

# 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,

pro-atherothrombotic and procoagulant state<sup>11</sup>. Conditions that cause acute serious stress such as COVID-19, when combined with underlying inflammation, can induce overactivation of sympathetic functions, and this sympathetic dominance can disturb the balance within the autonomic nervous system<sup>12</sup>. This alteration is probably unfavourable for cardiometabolic health, and potentially leads to worse outcomes and increased mortality. Thus, COVID-19 can be a triggering factor that initiates the harmful development of cardiorespiratory distress and, in particular in patients characterized by sympathetic overactivity, might lead to multiorgan failure.

We fully agree with Boccardi<sup>2</sup> that early identification of autonomic imbalance is critical in patients with diabetes mellitus to concentrate therapeutic measures on those at risk of deteriorating health. We also agree that the autonomic nervous system interacts with the immune system via neuroinflammatory pathways, which eventually might affect the function of cardiac and respiratory systems<sup>13</sup>. Moreover, we agree that therapeutic modulation of a disturbed autonomic nervous system to achieve an improved balance might improve the prognosis of COVID-19 in patients with diabetes mellitus. Although more evidence is needed, various methods, such as non-invasive electrical stimulation on the vagal nerve system, offer useful potential along these lines<sup>14</sup>. Thus, it has been reported that vagus nerve stimulation in the auricular area could be an effective modality to improve the acute respiratory distress conditions seen in patients with COVID-19 (REF.<sup>15</sup>).

As of 13 January 2021, the [World Health Organization](#) reports (see Related links) that

more than 91 million people have been infected with SARS-CoV-2 worldwide, and of those, 1.9 million have died. Fortunately, [vaccines](#) have been developed (see Related links) and are currently being administered to people at high risk, such as the elderly and medical personnel. Before the vaccination programme becomes effective, people at high risk of COVID-19, such as those with diabetes mellitus, cardiovascular diseases or immunocompromised disorders, should receive priority attention and treatment if they contract COVID-19. We hope that further medical approaches will be discovered to reduce the morbidity and mortality associated with COVID-19 in people at high risk.

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#### Competing interests

The authors declare no competing interests.

#### RELATED LINKS

WHO COVID-19 dashboard: <https://covid19.who.int/>  
WHO COVID-19 vaccine information: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines>