Adrenal Gland Function and Dysfunction During COVID-19

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Key words

SARS-CoV-2, CIRCI, PAI, adrenal insufficiency, HPA axis

received 21.03.2022
accepted after revision 01.06.2022

Bibliography

Horm Metab Res 2022; 54: 532–539
DOI 10.1055/a-1873-2150
ISSN 0018-5043

Georg Thieme Verlag, Rüdigerstraße 14,
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ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic is currently one of the major health concerns worldwide accounting for many deaths and posing a great social and economic burden. Early activation of adrenal hormone secretion is pivotal to surviving systemic microbial infections. In addition, clinical studies demonstrated that glucocorticoids might also be beneficial in reducing disease progression and life deterioration in certain patients with COVID-19. Recent studies demonstrated that SARS-CoV-2 might target the adrenal glands, raising the possibility that at least some COVID-19 complications may be associated with adrenal dysfunction. Whether SARS-CoV-2 infection might cause adrenal dysfunction remains unknown. Histopathological examinations provided evidence that SARS-CoV-2 infection might indeed cause certain structural damage to the adrenal glands, especially concerning its vascular system. However, since no widespread cellular damage to cortical cells was observed, it is less likely that those changes could lead to an immediate adrenal crisis. This assumption is supported by the limited number of studies reporting rather adequate cortisol levels in patients with acute COVID-19. Those studies, however, could not exclude a potential late-onset or milder form of adrenal insufficiency. Although structural damage to adrenal glands is a rarely reported complication of COVID-19, some patients might develop a critical illness-related corticosteroid insufficiency (CIRCI), or iatrogenic adrenal insufficiency resulting from prolonged treatment with synthetic glucocorticoids. In this mini-review article, we aimed at describing and discussing factors involved in the adrenal gland function and possible dysfunction during COVID-19.

Introduction

The coronavirus disease 2019 (COVID-19) is a multisystemic and dynamic disease caused by infection with Severe Acute Respiratory Syndrome Coronavirus type 2 (SARS-CoV-2). COVID-19 has been declared a pandemic by the World Health Organization in March 2020 and has accounted for more than 6 million deaths worldwide [1]. Approximately 10–14 % of individuals with symptomatic COVID-19 develop severe complications necessitating immediate hospitalization such as, for example, life-threatening pneumonia [2, 3]. People at risk of developing a severe COVID-19 are older persons (above 60 years of age) having one or more comorbidities, including hypertension, diabetes, obesity [4], chronic obstructive pulmonary disease (COPD), or cancer [5]. Moreover, COVID-19 severity was found to be higher in men than in women [6]. The pathogenesis of COVID-19 is complex and involves innate immune receptors (toll-like receptors), immune cells (particularly macrophages and neutrophils), and cytokine networks (including IL-6, TNF-α, and IFNs) as well as coagulation and complement pathways [7, 8].

Rapid and adequate release of glucocorticoids (GC) is crucial for the survival of systemic microbial infections, sepsis, and septic shock [9]. During critical illness, glucocorticoids are necessary to sustain high plasma glucose levels, protect from cardiovascular shock, and most importantly prevent the overactivation of the immune system. Therefore, patients with known or newly acquired adrenal insufficiency (AI) are advised to double glucocorticoid doses during COVID-19 [10, 11]. More importantly, glucocorticoids might also be effective in preventing clinical deterioration of certain patients with COVID-19 further indicating their protective actions [12].

Daily cortisol production and secretion are regulated by the hypothalamic-pituitary-adrenal (HPA) axis. In unstressed healthy individuals, plasma cortisol secretion occurs in an ultradian, and a circadian fashion regulated by a pulsatile release of adrenocorticotropic hormone (ACTH) from the pituitary gland [13]. ACTH secretion is in turn controlled by corticotrophin-releasing hormone (CRH) produced by the hypothalamus. In addition, several metabolic and inflammatory factors might influence cortisol production such as, for example, angiotensin II, antidiuretic hormone, prostaglandins, macrophage inhibitory factor (MIF), interleukins, for example, IL-6, and adipokines [14, 15]. To prevent possible side effects of GC overexposure in peripheral tissues most of the plasma cortisol is bound to corticosteroid-binding globulin (CBG).

During sepsis, the HPA function is often impaired [16]. In some patients, reduced glucocorticoid metabolism [17] and depletion of corticoid-binding globulins [18] enhance cortisol bioavailability, which might inhibit ACTH release as a part of the negative feedback mechanism. Furthermore, a substantial number of patients develop critical illness-related corticosteroid insufficiency (CIRCI), which describes an insufficient level of morning cortisol (< 10 µg/dl) or activity of glucocorticoid receptor alpha (GR-α) in relation to ongoing inflammation [16, 19]. Finally, some patients might develop adrenal insufficiency (AI), which could be induced by direct cytotoxic actions of pathogens [20, 21] or hemorrhages occurring within the HPA axis [22].

Considering similarities between bacterial sepsis and severe SARS-CoV-2 infection, a potential dysregulation and damage of the adrenal gland might also occur in patients with COVID-19. In fact, several studies and case reports described various forms of adrenal insufficiency in patients with mild and severe COVID-19 [23].

The major purpose of this review is to summarize current studies focusing on the adrenal gland function in patients with COVID-19. Moreover, we will present and discuss potential mechanisms contributing to the adrenal gland dysfunction found in some COVID-19 patients.

Adrenal gland damage associated with COVID-19

Due to the lack of specific biomarkers and limitations of the ACTH-stimulation test, assessment of adrenal gland function and damage in patients with ongoing sepsis and COVID-19 is challenging [24]. Some information might, however, be gained from histopathological analysis of the adrenal glands of patients who died due to COVID-19 (▶ **Table 1**).

Histopathological examination of adrenal glands obtained from autopsies revealed a high degree of local inflammation. While in some studies an inconspicuous [25] or sporadic focal inflammation [26] was found, other observations report a more pronounced and frequent infiltration of CD3- and CD8-lymphocytes in different layers of the adrenal cortex [27] or lymphoplasmacellular cells in perivascular regions of the adrenal gland [28]. Furthermore, one study reported a cellular hyperplasia in zona fasciculata of the adrenal cortex in 86 % of investigated patients, which might be an indicator of impaired hormone production [29].

However, vascular damage seems to be the most commonly confirmed complication of COVID-19 in adrenal glands. In particular, a high degree of endotheliitis of periadrenal adipose and parenchymal tissues was found [25, 28], along with acute fibroid necrosis and apoptotic debris of adrenal arteriole [30]. Moreover, histological [31] and routine computer tomography (CT) investigations [26, 32] reported thrombi formation, infarctions, and hemorrhages in the adrenal glands of patients with COVID-19 [33, 34]. Particularly, unilateral and bilateral acute adrenal infarctions were frequently (23 %) found during routine chest CT in patients with critical COVID-19 [33]. Similar observations were also made in another study reporting bilateral and unilateral gland infarctions in 13.4 and 2.6 % out of 343 patients with COVID-19, respectively [34]. Although adrenal insufficiency has not been evaluated in those patients, adrenal infarcts were associated with enhanced length of stay in ICU [33, 34] and higher mortality [34]. Adrenal infarctions might reflect the procoagulative and prothrombotic status of those patients [35]. Indeed, an increased risk of embolization of the adrenal cortex has been reported in patients with COVID-19 [36].

Several case studies of patients with COVID-19 demonstrated that bilateral adrenal hemorrhages or infarcts might indeed lead to adrenal insufficiency. For example, a patient, with positive serology against COVID-19 was admitted to hospital with fever, fatigue, abdominal pain, and nausea. The patient presented with low plasma sodium concentrations, but normal initial random cortisol and ACTH concentrations. The CT scan revealed enlarged adrenal glands with non-hemorrhagic infarction. Partial AI due to possible microvascular thrombi in the parenchyma was suspected and GCs therapy was initiated [35]. In another patient with no prior history of adrenal diseases, adrenal insufficiency was triggered by bilateral hemorrhage during hospitalization due to COVID-19 [37].

In some rare cases, primary adrenal insufficiency (PAI) caused by either bilateral adrenal hemorrhage or infarcts might not be exclusively attributed to COVID-19 and rather result from an autoim-

▶ **Table 1** Summary of the histopathological studies, which included the adrenal glands.

Author/Year Reference	Main findings	SARS-CoV-2 detection	No of cases
Wong et al. 2021 [25]	Adrenal glands of 62.5 % (5/8) patients showed inconspicuous chronic inflammation with perivascular distribution. Chronic inflammation was additionally found in one adrenal gland.	2/8 RT-qPCR, 3/3 FISH	8
Freire Santana et al. 2020 [26]	Adrenal lesions (12/28), necrosis (7/28), cortical lipid degeneration (4/28), hemorrhages (2/28), focal inflammation (4/28), and thrombosis (1/28).	ND	28
Zinserling et al. 2020 [27]	Infiltration of CD3 + and CD8 + lymphocytes in different layers of the adrenal cortex and in surrounding periglandular adipose tissue. Small groups of proliferating cells with enlarged nuclei.	ND	10
Kanczkowski et al. 2021 [28]	Endothellitis found in periadrenal fat tissue (6 low and 13 high) and in parenchymal tissue (10 low and 1 moderate). Immune infiltration (38/40).	18/40 ISH and IHC; 15/30 RT-qPCR	40
Iuga et al. 2020 [30]	Acute fibroid necrosis of adrenal arteriole in both the parenchyma and capsule. Adrenal parenchymal infarct or thrombosis.	ND	5
Hanley et al. 2020 [31]	Microinfarctions were detected in 33 % (3/9) of investigated adrenal glands.	ND	9
Paul et al. 2022 [32]	Lymphohistiocytic infiltrate in the adrenal cortex of COVID-19 patients composed of CD4 and CD8 cells. With apoptotic center (cleaved casp.3). In 11/19 (58 %) of COVID-19 patients adrenal capillaries were expanded and showed microthrombi. Disrupted adrenal zonation.	19/19 IHC, ISH, RT-RT-qPCR	19

ND: Not determined.

mune reaction. For example, adrenal insufficiency was reported in two patients, who developed either adrenal hemorrhage or infarction shortly after COVID-19 infection [38, 39]. The medical history of both patients suggested previously undiagnosed antiphospholipid syndrome (APLS), which progression might have been accelerated by SARS-CoV-2 infection. However, autoimmune destruction of adrenocortical cells might not always be associated with vascular damage. This is exemplified by a patient with no prior history of autoimmune diseases, who developed primary adrenal insufficiency within 5 months after recovery from COVID-19. The patient had low morning cortisol and aldosterone levels despite a clearly increased ACTH concentrations and normal appearance of both adrenal during CT imaging [40]. Further examination has linked the development of adrenal insufficiency in this patient with the presence of anti-21-hydroxylase antibodies.

In addition, histopathological examinations of adrenal glands from patients with COVID-19 revealed a possibility of direct SARS-CoV-2 action. In particular, evidence of degeneration and necrosis of adrenocortical cells [26, 28] was found, together with the presence of a small number of sporadically proliferating cells with enlarged nuclei [27]. Further evidence includes adrenal gland lesions and cortical lipid degeneration [26]. Adrenocortical necrosis albeit very limited was also observed in another study [28].

Detection of SARS-CoV-2 in the adrenal glands from COVID-19 patients

Many pathogenic microbes including fungi, viruses, and bacteria can target adrenal glands [41]. Some of those infections like in the case of *Mycobacterium tuberculosis* or cytomegalovirus might directly promote the development of Addison's disease, which is a manifestation of primary adrenal insufficiency [20]. In the case of other infections, destruction of the adrenal gland cortex might not reach 90 %, which is required for Addison's disease symptoms to manifest [42].

In order to be infected by SARS-CoV-2, adrenocortical cells should express angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2), which proteins are required for its binding and a cellular internalization, respectively [43]. Expression of those factors in human adrenal glands has been demonstrated using bulk and single-cell RNA sequencing [44] and immunohistochemistry [45]. In particular, high ACE2 protein expression was detected in stromal cells as well as in small capillaries of the adrenal glands [28, 32, 46], and to a laser extent in adrenocortical cells [32, 45]. Whereas TMPRSS2 protein expression was mostly found in adrenocortical cells [28, 45].

In addition to TMPRSS2, also other proteins found in the adrenal glands might facilitate SARS-CoV-2 cellular uptake. These are above all furins, neuropilin-1, C-type lectins [47], and scavenger receptor B type 1 (SRB1) [48]. Alternatively, SARS-CoV-2 can also enter cells through an endosomal route, which process requires cathepsin L expression and a low pH to promote its release from endosomes [49].

The expression of these key receptors in adrenal cells suggests that SARS-CoV-2 might target adrenal glands [45, 50]. Indeed, SARS-CoV-2 infection was detected in the adrenal glands of patients with COVID-19 using several techniques including in situ RNA and DNA hybridization, immunohistochemistry, and RT-qPCR [25, 28, 32]. In particular, SARS-CoV-2 was found in scattered cell populations of adrenocortical cells and in endothelial cells [28, 32]. Moreover, SARS-CoV-2 was also shown to infect human adrenocortical cell lines [28, 32].

However, a limited number of SARS-CoV-2 positive cells in the adrenal cortex and the lack of widespread damage to adrenocortical cells of COVID-19 patients, suggest that the development of AI due to direct cytopathic actions of this virus is less likely.

Adrenal gland function in patients with COVID-19

The mechanisms leading to the dysfunction of the HPA axis during critical illness are complex and poorly understood [51]. As indicated above, a subset of patients may have structural damage to the adrenal gland from either hemorrhage or infarction, leading to a primary insufficiency, whereas in other patients reduced cortisol production may be caused by secondary adrenal insufficiency resulting from damage to the pituitary glands or to the hypothalamus (tertiary AI). In fact, the cases of secondary adrenal insufficiency induced by sudden hemorrhages or infarctions of the pituitary gland (apoplexies) were already reported in patients with COVID-19 [52, 53].

Considering that the pituitary gland and hypothalamus express ACE2 and TMPRSS2, it is also highly plausible that SARS-CoV-2 can infect these components of the HPA axis [54]. Particularly because SARS-CoV-1 spike protein was already found to be able to cross the blood-brain barrier in experimental settings [55], and that SARS-CoV-1 had been already detected in both of these organs [56]. Although no direct evidence of SARS-CoV-2 infection in those organs exists up to date, some histopathological studies at least suggest such a possibility [57].

In many critically ill patients including patients with head trauma, skin burns, and major surgery but predominantly with sepsis and septic shock, a reversible impairment of the HPA axis is being diagnosed, which cannot be explained by structural damage to the adrenal gland, the pituitary, or the hypothalamus [58]. CIRCI is usually associated with systemic inflammation and is currently considered to result from the HPA axis dysfunction, reduced cortisol metabolism, and tissue resistance to glucocorticoids [16]. The prevalence and existence of CRICI remain controversial as well as the criteria used for its diagnosis, which are a delta total serum cortisol of < 9 µg/dl after ACTH administration (250 µg), or random total cortisol of < 10 µg/dl [24]. Although measurement of serum-free cortisol and cortisone, for example, in the saliva is increasingly considered a better indicator of stress, it is not yet fully implemented in routine diagnostics of stress levels in critically ill patients.

A limited number of studies employing a high number of patients, addressing adrenal hormone production during COVID-19 have been published so far. As summarized in ▶ **Table 2**, the results of those studies are also quite heterogeneous and require a careful interpretation. In particular, a study with 535 critically ill patients (403 with severe COVID-19 and 132 SARS-CoV-2 negative controls), revealed an adequate cortisol response [59]. However, since ACTH levels were not determined in those patients a potential AI might be concealed, for example, by reduced cortisol metabolism. Moreover, patients having cortisol levels exceeding 26.97 µg/dl (744 nmol/l) cut-off were more likely to die [59], suggesting that

▶ **Table 2** Summary of clinical studies showing the HPA activity in patients with COVID-19.

Author/Year/Reference	Number of patients and main findings	Mortality Risk and other correlations
Kumar et al. 2021 [23]	Adrenal insufficiency was found in 34/235 (14.5 %) patients. Cortisol level lower than 3 µg/dl was found in 7.2 % (17/235) of patients. Furthermore, 18.3 % of patients (3/17) had delta cortisol < 9 µg/dl.	Median serum total cortisol levels were 858 nmol/l in non-survivors and 676 nmol/l in survivors of severe COVID-19. Robust adrenal response correlated with severity of COVID-19.
Tan et al. 2020 [59–60]	Adequate total cortisol values were detected in 385/403 patients, whereas 18/403 patients matched the CIRCI criterion.	Among severely affected patients with COVID-19, those with cortisol levels exceeding 26.97 µg/dl (744 nmol/l; 135/403) had an increased risk of death.
Guven et al. 2021 [61]	Median cortisol levels among patients admitted to ICU with COVID-19 (n = 144) was higher than those without COVID-19 (n = 141) "21.84 µg/dl vs. 16.47 µg/dl".	Patients with COVID-19 having cortisol levels exceeding 31 µg/dl (855 nmol/l) (30/144) had enhanced mortality.
Alzahrani et al. 2021 [62]	9/28 (32 %) patients had morning cortisol levels below 10.8 µg/dl (300 nmol/l) indicating CIRCI.	Cortisol and ACTH levels were lower in patients with more severe COVID-19.
Ahmadi et al. 2022 [63]	Among 154 hospitalized patients, normal cortisol level (15.6 µg/dl) and ACTH (11.4 pg/ml) were observed. Lower cortisol level was observed in a non-survival group (11.4 µg/dl, 9.09 %) vs. Survivals (16.7 µg/dl).	Enhanced cortisol but not ACTH levels correlated with lower mortality among patients with COVID-19.
Das et al. 2021 [64]	In a group of patients with moderate-severe COVID-19 (n = 35), 38.5 % had hypocortisolism defined as cortisol < 15 µg/dl (414 nmol/l), vs. 6.8 % in a group with mild disease (n = 49) (cortisol < 6 µg/dl).	Secondary hypoadrenalism in the moderate-to-severe group suggests either hypophysitis or reduced cortisol clearance associated with GR resistance
Yavropoulou et al. 2022 [65]	Morning salivary free cortisol levels did not differ between the COVID-19 patients (n = 52) and the healthy group (n = 33), but the COVID-19 group had higher median levels of the evening and nocturnal salivary cortisol compared to controls [0.391 vs. 0.081 µg/dl, and 0.183 vs. 0.054 µg/dl, respectively]	Increased evening and nocturnal but not morning cortisol secretion may occur in even clinically mild COVID-19.

elevated GC levels might reflect the severity of the disease. In this cohort, only 18 patients with COVID-19 and 13 control ICU patients fulfilled the criteria of CIRCI [60]. Higher cortisol values among patients with severe COVID-19 were also observed in other studies [23, 61]. However, the frequency of CIRCI (14.5 %) in the latter cohort was higher [23].

Other authors reported partly opposite findings. For example, in one study patients with more severe COVID-19 had lower cortisol and ACTH concentrations, suggesting a direct link between the COVID-19 infection and impaired glucocorticoid response. Among them, 32 % (9/28) of patients had central adrenal insufficiency and fulfilled the criteria of CIRCI (< 10.8 µg/dl) [62]. Similarly, in another study with a larger number of COVID-19 patients (n = 154), significantly lower cortisol but not ACTH plasma levels were found among non-survivors [63]. Finally, adrenal hypocortisolism (cortisol < 15 µg/dl in moderate-to-severe group vs. < 6 µg/dl in mild group), was more frequently found (38.5 vs. 6.8 %) in patients with severe COVID-19 (n = 35) as compared to patients with mild disease group (n = 49) [64].

In contrast to the majority of studies that only measured morning total cortisol concentrations, a recent study determined the free salivary cortisol levels of COVID-19 patients at different time points. Interestingly, this study reported elevated levels of free cortisol also during the evening (0.391 vs. 0.081 µg/dl) and nocturnal (0.183 vs. 0.054 µg/dl) time points in the mild-to-moderate COVID-19 group compared to healthy individuals [65]. However, ACTH, DHEA, and aldosterone concentrations were not altered suggesting an intact adrenal structure [65]. On the contrary, a possible disruption of adrenocortical steroidogenesis in patients with more severe COVID-19 was recently reported [66]. Particularly, the measurement of adrenal steroids by a liquid chromatography-tandem mass spectrometry revealed a significantly increased 11-deoxycortisol concentrations compared to cortisol in those patients. However, these results require further validation [66].

Altogether, adrenal gland function during COVID-19 is mostly preserved among patients with COVID-19. Furthermore, elevated plasma levels of total cortisol might be a good indicator of acute COVID-19 disease progression and mortality risk. However, considering the heterogeneity of results from available clinical studies reporting cortisol levels in patients with COVID-19, the design of larger and multicenter studies might help to solve those discrepancies. Contrary to CIRCI, primary, secondary or tertiary adrenal insufficiency induced by hemorrhage or infarctions occurring within the HPA axis are relatively rare complications of COVID-19. Nevertheless, considering the high lethality related to the sudden onset of PAI, and the proinflammatory and thrombotic nature of COVID-19, it is crucial to raise awareness about AI diagnosis among intensive care physicians [67]. Moreover, it is important to sensitize patients with acute and post-acute COVID-19 about symptoms of adrenal insufficiency. Especially considering the possibility of late-onset of central hypocortisolism [68].

Glucocorticoid treatment and the HPA axis dysfunction

Many drugs and their combinations, including antivirals (remdesivir or paxlovid), hydroxychloroquine, interferons regiments, or anti-interleukin 6-receptor monoclonal antibody (tocilizumab) were approved by the Food and Drug Agency (FDA) in an emergency use authorization (EUA) mode. However, results of the first larger clinical studies demonstrated their limited effectiveness in reducing mortality, initiation of ventilation, or length of stay in hospital [69, 70]. In opposite, the use of SARS-CoV-2 neutralizing monoclonal antibodies was associated with a reduced incidence of COVID-19–related hospitalization and death among high-risk ambulatory patients [71], as well as a lower number of symptomatic COVID-19 cases [72], compared with a placebo group. Nonetheless, their high costs and low availability might limit their potential use [73]. On that account, the use of glucocorticoids, which are inexpensive and most commonly used drugs, got prompt attention.

Most importantly, results of recent clinical studies strongly suggest that GC treatment might be effective in preventing clinical deterioration in patients with COVID-19. Particularly, a single daily dose of dexamethasone (6 mg) for up to 10 days reduced 28-day mortality among patients requiring invasive mechanical ventilation [12]. Furthermore, an early inhalation with budesonide reduced the likelihood of needing urgent medical care and recovery time among patients with mild COVID-19 [74]. It has also reduced hospital admissions or deaths of symptomatic persons with COVID-19 in the community who are at higher risk of complications [75]. These studies collectively demonstrated the benefit of adrenal steroids in improving the outcome of patients with COVID-19.

Despite the protective role of glucocorticoids for the survival of some patients with COVID-19, excessive cortisol production (Cushing syndrome) or prolonged GC treatment might enhance COVID-19 – associated mortality through induction of immune deficiency, enhanced risk of secondary infections, and development of HPA axis dysfunction [50]. Prolonged or poorly monitored GCs intake have also other serious side effects, including among others psychosis, hyperglycemia and, the development of iatrogenic adrenal insufficiency [76]. In particular, patients with severe COVID-19, who received dexamethasone have enhanced risk of developing a tertiary adrenal insufficiency. Although low to moderate doses of this potent synthetic glucocorticoid such as those used in the Recovery study (6 mg daily for 10 days) should not cause HPA axis suppression upon withdrawal. However, development of AI following low doses and short durations of glucocorticoids was already described in the literature. Furthermore, it was shown that 50 % of patients who recovered from acute COVID-19 and received dexamethasone therapy experienced severe complications including severe fatigue. Therefore, higher doses of glucocorticoids, particularly dexamethasone, should be avoided in patients who do not require oxygen support.

Limited information is available regarding the HPA axis function and cortisol levels in patients who received glucocorticoids during COVID-19 hospitalization. To the best of our knowledge, only one study assessed cortisol concentrations and the HPA function in those patients and found rather normal ACTH and cortisol values as well as an adequate adrenal response to the ACTH test 3 months after presentation with COVID-19, regardless of reported symptoms [77]. However, in this study the possible induction of iatrogenic adrenal insufficiency was not taken into consideration. In fact, exclusion criteria prevented enrolment of patients with continuous glucocorticoid treatment after recovery from COVID-19. This could potentially explain opposite findings reported by a study with post

COVID patients infected by related coronavirus. In this report around 39.3 % (24/61) of patients who recovered from SARS-CoV-1 infection developed hypocortisolemia that lasted for at least 3 months and resolved after 1 year. In those patients, low cortisol levels were also associated with decreased ACTH concentrations, suggesting central adrenal insufficiency [78].

Due to an insufficient number of studies, which evaluated the function of the HPA axis in patients with COVID and especially in those receiving a prolonged GC treatment, it is currently impossible to estimate the true incidence of adrenal insufficiency. Providing such risk assessment is, however, of paramount importance because GC therapy might be continued for weeks in many patients with COVID-19 regardless of their infection status. Those patients are at risk of developing secondary or tertiary adrenal insufficiency, particularly when the GC therapy is poorly monitored in outpatient settings or was inadequately tapered off.

In summary, the adrenal gland is a pronounced target of SARS-CoV-2. The infection promotes local inflammation and vascular damage in this vital endocrine organ. However, limited and scattered pattern of SARS-CoV-2 infection and lack of widespread adrenocortical cell damage found at autopsies suggest that complete loss of adrenal gland function is less likely. The limited number of studies showing an adequate cortisol secretion supports this assumption. However, adrenal insufficiency may be an important and yet frequently undetected complication of COVID-19. As demonstrated by several case studies and clinical reports, various forms of AI may manifest during hospitalization and also in the recovery phase of COVID-19. Therefore, the potential development of AI in patients with COVID-19 and in particular after tapering off GC therapy should be considered. Furthermore, larger and multi-center studies are required to estimate the risk of AI development in those patients.

Conflict of Interest

The authors declare that they have no conflict of interest.

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