



Revisiting the endocrine and metabolic manifestations of COVID-19 two years into the pandemic

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Abstract

An extraordinary effort of the universal endocrine community has led to important insights into endocrine and metabolic aspects of COVID-19. In this Editorial, we introduce a special issue of Reviews in Endocrine and Metabolic Disorders that calls attention, through the efforts of internationally recognized experts in the field, to features that are now widely recognized as endocrine and metabolic manifestations of COVID-19. These advances in our knowledge have seminal implications for how we can prevent and manage these aspects of COVID-19.

Keywords COVID-19 · Vaccination · Endocrine Phenotype · Vitamin D · Calcium · Pituitary

1 Introduction

Two years into the COVID-19 pandemic, it is now apparent that it is an evolving clinical scenario in which, somewhat surprisingly, endocrinologists have discovered themselves heavily involved not only in waging the front-line battle against the pandemic [1] but also in describing endocrine and metabolic phenotypes of the disease including possible endocrine consequences of vaccination efforts [2, 3].

From the early days in 2020, when Coronavirus 2 (SARS-CoV-2) was primarily a respiratory syndrome, the disease is now known to harbor the potential to become a multi-system disorder. The extra-pulmonary signs, symptoms, and comorbidities contribute importantly to the morbidity and mortality of the disease [4]. Undoubtedly, the ubiquity of the angiotensin-converting enzyme 2 (ACE2), the cognate receptor for SARS-CoV-2, allows facile entry of viral particles to all organs and potentially to all cells [5].

Based upon the pervasive involvement of the endocrine system in many manifestations of COVID-19, as well as the

knowledge gained over the past two years, we are dedicating this special issue of Reviews in Endocrine and Metabolic Diseases to summarize these new insights. We are pleased that the contributors to this special issue are among the most authoritative and knowledgeable experts in the world.

2 Main components of the endocrine and metabolic phenotype of COVID-19 and their clinical impact

Several aspects of endocrine and metabolic involvement in COVID-19, to be reviewed in this special issue, have emerged as key features of the disease regarding epidemiological, mechanistic, and clinical features. Altogether, they form prognostic elements of COVID-19 outcomes [2, 3].

For example, poorly controlled diabetes mellitus and obesity were identified early in the pandemic as frequent comorbidities of the disease, affecting about 20% of hospitalized patients. Related to these metabolic disorders but also as an independent factor, low vitamin D levels increase the risk of severe manifestations of COVID-19 [6, 7]. SARS-Cov-2 can also directly damage beta cell pancreatic function leading to new onset diabetes and creating a sort of bidirectional relationship between viral infection and deranged glucose metabolism [8]. The increasingly recognized prognostic role of these common metabolic conditions has raised further attention to the importance of nutritional aspects before, during and after COVID-19 [9, 10]. Male sex and advanced

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age were also associated with disease severity although the role of sex hormones is not yet completely clarified [11, 12].

Other aspects of metabolic derangements in COVID-19, besides low vitamin D levels, are hypocalcemia and morphometric vertebral fractures among those hospitalized for the disease [13]. As many as two thirds of hospitalized patients have been reported with low vitamin D levels [14] and hypocalcemia [15–18]. These biochemical abnormalities may be related to an insufficient compensatory PTH response [19] due, at least in part, to the host inflammatory response and several clinical parameters of disease severity such as need for mechanical ventilation, ICU admission and mortality [20]. Interestingly, widespread lack of vitamin D in Southern European Countries [21] was suggested from the beginning of the pandemic as one of the possible risk factors for severe COVID-19 [22]. The relationship between hypovitaminosis D and these outcome data is likely to be related to impaired innate and adaptive immunity [23, 24]. Supporting this concept are studies that have demonstrated the efficacy of vitamin D supplementation in protecting against respiratory infections [25]. The mechanistic links between vitamin D insufficiency and higher risk and greater severity of SARS-CoV-2 infection are under active investigation [26]. To this point, vitamin D status, in several cross-sectional studies, predict the degree of pulmonary involvement [27]. Finally, vitamin D supplementation appears to have a key role in disease prevention although some, but not all, pilot trials, have shown that vitamin D administration to COVID-19 hospitalized patients also attenuate the severity of the disease [28, 29].

The osteo-metabolic phenotype of COVID-19 [13] also includes a high prevalence of radiological thoracic vertebral fracture (affecting one third of hospitalized patients [30]. Vertebral fractures were proposed as a marker of frailty in the disease and their severity significantly predicted mortality. These findings underscored the importance of maintaining any type of anti-osteoporosis therapy for those with osteoporosis and COVID-19 [31].

Pituitary diseases have also been reported to be clinically relevant in COVID-19 [32]. In fact, several studies reported that patients with Cushing's disease were at higher risk of SARS-Cov-2 infection as compared to the general population. Increased severity of COVID-19 was observed in patients with active disease [33] suggesting that chronic uncontrolled hypercortisolism may be mechanistically relevant in this clinical context [34].

Moreover, a specific involvement of the pituitary in the endocrine phenotype of COVID-19 was recently observed with hypopituitarism, pituitary apoplexy, hyponatremia and hypophysitis as main features [34, 35]. Furthermore, patients with hypopituitarism can be affected by comorbidities such as diabetes mellitus, obesity, and vertebral fractures which per se may predispose them to severe COVID-19 [36, 37].

3 The endocrine system and COVID-19 vaccination

As a result of an unprecedented world-wide effort, vaccination against COVID-19 has become universally available [38]. Related safety issues in patients with endocrine diseases particularly those with autoimmune problems as well as those with hypoadrenalism were of some concern for the endocrine community. According to an ESE statement [1], COVID-19 vaccination was endorsed for patients with stable endocrine conditions similar to the general population. Interestingly, an increased number of cases of post vaccine mild Graves disease has been recently reported in both men and women [39] possibly in the context of associated autoimmune responses to the adjuvants (ASIA). For example, in the case of mRNA vaccines, it could be related to polyethylene glycol-containing lipoids and for modified viral vaccines to oil-in-water excipients such as polysorbate. These very recent data suggest a consideration in vaccinating patients with Graves disease. In this regard, checking thyroid function in patients with prolonged post vaccine symptoms, if similar to thyrotoxicosis (e.g. fever, palpitations, asthenia) may be reasonable particularly if there is a positive history of autoimmune thyroid and non-thyroidal disease [39].

4 Conclusions

We have had the honor and pleasure to serve as Guest Editors of this special issue of Reviews in Endocrine and Metabolic Disease. It represents the efforts of many endocrinologists around the world. As a result, we hope you will gain new insights from these experts who have contributed so importantly to improved understanding of the endocrine and metabolic aspects of COVID-19.

Declarations

Conflicts of interest No sources of funding, financial or non-financial interests are declared. Due to the nature of the article (review) no study-specific approval by the appropriate ethics committee for research involving humans and/or animals, neither informed consent if the research involved human participants, and a statement on welfare of animals if the research involved animals is provided.

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