Abstract. COVID-19 is a global pandemic with devastating economic and public health impacts, which is particularly associated with increased incidence of respiratory and cardiovascular disease together with inflammation and oxidative stress as essential underlying features. Glucagon-Like Peptide-1 (GLP-1) receptor agonists are now routinely used for the clinical management of type 2 diabetes due to their established glucose-dependent insulinotropic actions. However, these agents also display a variety of pleiotropic functions, including the promotion of anti-inflammatory and anti-oxidant responses, highlighting likely therapeutic applications beyond glycemic control. Given that COVID-19 is particularly linked with adverse modulation of inflammatory and oxidative signaling, which are known to be impacted by GLP-1 receptor activation, it seems logical that GLP-1 receptor agonists may be beneficial for the clinical management of patients with SARS-CoV-2 infection. In this review, we discuss the specific role of inflammation and oxidative stress associated with COVID-19, including underlying pathogenic mechanisms, as the basis for the potential therapeutic application of GLP-1 receptor agonists to combat both acute and chronic complications of this devastating disease.

Key Words: Glucagon-like peptide-1, SARS-CoV-2, COVID-19, Inflammation, Oxidative stress.

Introduction

The 2019 coronavirus disease (COVID-19) first appeared in late December 2019 in Wuhan City, Hubei Province, among individuals who were diagnosed with pneumonia of unknown cause, and widespread throughout China by 30 January 2020. The World Health Organization subsequently classified COVID-19, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), as a global pandemic on 11th March 2020, with the disease widespread and persistent in over 220 nations around the world. Symptoms typically include fever, headache, dry cough, dyspnea, and disorientation, and can range from moderate to severe, including hypoxia and acute respiratory distress syndrome (ARDS), leading to death in extreme cases. As of October 2022, >618 million global SARS-CoV-2 infections and >6.5 million COVID-19-related deaths were confirmed. Notably, whilst largely a respiratory condition, COVID-19 is linked with cardiovascular complications, with a significant proportion of deaths occurring due to chronic heart failure subsequent to SARS-CoV-2 infection.

Further to the emergence of severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 and the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, SARS-CoV-2 is the third highly pathogenic and large-scale epidemic coronavirus to arise in the twenty-first century. SARS-CoV-2 was named after its genetically related predecessor, SARS-CoV (now known as SARS-CoV-1), and contains sequences not previously detected in human or animal viruses. Its structure comprises a protein envelope surrounding each SARS-CoV-2 virus particle, containing its single-stranded RNA genome, which encodes for four structural proteins: spike, membrane, envelope, and nucleocapsid proteins. Spike (S) protein interacts with the angiotensin-converting enzyme 2 (ACE2) receptor on the surface of human airway epithelial cells, with spike protein primed by the transmembrane protease serine 2 (TMPRSS2) serine protease, permitting virus entry and replication via integration into the cell’s RNA and protein synthesis machinery (Figure 1).

It has been demonstrated that SARS-CoV-2 binds to ACE2 receptor-expressed cells (Figure 1).
but not those cells without receptor expression\(^1\). The binding mechanism illustrated as the virus receptor binding domain presented in spike glycoprotein binds to ACE2 receptor mainly subdomain I\(^{12}\), causing virus-host cell membrane fusion, which subsequently releases the viral RNA to the cytoplasm, therefore establishing infection state\(^13\). While some transmembrane proteinases, such as transmembrane protease serine 2 (TMPRSS2) and metallopeptidase domain 17 (ADAM17), or other proteins, such as vimentin, may be contributed to virus receptor binding and fusion\(^14\). For example, protease serine 2 TMPRSS2 transmembrane proteinase can promote virus uptake by cleaving ACE2\(^15\).

Whilst angiotensin-converting enzyme (ACE), as a part of renin-angiotensin system (RAS), plays a significant role in maintaining electrolytes hemostasis and controlling blood pressure through angiotensin 2 formation, causing vasoconstriction and salt retention\(^16\). In addition, when angiotensin
2 binds to the angiotensin type 1 receptor (AT1R), it causes cell proliferation, extracellular matrix remodeling, and inflammatory responses17. Although a homology between ACE and ACE2 is established, ACE2 counteracts the Mas receptor physiological effects of RAS by catalyzing the conversion of angiotensin II to angiotensin-(1-7) that binds to induce vasodilation, anti-inflammatory, and anti-fibrosis effects18. Thereby, the interaction between SARS-CoV-2 and ACE2 receptor causes angiotensin II/AT1R activation inducing fibrosis, inflammation, and oxidative stress. Meanwhile, it has been established that AT1R activation by angiotensin II promotes epithelial lung alveolar cell apoptosis19, and endothelial cell dysfunction via generation of reactive oxygen species20. As well as the inflammatory mechanism of angiotensin II may involve nuclear factor (NF)-κB activation and interleukins as IL-6 transcription21. Therefore, SARS-CoV-2 induced immune system response in association with high angiotensin II level could promote the hyper-inflammatory state in infected patients.

The analysis of ACE2 protein expression has demonstrated that heart, lungs, kidney, colon, and small intestine are the tissues with the highest ACE2 expression, unlike blood cells22, and the presence of SARS-CoV-2 in heart, lung, and renal tissues was confirmed by Scanning Electron microscope (SEM) and transmission electron microscope (TEM)23. This indicates that SARS-CoV-2 may attack different organs with high ACE2 receptor expression besides the lungs, which may cause multiple organ dysfunction such as acute renal injury, and acute cardiac injury in addition to acute lung injury21.

Although precise mechanisms underlying COVID-19 pathophysiology are not defined, inflammation is established as a central feature, with abnormalities in immune cell profile and circulating inflammatory markers linked to disease severity and outcome24. Indeed, SARS-CoV-2 is typically associated with cytokine storm (also known as cytokine release syndrome), which is driven by pathogen-triggered inflammation and accentuated by a positive feedback loop25. Cytokine storm specifically involves inappropriate activation of the innate immune response, cell death, and excessive inflammatory cytokine secretion26,27, which is linked with increased severity of COVID-19 and mortality. Notably, immune dysregulation in COVID-19 is associated with oxidative stress, defined as an imbalance between oxidants and antioxidants, which plays a key role in viral pathogenesis28 and has been linked with worsened outcomes in COVID-19 patients29. Indeed, oxidative stress in COVID-19 is specifically associated with the amplification and persistence of cytokine storm, coagulopathy, and cellular hypoxia30, with considerable contributions from oxidative damage due to redox imbalance and iron dysregulation31.

Over recent years, a new class of drugs known as glucagon-like peptide-1 receptor (GLP-1R) agonists have emerged as an effective treatment for type 2 diabetes mellitus (T2DM) and obesity32. GLP-1 is a incretin peptide hormone of 30 or 31 amino acids that are primarily released by three tissues in the human body: enteroendocrine L cells in the distal intestine, pancreatic alpha cells, and the central nervous system33. Whilst GLP-1R activations exert effective glycemic control in a glucose-dependent manner, it also regulates a variety of pathophysiological processes associated with inflammation, including thrombosis, fibrosis, and adverse tissue remodeling34,35,36.

As a result, in addition to clinical management of metabolic disease, GLP-1R agonists, such as liraglutide and exenatide, show clear promise for the treatment of inflammatory disorders, particularly those linked with cardiovascular and renal disease37. Whilst the established metabolic effects of GLP-1R agonists make this pharmacological class the preferred option for treating many individuals with T2DM, its pleiotropic actions highlight potential additional benefits beyond glycemic control, which are likely to extend to SARS-CoV-2 infection38. Indeed, it was recently reported that pre-symptomatic use of GLP-1R agonists in T2DM patients was linked with decreased risk of severe disease and mortality after SARS-CoV-2 infection39.

Given continuing high numbers of reported COVID-19 cases and deaths, specific treatment options are urgently needed in order to reduce poor acute and chronic outcomes. In this regard, it is evident that effective management of inflammation associated with SARS-CoV-2 infection and COVID-19 holds the potential to limit disease severity and consequences23. As such, this review article specifically focuses on the central role of inflammation and oxidative stress in COVID-19 pathogenesis and the emerging potential of GLP-1 signaling as a candidate therapeutic target.

**Oxidative Stress in COVID-19**

Reactive oxygen species (ROS) comprise free radicals and non-free radicals, which are derived from oxygen and exhibit intense chemical reactivity due to unpaired electrons. Specific ROS
include superoxide anions, hydrogen peroxide, hydroxyl radicals, ozone, and singlet oxygen, which are extremely reactive oxygen-containing molecules resulting from the inadequate cellular reduction of molecular oxygen. Oxidative stress is defined as an imbalance between the generation of ROS within cells and tissues, and endogenous detoxification mechanisms, such as superoxide dismutase, catalase, and glutathione peroxidase. Whilst ROS signaling is vital to support homeostasis, it has the potential to become dysregulated and detrimental to normal physiology. Indeed, increased ROS levels are linked to oxidative damage of many cellular compartments and components, with ROS-related structural and functional abnormalities of membrane-associated macromolecules, such as lipids and proteins, identified in numerous tissues, including the brain.

Notably, ROS signaling is known to be particularly important in maintaining normal endothelial cell function and determining cardiovascular disease progression, whilst endothelial cells have emerged as significant drivers of inflammation associated with SARS-CoV-2 infection and COVID-19. Redox signaling within endothelial cells may be mediated by ROS derived from different sources, including xanthine oxidase, NOX NADPH oxidases, and dysfunctional nitric oxide synthase, but is predominantly determined by mitochondrial ROS (mtROS), which in excess quantities, promotes oxidative stress, inflammation, and chronic endothelial dysfunction. Interestingly, SARS-CoV-2 infection appears to be associated with significant induction of oxidative stress genes in both immune and pulmonary cells vs. other respiratory viruses, with a ten-fold higher affinity for alveolar cells compared to SARS-CoV-1. It is conceivable that disruption of normal gene expression due to free radical generation and subsequent oxidative stress may impact cellular replication of SARS-CoV-2 further to entry via the ACE2 receptor, radially changing virus structure.

Similar to other coronaviruses, SARS-CoV-2 has a strong capacity for mutation, affecting both non-structural and structural proteins. Notably, the S protein, which is required for ACE2-dependent entry of SARS-CoV-2 into host cells, may be particularly prone to mutation, thereby favoring virus evolution and persistence. Furthermore, SARS-CoV-2 may increase oxidative stress in COVID-19 patients either via inhibition of the conversion of angiotensin II to angiotensin-(1-7) with the resultant generation of superoxide or due to an increased ratio of neutrophils to lymphocytes which drives the production of superoxide and hydroxyl radicals. Given the established role of superoxide and ROS as key mediators of disease progression, it is notable that the impact of SARS-CoV-2 infection is often greater in patients with co-morbidities, such as diabetes and preexisting cardiovascular disease, which is likely to be at least partly determined by increased oxidative stress. Therefore, inhibition of viral protein binding to host cells has clear potential to reduce oxidative stress and confer substantial health benefits during the early stages of SARS-CoV-2 infection.

Inflammation in COVID-19

COVID-19 causes serious respiratory and extra-pulmonary complications, which are observed in tissues with varying levels of ACE2 receptor expression, with damage to those with low ACE2 expression likely mediated by the host inflammatory response rather than direct viral entry. Systemic inflammation associated with COVID-19 is typically characterized by increased circulating cytokines, often referred to as ‘cytokine storm’ or ‘cytokine release syndrome’, the severity of which is linked to deterioration of patient health. Several immune cell types, including innate macrophages, dendritic cells, natural killer cells, and adaptive T and B lymphocytes, produce cytokines in response to virus-specific binding of pathogen-associated molecular patterns (PAMPs) to pattern recognition receptors. The consequent innate immune response against the invading virus activates multiple signaling pathways and downstream transcription factors leading to the induction of genes encoding pro-inflammatory cytokines. In this regard, SARS-CoV-2 infection is linked with a specific inflammatory response profile, characterized by a delayed release of chemokines and cytokines from macrophages, airway epithelial cells, and dendritic cells during the early phase, followed by later phase secretion of high levels of pro-inflammatory cytokines (e.g., interleukins, tumor necrosis factor) and chemokines (e.g., CCL2, CCL3, CCL5) in parallel with low levels of antiviral factors (e.g., interferons). Indeed, it seems likely that activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) pathway is central to pro-inflammatory signaling driven by SARS-CoV-2 infection and may underlie increased susceptibility to COVID-19 progression. Specifically, NF-kB is the priming signal for nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) family pyrin domain containing 3 (NLRP3) inflammasome activation.
a critical component of host viral immune defense against a variety of viruses, and dysregulation of which is linked to the pathogenesis of inflammatory disorders, including auto-inflammatory diseases, ARDS, and acute lung injury, which are characterized by major pyroptosis75. Indeed, NF-κB activation boosts the generation of pro-inflammatory cytokines and ROS, both of which promote cellular damage and are characteristic features of SARS-CoV-2 infection58, whilst dysregulation of NF-κB signaling is reported to worsen and intensify COVID-1959. Furthermore, pro-inflammatory cytokines, such as interleukin-1 beta (IL-1β), IL-6, and tumor necrosis factor (TNF), which play established roles in ARDS pathogenesis, are also linked with severe cytokine storm in COVID-1959, which may promote NF-κB-dependent epithelial and endothelial cell apoptosis, together with vascular leakage, leading to the development of life-threatening complications including ARDS60, acute cardiac injury (e.g., myocarditis, myocardial infarction, cardiac arrest), sepsis, multi-organ failure, ischemic stroke, and acute pulmonary embolism, in addition to secondary infections such as bacterial pneumonia61. In this regard, it is notable that a significant proportion of COVID-19-related morbidity and mortality is linked with cardiovascular dysfunction, most likely occurring secondary to systemic inflammation. Indeed, multisystem inflammatory syndrome in children (MIS-C), which is observed in some individuals following SARS-CoV-2 infection and is clinically similar to Kawasaki Disease, provides direct evidence of the potential impact of inflammation related to COVID-19 on the cardiovascular system, with this condition characterized by cardiogenic shock and medium-sized artery vasculitis62,63. Indeed, circulating levels of C-reactive protein, an established inflammatory marker linked with cardiovascular disease, may independently predict severe or critical COVID-19, whilst D-dimer levels, indicative of thrombosis, may accurately predict in-hospital death due to COVID-1964. Furthermore, there is mounting evidence of increased risk of cardiovascular events post-acute COVID-19, which is not limited to patients hospitalized during the acute phase65,66.

**GLP-1 Receptor Agonists**

GLP-1 is a 30-31 amino acid incretin peptide hormone produced primarily by three tissues in the human body: enteroendocrine L-cells in the distal intestine, pancreatic alpha cells, and the central nervous system34. Enteroendocrine L-cells generate GLP-1 in two forms, GLP-1 (7-36) amide and GLP-1 (7-37), both of which are physiologically active, although the former is predominant. During fasting, circulating GLP-1 concentrations are low (5-10 pmol/L), but are significantly increased (15-50 pmol/L) by feeding in a glucose-dependent manner. The half-life of native GLP-1 in the circulation is only ~2 minutes due to the rapid cleavage of alanine at the second residue by dipeptidyl peptidase-4 (DPP-4), resulting in the generation of inactive GLP-1 (9-36) amide or GLP-1 (9-37). Indeed, only 10-15% of secreted GLP-1 reaches the systemic circulation67, resulting in a short period of biological activity. Once released, GLP-1 binds to and activates the GLP-1R, a seven-transmembrane G protein-coupled receptor, which is expressed in a variety of tissues, including pancreatic islets, heart, vasculature, liver, and central nervous system68, and in inflammatory cells with preferential macrophage expression70. Further to their established insulinotropic benefits in reducing hyperglycemia and insulin resistance, GLP-1R agonists are increasingly employed in clinical practice to treat patients with T2DM71,72. Six GLP-1R agonists are currently approved for clinical use: exenatide twice daily, lixisenatide once daily, liraglutide once daily, exenatide once weekly, dulaglutide once weekly, and semaglutide once weekly73. They are highly effective in controlling blood glucose levels in a glucose-dependent manner, thereby minimizing the risk of hypoglycemia, and are associated with limited side effects, of which gastrointestinal symptoms are most common but typically transient in nature34.

In addition to its metabolic actions, GLP-1 is widely reported to exert pleiotropic effects, particularly on the cardiovascular and central nervous systems, in both health and disease. For example, stress-induced increases in heart rate and blood pressure are linked to GLP-1 action in the brain, including stimulation of GLP-1-producing neurons75, whilst GLP-1Rs confers cardioprotection against remodeling stresses, such as ischemia and diabetes76,77. GLP-1R activation also has established neuroprotective properties with potential clinical applications, including prevention or treatment of neurodegenerative illnesses, such as Alzheimer’s and Parkinson’s disease, as well as post-stroke rehabilitation78. In this regard, it is important to note that individuals with COVID-19 and preexisting diabetes demonstrate a two-fold greater risk of mortality79, highlighting the significant influence of comorbidities on COVID-19.
disease progression and severity. Given that prognosis after SARS-CoV-2 infection may be determined by effective clinical management of cytokine storm and that GLP-1R agonists are known to preferentially reduce cytokine production and inflammation, which is associated with improved lung function\(^{60}\), it seems logical to suggest that these agents could be effective in improving outcomes in COVID-19 patients.

### Anti-Inflammatory and Antioxidant Effects of GLP-1R Agonists

Amongst the number of pleiotropic actions exerted by GLP-1R agonists, anti-inflammatory effects are significant and largely mediated by inhibition of NF-κB-dependent cytokine release\(^{38,81}\), a key driver of cytokine storm linked with SARS-CoV-2 infection. For example, in a rat model of experimental diabetes, renal NF-κB expression was inhibited by the GLP-1 analogue, exendin-4, and associated with attenuation of nephropathy\(^{82}\), whilst liraglutide reversed NF-κB-mediated vascular inflammation in angiotensin II infused hypertensive mice \(\text{via}\) reduced expression of endothelial adhesion molecules, including vascular cell adhesion protein \(1^{84}\). Notably, the anti-inflammatory benefits of exendin-4 are evident in both normoglycemia and hyperglycemia, as indicated by attenuation of adverse extracellular matrix remodeling and diastolic dysfunction in both experimental models of both myocardial infarction and diabetes, occurring independently of parallel metabolic changes and mediated \(\text{via}\) specific reduction of cardiac macrophage infiltration\(^{21,22}\). Similarly, liraglutide and exendin-4 are reported to mitigate atherosclerosis development in mice by inhibition of vascular monocyte adhesion and macrophage infiltration\(^{77,84}\), whilst liraglutide-mediated reduction of lipopolysaccharide-induced sepsis is not evident in GLP-1R \(^{-}\) mice\(^{85}\), indicating that the apparent anti-inflammatory effects of GLP-1R agonists are mediated by GLP-1R stimulation. Importantly, these actions, which are widely evident in experimental models, are also observed in the clinical setting. For example, GLP-1R agonists are reported to reduce circulating concentrations of pro-inflammatory cytokines, such as IL-1β and TNF-α, in obese type 2 diabetic patients \(\text{vs}\) patients receiving standard glycemic control therapy\(^{72}\). Similarly, both liraglutide and exendin-4 reduce the expression of pro-inflammatory cytokines, IL-1β, IL-6, TNF-α and MCP-1 in human mononuclear cells, in parallel with increased expression of adiponectin, which promotes established anti-inflammatory actions\(^{86,87}\). In this regard, exendin-4 attenuates macrophage-mediated adipose tissue inflammation \(\text{via}\) specific inhibition of NF-κB-dependent cytokine secretion\(^{88}\), suggesting that GLP-1R agonists modulate both immune cell and adipose tissue function independently of their well-established actions on glycemic control. Indeed, GLP-1R activation in T2DM may specifically inhibit NLRP3 inflammasome-dependent inflammation in perivascular adipose tissue, characterized by NF-κB-mediated upregulation of cleaved caspase-1, IL-1, and IL-18\(^{89}\). Consistent with this observation, T2DM patients treated with GLP-1R agonists display increased plasma levels of anti-inflammatory adipokines, such as adiponectin, together with reduced pro-inflammatory cytokines\(^{90}\).

In addition to their evident anti-inflammatory effects, emerging evidence indicates that GLP-1R agonists may also confer important antioxidant effects with significance to SARS-CoV-2 infection. For example, liraglutide is reported to promote antioxidant and anti-inflammatory properties in angiotensin II-treated mice, which is linked with the attenuation of hypertension-induced cardiac hypertrophy and vascular fibrosis\(^{83}\). Furthermore, treatment of human umbilical vein endothelial cells with native GLP-1 (7-36) reduced high glucose-induced oxidative stress \(\text{via}\) inhibition in NADPH oxidase activation\(^{90}\), whilst liraglutide promotes antioxidant effects on platelets, characterized by decreased ROS and increased nitric oxide generation, and associated with inhibition of platelet aggregation\(^{91}\). Consistent with its reported anti-inflammatory actions, exendin-4 reduces ROS formation in human monocytes, assessed by malondialdehyde levels\(^{8}\), \(\text{via}\) inhibition of NADPH oxidase activity and stimulation of antioxidant enzymes, glutathione peroxidase and superoxide dismutase\(^{92}\). Taken together, these findings support the emerging consensus that GLP-1R agonists hold significant therapeutic potential beyond their current application for glycemic control, by specifically targeting pro-inflammatory and pro-oxidative aspects, particularly in relation to diabetic vascular complications and cardiovascular disease.

### GLP-1 Receptor Agonists as Promising Drugs Against COVID-19

Given that preexisting T2DM is a significant determinant of poor prognosis in COVID-19 patients\(^{58}\), and GLP-1R agonists, which are now widely prescribed for glycemic control, have established
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anti-inflammatory and antioxidant actions, it is possible to suggest that they may also confer therapeutic benefit against SARS-CoV-2 infection and COVID-19 (Figure 2). As the GLP-1R is ubiquitously expressed, including in lungs, and the activation inhibits cytokine release, it has been proposed that increased systemic GLP-1 concentrations may be beneficial against the development and progression of acute obstructive pulmonary disease associated with severe COVID-1993. Although GLP-1R agonists are unlikely to directly impact respiratory SARS-CoV-2 infection, their potent anti-inflammatory properties hold clear potential to dampen the consequent excessive systemic inflammatory response38. It is particularly notable that GLP-1R activation appears to be highly significant in monocyte and macrophages, which represent the most abundant immune cell types in the lungs of COVID-19 patients. In this regard, GLP-1R agonists have been shown to inhibit cytokine production and reduce pulmonary inflammation, which may be particularly advantageous in COVID-19 patients with preexisting atherosclerosis, obesity, or T2DM, which are associated with aberrant inflammation and poor prognosis. Indeed, anti-inflammatory actions of liraglutide are associated with preserved respiratory function in rodents subjected to LPS-induced acute lung injury via inhibition of the NLRP3 pathway94, whilst improved lung function and mortality are evident in mice subjected to chronic obstructive pulmonary disease and liraglutide treatment95. Consistent with these experimental findings, native GLP-1 (7-36) is reported to stimulate protein kinase A-induced surfactant secretion by human type 2 pneumocytes, whose primary role is protection against inflammatory-mediated cellular damage, such as that observed after SARS-CoV-2 infection96. Similarly, pulmonary vascular remodeling, a key feature of severe COVID-19, is reduced by liraglutide treatment in experimental monocrotaline-induced pulmonary arterial hypertension via activation of endothelial nitric oxide synthase97. It is interesting to note that SARS-CoV-2 infection typically promotes a

Figure 2. Proposed mechanisms by which GLP-1R agonists may protect against inflammation and oxidative stress associated with COVID-19. Emerging evidence indicates that GLP-1R agonists (GLP-1 RA) may reduce (A) NF-κB-mediated proinflammatory signaling, (B) oxidative stress via inhibition of ROS generation and/or promotion of endogenous antioxidants, and (C) renin-angiotensin-aldosterone activation via ACE2 upregulation, which all appear to be central to SARS-CoV-2 pathogenesis and consequent thrombotic and inflammatory complications.
switch in cell metabolism towards a predominantly glycolytic phenotype, which promotes virus proliferation and is driven largely by mitochondrial ROS generation and subsequent stabilization of hypoxia-inducible factor-1α. It, therefore, seems possible that GLP-1R agonists, which impact both metabolic and oxidative signaling, may also reduce direct consequences of SARS-CoV-2 cell entry. Indeed, such metabolic changes in monocytes and macrophages, which are preferential targets for GLP-1R activation, further to SARS-CoV-2 infection, may also impair T cell responsiveness and diminish airway epithelial cell survival. Taken together, these initial data are intriguing and clearly supportive of the potential repurposing of GLP-1R agonists for the management of respiratory complications linked with SARS-CoV-2 infection.

In addition to the direct anti-inflammatory effects of GLP-1R agonists on pulmonary inflammation and function, it appears that these drugs may also reduce respiratory infection via modulation of ACE2, a cell-bound protease with abundant expression in alveolar epithelium, enterocytes, and blood vessels, which catalyzes the conversion of angiotensin II to angiotensin (1-7). Indeed, liraglutide is reported to upregulate the expression of ACE2 in the lungs of diabetic rats, thereby counteracting pro-inflammatory and pro-fibrotic actions of renin-angiotensin-aldosterone system activation. In this regard, it has been suggested that GLP-1R mediated induction of ACE2 could limit lung injury in COVID-19 by opposing SARS-CoV-2 infection and reducing consequent immune cell over-activation and ARDS. However, it is crucial to note that as the ACE2 receptor represents the primary mechanism by which SARS-CoV-2 enters and replicates within airway epithelium, there is a risk that induction of ACE2 expression by GLP-1R agonists could exacerbate COVID-19. As such, further experimental and clinical studies are needed to elucidate the precise relationship between ACE2 and ACE2 receptor expression in relation to SARS-CoV-2 infection and GLP-1R activation.

In addition to the likely direct anti-inflammatory and antioxidant actions of GLP-1R agonists in the context of SARS-CoV-2 infection, it is important to consider that obesity and T2DM, for which these drugs are recommended treatments, predispose to increased severity of COVID-19. Therefore, the established metabolic benefits of GLP-1R agonists in promoting weight loss via normalization of insulin and glucagon signaling, which are associated with reduction of systemic inflammation and improved immune function, are likely to enhance COVID-19 prognosis. In this regard, early reports of the clinical effects of GLP-1R agonists in this setting are encouraging. One large-scale study of 12,446 SARS-COV-2 positive T2DM patients, indicated that pre-existing prescription of either a GLP-1R agonist or sodium/glucose cotransporter-2 (SGLT2) inhibitor lowered both 60-day mortality and hospitalization in comparison to patients receiving DPP4 inhibitor therapy. Similarly, a meta-analysis of T2DM patients admitted to hospitals with COVID-19 indicated reduced mortality in those using GLP-1R agonists vs. standard glycemic control therapy, with particular benefits observed in patients with additional cardiovascular risk factors. Indeed, atherosclerosis, which is largely viewed as an inflammatory disease, may be considered a comorbidity contributing to an increased risk of COVID-19 infection and poor outcomes. In this regard, atherogenic inflammatory profiles, characterized by aberrant cytokine release and immune cell activation, are reported to determine COVID-19 severity, which may be impacted by established anti-inflammatory actions of GLP-1R agonists to reduce atherosclerotic disease. Although current data supporting the potential application of GLP-1R agonists for treatment of COVID-19 is limited to T2DM cohorts, this is likely to extend to non-diabetic patients given that their anti-inflammatory and antioxidant actions are also evident in normoglycemia. Nonetheless, further research is required to assess whether this class of drugs may represent a safe and effective therapeutic option for the management of both diabetic and non-diabetic patients exposed to SARS-CoV-2 infection.

**Conclusions**

COVID-19 continues to represent a significant public health concern that is evident worldwide and associated with severe complications driven by aberrant inflammatory responses and multi-organ dysfunction, which are particularly prominent in T2DM and obese individuals. Although some drugs have been shown to confer benefits against COVID-19, more specific and effective treatments, especially against chronic aspects, are urgently needed. In this regard, GLP-1R agonists, which are primarily used for the management of glycemia in T2DM, confer anti-inflammatory and antioxidant effects on multiple organ systems, including cardiovascular, respiratory, renal, and endocrine,
in addition to their established metabolic actions. These properties, which are apparent in both normoglycemic and hyperglycemic conditions, together with emerging clinical evidence, highlight GLP-1R agonists as a potential therapeutic option for SARS-CoV-2 and COVID-19, particularly in patients with comorbidities. Detailed mechanisms by which GLP-1R activation may interact with SARS-CoV-2 infection and impact the development and progression of COVID-19 remain still unclear. Nonetheless, it is important to recognize the significant additional potential benefits of GLP-1R agonists, beyond glucose control in T2DM, towards effective treatment of comorbidities and other inflammatory disorders, which appear to include both acute and chronic COVID-19.

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