Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

respiratory distress syndrome in COVID-19. Moreover, lung inflammation in COVID-19 can lead to fibrosis. Metformin is known to reverse established fibrosis in various lung models by facilitating the deactivation and apoptosis of myofibroblasts.[3]

Generally, metformin is considered to act as a cell protector; it modulates energy metabolism (thus attenuating the harmful effects of stress on mitochondrial function), activates AMP-activated protein kinase (potentiating the autophagic process), scavenges reactive oxygen species, and modulates dysbiosis. These characteristics might explain why metformin has been shown to be associated with a relative reduction in mortality among patients with diabetes in the intensive care unit.[4]

Finally, severe infections are associated with insulin resistance and hyperglycaemia (even in patients without diabetes), whereas tight blood glucose control is essential for reducing mortality among patients who are critically ill. Hence, we suggest that investigators in ongoing cohort studies should check whether metformin is associated with a favourable outcome in patients with diabetes. Pending these analyses, we recommend that metformin treatment should be maintained in patients with diabetes who are hospitalised for COVID-19, as long as they have not developed concomitant kidney and liver failure. Kidney failure leads to metformin accumulation and liver failure reduces lactate elimination, increasing the risk of lactic acidosis.[5]

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1 Bornstein SR, Rubino F, Khunti K, et al. Practical recommendations for the management of diabetes in patients with COVID-19. *Lancet Diabetes Endocrinol* 2020; **8:** 546–50.
2 Gordon DE, Jang GM, Bouhaddou M, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature* 2020; published online April 30. https://doi.org/10.1038/s41586-020-2286-9.
3 Rangarajan S, Bone NB, Zmijewska AA, et al. Metformin reverses established lung fibrosis in a bleomycin model. *Nat Med* 2018; **24:** 1121–27.
4 Christiansen C, Johansen M, Christensen S, O'Brien JM, Tønnesen E, Sørensen H. Preadmission metformin use and mortality among intensive care patients with diabetes: a cohort study. *Crit Care* 2013; **17:** R192.
5 Lalau J-D, Kajbaf F, Protti A, Christensen MM, De Broe ME, Wiernsperger N. Metformin-associated lactic acidosis (MALA): moving towards a new paradigm. *Diabetes Obes Metab* 2017; **19:** 1502–12.

We read with great interest the Personal View by Stefan Bornstein and colleagues[1] on the management of diabetes in patients with COVID-19. During these unprecedented times, more guidance is required to care for this high-risk population. The authors recommend intensification of glucose control to prevent COVID-19, suggesting an HbA_{1c} of less than 53 mmol/mol (<7%) and plasma glucose concentration of 4–8 mmol/L (72–144 mg/dL) for most patients, and 5–8 mmol/L (90–144 mg/dL) for frail patients. These glycaemic goals for the older population are much tighter than suggested in most guidelines. Older patients with diabetes are a heterogeneous population with varying levels of complexity, multimorbidity, geriatric syndromes, functional abilities, and life expectancy. Some patients rely on caregivers, whereas others live in assisted living facilities or long-term care facilities. Consideration of these factors when deciding on glycaemic goals is even more critical at this time because older adults are in isolation and support from family, caregivers, or nurses might be limited. Previous studies have shown that intensive control (HbA_{1c} <7%) in older adults with diabetes did not lead to a significant reduction in cardiovascular events, and conversely, increased the risk of hypoglycaemia and death.[2,3] In a study of older adults aged 75 years or older with type 2 diabetes and high complexity or comorbidities,[4] those who were treated with intensive glycaemic control (HbA_{1c} <7%) had double the risk of severe hypoglycaemia compared with those given standard treatment. Therefore, changes made to diabetes treatment plans must minimise the risk of hypoglycaemia, because it can lead to grave consequences such as increased falls, fractures, hospitalisations, cerebrovascular and cardiovascular events, cognitive dysfunction, and even death.[5] Although the practical recommendations provided by Bornstein and colleagues[1] serve as an important guide for clinicians treating patients with diabetes, a different approach is needed for older adults with functional and cognitive decline, as well as those living in long-term care facilities. This approach should include avoiding any intensification or changes in medications that could lead to hypoglycaemia and increased treatment burden. In addition, for many of these patients, self-care activities such as diet and exercise routines might have been interrupted. Providing reassurance to patients can be helpful to reduce feelings of stress or guilt if their routine has not been maintained. As the pandemic unfolds and life normalises to some extent, diabetes management and glycaemic goals can be revisited.

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1 Bornstein SR, Rubino F, Khunti K, et al. Practical recommendations for the management of diabetes in patients with COVID-19. *Lancet Diabetes Endocrinol* 2020; **8:** 546–50.
2 Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009; **360:** 129–39.
3 Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; **358:** 2545–59.

4 McCoy RG, Lipska KJ, Yao X, Ross JS, Montori VM, Shah ND. Intensive treatment and severe hypoglycemia among adults with type 2 diabetes. *JAMA Intern Med* 2016; **176:** 969–78.

5 Kirkman MS, Briscoe VJ, Clark N, et al. Diabetes in older adults. *Diabetes Care* 2012; **35:** 2650–64.

The recent Personal View by Stefan Bornstein and colleagues[1] highlights possible susceptibility factors in patients with diabetes and obesity that could predispose to severe COVID-19-related illness. The authors incorporated useful general management guidance, but we feel that the descriptions of acute presentations were not sufficiently detailed to aid clinical management. We wish to expand on the acute metabolic presentations related to hyperglycaemia, which have been challenging to manage in the acute setting. These considerations are based on observations from a large regional clinical network that informed a national diabetes COVID-19 response team to from the Association of British Clinical Diabetologists help produce new specific guidance to aid acute management.

For **guidance from the Association of British Clinical Diabetologists** see https://abcd.care/coronavirus

Our clinical network has reported severe acute glycaemic presentations associated with COVID-19 infections. An excess case incidence of diabetes-related ketoacidosis, often with concurrent significant hyperosmolality (>320 mOsm/L), was reported. In some cases, high levels of ketosis (>5 mmol/L) had rapid onset and appeared to be disproportionate to blood glucose levels.[2] These acute presentations have been noted in patients both with and without pre-existing diabetes and in patients of different ethnicities. Early measurement of capillary blood ketone concentration is therefore advised in all patients with acute hyperglycaemia to allow prompt diagnosis. Of note, use of SGLT2 inhibitors for diabetes, which can promote ketosis in a minority of individuals, does not appear to be a feature in the majority of cases (unpublished data). The article by Bornstein and colleagues[1] correctly hypothesises a possible direct COVID-19-related effect on pancreatic β cell function predisposing to ketosis, which has been reported with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), through increased expression of ACE2 receptor.

Fluid replacement decisions in individuals presenting with diabetes-associated emergencies have been complex. There have been concerns about the rapidity of the onset of ketosis, concurrent potential lung injury, and pronounced kidney injury, with reports of rhabdomyolysis. Thus, prudent use of intravenous fluid replacement judged on an individual basis is advised in managing cases of diabetes-related ketoacidosis and hyperosmolality to avoid adverse lung and renal complications.

Extreme insulin resistance was acknowledged by Bornstein and colleagues.[1] Compatible with this, our network have described significant insulin resistance with unusually high insulin requirements in ventilated patients, which is acknowledged in national guidance from the Association of British Clinical Diabetologists. We postulate that very high insulin requirements might be driven by the COVID-19-related hyperinflammatory state, with contribution from feeding regimens and glucotoxicity.

The observed uncontrolled hyperglycaemia in patients with diabetes and COVID-19 might be explained by higher levels of inflammation compared with patients without diabetes, as reported in a retrospective case series from China.[3] Indeed, our unpublished subset of patients presenting with hyperglycaemia consistently showed elevated concentrations of the acute phase protein ferritin, with a median concentration of 1049 μg/L and a range of 744–2594 μg/L (normal range 30–400 μg/L). Pro-inflammatory cytokines have been demonstrably elevated in people with type 2 diabetes.[4] In particular, IL-6, which coordinates the cytokine release syndrome, has been shown to increase blood glucose in a dose-dependent manner.[5]

We postulate that acute presentations of marked ketosis, mixed diabetes-related ketoacidosis with hyperosmolality, and severe insulin resistance might be reiterated in similar populations of diverse ethnicity within and beyond the UK. Although prevention of SARS-CoV-2 infection is a key strategy, early recognition and specific clinical management to mitigate acute manifestations of diabetes could lead to improved patient outcomes.

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1 Bornstein SR, Rubino F, Khunti K, et al. Practical recommendations for the management of diabetes in patients with COVID-19. *Lancet Diabetes Endocrinol* 2020; **8:** 546–50.

2 Diabetes UK. Guidance for inpatient diabetes care. 2020. https://www.diabetes.org.uk/resources-s3/public/2020-04/To%20the%20Diabetes%20Team_Final%20%28002%29.pdf (accessed June 27, 2020).

3 Guo W, Li M, Dong Y, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. *Diabetes Metab Res Rev* 2020; published online March 31. https://doi.org/10.1002/dmrr.3319.

4 Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 2001; **286:** 327–34.

5 Tsigos C, Papanicolaou DA, Kyrou I, Defensor R, Mitsiadis CS, Chrousos GP. Dose-dependent effects of recombinant human interleukin-6 on glucose regulation. *J Clin Endocrinol Metab* 1997; **82:** 4167–70.