Blood glucose levels and COVID-19. Reply to Sardu C, D'Onofrio N, Balestrieri ML et al [letter] and Lepper PM, Bals R, Jüni P et al [letter]

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Keywords Blood glucose · COVID-19 · Diabetes · Mortality · Prognosis

Abbreviations

CAP	Community-acquired pneumonia
COVID-19	Coronavirus disease-2019

To the Editor: We welcome the letters by Sardu et al [1] and Lepper et al [2] on our paper entitled 'Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study' [3]. Sardu et al found that the change in blood glucose concentration between admission and 24 h was associated with coronavirus disease-2019 (COVID-19) outcome in 132 Italian hyperglycaemic (i.e. blood glucose >7.7 mmol/l on admission) patients hospitalised for both severe and non-severe disease [1]. In addition, Lepper et al reported data on an impressive cohort of nearly 7000 patients with community-acquired pneumonia (CAP) and demonstrated that elevated blood glucose on admission was associated with an increased risk of death in individuals with or without pre-existing diabetes [2, 4]. Both studies emphasised the value of admission blood glucose on prognosis of COVID-19 and of CAP [2].

Sardu et al considered that we misinterpreted our data on admission blood glucose, since we claimed that we considered it to be a consequence of, rather than a contributor to COVID-19 severity. This point is of scientific and medical interest. They acknowledged a prognostic role for admission blood glucose, which is in line with our findings, and, furthermore, suggested that hyperglycaemia is more than a simple marker of the severity of the infection. We believe that their interesting results should not lead to any alteration of our conclusion on the value of admission blood glucose for several reasons. First, the study by Sardu et al was purely observational and so causation cannot be established: the greater decrease in blood glucose between those with a better outcome compared with the others does not imply that this improvement is causal. Second, Van den Berghe et al could not find evidence of a benefit on all-cause death of strict blood glucose control with insulin compared with conventional therapy in a study of 1200 patients admitted to the medical ICU, with half of the participants having respiratory conditions [5].

We fully agree with Lepper et al that admission blood glucose can be used as a stratification factor to identify patients at high risk of severe pneumonia [2, 4]. However, based on our results from the Coronavirus SARS-CoV-2 and

A complete list of the CORONADO trial investigators is provided in the Electronic supplementary material (ESM).

Bertrand Cariou, Samy Hadjadj and Matthieu Wargny contributed equally to this article.

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Diabetes Outcomes (CORONADO) study [3], other biomarkers, such as C-reactive protein, lymphocyte counts or aspartate aminotransferase, which outperformed blood glucose in multivariable analysis, could have adequate power for such a stratification and should not be forgotten.

In conclusion, whether blood glucose in COVID-19 is a causal factor requiring specific treatment or a mere marker remains to be established in future dedicated studies including randomised controlled trials.

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References

1. Sardu C, D'Onofrio N, Balestrieri ML et al (2020) Hyperglycaemia on admission to hospital and COVID-19. Diabetologia. https://doi.org/10.1007/s00125-020-05216-2
2. Lepper PM, Bals R, Jüni P, von Eynatten M (2020) Blood glucose, diabetes and metabolic control in patients with community-acquired pneumonia. Diabetologia. https://doi.org/10.1007/s00125-020-05225-1
3. Cariou B, Hadjadj S, Wargny M et al (2020) Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. Diabetologia 63:1500–1515. https://doi.org/10.1007/s00125-020-05180-x
4. Lepper PM, Ott S, Nüesch E et al (2012) Serum glucose levels for predicting death in patients admitted to hospital for community acquired pneumonia: prospective cohort study. BMJ 344:e3397. https://doi.org/10.1136/bmj.e3397
5. Van den Berghe G, Wilmer A, Hermans G et al (2006) Intensive insulin therapy in the medical ICU. N Engl J Med 354:449–461. https://doi.org/10.1056/NEJMoa052521

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