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-19.8,11 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 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 "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, 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, 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). While 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 to 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, 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 imbalance 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. 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.

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.

Sandro Gentile MD1, Felice Strollo MD2, Andrea Mambro MD3, Antonio Ceriello MD4

1Campania University, “Luigi Vanvitelli”, and Nefrocenter Research & Nyx Start-UP, Naples, Italy
2IRCCS San Raffaele Pisana, Rome, Italy
3Anesthesiology and Resuscitation Unit, CTO, Andrea Alesini Hospital, Rome, Italy
4IRCCS Multimedica, Sesto San Giovanni, Italy

REFERENCES
1. Caballero AE, Ceriello A, Misra A, et al. COVID-19 in people living with diabetes: an international consensus. J Diabetes Complicat. 2020;34:107671. https://doi.org/10.1016/j.jdiacomp.2020.107671.
2. Wu J, Wu J, Zhang J, et al. Influence of diabetes mellitus on the severity and fatality of SARS-CoV-2 (COVID-19) infection. Diabetes Obes Metab. 2020;1-8. https://doi.org/10.1111/dob.14105.
3. Singh AK, Gillies CL, Singh R, et al. Prevalence of co-morbidities and their association with mortality in patients with COVID-19: a systematic review and meta-analysis. Diabetes Obes Metab. 2020;1-10. https://doi.org/10.1111/dob.14124.
4. Li H, Tian S, Chen T, et al. Newly diagnosed diabetes is associated with a higher risk of mortality than known diabetes in hospitalized patients with COVID-19. Diabetes Obes Metab. 2020;1-10. https://doi.org/10.1111/dob.14099.
5. Gentile S, Strollo F, Ceriello A. COVID-19 infection in Italian people with diabetes: lessons learned for our future (an experience to be used). Diabetes Res Clin Pract. 2020:162;108137. https://doi.org/10.1016/j.diabres.2020.108137.
6. Rubino F, Amiel SA, Zimmet P, et al. New-onset diabetes in Covid-19. N Engl J Med. 2020;383:789-790. https://doi.org/10.1056/NEJMct2018688.
7. Vas P, Hopkins D, Feher M, Rubino F, Whyte MB. Diabetes, obesity and COVID-19: A complex interplay. Diabetes Obes Metab. 2020;1-5. https://doi.org/10.1111/dob.14134.
8. Palermo NE, Sadhu AR, McDonnell ME. Diabetic ketoacidosis in COVID-19: Unique concerns and considerations. J Clin Endocrinol Metab. 2020;105:dgaa360.
9. Fabiani S, Fallahi P, Ferrari SM, Miccoli M, Antonelli A. Hepatitis C virus infection and development of type 2 diabetes mellitus: systematic review and meta-analysis of the literature. Rev Endocr Metab Disord. 2018;19(4):405-420. https://doi.org/10.1007/s11154-017-9440-1.
10. Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol. 2010;47:193-199.
11. Li J, Wang X, Chen J, Zuo X, Zhang H, Deng A. COVID-19 infection may cause ketosis and ketoacidosis. Diabetes Obes Metab. 2020;1-7. https://doi.org/10.1111/dob.14057.
12. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet. 2020;395:1054-1062.
13. Zhu L, She ZG, Cheng X, et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. Cell Metab. 2020;31:1068-1077.
14. Li X, Xu S, Yu M, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020;146:110-118.
15. Ceriello A, De Nigris V, Prattichizzo F. Why is hyperglycaemia worsening COVID-19 and its prognosis? Diabetes F. Obes Metab. 2020;1-2. https://doi.org/10.1111/obm.13098.
16. Stenz FB, Umpierrez GE, Cuervo R, Kitabchi AE. Proinflammatory cytokines, markers of cardiovascular risks, oxidative stress, and lipid peroxidation in patients with hyperglycemic crises. Diabetes. 2004;53:2079-2086.
17. Ceriello A. Hyperglycemia and the worse prognosis of COVID-19. Why a fast blood glucose control should be mandatory. Diabetes Res Clin Pract. 2020;163:108186. https://doi.org/10.1016/j.diabres.2020.108186.
18. Ceriello A, Standl E, Catrinou D, et al. Issues for the management of people with diabetes and COVID-19 in ICU. Cardiovasc Diabetol. 2020;19(1):114. https://doi.org/10.1186/s12933-020-01089-2.
19. Gentile S, Strollo F, Ceriello A. The need for diabetes care customization in the ICU at the time of SARS-CoV-2 outbreak. Diabetes Ther. 2020;11(6):1-3. https://doi.org/10.1007/s13300-020-00824-y.