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Stefan Bornstein and colleagues[1] seem to be the first to react to an unprecedented challenge regarding management of diabetes in patients with COVID-19 by offering practical recommendations. The authors state that patients with diabetes have an increased risk of severe COVID-19 complications, including acute respiratory distress syndrome.

Because the practical recommendations also state that ACE2 has been identified as the receptor for the spike protein of severe acute respiratory syndrome coronavirus 2, Bornstein and colleagues discuss whether medications that increase ACE2 expression (ACE inhibitors and angiotensin II receptor blockers)[2] should be continued or discontinued for patients with COVID-19.

Bornstein and colleagues also mention that chronic hyperglycaemia downregulates ACE2 expression. However, the results of clinical observations are controversial; patients with diabetes have shown higher circulating ACE2 activities,[3] yet ACE2 expression, according to renal biopsy data in patients with type 2 diabetes and kidney ,disease is low.[4] Differences in results might be due to drug effects. Of note, clinical and experimental data indicate that diabetes is protective against the development of acute respiratory distress syndrome.[5] Thus, the recommended therapeutic aims for patients with diabetes and COVID-19 (plasma glucose concentration of 4–8 mmol/L and HbA_{1c} <53 mmol/mol [7%])[1] might end up being too strict. In addition, the recommendations do not mention glucose-lowering drugs as a possible specific influence on the expression of ACE2 and progression of COVID-19, which is currently a topic of discussion. Preliminary answers to most questions regarding diabetes and COVID-19 cannot be obtained earlier than the results of the first observational epidemiological studies, which should be the basis for clinical recommendations.

I declare no competing interests.

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Authors' reply

We are pleased to learn about the interest in our paper on the practical recommendations for the management of diabetes in patients with COVID-19.[1] These Correspondences address important aspects regarding the use of medications and the risk of hypoglycaemia or obesity, and we are thankful for these comments.

Jagat Mukherjee and colleagues suggest considering the role of sulfonylureas and PPAR-γ agonists in patients with diabetes and COVID-19 disease. They elaborate on a potential protective role of pioglitazone by three hypothetic mechanisms, including ACE2 regulation, inhibition of a protease in severe acute respiratory syndrome coronavirus 2 replication, and the drug's well-known anti-inflammatory effect. Although we restricted the list of anti-diabetes drugs to the most commonly used agents in modern diabetes management, several other glycaemia-modulating drugs, including pioglitazone, are discussed in a review by Ciaverella and colleagues.[2] Jean-Daniel Lalau and Abdallah Al-Salameh comment on the role of metformin, emphasising its antifibrotic, anti-inflammatory, and cell-protective effects. Furthermore, they mention a possible antimicrobial feature of metformin. Given these beneficial effects, they recommend maintaining metformin in hospitalised patients with COVID-19 who have not yet developed kidney or liver failure. Although Mukherjee and colleagues and Jean-Daniel Lalau and Abdallah Al-Salameh raise interesting points, we believe questions related to the role of metformin and pioglitazone on virus entry and effects on cell integrity and function will be better addressed in mechanistic studies on a cellular or subcellular level. To date, insulin must remain the first-choice agent in the management of critically ill hospitalised patients.

Medha Munshi and Sarah Sy discuss the glycaemic goals for older patients with diabetes and COVID-19 disease and suggest that older patients with functional and cognitive decline, as well as those living in long-term facilities, will require a different set of guidelines. We agree with the comment that hypoglycaemia is a critical risk factor, especially in the elderly, and treatment goals have to be adjusted to individual patient situations, considering comorbidities and the environmental conditions during the pandemic. We attempted to cover many levels of health care in many countries with different health-care systems and economies. Therefore, the recommendations should be read as a general line of action that must be adapted accordingly.

Adrian Li and colleagues emphasise that a disproportionately high frequency of acute diabetes-related complications, such as ketoacidosis, often with concurrent hyperosmolality, occur at the initial presentation of patients with or without pre-existing diabetes. We agree with this important note and stress the need for careful review of potential associations with mediating medications as well as investigating direct virus-related effects. Initial diagnostic routine should identify acute diabetes-related

complications and allow for early and adequate treatment. Furthermore, Li and colleagues discuss the prominent role of insulin resistance in the context of COVID-19. Particularly in serious cases of the virus-mediated hyperinflammatory state, a severe and unusually high insulin resistance is being described as a common denominator and certainly represents a key feature similar to age, obesity, and multimorbidity.

Mykola Khalangot raises the question of the appropriate time to give recommendations for the management of diabetes in patients with COVID-19. We truly believe that in the state of emergency of a pandemic of global dimension, involving millions of patients and many health-care providers, the need for immediate action is absolutely mandatory. Given that diabetes and metabolic syndrome had been identified early on as a major risk factor for severe COVID-19 disease and account for 20–50% of patients with severe or lethal outcomes,[3] raising awareness of optimal glycaemic management of patients with diabetes in the general population had to be done with the highest priority. In our clinical centres, we were confronted with an alarming insecurity of physicians to stop or continue certain medications. Likewise, care of chronic diseases had been seriously neglected in the height of the pandemic. Therefore, it was a duty for our panel of experienced clinicians with a broad responsibility and geographic representation of large clinical programmes to publish practical guidance to help save lives in this dramatic situation.

For the **CoviDiab registry** see http://covidiab.e-dendrite.com/index.html

We have elaborated on potential mechanisms of ACE2 upregulation and downregulation by various medications.[4] However, we agree with Mykola Khalangot that these virus-mediated interactions need to be studied at the cellular level. According to current evidence, we should not recommend discontinuation of ACE inhibitors or angiotensin II receptor blockers.[5] We also agree that these practical recommendations have to be seen as a work in progress considering the magnitude of the problem.

We are glad that our recommendations have been promoted and supported by many of the largest societies and health-care organisations around the world. Although it is crucial to provide qualified guidance for screening and management of patients with COVID-19 and diabetes in the acute phase of a pandemic, it is equally important to constantly acknowledge and implement new insights from the increasing experience in the field. In many regions, the current course of the pandemic allows for the execution of thoroughly designed and controlled clinical trials and it is the responsibility of experts to critically evaluate and revise diagnostic and therapeutic recommendations according to the latest knowledge.

Given the observation that COVID-19 could cause or trigger the onset of diabetes and newly diagnosed diabetes seems to be associated with a higher risk of mortality in patients with COVID-19,[6] we have initiated a global registry on new-onset COVID-19-related diabetes, the CoviDiab registry, to improve understanding of how the condition develops, its natural history, and best management practices.[7]

We declare no competing interests.

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