JBCR Journal of Biomedical & Clinical Research
Journal of Medical University of Pleven

Journal of Biomedical and Clinical Research 18(1): 11–21 (2025)
DOI: 10.3897/jbcr.e135548

Review Article

Changes in cortisol secretion and the role of the glucocorticoid receptor in the development of the immune response in patients with SARS-CoV-2 infection

Malvina Todorova[1], Katya Todorova[1]

1 *Clinic of Endocrinology and Metabolic Diseases, University Hospital "Dr G. Stranski", Faculty of Medicine, Medical University – Pleven, Pleven, Bulgaria*
Corresponding author: Malvina Todorova (malvinatodorova13@gmail.com)

Summary

With the outbreak of the COVID-19 pandemic, the scientific community has directed its attention towards studying the impact of the causative agent, SARS-CoV-2, on the endocrine system. It has been proven that the virus exhibits organotropism towards the cortex of the adrenal glands, causing tissue damage and hormonal dysfunction. The aim of this exposition is to address the question of whether SARS-CoV-2 causes disruptions in the hormonal regulation of glucocorticoid hormones. Based on a thorough review of the current literature, it is suggested that the virus could potentially directly damage the hypothalamus, leading to a disruption in the regulation of the hypothalamic-pituitary-adrenal axis. The decrease in cortisol secretion is a secondary effect. As a result, there is a loss of stress-induced cortisol elevation due to the inflammatory process and an increased risk of adrenal crisis. On the other hand, inflammatory cytokines synthesized during the inflammatory process could stimulate cortisol secretion through an ACTH-independent mechanism. The magnitude of the biological response is influenced by the newly emerged resistance of cortisol receptors, disturbances in intracellular cortisol signaling, and dysregulation between ACTH and cortisol secretion. The detailed study of functional changes in cortisol secretion in response to SARS-CoV-2-associated inflammation provides a new horizon for scientific research following recovery from COVID-19.

Key words: ACTH, adrenal gland, cortisol, SARS-CoV-2 infection

Academic editor: Galya Stavreva
Received: 27 August 2024
Accepted: 29 November 2024
Published: 5 February 2025

Citation: Todorova M, Todorova K (2025) Changes in cortisol secretion and the role of the glucocorticoid receptor in the development of the immune response in patients with SARS-CoV-2 infection. Journal of Biomedical and Clinical Research 18(1): 11–21. https://doi.org/10.3897/jbcr.e135548

Introduction

Coronaviruses are part of a large family of viruses. In addition to the two known forms of the virus, SARS-CoV-1, and MERS-CoV, the newly discovered SARS-CoV-2, the virus responsible for COVID-19, was identified in 2019. Numerous scientific publications have demonstrated the interrelationships between the inflammatory status associated with SARS-CoV-2 and adrenal dysfunction. It has also been proven that the most important element in initiating COVID-19 infection is the binding of the SARS-CoV-2 virus to the angiotensin-converting enzyme 2 (ACE2) receptor. It is expressed in various tissues, and multiple studies have shown increased expression of the ACE2 receptor in several endocrine glands, including the adrenal glands, suggesting that SARS-CoV-2 exhibits

some organotropism towards them, causing tissue damage and subsequent hormonal dysfunction (Oguz and Yildiz 2023).

The human adrenocortex expresses not only the ACE2 receptor but also transmembrane serine protease (TMPRSS2) (Jensterle et al. 2022), another key component for viral invasion. The latter synergizes with the ACE2 receptor to accelerate viral entry into adrenocortical cells. Expression of both key viral receptors has been found in the adrenal cortex, and more specifically in zona fasciculata and zona reticularis (Stefunkova et al. 2021), mainly in epithelial but also in mesenchymal and endothelial cells, making the hypothalamic-pituitary-adrenal axis (HPA) one of the main endocrine targets of SARS-CoV-2, determining further consequences for the organism (Mao et al. 2020; Wong et al. 2021; Jensterle et al. 2022).

The specific pathophysiological mechanisms of viral damage are diverse and can include:

1. Direct cytopathic effects of SARS-CoV-2 on the adrenal glands with the development of vasculitis or adrenal vessel thrombosis

A number of studies prove the possibility of the development of adrenal insufficiency during SARS-CoV-2 infection.

Evidence for such changes is provided by available autopsy studies reporting adrenal histomorphological changes that can be attributed to SARS-CoV-2 infection (Gu and Korteweg 2007).

The leading changes described in the adrenal glands include acute fibrinoid necrosis of small vessels, mainly affecting arterioles in the adrenal parenchyma, capsule, and periadrenal adipose tissue. Additional findings include subendothelial vacuolization and apoptosis, without significant signs of inflammation, parenchymal infarcts, or thrombosis.

Recently, there have also been reported cases of adrenal hemorrhage and infarction resulting from COVID-19 infection (Sharrack et al. 2020; Leyendecker et al. 2020), further highlighting that COVID-19 can affect the adrenal glands through multiple factors, including hypercoagulation, direct endothelial injury, microvascular thrombosis, and increased susceptibility of the adrenal glands to infarction or hemorrhage due to their vascular anatomy (Hashim et al. 2021).

2. Adrenal insufficiency is secondary to central dysfunction

Leow et al. (2005) conducted a follow-up study on individuals who had recovered from SARS-CoV-2 infection. Three months post-recovery, nearly half of the patients exhibited hypocortisolism, predominantly of central origin indicated by low ACTH levels (Hashim et al. 2021). Notably, the majority of these patients did not receive systemic steroids during their treatment for SARS-CoV-2 infection, excluding the possibility of HPA axis suppression due to exogenous corticosteroid administration. Interestingly, the hypocortisolism observed was transient and resolved within a year for approximately two-thirds of the patients (Hashim et al. 2021).

Another study also documented impaired adrenocortical response in 28 COVID-19 patients, demonstrating central hypocortisolism with decreased plasma cortisol and ACTH levels. Several potential mechanisms have been

proposed to explain COVID-19-associated central hypocortisolism. Given that the ACE2 and TMPRSS2 receptors, crucial for SARS-CoV-2 entry into host cells, are also present in the hypothalamus and pituitary gland, direct viral cytopathic effects on these areas are plausible. Autopsy studies of COVID-19 patients have reported necrosis and infarction in pituitary regions, supporting the hypothesis of direct viral damage. Moreover, genomic sequences of SARS-CoV-2 have been detected in the hypothalamus, further suggesting virus-induced damage to central nervous system structures (Alzahrani et al. 2020).

3. Immune-mediated inflammation

Several authors have proposed the occurrence of reversible immune-mediated hypophysitis. Recent research in male mice indicated that the S1 subunit of SARS-CoV-2 spike protein can traverse the blood-brain barrier, localizing in critical areas such as the cerebral cortex, hypothalamus, and hippocampus, which play pivotal roles in regulating the HPA axis. Autopsy studies on patients infected with severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) revealed reduced counts of somatotroph, thyrotroph, and corticotroph cells in the pituitary gland, along with altered immunoreactivity of their respective hormones, potentially indicating similar changes in SARS-CoV-2 infection. Conversely, no significant changes were observed in mammotroph and gonadotroph pituitary cells (Jensterle et al. 2022).

Considering the neurological manifestations, it is evident that both the hypothalamus and pituitary gland are impacted directly or via immune-mediated mechanisms in COVID-19 infection. Elevated production of proinflammatory cytokines, notably IL-1, IL-6, TNF-alpha, monocyte chemoattractant protein 1 (MCP-1), and granulocyte-colony stimulating factor (G-CSF), has been shown to suppress ACTH release, thereby attenuating its effects on adrenal tissue (Kunz-Ebrecht et al. 2003; Glaser and Kiecolt-Glaser 2005; Hänsel et al. 2010; DeSantis et al. 2012; Vakhshoori et al. 2021).

According to additional researchers, increased levels of inflammatory cytokines can stimulate the HPA axis and promote the release of cortisol. This cortisol release is thought to suppress the inflammatory response by inhibiting nuclear transcription factor-β (NF-β) signaling (Katz et al. 2022). Thus, cortisol is believed to serve as a crucial link between stress and inflammation, with levels of cortisol and cytokines potentially indicating an imbalance in the immune-endocrine system during stressful conditions (Wolkow et al. 2015). Multiple studies have illustrated the significance of a reciprocal feedback loop between cytokines and cortisol in maintaining the functionality of the HPA axis and immune system homeostasis (Reale et al. 2020).

4. Molecular mimicry

Another pathogenetic mechanism that has been suggested to inhibit the adrenal response to stress, causing relative adrenocortical insufficiency is the molecular mimicry of specific genomic sequences of SARS-CoV-2 and amino acid sequences of the ACTH molecule. This may lead to a cross-reactive immune response with a subsequent decrease in circulating levels of ACTH (Fox 1976; Jensterle et al. 2022; Vakhshoori et al. 2021).

5. A dissociation between cortisol and ACTH regulation

When assessing potential HPA axis dysregulation in COVID-19 patients, it's important to consider the phenomenon of cortisol and ACTH dissociation. In severe illness, cortisol secretion can depend on factors other than ACTH, leading to this dissociation. Cytokines, which are typically elevated in more severe cases, can independently stimulate cortisol production. Additionally, reduced peripheral metabolism of cortisol, which extends its systemic half-life, is another ACTH-independent mechanism that can elevate cortisol levels and subsequently reduce ACTH through feedback inhibition. A study noted that individuals with moderate to severe COVID-19 infection often had lower ACTH levels but higher cortisol levels, aligning with existing evidence of cortisol and ACTH dissociation in severe illnesses (Jensterle et al. 2022).

6. The anatomical location of the vascular network of the adrenal glands

The anatomical configuration of the adrenal glands' vascular network is unique. These glands receive blood from a network of arterioles branching from several major arteries, yet they have only one suprarenal vein for blood outflow (Fox 1976). During severe stress, such as that caused by COVID-19, venous drainage may be compromised due to ACTH-induced arteriolar dilation, resulting in vascular stasis and potential adrenal damage (Wepler et al. 2020; Vakhshoori et al. 2021;). Cholesterol, primarily in the form of high-density lipoprotein (HDL), is essential for cortisol production; therefore, reduced HDL-cholesterol levels in severe illnesses can contribute to adrenal insufficiency (Vassiliadi et al. 2021).

The interplay between SARS-CoV-2 and the host immune defense

1. Immune inflammation and COVID-19 infection

In numerous COVID-19 cases, the host's immune response struggles to properly regulate the increasing inflammation. This inadequate response may result in an overly intense inflammatory state, characterized by elevated levels of proinflammatory cytokines, which further amplify the inflammation. Consequently, coagulation pathways become activated, leading to a heightened risk of thrombotic events. This hyperinflammatory condition, often referred to as a cytokine storm, is commonly observed in patients who experience rapid clinical deterioration, frequently resulting in fatal outcomes (Savla et al. 2021).

Specific to the SARS-CoV-2 virus is that it can destabilize the Th1 helper T-lymphocyte response, mediated by the release of various interferons but unexpectedly shows an increase in the levels of various chemokines (Sher et al. 2023).

This specific feature may be the main weapon for virus invasion and replication.

Recent studies have shown that SARS-CoV-2 causes lesions and atrophy of lymphoid tissue in the human body, such as the lymph nodes and spleen, subsequently reducing the production and effects of T cells (Sher et al. 2023).

The main feature of both mild and severe COVID-19 infection is lymphocytopenia, characterized by significantly reduced peripheral T-cell levels, including low CD4+ and CD8+ T-lymphocytes, NK-cells, and B-lymphocytes. Lymphocytopenia

correlates with symptom severity and T-cell count, and may therefore serve as a predictor of adverse disease outcomes (Gil-Etayo et al. 2021).

The developing cytokine storm has been observed mainly in patients with severe infection and includes the synthesis of pro-inflammatory cytokines, the release of interleukins, and the activation of coagulation pathways, subsequently increasing the risk of thrombotic complications (Savla et al. 2021).

2. Imbalance between Th1 and Th2 in the setting of COVID-19 infection

According to some studies, the Th1 response is suppressed, while the Th2 response is enhanced in COVID-19. In severe cases, this suppression of Th1 responses may result in inadequate production of IFN-γ and other Th1 cytokines, weakening cell-mediated immunity, which is essential for controlling viral infections. Conversely, an increase in Th2 cytokines, such as IL-4, IL-5, and IL-10, has been observed in some patients with severe COVID-19. IL-10, a potent anti-inflammatory cytokine, can further suppress the Th1 response, contributing to immune system dysregulation (Hosseini et al. 2022).

Persistent viral stimulation and chronic inflammation can lead to the exhaustion and depletion of T-cells, including Th1 and Th2 cells, which further complicates the immune response and recovery. Additionally, the extent of lymphopenia is linked to the severity of the patient's condition. While many acute viral infections lead to temporary lymphopenia that typically resolves rapidly, lymphopenia associated with COVID-19 can be more pronounced and enduring compared to that seen in many other viral infections (Gil-Etayo et al. 2021).

From the above, it is clear that T-cells exhibit reduced functionality. Observed changes in individual T-cell subpopulations disrupt the balance between pro-inflammatory and anti-inflammatory responses. Despite the suppressed Th1 response in severe cases of COVID-19, the immune system reacts with the hyper-inflammatory response, leading to a massive release of pro-inflammatory cytokines and the subsequent development of a cytokine storm.

Impact of downstream effects of glucocorticoid receptor dysfunction on organ function in critical illness-associated systemic inflammation

1. Resistance to cortisol action at the glucocorticoid receptor level and changes in post-receptor signaling

Glucocorticoid hormones exert their immunological, metabolic, and hemodynamic effects through the intracellular glucocorticoid receptor (GCR), which is widely distributed throughout the body. This receptor is part of the nuclear transcription factor superfamily and is characterized by a carboxy-terminal region responsible for ligand binding, a central DNA-binding domain that interacts with specific DNA sequences in target genes, and a hypervariable N-terminal region (Wepler et al. 2020).

The human glucocorticoid receptor (hGR) gene is located on chromosome 5 and contains 9 exons. Alternative splicing at exon 9 gives rise to two highly similar isoforms of the receptor, known as α and β. The hGRα isoform is the classical glucocorticoid receptor, functioning as a ligand-dependent transcription factor (Wepler et al. 2020).

Glucocorticoid receptor – beta (hGRβ) does not bind to glucocorticoid hormones and exerts a dominant-negative effect on the transcriptional activity of hGRα.

After receptor binding to cortisol (Pal 2022), the receptor-ligand complex is translocated into the nucleus, where it binds to specific DNA sequences in the promoter regions of target genes and stimulates or represses gene transcription (Vassiliadi et al. 2021).

These sequences, known as glucocorticoid response elements (GREs), are often characterized by the palindromic sequence CGTACAnnnTGTACT. They play a crucial role in modulating the immune response by exerting strong anti-inflammatory effects. This is achieved through mechanisms that involve both the innate and adaptive immune systems. GREs contribute to the regulation of anti-inflammatory proteins via DNA-dependent processes, non-genomic modulation of inflammation, and direct interference with the transcription of factors like nuclear factor kappa beta. This results in the suppressed expression of proinflammatory cytokines, including IL-1, IL-2, IL-6, IL-8, tumor necrosis factor, interferon-gamma, vascular endothelial growth factor, and prostaglandins. These cytokines are closely linked to the severity of COVID-19 infection (Jensterle et al. 2022; Katz et al. 2022).

This transcriptional activation or repression ultimately leads to the termination of the inflammatory response.

In a recent investigation, researchers obtained sequencing data of the functionally active GR subunit mRNA from bronchoalveolar lavage samples in patients infected with SARS-CoV-2. The results indicated a reduction in this mRNA in patients with severe COVID-19 compared to those with milder cases. The authors proposed that this reduction might reflect a pathological down-regulation of the body's natural immunomodulatory mechanism in severe cases. They suggested that this mechanism could be pharmacologically restored through appropriate and timely corticosteroid treatment, potentially lowering the risk of long-term complications (Jensterle et al. 2022).

Moreover, because GR is widely expressed and has multiple effects, there are many documented side effects linked to glucocorticoid treatment, which primarily depend on the dosage and duration of the treatment (Pal and Banerjee 2020; Pal 2022).

The range of abnormalities may vary from early signs of hypercorticism in patients with individual hypersensitivity to extended suppression of the HPA axis following the discontinuation of glucocorticosteroid therapy (Ferraù et al. 2021).

Consequently, in January 2020, the World Health Organization (WHO) released provisional guidelines advising against the routine administration of glucocorticoids for treating COVID-19 patients (Katz et al. 2022).

2. Clinical significance of GCR in state of COVID-19 inflammation

Local glucocorticoid availability is determined by the amount of circulating ligands and the tissue-specific expression of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD 1), which converts inactive cortisone to active cortisol. The tissue-specific actions of glucocorticoids and the glucocorticoid receptor (GR) are influenced by local cellular cortisol levels, GR expression, and functionality (Bamberger et al. 1996).

In patients with COVID-19, evolving glucocorticoid resistance is characterized by an inadequate GR response to regulate GR-responsive gene transcription despite sufficient plasma cortisol levels. This resistance and the subsequent effect of cortisol may stem from reduced GR-α mRNA and protein expression, decreased expression of receptor subtypes, reduced GR affinity for cortisol, and issues with nuclear translocation and/or DNA binding (Bamberger et al. 1996).

Resistance to glucocorticoids is also observed in sepsis and may play a significant role in the ineffectiveness of glucocorticoids to improve the condition of septic patients. There is evidence indicating a correlation between the degree of glucocorticoid resistance and the severity and mortality of diseases, such as acute respiratory distress syndrome (ARDS) and septic shock (Pal 2022; Ilias et al. 2023).

In addition to intracellular glucocorticoid resistance due to insufficient GR-α-mediated anti-inflammatory activity, a combination with increased GR-β expression in circulating cells, which in turn leads to an imbalance between GRα and GRβ, has also been found in critically ill patients despite apparently adequate levels of circulating cortisol (Annane et al. 2017).

COVID-19-related diseases of the adrenal gland:

1. Cortisol insufficiency associated with critical illness (CIRCI)

CIRCI is a characteristic manifestation of SARS-CoV-2-induced inflammation. The consequence of this is the loss of the normal adaptive response, expressed in a stress-induced rise in cortisol secretion as a result of the inflammatory process, as well as an increased risk of the occurrence of an adrenal crisis (Hakan et al. 2021).

The basis of CIRCI is a dysregulation of the HPA axis during acute viral infection with SARS-CoV-2, which underlies an uncontrolled cytokine storm characterized by hyperinflammation and immunosuppression, changes in cortisol metabolism, and tissue resistance to the action of glucocorticoids at the receptor level (Hakan et al. 2021).

During severe COVID-19 infection, as well as in other acute conditions like sepsis, septic shock, acute respiratory distress syndrome (ARDS), severe community-acquired pneumonia, and various shock states, it has been observed that these conditions can contribute to critical illness-related corticosteroid insufficiency (CIRCI). Administering pharmacological corticosteroids has been shown to lower the risk of CIRCI and reduce the potential long-term effects related to severe COVID-19 infection (Hakan et al. 2021).

2. Adrenal insufficiency

Numerous studies tracking patients who have recovered from SARS-CoV-2 infection describe central hypocortisolism, confirmed by established low levels of ACTH and cortisol. Consequently, decreased cortisol secretion appears to be a secondary effect (Alzahrani et al. 2020). It is noteworthy that most of the studied patients had not received any systemic steroids during the treatment of SARS-CoV-2 infection, which rules out the possibility of HPA axis suppression due to the administration of exogenous corticosteroids. Interestingly, the developed hypocortisolism was transient and resolved in two-thirds of the patients within one year (Hashim et al. 2021).

Another study also reports impaired adrenal cortical response in 28 patients with COVID-19 infection, with plasma concentrations of cortisol and ACTH indicating central hypocortisolism. Hypotheses regarding the etiology of COVID-19-related central hypocortisolism are based on the fact that the expression of the two receptors through which SARS-CoV-2 enters host cells, namely ACE2 and TMPRSS2, are also found in the hypothalamus and pituitary gland, making them potential direct cytopathic targets of SARS-CoV-2 (Kanczkowski et al. 2022).

This is further supported by numerous autopsy studies of patients infected with the COVID-19 virus, where areas of infarction and necrosis in the pituitary gland, neuronal degeneration, and edema have been observed, along with genomic sequences of SARS-CoV-2 in the hypothalamus, demonstrating direct viral-induced damage (Abdel-Moneim and Hosni 2021; Kanczkowski et al. 2022).

Moreover, increased stimulation of the pituitary gland observed in the state of infectious stress may increase blood flow to the pituitary gland, leading to acute apoplexy with subsequent panhypopituitarism. Therefore, COVID-19-associated prothrombotic and endothelial systemic disorders could be accelerating risk factors for pituitary apoplexy, particularly in patients with pituitary adenomas, especially those undergoing anticoagulant therapy or those with prolactin-secreting macroadenomas on dopamine agonist therapy (Frara et al. 2021).

Conclusion

Clinical studies of changes in adrenocortical secretion in patients with COVID-19 are ongoing, and data on the dynamics of cortisol and ACTH secretion are not yet completely clear. However, clinicians should be vigilant for the possibility of developing relative adrenal insufficiency in patients who have had and survived COVID-19 infection and have a high index of suspicion for developing adrenal insufficiency in patients with COVID-19 exhibiting characteristic symptoms, such as hyponatremia, hyperkalemia, and hypotension (Mao et al. 2020).

The detailed study of the functional changes in cortisol secretion in response to SARS-CoV-2-induced inflammation provides a new horizon for research after surviving COVID-19. There are still many questions waiting to be answered, one of which is how the inflammatory status modulates adrenal glands function and to what extent adrenocortical impairments are temporary or permanent.

Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

Funding
No funding was reported.

Author contributions
Conceptualization: MST, KT.

Data availability
All of the data that support the findings of this study are available in the main text.

References

Abdel-Moneim A, Hosni A (2021) Insights into the possible impact of COVID-19 on the endocrine system. Archives of Physiology and Biochemistry 129: 998–1006. https://doi.org/10.1080/13813455.2021.1890131

Alzahrani AS, Mukhtar N, Aljomaiah A, Aljamei H, Bakhsh A, Alsudani N, Elsayed T, Alrashidi N, Fadel R, Alqahtani E, Raef H, Butt MI, Sulaiman O (2020) The Impact of COVID-19 Viral Infection on the Hypothalamic-Pituitary-Adrenal Axis. Endocrine Practice 27: 83–89. https://doi.org/10.1016/j.eprac.2020.10.014

Annane D, Pastores SM, Arlt W, Balk RA, Beishuizen A, Briegel J, Carcillo J, Christ-Crain M, Cooper MS, Marik PE, Umberto Meduri G, Olsen KM, Rodgers SC, Russell JA, Van den Berghe G (2017) Critical illness-related corticosteroid insufficiency (CIRCI): a narrative review from a Multispecialty Task Force of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM). Intensive Care Medicine 43: 1781–1792. https://doi.org/10.1097/CCM.0000000000002737

Bamberger M, Schulte M, Chrousos P (1996) Molecular determinants of glucocorticoid receptor function and tissue sensitivity to glucocorticoids. Endocrine Reviews 17: 245–261. https://doi.org/10.1210/edrv-17-3-245

DeSantis AS, DiezRoux AV, Hajat A, Aiello AE, Golden SH, Jenny NS, Seeman TE, Shea S (2012) Associations of salivary cortisol levels with inflammatory markers: The multi-ethnic study of atherosclerosis. Psychoneuroendocrinology 37: 1009–1018. https://doi.org/10.1016/j.psyneuen.2011.11.009

Ferraù F, Ceccato F, Cannavò S, Scaroni C (2021) What we have to know about corticosteroids use during SARS-CoV-2 infection. Journal of Endocrinological Investigation 44: 693–701. https://doi.org/10.1007/s40618-020-01384-5

Fox B (1976) Venous infarction of the adrenal glands. Journal of Pathology 119: 65–89. https://doi.org/10.1002/path.1711190202

Frara S, Allora A, Castellino L, di Filippo L, Loli P, Giustina A (2021) COVID-19 and the pituitary. Pituitary 24: 465–481. https://doi.org/10.1007/s11102-021-01148-1

Gil-Etayo FJ, Suárez-Fernández P, Cabrera-Marante O, Arroyo D, Garcinuño S, Naranjo L, Pleguezuelo DE, Allende LM, Mancebo E, Lalueza A, Díaz-Simón R, Paz-Artal E, Serrano A (2021) T-helper cell subset response is a determining factor in COVID-19 progression. Frontiers in Cellular and Infection Microbiology 26: 624483. https://doi.org/10.3389/fcimb.2021.624483

Glaser R, Kiecolt-Glaser JK (2005) Stress-induced immune dysfunction: Implications for health. Nature Reviews Immunology 5: 243–251. https://doi.org/10.1038/nri1571

Gu J, Korteweg C (2007) Pathology and pathogenesis of severe acute respiratory syndrome. American Journal of Pathology 170: 1136–1147. https://doi.org/10.2353/ajpath.2007.061088

Hakan S, Mehmet S, Kerem E, Hasan A (2021) Critical illness-related corticosteroid insufficiency is common in Covid-19 and treatment provide survival benefit. Research Square. https://doi.org/10.21203/rs.3.rs-391924/v1

Hänsel A, Hong S, Cámara RJ, von Känel R (2010) Inflammation as a psychophysiological biomarker in chronic psychosocial stress. Neuroscience and Biobehavioral Reviews 35: 115–121. https://doi.org/10.1016/j.neubiorev.2009.12.012

Hashim M, Athar S, Gaba WH (2021) New onset adrenal insufficiency in a patient with COVID-19. British Medical Journal case reports 14: e237690. https://doi.org/10.1136/bcr-2020-237690

Hosseini P, Fallahi MS, Erabi G, Pakdin M, Zarezadeh SM, Faridzadeh A, Entezari S, Ansari A, Poudineh M, Deravi N (2022) Multisystem inflammatory syndrome and autoimmune diseases following COVID-19: Molecular mechanisms and therapeutic opportunities. Frontiers in Molecular Biosciences 14: 804109. https://doi.org/10.3389/fmolb.2022.804109

Ilias I, Vassiliou AG, Keskinidou C, Vrettou CS, Orfanos S, Kotanidou A, Dimopoulou I (2023) Changes in cortisol secretion and corticosteroid receptors in COVID-19 and non COVID-19 critically ill patients with sepsis/septic shock and scope for treatment. Biomedicines 11: 1801. https://doi.org/10.3390/biomedicines11071801

Jensterle M, Herman R, Janež A, Mahmeed A, Al-Rasadi K, Al-Alawi K, Banach M, Banerjee Y, Ceriello A, Cesur M, Cosentino F, Galia M, Goh SY, Kalra S, Kempler P, Lessan N, Lotufo P, Papanas N, Rizvi AA, Santos RD, Stoian AP, Toth PP, Viswanathan V, Rizzo M (2022) The relationship between COVID-19 and hypothalamic–pituitary–adrenal axis: A large spectrum from glucocorticoid insufficiency to excess—The CAPISCO international expert panel. International Journal of Molecular Sciences 23: 7326. https://doi.org/10.3390/ijms23137326

Kanczkowski W, Gaba WH, Krone N, Varga Z, Beuschlein F, Hantel C, Andoniadou C, Bornstein SR (2022) Adrenal gland function and dysfunction during COVID-19. Hormone and Metabolic Research 54: 532–539. https://doi.org/10.1055/a-1873-2150

Katz A, Altshuler D, Papadopoulos J, Amoroso N, Goldenberg R, Tarras E, Krolikowski K, Hagedorn J, Fridman D, Chen XJC, Iturrate E, Brosnahan SB (2022) The use of high-dose corticosteroids versus low-dose corticosteroids with and without Tocilizumab in COVID-19 acute respiratory distress syndrome. The Annals of Pharmacotherapy 57: 5–15. https://doi.org/10.1177/10600280221094571

Kunz-Ebrecht R, Mohamed-Ali V, Feldman J, Kirschbaum C, Steptoe A (2003) Cortisol responses to mild psychological stress are inversely associated with proinflammatory cytokines. Brain Behavior and Immunity 17: 373–383. https://doi.org/10.1016/S0889-1591(03)00029-1

Leow MK, Kwek DS, Ng AW, Ong KC, Kaw GJ, Lee LS (2005) Hypocortisolism in survivors of severe acute respiratory syndrome (SARS). Clinical Endocrinology 63:197–202. https://doi.org/10.1111/j.1365-2265.2005.02325.x

Leyendecker P, Ritter S, Riou M, Wackenthaler A, Meziani F, Roy C, Ohana M (2020) Acute adrenal infarction as an incidental CT finding and a potential prognosis factor in severe SARS-CoV-2 infection: A retrospective cohort analysis on 219 patients. European Radiology 31: 895–900. https://doi.org/10.1007/s00330-020-07226-5

Mao Y, Xu B, Guan W, Xu D, Li F, Ren R, Zhu X, Gao Y, Jiang L (2020) The adrenal cortex, an underestimated site of SARS-CoV-2 infection. Frontiers in Endocrinology 8: 593179. https://doi.org/10.3389/fendo.2020.593179

Oguz SH, Yildiz BO (2023) Endocrine disorders and COVID-19. Annual Review of Medicine 74: 75–88. https://doi.org/10.1146/annurev-med-043021-033509

Pal R (2022) COVID-19, hypothalamo-pituitary-adrenal axis and clinical implications. Endocrine 68: 251–252. https://doi.org/10.1007/s12020-020-02325-1

Pal R, Banerjee M (2020) COVID-19 and the endocrine system: exploring the unexplored. Journal of Endocrinological Investigation 43: 1027–1031. https://doi.org/10.1007/s40618-020-01276-8

Reale M, Costantini E, D'Angelo C, Coppeta L, Mangifesta R, Jagarlapoodi S, Di Nicola M, Di Giampaolo L (2020) Network between cytokines, cortisol and occupational stress in gas and oilfield workers. International Journal of Molecular Sciences 21: 1118. https://doi.org/10.3390/ijms21031118

Savla SR, Prabhavalkar KS, Bhatt LK (2021) Cytokine storm associated coagulation complications in COVID-19 patients: Pathogenesis and management. Expert Review of Anti-Infective Therapy 19: 1397–1413. https://doi.org/10.1080/14787210.2021.1915129

Sharrack N, Baxter T, Paddock M, Uchegbu E (2020) Adrenal hemorrhage as a complication of COVID-19 infection. British Medical Journal Case Reports 13: e239643. https://doi.org/10.1136/bcr-2020-239643

Sher EK, Ćosović A, Džidić-Krivić A, Farhat EK, Pinjić E, Sher F (2023) Covid-19 as a triggering factor of autoimmune and multi-inflammatory diseases. Life Sciences 319: 121531. https://doi.org/10.1016/j.lfs.2023.121531

Stefunkova N, Massanyi M, Roychoudhury S, Guha P, Greifova H, Tokarova K, Jambor T, Massanyi P, Lukac N (2021) Is there impact of the SARS-CoV-2 pandemic on steroidogenesis and fertility? Physiological Research 70: 161–175. https://doi.org/10.33549/physiolres.934756

Vakhshoori M, Heidarpour M, Bondariyan N, Sadeghpour N, Mousavi Z (2021) Adrenal insufficiency in coronavirus disease 2019 (COVID-19)-infected patients without preexisting adrenal diseases: A systematic literature review. International Journal of Endocrinology 2021: 2271514. https://doi.org/10.1155/2021/2271514

Vassiliadi DA, Vassiliou AG, Ilias I, Tsagarakis S, Kotanidou A, Dimopoulou I (2021) Pituitary-adrenal responses and glucocorticoid receptor expression in critically ill patients with COVID-19. International Journal of Molecular Sciences 22: 11473. https://doi.org/10.3390/ijms222111473

Wepler M, Preuss JM, Merz T, McCook O, Radermacher P, Tuckermann JP, Vettorazzi S (2020) Impact of downstream effects of glucocorticoid receptor dysfunction on organ function in critical illness-associated systemic inflammation. Intensive Care Medicine Experimental 8: 37. https://doi.org/10.1186/s40635-020-00325-z

Wolkow A, Aisbett B, Reynolds J, Ferguson SA, Main LC (2015) Relationships between inflammatory cytokine and cortisol responses in firefighters exposed to simulated wildfire suppression work and sleep restriction. Physiological Reports 3: e12604. https://doi.org/10.14814/phy2.12604

Wong DWL, Klinkhammer BM, Djudjaj S, Villwock S, Timm MC, Buhl EM, Wucherpfennig S, Cacchi C, Braunschweig T, Knüchel-Clarke R, Jonigk D, Werlein C, Bülow RD, Dahl E, von Stillfried S, Boor P (2021) Multisystemic cellular tropism of SARS-CoV-2 in autopsies of COVID-19. Patients Cells 10: 1900. https://doi.org/10.3390/cells10081900

World Health Organization (2020) Clinical Management of Severe Acute Respiratory Infection when Novel Coronavirus (2019-nCoV) Infection is Suspected: Interim Guidance. World Health Organization: Geneva, Switzerland. https://apps.who.int/iris/handle/10665/330893