

# Autonomic dyshomeostasis in patients with diabetes mellitus during COVID-19

Virginia Boccardi

In November 2020, Soo Lim and collaborators published a complete Review on coronavirus disease 2019 (COVID-19) and diabetes mellitus (Lim, S., Bae, J. H., Kwon, H. S. & Nauck, M. A. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. *Nat. Rev. Endocrinol.* **17**, 11–30 (2021)<sup>1</sup>). In this Review, they clearly explained that hyperglycaemia might interact with other risk factors to modulate immune and inflammatory responses, thus predisposing patients with diabetes mellitus to severe COVID-19 and possible lethal outcomes. From the epidemiological data or from bedside experience on COVID-19 wards, we have learned that in patients with diabetes mellitus and its complications, infection with SARS-CoV-2 is associated with increased morbidity and mortality<sup>2</sup>. However, it is still impossible to predict which infected people will experience the rapid evolution to acute respiratory distress and multi-organ failure.

From the hard work in hospital wards, we know that there are some laboratory and clinical biomarkers that might indicate a high risk of progression to severe COVID-19; these biomarkers include hyperglycaemia as well as hyponatraemia, hyperinflammation, abnormal heart rate variability (from severe bradycardia to tachycardia and arrhythmia), haemodynamic instability and altered mental status. Thus, it seems that the pathophysiological processes of COVID-19 change the interplay of the immune, endocrine and nervous systems. These systems interact with each other by means of cytokines, hormones and neurotransmitters<sup>3</sup>.

Interestingly, the nervous systems communicate with the immune system and regulate its activity through the autonomic nervous system (via sympathetic and parasympathetic activity)<sup>3</sup>. It is well established that diabetes mellitus is a condition associated with autonomic dysfunction, where sympathetic activity is hyperactivated alongside withdrawal of parasympathetic activity<sup>4</sup>. Moreover, when the balance between the sympathetic and parasympathetic nervous systems is disturbed by certain events, such as serious stress and inflammation during COVID-19, a stronger sympathetic impulse might shift homeostasis

of the autonomic nervous system towards further sympathetic dominance, potentially leading to increased mortality. The autonomic nervous system interacts with the immune system via the neuro-inflammatory pathway and via the cholinergic anti-inflammatory pathway, and also controls the function of the respiratory system<sup>5</sup>. Thus, the early identification of autonomic dyshomeostasis in patients with diabetes mellitus and COVID-19 is clinically important. Indeed, it is possible to hypothesize that the modulation of autonomic nervous system homeostasis (such as with the use of non-invasive transcutaneous electrical vagal nerve stimulation) might

improve clinical outcomes in patients at risk of progressing to severe COVID-19.

There is a reply to this letter by Lim, S., Bae, J. H., Kwon, H. S. & Nauck, M. A. *Nat. Rev. Endocrinol.* <https://doi.org/10.1038/s41574-021-00467-4> (2021)

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#### Competing interests

The author declares no competing interests.

## Reply to: Autonomic dyshomeostasis in patients with diabetes mellitus during COVID-19

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My colleagues and I published a comprehensive Review on coronavirus disease 2019 (COVID-19) and diabetes mellitus in November 2020 (Lim, S., Bae, J. H., Kwon, H. S. & Nauck, M. A. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. *Nat. Rev. Endocrinol.* **17**, 11–30 (2021)<sup>1</sup>). In her correspondence on our Review, Virginia Boccardi suggested that, in patients with diabetes mellitus and COVID-19, we should also consider imbalances in the sympathetic and parasympathetic nervous systems occurring, for example, as a consequence of diabetes mellitus, as important factors that might contribute to COVID-19 severity (Boccardi, V. Autonomic dyshomeostasis in patients with diabetes mellitus during COVID-19. *Nat. Rev. Endocrinol.* <https://doi.org/10.1038/s41574-021-00466-5> (2021)<sup>2</sup>).

Dysregulated glucose metabolism is associated with autonomic nervous system dysfunction, leading to an imbalance between sympathetic and parasympathetic activity<sup>3</sup>. This lack of homeostatic control is affected

by acute infections, potentially augmenting instability in vital functions in patients affected by COVID-19 (REFS<sup>4,5</sup>). It is well known that patients with a loss of homeostatic control of glucose metabolism release potentially damaging cytokines, including IL-6 and tumour necrosis factor<sup>6</sup>, which are involved in the development of complications of diabetes mellitus as well as COVID-19 (REF<sup>7</sup>). The synthesis and secretion of other cytokines, such as plasminogen activator inhibitor 1 and adhesion molecules associated with overactive coagulation, are also increased in patients with hyperglycaemia<sup>8</sup>. All these phenomena are, likewise, induced by SARS-CoV-2 infection<sup>9</sup>.

In the DCCT–EDIC study, which included patients with type 1 diabetes mellitus, individuals diagnosed with autonomic neuropathy experienced an increased long-term risk of adverse cardiovascular events<sup>10</sup>. Another study of patients with diabetes mellitus reported that activation of the sympathetic nervous system resulted in diffuse endothelial dysfunction and an increased pro-inflammatory,