Physiology and Pharmacology 28 (2024) 363-388
Review Article

The impact of antidiabetic medications on COVID-19 outcomes in diabetic patients: an overview

Malek Zarei[1*], Navideh Sahebi Vaighan[2], Sepideh Shiravand[2], Sara Mohammadvali-samani[2], Mohammad Abbas Sheikholeslami[2], Zahra Roudbari[3]

1. Shahid Beheshti University of Medical Sciences, Tehran, Iran
2. Brigham and Women's Hospital, Boston, Massachusetts, United States
3. Shiraz University of Medical Sciences, Shiraz, Iran

ABSTRACT

The advent of Coronavirus Disease 2019 (COVID-19), first identified in Wuhan, China, has led to significant mortality and morbidity worldwide, disproportionately affecting individuals with comorbidities such as diabetes mellitus (DM), cardiovascular diseases (CVDs), and obesity. Evidence suggests a strong correlation between DM and heightened risk of severe COVID-19 complications, which is thought to be exacerbated by factors such as hyperglycemia, systemic inflammation, immune dysregulation, and the increased expression of the angiotensin-converting enzyme 2 (ACE2) receptor in pancreatic cells. The interaction of COVID-19 with antidiabetic medications is complex, with varying reports on how these drugs may influence the disease trajectory in diabetic patients. This article seeks to synthesize the current literature on the role of antidiabetic agents in managing COVID-19 in patients with diabetes, elucidating their potential protective or adverse effects and providing a comprehensive overview of the evolving understanding of this critical interface.

Keywords:
COVID-19
Diabetic patients
Antidiabetic agents
COVID-19 outcomes

Introduction

The onset of the Coronavirus Disease 2019 (COVID-19) pandemic, instigated by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has precipitated a global healthcare crisis, overwhelming healthcare systems across numerous nations (Chen et al., 2020b; Zhu et al., 2020). Initially presenting with mild symptoms, COVID-19 can escalate into severe illness within two weeks, manifesting as Acute Respiratory Distress Syndrome (ARDS), Systemic Inflammatory Response Syndrome (SIRS), multiorgan dysfunction, and even shock (Wu and McGoogan 2020). Notably, the risk of severe outcomes, including higher morbidity and mortality, is significantly elevated in certain demographics: older individuals, males, and those with pre-existing health conditions such as obesity, Diabetes Mellitus

* Corresponding author: Malek Zarei, m.zarei@sbmu.ac.ir
Received 24 November 2023; Revised from 6 May 2024; Accepted 7 May 2024

Citation: Zarei M, Sahebi vaihan N, Shiravand S, Mohammadvali-samani S, Sheikholeslami M.A., Roudbari Z. The Impact of Antidiabetic Medications on COVID-19 Outcomes in Diabetic Patients: An Overview. Physiology and Pharmacology 2024; 28: 363-388. http://dx.doi.org/10.61186/phypha.28.4.363

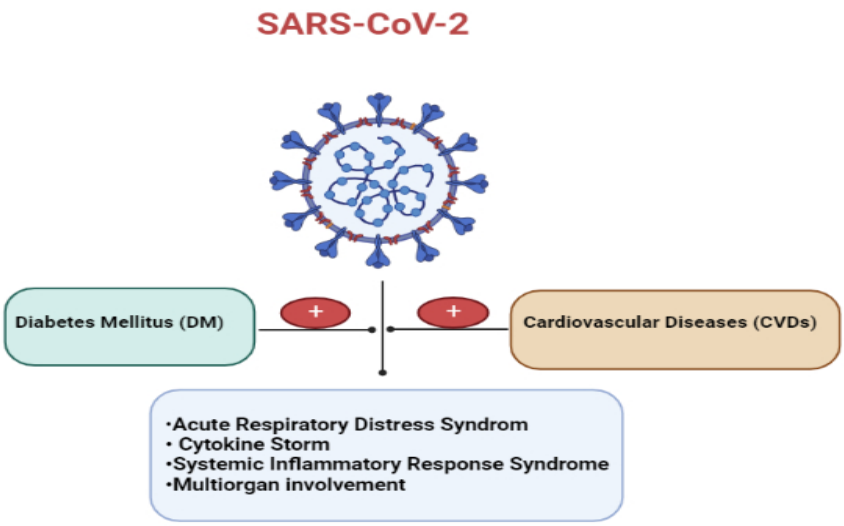

FIGURE 1. The impact of COVID-19 on the Diabetes Mellitus

(DM), and cardiovascular diseases (CVDs) (Goyal et al., 2020; Grasselli et al., 2020; Mortada et al., 2017) (Figure 1).

Data from various cohorts have underscored a stark correlation between DM and increased instances of COVID-19-related hospitalizations and fatalities (Stoian et al., 2020b). Diabetes not only heightens the probability of intense COVID-19 manifestations but also correlates with an uptick in hospital admissions and mortality rates (Stoian et al., 2020a). Several mechanisms are proposed to underpin this correlation: hyperglycemia induced by DM may exacerbate inflammation, immune dysregulation, and viral replication (Bojkova et al., 2020). Specifically, hyperglycemia could potentiate viral replication via the ACE2 receptor, which is integral to viral entry into host cells and is also expressed in pancreatic endocrine cells (Wang et al., 2015; Yang et al., 2010). Consequently, viral-induced damage to these cells can worsen pre-existing hyperglycemic conditions (Bojkova et al., 2020). Complicating matters, certain COVID-19 treatments, such as corticosteroids and antivirals, may further contribute to elevated blood sugar levels (Lim et al., 2021). Furthermore, inflammation, a hallmark of severe COVID-19, can precipitate insulin resistance by impacting the liver and skeletal muscles, both critical in glucose homeostasis (Šestan et al., 2018). It also increases the risk of macro- and microvascular complications in patients with Type 2 DM (T2DM) with pre-existed mild vascular inflammation due to chronic hyperglycemia (Cheema et al., 2020), putting them at a significantly higher risk of mortality due to COVID-19 compared to other patients (Basra et al., 2021; Holman et al., 2020) (Figure 2).

The dysregulation of immune responses in several diabetic patients is another factor exacerbating the clinical course of COVID-19 (Verma et al., 2021). Cytokine storm is the leading cause of inflammation-induced pulmonary damage, severe pneumonia, and subsequent death in severe COVID-19 (Zarei et al., 2021). In this context, the pharmacological profile of antidiabetic medications may significantly affect COVID-19 outcomes (Rizvi et al., 2021). Beyond glycemic control, certain antidiabetic agents have demonstrated anti-inflammatory effects in animal models, protecting lung function and modulating cytokine production (Groop et al., 1989; Šestan et al., 2018). However, some antidiabetic drugs have been contraindicated due to detrimental effects reported in the context of COVID-19 (Lim et al., 2021). This article provides a comprehensive overview of antidiabetic medications, exploring both their potential therapeutic benefits and adverse impacts on the clinical course of diabetic patients with COVID-19 (Table 1).

Oral antidiabetic agents

Metformin

Metformin, a biguanide derivative, is widely prescribed for the management of T2DM, CVDs, and various forms of cancer, and is noted for its roles in appetite

TABLE 1: Overview of Antidiabetic Agents and Their Effects on COVID-19 Outcomes

DRUG	Anti-inflammatory effect	Cardiovascular effect	Pulmonary effect	Nephrological effect	Mortality	Anti-viral
Metformin	Positive effect	-	Positive effect	-	Decrease	Positive effect
Sulfonylurea	Positive effect	-	-	-	No effect-Decrease	
TZDs	Positive effect	Positive effect/increase CVD-related mortality (only rosiglitazone)	Anti-fibrotic effect	Positive effect		Positive effect
GLP-1 and GIP	Positive effect	Positive effect	Positive effect	Positive effect	Decrease	Positive effect
DPP4 Inhibitors	Positive effect	-	-	-	Decrease	Positive effect
SGLT2 Inhibitors	Positive effect	Positive effect	Anti-fibrotic effect	Positive effect	Decrease	
Insulin	Positive effect	Positive effect	Negative effect	-	Paradoxical	
Bromocriptine	Positive effect	Positive effect	-	-	-	Positive effect

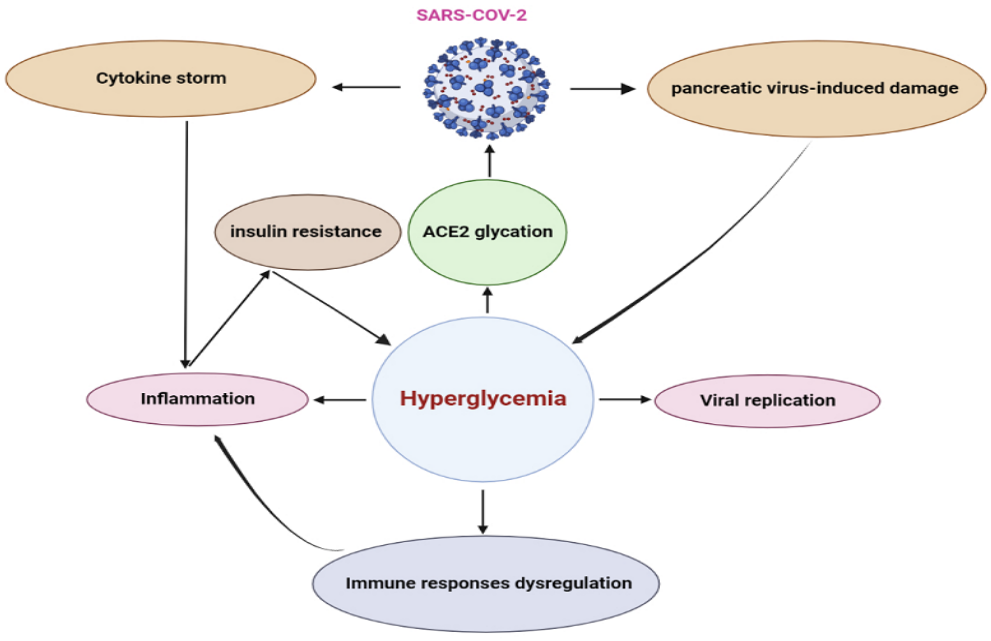

FIGURE 2. Mechanisms of SARS-CoV-2 Induced Hyperglycemia.

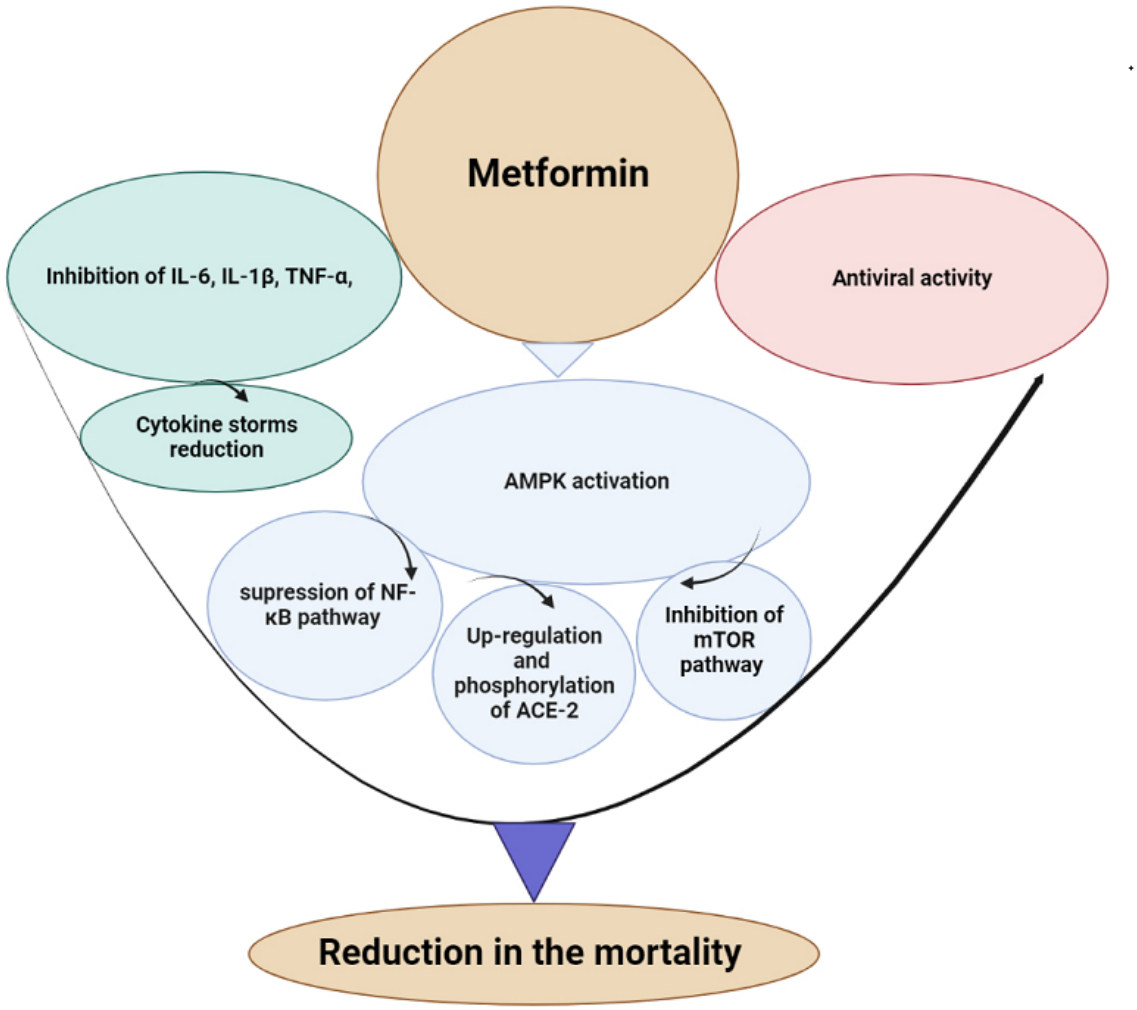

FIGURE 3. Evaluating the Therapeutic Benefits of Metformin in Managing COVID-19 in Diabetic Patients.

reduction and potential anti-aging benefits (Lv and Guo 2020). Recent studies advocate for metformin's efficacy in treating patients with these conditions (Chen et al., 2020c; Luo et al., 2020). attributing its therapeutic effects to hypoglycemic, anti-inflammatory, and antiviral mechanisms. Given the pivotal role of inflammation in COVID-19 severity and complications, metformin's anti-inflammatory action is particularly valuable, although some studies report conflicting results regarding these benefits (Sharma et al., 2020).

Metformin's direct anti-inflammatory effect is evidenced by its modulation of metabolic parameters (Bharath and Nikolajczyk 2021) and reduction in pro-inflammatory cytokines such as IL-1β and Tumor Necrosis Factor α (TNF-α), as observed in the lung tissue of rats with pulmonary inflammation and fibrosis. It also impedes the fibrosis process via the AMP-activated Protein Kinase (AMPK)-mTOR pathway (Li et al., 2021). In vitro studies reveal that metformin suppresses IL-6 production in monocytes infected with SARS-CoV-2 (Cory et al., 2021a), mitigates ARDS by curtailing cytokine release from lung macrophages (Xian et al., 2021), and curbs chronic inflammation by augmenting AMPK activity alongside antioxidant defenses (Martin-Montalvo et al., 2013). Metformin's activation of AMPK also leads to phosphorylation of ACE-2, altering the receptor's conformation and function, which may hinder SARS-CoV-2's cellular entry and enhance ACE2's stability, thus exerting a lung-protective effect (Malhotra et al., 2020). Additionally, the activation of AMPK by metformin can suppress the Nuclear Factor κB (NF-κB) pathway, implicated in acute lung injury (Zhang et al., 2011), and might modify mitochondrial or microbial functions (Malhotra et al., 2020).

Metformin has been documented to possess antiviral activities against both DNA and RNA viruses, facilitated by AMPK activation. This includes action against Hepatitis B and C Viruses (HBV, HCV) (Xun et al., 2014), dengue virus, Coxsackievirus B3 (CVB3) (Xie et al., 2015) and Kaposi sarcoma herpesvirus (Cheng et al., 2016). Notably, metformin impedes the production of HBV surface antigens and enhances the inhibitory effects of interferon-α2b and lamivudine on HBV antigen expression (Xun et al., 2014). When used alongside antiviral drugs such as peginterferon or ribavirin, metformin has been shown to improve HCV clearance (Romero-Gómez et al., 2009). Additionally, metformin diminishes viral replication and related myocarditis in CVB3-infected mice, thus improving survival rates (Xie et al., 2015). These observations suggest that metformin could play a beneficial role in SARS-CoV-2 infection management, especially when combined with other antiviral medications.

Epidemiological and clinical studies have explored the impact of metformin on diabetic patients with COVID-19. Epidemiological data indicate that pre-diagnostic metformin use may reduce mortality by as much as threefold (Cory et al., 2021b; Crouse et al., 2021). A retrospective study of 120 diabetic patients hospitalized with COVID-19 showed a significant mortality reduction among those treated with metformin (Chen et al., 2020c). Luo et al.'s multivariate analysis supports the direct benefits of metformin, demonstrating a fourfold decrease in mortality, independent of its glycemic control effects (Luo et al., 2020). Mortality reduction rates have varied across studies, from 20% to 80%. A meta-analysis by Hariyanto et al. indicated an average mortality decrease of 46%. Conversely, some studies have not found metformin to reduce disease severity or mortality (Izzi-Engbeaya et al., 2020; Kim et al., 2020; Philipose et al., 2020). and in certain cases, it has been linked to an increase in life-threatening complications (Gao et al., 2020). Concerns also exist regarding metformin's use in patients with concurrent T2DM and COVID-19 due to the potential for metabolic acidosis (Scheen 2020), leading to recommendations against its use in patients with acute respiratory distress and renal insufficiency (Samuel et al., 2021).

In summary, metformin may offer multiple therapeutic effects, including antiviral, vasculoprotective, immunosuppressive, and anti-inflammatory actions, beyond its hypoglycemic benefits. Consequently, its administration is advocated for diabetic patients with COVID-19, provided there is no heightened risk of acidosis (Figure 3).

Sulfonylureas

Sulfonylureas (SUs) and Glinides, pivotal in the pharmacotherapy of Type 2 Diabetes Mellitus (T2DM), are renowned for stimulating insulin secretion. They achieve this by inhibiting ATP-sensitive K+ channels in pancreatic beta cells, leading to the activation of voltage-gated $Ca2^{+}$ channels (Sola et al., 2015). Beyond their primary hypoglycemic action, these agents also exhibit anti-inflammatory effects. Hypoglycemia indirectly mediates anti-inflammatory responses (Kothari et al., 2016), while their direct anti-inflammatory effects are mediated by targeting the potassium channels abundantly expressed on the surfaces of monocytes and macrophages (Ji et al., 2014; Kothari et al., 2016). This dual mechanism allows SUs to dampen cytokine secretion from activated macrophages (Kewcharoenwong et al., 2013; Pompermayer et al., 2005), and leverage their antioxidant properties to enhance anti-inflammatory responses (Abdallah et al., 2011). Glibenclamide, in particular, has been noted to mitigate pulmonary inflammation by curbing cytokine release from type 2 T-helpers (Cui et al., 2015).

Furthermore, SUs have been implicated in the inhibition of the NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome, a key pro-inflammatory mediator in numerous inflammatory disorders (Hill et al., 2017; Lamkanfi et al., 2009; Yaribeygi et al., 2019). Glibenclamide's benefits extend to reducing inflammation in melioidosis and bronchopulmonary dysplasia in animal models, attributable to its inhibition of caspase-1 activation, reduction in IL-1β secretion, and suppression of neutrophil and macrophage influx. Studies in asthmatic animal models have demonstrated its efficacy in reducing airway inflammation through the attenuation of IL-5 and IL-13 levels (Zhang et al., 2017).

Despite the promising anti-inflammatory potential of SUs and Glinides, clinical outcomes in COVID-19 cases remain uncertain. Dalan et al.'s multivariate analysis showed no significant improvement in mechanical ventilation needs among SU users (Dalan et al., 2021). Moreover, another study by Kim et al. found no difference in mortality between the patients who used SUs and those who did not (Kim et al., 2020). Similarly, Coronavirus SARS-CoV-2 and Diabetes Outcomes (CORONADO)

reported no difference in the primary or secondary outcomes on days 8 and 28 between the patients receiving combinational therapy with SUs and glinide and those who did not (Cariou et al., 2020; Wargny et al., 2021). Further retrospective studies across the UK, Italy, and Belgium corroborate these findings, showing no substantial impact of SU/Glinide therapy on mortality risk in diabetic COVID-19 patients (Izzi-Engbeaya et al., 2020; Orioli et al., 2021; Silverii et al., 2021). However, isolated studies, such as those indexed in PROSPERO, suggest a potential mortality reduction associated with SUs in this patient demographic (Kan et al., 2021). An observational cohort even indicated a decreased risk of COVID-19-related mortality in diabetics on SU therapy (Khunti et al., 2021).

Considering the overall inconclusive impact of SUs on COVID-19, these drugs remain a viable option for glycemic management in diabetic patients with COVID-19. They can be prescribed as monotherapy or in conjunction with other antidiabetic agents like metformin, ensuring individualized patient care based on clinical judgment and patient-specific factors.

Thiazolidinediones (TZDs)

Thiazolidinediones (TZDs), specifically rosiglitazone and pioglitazone, are well-established oral hypoglycemic agents in the monotherapy or combined regimen for T2DM (Rosak et al., 2005). These agents function primarily through the modulation of Peroxisome Proliferator-Activated Receptors (PPARs), specifically targeting the PPAR-γ isoform. This interaction facilitates their regulatory effects on β cell function, lipid metabolism, and inflammatory processes (Inzucchi SE 2012). Additionally, TZDs are recognized for their role in mitigating urinary protein excretion and delaying diabetic nephropathy progression (P.A. Sarafidis 2010).

Among their notable properties, TZDs exhibit a pronounced impact on chronic inflammation, outperforming metformin and other insulinotropic agents like meglitinides and sulfonylureas in reducing inflammatory markers (Erem C 2014; Nissen SE 2008). Clinical investigations have illuminated the capacity of TZDs to significantly attenuate pro-inflammatory cytokines such as TNF-α and IL-6 (Xie X 2017). Extended treatment with pioglitazone has been demonstrated to downregulate IL-8, IL-6, and IL-1β in monocytes and lymphocytes (Zhang WY 2008). and it has been credited with reducing pulmonary fibrosis in rat models (Barbarin V. 2005). The pro-inflammatory cytokines elevated in severe COVID-19, like IL-6 and TNF-α, are among those modulated by TZDs, suggesting a potential therapeutic angle for managing inflammation in COVID-19 patients (Han et al., 2020).

Furthermore, TZDs wield a spectrum of cardioprotective effects, influencing tissue remodeling, cellular proliferation, and cytokine secretion, thereby playing a role in the inflammatory myocardial response (Turner NA 2007). PPAR-γ activation has been shown to suppress inflammatory gene expression in endothelial cells (Gao M 2011), and improve vascular function markers (Horio T 2005) highlighting their potential beyond glycemic control. Moreover, these drugs have various effects on myocardial perfusion, intimal proliferation in large vessels, thrombotic events, microalbuminuria, micro- and macro-vasculature, and lipid profile (Prigeon RL 1998). They also reduce systolic and diastolic blood pressures in comparison to other oral hypoglycemic medications or placebo, which can be explained by their improving effect on endothelial function and the Renin-Angiotensin-Aldosterone System (RAAS) (Ajjan RA 2016).

Pulmonary complications of COVID-19, including progressive consolidation and fibrosis, may be attenuated by $PPAR_c$ agonists through interference with the Tissue Growth Factor (TGF-β) signaling and myofibroblast differentiation, showcasing their anti-fibrotic potential (Turner NA 2007). Moreover, the antiviral capabilities of PPAR agonists, such as countering severe viral diseases (Darwish 2011), and improving outcomes in influenza models, also underscore their potential utility in COVID-19 treatment(Darwish et al., 2011).

Despite their benefits, caution is warranted due to TZDs' association with complications similar to diabetes sequelae, particularly concerning congestive heart failure and myocardial infarction risks (Davidson et al., 2018). Rosiglitazone, in particular, has come under scrutiny for its potential to increase cardiovascular mortality, whereas pioglitazone does not exhibit these adverse effects when used in monotherapy (Komajda M 2005).

With their pronounced anti-inflammatory effects, glucose-lowering capabilities, and emerging antiviral properties, TZDs, particularly pioglitazone, may offer therapeutic benefits in the management of diabetic patients with COVID-19. However, a patient-specific approach must be adopted, weighing the benefits against the risks,

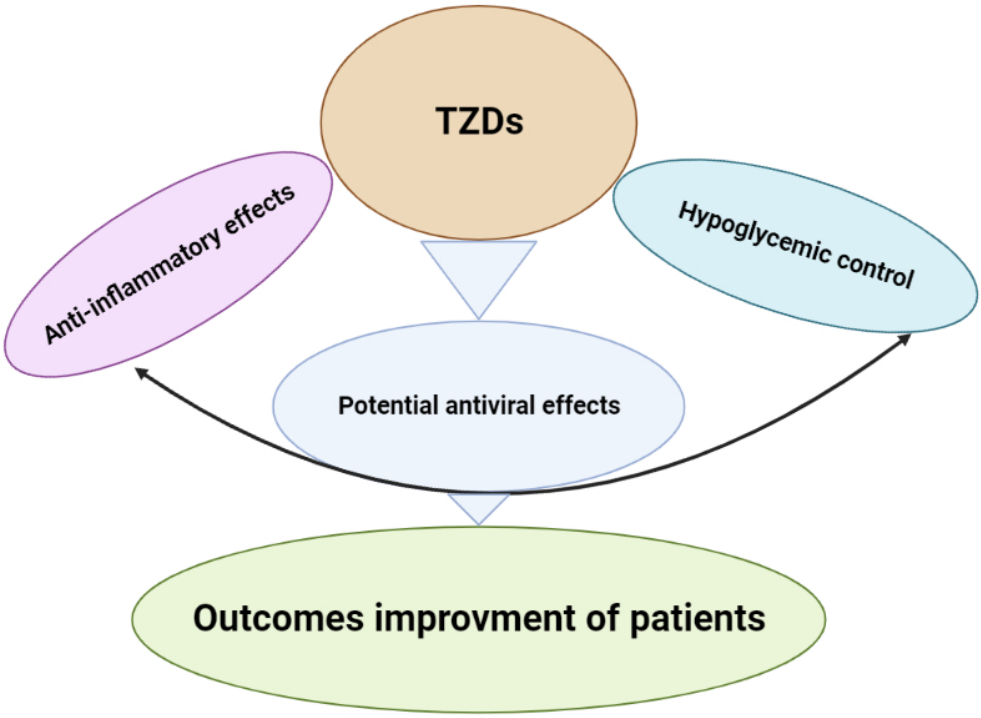

FIGURE 4. Assessing the Effects of Thiazolidinediones on COVID-19 Outcomes in Patients with Diabetes Mellitus.

especially in the context of cardiovascular disease (Figure 4).

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

Dipeptidyl Peptidase-4 (DPP-4) inhibitors represent a class of novel antihyperglycemic agents that, when combined with established diabetes medications, enhance therapeutic outcomes. DPP-4's primary role involves the degradation of incretin hormones, which regulate glucose metabolism and insulin secretion. By inhibiting DPP-4, these medications prolong the action of incretins, thereby bolstering postprandial insulin secretion and tackling insulin resistance (Bassendine MF 2020), while also modulating inflammatory processes through M1/M2 macrophage polarization and GLP-1-mediated pathways (Iacobellis 2020). Interestingly, studies have shown that the spike protein of the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), a close relative of SARS-CoV-2, has an affinity for DPP-4 (Lu et al., 2013). Although the molecular studies have not fully confirmed the cellular entry of SARS-CoV-2 mediated by DPP-4, structural models suggest the interaction of the spike protein of SARS-CoV-2 with CD26, which is the membrane-bound DPP-4 (Vankadari N 2020). This molecule is found on the surface of several cell types, such as lymphocytes, and has an immunoregulatory interaction with adenosine deaminase (Morimoto C 1998). Considering these findings, DPP-4 inhibitors may prevent the cellular entry of SARS-CoV-2, thereby improving the subsequent pulmonary inflammation and cytokine storm (Kawasaki et al., 2018; Shao et al., 2020). However, the functional assay study refused the role of DPP-4 in the internalization of SARS-CoV-2 into host cells (Hoffmann et al., 2020).

It has been shown that immune system hyperactivation is the key to the pathogenesis of critical COVID-19 and its severe complications, including sepsis, cardiorespiratory collapse, Disseminated Intravascular Coagulation (DIC), and multiorgan failure (Lim MA 2020). Such hyperactivation leads to cytokine storm, characterized by elevated levels of cytokines and inflammatory markers, such as interleukins, TNF-α, CRP, D-dimer, ferritin, and procalcitonin (Huang et al., 2020). It is known that DPP-4 is involved in immunoregulation by increasing lymphocyte proliferation, activating T cells, modifying the NF-κB pathway, increasing the CD86 expression (Bassendine MF 2020), and promoting the cleavage of certain growth factors, chemokines, and cytokines (Iacobellis 2020). According to a study on transgenic obese mice expressing human DPP-4, as well as a

genetic association study on humans, the higher severity of MERS-CoV in patients with T2DM may be due to an immune dysregulation mediated by DPP-4 (Li K 2016). Moreover, it is suggested that DPP-4 inhibitors can inhibit the overexpression of inflammatory cytokines and markers, including CRP, TNF-α, IL-6, and IL-1, improving the clinical outcomes of COVID-19 (Liu X 2017). Some human studies have reported the effect of sitagliptin (the first DPP4 inhibitor approved for DM therapy) on decreasing the plasma levels of CRP and IL-6 (Makdissi A 2012). Besides, vildagliptin significantly reduced the levels of IL-6 (Birnbaum et al., 2016), while another study reported the effectiveness of saxagliptin in decreasing the serum levels of IL-6, IL-18, IL-1β, TNF-α, and CRP and attenuating the inflammasome activation (Birnbaum et al., 2016). However, other studies have not shown the effect of DPP-4 inhibitors on inflammatory marker levels (Nomoto H 2017; Sromova et al., 2016; Tsurutani et al., 2017). Furthermore, Baggio et al. did not find a significant change in the plasma levels of soluble DPP-4, CRP, TNF-α, and IL-6 in COVID-19 patients after administrating sitagliptin compared to baseline values (Baggio et al., 2020). Considering the above, it is recommended to prescribe these drugs based on the individual needs of the patients (Hariyanto and Kurniawan 2021).

According to the adverse drug reaction database of the World Health Organization (WHO) in 2011, upper respiratory tract infections are more prevalent in patients taking DPP-4 inhibitors compared to those using other drugs for DM (Willemen MJ 2011). However, available observational studies or randomized controlled trials demonstrate that DPP-4 inhibitors do not increase the risk of contracting respiratory tract infections (Nomoto H 2017). Also, previous studies reported no relationship between the use of DPP-4 inhibitors and the prevalence of community-acquired pneumopathy due to any reason (Pascal KE 2015). Also, a large cohort on the safety of DPP-4 inhibitors reported that these drugs were safe in patients with T2DM before being admitted to the hospital for COVID-19 (Fadini GP 2020).

According to the CORONADO study, no independent correlation between DPP-4 inhibitors and the severe course and prognosis of COVID-19 was reported (Cariou et al., 2020), which is consistent with the results of a meta-analysis reporting no effect of DPP-4 inhibitors on severity or mortality of patients with COVID-19 (Hariyanto and Kurniawan 2021). Moreover, an observational study in Italy reported that there were no outcome differences between diabetic patients hospitalized for COVID-19 who have already had DPP-4 inhibitors and those without these drugs (Willemen MJ 2011). On the contrary, a multicenter retrospective observational study by Solerte on patients with COVID-19 who were hospitalized and receiving sitagliptin showed a reduced rate of mortality, an improvement in outcome, and a higher discharge rate compared to those receiving standard care (Solerte SB 2020). Moreover, in a meta-analysis by Rakhmat et al., DPP-4 inhibitors could reduce the mortality of patients with COVID-19, although this effect was weaker in patients using ACE Inhibitors (ACE-I) or metformin. However, since ACEIs, Angiotensin Receptor Blockers (ARBs), and metformin can decrease COVID-19-related mortality, these drugs were usually administered to diabetic patients. Therefore, further analyses are needed to illustrate whether the effect of DPP-4 inhibitors is dependent on metformin, ACEIs, or ARBs (Rakhmat et al., 2021). Other recent studies showed that the DPP-4 inhibitors reduced (Mirani et al., 2020; Solerte SB 2020) or did not (Kim et al., 2020; Yan et al., 2020) change the mortality of diabetic patients with COVID-19 before or during hospital admission.

Bearing the aforementioned points in mind, DDP-4 inhibitors can be prescribed for or be continued in patients with DM and COVID-19 based on their needs with no concern of deleterious effects on the outcome of COVID-19.

Sodium-Dependent Glucose Cotransporter-2 (SGLT2) Inhibitors

Sodium-Glucose co-Transporters (SGLTs) and Glucose Transporters (GLUTs) are two groups of transporters involved in all kinds of glucose transportation, including cellular glucose release and uptake, glucose transport across the blood-brain barrier, renal glucose reabsorption, and enteral glucose absorption (Cure E 2020). Among all types of SGLTs, SGLT-2 contributes to renal glucose reabsorption and is found in the S1 and S2 segments of the renal proximal convoluted tubules (Wright EM 2004). Beyond their antidiabetic effects, SGLT-2 inhibitors exert various beneficial effects, including cardioprotective, anti-inflammatory, and nephroprotective effects in diabetic patients with or without COVID-19.

SGLT-2 inhibitors exert cardioprotective effects, probably independent of their hypoglycemic control. These effects are through different mechanisms, including decreasing cardiac inflammation and fibrosis, increasing the ketone body use for cardiac metabolism, inhibiting the myocardial sodium-hydrogen exchanger, and inducing osmotic diuresis and natriuresis (Cowie and Fisher 2020). Studies have reported the significantly decreasing effect of these drugs on new-onset arrhythmias and their improving effects on heart failure with preserved ejection fraction, which is not common in obese and diabetic patients (Chen et al., 2020a). Moreover, the DARE-19 trial (NCT04350593) and another clinical trial (NCT04393246) on patients admitted to the hospital with decompensated heart failure have shown that SGLT-2 inhibitors can exert their nephroprotective and cardioprotective effects under acute conditions, such as in patients with COVID-19, without causing additional risks. Thus, they can be administered during COVID-19 for facilitated recovery, decreased mortality and morbidity, and organ protection. However, this hypothesis requires more investigations on patients hospitalized due to COVID-19.

It has been reported that about 75% of COVID-19 patients have a type of renal involvement (hematuria, proteinuria, or AKI), which can increase mortality significantly (Ronco and Reis 2020). The renal problems in COVID-19 patients can be due to renal tissue inflammation or cardiomyopathy leading to endothelial injury and subsequent cardiorenal syndrome type 1. Moreover, there is a possibility that the virus can directly cause tubulointerstitial damage and tubulopathy (Verma et al., 2019). A study by Menon et al. reported that COVID-19 and diabetes had common underlying mechanisms of renal disorders. According to their results, expression patterns of ACE-2-positive epithelial cells of the proximal tubule in diabetic renal disease overlap with those observed in cells infected with SARS-CoV-2. According to some preclinical studies, SGLT-2 inhibitors can temporarily activate the intra-renal and systemic RAAS for water and sodium loss compensation, especially after the therapy initiation in patients with COVID-19 (Menon et al., 2020). This may increase the angiotensin II levels, causing inflammation. However, these drugs seem to have organ-protective effects in combination with ACE despite causing volume depletion leading to RAAS activation. It is unclear whether such activation occurs in patients with the recent initiation of SGLT-2 inhibitors or those with long-term use of these drugs (Li et al., 2018). In addition, it has been reported that canagliflozin could decrease the levels of fibronectin, Matrix Metalloproteinases (MMPs), IL-6, and TNF receptor 1 in an experimental model of diabetic renal disease indicating the effect of SGLT-2 inhibitors in reversing the molecular processes leading to kidney fibrosis and inflammation (Heerspink et al., 2019).

On the other hand, SGLT-2 inhibitors can decrease the levels of inflammatory cytokines, especially those with direct roles in cytokine storms induced by COVID-19, regardless of the blood glucose levels of the patients. These drugs have potential anti-inflammatory effects and decrease the volume of the interstitial fluid selectively, which may improve the condition of COVID-19 patients (Sarafidis et al., 2019). Moreover, preclinical studies have shown the lung-protective effect of SGLT-2 inhibitors by reducing tissue inflammation, hypoxia, and oxidative stress (Sarafidis et al., 2019). A study investigated the effect of daily administration of empagliflozin (10 mg for 5-7 days) on 3 non-diabetic patients admitted to the hospital with COVID-19 who had severe bilateral viral pneumonia, showing the ineffectiveness of the intervention. However, the mentioned study did not have a control group, and all 3 patients survived (Bossi et al., 2020).

Previous studies have reported a strong relationship between COVID-19 and long-lasting ketosis and DKA in diabetic patients. SARS-CoV-2 can bind to hemoglobin, it can result in a state of tissue hypoxia that further elevates the production of lactate. Moreover, SARS-CoV-2 may have direct diabetogenic effects, exerted by injuring pancreatic beta cells and subsequently disrupting insulin secretion. These problems, together with increased insulin resistance caused by systemic inflammation, may lead to insulin deficiency and DKA (Batista et al., 2021). On the other hand, SGLT-2 inhibitors are reported to increase the risk of Diabetic Ketoacidosis (DKA) by 2 times compared to other hypoglycemic agents or placebo(Scheen 2019). This effect has especially been observed in the elderly with long-term T2DM and decreased insulin secretion. Hence, several healthcare institutions have declared their concerns regarding the SGLT-2 inhibitor administration in diabetic patients with COVID-19 (Li et al., 2020; Rayman et al., 2020). However, the significance of the effect of SGLT-

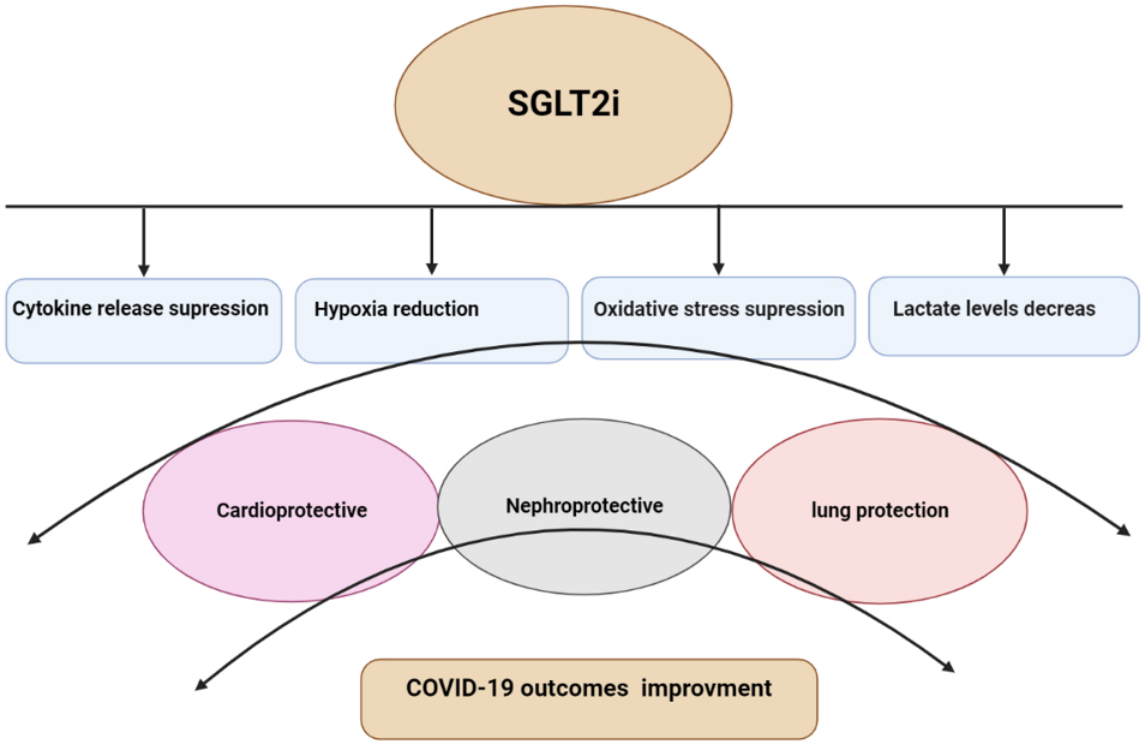

FIGURE 5. The relationship between SGLT2 Inhibitors and COVID-19.

2 inhibitors on increasing the DKA risk in COVID-19 patients, particularly those with severely decreased insulin levels, is still unknown (Fernandez-Fernandez et al., 2020). Dapagliflozin can prevent cellular injury and death through lactate level decrease and tissue oxygenation improvement. In addition, it exerts cytoprotective effects by Na^+/H^+ exchanger inhibition and preventing cellular pH decrease (Cure and Cure 2020). According to a systematic review of COVID-19 patients who had combined hyperglycemic hyperosmolar syndrome and DKA or DKA alone, a minimal number of 7 out of 110 were using SGLT-2 inhibitors (Górriz et al., 2020). On the other hand, some clinicians believe SGLT-2 inhibitors should be discontinued in patients admitted to the hospital with COVID-19 (Bornstein et al., 2020; Cerielloet al., 2020a; Mirabelli et al., 2020; Palermo et al., 2020). Also, it is recommended to stop SGLT-2 inhibitors in all patients at high risk for severe COVID-19, such as those with a history of T2DM, hypertension, atherosclerosis, heart failure, CVDs, or renal disease (GFR < 25 mL/min/1.73 m2). However, no study has ever supported this recommendation. Patients with COVID-19 may have decreased oral intake or dehydration due to fluid loss through breathing, fever, or diarrhea, which may increase the chance of DKA. Therefore, it is better to personalize this recommendation to patients with COVID-19 who are at increased risk of fluid depletion to minimize the risk of renal problems and DKA (Fernandez-Fernandez et al., 2020).

In general, it seems that SGLT-2 inhibitors exert anti-inflammatory, lactate-decreasing, and organ-protective effects, such as cardio- and nephro-protection. All these effects can be beneficial for diabetic patients with COVID-19. However, it should be noted that these drugs may increase the risk of DKA, especially in diabetic patients with COVID-19 (Figure 5).

Central-Acting Dopamine Agonist (Bromocriptine)

Dopamine-related pathways play an important role in the metabolisms of lipids and carbohydrates (Al-lami et al., 2018). Bromocriptine-QR (B-QR), a central-acting dopamine agonist has been approved in the United States for the treatment of T2DM and exerts its effects through sympathetic and dopaminergic tone resetting inside the central nervous system (Kumar et al., 2013). Moreover, it is generally safe, does not bear a risk of hypoglycemia or weight gain, and can potentially decrease the risk of cardiovascular accidents in patients (Gaziano

et al., 2010; Gaziano et al., 2012).

Regardless of the antidiabetic effects of bromocriptine, the studies by Chan et al. (2017) and Kato (2016) reported its antiviral effects on the zika and dengue viruses, respectively (Chan et al., 2017; Kato et al., 2016). Moreover, studies investigating the promising drugs for the treatment of COVID-19, such as tadalafil, ergotamine, and simeprevir, have reported the antiviral effect of bromocriptine on the SARS-CoV-2 through noncovalent interactions with one of its main proteases (Bibi et al., 2021; Rahman et al., 2021). Additionally, it has been shown that bromocriptine can significantly reduce the levels of high-sensitivity C-reactive protein (hsCRP) and TNF-α after a 12-week course of treatment, suppressing the metabolic inflammatory response associated with obesity (Al-lami et al., 2018). The inhibitory effect of bromocriptine and cabergoline on the low-grade systemic inflammatory response has been previously reported in two studies (Krysiak and Okopien 2015; Krysiak et al., 2014). Moreover, evidence has shown that bromocriptine has protective effects against CVDs by modulating the circadian functions of the hypothalamus, leading to decreased sympathetic drive and activity of the hypothalamus-pituitary-adrenal axis. Subsequently, the related cardiometabolic effects that may lead to vasoconstriction, production of nitrogen and oxygen-reactive species, inflammation, arteriosclerosis, and endothelial dysfunction are attenuated (Chamarthi et al., 2015; Lambert et al., 2010). Several studies have shown the inhibiting effect of B-QR on metabolic disturbances and CVDs in patients with T2DM (Chamarthi et al., 2016; Chamarthi et al., 2015; Gaziano et al., 2012). Furthermore, bromocriptine improves the lipid profile in obese patients by causing significant reductions in TG and LDL levels (Al-lami et al., 2018; Kamath et al., 1997), which can be explained by resetting the abnormally elevated hypothalamic noradrenergic tone, leading to lipolysis inhibition and FFA and TG level reduction (Kamath et al., 1997). Considering the above effects, bromocriptine can be particularly useful for diabetic patients with CVDs or non-diabetic patients with CVD risk factors (Krysiak and Okopien 2015).

Besides the mentioned points, the potential therapeutic effects of bromocriptine on COVID-19 can be explained by the effect of this drug on the patients' Body Mass Index (BMI), which can independently increase the risk of critical illness (Petrilli et al., 2020), need for mechanical ventilation, and mortality in the COVID-19 patients (Cariou et al., 2020). Also, another independent risk factor for critical COVID-19 is the blood glucose level upon admission (Wu et al., 2020a), which can be affected by bromocriptine administration. However, to the best of our knowledge, no study has ever evaluated the effect of bromocriptine in patients with COVID-19. Therefore, we recommend investigating the potential efficacy of this drug in diabetic patients with COVID-19. It is expected that it is most beneficial in diabetic patients with COVID-19 who have already been using that for other indications.

Insulin

Insulin, a critical physiological hormone, plays a key role in modulating serum glucose levels. Various recombinant insulin formulations, differentiated by their action durations, are employed to manage different types of DM (Chisholm-Burns et al., 2019). For instance, long-acting insulin analogs such as insulin glargine are suggested for managing hyperglycemia in diabetic patients with COVID-19, especially for those experiencing respiratory distress. Such analogs avoid the peak action delay characteristic of endogenous and regular insulin preparations (Bornstein et al., 2020; Gupta et al., 2020; Kalbhande and Kuldeep; Kosinski et al., 2020; Longo et al., 2020). However, there is an associated risk of hypoglycemia, a concern particularly acute for patients in the Intensive Care Unit (ICU) (Control and Group 1997; Group 2008). Indeed, insulin-induced hypoglycemia, documented in approximately 10% of Wuhan's diabetic COVID-19 patient population, could potentially compromise immune function(Iqbal et al., 2019; Zhou and Tan 2020), increasing the risk of shock, the need for dialysis, and mechanical ventilation requirements in ICU patients (Finfer et al., 2009; Riahi et al., 2021; Yu et al., 2021). The efficacy and safety of insulin therapy in diabetic patients with COVID-19 remain subjects of debate.

A retrospective analysis suggested that insulin therapy correlates with higher mortality, even after adjusting for confounding factors influencing disease severity. Moreover, insulin therapy enhanced inflammation and multiorgan damage in diabetic patients with COVID-19 (Yu et al., 2021). Some mechanisms proposed for the poorer prognosis in COVID-19 associated with insulin therapy include an elevated risk of hypoglycemia

(Yu et al., 2021), heightened levels of pro-inflammatory cytokines such as IL-6 and IL-1β-dependent CRP (Donath 2021), Moreover, in diabetic rats with sepsis insulin increased inflammation in lungs (Filgueiras et al., 2014), and exacerbated pulmonary inflammation — particularly concerning as the lungs are a primary target for SARS-CoV-2(Yang et al., 2021). Insulin may amplify pro-IL-1β maturation in activated macrophages via the NLRP3 inflammasome (Dror et al., 2017), which is implicated in the COVID-19 inflammatory response (Siu et al., 2019). Moreover, as an anabolic hormone, insulin leads to weight gain, increased appetite, and suppressed lipolysis in the muscle and adipose tissue, contributing to the development of obesity (Jacob et al., 1999; Kolb et al., 2020). Additionally, insulin's anabolic effects may contribute to obesity—a condition marked by chronic inflammation and an increased risk of severe COVID-19—thus potentially exacerbating the disease's severity. Therefore, the immune disturbances caused by insulin therapy and obesity may explain the association observed between insulin therapy and adverse outcomes in COVID-19 (Wu et al., 2020b).

On the other hand, it is suggested that insulin's anti-inflammatory properties, distinct from its glucose-lowering capabilities, may confer benefits in the context of the excessive inflammation seen in COVID-19 (Avogaro et al., 2021). Insulin has been shown to modulate ACE2-R/SARS-CoV-2 binding by altering ACE2-R glycosylation, enhancing immune function, and mitigating cytokine storms by dampening inflammatory mediator synthesis (Kalbhande and Kuldeep). Although direct interactions with ACE2 have not been conclusively demonstrated, insulin has been observed to reduce ADAM-17 expression, a sheddase that regulates ACE2 activity, in diabetic Akita mice (Salem et al., 2014); however, this effect has yet to be confirmed in pulmonary tissues (Pal and Bhadada 2020). Insulin's anti-inflammatory effects are extensive, including the inhibition of ROS production, NF-κB activity, and the expression of various inflammatory markers such as MCP-1 and ICAM-1 (Aljada et al., 2002; Dandona et al., 2003). It also downregulates inflammatory mediators like MIP-1β and CCL5 (Ghanim et al., 2010). In this regard, some studies have linked insulin therapy in diabetic patients with COVID-19 to a reduced risk of severe disease, less frequent hospital admissions, and lower mortality rates (Chaudhuri and Umpierrez 2012; Dandona and Ghanim 2021; Marfella et al., 2009; Sardu et al., 2020). Notably, insulin may mitigate COVID-19-associated hypercoagulability by modulating PAI-1 levels, enhancing thrombolysis, and inhibiting platelet aggregation (Kahn et al., 1993; Yudkin 1999). Diabetic COVID-19 patients on insulin therapy have also demonstrated improved glycemic control and reduced D-dimer levels (Sardu et al., 2020).

Despite these insights, insulin remains indispensable for managing diabetes and preventing its complications. Abrupt cessation of insulin therapy in diabetic patients with COVID-19 is not advisable without a viable alternative for glucose management. Furthermore, patients with severe COVID-19 may require higher insulin doses and longer periods to achieve normoglycemia due to the inflammatory state (Wu et al., 2020b). Thus, insulin therapy is essential for COVID-19 patients with advanced COVID-19. Additionally, the potential for insulin to exacerbate hypokalemia, an issue in COVID-19 patients possibly due to elevated aldosterone levels induced by high serum angiotensin II, must be monitored closely (Bornstein et al., 2020).

Non-insulin injectable agents

Glucagon-Like Peptide 1 (GLP-1) Agonists

As an incretin secreted from the intestine, GLP-1 is involved in serum glucose level regulation by stimulating the secretion of insulin and suppressing the secretion of glucagon (Lee 2022). GLP-1, an incretin hormone secreted by the intestine, plays a crucial role in the regulation of blood glucose levels by stimulating insulin secretion and inhibiting glucagon release (Belančić et al., 2021). These agents effectively mitigate hyperglycemia and glucose variability without significantly increasing hypoglycemia risk (Lee 2022).

COVID-19 disrupts immune responses, causing excessive inflammation marked by elevated levels of cytokines like Interferon gamma-induced Protein 10 (IP-10), MCP-1, TNF-α, IL-6, and IL-1β. This heightened inflammatory response accelerates disease progression (Liu et al., 2020; Zhang et al., 2020). Moreover, SARS-CoV Unique Domain (SUD) directly activates the NLRP3 inflammasome in alveolar epithelial cells, modulating the C-X-C motif chemokine Ligand 10 (CXCL10)-mediated pulmonary inflammation (Chang et al., 2020). On the other hand, the binding of GLP-1R to the GLP-1 or GLP-1RA inactivates the protein kinase C or NF-κB, leading to the underexpression of MCP-1,

Interferon γ (IFN-γ), Vascular Cell Adhesion Molecule 1 (VCAM-1), IL-6, TNF-α, IL-1β, and NLRP3, as well as monocyte adhesion inhibition through activating the phosphorylated AMPK, Ca^{2+}/Calmodulin-dependent protein Kinase Kinases β (CaMKKβ), and cAMP/Ca^{2+} (Lee and Jun 2016). GLP-1RAs have demonstrated significant anti-inflammatory effects, including modulation of eNOS/sGC/PKG signaling pathways and suppression of pro-inflammatory cytokines (Jin and Liu 2020). In animal studies, GLP-1RAs like liraglutide have shown efficacy in reducing oxidative stress, inflammatory mediators, and mortality, and in preventing thrombocytopenia and microvascular thrombosis in the pulmonary vasculature (Shah et al., 2019). Moreover, studies have reported the effect of GLP-1RAs on reducing CRP levels (Mazidi et al., 2017) and in vitro anti-inflammatory and antioxidant properties of liraglutide (Mei et al., 2019; Shiraki et al., 2012), especially in patients with T2DM (Zhang et al., 2018) or those with myocardial infarction without ST-segment elevation (Chen et al., 2016).

Furthermore, there are reports that GLP-1RAs improve pulmonary function in diabetic patients by directly affecting the pulmonary tissue, which is not related to the serum glucose levels of these patients (Rogliani et al., 2019). Moreover, they alleviate lung inflammation, decrease the production of cytokines, and preserve pulmonary function in rat and mouse models affected with experimental pulmonary damage (Toki et al., 2018; Viby et al., 2013; Zhou et al., 2016). Animal studies have shown that liraglutide can prevent acute lung injury and extravasation of neutrophils induced by lipopolysaccharides by strengthening the tight junctions, preventing the adhesion of neutrophils, and inhibiting their migration (Xu et al., 2019). Rogliani et al., reported that GLP-1RA administration can improve the spirometry parameters in diabetic patients with no obstructive pulmonary problems, regardless of the glucose levels of the patients (Rogliani et al., 2019). Moreover, these drugs reduce the mortality and complications within one month from the COVID-19 diagnosis (Rogliani et al., 2019) and are not accompanied by an increased risk of pneumonia, respiratory tract infections, or ARDS in patients with cardiovascular diseases, diabetes, or other comorbidities, especially during the COVID-19 pandemic (Patoulias et al., 2021). Also, the patients taking both SGLT2 inhibitors and GLP-1RAs had a lower chance of mortality and hospital admission due to COVID-19 compared to those only taking DPP-4 inhibitors (Kahkoska et al., 2021). A study investigating lung fibrosis in mice reported that GLP-1RAs decreased the hydroxyproline and collagen expression, inhibited the enzymes related to idiopathic pulmonary fibrosis, increased surfactant production, and suppressed inflammation (Fandiño et al., 2020). In addition, it is suggested that GLP-1RAs can alleviate the IPF by inhibiting the NF-κB pathway (Si et al., 2014). This mechanism is probably mediated by reduced levels of TGF-β (Li et al., 2012; Oda et al., 2016). Therefore, GLP-1 is involved in both chronic and acute lung injury. Moreover, several clinical studies reported that SARS-CoV-2 can decrease the level of surfactants (Sazgarnejad et al., 2021), while GLP-1RAs not only can inhibit the cellular entry of SARS-Cov-2 through binding to ACE2-R (Catrinoiu et al., 2020; Lee and Jun 2016) but, the subsequent ACE2 overexpression could increase the production of Surfactant Proteins A and B (SP-B, SP-A) in the pulmonary tissue (Romaní-Pérez et al., 2015), decreasing the breathing work (McCormack and Whitsett 2002).

As previously mentioned, patients with CVDs and diabetes are at a higher risk of severe COVID-19 and related mortality. GLP-1R is present in the heart tissue (Wei and Mojsov 1995), through which the GLP-1 exerts its cardiovascular effects (Mudaliar and Henry 2010), including blood pressure decrease through stimulating the Atrial Natriuretic Peptide (ANP) secretion (Kim et al., 2013) and endothelial function improvement in the patients with diabetes (Ceriello et al., 2011). Moreover, it can stimulate endogenous antioxidant production, protecting the cardiac cells against apoptosis (Saraiva and Sposito 2014). Therefore, regardless of their glucose-lowering effects, SGLT2 inhibitors and GLP1-RAs are recommended by the American Diabetes Association as a suitable second-line treatment for diabetic patients who are at high risk for cardiovascular diseases or have confirmed atherosclerotic cardiovascular disease (Association 2020). It has been shown that COVID-19 patients with cardiovascular disease have a worse prognosis compared to other patients, and GLP1-RAs have beneficial and cardioprotective effects (Ceriello et al., 2020b). Therefore, they are expected to be useful for these patients. Nevertheless, it has been shown that GLP-1 levels have a positive relationship with the atherosclerosis of the coronary arteries, an important comorbidity in patients with COVID-19 (Grze-

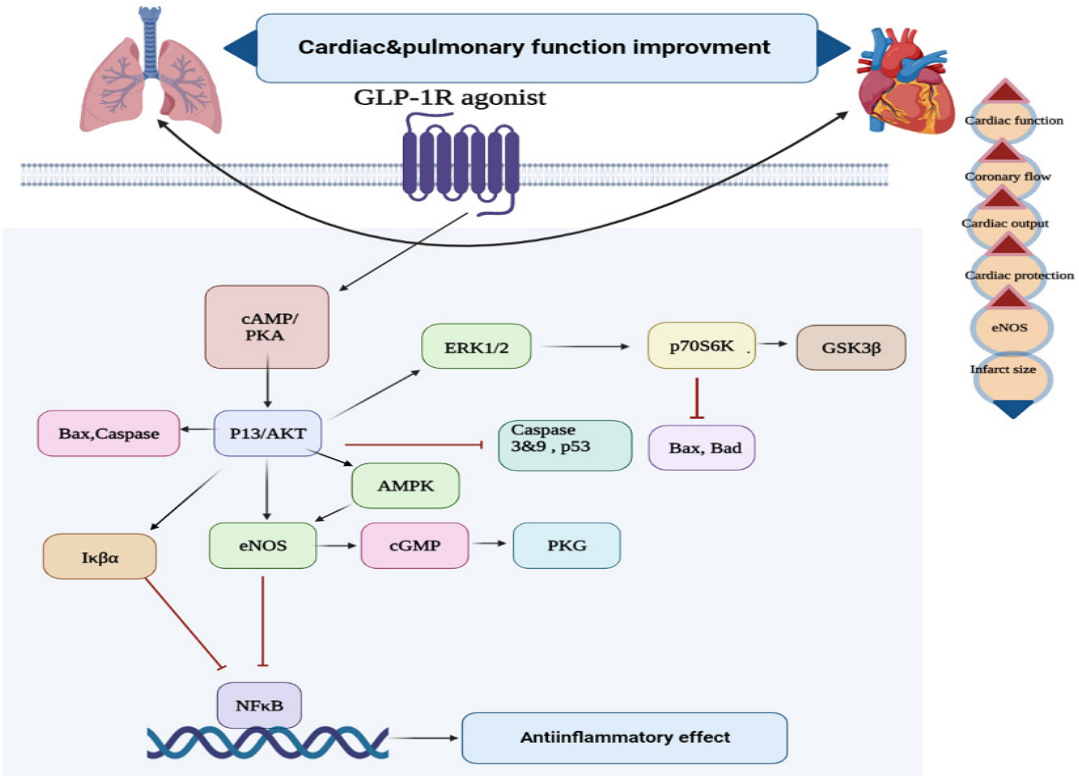

FIGURE 6. GLP-1 Agonists in COVID-19: Cardiovascular, Renal, and Pulmonary Protective Effects and Their Impact on Patient Outcomes.

gorowska and Lorkowski 2020; Piotrowski et al., 2013), which needs to be further investigated.

GLP-1 is involved in the olfactory and taste signaling pathways as a neurotransmitter coordinating between the Central Nervous System (CNS) and peripheral organs (Martin et al., 2009). It is expressed in type I and II taste cells, while its receptor is expressed in nerve fibers involved in taste in rodents and mice (Takai et al., 2015). According to studies, mice without GLP-1R have a remarkably decreased ability to taste sweet things (Müller et al., 2019). Moreover, the mRNAs of GLP-1R and the GLP-1 precursor, pre-proglucagon, are expressed in the olfactory bulb cells. Therefore, GLP-1 is probably involved in signal transmission from the olfactory epithelium to the CNS (Merchenthaler et al., 1999). On the other hand, several patients with COVID-19 may develop anosmia and dysgeusia, which are not associated with nasal congestion. The mechanisms of these symptoms are not illustrated yet; however, it has been suggested that low levels of serum GLP-1 may increase the risk of these symptoms in patients with COVID-19 (Ben-Chetrit et al., 2021).

In summary, GLP-1RAs offer a range of beneficial cardiovascular, pulmonary, and anti-inflammatory effects for patients with diabetes and COVID-19. While some studies have debated the superiority of GLP-1RAs over SGLT2 inhibitors due to concerns about ACE-2 overexpression, the overall evidence supports their use in managing these patients (Israelsen et al., 2021; Romaní-Pérez et al., 2015; Sandooja et al., 2020) (Figure 6).

Conclusion

Diabetes mellitus (DM) exacerbates both the mortality and morbidity associated with COVID-19. Beyond glycemic control, antidiabetic drugs may confer additional benefits through their anti-inflammatory, antiviral, and organ-protective properties, potentially improving COVID-19 outcomes. The selection of an appropriate antidiabetic regimen should be personalized, considering the unique conditions of each patient.

Metformin, barring contraindications such as the risk of acidosis, may be advantageous in diabetic COVID-19 patients due to its diverse beneficial effects, including antiviral and vasculoprotective actions. Sulfonylureas remain a viable option for managing hyperglycemia,

alone or in combination with other drugs like metformin. Thiazolidinediones (TZDs) show promise with their anti-inflammatory and potential antiviral activities, but caution is advised due to cardiovascular risks associated with drugs like rosiglitazone.

DPP-4 inhibitors, while useful for glycemic management, require careful consideration in the COVID-19 context due to a lack of conclusive evidence on their benefits. SGLT-2 inhibitors are recommended for their anti-inflammatory and organ-protective effects, except in patients with a heightened risk of diabetic ketoacidosis (DKA).

The role of bromocriptine in COVID-19 management is yet to be determined, but its known anti-inflammatory and glycemic properties warrant further research. Similarly, the effect of

Insulin therapy, despite debates over its anti-inflammatory effects, remains indispensable for critical glycemic management and the prevention of diabetes-related complications. It is uniquely suited for intravenous use in severe cases, such as DKA precipitated by COVID-19, underscoring its essential role in advanced disease management.

Finally, GLP1-Ras have demonstrated anti-inflammatory, cardioprotective, and nephroprotective benefits and may enhance pulmonary function, making them suitable for diabetic patients with a high risk of cardiovascular complications or established atherosclerotic cardiovascular disease. However, their comparative effectiveness with SGLT-2 inhibitors is uncertain, particularly in light of concerns about ACE-2 overexpression.

In conclusion, while the therapeutic landscape for managing diabetes in the context of COVID-19 continues to evolve, a nuanced understanding of the pharmacological profiles of antidiabetic agents and their intersection with the pathophysiology of COVID-19 is crucial for optimizing patient outcomes.

References

Abdallah D M, Nassar N N, Abd-El-Salam R M. Glibenclamide ameliorates ischemia-reperfusion injury via modulating oxidative stress and inflammatory mediators in the rat. hippocampus. Brain Res 2011; 1385: 257-262. https://doi.org/10.1016/j.brainres.2011.02.007

Ajjan RA G P. Cardiovascular disease prevention in patients with type 2 diabetes: the role of oral antidiabetic agents. Diab Vas Dis Res 2006; 3: 147-158. https://doi.org/10.3132/dvdr.2006.023

Al-lami H C A, Rizij F A, Hussein A A. Effect of bromocriptine on anthropometric, metabolic and inflammatory parameters in obese women. Thi-Qar Medical Journal 2018; 16.

Aljada A, Ghanim H, Mohanty P, Kapur N, Dandona P. Insulin inhibits the pro-inflammatory transcription factor early growth response gene-1 (Egr)-1 expression in mononuclear cells (MNC) and reduces plasma tissue factor (TF) and plasminogen activator inhibitor-1 (PAI-1) concentrations. J Clin Endocrinol Metab 2002; 87: 1419-1422. https://doi.org/10.1210/jcem.87.3.8462

Association A D. 9. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes-2020. Diabetes care 2020; 43: S98-S110. https://doi.org/10.2337/dc20-S009

Avogaro A, Bonora B, Fadini G P. Managing diabetes in diabetic patients with COVID: where do we start from? Acta Diabetol 2021; 58: 1441-1450. https://doi.org/10.1007/s00592-021-01739-1

Baggio L L, Varin E M, Koehler J A, Cao X, Lokhnygina Y, Stevens S R, et al. Plasma levels of DPP4 activity and sDPP4 are dissociated from inflammation in mice and humans. Nat Commun 2020; 11: 3766. https://doi.org/10.1038/s41467-020-17556-z

Barbarin V. N A, Misson P. The role of pro- and anti-inflammatory responses in silica-induced lung fibrosis Respir Res 2005; 6: 112. https://doi.org/10.1186/1465-9921-6-112

Basra R, Whyte M, Karalliedde J, Vas P. What is the impact of microvascular complications of diabetes on severe COVID-19? Microvasc Res 2021: 104310. https://doi.org/10.1016/j.mvr.2021.104310

Bassendine MF B S, McCaughan G W, Gorrell M D. COVID-19 and comorbidities: a role for dipeptidyl peptidase 4 (DPP4) in disease severity? J Diabetes 2020; 12: 649_658. https://doi.org/10.1111/1753-0407.13052

Batista D V, Vieira C A F d A, Costa T A, Lima E G. COVID-19-associated euglycemic diabetic ketoacidosis in a patient with type 2 diabetes on SGLT2 inhibitor: a case report. Diabetol Int 2021; 12: 313-316. https://doi.org/10.1007/s13340-020-00473-3

Belančić A, Kresović A, Troskot Dijan M. Glucagon-like peptide-1 receptor agonists in the era of COVID-19: Friend or foe? Clin Obes 2021; 11: e12439. https://doi.org/10.1111/cob.12439

Ben-Chetrit E, Ben-Ya'acov A, Quitina A, Atia O, Regev E, Shteyer E, et al. Anosmia and dysgeusia amongst COVID-19 patients are associated with low levels of se-

rum glucagon-like peptide 1. Int J Clin Pract 2021: e14996. https://doi.org/10.22541/au.162580954.40299908/v1

Bharath L P, Nikolajczyk B S. The intersection of metformin and inflammation. Am J Physiol Cell Physiol 2021; 320: C873-C879. https://doi.org/10.1152/ajpcell.00604.2020

Bibi N, Farid A, Gul S, Ali J, Amin F, Kalathiya U, et al. Drug repositioning against COVID-19: a first line treatment. J Biomol Struct Dyn 2021: 115. https://doi.org/10.1080/07391102.2021.1977698

Birnbaum Y, Bajaj M, Qian J, Ye Y. Dipeptidyl peptidase-4 inhibition by Saxagliptin prevents inflammation and renal injury by targeting the Nlrp3/ASC inflammasome. BMJ Open Diabetes Res Care 2016; 4: e000227. https://doi.org/10.1136/bmjdrc-2016-000227

Bojkova D, Klann K, Koch B, Widera M, Krause D, Ciesek S, et al. Proteomics of SARS-CoV-2-infected host cells reveals therapy targets. Nature 2020; 583: 469-472. https://doi.org/10.1038/s41586-020-2332-7

Bornstein S R, Rubino F, Khunti K, Mingrone G, Hopkins D, Birkenfeld A L, et al. Practical recommendations for the management of diabetes in patients with COVID-19. Lancet Diabetes Endocrinol 2020; 8: 546-550. https://doi.org/10.1016/S2213-8587(20)30152-2

Bossi A C, Forloni F, Colombelli P L. Lack of efficacy of SGLT2-i in severe pneumonia related to novel coronavirus (nCoV) infection: no little help from our friends. Diabetes Therapy 2020; 11: 1605-1606. https://doi.org/10.1007/s13300-020-00844-8

Cariou B, Hadjadj S, Wargny M, Pichelin M, Al-Salameh A, Allix I, et al. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. Diabetologia 2020; 63: 1500-1515. https://doi.org/10.1007/s00125-020-05180-x

Catrinoiu D, Ceriello A, Rizzo M, Serafinceanu C, Montano N, Stoian A P, et al. Diabetes and renin-angiotensin-aldosterone system: implications for covid-19 patients with diabetes treatment management. Farmacia 2020; 68: 377-383. https://doi.org/10.31925/farmacia.2020.3.1

Ceriello A, Esposito K, Testa R, Bonfigli A R, Marra M, Giugliano D. The possible protective role of glucagon-like peptide 1 on endothelium during the meal and evidence for an "endothelial resistance" to glucagon-like peptide 1 in diabetes. Diabetes care 2011; 34: 697-702. https://doi.org/10.2337/dc10-1949

Ceriello A, Standl E, Catrinoiu D, Itzhak B, Lalic N M, Rahelic D, et al. Issues of cardiovascular risk management in people with diabetes in the COVID-19 era. Diabetes Care 2020a; 43: 1427-1432. https://doi.org/10.2337/dc20-0941

Ceriello A, Stoian A P, Rizzo M. COVID-19 and diabetes management: What should be considered? Diabetes Res Clin Pract 2020b; 163. https://doi.org/10.1016/j.diabres.2020.108151

Chamarthi B, Ezrokhi M, Rutty D, Cincotta A H. Impact of bromocriptine-QR therapy on cardiovascular outcomes in type 2 diabetes mellitus subjects on metformin. Postgrad Med 2016; 128: 761-769. https://doi.org/10.1080/00325481.2016.1243003

Chamarthi B, Gaziano J M, Blonde L, Vinik A, Scranton R E, Ezrokhi M, et al. Timed bromocriptine-QR therapy reduces progression of cardiovascular disease and dysglycemia in subjects with well-controlled type 2 diabetes mellitus. J Diabetes Res 2015; 2015. https://doi.org/10.1155/2015/157698

Chan J F-W, Chik K K-H, Yuan S, Yip C C-Y, Zhu Z, Tee K-M, et al. Novel antiviral activity and mechanism of bromocriptine as a Zika virus NS2B-NS3 protease inhibitor. Antiviral Res 2017; 141: 29-37. https://doi.org/10.1016/j.antiviral.2017.02.002

Chang Y-S, Ko B-H, Ju J-C, Chang H-H, Huang S-H, Lin C-W. SARS unique domain (SUD) of severe acute respiratory syndrome coronavirus induces NLRP3 inflammasome-dependent CXCL10-mediated pulmonary inflammation. Int J Mol Sci 2020; 21: 317-319. https://doi.org/10.3390/ijms21093179

Chaudhuri A, Umpierrez G E. Oxidative stress and inflammation in hyperglycemic crises and resolution with insulin: implications for the acute and chronic complications of hyperglycemia. J Diabetes Complications 2012; 26: 257. https://doi.org/10.1016/j.jdiacomp.2012.04.016

Cheema A K, Kaur P, Fadel A, Younes N, Zirie M, Rizk N M. Integrated datasets of proteomic and metabolomic biomarkers to predict its impacts on comorbidities of type 2 diabetes mellitus. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2020; 13: 2409. https://doi.org/10.2147/DMSO.S244432

Chen H-Y, Huang J-Y, Siao W-Z, Jong G-P. The association between SGLT2 inhibitors and new-onset arrhythmias: a nationwide population-based longitudinal cohort study. Cardiovasc Diabetol 2020a; 19: 1-8. https://doi.org/10.1186/s12933-020-01048-x

Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The lancet 2020b; 395: 507-513. https://doi.org/10.1016/S0140-6736(20)30211-7

Chen W-R, Shen X-Q, Zhang Y, Chen Y-D, Hu S-Y, Qian G, et al. Effects of liraglutide on left ventricular function in patients with non-ST-segment elevation myocardial infarction. Endocrine 2016; 52: 516-526. https://doi.org/10.1007/s12020-015-0798-0

Chen Y, Yang D, Cheng B, Chen J, Peng A, Yang C, et al. Clinical characteristics and outcomes of patients with diabetes and COVID-19 in association with glucose-lowering medication. Diabetes care 2020c; 43: 1399-1407. https://doi.org/10.2337/dc20-0660

Cheng F, He M, Jung J U, Lu C, Gao S-J. Suppression of Kaposi's sarcoma-associated herpesvirus infection and replication by 5′-AMP-activated protein kinase. J Virol 2016; 90: 6515-6525. https://doi.org/10.1128/JVI.00624-16

Chisholm-Burns M A, Schwinghammer T L, Malone P M, Kolesar J M, Lee K C, Bookstaver P B. Pharmacotherapy principles and practice: McGraw Hill Professional, 2019.

Control D, Group C T R. Hypoglycemia in the diabetes control and complications trial. Diabetes 1997; 46: 271-286. https://doi.org/10.2337/diab.46.2.271 https://doi.org/10.2337/diabetes.46.2.271

Cory T J, Emmons R S, Yarbro J R, Davis K L, Pence B D. Metformin suppresses monocyte immunometabolic activation by SARS-CoV-2 spike protein subunit 1. Front Immunol 2021a; 12: 733921. https://doi.org/10.3389/fimmu.2021.733921

Cory T J, Emmons R S, Yarbro J R, Davis K L, Pence B D. Metformin suppresses monocyte immunometabolic activation by SARS-CoV-2 spike protein subunit 1. Front Immunol 2021b: 4785. https://doi.org/10.1101/2021.05.27.445991

Cowie M R, Fisher M. SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control. Nat Rev Cardiol 2020; 17: 761-772. https://doi.org/10.1038/s41569-020-0406-8

Crouse A B, 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: 1081. https://doi.org/10.1101/2020.07.29.20164020

Cui W, Zhang S, Cai Z, Hu X, Zhang R, Wang Y, et al. The antidiabetic agent glibenclamide protects airway hyperresponsiveness and inflammation in mice. Inflammation 2015; 38: 835-845. https://doi.org/10.1007/s10753-014-9993-z

Cure E C C M. Comment on: "High released lactate by epicardial fat from coronary artery disease patients is reduced by dapagliflozin treatment". Atherosclerosis 2020; 292, 60-69. https://doi.org/10.1016/j.atherosclerosis.2019.11.016

Cure E, Cure M C. Can dapagliflozin have a protective effect against COVID-19 infection? A hypothesis. Diabetes and Metabolic Syndrome: Clinical Research and Reviews 2020; 14: 405-406. https://doi.org/10.1016/j.dsx.2020.04.024

Dalan R, Ang L W, Tan W Y, Fong S-W, Tay W C, Chan Y-H, et al. The association of hypertension and diabetes pharmacotherapy with COVID-19 severity and immune signatures: an observational study. Eur Heart J Cardiovasc Pharmacother 2021; 7: e48-e51. https://doi.org/10.1093/ehjcvp/pvaa098

Dandona P, Aljada A, Mohanty P, Ghanim H, Bandyopadhyay A, Chaudhuri A. Insulin suppresses plasma concentration of vascular endothelial growth factor and matrix metalloproteinase-9. Diabetes care 2003; 3310-3314. https://doi.org/10.2337/diacare.26.12.3310

Dandona P, Ghanim H. Diabetes, obesity, COVID-19, Insulin, and other antidiabetes drugs. Diabetes care 2021; 44: 1929-1933. https://doi.org/10.2337/dci21-0003

Darwish I, Mubareka S, Liles W C. Immunomodulatory therapy for severe influenza. Expert Rev Anti Infect Ther 2011; 9: 807-822. https://doi.org/10.1586/eri.11.56

Darwish I M, S.; Liles, W.C. Immunomodulatory therapy for severe influenza. Expert Rev Anti-Infect Ther 2011; 9: 807-822. https://doi.org/10.1586/eri.11.56

Davidson M A, Mattison D R, Azoulay L, Krewski D. Thiazolidinedione drugs in the treatment of type 2 diabetes mellitus: past, present and future. Critical reviews in toxicology 2018; 48: 52-108. https://doi.org/10.1080/10408444.2017.1351420

Donath M Y. Glucose or insulin, which is the culprit in patients with covid-19 and diabetes? Cell Metabolism 2021; 33: 2-4. https://doi.org/10.1016/j.cmet.2020.11.015

Dror E, Dalmas E, Meier D T, Wueest S, Thévenet J, Thienel C, et al. Postprandial macrophage-derived IL-1β stimulates insulin, and both synergistically promote glucose disposal and inflammation. Nat Immunol 2017; 18: 283-292. https://doi.org/10.1038/ni.3659

Erem C O H, Nuhoglu I, Deger O, Civan N, Ersoz H O. Comparison of effects of gliclazide, metformin and pioglitazone monotherapies on glycemic control and cardiovascular risk factors in patients with newly diagnosed uncontrolled type 2 diabetes mellitus. Exp Clin Endocrinol Diabetes 2014; 122: 295-302. https://doi.org/10.1055/s-0034-1370989

Fadini GP M M, 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: 1946-1950. https://doi.org/10.1111/dom.14097

Fandiño J, Toba L, González-Matías L C, Diz-Chaves Y, Mal-

lo F. GLP-1 receptor agonist ameliorates experimental lung fibrosis. Sci Rep 2020; 10: 1-15. https://doi.org/10.1038/s41598-020-74912-1

Fernandez-Fernandez B, D'Marco L, Górriz J L, Jacobs-Cacha C, Kanbay M, Luis-Lima S, et al. Exploring sodium glucose co-transporter-2 (SGLT2) inhibitors for organ protection in COVID-19. J Clin Med 2020; 9: 2030. https://doi.org/10.3390/jcm9072030

Filgueiras L R, Capelozzi V L, Martins J O, Jancar S. Sepsis-induced lung inflammation is modulated by insulin. BMC pulmonary medicine 2014; 14: 1-8. https://doi.org/10.1186/1471-2466-14-177

Finfer S, Chittock D, Yu-Shuo S. Intensive versus Conventional Glucose Control in Critically Ill Patients. n engl j med. 2009; 36013360 (26): 1283-1297. https://doi.org/10.1056/NEJMoa0810625

Gao M H Z, Zheng Y, Zeng Y, Shen X, Zhong D, He F. Peroxisome proliferator activated receptor c agonist troglitazone inhibits high mobility group box 1 expression in endothelial cells via suppressing transcriptional activity of nuclear factor jB and activator protein 1. Shock 2011; 36: 228-234. https://doi.org/10.1097/SHK.0b013e318225b29a

Gao Y, Liu T, Zhong W, Liu R, Zhou H, Huang W, et al. Risk of metformin in patients with type 2 diabetes with COVID-19: a preliminary retrospective report. Clin Transl Res 2020; 13: 1055-1059. https://doi.org/10.1111/cts.12897

Gaziano J M, Cincotta A H, O'Connor C M, Ezrokhi M, Rutty D, Ma Z, et al. Randomized clinical trial of quick-release bromocriptine among patients with type 2 diabetes on overall safety and cardiovascular outcomes. Diabetes care 2010; 33: 1503-1508. https://doi.org/10.2337/dc09-2009

Gaziano J M, Cincotta A H, Vinik A, Blonde L, Bohannon N, Scranton R. Effect of bromocriptine-QR (a quick-release formulation of bromocriptine mesylate) on major adverse cardiovascular events in type 2 diabetes subjects. J Am Heart Assoc 2012; 1: e002279. https://doi.org/10.1161/JAHA.112.002279

Ghanim H, Korzeniewski K, Sia C L, Abuaysheh S, Lohano T, Chaudhuri A, et al. Suppressive effect of insulin infusion on chemokines and chemokine receptors. Diabetes care 2010; 33: 1103-1108. https://doi.org/10.2337/dc09-2193

Górriz J L, Navarro-González J F, Ortiz A, Vergara A, Nunez J, Jacobs-Cachá C, et al. Sodium-glucose cotransporter 2 inhibition: towards an indication to treat diabetic kidney disease. Nephrol Dial Transplant 2020; 35: i13-i23. https://doi.org/10.1093/ndt/gfz237

Goyal P, Choi J J, Pinheiro L C, Schenck E J, Chen R, Jabri A, et al. Clinical characteristics of Covid-19 in New York city. N Engl J Med 2020; 382: 2372-2374. https://doi.org/10.1056/NEJMc2010419

Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. Jama 2020; 323: 1574-1581. https://doi.org/10.1001/jama.2020.5394

Groop L C, Bonadonna R C, DelPrato S, Ratheiser K, Zyck K, Ferrannini E, et al. Glucose and free fatty acid metabolism in non-insulin-dependent diabetes mellitus. Evidence for multiple sites of insulin resistance. J Clin Invest 1989; 84: 205-213. https://doi.org/10.1172/JCI114142

Group A t C C R i D S. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008; 358: 2545-2559. https://doi.org/10.1056/NEJMoa0802743

Grzegorowska O, Lorkowski J. Possible correlations between atherosclerosis, acute coronary syndromes and COVID-19. J Clin Med 2020; 9: 3746. https://doi.org/10.3390/jcm9113746

Gupta R, Ghosh A, Singh A K, Misra A. Clinical considerations for patients with diabetes in times of COVID-19 epidemic. Diabetes Metab Syndr 2020; 14: 211-212. https://doi.org/10.1016/j.dsx.2020.04.023 https://doi.org/10.1016/j.dsx.2020.03.002

Han H, Ma Q, Li C, Liu R, Zhao L, Wang W, et al. Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors. Emerg Microbes Infect 2020; 9: 1123-1130. https://doi.org/10.1080/22221751.2020.1770129

Hariyanto T I, 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. Journal of Diabetes & Metabolic Disorders 2021; 20: 543-550. https://doi.org/10.1007/s40200-021-00777-4

Heerspink H J, Perco P, Mulder S, Leierer J, Hansen M K, Heinzel A, et al. Canagliflozin reduces inflammation and fibrosis biomarkers: a potential mechanism of action for beneficial effects of SGLT2 inhibitors in diabetic kidney disease. Diabetologia 2019; 62: 1154-1166. https://doi.org/10.1007/s00125-019-4859-4

Hill J R, Coll R C, Sue N, Reid J C, Dou J, Holley C L, et al. Sulfonylureas as concomitant insulin secretagogues and NLRP3 inflammasome inhibitors. Chem Med Chem 2017; 12: 1449-1457. https://doi.org/10.1002/cmdc.201700270

Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Her-

rler 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. e8. https://doi.org/10.1016/j.cell.2020.02.052

Holman N, Knighton P, Kar P, O'Keefe J, Curley M, Weaver A, et al. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. Lancet Diabetes Endocrinol 2020; 8: 823-833. https://doi.org/10.1016/S2213-8587(20)30271-0

Horio T S M, Takamisawa I, Suzuki K, Hiuge A, Yoshimasa Y, Kawano Y. Pioglitazone-induced insulin sensitization improves vascular endothelial function in nondiabetic patients with essential hypertension. Am J Hypertens 2005; 18: 1626-1630. https://doi.org/10.1016/j.amjhyper.2005.02.003
https://doi.org/10.1016/j.amjhyper.2005.05.035

Huang I, Pranata R, Lim M A, Oehadian A, Alisjahbana B. C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: a meta-analysis. Ther Adv Respir Dis 2020; 14:1753466620937175. https://doi.org/10.1177/1753466620937175

Iacobellis G. COVID-19 and diabetes: can DPP4 inhibition play a role? Diabetes Res Clin Pract 2020; 162. https://doi.org/10.1016/j.diabres.2020.108125

Inzucchi SE B R, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2012; 55: 1577-1596. https://doi.org/10.1007/s00125-012-2534-0

Iqbal A, Prince L R, Novodvorsky P, Bernjak A, Thomas M R, Birch L, et al. Effect of hypoglycemia on inflammatory responses and the response to low-dose endotoxemia in humans. J Clin Endocrinol Metab 2019; 104: 1187-1199. https://doi.org/10.1210/jc.2018-01168

Israelsen S B, Pottegård A, Sandholdt H, Madsbad S, Thomsen R W, 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, Obesity and Metabolism2021; 23: 1397-1401. https://doi.org/10.1111/dom.14329

Izzi-Engbeaya C, Distaso W, Amin A, Yang W, Idowu O, Kenkre J S, et al. Severe COVID-19 and diabetes-A retrospective cohort study from three London Teaching Hospitals. medRxiv 2020. https://doi.org/10.1101/2020.08.07.20160275

Jacob S, Hauer B, Becker R, Artzner S, Grauer P, Löblein K, et al. Lipolysis in skeletal muscle is rapidly regulated by low physiological doses of insulin. Diabetologia 1999; 42: 1171-1174. https://doi.org/10.1007/s001250051288

Ji M-H, Jiao-Jiao Y, Lin-Sha J, Zhu S-H, Yang J-J. Glibenclamide pretreatment attenuates acute lung injury by inhibiting the inflammatory responses and oxidative stress in a polymicrobial sepsis animal model. J Educ Perioper Med 2014; 1: 36. https://doi.org/10.24015/JAPM.2014.0006

Jin T, Liu M. Letter to the editor: Comment on GLP-1-based drugs and COVID-19 treatment. Acta Pharmacol Sin 2020; 10: 1249. https://doi.org/10.1016/j.apsb.2020.05.006

Kahkoska A R, Abrahamsen T J, Alexander G C, Bennett T D, Chute C G, Haendel M A, 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: 1564-1572. https://doi.org/10.2337/dc21-0065

Kahn N N, Bauman W A, Hatcher V B, Sinha A K. Inhibition of platelet aggregation and the stimulation of prostacyclin synthesis by insulin in humans. Am J Physiol Heart Circ Physiol 1993;265: H2160-H2167. https://doi.org/10.1152/ajpheart.1993.265.6.H2160

Kalbhande J G, Kuldeep V. Use of Insulin in treatment of COVID-19: A proposal to explore feasibility. Journal of Medical Science And clinical Research 2020; 8: 628-634. https://dx.doi.org/10.18535/jmscr/v8i7.103

Kamath V, Jones C N, Yip J C, Varasteh B B, Cincotta A H, Reaven G M, et al. Effects of a quick-release form of bromocriptine (Ergoset) on fasting and postprandial plasma glucose, insulin, lipid, and lipoprotein concentrations in obese nondiabetic hyperinsulinemic women. Diabetes Care 1997; 20: 1697-1701. https://doi.org/10.2337/diacare.20.11.1697

Kan C, Zhang Y, Han F, Xu Q, Ye T, Hou N, et al. Mortality risk of antidiabetic agents for type 2 diabetes with COVID-19: a systematic review and meta-analysis. Front Endocrinol 2021: 1158. https://doi.org/10.3389/fendo.2021.708494

Kato F, Ishida Y, Oishi S, Fujii N, Watanabe S, Vasudevan S G, et al. Novel antiviral activity of bromocriptine against dengue virus replication. Antiviral research 2016; 131: 141-147. https://doi.org/10.1016/j.antiviral.2016.04.014

Kawasaki T, Chen W, Htwe Y M, Tatsumi K, Dudek S M. DPP4 inhibition by sitagliptin attenuates LPS-induced lung injury in mice. Am J Physiol Lung Cell Mol Physiol 2018; 315: L834-L845. https://doi.org/10.1152/ajplung.00031.2018

Kewcharoenwong C, Rinchai D, Utispan K, Suwannasaen D, Bancroft G J, Ato M, et al. Glibenclamide reduces pro-inflammatory cytokine production by neutrophils of diabetes patients in response to bacterial infection. Sci. Rep 2013; 3: 1-8. https://doi.org/10.1038/srep03363

Khunti K, Knighton P, Zaccardi F, Bakhai C, Barron E, Holman N, et al. Prescription of glucose-lowering therapies and risk of COVID-19 mortality in people with type 2 diabetes: a nationwide observational study in England. Lancet Diabetes Endocrinol 2021; 9: 293-303. https://doi.org/10.1016/S2213-8587(21)00050-4

Kim M, Platt M J, Shibasaki T, Quaggin S E, Backx P H, Seino S, et al. GLP-1 receptor activation and Epac2 link atrial natriuretic peptide secretion to control of blood pressure. Nat Med 2013; 19: 567-575. https://doi.org/10.1038/nm.3128

Kim M K, Jeon J-H, Kim S-W, Moon J S, Cho N H, Han E, 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: 602-613. https://doi.org/10.4093/dmj.2020.0146

Kolb H, Kempf K, Röhling M, Martin S. Insulin: too much of a good thing is bad. BMC medicine 2020; 18: 1-12. https://doi.org/10.1186/s12916-020-01688-6

Komajda M G J, Biswas N, Jones N P. Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD): study design and protocol. Diabetologia 2005; 48: 1726-1735. https://doi.org/10.1007/s00125-005-1869-1

Kosinski C, Zanchi A, Wojtusciszyn A. Diabetes and COVID-19 infection. Rev Med Suisse 2020; 16: 939-943. https://doi.org/10.53738/REVMED.2020.16.692.0939

Kothari V, Galdo J A, Mathews S T. Hypoglycemic agents and potential anti-inflammatory activity. Journal of inflammation research 2016; 9: 27. https://doi.org/10.2147/JIR.S86917

Krysiak R, Okopien B. Different effects of cabergoline and bromocriptine on metabolic and cardiovascular risk factors in patients with elevated prolactin levels. Basic Clin Pharmacol Toxicol 2015; 116: 251-256. https://doi.org/10.1111/bcpt.12307

Krysiak R, Samborek M, Stojko R. Anti-inflammatory effects of bromocriptine in a patient with autoimmune polyglandular syndrome type 2. Neuroendocrinol Lett 2014; 35.

Kumar V, Aithal S, Baleed S, Patil U. Bromocriptine, a dopamine (d2) receptor agonist, used alone and in combination with glipizide in sub-therapeutic doses to ameliorate hyperglycaemia. J Clin Diagn Res 2013; 7: 1904-1907.

Lambert G W, Straznicky N E, Lambert E A, Dixon J B, Schlaich M P. Sympathetic nervous activation in obesity and the metabolic syndrome-causes, consequences and therapeutic implications. Pharmacology & therapeutics 2010; 126: 159-172. https://doi.org/10.1016/j.pharmthera.2010.02.002

Lamkanfi M, Mueller J L, Vitari A C, Misaghi S, Fedorova A, Deshayes K, et al. Glyburide inhibits the Cryopyrin/Nalp3 inflammasome. J Cell Biol 2009; 187: 61-70. https://doi.org/10.1083/jcb.200903124

Lee J H. Potential therapeutic effect of glucagon-like peptide-1 receptor agonists on COVID-19-induced pulmonary arterial hypertension. Medical hypotheses 2022; 158: 110739. https://doi.org/10.1016/j.mehy.2021.110739

Lee Y-S, Jun H-S. Anti-inflammatory effects of GLP-1-based therapies beyond glucose control. Mediators Inflamm 2016; 2016. https://doi.org/10.1155/2016/3094642

Li J, Wang X, Chen J, Zuo X, Zhang H, Deng A. COVID-19 infection may cause ketosis and ketoacidosis. Diabetes Obes Metab 2020; 22: 1935-1941. https://doi.org/10.1111/dom.14057

Li K W-L C, Perlman S, et al. Middle east respiratory syndrome coronavirus causes multiple organ damage and lethal disease in mice transgenic for human dipeptidyl peptidase 4. J Infect Dis 2016; 213: 712-722. https://doi.org/10.1093/infdis/jiv499

Li L, Konishi Y, Morikawa T, Zhang Y, Kitabayashi C, Kobara H, et al. Effect of a SGLT2 inhibitor on the systemic and intrarenal renin-angiotensin system in subtotally nephrectomized rats. J pharmacol sci 2018; 137: 220-223. https://doi.org/10.1016/j.jphs.2017.10.006

Li S-x, Li C, Pang X-r, Zhang J, Yu G-c, Yeo A J, et al. Metformin Attenuates Silica-Induced Pulmonary Fibrosis by Activating Autophagy via the AMPK-mTOR Signaling Pathway. Front pharmacol 2021: 2010. https://doi.org/10.3389/fphar.2021.719589

Li W, Cui M, Wei Y, Kong X, Tang L, Xu D. Inhibition of the Expression of TGF-β1 and CTGF in Human Mesangial Cells byExendin-4, a Glucagon-like Peptide-1Receptor Agonist. Cell Physiol Biochem 2012; 30: 749-757. https://doi.org/10.1159/000341454

Lim MA P R, Huang I, Yonas E, Soeroto AY, Supriyadi R. Multiorgan failure with emphasis on acute kidney injury and severity of COVID-19: systematic review and meta-analysis. Can J Kidney Heal Dis 2020; 7: 7-11. https://doi.org/10.1177/2054358120938573

Lim S, Bae J H, Kwon H-S, Nauck M A. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. Nat Rev Endocrinol 2021; 17: 11-30. https://doi.org/10.1038/s41574-020-00435-4

Liu J, Li S, Liu J, Liang B, Wang X, Wang H, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. EBioMedicine 2020; 55: 102763. https://doi.org/10.1016/j.ebiom.2020.102763

Liu X M T, Chen W, Ye S. Comparison of antidiabetic medications during the treatment of atherosclerosis in T2DM patients. Mediators Inflamm 2017; 55. https://doi.org/10.1155/2017/5032708

Longo M, Caruso P, Maiorino M I, Bellastella G, Giugliano D, Esposito K. Treating type 2 diabetes in COVID-19 patients: the potential benefits of injective therapies. Cardiovascular Diabetology 2020; 19: 1-5. https://doi.org/10.1186/s12933-020-01090-9

Lu G, Hu Y, Wang Q, Qi J, Gao F, Li Y, et al. Molecular basis of binding between novel human coronavirus MERS-CoV and its receptor CD26. Nature 2013; 500: 227-231. https://doi.org/10.1038/nature12328

Luo P, Qiu L, Liu Y, Liu X-l, Zheng J-l, Xue H-y, et al. Metformin treatment was associated with decreased mortality in COVID-19 patients with diabetes in a retrospective analysis. Am J Trop Med Hyg 2020; 103: 69. https://doi.org/10.4269/ajtmh.20-0375

Lv Z, Guo Y. Metformin and its benefits for various diseases. Front Endocrinol 2020; 11: 191. https://doi.org/10.3389/fendo.2020.00191

Makdissi A G H, Vora M, Green K, Abuaysheh S, Chaudhuri A et al Sitagliptin exerts an antinflammatory action. J Clin Endocrinol Metab 2012; 97: 3333-3341. https://doi.org/10.1210/jc.2012-1544

Malhotra A, Hepokoski M, McCowen K C, Shyy J Y. ACE2, metformin, and COVID-19. Iscience 2020; 23: 101425. https://doi.org/10.1016/j.isci.2020.101425

Marfella R, Di Filippo C, Portoghese M, Ferraraccio F, Rizzo M R, Siniscalchi M, et al. Tight glycemic control reduces heart inflammation and remodeling during acute myocardial infarction in hyperglycemic patients. J Am Coll Cardiol 2009; 53: 1425-1436. https://doi.org/10.1016/j.jacc.2009.01.041

Martin-Montalvo A, Mercken E M, Mitchell S J, Palacios H H, Mote P L, Scheibye-Knudsen M, et al. Metformin improves healthspan and lifespan in mice. Nat Commun 2013; 4: 1-9. https://doi.org/10.1038/ncomms3192

Martin B, Maudsley S, White C M, Egan J M. Hormones in the naso-oropharynx: endocrine modulation of taste and smell. Trends Endocrinol Metab 2009; 20: 163-170. https://doi.org/10.1016/j.tem.2009.01.006

Mazidi M, Karimi E, Rezaie P, Ferns G A. Treatment with GLP1 receptor agonists reduce serum CRP concentrations in patients with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. J Diabetes Complications 2017; 31: 1237-1242. https://doi.org/10.1016/j.jdiacomp.2016.05.022

McCormack F X, Whitsett J A. The pulmonary collectins, SP-A and SP-D, orchestrate innate immunity in the lung. The Journal of clinical investigation 2002; 109: 707-712. https://doi.org/10.1172/JCI0215293

Mei J, Sun J, Wu J, Zheng X. Liraglutide suppresses TNF-α-induced degradation of extracellular matrix in human chondrocytes: a therapeutic implication in osteoarthritis. Am J Transl Res 2019; 11: 4800.

Menon R, Otto E A, Sealfon R, Nair V, Wong A K, Theesfeld C L, et al. SARS-CoV-2 receptor networks in diabetic and COVID-19-associated kidney disease. Kidney international 2020; 98: 1502-1518. https://doi.org/10.1016/j.kint.2020.09.015

Merchenthaler I, Lane M, Shughrue P. Distribution of pre-pro-glucagon and glucagon-like peptide-1 receptor messenger RNAs in the rat central nervous system. J Comp Neurol 1999; 403: 261-280. https://doi.org/10.1002/(SICI)1096-9861(19990111)403:2<261::AID-CNE8>3.0.CO;2-5

Mirabelli M, Chiefari E, Puccio L, Foti D P, Brunetti A. Potential benefits and harms of novel antidiabetic drugs during COVID-19 crisis. I Int J Environ Res Public Health 2020; 17: 3664. https://doi.org/10.3390/ijerph17103664

Mirani M, Favacchio G, Carrone F, Betella N, Biamonte E, Morenghi E, et al. Impact of comorbidities and glycemia at admission and dipeptidyl peptidase 4 inhibitors in patients with type 2 diabetes with COVID-19: a case series from an academic hospital in Lombardy, Italy. Diabetes Care 2020; 43: 3042-3049. https://doi.org/10.2337/dc20-1340

Morimoto C S S. The structure and function of CD26 in the T-cell immune response. Immunol Rev 1998; 161: 55-70. https://doi.org/10.1111/j.1600-065X.1998.tb01571.x

Mortada Y, Khojasteh K, Zarei M, Mansouri A, Jorjani M. How nitric oxide increases in diabetic morphine tolerated male rats. Iran J Pharm Res 2017; 16: 630.

Mudaliar S, Henry R R. Effects of incretin hormones on β-cell mass and function, body weight, and hepatic and myocar-

dial function. Am J Med 2010; 123: S19-S27. https://doi.org/10.1016/j.amjmed.2009.12.006

Müller T D, Finan B, Bloom S, D'Alessio D, Drucker D J, Flatt P, et al. Glucagon-like peptide 1 (GLP-1). Mol Metab 2019; 30: 72-130. https://doi.org/10.1016/j.molmet.2019.09.010

Nissen SE N S, Wolski K, Nesto R, Kupfer S, Perez A, Jure H, De Larochelli_ere R, Staniloae CS, Mavromatis K, et al. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. JAMA 2008; 299: 1561-1573. https://doi.org/10.1001/jama.299.13.1561

Nomoto H K K, Miyoshi H, Kameda H, Cho KY, Nakamura A et al Effects of 50 mg vildagliptin twice daily vs 50g sitagliptin once daily on blood glucose fluctuations evaluated by long-term self-monitoring of blood glucose. Endocr J 2017; 64: 417-424. https://doi.org/10.1507/endocrj.EJ16-0546

Oda K, Yatera K, Izumi H, Ishimoto H, Yamada S, Nakao H, et al. Profibrotic role of WNT10A via TGF-β signaling in idiopathic pulmonary fibrosis. Respir Res 2016; 17: 1-14. https://doi.org/10.1186/s12931-016-0357-0

Orioli L, Servais T, Belkhir L, Laterre P-F, Thissen J-P, Vandeleene B, et al. Clinical characteristics and short-term prognosis of in-patients with diabetes and COVID-19: a retrospective study from an academic center in Belgium. Diabetes & Metabolic Syndrome: Clinical Research & Reviews 2021; 15: 149-157. https://doi.org/10.1016/j.dsx.2020.12.020

P.A. Sarafidis P C S, P.I. Georgianos, A.N. Saratzis, A.N. Lasaridis. Effect of thiazolidinediones on albuminuria and proteinuria in diabetes: A meta-analysis. Am. J. Kidney Dis 2010; 55: 835-847. https://doi.org/10.1053/j.ajkd.2009.11.013

Pal R, Bhadada S K. Should anti-diabetic medications be reconsidered amid COVID-19 pandemic? Diabetes Res Clin Pract 2020; 163. https://doi.org/10.1016/j.diabres.2020.108146

Palermo N E, Sadhu A R, McDonnell M E. Diabetic ketoacidosis in COVID-19: unique concerns and considerations. J Clin Endocrinol Metab 2020; 105: 2819-2829. https://doi.org/10.1210/clinem/dgaa360

Pascal KE C C, Mujica AO, et al. pre-and postexposure efficacy of fully human antibodies against spike protein in a novel humanized mouse model of MERS-CoV infection. Proc Natl Acad Sci U S A 2015; 112: 8738-8743. https://doi.org/10.1073/pnas.1510830112

Patoulias D, Boulmpou A, Imprialos K, Stavropoulos K, Papadopoulos C, Doumas M. Meta-analysis evaluating the risk of respiratory tract infections and acute respiratory distress syndrome with glucagon-like peptide-1 receptor agonists in cardiovascular outcome trials: Useful implications for the COVID-19 pandemic. Revista Clínica Española (English Edition) 2021. https://doi.org/10.1016/j.rceng.2021.04.002

Petrilli C M, Jones S A, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. Bmj 2020; 369. https://doi.org/10.1136/bmj.m1966

Philipose Z, Smati N, Wong C S J, Aspey K, Mendall M. Obesity, old age, and frailty are the true risk factors for COVID-19 mortality and not chronic disease or ethnicity. MedRxiv 2020. https://doi.org/10.1101/2020.08.12.20156257

Piotrowski K, Becker M, Zugwurst J, Biller-Friedmann I, Spoettl G, Greif M, et al. Circulating concentrations of GLP-1 are associated with coronary atherosclerosis in humans. Cardiovasc Diabetol 2013; 12: 1-5. https://doi.org/10.1186/1475-2840-12-117

Pompermayer K, Souza D G, Lara G G, Silveira K D, Cassali G D, Andrade A A, et al. The ATP-sensitive potassium channel blocker glibenclamide prevents renal ischemia/reperfusion injury in rats. Kidney international 2005; 67: 1785-1796. https://doi.org/10.1111/j.1523-1755.2005.00276.x

Prigeon RL K S, Porte D Jr. Effect of troglitazone on B cell function, insulin sensitivity, and glycemic control in subjects with type 2 diabetes mellitus. J Clin Endocrinol Metab. 1998; 83: 819-823. https://doi.org/10.1210/jc.83.3.819 https://doi.org/10.1210/jcem.83.3.4641

Rahman M M, Saha T, Islam K J, Suman R H, Biswas S, Rahat E U, et al. Virtual screening, molecular dynamics and structure-activity relationship studies to identify potent approved drugs for Covid-19 treatment. J Biomol Struct Dyn 2021; 39: 6231-6241. https://doi.org/10.1080/07391102.2020.1794974

Rakhmat I I, Kusmala Y Y, Handayani D R, Juliastuti H, Nawangsih E N, Wibowo A, 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 & Metabolic Syndrome: Clinical Research & Reviews 2021; 15: 777-782. https://doi.org/10.1016/j.dsx.2021.03.027

Rayman G, Lumb A, Kennon B, Cottrell C, Nagi D, Page E, et al. Guidance on the management of Diabetic Ketoacidosis in the exceptional circumstances of the COVID-19

pandemic. Diabetic Medicine 2020; 37: 1214-1216. https://doi.org/10.1111/dme.14328

Riahi S, Sombra L R S, Lo K B, Chacko S R, Neto A G M, Azmaiparashvili Z, et al. Insulin use, diabetes control, and outcomes in patients with COVID-19. Endocrine Research 2021; 46: 45-50. https://doi.org/10.1080/07435800.2020.1856865

Rizvi A A, Stoian A P, Lessan N, Rizzo M. Endocrinology in the time of COVID-19: a rapid evolution of knowledge and care. Medicina 2021; 57: 805. https://doi.org/10.3390/medicina57080805

Rogliani P, Matera M G, Calzetta L, Hanania N A, Page C, Rossi I, et al. Long-term observational study on the impact of GLP-1R agonists on lung function in diabetic patients. Respir Med 2019; 154: 86-92. https://doi.org/10.1016/j.rmed.2019.06.015

Romaní-Pérez M, Outeiriño-Iglesias V, Moya C M, Santisteban P, González-Matías L C, Vigo E, et al. 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: 3559-3569. https://doi.org/10.1210/en.2014-1685

Romero-Gómez M, Diago M, Andrade R J, Calleja J L, Salmerón J, Fernández-Rodríguez C M, et al. Treatment of insulin resistance with metformin in naïve genotype 1 chronic hepatitis C patients receiving peginterferon alfa-2a plus ribavirin. Hepatology 2009; 50: 1702-1708. https://doi.org/10.1002/hep.23206

Ronco C, Reis T. Kidney involvement in COVID-19 and rationale for extracorporeal therapies. Nat Rev Nephrol 2020; 16: 308-310. https://doi.org/10.1038/s41581-020-0284-7

Rosak C, Petzoldt R, Wolf R, Reblin T, Dehmel B, Seidel D. Rosiglitazone plus metformin is effective and well tolerated in clinical practice: results from large observational studies in people with type 2 diabetes. Int J Clin Pract 2005; 59: 1131-1136. https://doi.org/10.1111/j.1368-5031.2005.00652.x

Salem E S, Grobe N, Elased K M. Insulin treatment attenuates renal ADAM17 and ACE2 shedding in diabetic Akita mice. Am J Physiol Renal Physiol 2014; 306: F629-F639. https://doi.org/10.1152/ajprenal.00516.2013

Samuel S M, Varghese E, Büsselberg D. Therapeutic potential of metformin in COVID-19: reasoning for its protective role. Trends Microbiol 2021; 29: 894-907. https://doi.org/10.1016/j.tim.2021.03.004

Sandooja R, Vura N V R K, Morocco M. Heightened ACE activity and unfavorable consequences in COVID-19 diabetic subjects. Int J Endocrinol 2020; 2020. https://doi.org/10.1155/2020/7847526

Sarafidis P, Ferro C J, Morales E, Ortiz A, Malyszko J, Hojs R, et al. SGLT-2 inhibitors and GLP-1 receptor agonists for nephroprotection and cardioprotection in patients with diabetes mellitus and chronic kidney disease. A consensus statement by the EURECA-m and the DIABESITY working groups of the ERA-EDTA. Nephrol Dial Transplant 2019; 34: 208-230. https://doi.org/10.1093/ndt/gfy407

Saraiva F K, Sposito A C. Cardiovascular effects of glucagon-like peptide 1 (GLP-1) receptor agonists. Cardiovasc Diabetol 2014; 13: 1-11. https://doi.org/10.1186/s12933-014-0142-7

Sardu C, D'Onofrio N, Balestrieri M L, Barbieri M, Rizzo M R, Messina V, et al. Outcomes in patients with hyperglycemia affected by COVID-19: can we do more on glycemic control? Diabetes care 2020; 43: 1408-1415. https://doi.org/10.2337/dc20-0723

Sazgarnejad S, Yazdanpanah N, Rezaei N. Anti-inflammatory effects of GLP-1 in patients with COVID-19. Expert Rev Anti Infect Ther 2021: 1-9. https://doi.org/10.1080/14787210.2021.1964955

Scheen A. Metformin and COVID-19: from cellular mechanisms to reduced mortality. Diabetes Metab 2020; 46: 423-426. https://doi.org/10.1016/j.diabet.2020.07.006

Scheen A J. An update on the safety of SGLT2 inhibitors. Expert Opin Drug Saf 2019;18: 295-311. https://doi.org/10.1080/14740338.2019.1602116

Šestan M, Marinović S, Kavazović I, Cekinović Đ, Wueest S, Wensveen T T, et al. Virus-induced interferon-γ causes insulin resistance in skeletal muscle and derails glycemic control in obesity. Immunity 2018; 49: 164-177. e6. https://doi.org/10.1016/j.immuni.2018.05.005

Shah F A, Mahmud H, Gallego-Martin T, Jurczak M J, O'Donnell C P, McVerry B J. Therapeutic effects of endogenous incretin hormones and exogenous incretin-based medications in sepsis. J Clin Endocrinol Metab 2019; 104: 5274-5284. https://doi.org/10.1210/jc.2019-00296

Shao S, Xu Q, Yu X, Pan R, Chen Y. Dipeptidyl peptidase 4 inhibitors and their potential immune modulatory functions. Pharmacology & therapeutics 2020; 209: 107503. https://doi.org/10.1016/j.pharmthera.2020.107503

Sharma S, Ray A, Sadasivam B. Metformin in COVID-19: a possible role beyond diabetes. Diabetes research and clinical practice 2020; 164: 108183. https://doi.org/10.1016/j.diabres.2020.108183

Shiraki A, Oyama J-i, Komoda H, Asaka M, Komatsu A, Sakuma M, et al. The glucagon-like peptide 1 analog liraglutide reduces TNF-α-induced oxidative stress and inflammation in endothelial cells. Atherosclerosis 2012; 221: 375-382. https://doi.org/10.1016/j.atherosclerosis.2011.12.039

Si G, Tao Z, Wei W, Min X, Wang X-c, Chen Z-h. Glucagon like peptide-1 attenuates bleomycin-induced pulmonary fibrosis, involving the inactivation of NF-κB in mice. Int Immunopharmacol 2014; 22: 498-504. https://doi.org/10.1016/j.intimp.2014.07.010

Silverii G A, Monami M, Cernigliaro A, Vigneri E, Guarnotta V, Scondotto S, et al. Are diabetes and its medications risk factors for the development of COVID-19? Data from a population-based study in Sicily. Nutr Metab Cardiovasc Dis 2021; 31: 396-398. https://doi.org/10.1016/j.numecd.2020.09.028

Siu K L, Yuen K S, Castano-Rodriguez C, Ye Z W, Yeung M L, Fung S Y, et al. Severe acute respiratory syndrome Coronavirus ORF3a protein activates the NLRP3 inflammasome by promoting TRAF3-dependent ubiquitination of ASC. FASEB J 2019; 33: 8865-8877. https://doi.org/10.1096/fj.201802418R

Sola D, Rossi L, Schianca G P C, Maffioli P, Bigliocca M, Mella R, et al. Sulfonylureas and their use in clinical practice. Arch Med Sci 2015; 11: 840. https://doi.org/10.5114/aoms.2015.53304

Solerte SB D A 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 multicentre, case-control, retrospective, observational study. Diabetes Care 2020; 43: 2999- 3006. https://doi.org/10.2337/dc20-1521

Sromova L, Busek P, Posova H, Potockova J, Skrha P, Andel M, et al. The effect of dipeptidyl peptidase-IV inhibition on circulating T cell subpopulations in patients with type 2 diabetes mellitus. Diabetes Res Clin Pract 2016; 118: 183-192. https://doi.org/10.1016/j.diabres.2016.06.020

Stoian A P, Banerjee Y, Rizvi A A, Rizzo M. Diabetes and the COVID-19 pandemic: how insights from recent experience might guide future management. Metab Syndr Relat Disord 2020a; 18: 173-175. https://doi.org/10.1089/met.2020.0037

Stoian A P, Pricop-Jeckstadt M, Pana A, Ileanu B-V, Schitea R, Geanta M, et al. Death by SARS-CoV 2: a Romanian COVID-19 multi-centre comorbidity study. Sci Rep 2020b; 10: 1-11. https://doi.org/10.1038/s41598-020-78575-w

Takai S, Yasumatsu K, Inoue M, Iwata S, Yoshida R, Shigemura N, et al. Glucagon-like peptide-1 is specifically involved in sweet taste transmission. FASEB J 2015; 29: 2268-2280. https://doi.org/10.1096/fj.14-265355

Toki S, Goleniewska K, Reiss S, Zhang J, Bloodworth M H, Stier M T, et al. Glucagon-like peptide 1 signaling inhibits allergen-induced lung IL-33 release and reduces group 2 innate lymphoid cell cytokine production in vivo. J Allergy Clin Immunol 2018; 142: 1515-1528. e8. https://doi.org/10.1016/j.jaci.2017.11.043

Tsurutani Y, Omura M, Matsuzawa Y, Saito J, Higa M, Taniyama M, et al. Efficacy and safety of the dipeptidyl Peptidase-4 inhibitor Sitagliptin on atherosclerosis, β-cell function, and glycemic control in Japanese patients with type 2 diabetes mellitus who are treatment Naïve or poorly responsive to Antidiabetes agents: a multicenter, prospective observational, uncontrolled study. Cur The Res 2017; 84: 26-31. https://doi.org/10.1016/j.curtheres.2016.12.002

Turner NA M R, Warburton P, O'Regan DJ, Ball SG, Porter KE. Mechanism of TNFalpha-induced IL-1alpha, IL-1beta and IL-6 expression in human cardiac fibroblasts: effects of statins and thiazolidinediones. Cardiovasc Res 2007; 76: 81-90. https://doi.org/10.1016/j.cardiores.2007.06.003

Vankadari N W J. Emerging WuHan (COVID-19) coronavirus: glycan shield and structure prediction of spike glycoprotein and its interaction with human CD26. Emerg Micro & Infec 2020; 9: 601-604. https://doi.org/10.1080/22221751.2020.1739565

Verma A K, Beg M M A, Bhatt D, Dev K, Alsahli M A, Rahmani A H, et al. Assessment and Management of Diabetic Patients During the COVID-19 Pandemic. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2021; 14: 3131. https://doi.org/10.2147/DMSO.S285614

Verma S, Jüni P, Mazer C D. Pump, pipes, and filter: do SGLT2 inhibitors cover it all? The Lancet 2019; 393: 3-5. https://doi.org/10.1016/S0140-6736(18)32824-1

Viby N-E, Isidor M S, Buggeskov K B, Poulsen S S, Hansen J B, Kissow H. Glucagon-like peptide-1 (GLP-1) reduces mortality and improves lung function in a model of experimental obstructive lung disease in female mice. Endocrinology 2013; 154: 4503-4511. https://doi.org/10.1210/en.2013-1666

Wang L, Liang J, Leung P S. The ACE2/Ang-(1-7)/Mas axis regulates the development of pancreatic endocrine cells in mouse embryos. PLoS One 2015; 10: e0128216. https://doi.org/10.1371/journal.pone.0128216

Wargny M, Potier L, Gourdy P, Pichelin M, Amadou C, Benhamou P-Y, 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: 778-794. https://doi.org/10.1007/s00125-020-05351-w

Wei Y, Mojsov S. Tissue-specific expression of the human receptor for glucagon-like peptide-I: brain, heart and pancreatic forms have the same deduced amino acid sequences. FEBS letters 1995; 358: 219-224. https://doi.org/10.1016/0014-5793(94)01430-9

Willemen MJ M-T A, Straus SM, Meyboom RH, Egberts TC, Leufkens HG. Use of dipeptidyl peptidase-4 inhibitors and the reporting of infections: a disproportionality analysis in the World Health Organization VigiBase. Diabetes Care 2011; 34: 369-374. https://doi.org/10.2337/dc10-1771

Wright EM T E. The sodium/glucose cotransport family SLC5. Pflugers Arch 2004; 447: 510-518. https://doi.org/10.1007/s00424-003-1063-6

Wu J, Huang J, Zhu G, Wang Q, Lv Q, Huang Y, et al. Elevation of blood glucose level predicts worse outcomes in hospitalized patients with COVID-19: a retrospective cohort study. BMJ Open Diabetes Res Care 2020a; 8: e001476. https://doi.org/10.1136/bmjdrc-2020-001476

Wu L, Girgis C M, Cheung N W. COVID-19 and diabetes: insulin requirements parallel illness severity in critically unwell patients. Clinical Endocrinology 2020b; 93: 390-393. https://doi.org/10.1111/cen.14288

Wu Z, McGoogan J M. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. Jama 2020; 323: 1239-1242. https://doi.org/10.1001/jama.2020.2648

Xian H, Liu Y, Nilsson A R, Gatchalian R, Crother T R, Tourtellotte W G, et al. Metformin inhibition of mitochondrial ATP and DNA synthesis abrogates NLRP3 inflammasome activation and pulmonary inflammation. Immunity 2021; 54: 1463-1477. e11. https://doi.org/10.1016/j.immuni.2021.05.004

Xie W, Wang L, Dai Q, Yu H, He X, Xiong J, et al. Activation of AMPK restricts coxsackievirus B3 replication by inhibiting lipid accumulation. J Mol Cell Cardiol 2015; 85: 155-167. https://doi.org/10.1016/j.yjmcc.2015.05.021

Xie X S S, Yi Z, et al. Role of adipocyte mitochondria in inflammation, lipemia and insulin sensitivity in humans: effects of pioglitazone treatment. Int J Obes 2017. https://doi.org/10.1038/ijo.2017.192

Xu J, Wei G, Wang J, Zhu J, Yu M, Zeng X, et al. Glucagon-like peptide-1 receptor activation alleviates lipopolysaccharide-induced acute lung injury in mice via maintenance of endothelial barrier function. Laboratory Investigation 2019; 99: 577-587. https://doi.org/10.1038/s41374-018-0170-0

Xun Y H, Zhang Y J, Pan Q C, Mao R C, Qin Y L, Liu H Y, et al. Metformin inhibits hepatitis B virus protein production and replication in human hepatoma cells. J Viral Hepat 2014; 21: 597-603. https://doi.org/10.1111/jvh.12187

Yan H, Valdes A M, Vijay A, Wang S, Liang L, Yang S, et al. Role of drugs used for chronic disease management on susceptibility and severity of COVID19: a large case-control study. Clin Pharmacol Ther 2020; 108: 1185-1194. https://doi.org/10.1002/cpt.2047

Yang J-K, Lin S-S, Ji X-J, Guo L-M. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta diabetologica 2010; 47: 193-199. https://doi.org/10.1007/s00592-009-0109-4

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. Frontiers in Endocrinology 2021; 12. https://doi.org/10.3389/fendo.2021.696087

Yaribeygi H, Katsiki N, Butler A E, Sahebkar A. Effects of antidiabetic drugs on NLRP3 inflammasome activity, with a focus on diabetic kidneys. Drug discovery today 2019; 24: 256-262. https://doi.org/10.1016/j.drudis.2018.08.005

Yu B, Li C, Sun Y, Wang D W. Insulin treatment is associated with increased mortality in patients with COVID-19 and type 2 diabetes. Cell metabolism 2021; 33: 65-77. e2. https://doi.org/10.1016/j.cmet.2020.11.014

Yudkin J S. Abnormalities of coagulation and fibrinolysis in insulin resistance: evidence for a common antecedent? Diabetes care 1999; 22: C25.

Zarei M, Sahebi Vaighan N, Ziai S A. Purinergic receptor ligands: the cytokine storm attenuators, potential therapeutic agents for the treatment of COVID-19. Immunopharmacology and Immunotoxicology 2021; 43: 633-643. https://doi.org/10.1080/08923973.2021.1988102

Zhang B, Liu Z-Y, Li Y-Y, Luo Y, Liu M-L, Dong H-Y, et al. Antiinflammatory effects of matrine in LPS-induced acute lung injury in mice. Eur J Pharm Sci 2011; 44: 573-579. https://doi.org/10.1016/j.ejps.2011.09.020

Zhang B, Zhou X, Zhu C, Song Y, Feng F, Qiu Y, et al. Immune phenotyping based on the neutrophil-to-lymphocyte ratio and IgG level predicts disease severity and outcome for patients with COVID-19. Front Mol Biosci 2020; 7: 157. https://doi.org/10.3389/fmolb.2020.00157

Zhang G, Lin X, Zhang S, Xiu H, Pan C, Cui W. A pro-

tective role of glibenclamide in inflammation-associated injury. Mediators Inflamm 2017; 2017. https://doi.org/10.1155/2017/3578702

Zhang W-q, Tian Y, Chen X-m, Wang L-f, Chen C-c, Qiu C-m. Liraglutide ameliorates beta-cell function, alleviates oxidative stress and inhibits low grade inflammation in young patients with new-onset type 2 diabetes. Diabetol Metab Syndr 2018; 10: 1-8. https://doi.org/10.1186/s13098-018-0392-8

Zhang WY S E, Permana PA, Reaven P D. Pioglitazone inhibits the expression of inflammatory cytokines from both monocytes and lymphocytes in patients with impaired glucose tolerance. Arterioscler Thromb Vasc Biol 2008; 28: 2312-8. https://doi.org/10.1161/ATVBAHA.108.175687

Zhou F, Zhang Y, Chen J, Hu X, Xu Y. Liraglutide attenuates lipopolysaccharide-induced acute lung injury in mice. Eur J Pharmacol 2016; 791: 735-740. https://doi.org/10.1016/j.ejphar.2016.10.016

Zhou J, Tan J. Diabetes patients with COVID-19 need better blood glucose management in Wuhan, China. Metabolism 2020; 107: 154216. https://doi.org/10.1016/j.metabol.2020.154216

Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020. https://doi.org/10.1056/NEJMoa2001017