

SPECIAL REPORT



The role of GLP-1 receptor agonists during COVID-19 pandemic: a hypothetical molecular mechanism

Yajnavalka Banerjee^{a,b,*}, Anca Pantea Stoian^{c,*}, José Silva-Nunes^{d,e,f}, Alper Sonmez^g, Ali A. Rizvi^{h,i}, Andrej Janež^j and Manfredi Rizzo^{b,c,i,k}

^aBiochemistry, Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai, United Arab Emirates; ^bCentre of Medical Education, University of Dundee, UK; ^cDepartment of Diabetes, Nutrition and Metabolic Diseases, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; ^dDepartment of Endocrinology, Diabetes and Metabolism, Centro Hospitalar Universitário De Lisboa Central, Lisbon, Portugal; ^eNova Medical School-Faculdade De Ciências Médicas, New University of Lisbon, Lisbon, Portugal; ^fHealth and Technology Research Center (H&TRC), Escola Superior De Tecnologia Da Saude De Lisboa, Lisbon, Portugal; ^gDepartment of Endocrinology and Metabolism, Gulhane School of Medicine, University of Health Sciences, Ankara, Turkey; ^hDivision of Endocrinology, Metabolism, and Lipids Emory, University School of Medicine, Atlanta, GA, USA; ⁱDivision of Endocrinology, Diabetes and Metabolism, University of South Carolina School of Medicine, Columbia, SC, USA; ^jDepartment of Endocrinology, Diabetes and Metabolic Diseases, University Medical Centre Ljubljana, Faculty of Medicine, University of Ljubljana, Slovenia; ^kDepartment of Health Promotion Sciences Maternal and Infantile Care, Internal Medicine and Medical Specialties (PROMISE), University of Palermo, Palermo, Italy

ABSTRACT

Introduction: A number of anti-diabetic treatments have been favored during the continuing spread of the current SARS-CoV-2 pandemic. Glucagon like peptide-1 receptor agonists (GLP1-RAs) are a group of antidiabetic drugs, the glucose reducing effect of which is founded on augmenting glucose-dependent insulin secretion with concomitant reduction of glucagon secretion and delayed gastric emptying. Apart from their glucose lowering effects, GLP1-RAs also exert a plethora of pleiotropic activities in the form of anti-inflammatory, anti-thrombotic and anti-obesogenic properties, with beneficial cardiovascular and renal impact. All these make this class of drugs a preferred option for managing patients with type 2 diabetes (T2D), and potentially helpful in those with SARS-CoV2 infection.

Areas covered: In the present article we propose a hypothetical molecular mechanism by which GLP1-RAs may interact with SARS-CoV-2 activity.

Expert Opinion: The beneficial properties of GLP1-RAs may be of specific importance during COVID-19 infection for the most fragile patients with chronic comorbid conditions such as T2D, and those at higher cardiovascular and renal disease risk. Yet, further studies are needed to confirm our hypothesis and preliminary findings available in the literature.

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1. Introduction

Since the beginning of 2020, the global community has been facing a challenging pandemic caused by the coronavirus SARS-CoV-2 and its related disease COVID-19, with more than 180 million reported cases and about four million deaths as of 3 October 2020 [1]. The actual impact of COVID-19 is probably much larger than what has been assessed by official reports secondary to the reduced access of patients with acute and chronic diseases to health care facilities due to fear of contracting the virus [2]. Older individuals with chronic health conditions are more likely to develop severe symptoms and complications; for example, the presence of Type-2 diabetes (T2D) is associated with higher mortality and increased need for intensive care [3,4]. An effective and timely prevention strategy is, therefore, imperative [5].

Some international recommendations and shared practice on clinical experience and key learnings, for a better management

of diabetic patients during the pandemic, are already available [6,7]. Other authors have also proposed potential mechanisms beyond the susceptibility for COVID-19 in patients with T2D [8]; indeed, the exposure to high glucose levels is a significant predictor of adverse outcome in COVID patients [9]. Such finding is not surprising since acute glucose variability can enhance oxidative stress, triggering the production of inflammatory cytokines and amplifying the inflammatory process [10]. Poor glycaemic control has also been linked to negative changes in the innate-mediated and the cell-mediated adaptive immunity [11]. Finally, some authors have suggested that raised glucose levels may directly stimulate the replication of SARS CoV-2 virus [12,13].

In the present article we first discuss the close association between diabetes and COVID-19 hospitalization and mortality that has been reported in multiple cohorts across different countries, globally. Then, we discuss potential mechanisms by which GLP1-RAs may modulate SARS-CoV-2 activity, reducing viral entry and attenuating the infection. We indeed aim to

CONTACT Anca Pantea Stoian ✉ ancastoian@yahoo.com 📧 Department of Diabetes, Nutrition and Metabolic Diseases, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

*These two authors contributed equally to the present work.

Article highlights

- Diabetes represents a comorbidity very closely associated with COVID-19,
- Hyperglycemia is associated with the severity of prognosis in patients with COVID-19.
- Novel anti-diabetic drugs seem to have a greater role in the management of patients with T2D during COVID-19 era, due to their glyco-cardio-metabolic benefit.

We hypothesize that GLP1-RAs may modulate SARS-CoV-2 activity.

provide a timely contribution useful for the medical and scientific community during this terrible pandemic.

2. Diabetes and COVID-19

Poor COVID-19 outcomes in patients with T2D has been shown since the beginning of the pandemic in many studies, highlighting immediately the need of tight control of diabetic patients, now more than ever, during this terrible pandemic [14,15]. Indeed, initial reports from Wuhan and from other regions in China have shown some divergent rates in the prevalence of T2D amongst COVID patients [16]. However, after the first smaller reports, findings from larger Chinese studies indicated more consistency, and in two multicenter reports, T2D was present in about 8% of subjects hospitalized for COVID [17,18]. Still from China, Zhu and colleagues [19] have also emphasized the importance of proper glycemic control for COVID outcome; in a retrospective multicenter study performed in patients with T2D and COVID-19, the authors reported that glycemic control was associated with significantly lower mortality.

Regarding early European reports, the first data were available from Italy, as the first hard-hit country in Europe: in Padua, Veneto, and in Milan, Lombardy, the prevalence of diabetes among hospitalized individuals with COVID-19 was 9% [20] and 15%, respectively [21]. Some other early reports were consistent with these findings, although higher prevalence rates of about 25% were reported in other European countries, like Spain [22], and the US [23]. In summary, making a comparative analysis of the prevalence of T2D in the above-mentioned large cohort studies conducted in different countries, the main early learnings were that diabetes represents a comorbidity very closely associated with COVID-19, its more severe forms that may also require hospitalization in intensive care units, and related mortality [24–26].

In consistent to that, Holman et al. [27] in a population-based cohort study in England, have later shown a strong association between prior hyperglycemia and COVID-19 associated death after adjustment for other risk factors. In subjects with T2D, COVID-19 linked mortality was significantly higher in those with HbA1c $\geq 7.6\%$ than in those with an HbA1c of 6.5–7.0%). However, it should also be highlighted that low HbA1c was also associated with significantly increased COVID-19 mortality, which reinforces the clinical importance to avoid severe hypoglycemia. Another study from Italy has also shown that hyperglycemia at hospital admission is associated with the

severity of COVID-19 prognosis [28]. Overall, these studies allude to a major role of T2D and the associated comorbidities/complications in conferring an increased susceptibility to develop COVID-19, and therefore require the adoption and implementation of international scientific guidelines would ensure use of appropriate drugs with proven benefit and safety [29].

3. GLP1-RAs in patients with T2D and SARS-CoV2 infection

GLP1-RAs, are incretin mimetics, whose anti-hyperglycemic effect is based on preserving pharmacologic levels of GLP1 which then increases glucose-dependent insulin secretion, decreases glucagon secretion, and delays gastric emptying. GLP1-RAs can be classified into long-acting (e.g. liraglutide, exenatide once weekly, dulaglutide, albiglutide, semaglutide) and short-acting (e.g. exenatide, lixisenatide) compounds [30]; furthermore, semaglutide is now also available as a pill, being the first oral GLP1-RA for the treatment of T2D [31]; GLP1-RAs have been shown to reduce HbA1c by approximately 0.8% to 1.6% [30,31] and some of these agents have increased homology to human GLP1 and therefore named as ‘GLP1-analogues’ (e.g. liraglutide, dulaglutide, albiglutide and semaglutide); the latter, beyond significant gluco-metabolic beneficial effects, have a favorable cardiovascular outcome, reducing cardiovascular events and mortality [32]. Yet, this may be not uniform among the class of GLP-1 RAs, since other agents have been discontinued due to adverse safety profiles [33,34].

GLP-1 RAs exert significant anti-inflammatory effects [35,36], which could theoretically blunt the exaggerated inflammatory response induced by pulmonary SARS-CoV2 infection, but not to reduce the infection per se. Given the GLP-1RAs beneficial role in patients with T2D at high risk for cardiovascular diseases, both diabetologists and cardiologists are now in agreement that represent first therapeutical choice for patients at such risk [37], which is of greater importance during COVID era [38]. Yet, there is still insufficient evidence to clarify the benefit of GLP-1RAs in patients with T2D and SARS-CoV2 infection, so far mainly limited to data obtained from retrospective analyses of few databases. In the US, the National COVID Cohort Collaborative (N3C) Consortium have performed the analysis of observational data from SARS-CoV-2-positive adults with a prescription for GLP1-RAs, sodium-glucose cotransporter 2 inhibitors (SGLT2i) inhibitors or dipeptidyl peptidase 4 inhibitors (DPP4i) within 24 months of positive SARS-CoV-2 PCR test [39]. Interestingly, the authors have very recently reported that premonitory GLP1-RAs and SGLT2i use, compared with DPP4i usage, was associated with lower odds of mortality and other adverse outcomes, such as emergency room visits and hospitalizations [39].

By contrast, an earlier retrospective study performed in Denmark have suggested that the use of incretin-based therapies in individuals with diabetes and SARS-CoV-2 was not associated with improved clinical outcomes [40]. Yet, this study suffers of a limited sample size. A neutral benefit with the use of GLP1-RAs has been also shown by Khunti et al in an observational nationwide study in England, where pre-COVID

-19 prescription of glucose-lowering therapies and mortality risk of COVID-19 was analyzed in 2,85 million people with T2D. Metformin, SGLT2i, and sulfonylureas were associated with reduced risks of the COVID-19-related mortality, whereas insulin and DPP-4i were associated with increases in risk; neutral results were observed for GLP1-RAs and thiazolidinediones [41]. Other reports have shown a beneficial impact on COVID hospitalizations and mortality with the use of GLP1-RAs [42], and we cannot exclude that weight loss obtained with GLP1-RAs may be a protective mechanism in patients with T2D and COVID-19. In summary, available evidence suggest a beneficial impact of GLP1-RAs on hospitalizations and mortality in patients with T2D and COVID-19; yet, to date, no prospective studies investigating the association between GLP1-RAs use and COVID-19 outcome have been published.

4. Mechanisms by which GLP1-RAs may attenuate with SARS-CoV-2 infection

GLP1-RAs have been shown to exert several beneficial pleiotropic effects, beyond glycemic control [43,44]. One of them is the systemic anti-inflammatory effect, which is mediated as a consequence of the inhibitory effect on cytokine release due to their interference with the NF- κ B signaling pathways [45]. This anti-inflammatory effect of GLP1 RA could theoretically blunt the exaggerated inflammatory response induced by

pulmonary SARS-CoV-2 infection, but not reduce the infection per se.

The anti-inflammatory aspect of GLP1-RAs has been well demonstrated in animal model studies [46]. For example, the administration of liraglutide in lipopolysaccharide induced endotoxemia in animal models has been shown to improve survival and vascular dysfunction, along with salubrious actions on inflammatory and hemostatic parameters [47]. This pleiotropic activity of GLP1-RAs may be advantageous when it comes to the management of SARS-CoV-2 infection, as it may potentially reduce the severity of the viral infection (Figure 1). NF- κ B is also the key and central mediator of the priming signal for NLR family pyrin domain containing 3 (NLRP3) inflammasome activation, and functions by stimulating the transcriptional expression of NLRP3 in response to multifarious Pattern Recognition Receptors (PRR) ligands and cytokines [48]. NLRP3 inflammasome is composed of NLRP3, the apoptosis-associated speck-like protein containing a CARD (ASC) and procaspase-1, as well as an essential regulatory protein, NIMA-related kinase 7 (NEK7) [49]. The NLRP3 gene is a direct target of NF- κ B, which contains NF- κ B-binding sites in its promoter region. Upon stimulation by NF- κ B, the inflammasome receptors oligomerize and recruit pro-caspase 1 via ASC, thus stimulating pro-caspase 1 processing and conversion to active caspase 1. Activated caspase 1, then cleaves pro-IL-1 β and pro-IL-18 into their mature forms [50]. Hence, NF- κ B mediated secretion of

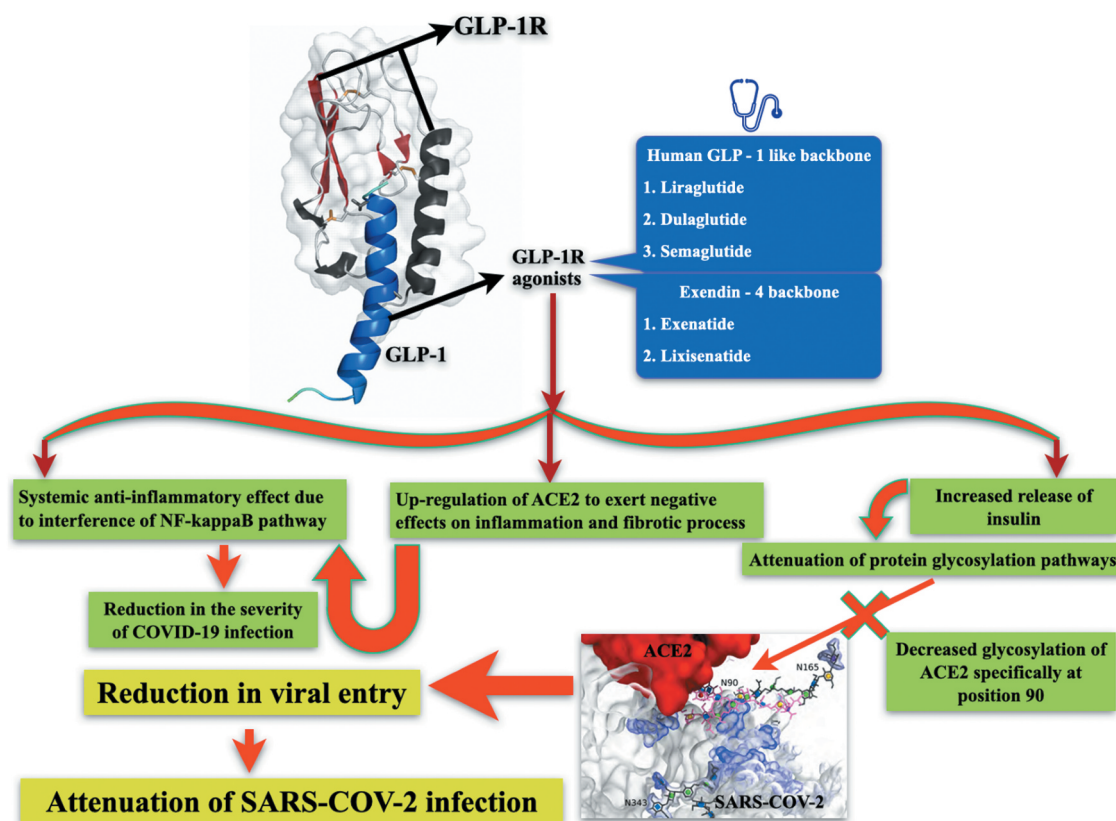


Figure 1. Potential mechanism by which GLP1-RAs may interact with SARS-CoV-2 activity.

The structural coordinates of GLP-1 receptor complex (represented in the form of ribbon diagram) was downloaded from protein data bank (PDB ID: 5VEX). The details of the structure can be obtained from Song et al. Nature 2017;546:312–315. The concept of ACE2 and SARS-CoV-2 interaction was adopted with minor modifications from bioRxiv: the preprint server for biology 2020.06.25.172403. 24 July 2020, doi:10.1101/2020.06.25.172403.

these pro-inflammatory cytokines through NLRP3 priming attests to increase in the disease severity in SARS-CoV-2 infection. As GLP1-RAs interfere with the NF- κ B signaling pathways, they could also attenuate NLRP3 mediated inflammation. However, this area requires further investigation.

SARS-CoV-2 infection through NF- κ B mediated pathways induces a hyper-inflammatory state designated as 'cytokine storm' [51], involving significant systemic perturbations. These include iron dysregulation manifested as hyperferritinemia associated with disease severity [52]. Hyperferritinemia induces reactive oxygen species (ROS) production and promotes oxidative stress, which leads to mitochondrial damage [53]. Downstream to this mitochondrial damage, platelet issues and apoptosis may occur. The interaction of dysfunctional platelets with coagulation cascades aggravate clotting events and thrombus formation, the latter being one of the major causes of death in SARS-CoV-2 infection [54]. Since GLP1-RAs mitigate NF- κ B signaling pathways, they could also induce mitochondrial protection leading to favorable anti-thrombotic effects. This possibility is supported through observations in ex vivo whole blood microfluidics model, where native GLP-1(7–36) has been shown to reduce entire blood thrombus formation at both venous and arterial flow shear rates, resulting in the formation of smaller and less contracted thrombi [55].

It is well known that GLP1-RAs stimulate the secretion of insulin from pancreatic beta-cells [56]. Insulin plays a key role in protein glycosylation [57], and glycosylation has been shown to play a pivotal role in SARS-CoV-2 infection. SARS-CoV-2 utilizes its highly glycosylated trimeric Spike protein to bind to the cell surface receptor ACE2 glycoprotein and facilitate host cell entry [58]. In fact, glycosylation of the ACE2 receptor at specific amino acid residues (such as at position 90) (Figure 1) is important for its binding to the SARS-CoV-2 Spike protein [58]. One of the key pathways for glycosylation is the hexosamine biosynthesis pathway [59]. This pathway functions in part as a glucose sensor and regulates cellular responses to insulin by controlling the levels of UDP-GlcNAc-mediated glycosylation of targets related to insulin activity [60]. The hexosamine biosynthesis pathway is highly responsive to glucose levels, and its flux is significantly increased in some tissues of patients with diabetes, leading to increased levels of UDP-GlcNAc and, thus, elevated glycosylation. Long-term exposure to high glucose increases O-GlcNAc modifications and, therefore, its biological effects; for example, in the context of diabetes, increases O-GlcNAc glycosylation of proteins, such as glycosylation of AKT, can lead to enhanced β -cell death [61]. Based on these observations, one can surmise that decreased insulin levels may increase glycosylation of the ACE2 receptor, augmenting its affinity for SARS-CoV-2 spike protein. Therefore, GLP1-RAs, apart from their favorable effect mediated through its impact on NF- κ B signaling pathways during SARS-CoV-2 infection, may also impede virus entry through their modulatory effect on protein glycosylation, especially that of ACE2.

5. GLP1-RAs and ACE2 conundrum

It has been shown that GLP1 receptors contribute to airway remodeling [62]. Numerous clinical trials are currently underway to investigate the theoretical potential of GLP1-RAs for the improvement of chronic obstructive respiratory disease [63]. In animal studies, liraglutide has been associated with the upregulation of ACE2, abundantly expressed in alveolar epithelial cells, enterocytes and vessels upstream of the counter-regulatory RAS pathway, which exercises a negative effect on inflammatory and fibrotic processes [64]. Although still uncorroborated by well-defined translational substantiation, the GLP1-RAs-induced upregulation of ACE2 could ameliorate lung injury, antagonizing the reduction of ACE2 expression levels that are hallmarks of SARS-CoV-2 infection progression [65] and precluding the over-activated immune response critical for acute respiratory distress syndrome [66] (Figure 1). On the other hand, ACE2 enables virus entry into host target cells [67], raising speculation of augmented vulnerability to SARS-CoV-2 infection in the case of ACE2 overregulation, as an outcome of long-term treatment with ACE inhibitors and/or ANGII receptor blockers, GLP1-RAs or a combination of both in hypertensive patients with diabetes [68]. However, robust clinical/epidemiological studies which support the correlation between these medications, especially GLP1-RAs use, and SARS-CoV-2 infection severity, and adjusted for conceivable confounding variables such as sex, age and comorbidities possibly modulating the expression of ACE2, are unavailable. The subject of whether GLP1-RAs treatment-induced overregulation of ACE2 in target tissues would lead to an increased risk of SARS-CoV-2 infection, or their proposed protective activity (Figure 1) would predominate, is a conundrum yet to be solved.

6. Conclusions

We discussed in the present article about the importance of the anti-inflammatory properties and the beneficial metabolic and cardio-renal effects of GLP1-RAs, together with their safety. Further, we proposed potential mechanisms by which GLP1-RAs may modulate SARS-CoV-2 activity, albeit subject to confirmation in future studies. This is of particular importance due to the continuous spread of the virus and its related disease COVID-19, with increased number of cases, severe forms and complications, and related deaths.

7. Expert opinion

Our globe is facing a very difficult and challenging pandemic since the beginning of 2020, caused by the new coronavirus SARS-CoV-2 and its related disease COVID-19. All the continents have been seriously hit by the virus, starting from the town of Wuhan in China, and with billions of people worldwide following very strict social distancing regulations, as well as partial or full lockdowns. Currently, there is continuous spread of the virus and the actual impact of COVID-19 seems to be much larger than what assessed by official reports, for

instance for the significant reduced access of patients with acute and chronic diseases to health care facilities due to fear of contracting the virus.

Older individuals with chronic health conditions are those more likely to develop severe symptoms and complications; for example, the presence of diabetes is associated with higher mortality and increased need for intensive care. A number of anti-diabetic treatments have been favored during the continuing spread of the current SARS-CoV-2 pandemic [69], and early use of GLP1-RAs has been advocated. Distinct and unique pharmacokinetic, metabolic and cardio-renal properties are present in the different GLP1-RAs approved for subcutaneous administration for the management of T2D and currently available in the markets, including twice-daily exenatide, once-daily liraglutide and lixisenatide, once-weekly exenatide, dulaglutide albiglutide and semaglutide, as well as semaglutide in the new daily oral formulation, the latest agent available.

Indeed, this class of novel anti-diabetic agents has beneficial effects on glucose metabolism, and some GLP1-RAs have also shown a beneficial cardiovascular and renal impact. This is of particular importance during COVID-19 infection for the most fragile patients with chronic conditions such as diabetes and those at higher cardiovascular and renal disease risk. In addition, some GLP1-RAs have significant anti-inflammatory properties that are also of importance during the COVID-19 era [70], since the latter has been shown to contribute to systemic inflammation that seems to underlie organ impairment, including myocardial injury [71].

Certain scientific recommendations issued during the COVID-19 pandemic have highlighted the safety of insulin therapy in patients with SARS-CoV-2 infection and diabetes, while exercising care when considering other oral/injectable therapies. On the other hand, it has also been suggested that patients with type 2 diabetes and SARS-CoV2 could reach better metabolic balance, decrease inflammation, and possibly avoid complications using a fixed combination with basal insulin and GLP1-RAs [6]. The latter provides good glycemic control while avoiding hypo and hyperglycemia and promoting an anti-inflammatory effect for patients with type 2 diabetes affected by SARS-CoV-2 infection [9].

In the present article we discussed on potential mechanisms by which GLP1-RAs may modulate SARS-CoV-2 activity, albeit subject to confirmation in future studies. Nevertheless, the beneficial anti-inflammatory properties as well as the metabolic and cardio-renal effects of GLP1-RAs, together with their safety, make this class of drugs as one of the best options for managing type 2 diabetes patients in the face of the COVID-19 pandemic.

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ORCID

Manfredi Rizzo  <http://orcid.org/0000-0002-9549-8504>

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Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.

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