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.

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Management of diabetes in patients with COVID-19

We read with interest the practical recommendations for management of diabetes in patients with COVID-19 by Stefan Bornstein and colleagues[1] in *The Lancet Diabetes & Endocrinology*. However, in the panel describing special considerations for anti-diabetic drugs, we note that two commonly used groups, sulfonylureas and pioglitazone, are missing. Of these, pioglitazone, a PPAR-γ agonist, merits further discussion because it interacts with both the mechanisms that might play a role in patients with diabetes with COVID-19, as described by Bornstein and colleagues.[1] In addition, a substantial minority of people with diabetes in the UK,[2] and a considerable proportion worldwide, use pioglitazone.

Pioglitazone upregulates expression of ACE2 in rat tissues,[3] leading to speculation that its use might increase susceptibility to, and severity of, COVID-19, because ACE2 acts as a co-receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to enter the cell. However, apart from ACE2 upregulation in insulin-sensitive tissues in animals, namely the liver, adipose tissue, and skeletal muscle, there is no evidence that pioglitazone upregulates expression of ACE2 in alveolar cells. Alternatively, as described by Bornstein and colleagues,[1] by increasing ACE2 expression in insulin-sensitive tissues, pioglitazone might help ameliorate the harmful effects of excess angiotensin II. In addition, using homology modelling and molecular docking techniques, Wu and colleagues[4] have shown that pioglitazone is a potential inhibitor of 3-chymotrypsin-like protease, which is essential for RNA synthesis and replication of SARS-CoV-2. However, this software-based prediction of pioglitazone as a potential inhibitor of SARS-CoV-2 RNA synthesis and replication needs validation in both in-vitro and in-vivo studies.

People with diabetes and COVID-19 are at a higher risk of SARS-CoV-2-driven hyperinflammation and cytokine storm syndrome.[5] Pioglitazone might play an important role by moderating the host inflammatory response on multiple fronts. PPAR-γ agonists decrease the secretion of various pro-inflammatory cytokines, including TNF-α, IL-1, and IL-6 in the monocytes and macrophages. Furthermore, animal studies have shown that pioglitazone can suppress TNF-α and IL-6 generation in adipose tissue. However, more research is needed to substantiate these benefits in humans.

Pioglitazone is an inexpensive anti-diabetic drug, used widely around the globe. It has the potential to do more benefit than harm, and , in our view, it can be safely continued in people with diabetes and COVID-19, except in specific conditions in which its use is not recommended, including symptomatic heart failure and liver dysfunction with significantly elevated transaminases.

We declare no competing interests.

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We read with interest the recommendations on the management of diabetes in patients with COVID-19 by Stefan Bornstein and colleagues.[1] However, their suggestion of discontinuing metformin in patients with severe symptoms of COVID-19 (to reduce the risk of lactic acidosis) raises a number of issues. We believe that it is important to maintain a thoughtful approach to metformin therapy in patients with diabetes and COVID-19.

After the synthesis of the first glucose-lowering biguanides in the 1920s, metformin was rediscovered in the 1940s for the treatment of malaria. In 1949, a dimethylbiguanide preparation (flumamine) was used to treat influenza virus infections. Since then, metformin has shown adjuvant efficacy in malaria, tuberculosis, hepatitis C virus infection, and Zika virus infection, indicating that it has considerable potential as an antimicrobial. Of note, metformin is reportedly one of the drugs that targets human host factors of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) via the mTOR pathway.[2]

Metformin has direct and indirect immunosuppressive effects. In particular, metformin reduces the secretion of pro-inflammatory cytokines (IL-6, IL-1β, CXCL1, and CXCL2) by macrophages. These cytokines are involved in the development of acute

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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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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