therefore, this review assessed the benefits and safety of sitagliptin in the treatment of COVID-19. **Methods**: A detailed literature review using the electronic databases of Pubmed and Google Scholar was conducted during July and August 2021 to find out studies that published in English language and discussed the role of sitagliptin for COVID-19 patients. **Results**: 14 articles were eligible and thus included in this narrative review. Nine of these articles agreed to the benefit of sitagliptin in the treatment of COVID-19, while 3 studies considered sitagliptin as non useful or even risky, and one study was neutral in its conclusion towards the usage of sitagliptin in COVID-19. Only one study focused on the safety of sitagliptin and found that it is safe. **Conclusion**: Sitagliptin has anti-inflammatory, antifibrotic and antiapoptotic properties; such effects may be beneficial in reducing risks of COVID-19. Sitagliptin has good safety and fair benefits to reduce mortality among DM patients with COVID-19. Further randomized clinical trials are needed to confirm these benefits especially among patients without DM.

Keywords
Sitagliptin; COVID-19

Introduction

The world is facing a pandemic of coronavirus disease 2019 (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] COVID-19 is associated with a risk of high mortality, especially among patients with chronic diseases such as diabetes mellitus (DM).[2] DM patients with COVID-19 have a longer hospitalization stay and worse clinical scores and respiratory parameters as compared to patients with non-diabetic patients.[3]

COVID-19 vaccines have been shown to significantly reduce the infection rate and severity of the infection among most COVID-19 patients[4,5]; however, their effectiveness may be reduced against newer variants of SARS-CoV-2 viruses (e.g., delta), which become the dominated ones in many countries.[6] Therefore, effective treatment against COVID-19 is still needed and can complement the vaccination effort worldwide. Unfortunately, till now, no drug was approved to treat COVID-19.[7,8]

Since drug approval is costly and takes a long time, many drugs are repurposed to help in treating patients with COVID-19,[8] such as hydroxychloroquine, remdesivir, favipravir, and tocilizumab; however, only few of them had a proven significant benefit.[9] Therefore, research continued to find out other drugs that can be repurposed for COVID-19 treatment. Human dipeptidyl peptidase 4 (DPP4) was found to be as a functional receptor for the spike protein of the Middle East respiratory syndrome (MERS)-CoV.[10] This finding raised the attention of Iacobellis G during early days of COVID-19, to write a commentary on the possible role of the dipeptidyl peptidase-4 (DPP-4) enzyme in being a functional receptor of the SARS-CoV-2 virus spike protein, besides its important role in regulating immune response and inducing inflammation. DPP-IV inhibitors such as sitagliptin, saxagliptin, vildagliptin, alogliptin, and linagliptin present a potential therapy that could be investigated for repurposing for the treatment of COVID-19.[2]

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Review and meta-analysis articles studied the benefits of the DPP-4 among COVID-19 patients and found conflicting results. Some showed benefits of reducing disease progression,[11,12] the need for intensive care,[13] and even mortality,[11,13,14] while other reviews were either neural to the benefit of DPP-4 inhibitors[15] or found no improvement in clinical outcomes of COVID-19 by the usage of DPP-4 inhibitors.[16] This heterogeneity in results may be because different DPP-4 inhibitors act on different binding sites of the DPP-4 enzymes, thus have different systemic effects and possibly different pleiotropic effects.[17] In this regard, sitagliptin anti-inflammatory and antithrombotic effects appears to be greater or at least similar to other DPP-4 inhibitors.[17,18] Therefore, this review assessed the benefits and safety of sitagliptin in the treatment of COVID-19.

Methods

Search Strategy

A detailed literature review using the electronic databases of Pubmed and Google Scholar was conducted from 20th July to 25th August 2021 based on the following set of keywords: "Sitagliptin" and "COVID-19".

Inclusion Criteria and Study Selection

All articles with exception of review studies that published in English language and focused on the role of sitagliptin for COVID-19 patients were included in the current narrative review study. Studies that discussed the role of DPP4 inhibitors on COVID-19 with no mentioning of sitagliptin in specific were excluded.

Review Method

A manual review for all titles appeared during database search was done by the main authors of this review. Relevant articles in which their titles implied the presence of any indication for studying sitagliptin in COVID-19 through inclusion of certain words such as DPP4 inhibitors, antidiabetics, incretin mimetics, gliptins, sitagliptin, and COVID-19 were retrieved and reviewed. On the other hand, articles were not reviewed if their titles indicated that they

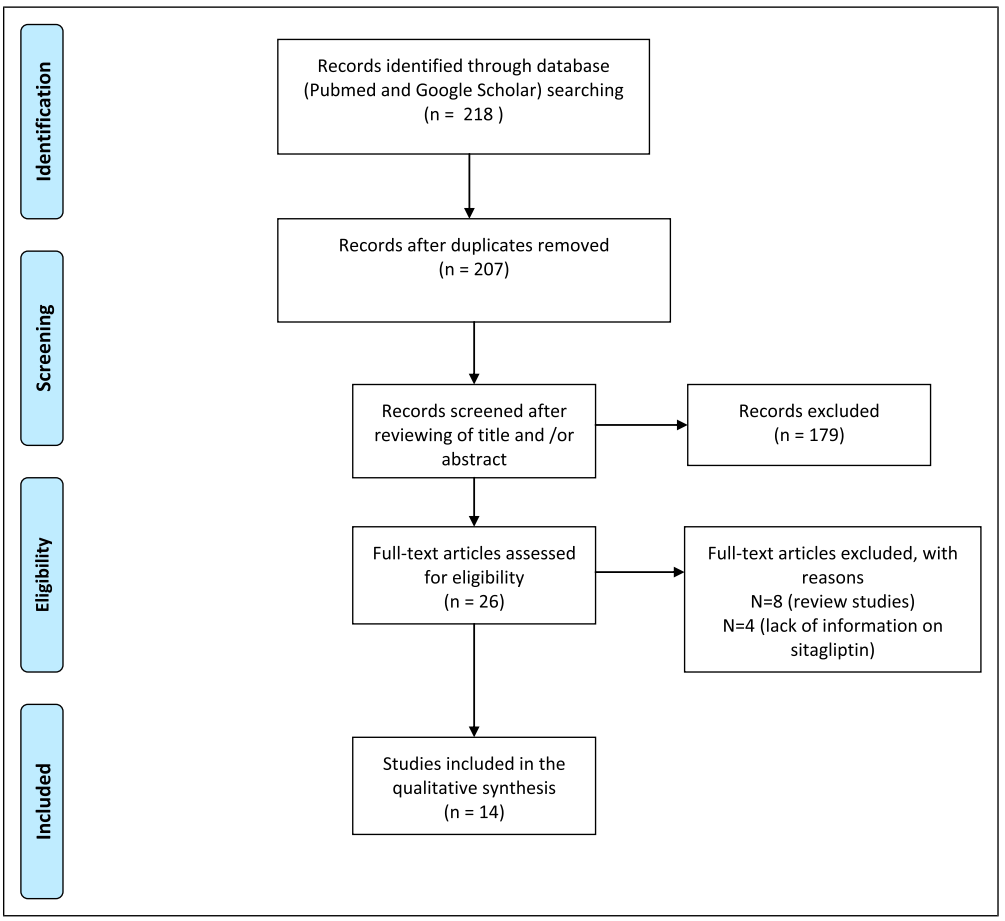

Figure 1. PRISMA 2009 flow diagram.[19]

had been focusing on diseases other than COVID-19 (Figure 1).

Results

We included 14 articles in this narrative review. These included 2 observational studies, 5 letters to the editor, 3 commentaries, 2 communications, 1 perspective, and 1 hypothesis study. Nine of these articles agreed to the benefit of sitagliptin in the treatment of COVID-19, while 3 studies considered sitagliptin as non useful or even risky during COVID-19, and one study was neutral in its conclusion toward the usage of sitagliptin in COVID-19. Only one study focused on the safety of sitagliptin during COVID-19 and found that it is safe (Table 1).

Table 1: Included articles about sitagliptin usage in COVID-19.

Authors' Opinion	Authors of the Study, and year of Publication	Article Type	Main Conclusion
Positive	Dastan F, Abedini A, Shahabi S et al, 2020	Letter to the editor	Sitagliptin may be an effective medication for COVID-19 by directly blocking or indirectly downregulating the expression of SARS-CoV-2 receptors (e.g. CD-26 and ACE-2), in addition to its anti-apoptotic and anti-inflammatory characteristics
	Nauck MA and Meier JJ, 2020	Commentary	Potentially substantial benefits of sitagliptin treatment in COVID-19 patients with type 2 DM. Benefits need confirmation by clinical trial
	Solerte SB, D'Addio F, Trevisan R, et al, 2020	Case-control retrospective study	Sitagliptin treatment at the time of COVID-19 hospitalization was associated with reduced mortality and improved clinical outcomes as compared with standard-of-care treatment. Benefits need confirmation by clinical trial
	Bardaweel SK, Hajjo R, Sabbah DA, 2021	Preliminary communication	Sitagliptin may be beneficial for the treatment of COVID-19 disease, either as monotherapy or in combination with other therapies, especially for diabetic patients and patients with pre-existing cardiovascular conditions who are already at higher risk of COVID-19 mortality
	Solerte SB, D'Addio F, Fiorina P, 2021	Letter to the editor	Sitagliptin may represent a therapeutic option to be considered in patients with type 2 DM who develop COVID-19. It must be used with caution for non-diabetic patients with COVID-19
	Solerte SB, Di Sabatino A, Galli M, Fiorina P, 2020	Perspective	The use of DPP4 inhibitors, such as sitagliptin, in patients with COVID-19 with, or even without type 2 DM may offer a simple way to reduce the virus entry and replication into the airways and to hamper the sustained cytokine storm and inflammation within the lung in patients diagnosed with COVID-19 infection
	Memiş H, Çakır A, DURMUŞ M, et al, 2021	Letter to the editor	Sitagliptin could have beneficial effects in patients with COVID-19, but this needs to be confirmed in randomised controlled trials
	Strollo R and Pozzilli P, 2020	Commentary	There is a potential role for DPP4 inhibition or modulation in one or more steps of COVID-19 immunopathogenesis
	Mozafari N, Azadi S, Mehdi-Alamdarlou S, et al, 2020	Hypothesis study	Sitagliptin might reduce COVID-19 severity because of its multidimensional anti-inflammatory effects among diabetic patients
	Roussel R, Darmon P, Pichelin M, et al, 2021	Retrospective cohort study	The use of DPP-4i (including sitagliptin) for DM management during the COVID-19 pandemic is safe and such drugs should not be discontinued
Negative	Males VK, 2020	Letter to the editor	It should not be presumed that DPP4 inhibitors can reduce the risk of acute respiratory complications in type 2 DM with COVID-19 infection
	Kow CS and Hasan SS, 2020	Letter to the editor	It may be unwise to repurpose sitagliptin for the treatment of COVID-19 because of its thromboembolic risk
	Nar H, Schnapp G, Hucke O, et al, 2021	Communication	This study did not preclude any observed activity of gliptins against SARS-CoV-2
Neutral	Dalan R, 2020	Commentary	No definite conclusions can be made with regards to whether DPP4 inhibitors are beneficial, neutral or harmful in the setting of COVID-19 infection

ACE2 = Angiotensin converting enzyme 2; CD 26 = cluster of differentiation 26; COVID-19 = Coronavirus disease of 2019; DPP4 = Dipeptidyl peptidase 4; DM = Diabetes mellitus; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2.

Effectiveness of Sitagliptin

Suggested Mechanisms for the Effect of Sitagliptin in Patients with COVID-19. Sitagliptin is a DPP4 inhibitor.[20] Animal studies found that DPP4 inhibition can result in a significant rise in soluble DPP-4. The relative abundance of soluble DPP-4 bind Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and thus, can prevent the attachment of coronaviruses to membrane-bound DPP-4, which is known as cluster of differentiation 26 (CD26), in pneumocytes or other cells relevant for viral spread and replication in COVID-19 (Figure 2).[21]

Additionally, it is well known that angiotensin converting enzyme 2 (ACE2) is an important binding site for SARS-Co-V-2 spike protein that is needed for viral entry into the cells.[23] Meanwhile there is a high homology of ACE2 with DPP-4 sequence,[23] in which the expression pattern of DPP4 receptor is analogous with ACE2 across 13 human tissues.[24] On the other hand, many bioinformatic models have been developed, such as models involving a prediction of human-virus protein interaction besides protein docking based on crystal structures. These models found that the SARS-CoV-2 interacts with DPP4 enzyme as a co-receptor, yet, this interaction is less strong than that of SARS-Cov-2 with ACE2.[25] Therefore, two articles suggested that DPP4 may be a co-receptor for SARS-CoV-2 viral entry[24,26] and there is a possible role for sitagliptin to prevent the binding of spike protein and thus viral hijacking and virulence,[20,23,27-29] thereby preventing the injury to the lung and multiorgan failure.[23]

However, Strollo and Pozzilli raised the issue of the low ability of sitagliptin to block SARS-CoV-2 viral entry than linagliptin and alogliptin because it acts as a substrate competitive inhibitor of DPP4 and has a shorter distance (17 amino acids) from one of the predicted binding sites (V341) of SARS-CoV-2. Previous studies showed that sitagliptin was unable to block Middle East respiratory syndrome coronavirus (MERS-CoV) infection.[29] Furthermore, the experimental model of human coronavirus- Erasmus Medical Center (EMC) showed that DPP4 inhibitors did not have the ability to reduce the viral entry and viral receptor interaction was independent of peptidase activity of DPP4.[25] Therefore, sitagliptin may have a limited role in preventing viral entry to the cells and also in decreasing the infection transmission.[25,29]

Anti-inflammatory Immunomodulatory Mechanism. Sitagliptin can block the interaction between caveolin-1 (CAV-1), an integral protein on the membrane of smooth muscle cells, macrophages, and endothelial cells, and DPP4 on antigen presenting cells. The interaction between CAV-1 and DPP4 leads to phosphorylation of caveolin-1; this in turn leads to interleukin-1 receptor-associated serine/threonine kinase 1 (IRAK-1) and Toll-interacting protein (Tollip) dissociation from caveolin-1.[30] NF-kappa-B can be activated after phosphorylation of IRAK-1 (dependent activiation).[30] Additionally, Tollip and IRAK-1 are involved in the signaling pathway of the toll-like receptor (TLR). Therefore, sitagliptin by inhibiting DPP4 has an anti-inflammatory and immunomodulatory properties[20,29,30] through suppressing nuclear factor kappa beta (NF-κB) activation and inflammatory cytokines expression.[20,30] Additionally, experimental model of acute respiratory distress syndrome (ARDS), which represents the

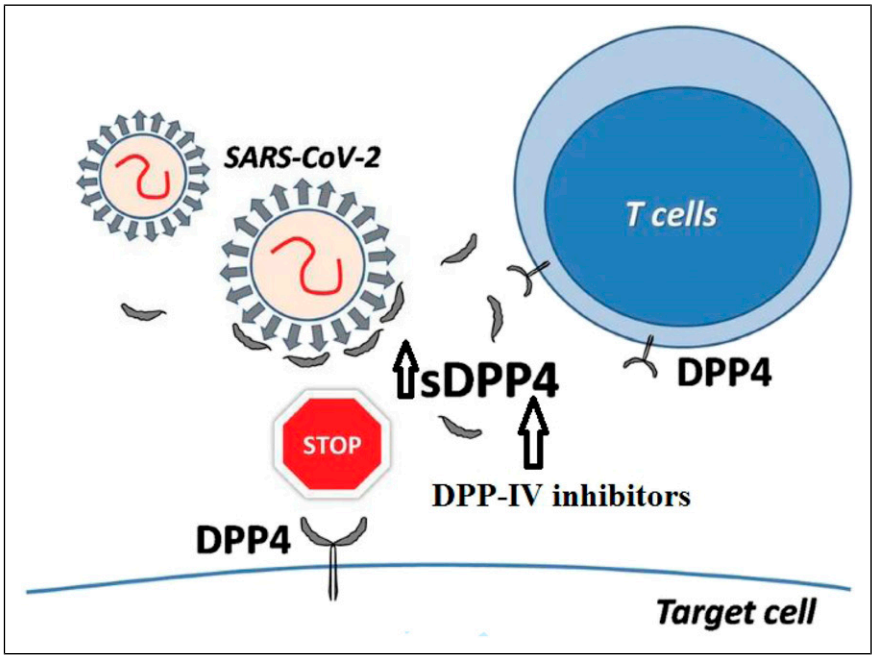

Figure 2. The effect of DPP-4 inhibition on SARS-CoV-2 spread and viral replication.[22]

main death cause of SARSCoV-2 infected patients, showed that DPP4 inhibition by sitagliptin alleviated histological findings of lung injury by inhibiting proinflammatory cytokines IL-1β, TNFα, and IL-6.[25,29] Furthermore, sitagliptin was found to increase the level of anti-inflammatory cytokines like IL-10.[20] Therefore, anti-inflammatory effects of sitagliptin may be effective in preventing the deterioration in lung function[30] and possible progression to extensive tissue damage, organ failure, and death that can result from the cytokine storm,[20,23,26] which is caused by overactive immune response in pneumonia caused by SARS-CoV-2.[20,23] Thus these effects may contribute to the improvement of patient's prognosis when used in early stages of the disease (at the time of hospitalization).[23]

Other Possible Mechanisms of Sitagliptin in COVID-19. In vitro and animal studies showed that sitagliptin may exert antifibrotic properties by inhibiting TGF-ß-induced lung fibroblasts activation.[25,29] Besides that, sitagliptin has antiapoptotic effects, which can be related to the activation of the glucagon like peptide – 1 (GLP-1) receptor. GLP-1 has antiapoptotic actions via the upregulation of B-cell lymphoma protein 2 (Bcl-2) and inhibition of Bcl2 associated X protein (BAX) expression.[20] Since SARS-CoV-2 when infect the lung lead to lung damage through inducing apoptosis of lung epithelial cells, sitagliptin, by its anti-apoptotic properties, may improve the survival of lung cells in COVID-19 patients.[20] Sitagliptin also has the ability to suppress the production of interferon gamma-induced protein 10 (CXCL10) chemokine among AIDS patients; such chemokine is expressed at a high level in the lung bronchoalveolar microenvironment of COVID-19 patients; thus, authors concluded that sitagliptin may be useful in the treatment of COVID-19.[24] In contrast to all of the above benefits of sitagliptin, scientists did an enzymatic assay and found that sitagliptin has limited ability to inhibit the main protease of the Novel SARS-CoV-2 Virus (Mpro) catalytic activity. Thus authors of that study conclude that sitagliptin may not be useful for the treatment of COVID-19.[31]

Human Studies for the Role of Sitagliptin in COVID-19. A case-control multicenter study[23] included 338 patients with type 2 and had COVID-19 pneumonia; such patients exhibited an oxygen saturation <95% when breathing ambient air or when receiving oxygen support who admitted to hospitals in Northern of Italy from the first of March to the end of April 2020. The treatment of all T2DM patients was shifted to insulin as a standard of care for hospitalized T2DM patients due to COVID-19. Insulin therapy was administered according to the "modified Yale insulin infusion protocol." Sitagliptin was added to insulin therapy at the time of hospitalization for 169 patients, while 169 patients were treated by a standard of care. Treatment with sitagliptin was associated with reduced mortality (18% vs. 37% deaths; hazard ratio .44 [95% CI 0.29-.66]; P = .0001), this benefit was also confirmed after adjustment for clinically relevant factors (age, sex, comorbidities, and ongoing treatments), and with an improvement in clinical outcomes, defined as an increase in at least two points on a seven-category modified ordinal scale (60% vs. 38% of improved patients; P = .0001), and with a greater number of hospital discharges (120 vs. 89; P = .0008) compared with patients receiving standard of care, respectively. Besides that, laboratory findings including C-Reactive protein, D-Dimer, and lactate dehydrogenase (LDH) were significantly lower in sitagliptin treated patients. This study had many limitations such as its observational study design, the baseline difference in some of the inflammatory markers between the two studied groups, and the lack of information about the need for mechanical ventilator among the enrolled participants.[23]

Another study involved a secondary analysis of the CORONADO study (CORONAvirus and Diabetes Outcomes).[32] The CORONADO study was a retrospective cohort study to determine the prognosis of people with type 2 DM admitted to French hospitals for COVID-19 and diabetes from 10 March to 10 April 2020. The study population consisted of 2449 patients with T2DM who used at least one anti-diabetic agents; among them, 596 were using DPP-4 inhibitors (24.3%), mainly sitagliptin (n = 424; 17.2%). Patients were divided into 2 groups: those using DPP4 inhibitors and those using anti-diabetic agents other than DPP4 inhibitors. On the day of admission there was no major significant difference at baseline level in clinical (sign and symptoms of COVID-19) and laboratory (D-Dimer, lymphocyte count, LDH, fibrinogen, and platelet count) parameters with the exception of slightly higher blood glucose and CRP values for patients on DPP4 inhibitors [28 = 31]. In this secondary analysis, the need for mechanical ventilation and mortality rate within 7-28 days of admission were the main studied outcomes.[32] There was a trend toward a mild and non significant reduction in death and non significant increase in the need for intermittent mechanical ventilator (9.7% vs. 11.7%, P value = .2048; 19.1 vs. 18.5%, P value = .7169) on day 7 and day 28 (18.1% vs. 21.8%, P value = .0561; 20.3% vs. 19.2% P value = .5527), respectively among sitagliptin users as compared with non-sitagliptin users.[32] However, the association between the use of DPP-4 inhibitors and these outcomes was not found after doing propensity analysis, even after further adjustment for kidney function (i.e. estimated glomerular filtration rate values), DM duration, and HbA1c at day 7 after admission. Therefore, the current findings did not identify any association between treatment with sitagliptin (or any DPP-4 inhibitors) and severe outcomes of COVID-19 in patients with T2DM admitted to hospitals.[32] However, there are major limitations in this study including its observational design and inability to study the relationship between in-hospital exposure to any specific drug, including DPP-4 inhibitors and outcomes, besides that about 20% of patients were shifted from DPP-4

inhibitors to insulin therapy upon admission to hospital.[32] On the other hand, adherence to DPP-4 inhibitors during hospital admission for included patients was not calculated.[32]

Safety of Sitagliptin

The action of sitagliptin to suppress T cell proliferation and production of proinflammatory cytokine may be a double edge sword because in COVID-19 infection, SARS Co-V has been shown to infect T cells by its spike protein although it is not clear whether the virus replicates inside the T cells or it leads to apoptosis. Moreover, decreases in the counts of CD3 +, $CD4^+$, $CD8^+$ T cells, and NK cells, as well as increases in the CD4/CD8 ratio in COVID-19 have been reported to correlate with the severity of infection. Besides that regulatory T cells which have a significant role in autoimmune diseases did not have an important role in COVID-19. Therefore, it is possible that the baseline suppressed T cell immunity secondary to sitagliptin may be a disadvantage in COVID-19 infection and lead to a more severe disease.[25] The issue of increasing the risk of infection by the use of sitagliptin was raised by Males VK in his letter to editor based on the results of pharmacovigilance study and two in vitro studies that found a reduction of T-cell activity by these agents.[33] However, such result was not confirmed by meta-analysis of randomized controlled clinical trials.[34] Additionally, the increase in infection risk was not detected in human studies, at which no significant difference was found in sign and symptoms of COVID-19 between T2DM patients on DPP4 inhibitors (sitagliptin, vildagliptin, and saxagliptin) and those using other anti-diabetic agents.[32]

The issue for hypercoagulability risk due to the use of sitagliptin in COVID-19 patients was raised in a commentary article. The loss of DPP4 activity is associated with a prothrombotic state in myocardial microvessels and in human umbilical vein endothelial cells due to the upregulation of the procoagulant tissue factor. This factor may be a risk in COVID-19 patients who were at high risk of developing arterial and venous thrombosis.[25] However, such thrombotic risk by sitagliptin was based on results from diseases other than COVID-19 such as myocardial infarction. Additionally, a pharmacovigilance study found a higher reporting of venous thromboembolism events among patients using DPP-4 inhibitors compared with other antidiabetic agents except for insulin, with a proportional reporting ratio of 2·0 for DPP4i and 3.2 for sitagliptin (95% confidence interval 2.8-3.7).[35] However, only limited information can be obtained from the pharmacovigilance studies about the medical and medication histories for patients with the reported side effects make the guaranteed conclusions impossible.[35] Indeed, the hypercoagulability state has been associated with a late stage of COVID-19, and it has not been clarified whether it is directly induced by a viral infection of endothelial cells or indirectly through the inflammatory and immune processes.[26] In both cases, the use of sitagliptin may have some benefits by reducing viral entry and the inflammatory response.[26] Additionally, there was no major significant difference at baseline level in the value of main laboratory tests of coagulation among COVID-19 patients (D-Dimer and fibrinogen) at the day of hospital admission between T2DM patients using DPP4i and those using other anti-diabetic agents.[32] Furthermore, in a retrospective cohort study, D-Dimer level was significantly reduced when sitagliptin used as add-on therapy to standard of care for T2DM patients who admitted to hospital with COVID-19.[23]

> "These data supported the safe use of sitagliptin for treating DM during the COVID-19 pandemic and it should not be discontinued".[32]

Conclusion

Sitagliptin has many pleiotropic effects including anti-inflammatory, antifibrotic and antiapoptotic properties; such effects may be beneficial in reducing risks of COVID-19. Limited observational studies revealed safety and fair benefits to reduce mortality among diabetic patients with COVID-19. Randomized clinical trials are needed to confirm these benefits of sitagliptin in the treatment of COVID-19 among patients with or without type 2 DM.

Declaration of conflicting interests

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