

Metabolic Syndrome and COVID-19: Endocrine–Immune Vascular Interactions Shape the Clinical Course

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This excellent review by Bansal and co-authors (1) is a brief, timely, and comprehensive article summarizing our current understanding of the pathophysiological mechanisms and the clinical consequences for COVID-19-patients with the metabolic syndrome. Based on the fact that patients with obesity, diabetes, and hypertension are at substantially increased risk for a severe course of COVID-19 and that about a quarter of the COVID-19 cases with fatal outcome are associated with diabetes, the authors expand our previous recommendations for the practical management of diabetic patients with COVID-19 (2).

The pathophysiological background of the observed association between endocrine and metabolic factors, cardiovascular disease, diabetes mellitus, and COVID-19 has been discussed extensively and we have realized that many lessons still need to be learned. For example, recognition of the interaction of SARS-CoV-2 with the angiotensin-converting enzyme (ACE2) in the context of virus entry into host cells triggered one of the first striking questions with high practical implications in this setting: should the widely used treatment with ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in patients with the metabolic syndrome and COVID-19 be continued or stopped (3)?

The best strategy to make wise decisions in insecure times characterized by the absence of evidence is to hang on a moment, taking the time to browse for robust facts before providing definitive answers and performing fundamental changes of commonly established therapies with proven benefit. The same is true with regard to unestablished therapies that have been recently discussed on a popular basis, such as treatment of COVID-19 patients with the antimalarial and rheumatoid arthritis drug hydroxychloroquine. However, since drug development is extremely time consuming and expensive, it would be very helpful to have effective drugs useful for the treatment of COVID-19 patients ready to hand on the shelf. Therefore, it may be worthwhile to consider potential beneficial effects of approved drugs already in clinical use.

Consequently, it has recently been speculated that the widely used antidiabetic compound metformin may also be useful as an antiviral compound and that the well-known anti-inflammatory effects of the peroxisome proliferator-activated receptor- γ -agonist pioglitazone may have potential benefit in COVID-19.

This is an interesting perspective because metformin was originally introduced as a compound for the treatment of influenza virus infections, and it is well established that type-2 diabetes and insulin resistance are associated with a state of chronic inflammation. Most of the severe and life-threatening complications of COVID-19 are thought to be pathophysiologically based on a hyperinflammatory state with an uncontrolled systemic

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surge of excessive cytokines, commonly termed as a “cytokine storm.” Therefore, in the current situation it is reasonable to give established anti-inflammatory treatments a trial, and the first results using dexamethasone in critically ill COVID-19 patients are highly promising.

Interestingly, insulin resistance appears to be associated with the dimension of the cytokine storm and can therefore be related to the severity of complications in COVID-19. One of the major problems in COVID-19-patients with potential life-threatening or even fatal consequences is due to thromboembolic complications supposed to be based on overactivation of the complement cascade and consecutive activation of extrinsic and intrinsic coagulation pathways. Also, mechanisms involved in the formation of diabetic vascular complications like the advanced glycation end-products/receptor for advanced glycation end-products signaling pathway may be of potential relevance in the pathophysiology of organ damage related to COVID-19 and have been currently considered in this context. In addition to metabolic associations, multiple links of COVID-19 to endocrine functions have been discussed (4). For instance, COVID-19 may affect the neuroendocrine stress axis at several levels. Along with obvious general effects of a situational psychological burden, COVID-19 may have a direct impact on the function of the hypothalamic–pituitary–adrenal–axis due to specific structural damage caused by the viral infection. Interestingly, infection of the adrenals with SARS-CoV-2 may be fostered by the high level of expression of ACE2 in this organ (5, 6). Finally, it seems that COVID-19 may induce a new onset of type 1 and type 2 diabetes in so far healthy people or a novel subform of diabetes. Therefore, we have initiated the establishment of a global registry based on routinely collected clinical data to investigate and follow up new cases of diabetes in COVID-19 patients (7).

We need to continue our joint efforts to elucidate the association between the metabolic syndrome and COVID-19 and need to realize that work is still in

progress to shed more light on the picture in order to make evidence-based decisions. For the time being, it is best to keep patients with the metabolic syndrome at the lowest possible risk by optimizing all available preventive and therapeutic options including drug treatment and even bariatric surgery (8).

Additional Information

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