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LETTER TO THE EDITOR

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COVID-19, ketoacidosis and new-onset diabetes: Are there possible cause and effect relationships among them?

Since the beginning of the SARS-CoV-2 pandemic that emerged at the turn of 2019 and 2020 in China, the large number of scientific reports published in the latest issues of *Diabetes, Obesity and Metabolism* and elsewhere almost all showed that patients with diabetes mellitus faced a more severe form of COVID-19 and a high mortality rate.[1–4] However, intriguingly, COVID-19 patients with newly diagnosed diabetes had the highest risk of all-cause mortality compared with COVID-19 patients with known diabetes or those with hyperglycaemia without diabetes.[3,4] As described in one of the first Italian reports on the disease, according to daily-recorded data from the *Istituto Superiore di Sanità*, this was the case in Italy, the first European country to be severely affected by the epidemic.[5] Moreover, more severe multi-organ failure was present in adults with diabetes, providing further explanation for the higher mortality rate observed.[1]

COVID-19-specific metabolic complications, however, are not yet well characterized. We were intrigued therefore by the proposal to establish an international registry of newly diagnosed diabetes put forward by an international group of experts.[6] The aim of this registry will be (1) to establish the extent and phenotype of new-onset COVID-19-related diabetes, defined by SARS-CoV-2 infection and hyperglycaemia without any history of diabetes or elevated glycated haemoglobin levels, and (2) to provide reliable answers to the many questions raised by the association of diabetes with COVID-19.[6,7] A significant reason for this proposal was the high prevalence of diabetic ketoacidosis and hyperosmolarity warranting exceptionally high doses of insulin that has been reported in patients with COVID-19.[6] This leads to the hypothesis that SARS-Co2 infection might either precipitate a new type of diabetes by a direct impact on pancreatic cells or might trigger new pathophysiological diabetes-related mechanisms.[6]

Viral infection and its association with diabetes is a familiar concept. Indeed, the scientific community attributes a role in triggering type 1 diabetes events to infections from several viruses (Epstein–Barr and entero-/coxsackieviruses, among others).[8] Similarly, hepatitis C infection is a well-known risk factor for type 2 diabetes, which is also associated with β-cell dysfunction.[9] With regard to coronaviruses, SARS-CoV-1 binds to the ACE2 receptor in the pancreatic islets, eventually causing cell damage and precipitating diabetes onset. If this is also the case for SARS-CoV-2, insulin deficiency and increased risk of diabetic ketoacidosis (DKA) might follow for those already diagnosed with type 2 diabetes.[10] However, as data on SARS-CoV-2 binding to the ACE2 receptor are still scarce, such a mechanism remains speculative, and there is insufficient evidence, at the moment, to establish whether DKA is more prevalent than usual in the case of COVID-19 and whether SARS-CoV-2 poses an increased risk of DKA compared with other severe infectious diseases.

To date, only one study has described the prevalence of acidosis and ketoacidosis in a large number (n = 658) of hospitalized patients with confirmed COVID-19.[11] Of that cohort, 42 (6.4%) presented with positive urine or serum ketones, with only three of the 42 (7%) meeting the American Diabetes Association criteria for DKA. Those with ketosis were approximately twice as likely to have diabetes at baseline, and the three individuals who developed DKA had underlying diabetes. Patients with ketosis, with or without acidosis, were younger (median age 47 vs. 58 years; $P = 0.003$), and had higher rates of acute respiratory distress syndrome (28.6% vs. 13.5%; $P = 0.007$), acute liver injury (14.3% vs. 5.4%; $P = 0.042$), and digestive disorders (31.0% vs. 12.0%; $P = 0.0012$).

Based on the above, then, when looking at ketoacidosis in people with diabetes, we should try to accurately distinguish "true" from "spurious" newly diagnosed diabetes. To do so, several clinical and logistic considerations should be taken into account. Indeed, various completely different conditions might have led to the inclusion of diabetes on the list of hospital discharge diagnosis-related groups (DRGs), on which the many retrospective analyses conducted so far are based.[12–14] Specifically, when focusing on new-onset diabetes, such conditions might include (1) the so-called prediabetic state (impaired fasting glucose and impaired glucose tolerance), which are associated with persistently normal glycated haemoglobin levels, (2) the temporary hyperglycaemic effect typically observed with any acute or severe inflammatory disease, or (3) the symptoms and signs of ketoacidosis affecting people with diabetes.[8,11] With regard to the latter, at a time when they were overwhelmed by emergency intensive care unit (ICU) admissions, doctors might have classified any event occurring in people with high blood sugar levels as DKA, regardless of whether these were real cases of DKA or no more than respiratory acidosis with superimposed malnutrition-driven ketosis. A confounder may also be the high blood concentrations attained by inflammatory markers in patients with COVID-19, which is also typical of DKA, independent of accompanying illness.[15,16] It is still unclear whether the inflammatory cascades occurring in DKA and severe COVID-19 cases act synergistically to worsen clinical outcomes. However, despite being elevated in DKA, interleukin-6 seems to be a driver rather than a consequence of ketosis, and is likely to play a significant role in maladaptive immune responses to the SARS-CoV-2 virus.[15]

During the most dramatic phases of the epidemic, a huge number of patients were admitted the hospital wards in Italy (as well as in other countries), with these numbers exceeding the available number of ICU

beds and breathing devices. Therefore, as reported in some interviews appearing in the media throughout the first part of the lockdown period, most ICU staff admitted to having given top priority to vital function preservation. As a consequence, similarly to what happens during any severe acute illnesses, such as myocardial infarction or surgical stress,[17] those patients either already known to have diabetes or who were unexpectedly hyperglycaemic posed a minimal problem. In other words, physicians strived hard mainly to save lives by using insulin as planned, without getting lost in unnecessary and risky time-consuming classification dilemmas. In such a context, they did what they were expected to do by sticking to well-established protocols for severe acid-base immbalance *per se* and adding insulin as needed in case of hyperglycaemia, leaving aside subtle underlying mechanisms. Therefore, when completing medical records, they might sometimes have included DKA among the primary or secondary DRGs, thus contributing to an increase in the percentage of diabetes-related death rates associated with COVID-19 (unpublished, anecdotal and personal data). Should this have happened on a large scale, such an increase might have easily turned out to be an artifact.

Nevertheless, healthcare personnel from the ICU should be trained to identify and treat DKA promptly in critically ill and medically complex patients. In patients with severe metabolic imbalance and nutritional defects caused by diabetes *per se* and further aggravated by SARS-CoV-2 infection, such an attitude could ensure success.[18] In any case, recognition and prompt treatment of real DKA in the ICU setting is essential to enable healthcare personnel to implement the best individually tailored treatment strategy for critically ill and medically complex patients.[19]

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

S.G. wrote, revised and approved the final version of the manuscript. F.S., A.M. and A.C. revised and approved the final version of the manuscript.

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