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Challenge of Administering Antidiabetic Medications to Patients with Diabetes Who Have COVID-19

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Abstract

The coronavirus disease 2019 (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a previously unrecognized viral illness with high infectivity that has sparked a global crisis. Poorly controlled diabetes was demonstrated to be a crucial risk factor for poor COVID-19 outcomes. COVID-19 infections are associated with severe metabolic dysfunctions, new-onset diabetes, and increased thrombotic events against the backdrop of aberrant endothelial function. The current body of evidence suggests that when hyperglycemia interacts with other risk factors, it might modify immune and inflammatory responses such that individuals become susceptible to severe COVID-19 infection and worse outcomes including higher mortality. Apart from their glucose-lowering actions, the pleiotropic effects of antidiabetic medications can inhibit viral action, attenuate endothelial dysfunction, ameliorate oxidant effects, and modulate inflammatory and immune responses during COVID-19 infections. These actions make antidiabetic medications feasible candidates for drug repurposing to combat the SARS-CoV-2-induced tsunami in diabetic COVID-19 patients. This review discusses the association between diabetes and COVID-19, pathophysiology of the disease in diabetes, and therapeutic potential of antidiabetic medications for diabetic patients during the current COVID-19 pandemic. Given the short history of human infection with SARS-CoV-2, the information provided by recent studies is limited. Hence, further investigations of the optimal management of patients with diabetes who are affected by COVID-19 are warranted. (J Intern Med Taiwan 2022; 33: 110-127)

Key Words: Diabetes, COVID-19, SARS-CoV-2, Antidiabetic medications, Hyperglycemia

Introduction

In early 2020, the new highly infectious organism known as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is the novel coronavirus that causes coronavirus disease 2019 (COVID-19), was formally declared as a public health emergency by the World Health Organization[1]. The prevalence of diabetes is high, and diabetes is among the most common comorbidities observed in patients infected with COVID-19[2]. Angiotensin-converting enzyme 2 (ACE2) in human cells is the main entry receptor for SARS-CoV-2, which are highly expressed in multiple organ systems[3]. Hence, SARS-CoV-2 may cause pleiotropic alterations of glucose metabolism that complicate the pathophysiology of pre-existing diabetes or give rise to a new disease mechanism.

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Patients with diabetes infected with COVID-19 are more prone to progress to severe or critical conditions with higher mortality rates relative to patients without diabetes, and both hyperglycemia and pre-existing diabetes are independent predictors for COVID-19 mortality[4]. An initial mild presentation of SARS-CoV-2 infection may be hidden during the assessment of COVID-19 severity among patients with diabetes, suggesting the absence of classic signs and clinical symptoms, and this may lead to a life-threatening delay in the provision of required care[5]. Moreover, diabetes-induced abnormalities, such as underlying metabolic disorders, immunological changes, and low-grade systemic inflammation may predispose these patients to infectious events of greater severity[6].

This review discusses the basic and clinical science spanning the intersections of diabetes with COVID-19, and it emphasizes clinical relevance, pathophysiology of COVID-19 in diabetes, and therapeutic potential of antidiabetic medications during the current COVID-19 pandemic.

Potential mechanisms

Although the mechanisms linking COVID-19 infection and increased susceptibility to worsening diabetic complications remain largely unclear, many hypotheses were proposed to explain how COVID-19 infection damages beta-cell function, including direct attack of beta cells, bystander effects on beta cells due to infection of surrounding cells, and systemic effects of COVID-19 with either direct or indirect effects on beta cells[7]. The virus was demonstrated to be capable of entering islet cells through the use of ACE2 as its receptor, leading to damage of insulin-producing beta cells and, subsequently, insulin deficiency that causes acute diabetes in patients with SARS-CoV-2 infections[8]. Moreover, proinflammatory cytokines play essential roles in the pathogenesis of both diabetes and COVID-19, driving beta cell dysfunction, damage, and death in diabetes through intrinsic cellular signaling pathways and the augmentation of the islet immune cell response[7]. Hence, in predisposed individuals, local islet inflammation associated with COVID-19 may theoretically result in increased islet autoimmunity. Finally, research suggests that severe acute illness and chronic systemic inflammation lead to increased systemic insulin resistance (IR) and gluconeogenic stress hormones, which give rise to increased demand on beta cells and influence insulin secretion[9].

Inflammation

Diabetes can increase susceptibility and exacerbate disease severity following COVID-19 infection because of a compromised innate immune response. SARS-CoV-2 infection can increase the levels of inflammatory mediators, which can increase the interstitial and/or vascular permeability of proinflammatory products[10]. Moreover, SARS-CoV-2 infection is associated with increased reactive oxygen species (ROS) production[10]. ROS production and viral activation of the renin–angiotensin–aldosterone system (RAAS) causes IR, hyperglycemia, and even vascular endothelial damage, all of which contribute to cardiovascular and all-cause mortality following SARS-CoV-2 infection[10].

Glucose metabolism

Both beta cells and hepatocytes can be infected by SARS-CoV-2 through ACE2, which may result in the progression of IR and impaired insulin secretion and, consequently, worsening hyperglycemia during an acute infection[11]. Moreover, in the long term, infected beta cells can trigger beta-cell autoimmunity, which may elicit new-onset diabetes (NOD) in susceptible subjects[11]. SARS-CoV-2 infection in an individual with diabetes can trigger stress and increase the secretion of glucocorticoid and catecholamines, which may result in increased blood glucose, abnormal glucose variability, and

diabetic complications[12]. COVID-19 infection can increase the risk of both diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state in individuals with or without pre-existing diabetes[13]. Nevertheless, further investigations must be conducted to clarify whether such alterations of glucose metabolism that occur with the sudden onset of severe COVID-19 will persist or remit when the infection resolves.

New-onset diabetes

Studies have explored the concept of virus-associated diabetes. Viral infections play a causative role in type 1 diabetes[14]. Similarly, despite the absence of pre-existing diabetes, the occurrence of NOD was reported in patients with COVID-19 following SARS-CoV-2 infection[15,16]. Studies have indicated that SARS-CoV-2 infection downregulates ACE2, resulting in the overactivation of angiotensin II and reduction of angiotensin 1-7 through the activation of the RAAS pathway; this can lead to a cytokine storm, which results in the excessive synthesis and secretion of proinflammatory cytokines/markers, leading to damage of the insulin-producing beta cells[17]. Subsequently, insulin deficiency will occur, which may partially elucidate NOD in patients with SARS-CoV-2 infections[8].

In a study of 184 patients hospitalized for COVID-19, 29 patients developed new and persistent hyperglycemia during COVID-19 treatment, and some of them presented with normal glycated hemoglobin (HbA1c) concentration on admission[18]. During the COVID-19 pandemic, more patients presented with ketoacidosis than expected, suggesting an increase in the numbers of patients with NOD[19]. Notably, studies have reported that relative to pre-existing diabetes, COVID-19-induced hyperglycemia without diabetes may result in a significant increase in mortality[20,21]. Nevertheless, the role of COVID-19 in altering the underlying pathophysiology and natural history of diabetes has yet to be clarified. Notably, SARS-CoV infection in patients with undiagnosed diabetes is associated with the development of hyperglycemia that was demonstrated to persist for 3 years after SARS recovery, suggesting insulin deficiency owing to damage in beta cells[8].

Although the coronaviruses are not on the list of viruses involved in the etiopathogenesis of diabetes, SARS-CoV-2 may be a causative environmental stimulus for the development of diabetes. Given the short history of human infection with SARS-CoV-2, further large-scale studies are necessary to clarify the development of COVID-19-induced diabetes, nature history of the disease's progression, and appropriate management measures.

Susceptibility and SARS-CoV-2 severity

Two case series examined critically ill patients with COVID-19 infection who were admitted to intensive care unit (ICU), and a diabetes prevalence of 33% and 58% was reported[22,23], suggesting an association between severe COVID-19 and diabetes. Drugs used to treat SARS-CoV-2 infection were reported to induce beta-cell damage, IR, and lipodystrophy, thereby contributing to worsening hyperglycemia[24]. Moreover, ROS, endothelial damage, and glucotoxicity caused by inflammatory cytokines contribute to an increased risk of thromboembolic complications and damage to vital organs in patients with diabetes who are infected with COVID-19[10]. Notably, the risk of COVID-19 reinfection may be high in patients with uncontrolled diabetes because of the impairment of the adaptive immune response[24]. However, studies have not yet verified whether diabetes-related changes that occur during severe COVID-19 will disappear or persist after the disease has resolved[25]; to this end, long-term studies should be conducted.

Antidiabetic medications

Antidiabetic medications used to control dia-

betes may have effects on COVID-19 pathogenesis, and these effects can extend beyond their glucose-lowering actions and play a role in mitigating progression to severe complications. These potential benefits stem from the modification of mechanisms associated with the pathophysiology of adverse complications of COVID-19, which modulates ACE2 expression to lower inflammatory markers and improve coagulopathy. Moreover, some antidiabetic medications may also provide protection to major organs commonly affected by COVID-19. During the ongoing COVID-19 pandemic, no standard recommendations are available to guide diabetes management to minimize the disruption of stable metabolic state, maintain optimal glycemic control, and prevent adverse glycemic events, particularly for patients with diabetes who have concurrent COVID-19 infection. A study reported that every 1% reduction in HbA1c automatically translates to a 21% decreased risk of developing severe COVID-19[26]. Hence, it is necessary to re-examine current knowledge of these agents and investigate their potential benefits in treating diabetic patients during the pandemic (Table 1).

Metformin

Metformin, which is the most prescribed oral antidiabetic medication, may have multiple beneficial effects beyond its glucose-lowering actions, such as the suppression of the production of proinflammatory cytokines through activated macrophages, the formation of neutrophil extracellular traps, and the immune responses of pathogenic T helper (Th) 1 and Th17; therefore, metformin could suppress the cytokine storm associated with severe COVID-19[27]. Metformin may reduce plasminogen activator inhibitor-1, factor VII levels, and C-reactive proteins (CRPs), and it may have direct effects on fibrin structure/function and platelet stabilization, contributing to a lower coagulation risk[28]. Moreover, metformin stimulates adenosine monophosphate (AMP) activated protein kinase, leading to the direct phosphorylation of the ACE2 receptor[29]. Hence, this modification of ACE2 may lead to conformational changes of the SARS-CoV-2 binding site to ACE2 receptors and, subsequently, reduce SARS-CoV-2 viral recognition[29]. Several studies have demonstrated that metformin can directly work on Na^+/H^+ exchangers and/or vacuolar ATPase, which are 2 crucial membrane compartments for the maintenance and regulation of endosomal acidic pH; this results in the inhibition of viral infection through an increase in the cellular pH that interferes with the endocytic cycle[30]. Moreover, metformin can reverse established lung fibrosis; therefore, it was proposed as an effective treatment for COVID-19-related pulmonary fibrosis[30].

Several meta-analyses have assessed metformin use for patients with diabetes who have COVID-19[31-33]. Several retrospective studies of patients with Type 2 diabetes (T2D) who were hospitalized for COVID-19 have suggested that metformin is associated with a reduced mortality rate[31]. Moreover, a meta-analysis reported that metformin users exhibited a 25% overall reduction of mortality ($P < 0.00001$) relative to non-metformin users[31]. Similarly, a meta-analysis of 5 retrospective cohort studies revealed that metformin is associated with a significant 46% reduction in mortality ($P = 0.02$) among patients with COVID-19[32]. A meta-analysis of 32 observational studies indicated that metformin reduces the risk of SARS-CoV-2 mortality (odds ratio [OR], 0.56; $P < 0.001$; 22 studies) but not disease severity (OR, 0.85; $P = 0.077$; 15 studies) [33]. Moreover, in the subgroup analysis, metformin reduced the risk of mortality (OR, 0.69; $P = 0.002$) and severity (OR, 0.83; $P = 0.023$) in patients aged 70 years or older[33].

A retrospective cohort study demonstrated that metformin use significantly reduces hospitalization rates (relative hazard [RH] = 0.71), mortality (RH = 0.34) and severe coronavirus infection (RH = 0.32)

Table 1. Antidiabetic medication recommendations for patients with type 2 diabetes and concurrent COVID-19

Drug class	Possible mechanisms of protection	Beneficial effects	Adverse effects	Recommendations
Metformin	Decreases various proinflammatory cytokines[27] Lowers coagulation to reduce thrombosis[28] Reduces viral recognition through ACE2 receptor phosphorylation [29] Influences endosomal Na^+/H^+ exchanger to inhibit viral endocytosis[30] Reverses established lung fibrosis[30]	Reduction in mortality rate[31-35,37] Reduction in hospitalization and severe infection[34]	Higher incidence of acidosis because of likelihood of hemodynamic instability among hospitalized patients; acidosis is significantly correlated with dosage, compromised kidney, and severe COVID-19 illness[36]	Continue metformin therapy and monitoring of patient for acidosis and deterioration of renal function Adhere to standard guidelines on sick-day rules that increases the risk of dehydration; however, remains strongly advised if the patient is at risk of dehydration
Thiazolidinediones	Inhibits inflammatory immune responses[38] Reduces risk of thrombosis through influence of platelet and coagulation pathways[39] Upregulates ACE2 expression to control the ongoing inflammation[40]	No clinical data	May precipitate peripheral edema and increase risk of heart failure because of fluid retention[42]	Although both beneficial and harmful effects reported, thiazolidinediones should be discontinued for hospitalized patients with COVID-19 who are at risk of acute heart failure and for patients with moderate-to-severe symptoms or signs of angina or advanced heart failure
Sulfonylureas	No clinical data	No clinical data	Risk of hypoglycemia Potential adverse cardiovascular effect in patients with severe illnesses who are at increased risk of myocardial injury, particularly those taking nonselective drugs[51,52]	Discontinue sulfonylureas for hospitalized patients with COVID-19, particularly those who have irregular diets or exhibit COVID-19-associated cardiovascular risk and severe illnesses
Glinide	No clinical data	No clinical data	Potential adverse cardiovascular effect because of mechanisms similar to those of sulfonylureas[51,52]	Discontinue glinide for hospitalized patients with COVID-19, particularly in those who have irregular diets or exhibit COVID-19-associated cardiovascular risk and severe illnesses
Alpha-glucosidase inhibitors	Reduces oxidative stress, carotid intima-media thickening, inflammation, and cardiac interstitial fibrosis and improves endothelial function[53]	No clinical data	Mainly affects postprandial glucose; effects on fasting glucose are limited	May be temporarily discontinued for all hospitalized patients (except stable patients) with COVID-19 who are expected to eat regularly
DPP-4 inhibitors	Interferes with the interaction between SARS-CoV-2 spike S1 protein and human DPP-4 [61] Limits COVID-19 viral proliferation[61] Reduces proinflammatory cytokines and curbs the inflammatory storm [61]	Controversial; some reported reduction in mortality[59-62], whereas other reported no alteration in severity and mortality[64] No changes to mortality for preadmission use[61] No reduction in mortality for ICU admission use[46,63]	Mainly affects postprandial glucose[54] Sitagliptin may increases risk of venous thromboembolism[55] Vildagliptin may increase interstitial lung injury[56]	Continue DPP-4 inhibitor therapy for patients with COVID-19; but caution is advised for patients who are at risk of venous thromboembolism and interstitial lung injury

Table 1. Antidiabetic medication recommendations for patients with type 2 diabetes and concurrent COVID-19 (Continued)

Drug class	Possible mechanisms of protection	Beneficial effects	Adverse effects	Recommendations
GLP-1 receptor agonists	Reduces inflammatory cytokines and infiltration of immune cells in multisystem organs[10] Modifies risk factors for severe COVID-19 complications[66] and reduces mortality[69]	No clinical data	May sustain attenuation in appetite sensations and dietary energy intake, increase risk of dehydration, and cause gastrointestinal intolerance[72]	Temporary suspension of GLP-1 receptor agonist is advised for all hospitalized patients with COVID-19 (except stable patients) who are expected to eat regularly and do not exhibit associated gastrointestinal symptoms Ensure adequate fluid intake if there is no contraindication
SGLT-2i	Exerts anti-inflammatory action to reduce the dysregulated process of cytokine storms[29,73] Reduces COVID-19 viral load[73] Improves interstitial lung oedema and hypoxemia and provides cellular protection[74]	Favorable[73,74] or deleterious effects[10] on clinical outcomes remains unclear	May precipitate DKA, thereby increasing risk of acute kidney injury, volume depletion, and urinary tract infection[10]	SGLT-2i may be continued for patients with asymptomatic or mild COVID-19 to control blood glucose and take advantage of its potential mechanistic effects beyond its glucose-lowering effect. However, caution is recommended for patients with more severe COVID-19 who require hospitalization. SGLT-2i should also be suspended for patients who could be at increased risk of DKA
Insulin	Reduces inflammatory markers[78] Downregulates ACE2 receptors[79]	Beneficial[81] or harmful[82–84] effects remains unclear and controversial	Risk of hypoglycemia Potential weight-gain effect	Continue insulin therapy for patients with COVID-19, particularly those who are critically unwell or have late-stage COVID-19 Intensive self-monitoring of blood glucose or implementation of continuous glucose monitoring during insulin therapy Adjust insulin dose with caution according to diabetes type and comorbidity and severity of infection to achieve therapeutic goal

Abbreviations: ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; ICU, intensive care unit; GLP-1, glucagon-like peptide-1; DPP-4, dipeptidyl peptidase-4; SGLT-2i, sodium-glucose co-transporter 2 inhibitor; DKA, diabetic ketoacidosis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

among older minority patients with COVID-19[34]. Similar results were observed among nursing home residents with SARS-CoV-2 infection, indicating that metformin is associated with decreased 30-day mortality, which could be related to its mammalian targeting of rapamycin inhibition[35]. However, a retrospective cohort study of 1213 hospitalized patients with pre-existing diabetes who have COVID-19 suggested that metformin treatment is significantly associated with a higher incidence of acidosis (particularly for patients with severe COVID-19) but not mortality, which is significantly correlated with high metformin dosage, compromised kidney function, and severe COVID-19[36].

Although metformin can reduce inflammation and provide cardioprotection for patients with diabetes who have COVID-19, researchers have recommended the continuation of metformin therapy in conjunction with the continual monitoring of patients for acidosis and deterioration of renal function[36]. Notably, metformin use prior to COVID-19 diagnosis was reported to be significantly associated with reduced mortality among patients with diabetes who have COVID-19 (OR, 0.33; $P = 0.0210$), whereas prior insulin use did not affect mortality[37]. Moreover, the beneficial effect of metformin persisted even after correcting for other COVID-19 risk factors such as age, sex, obesity, hypertension, chronic kidney disease (CKD) and heart failure (HF) [37].

Because of the possible biases in retrospective observational studies, and the divergent findings derived from such studies, definitive answers will only be provided by randomized controlled trials (RTCs). For this reason, at least two parallel-group RTCs investigating the effects of metformin on the prognosis for COVID-19 are currently ongoing. One is the COVID-OUT: Early Outpatient Treatment for SARS-CoV-2 Infection trial (NCT04510194). The investigators intend to evaluate whether metformin treatment in non-hospitalized patients with SARS-CoV-2 can (1) prevent decreased oxygenation and emergency department utilization, (2) prevent COVID-19 disease progression, and (3) improve viral load and serologic markers associated with COVID-19. The other is the Pilot Study Into the Use of Metformin and Low Dose Naltrexone for Patients With COVID-19 trial (NCT04604678). The investigators intend to study the effect of a combination of metformin and low dose naltrexone on the attenuation of symptoms and disease severity, recovery time, hospitalization rates, and mortality in COVID-19 patients at definite intervals over 4 weeks.

Collectively, the aforementioned results indicate that metformin may provide protective effects through several mechanisms beyond glucose-lowering actions during COVID-19 infection and could subsequently reduce mortality. However, further studies are necessary to explore how metformin can confer these benefits, provide a thorough risk–benefit assessment, and determine whether the indications of metformin use should be broadened given the ongoing COVID-19 pandemic.

Thiazolidinediones

Thiazolidinediones (TZDs) can inhibit inflammatory nuclear factor-κB and mitogen-activated protein kinase pathways by reducing the expression of caspase recruitment domain-containing protein 9 and attenuating the dendritic cell trafficking, antigen uptake and dendritic cell–T cell interactions at the initiation of immune response[38]. TZDs can positively influence platelet function and coagulation pathways, which may benefit the treatment of the prothrombotic state in patients with T2D[39]. Moreover, TZDs can upregulate ACE2 expression to support the control of ongoing inflammation[40]. A study suggested that a subtherapeutic TZD dose reduces the expression of inflammatory adipokines by suppressing interleukin (IL)-6 and tumor necrosis factor-α (TNF-α)[41]. Hence, TZDs was suggested as an anti-inflammatory treatment option for

patients with COVID-19[38]. Nevertheless, TZDs are associated with peripheral edema, weight gain, and, crucially, increased risk of HF due to fluid retention[42]. These results do not support TZD treatment for patients with COVID-19. A dedicated ongoing RCT, the Effect of Pioglitazone on T2D Patients With COVID-19 trial (NCT04604223), is being collected to investigate whether pioglitazone treatment in T2D with moderate-to-severe COVID-19 can improve the clinical outcome of their COVID-19 disease. Currently, no clinical study has verified the benefits of TZD use for patients with diabetes who have COVID-19. Further clinical studies are necessary to clarify the risk–benefit ratio of TZD use for patients with COVID-19.

Sulfonylureas

Sulfonylureas (SUs) can substantially improve glycemic control by stimulating insulin secretion, but they may also increase the risk of hypoglycemia, which can be severe and prolonged[43]. For COVID-19, retrospective studies have reported that SU use does not have beneficial or detrimental effects on ICU admissions[44], moderate-to-severe COVID-19 infection[45], and primary outcome of mortality or ICU admissions within 30 days[46]. Similar results were reported in a prospective study of patients with diabetes who have COVID-19; the study suggested that the combined use of SUs and glinide is not beneficial or harmful with respect to primary and secondary outcomes at days 7 (interim report) and 28 (final report)[47,48]. Moreover, in an age-adjusted analysis, SU/glinide use did not affect discharge rates or mortality within 28 days[48].

Controversy has arisen over the safety of SUs for patients with myocardial infarction (MI). Some studies have reported that SU use does not influence mortality and MI[49], whereas others have demonstrated that SU use is linked to poorer outcomes in patients with MI[50]. Studies have suggested that COVID-19 results in myocardial injury, which could be attributed to the associated cytokine storm or myocardial dysfunction linked to the direct effect of SARS-CoV2 on the heart[51,52]. In this context, caution is advised with regard to the potential adverse cardiovascular effect of SU use for hospitalized patients with severe illness who have an increased risk of myocardial injury, particularly those receiving nonselective drugs.

Glinides are short-acting drugs that act similarly to SUs. Nevertheless, they should be used with caution, particularly for patients with COVID-19-associated myocardial injury because their mechanism is similar to that of SUs and may, consequently, pose similar cardiovascular risk.

No ongoing RCT thus far has evaluated the benefits or harms of SUs or glinides treatment on T2D patients with COVID-19 infection.

Collectively, the aforementioned findings indicate that SUs and glinides should be avoided for hospitalized patients with COVID-19 infection, particularly those with COVID-19-associated cardiovascular risk and severe illnesses, on the basis of the risk of severe hypoglycemia and cardiovascular safety.

Alpha-glucosidase inhibitors

Alpha-glucosidase inhibitors (AGIs) delay the absorption of carbohydrates in the small intestine and, thus, reduce postprandial hyperglycemia and improve glycemic control. Several studies have suggested that AGIs exhibit promising effects beyond their glucose-lowering action on oxidative stress, inflammation, cardiac interstitial fibrosis, carotid intima-media thickening, and endothelial function pathways[53]. Nevertheless, no ongoing RCT has evaluated the efficacy and safety of AGIs treatment to date and the existing clinical studies have yet to verify the beneficial or harmful effects of AGI use on patients with diabetes who have COVID-19.

Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase-4 (DPP-4) inhibitors (DPP-4is) block the degradation of incretins and subsequently prolong the response of insulin stimulation in response to elevated blood glucose levels[54]. DPP-4is are commonly used to treat T2D; however, a disproportionately higher number of venous thromboembolism events have occurred following DPP-4i use relative to the use of other noninsulin antidiabetic medications, and such events occurred mainly at the gastrointestinal level and with sitagliptin use (relative to the use of other DPP-4is) [55]. Moreover, vildagliptin was reported to increase the risk of interstitial lung injury, although the precise mechanism remains uncertain[56]. Hence, patients who use DPP-4is and also present with risk factors for venous thromboembolism or interstitial lung injury should be carefully monitored given the ongoing COVID-19 pandemic.

Although ACE2 is the main entry receptor for SARS-CoV-2[3], a crystallographic study reported that the DPP-4 can act as a candidate-binding target or co-receptor of SARS-CoV-2[57]. Moreover, studies have suggested that although SARS-CoV-2 does not directly involve DPP-4, its interaction with DPP-4 in conjunction with ACE2 (and probably mutations resulting in involvement) cannot be entirely ruled out[58].

Numerous studies have suggested that DPP-4i has beneficial effects on coagulation and inflammatory pathways, which may contribute to the reduction of the risks of adverse outcomes associated with COVID-19[29]. More crucially, DPP-4i can reduce virus entry and replication in the airways and hamper sustained cytokine storms and inflammation within the lung in patients with COVID-19[29].

However, more recent studies do not suggest that DPP-4i use poses safety problems for patients with diabetes who have COVID-19[46,59–64]. Observational studies have suggested that DPP-4i use has protective effects on patients with diabetes who have COVID-19[59,60]. In a meta-analysis of patients with diabetes who have COVID-19, in-hospital use of DPP-4i was associated with a reduction of COVID-19 mortality by 63% and 73% for unadjusted and adjusted analyses, respectively[61]. However, preadmission use of the drug did not result in any change in mortality[61]. In this context, the potential mechanisms that allow DPP-4i use to improve clinical outcomes in patients with diabetes who have COVID-19 are speculative. First, DPP-4i can induce a conformational change in DPP-4 molecules and thereby interfere with the interaction between SARS-CoV-2 spike S1 protein and human DPP-4. Second, circulating levels of soluble dipeptidyl peptidase-4 (sDPP-4) were reduced in patients who were hospitalized for severe COVID-19. sDPP-4 could act as a decoy receptor for SARS-CoV-2 and prevent vital replications. Moreover, an experimental model of mice demonstrated that DPP-4i can increase levels of sDPP-4 by 50%–100%. Hence, apart from interfering with viral entry, DPP-4i can promote sequestration of viral particles in circulation by increasing sDPP-4 levels and consequently limiting viral proliferation. Finally, both human and experimental studies have suggested that DPP-4i has a potent anti-inflammatory effect on reducing proinflammatory cytokines, which may be instrumental in curbing the inflammatory storm observed in patients with severe COVID-19[61]. Similarly, another meta-analysis demonstrated that DPP-4i use is associated with lower mortality in patients with COVID-19, and this association is weaker in patients who also take metformin and/or angiotensin converting enzyme inhibitors[62].

By contrast, several retrospective case–control studies have assessed the effects of exposure to DPP-4i in hospitalized patients with diabetes who have COVID-19 and have reported no significant differences in ICU admission and mortality[63] and the primary outcome of mortality or ICU admission within 30 days in DPP-4i users compared with the

nonusers[46]. Moreover, a comprehensive meta-analysis of 10 studies revealed that DPP-4i use does not lead to significant improvements in the composite poor outcome of COVID-19; hence, it does not alter the COVID-19 severity and mortality, regardless of gender, age, cardiovascular disease (CVD), hypertension, and admission blood glucose level[64]. In this context, several contradicting reasons were proposed to explain these inconsistencies. First, although the S1 domain of the SARS-CoV-2 spike glycoprotein may interact with membrane-bound human DPP-4, a functional assay study reported that ACE2 is a major binding partner for COVID-19 and that DPP-4 does not play a significant role for SARS-CoV-2 internalization in host cells. Thus, DPP-4i does not significantly change the course of COVID-19. Second, a recent experimental study demonstrated that proinflammatory cytokines levels did not differ between mice that were subjected to a calorie deficit and mice that consumed a high-fat and high-cholesterol diet after a 2-week administration of DPP-4i, which suggests that DPP-4 and sDPP-4 levels are not associated with cytokine levels in the plasms, liver, or adipose tissue of high-fat-diet-fed mice treated with DPP-4i and brings into question the anti-inflammatory effect of DPP-4i. Finally, relative to non-DPP-4i users, no difference in the markers of severe-COVID-19 (e.g., sDPP-4 protein levels and circulating levels of IL-6, TNF-α, and CRP relative to baseline values) was observed in patients who received DPP-4i at 12 months. Hence, DPP-4i treatment in patients with diabetes who have COVID-19 cannot reduce inflammation and prevent the cytokine storm associated with COVID-19; consequently, DPP-4i use does not alter the severity and mortality outcomes of COVID-19[64].

At least three ongoing parallel-group RCTs are conducted to investigate the effects of DPP-4is on the prognosis for COVID-19. One is an open-label Effect of Sitagliptin Treatment in COVID-19-Positive Diabetic Patients trial (NCT 04365517) to evaluate the effect of sitagliptin as an add-on to standard care with nutritional therapy with or without insulin treatment. The other two are to investigate whether linagliptin added to background insulin therapy can help with diabetes control and reduce the severity of the COVID-19 infection (NCT 04341935; NCT 04371978).

Collectively, the aforementioned body of evidence suggests that DPP-4 is associated with multiple biological processes, such as inflammatory and immune mechanisms, and a hypothesis was proposed that DPP-4i can moderate outcomes in patients with diabetes who have SARS-CoV-2. Nevertheless, several mechanisms appear to be deleterious, whereas others may be associated with favorable effects on patients with COVID-19. Hence, whether DPP-4i affects COVID-19 activity and produces beneficial, neutral, or harmful effects is a topic that requires further clarification.

Glucagon-like peptide-1 receptor agonist

Glucagon-like peptide-1 receptor agonist (GLP-1 RA) contributes to glucose homeostasis in patients with diabetes through the stimulation of glucose-dependent insulin secretion, delayed gastric emptying, and increased postprandial satiety[65]. Moreover, GLP-1 RA was suggested to reduce the production of various inflammatory cytokines and infiltration of immune cells in multisystem organs, which produces beneficial effects for chronic inflammatory diseases such as atherosclerosis neurodegenerative disorders and nonalcoholic fatty liver disease (NAFLD) because of a reduction in the activity of inflammatory pathways[10]. GLP-1 RA may be useful in modifying risk factors for severe COVID-19 complications such as CVD, obesity, and NAFLD[66]. Furthermore, GLP-1 RA was proposed as a potential therapeutic candidate for acute COVID-19 infection to reduce respiratory injuries[66]. However, animal studies have demonstrated that GLP-1 RA liraglutide is associ-

ated with increased ACE2 expression, which has a negative effect on inflammatory and fibrotic processes[67]. Moreover, a follow-up study reported that liraglutide treatment prevents the alteration of lung function and promotes the positive effects of the ACE2-angiotensin system in restoring lung function[68]. Thus, the aforementioned studies indicate that GLP-1 RA is a double-edged sword with respect to the treatment of patients with diabetes who have COVID-19. GLP-1 RA may facilitate the infection and replication of SARS-CoV-2 through the stimulation of ACE2 expression. Alternatively, it may result in the generation of soluble ACE2, which serves as decoy receptor that can efficiently block or mitigate SARS virus infection[68].

The current body of evidence is inadequate to support the use of GLP-1 RA as a therapeutic drug for patients with diabetes who have COVID-19. In an observational study, premorbid GLP-1 RA use was associated with lower mortality and other clinical adverse outcomes relative to DPP-4i use among patients with SARS-CoV-2 (OR, 0.54) [69]. A case report reported a good outcome for GLP-1 RA use in patients with diabetes who have COVID-19[70]. In a retrospective study, GLP-1 RA use in individuals with diabetes who have COVID-19 was not associated with improved clinical outcomes[71]. Similar results were reported in a prospective study of patients with diabetes who have COVID-19, indicating that GLP-1 RA use does not have a beneficial or harmful effect on discharge rate (OR, 1.11; $P = 0.45$) or mortality (OR, 0.78; $P = 0.21$) relative to GLP-1 RA nonusers in an age-adjusted analysis[48]. Moreover, given the sustained attenuation in appetite sensations and dietary energy intake and the presence of gastrointestinal intolerance, a temporary suspension of GLP-1 RA is recommended for patients with COVID-19 who are severely ill because of the further delay of patient recovery[72]. Hence, these findings do not indicate the preventive or attenuation effect of the current use of GLP-1 RA in patients with diabetes who have COVID-19. No ongoing RCT thus far has evaluated the benefits or harms of GLP-1 RA treatment on T2D patients with COVID-19 infection.

GLP-1 RA is involved in many biologic processes such as inflammatory and immune pathways; however, the nature of the effects of GLP-1 RA use (beneficial, natural, or harmful) on patients with diabetes who have COVID-19 is inconclusive based on the current body of evidence. Hence, prospective RCTs involving such patients are necessary to investigate the potential benefits associated with GLP-1 RA use in patients with diabetes who have COVID-19.

Sodium-glucose cotransporter-2 inhibitor

The current body of evidence suggests that sodium-glucose cotransporter-2 inhibitor (SGLT-2i) has anti-inflammatory properties that have beneficial effects on oxidative stress, tissue hypoxia, autophagy, thrombosis, and energy metabolism[29], all of which may have a positive effect on the dysregulated process of cytokine storms associated with COVID-19[73]. Moreover, SGLT2i can produce other positive effects that can benefit COVID-19 patients with interstitial lung oedema and hypoxemia through increased hematocrit, reduction of interstitial volume without changes in blood volume, and cellular protection due to reductions in cytoplasmic Na^+ and Ca^{++} concentration[74]. SGLT-2i was suggested to increase lactate concentration and reduce intracellular pH, which can reduce the COVID-19 viral load[73]. Because COVID-19 disproportionately affects individuals with cardiovascular/cardiometabolic comorbidities, the significant cardiorenal benefit of SGLT-2i use for patients with T2D who have CKD and high cardiovascular risk suggests potential positive effects on COVID-19 patients. However, DKA, acute kidney injury, and risk of increased volume depletion were documented in patients with T2D who took SGLT-2i[10],

particularly patients who were severely ill. The aforementioned concerns led to recommendations from expert groups to temporarily suspend SGLT-2i use for patients with COVID-19 at admission to reduce the risk of metabolic decompensation (even though they have conditions for which SGLT-2i use was proven to produce substantial benefits) [75].

Whether SGLT-2i use has favorable or deleterious effects on clinical outcomes in patients with diabetes who have COV-ID-19 remains unclear. In a 1:1 propensity score-matched multivariate analysis of patients with COVID-19 who have diabetes, a higher prevalence was observed for disease severity (OR, 1.75; $P = 0.59$) and mortality (OR, 5.05; $P = 0.18$) in SGLT-2i users compared with the nonusers; however, these findings were not statistically significant[45]. In a retrospective cohort study of patients with diabetes who have COVID-19, lower ICU admission or death within 30 days was observed in SGLT-2i users compared with nonusers (OR, 0.66; $P = 0.40$) [46]. By contrast, in a retrospective study that involved a multivariate analysis, SGLT-2i users exhibited a marginally lower risk of mechanical ventilation (adjusted relative risk, 0.03; $P = 0.03$) compared with SGLT-2i nonusers[44]. In an observational study of patients with COVID-19, SGLT-2i use was associated with lower 60-day mortality and decreased total mortality, emergency room visits, and hospitalization relative to DPP-4i use[69]. The Dapagliflozin in Respiratory Failure in Patients with COVID-19 (DARE-19) trial provided encouraging but inconclusive evidence that dapagliflozin (compared with a placebo) reduces the risk of organ dysfunction or mortality in patients with cardiometabolic risk factors who were hospitalized with COVID-19[76]. Moreover, the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial (NCT04381936)[77], which is a dedicated ongoing COVID-19 trial of SGLT-2i, is assessing whether empagliflozin reduces the risk of mortality among patients hospitalized for COVID-19. It is also investigating whether the treatment shortens the length of hospital stay and reduces the need for a mechanical ventilator. In contrast to the DARE-19 trial, the RECOVERY trial further includes empagliflozin in a much larger comparison; therefore, the results of the RECOVERY trial will be able to determine whether SGLT-2i provides organ protection and improves the chances of recovery for hospitalized patients with COVID-19.

Collectively, the aforementioned findings indicate that the pleiotropic benefits of SGLT-2i use can favorably influence outcomes in patients with COVID-19, although this hypothesis has yet to be demonstrated in ongoing prospective RCTs. However, concerns regarding the potential increase in DKA risk should not be ignored. SGLT-2i use may be continued in patients in asymptomatic or mild COVID-19 to control blood glucose and take advantage of its potential mechanistic effects beyond its glucose-lowering effect. However, caution is recommended for patients with more severe COVID-19 who require hospitalization, and the suspension of SGLT2i is recommended because of a possible increase in DKA risk[74].

Insulin

For patients with a severe or critical course of illness, insulin is regarded as the most appropriate pharmacologic agent for achieving and maintaining glycemic control effectively. Insulin also has anti-inflammatory effects and reduces the biomarkers of inflammation in hospitalized patients with critical illnesses[78].

An experimental model using non-obese diabetic mice reported that insulin downregulated ACE2 receptors[79], which might reduce the risk of COVID-19 infection. Furthermore, an observational study showed tremendous insulin requirement among COVID-19 patients[80], which might be attributed to the beta-cell dysfunction induced by SARS-CoV2. To what extent COVID-19 plays a direct role

in this high IR remains unclear. Further research is needed to clarify the clinical influence of insulin in the context of COVID-19.

Although no ongoing RCT thus far has evaluated the benefits or harms of insulin treatment on T2D patients with COVID-19 infection, several recent retrospective studies have assessed the effects of insulin treatment in hospitalized patients with COVID-19-related complications and reported conflicting results[81-84]. In a study of patients with diabetes who have COVID-19 and also presented with hyperglycemia, insulin users exhibited a lower risk of severe disease relative to insulin nonusers (P = 0.027)[81]. By contrast, several studies have suggested that insulin treatment is associated with worse outcomes[82-84]. In a retrospective observational study of patients with diabetes who have COVID-19, patients who underwent insulin treatment at home exhibited significantly higher mortality relative to those who did not receive insulin treatment (OR, 2.65; P = 0.013) after adjustment for confounders[82]. Moreover, peak daily inpatient insulin requirements for COVID-19 was suggested as a marker for poor prognosis[82] that can be used to identify patients who require more aggressive treatments to prevent mortality[85]. However, a study suggested that the reported association between outpatient or inpatient insulin therapy and increased risk of mortality can mainly be attributed to the confounding effects of baseline glycemic control, metformin use, and other unadjusted confounders[85]. Similarly, in another retrospective cohort study of patients with diabetes who have COVID-19, insulin users exhibited a significant increase in mortality relative to insulin nonusers (adjusted hazard ratio, 5.38)[83]. Moreover, insulin treatment enhances systemic inflammation and aggravates vital organ injuries[83], which contradicted previous findings[78]. A meta-analysis suggested that insulin treatment is associated with increased mortality (OR, 2.10), severe/critical complications (OR, 2.56), and in-hospital admission (OR, 1.61) in patients with diabetes who have COVID-19[84]. However, given the high heterogeneity, presence of multiple confounders, limited amount of prospective data, and lack of clarity regarding diabetes type that were discussed in the present study, further large-scale RCTs are necessary to verify the aforementioned finding.

Although the beneficial or harmful effects of insulin treatment on patients with diabetes who have COVID-19 remain unclear and controversial, given the unique role of insulin in the management of diabetes and its complications, insulin treatment should not be abandoned until better and safer antidiabetic medications can be identified for patients with diabetes who have COVID-19. Furthermore, patients with diabetes who have COVID-19 and are critically unwell have high insulin requirements and poorer time in the optimal target range for blood glucose during a peak inflammatory response[86], which suggests that insulin use is necessary during the late stage of COVID-19. Finally, the results of existing studies should be interpreted with caution because of the complexity associated with the effectiveness of insulin in controlling glycemic levels at various stages of diabetes; therefore, more well-designed RCTs are necessary to establish clearer conclusions regarding insulin use for COVID-19 progression[84].

Conclusion

Patients with diabetes are susceptible to severe complications from COVID-19. Several underlying physiological mechanisms in individuals with diabetes may contribute to worsening outcomes during a COVID-19 infection. Maintaining optimal glycemia control and avoiding glucose fluctuations are the cornerstone of care for patients with diabetes who have COVID-19. Several antidiabetic medications are discussed because of their immunomodulating properties beyond their glucose-lowering effects, and these properties are crucial in combating COVID-19-associated hyperinflammatory syn-

drome. However, the benefits of the medications must be assessed against their potential risks.

Metformin may provide protective effects through several mechanisms beyond its glucose-lowering actions during a COVID-19 infection; therefore, it can reduce mortality. This suggests that patients with COVID-19 should continue using metformin unless they exhibit deteriorating renal function, increasing hypoxemia, multiple organ failure. Although no clinical data support the beneficial effects of TZDs, they should not be administered to hospitalized patients with COVID-19 who are at risk of acute HF because of their current illness. Given the risk of severe hypoglycemia and cardiovascular safety, SUs and glinides should be avoided for hospitalized individuals with COVID-19, particularly those with COVID-19-associated cardiovascular risk and severe illnesses. No existing data currently support AGIs; thus, their safety for patients with diabetes who have COVID-19 remains unclear. Further studies are required to verify whether DPP-4i affects COVID-19 activity and has beneficial, neutral, or harmful effects. For GLP-1 RA and SGLT-2i, existing data have not verified any significant beneficial or harmful effects. Nevertheless, a temporary suspension of GLP-1 RA is recommended for patients with COVID-19 who are severely ill because of the further delay of patient recovery. Similarly, SGLT-2i should not be continued in hospitalized patients with multiple organ failure or in the presence of another contraindication that may preclude SGLT-2i use. For critically unwell patients with diabetes who have COVID-19 and high insulin requirements, the body of evidence does not support the suspension of insulin treatment unless better and safer antidiabetic medications can be identified for such patients.

Future research will improve our understanding of COVID-19 and how we can maximize the benefits of antidiabetic medications for patients with diabetes who have COVID-19. Because of the limitations of real-world studies, further RCTs are required to verify the clinical relevance and applicability of the findings discussed in the present study.

References

1. World Health Organization. WHO Director-General's statement on IHR Emergency Committee on Novel Coronavirus (2019-nCoV). Accessed 16 October 2020. Available from https://www.who.int/dg/speeches/detail/who-director-general-s-statement-on-ihr-emergency-committee-on-novel-coronavirus-(2019-ncov).
2. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet 2020; 395: 1054-62.
3. Ma RCW, Holt RIG. COVID-19 and diabetes. Diabet Med 2020 Apr 3: 10.1111/dme.14300. doi: 10.1111/dme.14300 [Epub ahead of print].
4. Zhou Y, Chi J, Lv W, Wang Y. Obesity and diabetes as high-risk factors for severe coronavirus disease 2019 (Covid-19). Diabetes Metab Res Rev 2021; 37: e3377.
5. Guo W, Li M, Dong Y, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev 2020; 36: e3319.
6. Toniolo A, Cassani G, Puggioni A, et al. The diabetes pandemic and associated infections: suggestions for clinical microbiology. Rev Med Microbiol 2019; 30: 1-17.
7. Ibrahim S, Monaco GS, Sims EK. Not so sweet and simple: Impacts of SARS-CoV-2 on the β cell. Islets 2021; 13: 66-79.
8. Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol 2010; 47: 193-9.
9. De Luca C, Olefsky JM. Inflammation and insulin resistance. FEBS Lett 2008; 582: 97-105.
10. 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.
11. Maddaloni E, Buzzetti R. Covid-19 and diabetes mellitus: unveiling the interaction of two pandemics. Diabetes Metab Res Rev 2020; 36: e33213321.
12. Wang A, Zhao W, Xu Z, Gu J. Timely blood glucose management for the outbreak of 2019 novel coronavirus disease (COVID-19) is urgently needed. Diabetes Res Clin Pract 2020; 162: 108118.
13. England N, Improvement N. After-care needs of inpatients recovering from COVID-19. 2020; 001559.
14. Yang L, Han Y, Nilsson-Payant BE, et al. A human pluripotent stem cell-based platform to study SARS-CoV-2 tropism and model virus infection in human cells and organoids. Cell Stem Cell 2020; 27: 125-36.
15. Potier L, Julla JB, Roussel R, et al. COVID-19 symptoms masking inaugural ketoacidosis of type 1 diabetes. Diabetes Metab 2021; 47: 101162.
16. Marchand L, Pecquet M Luyton C. Type 1 diabetes onset triggered by COVID-19. Acta Diabetol 2020; 57: 1265-6.
17. Samuel SM, Varghese E, Büsselberg D. Therapeutic potential of metformin in COVID-19: Reasoning for its pro-

tective role. Trends in Microbiology 2021. DOI:https://doi.org/10.1016/j.tim.2021.03.004.
18. Smith SM, Boppana A, Traupman JA, et al. Impaired glucose metabolism in patients with diabetes, prediabetes, and obesity is associated with severe COVID-19. J Med Virol 2021; 93: 409-15.
19. Unsworth R, Wallace S, Oliver N S, et al. New-onset type 1 diabetes in children during COVID-19: multicenter regional findings in the UK. Diabetes Care 2020; 43: 11: e170-1.
20. Singh, A.K. and Singh, R. Hyperglycemia without diabetes and new-onset diabetes are both associated with poorer outcomes in COVID-19. Diabetes Res Clin Pract 2020; 167: 108382.
21. Bode B, Garrett V, Messler J, et al. Glycemic characteristics and clinical outcomes of COVID-19 patients hospitalized in the United States. J Diabetes Sci Technol 2020; 14: 813-21.
22. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in critically ill patients in the Seattle region—case series. N Engl J Med 2020; 382: 2012-22.
23. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. JAMA 2020; 323: 1612-4.
24. Abdel-Moneim A, Hosni A. Insights into the possible impact of COVID-19 on the endocrine system. Arch Physiol Biochem 2021: 1-9.
25. Mahrooz A, Muscogiuri G, Buzzetti R, Maddaloni E. The complex combination of COVID-19 and diabetes: Pleiotropic changes in glucose metabolism. Endocrine 2021; 72: 317-25.
26. Hayek S, Ben-Shlomo Y, Balicer R, et al. Preinfection glycaemic control and disease severity among patients with type 2 diabetes and COVID-19: A retrospective, cohort study. Diabetes Obes Metab 2021. DOI: 10.1111/dom.14393.
27. Chen X, Guo H, Qiu L, Zhang C, Deng Q, Leng Q. Immunomodulatory and antiviral activity of metformin and its potential implications in treating coronavirus disease 2019 and lung injury. Front Immunol 2020; 11: 2056.
28. Grant PJ. Beneficial effects of metformin on haemostasis and vascular function in man. Diabetes Metab 2003; 29: 6S44-52.
29. Berlie HD, Kale-Pradhan PB, Orzechowski T, Jaber LA. Mechanisms and Potential Roles of Glucose-Lowering Agents in COVID-19: A Review. Ann Pharmacother 2021; 1060028021999473.
30. Esam Z. A proposed mechanism for the possible therapeutic potential of Metformin in COVID-19. Diabetes Res Clin Pract 2020; 167: 108282.
31. Singh AK, Singh R. Is metformin ahead in the race as a repurposed host-directed therapy for patients with diabetes and COVID-19? Diabetes Res Clin Pract 2020;165: 108268.
32. Hariyanto, TI, Kurniawan A. Metformin use is associated with reduced mortality rate from coronavirus disease 2019 (COVID-19) infection. Obes Med 2020; 19: 100290.
33. Oscanoa TJ, Amado J, Vidal X, Savarino A, Romero-Ortuno R. Metformin therapy and severity and mortality of SARS-CoV-2 infection: A meta-analysis. Clin Diabetol 2021; 10: 1-13.
34. Ghany R, Palacio A, Dawkins E, et al. Metformin is associated with lower hospitalizations, mortality and severe coronavirus infection among elderly medicare minority patients in 8 states in USA. Diabetes & Metabolic Syndrome: Clin Res Rev 2021; 15: 513-8.
35. Lally MA, Tsoukas P, Halladay CW, O'Neill E, Gravenstein S, Rudolph JL. Metformin is associated with decreased 30-day mortality among nursing home residents infected with SARS-CoV2. J Am Med Dir Assoc 2021; 22: 193-8.
36. Cheng X, Liu YM, Li H, et al. Metformin is associated with higher incidence of acidosis, but not mortality, in individuals with COVID-19 and pre-existing type 2 diabetes. Cell Metab 2020; 32: 537-47.
37. Crouse AB, Grimes T, Li P, Might M, Ovalle F, Shalev A. Metformin use is associated with reduced mortality in a diverse population with COVID-19 and diabetes. Front Endocrinol 2021; 11: 1081.
38. Erol A. Pioglitazone treatment for the COVID-19-associated cytokine storm. Preprint. OSF Preprints. 2020. DOI: 10.31219/osf.io/avfpb.
39. Borchert M, Schöndorf T, Lübben G, Forst T, Pfützner A. Review of the Pleiotropic Effects of Peroxisome Proliferator-Activated Receptor γ Agonists on Platelet Function. Diabetes Technol Ther 2007; 9: 410-20.
40. Zhang W, Xu YZ, Liu B, et al. Pioglitazone upregulates angiotensin converting enzyme 2 expression in insulin-sensitive tissues in rats with high-fat diet-induced nonalcoholic steatohepatitis. Sci World J 2014; 2014: 603409.
41. Mohapatra J, Sharma M, Singh S, et al. Subtherapeutic dose of pioglitazone reduces expression of inflammatory adipokines in db/db mice. Pharmacology 2009; 84: 203-10.
42. Kernan WN, Viscoli CM, Furie KL, et al. Pioglitazone after ischemic stroke or transient ischemic attack. N Engl J Med 2016; 374: 1321-31.
43. Schopman JE, Simon AC, Hoefnagel SJ, et al. The incidence of mild and severe hypoglycemia in patients with type 2 diabetes mellitus treated with sulfonylureas: A systematic review and meta-analysis. Diabetes Metab Res Rev 2014; 30: 11-22.
44. Dalan R, Ang LW, Tan WY, et al. The association of Hypertension and Diabetes Pharmacotherapy with COVID-19 severity and immune signatures: an observational study. Eur Heart J Cardiovasc Pharmacother 2020 Aug 7. https://doi.org/10.1093/ehjcvp/pvaa098.
45. Kim MK, Jeon JH, Kim SW, et al. 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: 602-13.
46. Izzi-Engbeaya C, Distaso W, Amin A, et al. Severe COVID-19 and diabetes - a retrospective cohort study from three london 2 teaching hospitals. medRxiv preprint doi, https://doi.org/10.1101/2020.08.07.20160275; 2020.
47. Cariou B, Hadjadj S, Wargny M, et al. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the Coronado study. Diabetologia 2020; 63: 1500-15.
48. Wargny M, Potier L, Gourdy P, et al. Predictors of hospital discharge and mortality in patients with diabetes and

COVID-19: updated results from the nationwide Coronado study. Diabetologia 2021; 64: 778-94.
49. Garratt KN, Brady PA, Hassinger NL, et al. Sulfonylurea drugs increase early mortality in patients with diabetes mellitus after direct angioplasty for acute myocardial infarction. J Am Coll Cardiol 1999; 33: 119-24.
50. American Diabetes Association. A study of the effects of hypoglycemia agents on vascular complications in patients with adult-onset diabetes. VI. Supplementary report on nonfatal events in patients treated with tolbutamide. Diabetes 1976; 25: 1129-53.
51. Vakhshoori M, Heidarpour M, Shafie D, Taheri M, Rezaei N, Sarrafzadegan N. Acute cardiac injury in COVID-19: A systematic review and meta-analysis. Arch Iran Med 2020; 23: 801-12.
52. Clerkin KJ, Fried JA, Raikhelkar J, et al. COVID-19 and Cardiovascular Disease. Circulation. 2020; 141: 1648-55.
53. Standl E, Theodorakis MJ, Erbach M, Schnell O, Tuomilehto J. On the potential of acarbose to reduce cardiovascular disease. Cardiovasc Diabetol 2014; 13: 1-12.
54. Drucker DJ, Nauck MA. The incretin system: Glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 2006; 368: 1696-705.
55. Gouverneur A, Lair A, Arnaud M, et al. DPP-4 inhibitors and venous thromboembolism: An analysis of the WHO spontaneous reporting database. Lancet Diabetes Endocrinol 2020; 8: 365-7.
56. Ohara N, Kaneko M, Sato K, et al. Vildagliptin-induced acute lung injury: A case report. J Med Case Rep 2016; 10: 1-5.
57. Li Y, Zhang Z, Yang L, et al. The MERS-CoV receptor DPP4 as a candidate binding target of the SARS-CoV-2 spike. iScience 2020; 23: 101160.
58. Singh AK, Singh R, Saboo B, Misra A. Non-insulin anti-diabetic agents in patients with type 2 diabetes and COVID-19: A critical appraisal of literature. Diabetes Metab Syndr 2021; 15: 159-67.
59. 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: 251-9.
60. 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; 43: 2999-3006.
61. 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.
62. Rakhmat II, Kusmala YY, Handayani DR, et al. 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: 777-82.
63. Fadini GP, Morieri ML, Longato 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; 22: 1946-50.
64. Hariyanto TI, Kurniawan A. Dipeptidyl peptidase 4 (DPP4) inhibitor and outcome from coronavirus disease 2019 (COVID-19) in diabetic patients: a systematic review, meta-analysis, and meta-regression. J Diabetes Metab Disord 2021; 20: 543-50.
65. Mirabelli M, Chiefari E, Caroleo P, et al. Long-term effectiveness of liraglutide for weight management and glycemic control in type 2 diabetes. Int J Environ Res Public Health 2020: 17: 207.
66. Sazgarnejad S, Yazdanpanah N, Rezaei N. Anti-inflammatory effects of GLP-1 in patients with COVID-19. Expert Rev Anti Infect Ther 2022;20(3):373-81.
67. Romaní-Pérez M, Outeiriño-Iglesias V, Moya CM, et al. F. Activation of the GLP-1 receptor by liraglutide increases ACE2 expression, reversing right ventricle hypertrophy, and improving the production of SP-A and SP-B in the lungs of type 1 diabetes rats. Endocrinology 2015; 156: 3559-69.
68. Pang J, Liu M, Ling W, Jin T. Friend or Foe? ACE2 inhibitors and GLP-1R agonists in COVID-19 treatment. Obes Med 2021; 22: 100312.
69. Kahkoska AR, Abrahamsen TJ, Alexander GC, et al. Association between glucagon-like peptide 1 receptor agonist and sodium–glucose cotransporter 2 inhibitor use and COVID-19 outcomes. Diabetes Care 2021; 44: 1564-72.
70. Chen S, Lin W, Weng J, et al. Is GLP-1R agonists effective and safe in severe COVID-19 patients with type 2 diabetes? - A case report and literature review. Preprint SSRN. 2020. https://doi.org/10.2139/ssrn.3654086.
71. 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: 1397-401.
72. Mirabelli M, Chiefari E, Puccio L, Foti DP, Brunetti A. Potential benefits and harms of novel antidiabetic drugs during COVID-19 crisis. Int J Environ Res Public Health 2020; 17: 3664.
73. Cure E, Cure M. Can dapagliflozin have a protective effect against COVID-19 infection? A hypothesis. Diabetes & Metabolic Syndrome. Clin Res Rev 2020; 14: 405-6.
74. Scheen AJ. SGLT2 inhibition during the COVID-19 epidemic: Friend or foe?. Diabetes Metab 2020; 46: 343-4.
75. Diabetes UK. Concise advice on inpatient diabetes (COVID: Diabetes)—front door guidance.https://diabetes-resources-production.s3.eu-west-1.amazonaws.com /resources-s3/public/2020-12/COvID_Front_Door_v3.1%20%28003%29.pdf. July 14, 2021.
76. Kosiborod MN, Esterline R, Furtado RH, et al. Dapagliflozin in patients with cardiometabolic risk factors hospitalised with COVID-19 (DARE-19): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Diabetes Endocrinol 2021. Published Online July 21, 2021. https://doi.org/10.1016/S2213-8587(21)00180-7.

77. Horby P. Randomised evaluation of COVID-19 therapy-full text view-ClinicalTrials. gov [Internet]. 2020 [cited 2020 Jul 5].https://clinicaltrials. gov/ct2/show/NCT04381936.
78. Hansen TK, Thiel S, Wouters PJ, Christiansen JS, Van den Berghe G. Intensive insulin therapy exerts anti-inflammatory effects in critically ill patients and counteracts the adverse effect of low mannose-binding lectin levels. J Clin Endocrinol Metab 2003; 88: 1082-8.
79. Roca-Ho H, Riera M, Palau V, et al. Characterization of ACE and ACE2 expression within different organs of the NOD mouse. Int J Mol Sci 2017; 18: 563.
80. Bornstein SR, Rubino F, Khunti K, et al. Practical recommendations for the management of diabetes in patients with COVID-19. Lancet Diabetes Endocrinol 2020; 8: 546-550.
81. Sardu C, D'Onofrio N, Balestrieri ML, et al. Outcomes in patients with hyperglycemia affected by COVID-19: can we do more on glycemic control? Diabetes Care 2020; 43: 1408-15.
82. Riahi S, Sombra LRS, Lo KB, et al. Insulin use, diabetes control, and outcomes in patients with COVID-19. Endocr Res 2021; 46: 45-50.
83. Yu B, Li C, Sun Y, Wang DW. Insulin treatment is associated with increased mortality in patients with COVID-19 and type 2 diabetes. Cell Metab 2021; 33: 65-77.
84. Yang Y, Cai Z, Zhang J. Insulin Treatment May Increase Adverse Outcomes in Patients With COVID-19 and Diabetes: A Systematic Review and Meta-Analysis. Front Endocrinol 2021; 12: 696087.
85. Kow CS, Hasan SS. Insulin Treatment May Not Be Associated with Increased Mortality in Patients with COVID-19 and Concurrent Diabetes. Endocr Res 2021; 46: 51-2.
86. Wu L, Girgis C M, Cheung NW. COVID-19 and diabetes: Insulin requirements parallel illness severity in critically unwell patients. Clin Endocrinol 2020; 93: 390-3.

服用抗糖尿病藥在2019年新型冠狀病毒感染症之糖尿病人的挑戰

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摘　要

由嚴重急性呼吸道症候群冠狀病毒2型(severe acute respiratory syndrome coronavirus 2)所造成之2019年新型冠狀病毒感染症(coronavirus disease 2019)是一種先前未被發現並具有高度感染力的病毒性疾病，業已引發了全球性感染的危機。糖尿病控制不佳已被認為是2019年新型冠狀病毒感染症之預後不良的一個關鍵性危險因子。2019年新型冠狀病毒感染症會導致嚴重代謝功能失常、新發糖尿病與在內皮細胞功能異常的背景下所增加的血栓事件。目前有具體證據顯示當高血糖與其相關危險因子交互作用之下，將導致免疫系統與發炎反應的改變，如此一來，將使得個體容易感染到嚴重的2019年新型冠狀病毒感染症因而導致結果的惡化，其中包括有較高的死亡率在內。除了降血糖的作用之外，在感染2019年新型冠狀病毒感染症期間，抗糖尿病藥的多樣性效應(pleiotropic effects)能夠抑制病毒的活動、減輕內皮細胞功能的異常、緩解氧化效應和調解發炎與免疫系統的反應。這些作用使得抗糖尿病藥被重新思考使用作為糖尿病人感染2019年新型冠狀病毒感染症後之選擇用藥，用以對抗嚴重急性呼吸道症候群冠狀病毒2型所引起的海嘯。本篇綜論旨在探討糖尿病與2019年新型冠狀病毒感染症之間的關聯和這個疾病的病生理學對糖尿病的影響以及施用抗糖尿病藥對於糖尿病人當前2019年新型冠狀病毒感染症流行期間的潛在治療效果。鑒於人類感染嚴重急性呼吸道症候群冠狀病毒2型的短暫歷程，使得近期相關之研究所提供的資訊是有其受限制的。因此，進一步探討糖尿病人在感染2019年新型冠狀病毒感染症之後的最適當的血糖管理是有其必要性的。