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REVIEW

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Glucagon-like peptide-1 receptor agonists in the era of COVID-19: Friend or foe?

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Summary

The aim of the present manuscript is to discuss on potential pros and cons of glucagon-like peptide-1 receptor agonists (GLP-1RAs) as glucose-lowering agents during COVID-19 pandemic, and what is more to evaluate them as potential candidates for the treatment of patients, affected by COVID-19 infection, with or even without diabetes mellitus type 2. Besides being important glucose-lowering agents, GLP-1RAs pose promising anti-inflammatory and anti-obesogenic properties, pulmonary protective effects, as well as beneficial impact on gut microbiome composition. Hence, taking everything previously mentioned into consideration, GLP-1RAs seem to be potential candidates for the treatment of patients, affected by COVID-19 infection, with or even without type 2 diabetes mellitus, as well as excellent antidiabetic (glucose-lowering) agents during COVID-19 pandemic times.

KEYWORDS

antidiabetics, coronavirus, diabetes mellitus, glucagon-like peptide 1, obesity

1 | INTRODUCTION

Up to October 26th 2020, the World Health Organization has recorded 42 966 344 cases of COVID-19 causing 1 152 604 deaths. Diabetes mellitus and obesity are significant and increasing worldwide health concerns, both characterized by presence of low-grade chronic inflammation and consequent immune system dysfunction leading to increased overall risk for various infections, (post)infectious complications and mortality.[1] Therefore, it is not surprising that both diabetes mellitus and obesity, in addition to arterial hypertension and old age, have been identified as most significant risk factors for COVID-19 infection and worse clinical outcomes.[2-4] Given the significance of the connection between COVID-19 and diabetes mellitus, providing the international guidelines and practical recommendations for its management during the pandemic times was of high importance. Hence, Bornstein et al. (international expert panel) provided them in the early beginnings of COVID-19 pandemic; extensively presented elsewhere.[5] It is noteworthy that no substantial considerations of potential metabolically interfering effects of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in suspected or COVID-19 positive patients with diabetes mellitus type 2 have been reported.[5] Only minor concern regarding potential GLP-1RAs-associated angiotensin converting enzyme-2 (ACE-2) upregulation has been raised, mostly because of the observations from a previous preclinical study on diabetes Sprague-Dawley rats.[6] Insulin is definitely a glucose-lowering agent of choice for patients with diabetes who are affected by most severe clinical forms of COVID-19 disease.[5]

GLP-1RAs' glucose lowering effect is based on maintaining pharmacologic level of GLP-1 which then increases glucose-dependent insulin secretion, reduces glucagon secretion, and delays gastric emptying. They can be categorized as either short-acting (exenatide, lixisenatide) or long-acting (liraglutide, semaglutide, dulaglutide, exenatide extended-release, albiglutide) and are currently only approved for use as subcutaneous injections.[7] In addition, Food and Drug Administration recently approved first oral GLP-1RA for the treatment of type 2 diabetes (semaglutide-Rybelsus).[8] GLP-1RAs have been shown to reduce glycated haemoglobin (HbA1c) by approximately 0.8% to 1.6%.[9] Besides substantial glucose-lowering effect, it

Abbreviations: ACE-2, angiotensin converting enzyme-2; BMI, body mass index; COVID-19, Coronavirus disease 2019; FBG, fasting blood glucose; GLP-1RA, glucagon-like peptide-1 receptor agonist; LPS, lipopolysaccharide; NF-κb, nuclear factor-κB; SARS CoV-2, severe acute respiratory syndrome coronavirus-2; SP, surfactant protein.

is worth mentioning that GLP-1RA administration is associated with anti-obesogenic properties, a low risk of hypoglycaemia, as well as non-serious adverse events only (predominantly gastrointestinal-e.g. nausea, vomiting, diarrhoea). On top of that, liraglutide and semaglutide pose significant favourable cardiovascular benefit and are approved for use in patients with severe renal impairment (eGFR≥15).[10-12]

The aim of the present narrative literature review is to discuss on potential pros and cons of GLP-1RAs as glucose-lowering agents during COVID-19 pandemic, and what is more to evaluate them as potential candidates for the treatment of patients, affected by COVID-19 infection, with or even without diabetes mellitus type 2. Finally, to conclude if GLP-1RA therapy is a friend or foe in the present pandemic times.

2 | THE INCREASING IMPORTANCE OF GLP-1RAS' GLUCOSE-LOWERING PROPERTIES IN COVID-19 PANDEMIC TIMES

Potential mechanisms that may increase the susceptibility for COVID-19 in patients with diabetes have extensively been proposed elsewhere by Muniyappa and Gubbi.[13] Hyperglycaemia, hypoglycaemia, as well as exposure to high glucose variability are predictors of worse/adverse outcomes in patients hospitalized for COVID-19.[14,15] This is not unexpected since acute hyperglycaemia, hypoglycaemia, as well as hyperglycaemia post-hypoglycaemia all produce oxidative stress and are followed by enormous production of inflammatory cytokines and by enhancement of the inflammatory/infectious process.[15] Poor glycaemic control has also been connected to alterations in innate-mediated and cell-mediated adaptive immunity.[16] Moreover, it is also speculated that elevated glucose levels directly promote SARS CoV-2 viral replication.[17,18]

Apicella et al. extensively overviewed the reasons for worse COVID-19 outcomes in patients with diabetes, as well as relevant studies on COVID-19 outcomes according to glycaemic control.[19] For instance, Zhu et al. in their retrospective, longitudinal, multi-centered study demonstrated that well-controlled blood glucose (glycaemic variability within 3.9 to 10.0 mmol/L) was associated with markedly lower mortality (adjusted HR 0.14) compared to poorly controlled blood glucose (upper limit of glycaemic variability exceeding 10.0 mmol/L) among patients with pre-existing type 2 diabetes during hospitalization for COVID-19.[20] An American retrospective observational study also demonstrated significantly longer length of stay and higher mortality in COVID-19 patients with diabetes and/or uncontrolled hyperglycaemia when comparing to patients without diabetes or uncontrolled hyperglycaemia.[21] What is more, Holman et al. in their population-based cohort study, of people diagnosed with diabetes who were registered with a general practice in England, reported a strong association between preceding hyperglycaemia and COVID-19 related death after adjustment for other risk factors. In people with type 2 diabetes, COVID-19 related mortality was significantly higher in those with HbA1c ≥59 mmol/mol (7.6%) than in those with an HbA1c of 48-53 mmol/mol (6.5-7.0%), and the risk increased significantly with increasing HbA1c levels (HR 1.22 for 59-74 mmol/mol [7.6-8.9%] and HR 1.36 for 75-85 mmol/mol [9.0-9.9%]). It is worth mentioning that low HbA1c (<48 mmol/mol) was also associated with significantly increased COVID-19 mortality.[22] Thus, an overly rigid glucose control is also probably not the best solution since it may increase the risk of hypoglycaemia (in hospitalized patients with diabetes), which can also result in increased length of hospitalization and in-hospital mortality.[23,24]

In addition, a retrospective study by Wang et al. highlighted fasting blood glucose (FBG) ≥7 mmol/L at admission as an independent predictor for 28-day mortality in patients with COVID-19 without previous diagnosis of diabetes. On top of that, patients with admission FBG ≥7 mmol/L and 6.1-6.9 mmol/L had higher levels of in-hospital complications when compared with patients with admission FBG <6.1 mmol/L (OR 3.99 and OR 2.61, respectively).[25] Similarly, admission blood glucose was an independent risk factor for predicting the progression to critical cases/death from non-critical cases, and initial blood glucose level of critical diagnosis was an independent risk factor for in-hospital mortality in critical cases in the study by Wu et al. Furthermore, higher median glucose level during hospital stay or after critical diagnosis was associated with poorer clinical outcomes, both in COVID-19 patients with diabetes and those without a history of diabetes.[26]

Bearing previously mentioned in mind, the preferred glucose-lowering therapeutic options, especially now during COVID-19 pandemic, should be efficient in reducing ambient hyperglycaemia and glycaemic variability without increasing the risk of hypoglycaemia.[27] Hence, GLP-1RAs impose themselves as excellent antidiabetic agents during COVID-19 pandemic times (for non-critically ill COVID-19 patients), since they have demonstrated high glycaemic efficacy with minimal risk of hypoglycaemia in multiple placebo-controlled and active-controlled studies.[28] Last but not least, it is worth mentioning that GLP-1RA therapy even in combination with long-acting basal insulin results in lowest glucose variability and hypoglycaemia whether measured by frequency, duration, or daily percentage of time.[14,29]

3 | ANTI-INFLAMMATORY PROPERTIES AND PULMONARY PROTECTIVE EFFECTS OF GLP-1RAS

Besides glucose-lowering effects, a growing body of literature indicates that GLP-1RAs pose significant anti-inflammatory properties and pulmonary protective effects. Anti-inflammatory properties (with a focus on impact on CRP, IL-6 and ferritin concentrations) of individual GLP-1RAs have recently been extensively overviewed elsewhere by Katsiki and Ferrannini.[30]

In addition to the pancreas, expression of the GLP-1R has been detected in various cells and organs including brain, kidney, stomach, heart, endothelium, as well as lung and certain immune cells.[31-33] The result of the binding of GLP-1/GLP-1RA to the GLP-1R is the

blockage of the protein kinase C or nuclear factor-κB (NF-κB) activation and subsequent reduction in the expression of NLRP3, IL-1β, TNF-α, IL-6, VCAM-1, IFN-γ, and MCP-1. Anti-inflammatory effects on monocyte adhesion are triggered by cAMP/Ca^{2+}, CAMKKβ, and pAMPK activation.[32] Altogether, GLP-1RAs anti-inflammatory properties are predominantly based on stimulation of eNOS/sGC/PKG signalling pathway and the inactivation of the NF-κB signalling, as well as attenuation of thioredoxin-interacting protein levels and repression of proinflammatory cytokine and chemokine expression.[33] What is more, multiple preclinical studies demonstrated that GLP-1RAs attenuate pulmonary/airway inflammation, reduce cytokine production and mucus secretion, and preserve lung function in mice with experimental lung injury.[34-38] To elaborate, stimulation of local expression of potent pulmonary vasodilator atrial natriuretic peptide, facilitation of surfactant protein A (SP-A) and thyroid transcription factor 1 expression, prevention of polymorphonuclear leukocyte-endothelial adhesion, and inhibition of multiple cytokines and chemokines in the lung have all been connected to GLP-1RAs administration.[33] On top of that, Rogliani et al. recently reported that the treatment with GLP-1RAs improves airway function (forced expiratory volume in 1 s - FEV_1, forced vital capacity - FVC, maximal expiratory flow at 75% and 50% - MEF_{75} and MEF_{50}), regardless of the blood glucose levels, in patients with diabetes mellitus type 2 with no underlying obstructive pulmonary disorders.[39]

4 | GLP-1RAS AND ANTI-OBESOGENIC PROPERTIES

Preclinical studies suggest that GLP-1RAs lower body weight predominantly by direct interaction with diverse GLP-1R populations and by directly and indirectly affecting the activity of neural pathways involved in food intake, reward, and energy expenditure.[40] Relevant clinical data is generally consistent that long-acting GLP-1RA usage results in significant weight loss (most probably and predominantly due to modulated food preference and reduced energy intake).[41-48] Change in weight with different GLP-1RAs in head-to-head clinical studies, was extensively reviewed by Trujillo et al.[49] In addition, due to clinically meaningful weight loss in patients with obesity/overweight, reductions in glycaemic variables and multiple cardiometabolic risk factors, as well as improvements in health-related quality of life demonstrated in SCALE clinical trials, liraglutide in once-daily subcutaneous dose of 3.0 mg was finally registered as Saxenda for treating obesity (body mass index - BMI ≥30 kg/m^2) or excess weight (BMI ≥27 kg/m^2) accompanied with one or more weight-related comorbidities (e.g. hypertension, dyslipidemia, diabetes), as an adjunct to diet and exercise.[42-45,50] Anti-obesogenic properties of long-acting GLP-1RAs are even more desirable now during the times of COVID-19 pandemic, since obesity is associated with increased COVID-19 susceptibility and severity due to low-grade chronic inflammation, higher expression of ACE-2 and pathway associated components, as well as decreased vitamin D bioavailability and gut microbiome dysbiosis.[51,52] To clarify, a decrease in BMI and fat mass due to GLP-1RA usage has a beneficial effect on previously mentioned components, which finally results in reduction of overall COVID-19 susceptibility and risk for development of its more severe clinical forms.

5 | GLP-1RAS AND THE EFFECT ON GUT MICROBIOME COMPOSITION

In addition to all previously described, GLP-1RAs also seem to have beneficial effect on gut microbiota.[53,54] To elaborate, the human gut microbiota is mostly composed by two dominant bacterial phyla - *Bacteroidetes* (Gram-negative bacteria) and *Firmicutes* (mostly Gram-positive bacteria).[55] On top of that, total lipopolysaccharide (LPS) produced in the healthy human gut (*Bacteroidetes* contribute 79%-92.4% of the overall LPS biosynthesis) is immunosilent/immunoinhibitory (has a very limited capacity to activate TLR4 - NF-κB pathway and elicit the production of inflammatory cytokines).[56] Accumulating body of literature is generally consistent that individuals with diabetes mellitus type 2 and/or obesity have altered intestinal microbiota which is characterized by significantly higher level of *Firmicutes* and lower level of *Bacteroidetes* (decreased B/F ratio), compared to healthy/normal-weight individuals.[57-63] Hence, the intestinal LPS in the individuals with diabetes mellitus type 2 and/or obesity could be shifted away from immunosilent/immunoinhibitory *Bacteroidetes* LPS subtypes, in favour of various proinflammatory LPS subtypes (phyla producing more inflammatory LPS).[52,56] As recently extensively described, latter shift accompanied by enhanced intestinal permeability may then result in endotoxemia and activation of proinflammatory pathways (predominantly NF-κB).[52] To deduce, gut microbiome dysbiosis can finally lead to more severe forms of infectious diseases such as COVID-19. Thus, at this point of time it is important to highlight that Zhao et al. demonstrated that liraglutide positively changed the structure of gut microbiota (increased *Bacteroidetes*/*Firmicutes* ratio) in both simple obese and diabetic obese rats, which was also accompanied with beneficial effects on metabolic parameters.[53] The exact mechanism how liraglutide modulates the structure of gut microbiota is still a matter of debate; however there are few possible explanations: (a) GLP-1 delays the gastric emptying rate and gut transit time and subsequently affects the gut lumen internal environment (e.g. the local pH value and nutrient composition), (b) GLP-1RA can cross the blood-brain barrier and bind to neurons within the arcuate nucleus and other sites within the hypothalamus (the role of gut-brain axis), (b) GLP-1RA promotes weight loss, modulates appetite and orchestrates glucose homeostasis, etc.[53] Altogether, the relevant body of literature regarding GLP-1RAs' effect on gut microbiome composition is currently scarce and predominantly based on findings with liraglutide. Hence, additional well-designed studies are needed to draw the certain conclusions.

It seems that liraglutide/GLP-1RAs can preserve healthy gut microbiota (prevent microbiome dysbiosis) and/or positively modulate its structure if already altered. Hence, activation of main

proinflammatory pathways (such as TLR4-NF-κB) due to endotoxemia (proinflammatory LPS) could be prevented during the initial step of the pathophysiological cascade described by Belančić.[52] It is plausible that more severe forms of the infectious diseases (e.g. cytokine storm in patients with COVID-19) could be prevented/avoided in such a way.

6 | GLP-1RAS AND ACE-2 EXPRESSION

In the early beginnings of the COVID-19 pandemic, Fang et al. published a hypothesis in Lancet journal regarding the increased risk for COVID-19 infection in patients with hypertension and diabetes mellitus taking ACE inhibitors or angiotensin II receptor blockers (ACE-2 upregulating drugs), since SARS CoV-2 uses ACE-2 as the cell entry receptor.[64] Since then, there are constant speculations whether consumption of all identified ACE-2 upregulating drugs may increase the susceptibility for COVID-19 infection and/or the risk for more severe forms of the disease.[65] Up to the present date, the findings regarding GLP-1RAs-associated ACE-2 respiratory upregulation are scarce and based on few preclinical/animal studies only. To elaborate, Romaní-Pérez et al. demonstrated that GLP-1R activation by liraglutide increases the ACE-2 expression and improves production of SP-A and SP-B in the lungs of streptozotocin-induced diabetes Sprague-Dawley rats, while Fandiño et al. reported that liraglutide enhances the activity of the ACE-2/Ang(1-7)/Mas receptor pathway in lungs of male pups from food-restricted mothers.[6,66] To the best of our knowledge, no human studies demonstrating the respiratory ACE-2 upregulation due to GLP-1R agonists have been reported yet.[67,68] Thus, practical significance of potential changes in ACE-2 levels and associated COVID-19 susceptibility is another conundrum.[69] At this point of time it is definitely worth mentioning that, on the other hand, there are some speculations that ACE-2 raising drugs might even lead to beneficial outcomes in patients with SARS CoV-2 infection, since it is thought that increased ACE-2 activity could result in shifting of the balance within the renin-angiotensin-aldosterone system towards ACE-2/Ang(1-7)/Mas receptor pathway, which is known to exert anti-inflammatory, anti-oxidative, and anti-fibrotic stress signals.[67] However; in order to draw the final conclusions on the present topic, further well-conducted clinical and experimental studies are still needed.

7 | CONCLUSIONS

Besides being important glucose-lowering agents, GLP-1RAs pose promising anti-inflammatory and anti-obesogenic properties, pulmonary protective effects, as well as beneficial impact on gut microbiome composition. In conclusion, taking everything previously mentioned into consideration, GLP-1RAs seem to be potential candidates for the treatment of patients, affected by COVID-19 infection, with or even without type 2 diabetes mellitus, as well as excellent antidiabetic (glucose-lowering) agents during COVID-19 pandemic times.[70] Last but not least, it is of high importance to constantly evaluate new scientific data/evidence regarding pharmacotherapy in COVID-19 pandemic times, based on evidence-based medicine principles.

CONFLICTS OF INTEREST

Andrej Belančić, Andrea Kresović, and Marija Troskot Dijan declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Andrej Belančić, Andrea Kresović, and Marija Troskot Dijan contributed substantially to this work. All authors were involved in data acquisition, analysis and interpretation of data, and drafting the manuscript. Andrej Belančić contributed to the manuscript conception and design, supervision and critical revision as well. All authors had final approval of the submitted version.

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