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