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EDITORIAL ARTICLE

# GLP-1 receptor agonists in the management of COVID-19 and long COVID for patients with underlying metabolic disorders

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## Introduction

The COVID-19 pandemic has highlighted the vulnerability of individuals with underlying metabolic conditions, such as obesity and type 2 diabetes (T2D), to severe illness, mortality and long-term complications.<sup>1,2</sup> Recent studies, including findings from the SELECT trial of semaglutide on patients with obesity and cardiovascular disease, suggest that GLP-1 receptor agonists (GLP-1RAs), medications primarily used to treat obesity and T2D,<sup>3</sup> may play a significant role in improving outcomes for these high-risk patients. We present the case for exploring the use of GLP-1RAs in managing not only the acute effects of COVID-19, but also in mitigating the long-term effects of the virus (long COVID) and propose future research directions.

## GLP-1 receptor agonists and acute COVID-19

Glucagon-like peptide-1 (GLP-1) is a short-acting incretin hormone that plays an important role in glucose homeostasis and appetite regulation.<sup>4</sup> GLP-1RAs activate GLP-1 receptors but are longer-acting, and therefore potentiate meal-stimulated insulin secretion and slow gastric emptying to improve glucose homeostasis, while reducing appetite and body weight. GLP-1RA therapy also impacts immune function, resulting in a wide range of benefits including reductions in blood pressure and inflammation.<sup>5</sup>

There is growing evidence that patients who are taking GLP-1RA medications for T2D or obesity have better outcomes from acute COVID-19. Early retrospective analyses from the COVID-19 pandemic showed that patients who were taking GLP-1RAs for T2D had a reduced risk of hospitalisation and mortality.<sup>6,7,8</sup> More recently, results from the SELECT trial have shown that individuals with obesity and cardiovascular disease, who were taking the GLP-1RA semaglutide when they contracted COVID-19, had a reduced risk of death or serious adverse events from COVID-19.<sup>3</sup>

## MECHANISMS OF GLP-1 RECEPTOR AGONIST ACTION IN COVID-19

Obesity and T2D are chronic inflammatory conditions which exacerbate the hyperinflammatory states and pathological processes that characterise COVID-19. These include activation of the Nuclear Factor-Kappa B (NF-κB) inflammation pathway, increased levels of pro-inflammatory cytokines such as IL-6 and TNFα, impaired immune response, altered redox balance, a pro-thrombotic state and endothelial dysfunction.<sup>9,10</sup>

GLP-1RAs have demonstrated significant anti-inflammatory effects in vitro, in animal models and in humans. They inhibit the NF-κB pathway, reduce pro-inflammatory cytokines including IL-6 and TNFα, reduce oxidative stress and improve immune and endothelial function,<sup>11,12</sup> all of which are critical in mitigating severe respiratory and cardiovascular complications of COVID-19. The glucose-lowering effects of GLP-1RAs could also be important in reducing the severity of disease in COVID-19. Hospitalised COVID-19 patients with poorly controlled diabetes, or who are pre-diabetic or hyperglycaemic, are at greater risk of mortality and COVID-19 complications compared to those who are normoglycaemic.<sup>13</sup> As hypoglycaemia is also a risk factor for COVID-19 mortality,<sup>14</sup> it is important that any glucose-lowering agent does not lower blood glucose excessively. GLP-1RAs are excellent in this regard, with almost negligible risk of inducing hypoglycaemia.<sup>15</sup>

## POTENTIAL ROLE OF GLP-1 RECEPTOR AGONISTS IN MANAGEMENT OF COVID-19

The consistent results of retrospective analyses and the findings of the SELECT trial indicate that GLP-1RA therapy could reduce the severity of disease and reduce the risk of mortality and complications in these high-risk groups. The new 'advanced GLP-1RAs', like semaglutide, have stronger glucose-lowering and weight loss effects than those being used at the time of the COVID-19 pandemic, suggesting the newer GLP-1RAs may also be more effective in improving COVID-19 outcomes.

For future pandemics or epidemics of highly virulent respiratory infections, similar to SARS-CoV-2, GLP-1RAs could be considered as a preventive measure for high-risk groups such as those with obesity, pre-diabetes, T2D, or overweight with additional metabolic risk factors such as hypertension or central adiposity. This could help reduce the risks of severe illness, hospitalisation, complications and mortality in a large number of potentially vulnerable individuals before a safe and effective vaccine is available.

## Long COVID

Long COVID, or post-acute sequelae of COVID-19 (PASC), is the term used to describe a broad spectrum of signs and symptoms that persist or develop in COVID-19 survivors and continue for at least 3 months.<sup>16</sup> The most common symptoms are fatigue, dyspnea and cognitive dysfunction ('brain fog'), but can also include loss of smell or taste, gastro-intestinal symptoms, pain, anxiety and depression among many others.<sup>17</sup>

Obesity and T2D have been identified as risk factors for long COVID,<sup>18,19</sup> and there is also evidence that new-onset hyperglycaemia and diabetes are among the post-acute COVID-19 sequelae,<sup>20,21,22</sup> characterised by insulin resistance and abnormal cytokine profiles, notably raised IL-6 levels. Similar to acute COVID, chronic inflammation, a dysregulated immune response, endothelial abnormalities and immune thrombosis have all been identified in people with persistent and severe long COVID symptoms.<sup>17,23,24</sup>

### POTENTIAL ROLE OF GLP-1 RECEPTOR AGONISTS IN MANAGEMENT OF LONG COVID

GLP-1RAs should be considered for treatment of long COVID, as they are known to act on several of the mechanisms involved in long COVID pathology. Firstly, they regulate endothelial function and immune function and are anti-inflammatory, specifically reducing the level of cytokines, including IL-6 and TNF $\alpha$ ,<sup>11,25,26</sup> which have been identified as potential biomarkers of long COVID.<sup>27</sup>

Secondly, GLP-1RAs are a treatment for T2D and obesity, which are risk factors for long COVID. A recent retrospective analysis of patients with T2D who contracted COVID-19 showed a reduced risk of mortality and long COVID-associated conditions one year later for those who were on GLP-1RAs compared to other T2D treatments.<sup>28</sup> They had lower risks of cognitive deficits, cerebrovascular complications, inflammatory and ischaemic heart diseases, thrombotic diseases and mental health problems. This suggests GLP-1RAs could be an effective intervention for long COVID prevention in patients with underlying metabolic disorders. The glucose-lowering and anti-inflammatory effects of GLP-1RAs also mean they could be an effective treatment for individuals who develop hyperglycaemia or T2D post-COVID-19.

Thirdly, there is evidence that GLP-1RAs are neuroprotective and improve cognition and neurologic signalling in cognitively impaired mice by reducing oxidative stress and neuroinflammation,<sup>29</sup> which may also be mechanisms involved in cognitive impairment associated with long COVID.<sup>30</sup> The GLP-1RA liraglutide has been shown to improve memory in patients with obesity and pre-diabetes or early T2D.<sup>31</sup> GLP-1RAs could therefore help mitigate cognitive dysfunction ('brain fog') in patients with long COVID.

Despite these promising insights, there have been no clinical trials designed to assess the effects of GLP-1RAs on long COVID patients. The available evidence does, however, warrant further research to explore the validity of GLP-1RAs in the treatment of long COVID in different patient groups.

## Further research

Evidence is mounting that points towards the potential of GLP-1RAs in reducing mortality and improving outcomes for individuals with obesity or T2D and acute COVID-19 or long COVID. To build on these findings, we propose research in the following areas:

1. Further retrospective studies to analyse long-term outcomes in patients already on

GLP-1RA therapy prior to COVID-19 infection to assess its impact on COVID-19 severity and long COVID

2. Clinical trials to evaluate the efficacy of GLP-1RAs in improving outcomes in acute COVID-19 and prevention of long COVID for patients with underlying metabolic conditions
3. Clinical trials to evaluate the efficacy of GLP-1RAs for different patient groups in treatment of long COVID
4. Interdisciplinary collaboration between endocrinologists, immunologists, and virologists to explore the mechanisms by which GLP-1RAs modulate metabolic and inflammatory pathways in viral illnesses.

## Conclusion

GLP-1 receptor agonists represent a promising adjunctive therapy in the management of COVID-19 and long COVID. Their ability to modulate immune, endothelial and metabolic functions highlights their potential to address the effects of COVID-19 and long COVID, particularly for high-risk populations with underlying metabolic diseases. By integrating GLP-1RAs into COVID-19 and long COVID management, we might not only improve outcomes for vulnerable individuals, but also pave the way for innovative therapeutic approaches in future pandemics.

## Conflicts of interest:

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