# Long COVID — metabolic risk factors and novel therapeutic management

*Kamlesh Khunti*[1] ✉, *Melanie J. Davies*[1], *Mikhail N. Kosiborod*[2,3] *and Michael A. Nauck*[4]

Cardiometabolic conditions, including type 1 and type 2 diabetes mellitus, are associated with severe COVID-19 and long COVID. Interventions to target multiple risk factors, combined with use of novel glucose-lowering agents that improve metabolic function and the key processes that are impaired in COVID-19, should be the preferred therapeutic options for management of people with long COVID.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is responsible for the current COVID-19 pandemic, has devastated both human health and economies globally. As of April 2021, COVID-19 has affected >120 million people worldwide, resulting in >2.8 million deaths (see Related links). Elderly people, individuals from lower socioeconomic backgrounds, ethnic minority groups and those with certain chronic comorbidities have been disproportionately affected. Cardiometabolic risk factors, including type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), atherosclerotic cardiovascular disease, chronic kidney disease, hypertension, heart failure and obesity have been consistently identified as the most common comorbidities associated with risk of severe COVID-19 and mortality[1].

A nationwide study in England of >61 million people showed that 31.4% and 1.5% of deaths in hospitals attributed to COVID-19 occurred in people with T2DM and T1DM, respectively[2]. In adjusted analysis, compared with people without diabetes mellitus, the odds ratios for in-hospital COVID-19-related deaths were 3.51 (95% CI, 3.16–3.90) in people with T1DM and 2.03 (95% CI, 1.97–2.09) in people with T2DM[2].

Although the short-term outcomes in people hospitalized with COVID-19 are of concern, another worrying aspect is the effect of long COVID (or post-COVID syndrome). Long COVID, which is estimated to affect 10% of patients with COVID-19, is defined as the persistence of symptoms beyond 3 months after infection due to the multi-organ damage caused by acute infection[3,4]. Long COVID still needs to be clearly defined, mainly owing to lack of understanding of its varying symptoms and pathophysiology[3,4], but it might be caused by the immune and inflammatory responses that occur in many severe acute viral infections[4].

In addition to cardiometabolic diseases that are risk factors for severe COVID-19 and mortality, the risks of acute cardiorenal complications are also high in people admitted to hospital with COVID-19. A meta-analysis of 44 studies with 14,866 cases of COVID-19 that was published in 2020 showed that acute cardiac injury occurred in 15% of patients (95% CI, 5–38%), venous thromboembolism in 15% of patients (95% CI, 0–100%) and acute kidney injury in 6% of patients (95% CI, 1–41%)[5]. Many of these acute complications will persist as long COVID. A UK study of 201 individuals (mean age 44 years) that included detailed assessments using MRI showed that at median follow-up of 140 days following an infection, 98% of people had fatigue, 88% had muscle ache and 87% had breathlessness. Of concern, there was evidence of mild organ impairment in the heart (32%), lungs (33%), kidneys (12%), liver (10%) and pancreas (17%) and multi-organ impairment was present in 25% of individuals[3]. Therefore, even in young low-risk populations, nearly two-thirds of people have persistent damage of one or more organs 4 months after initial symptoms of SARS-COV-2 infection, which will have implications for the long-term health of these patients.

The exact reasons for cardiometabolic diseases being associated with severe COVID-19 mortality are not known. Acute respiratory viral infections such as COVID-19 have been shown to lead to the development of transient insulin resistance in individuals with T1DM and T2DM, and hyperglycaemia is also an independent risk factor for severe COVID-19 and mortality in people with T2DM[6]. One popular theory is that these patients have a state of chronic metabolic inflammation that predisposes them to an excessive release of cytokines, the so-called cytokine storm. These elevated levels of inflammatory cytokines might in turn trigger multi-organ failure[6]. The main entry receptor for SARS-CoV-2 is angiotensin-converting enzyme 2 (ACE2). SARS-CoV-2 can bind to the pancreatic ACE2 receptors, damaging the islets while reducing the capacity of the pancreas to release insulin in response to the resultant hyperglycaemia[6]. There are a number of additional pathophysiological mechanisms that have been proposed, including increased levels of tissue-related enzymes, altered ACE2 receptor expression, immune

[1]*Leicester Diabetes Centre, University of Leicester, Leicester, UK.*

[2]*Saint Luke's Mid America Heart Institute, Kansas City, MO, USA.*

[3]*University of Missouri-Kansas City, Kansas City, MO, USA.*

[4]*Diabetes Center Bochum-Hattingen, St. Josef-Hospital, Ruhr-University, Bochum, Germany.*

✉*e-mail: kk22@le.ac.uk*

https://doi.org/10.1038/s41574-021-00495-0

dysregulation, pulmonary and endothelial dysfunction, systematic inflammation and hypercoagulation. In addition, an increased level of anti-inflammatory biomarkers, such as C-reactive proteins, D-dimer and IL-6 could be involved. In patients with T1DM or T2DM, all of these pathophysiological disturbances might contribute to an accentuated inflammatory cytokine storm response, which could lead to more severe courses of COVID-19 (REF.[6]). A systematic review of eight retrospective cohort studies published in 2020 also showed that excess adiposity was associated with severe disease and mortality in people with COVID-19 (REF.[7]). The majority of people with cardiometabolic diseases also have obesity and low-grade systemic inflammation, which might be a potential mechanism linking severe COVID-19 with insulin resistance, T2DM, hypertension and cardiovascular disease.

In terms of management of long COVID, it is important to control risk factors, including blood pressure, lipid levels and obesity, after having COVID-19. In addition, clinicians could advocate the improvement of physical function through lifestyle change and smoking cessation. There is now clear evidence that management of risk factors such as blood pressure, dyslipidaemia and glucose levels can lead to reduced microvascular and macrovascular complications in the chronic management of people with T2DM[8]. There is also evidence of the legacy benefits of multifactorial risk factor interventions on renal, cardiovascular and mortality outcomes[8], and, in our opinion, these findings might analogously apply to people with long COVID.

As factors associated with worse outcomes in people with COVID-19 and with long COVID include obesity, hyperglycaemia and cardiovascular and renal disease[1,3,6], glucose-lowering agents that improve metabolic function, along with having other advantages on the key processes that are impaired in COVID-19, would be preferable for the long-term management of people with long COVID. In terms of novel therapeutic options, cardiovascular outcome trials in people with T2DM have confirmed benefits of sodium–glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 receptor agonists (GLP1RA) on weight, glycaemic control and cardiovascular events, including cardiovascular death, and renal outcomes[9]. SGLT2 inhibitors also lead to reduced hospitalization for heart failure, and might reduce the risk of death from non-cardiovascular causes[9]. Most guidelines have suggested that SGLT2 inhibitors and GLP1RA are safe for clinical use during the pandemic, but SGLT2 inhibitors should be stopped in symptomatic individuals infected with SARS-CoV-2, who might be at risk of altered fluid homeostasis or (euglycaemic) ketoacidosis. The DARE trial is currently investigating the efficacy of dapagliflozin in hospitalized patients with COVID-19 (NCT04350593). There are a number of mechanisms by which SGLT2 inhibitors and GLP1RA might potentially improve long COVID, including improvements in hyperglycaemia, blood pressure, weight, oxidative stress, insulin resistance and low-grade inflammation[8].

The benefits observed in patients with COVID-19 following treatment with SGLT2 inhibitors are glucose independent and also include effects on myocardial metabolism and adipokine and vascular functions[10]. Studies have now also confirmed that the cardiovascular and renal benefits observed in people with T2DM treated with SGLT2 inhibitors also extend to people without T2DM[10]. In view of the pathophysiology of COVID-19 and the reported benefits of SGLT2 inhibitors and GLP1RA, these therapies could have special advantages relative to therapeutic alternatives for people with T2DM and long COVID and, perhaps, even individuals without diabetes mellitus. There is, however, an urgent need for randomized trials and real-world studies to determine whether the potential benefits of tight multifactorial risk factor control and use of novel therapies are translated in routine clinical practice in people with long COVID.


1. Singh, A. K. et al. Prevalence of co-morbidities and their association with mortality in patients with COVID-19: A systematic review and meta-analysis. *Diabetes Obes. Metab.* **22**, 1915–1924 (2020).
2. Barron, E. et al. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. *Lancet Diabetes Endocrinol.* **8**, 813–822 (2020).
3. Dennis, A. et al. Multi-organ impairment in low-risk individuals with long COVID. *BMJ Open* **11**, e048391 (2021).
4. Altmann, D. M. & Boyton, R. J. Decoding the unknowns in long covid. *BMJ* **372**, n132 (2021).
5. Potere, N. et al. Acute complications and mortality in hospitalized patients with coronavirus disease 2019: a systematic review and meta-analysis. *Crit. Care* **24**, 389 (2020).
6. Lim, S. et al. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. *Nat. Rev. Endocrinol.* **17**, 11–30 (2020).
7. Seidu, S. et al. The impact of obesity on severe disease and mortality in people with SARS-CoV-2: A systematic review and meta-analysis. *Endocrinol. Diabetes Metab.* **4**, e00176 (2020).
8. Khunti, K., Kosiborod, M. & Ray, K. K. Legacy benefits of blood glucose, blood pressure and lipid control in individuals with diabetes and cardiovascular disease: Time to overcome multifactorial therapeutic inertia? *Diabetes Obes. Metab.* **20**, 1337–1341 (2018).
9. Zelniker, T. A. et al. Comparison of the effects of glucagon-like peptide receptor agonists and sodium-glucose cotransporter 2 inhibitors for prevention of major adverse cardiovascular and renal outcomes in type 2 diabetes mellitus. *Circulation* **139**, 2022–2031 (2019).
10. Khunti, K. Type 2 diabetes mellitus in 2020: SGLT2 inhibitors in people with and without T2DM. *Nat. Rev. Endocrinol.* **17**, 75–76 (2021).



**Acknowledgements**
K.K. and M.J.D. are supported by the National Institute for Health Research (NIHR) Applied Research Collaboration East Midlands (ARC EM) and the NIHR Leicester Biomedical Research Centre (BRC).


**Competing interests**
K.K. has acted as a consultant, speaker or received grants for investigator-initiated studies for AstraZeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly and Merck Sharp & Dohme, Boehringer Ingelheim, Bayer, Berlin-Chemie AG / Menarini Group, Janssen and Napp. M.J.D. reported board membership and consultancy fees from Novo Nordisk, Sanofi-Aventis, Lilly, Merck, Sharp & Dohme, Boehringer Ingelheim, AstraZeneca, Servier and Janssen. M.J.D. reported institutional grants from Novo Nordisk, Sanofi-Aventis, Lilly, Boehringer Ingelheim and Janssen. M.J.D. reported payment for lectures or speakers bureaus from Novo Nordisk, Sanofi-Aventis, Lilly, Merck, Sharp & Dohme, Boehringer Ingelheim, AstraZeneca, Janssen, Mitsubishi Tanabe Pharma and Takeda Pharmaceuticals International. M.K. has received grants, honoraria and other research support from AstraZeneca, grants and honoraria from Boehringer Ingelheim, and honoraria from Sanofi, Amgen, Novo Nordisk, Merck (Diabetes), Eisai, Janssen, Bayer, GlaxoSmithKline, Glytec, Intarcia, Novartis, Applied Therapeutics, Amarin and Eli Lilly. M.K. is CI for the DARE Trial. M.A.N. has been member on advisory boards or has consulted with AstraZeneca, Boehringer Ingelheim, Eli Lilly & Co., Menarini/Berlin Chemie, Merck, Sharp & Dohme, NovoNordisk and Servier/Versatis. M.A.N. has received grant support from Afimmune, Eli Lilly & Co., Menarini/Berlin-Chemie and Merck, Sharp & Dohme. M.A.N. has also served on the speakers' bureau of AstraZeneca, Boehringer Ingelheim, Eli Lilly & Co., Menarini/Berlin Chemie, Merck, Sharp & Dohme, NovoNordisk and Sun Pharma.

**RELATED LINKS**
**Worldometer:** https://www.worldometers.info/coronavirus/