COMMENTARY

New-Onset Diabetes in COVID-19: Time to Frame Its Fearful Symmetry

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ABSTRACT

There is increasing evidence that coronavirus disease 2019 (COVID-19) may lead to new-onset diabetes mellitus (DM). This may occur even in patients without predisposing factors for impaired glucose metabolism. Both impaired pancreatic insulin secretion and insulin resistance have been implicated as underlying mechanisms. Importantly, new-onset hyperglycaemia is associated with worse prognosis in patients with COVID-19. Indeed, its prognosis may be even more sinister than in patients with pre-existing DM. More research data and knowledge are currently being collected to improve our insights into this constellation and to guide therapies in clinical reality.

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EDITORIAL

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exhibits increased mortality and morbidity in elderly individuals, especially in those with comorbidities, such as diabetes mellitus (DM) [1]. Previously, DM was identified as an independent factor predisposing to poor outcomes in patients infected by other coronaviruses, such as severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) [2] and Middle East respiratory syndrome coronavirus (MERS-CoV) [3]. Moreover, during the SARS-CoV-1 outbreak, acute DM was commonly observed in individuals with no history of DM or glucocorticoid use, and was an independent predictor of mortality [2].

Interestingly, DM may also be associated with severe coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2. Of note, "new-onset" hyperglycaemia and acute metabolic decompensation of pre-existing DM are now emerging as a complication of COVID-19, especially among hospitalised patients.

Impressively, this "new-onset" hyperglycaemia is not associated with any other risk factors, notably obesity, prediabetes, DM, or corticosteroid administration. These findings point to a bidirectional relationship between DM and COVID-19 [4].

First, some patient cases have illustrated that COVID-19 may accelerate diabetic ketoacidosis (DKA) in subjects with new-onset or pre-existing DM [5]. Early recognition of DKA symptoms is required to improve the prognosis of COVID-19-related DKA [5].

Moreover, it is known that SARS-CoV-2 may enter the pancreatic beta cells via the expression of angiotensin-converting enzyme 2 (ACE2) receptors [6]. It would be possible that the virus impairs pancreatic insulin secretion, thereby either aggravating DM or triggering new-onset DM [6]. A further underlying mechanism appears to be insulin resistance due to the high levels of interleukin-6 (IL-6) and tumour necrosis factor alpha (TNFα) in subjects with severe COVID-19 [7, 8].

Vice versa, this new-onset hyperglycaemia is linked to important perturbations. The latter include glycation of ACE2 receptors [9], excess cytokine release [10, 11], and a pro-thrombotic state via increased antithrombin III production [12], ultimately leading to a more sinister prognosis [10]. Indeed, a strong association of plasma glucose at admission with intubation and death has been demonstrated in DM [13]. Similarly, a correlation of plasma glucose on admission with radiographic evidence of acute respiratory distress syndrome (ARDS) irrespective of prior DM or no DM has been documented [14]. Perhaps, the latter is hardly surprising, given the established observation that new-onset hyperglycaemia may result from various clinical conditions, notably HIV and other viral infections [15, 16], organ transplantation [17], stroke [18] and myocardial infarction [19]. Of note, in such conditions new hyperglycaemia portends a very sinister prognosis.

In this context, there is accumulating evidence that hyperglycaemia at admission, both in DM subjects and in those with secondary hyperglycaemia, indicates a poor prognosis [20–22]. Importantly, newly diagnosed DM is linked to increased mortality, as compared with known DM and normal glucose levels in patients with COVID-19 [21]. In the light of these findings, several leading diabetologists have established a global registry of patients with COVID-19-related new DM to further investigate the intricacies and implications of these associations [23].

In conclusion, not only is DM associated with worse prognosis in COVID-19 but, vice versa, the latter may lead to new-onset DM, as well [5, 6]. Some mechanisms mediating this new hyperglycaemia have been implicated [6–8]. From a practical viewpoint, new hyperglycaemia is linked to unfavourable prognosis [20–23], perhaps even more than in pre-existing DM [21]. Hence, we need more knowledge [23], but we also need to deal with the emerging clinical implications, mastering the "fearful symmetry" [24] of these new conditions.

ACKNOWLEDGEMENTS

participated in advisory boards, and clinical trials sponsored by various pharmaceutical companies and she is currently Vice President of the National Diabetes Commission, Ministry of Health, Romania. Stella Papachristou and Iliana Stamatiou have nothing to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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