REVIEW

Endocrine and metabolic complications of COVID-19: lessons learned and future prospects

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Abstract

Coronavirus disease 2019 (COVID-19) is well known for its respiratory complications; however, it can also cause extrapulmonary manifestations, including cardiovascular, thrombotic, renal, gastrointestinal, neurologic, and endocrinological symptoms. Endocrinological complications of COVID-19 are rare but can considerably impact the outcome of the patients. Moreover, preexisting endocrinologic disorders can affect the severity of COVID-19. Thyroid, pancreas, adrenal, neuroendocrine, gonadal, and parathyroid glands are the main endocrinologic organs that can be targeted by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Endocrinological complications of COVID-19 are rare but can significantly deteriorate the patients' prognosis. Understanding the interaction between COVID-19 and the endocrine system can provide a potential treatment option to improve the outcome of COVID-19. In this article, we aim to review the short-term and long-term organ-based endocrinological complications of COVID-19, the pathophysiology, the influence of each complication on COVID-19 prognosis, and potential therapeutic interventions based on current published data. Moreover, current clinical trials of potential endocrinological interventions to develop therapeutic strategies for COVID-19 have been discussed.

Introduction

Coronavirus disease 2019 (COVID-19) pandemic has infected more than 243 million individuals so far. The most common presentation of COVID-19 is an upper respiratory infection that can progress to pneumonia and acute respiratory distress syndrome (ARDS) (Elahi et al. 2022). Extrapulmonary organ involvement, including cardiac, gastrointestinal (GI), renal, hematological, hepatic, neurological, and endocrinological organs is also possible (Ghaebi et al. 2021, Thakur et al. 2021). The endocrinological complications of COVID-19, which can significantly affect the prognosis of the patients, are less studied and require specific attention.

COVID-19 is caused by severe acute respiratory virus-2 (SARS-CoV-2). SARS-CoV-2 includes a spike (S) protein in its structure (Esmaeilzadeh et al. 2021a). The interaction between S protein and angiotensin-converting enzyme 2 (ACE2) receptor (ACE2-R) contributes to the in-cell entry of the virus. The transmembrane serine protease type 2 (TMPRSS 2) cleavages the spike protein which is necessary for its binding to ACE2-R (Mohamadian et al. 2021). The co-expression of ACE-2 and TMPRSS2 is necessary for the entrance of the virus to the host cell (Fig. 1). Current studies have demonstrated the extensive expression of ACE2-R in various tissues including the lung, GI epithelium,
Figure 1
The expression of ACE-2 and TMPRSS2 by endocrine tissues and their role in the pathogenesis of SARS-CoV-2. Created by Esmaeilzadeh et al. Refer to https://www.proteinatlas.org/ENSG00000130234-ACE2/tissue and https://www.proteinatlas.org/ENSG00000184012-TMPRSS2/tissue for more information on ACE-2 and TMPRSS2 expression by different endocrinologic tissues. A full color version of this figure is available at https://doi.org/10.1530/JME-22-0036.
neuroendocrine system, thyroid, adrenal, pancreas, testis, and ovaries (Pham et al. 2020). The primary infected cells by SARS-CoV-2 are type-I pneumocytes of the alveoli. Studies have detected the presence of SARS-CoV-2 in the blood samples of the patients (Aguiar et al. 2020). Moreover, ACE2-R is expressed on endocrine glands, and studies have reported the existence of viral particles and viral genome in endocrinological tissues (Peng et al. 2020). Therefore, the endocrinological involvement of COVID-19 has been suspected since its emergence. COVID-19 can affect different endocrine organs (Fig. 2). The general pathophysiologic mechanisms of endocrine dysfunction in COVID-19 include (1) direct viral injury, (2) endothelial dysfunction secondary to the SARS-CoV-2-induced endothelitis, (3) immune-mediated organ injury caused by the uncontrolled release of the cytokines, and (4) the dysregulation of the renin-angiotensin-aldosterone system (RAAS) (Lisco et al. 2021). In thyroid, subacute thyroiditis (SAT) and non-thyroidal illness syndrome (NTIS) are the most common complications. Considering adrenal glands, adrenal insufficiency (AI) can occur as a result of adrenal vein thrombosis and adrenal infarction secondary to COVID-19. In the pancreas, acute pancreatitis, necrotizing pancreatitis, new-onset diabetes/diabetic ketoacidosis (DKA), and impaired glucose tolerance are reported. In the gonads, orchitis, epididymitis, epididymo-orchitis, necrotizing orchitis, gonadal vein thrombosis, impaired semen parameters and spermatogenesis are the reported complications. Moreover, there could be alterations in the production of the hypothalamus–pituitary (HP) axis hormones, growth hormone (GH), and prolactin. Hypophysitis, syndrome of inappropriate antidiuretic hormone secretion, central diabetes insipidus (CDI), and pituitary apoplexy are other HP-related complications of COVID-19 (Gianotti et al. 2021). According to the crucial immune-modulatory role of hormones and their interaction with the immune response (Bilezikian et al. 2020), specific attention must be paid to the endocrinopathies in COVID-19. This can improve the prognosis and ameliorate the outcome of severely ill patients (Puig-Domingo et al. 2020, Esmaeilzadeh & Elahi 2021).

In this article, we aim to review the risk of developing acute/late endocrine complications after COVID-19, the organ-specific dysfunction of COVID-19 in different endocrine organs, different endocrinological presentations of each organ, and possible therapeutic interventions for each complication. Moreover, we discuss the current
clinical studies and ongoing clinical trials that aim to develop a clinical attitude to improve the outcome of endocrinopathies in COVID-19.

Thyroid complications of COVID-19

The thyroid gland influences metabolic processes by secreting thyroid hormones, triiodothyronine (T3), and thyroxin (T4). Meanwhile, normal thyroid function is crucial for an appropriate innate immune response. Chiiovato et al. demonstrated ACE2 mRNA expression at a significant level in thyroid tissue (Rotondi et al. 2021). Lazartigue et al. showed that TMPRSS2 is expressed by thyroid tissue at a high level regardless of gender (Lazartigues et al. 2020). Therefore, thyroid tissue is a potent target for SARS-CoV-2. In COVID-19 patients, reduced levels of thyroid-stimulating hormone (TSH) are accompanied by an increase in viral load. TSH levels have been reported to be decreased in COVID-19 (Esmaeilzadeh & Elahi 2021). Moreover, dysregulation of thyroid hormones increases the risk of severe COVID-19 (Zhang et al. 2021). The underlying mechanisms are increased levels of interleukin-6 (IL-6) and TNF-α, which are pro-inflammatory cytokines, and increased ACE2 expression in vascular endothelium (Kumari et al. 2020). Thyroid involvement in COVID-19 can present with the sick euthyroid syndrome, SAT, Graves’ disease (GD), postpartum thyroiditis (PT), Hashimoto’s syndrome, and silent thyroiditis (ST). Here, we aim to discuss every complication in detail.

Subacute thyroiditis (SAT)

SAT also named de Quervain or giant cell thyroiditis, is the self-limited inflammation of the thyroid gland that can impact the production of thyroid hormones that usually occurs after a recent viral infection (Desai & Hofer 2009). Typically, SAT has three phases. The first phase is thyrotoxicosis which is recognized by low TSH with or without increased T3 and T4. The second phase is hypothyroidism due to discharged thyroid hormones as a result of inflammatory damage to thyroid follicular cells. During the last phase, the thyroid retrieves its normal function. Common clinical signs and symptoms of SAT include anterior neck pain that may radiate to the jaw, ear, or mediastina, fever, fatigue, and muscle pain. Thyrotoxicosis manifestations such as palpitation and unintentional weight loss could occur in the first phase of SAT as a result of thyroid follicular destruction (Stasiak et al. 2018). SARS-CoV-2 could be a triggering factor for SAT. Several cases of COVID-19-associated SAT have been reported. Kalkan et al. reported a 41-year-old female with no past medical history to present with acute neck pain and fever. The laboratory analysis revealed that TSH was reduced, C-reactive protein (CRP) was elevated, and T4 and T3 were mildly increased. The patient had two positive RT-PCR tests for SARS-CoV-2. After being diagnosed with COVID-19-associated SAT, she was treated with 16 mg prednisolone daily for 4 weeks and successfully recovered (Asfuroglu Kalkan & Ates 2020). Consistently, other studies have reported COVID-19 to present with typical signs and symptoms of COVID-19-associated SAT (Muller et al. 2020). Importantly, COVID-19 can be manifested only by SAT and not any other common SARS-CoV-2 manifestation (San Juan et al. 2021). Moreover, a study by Muller et al. revealed that SAT prevalence is 20-folds higher in COVID-19 compared to non-COVID-19 intensive care unit (ICU) patients (Ruggeri et al. 2021). In severely ill COVID-19 patients, there might be a pattern of reduced TSH, free T3, and increased free T4, which represents the co-occurrence of SAT and NTIS (Muller et al. 2020).

Non-thyroidal illness syndrome (NTIS)

NTIS is the most common thyroid dysfunction in COVID-19 hospitalized patients. It is well known that many acute or chronic illnesses can result in alterations in thyroid function, which is known as NTIS, low T3 syndrome, or sick euthyroid syndrome. NTIS is a reactive condition and is defined by reduced serum T3 levels, normal or reduced T4 levels, and increased reverse T3. The level of TSH may be reduced or unchanged, representing an altered central hypothalamic–pituitary–thyroid axis negative feedback. The range of these changes is affected by the severity of the illness. Usually, these changes do not reflect a clinically underlying thyroid disease. Nevertheless, these alterations are presumed as a response to systemic stress and illness to conserve energy (Warner & Beckett 2010). Studies have proposed several mechanisms for NTIS including a reduction in deiodinase 1 activity, increment in deiodinase 3 activity (Farwell 2013), and alterations in serum thyroid-binding proteins and affinity of these proteins to thyroid hormones (Haddady & Farwell 2011). Moreover, there are several causes for low TSH levels including hypoxemia or increased endogenous or exogenous glucocorticoids. After recovery, the amount of T3, T4, and TSH return to baseline (Khoo et al. 2021). Although data show that NTIS leads to poor prognosis, thyroid hormones replacement therapy has not shown benefits in improving the prognosis, so far (Kaptein et al. 2010).

NTIS has been reported in 7.45% of hospitalized COVID-19 patients, even in mild to moderate patients. Moreover,
the presence of NTIS on admission was independently associated with poor COVID-19 outcomes. Therefore, the authors have concluded that NTIS on admission could serve as a prognostic factor in COVID-19 (Lui et al. 2021). There could be a correlation between the level of free T3 and TSH and the severity of COVID-19. Gong et al. found that low TSH and low T4 were associated with higher mortality of COVID-19 patients who suffered from NTIS (Gong et al. 2021). In a cohort study, Khoo et al. understood that most of the COVID-19 patients were euthyroid. Although COVID-19 patients had a small reduction in the level of T4 and TSH on admission due to COVID-19 compared to their recorded past thyroid function tests. Notably, non-COVID-19 patients did not show such a reduction in the level of T4 and TSH (Khoo et al. 2021). There is a phase II clinical trial to assess the effect of treatment with T3 in critically ill COVID-19 patients (NCT04348513).

**Hashimoto’s thyroiditis (HT)**

Hashimoto’s thyroiditis (HT) is an autoimmune disease associated with other autoimmune diseases like type 1 diabetes mellitus (DM) and vitiligo (Travaglino et al. 2020). SARS-CoV-2 could act as a trigger in genetically susceptible individuals for autoimmune disorders like HT. Up to now, one study has reported HT after COVID-19 infection. The patient was a 45-year-old male who experienced an acute onset of severe fatigue and muscle weakness 7 days after a mild COVID-19 infection. The authors declared that he did not have any personal or familial history of autoimmune disease without any considerable drug history. In further workup, the patient had an elevated TSH (6.49 µIU/ml) and low free T4 (9.19 pmol/L), suggesting primary hypothyroidism. Anti-thyroid peroxidase (TPO) antibody was reported potently positive, confirming the diagnosis of HT (Tee et al. 2020). Further investigation regarding the occurrence of autoimmune disorders, such as HT, after COVID-19 infection, is warranted.

**Silent thyroiditis (ST)**

ST, also named subacute lymphocytic thyroiditis, is a painless inflammation of the thyroid gland that occurs secondary to lymphocytic infiltration of the thyroid (Samuels 2012). Chan et al. reported a 32-year-old female with a history of weakness, fatigue, and inferior limb edema, without neck pain, for several weeks after COVID-19 infection to be diagnosed with hypothyroidism and positive anti-TPO. According to the positive antibody test and no past medical history, the authors concluded that hypothyroidism occurred due to COVID-19-associated thyroiditis (Chan et al. 2021). It should be noted that the authors were not able to differentiate between ST and atypical SAT in this case. Considering the increased frequency of painless SAT following COVID-19, the differentiation between ST and painless SAT needs more attention. The first point is that SAT usually comes following viral infection while the etiology of ST is considered to be autoimmune related. Consistently, thyroid autoimmune antibodies in SAT are usually negative, but in ST, about 50% of cases have positive anti-TPO antibodies (Muller et al. 2020). Therefore, ST must be considered in post-COVID-19 individuals presented with signs and symptoms of thyroiditis who do not experience neck pain.

**Postpartum thyroiditis (PT)**

PT is a type of thyroiditis that occurs in women without previous thyroid disorder within 12 months after delivery. About 25–40% of patients in PT experience the triphasic course like SAT and ST; however, 30% and 40% of patients experience only thyrotoxicosis or hypothyroidism, respectively (Lazarus 2011). The etiology of PT is considered autoimmune and up to 80% of patients have positive anti-TPO antibodies (Stagnaro-Green et al. 2011). Up to now, there has been a case of PT possibly associated with COVID-19 infection. A 29-year-old female with a past medical history of HT who had childbirth 3.5 months before being infected with SARS-CoV-2 had a positive RT-PCR on day 104 after delivery. During the next day, she developed a 39-degree fever and sore throat that ameliorated after 3 days without any specific treatment. On day 127 after delivery, she developed two separate negative RT-PCR tests. Almost 1 month after the positive SARS-CoV-2 RT-PCR test (4.5 months after childbirth), she presented with severe generalized fatigue. No goiter or tenderness was found in the physical examination. Laboratory findings revealed a normal white blood cell count (4800/µL) and lymphocyte (35.6%), and thyroglobulin was in the normal range despite elevated levels of anti-TG antibody. Other thyroid autoantibodies were negative. Without any specific interventions, she recovered after 36 days from the onset of PT (Mizuno et al. 2021). Therefore, PT is a probable complication of COVID-19 in women in their post-pregnancy period.

**Graves’ disease (GD)**

The most reported cause of hyperthyroidism is GD. The peak of incidence is between age 30 and 50 years, and females
are 6-fold more involved than males. In GD, the immune system produces TSH receptor-stimulating antibodies which result in the overproduction of thyroid hormones. The manifestations of GD are related to thyrotoxicosis, including weight loss, tremors, heat intolerance, fatigue, and palpitation. GD can have extrathyroidal manifestations, including ophthalmopathy, dermopathy, and acropachy (Negro et al. 2016). There are some reports of GD in probable association with SARS-CoV-2 (Harris & Al Mushref 2021, Moreno et al. 2021). The age of patients was between 21 and 61 years and all of them were female. Some of them had a past medical history of GD that had been in remission; however, after COVID-19 infection, they experienced an exacerbation of the GD (Mateu-Salat et al. 2020). Interestingly, some of them were new cases of GD diagnosed after COVID-19 infection. The time from the onset of SARS-CoV-2 infection and onset of GD signs and symptoms can differ from a week to 2 months. Major laboratory findings included thyrotoxicosis pattern, suppressed TSH and elevated free T4 and/or free T3, and positive anti-TSH receptor antibodies. Some patients also had positive titers of anti-TPO and anti-TG antibodies. Main imaging findings were hypeochogenic areas, increase in vascularization observed in ultrasonography, and increased radioiodine uptake of about 30–62%. Treatment was with anti-thyroid drugs, such as methimazole and thiamazole, and beta-blockers like propranolol. No correlation was detected between COVID-19 severity and risk of GD development (Harris & Al Mushref 2021, Lanzolla et al. 2021).

However, it is not possible to conclude that these disorders are caused by SARS-CoV-2 or are just incidental co-occurrence. Thus, further studies are warranted to clarify the basic mechanisms behind that. There might be a challenge in differentiating between thyrotoxicosis resulting from GD and SAT. Thus, indexes like platelet–lymphocyte ratio, neutrophil–lymphocyte ratio, monocyte–eosinophil ratio, and free T4/free T3 ratio are suggested to be useful. These parameters are more increased in SAT compared to GD or healthy controls (Stasiak & Lewinski 2021).

Management of previous thyroid dysfunction in superimposed COVID-19 infection is of great importance. European Society of Endocrinology has proposed a management strategy for thyroid dysfunction in COVID-19 pandemic. Based on this, hypothyroid patients should continue their oral hormone replacement therapy with the previous dose. In thyrotoxicosis adult patients who develop COVID-19 infection, it is recommended that if free T4 is upper limit normal, the patient receives 20 mg carbimazole or 15 mg methimazole oral daily. However, if the free T4 is greater than 30 pmol/L, higher doses should be administered (40 mg carbimazole or 30 mg methimazole OD). For further information, the authors recommend referring to the original article (Boelaert et al. 2020, Pal & Bhadada 2020).

### Adrenal complications of COVID-19

The adrenal gland plays a crucial role in the physiology of the stress response, regulation of the immune response (by controlling cytokine release), regulation of the fluid hemostasis, blood pressure control, and production of the sex hormones. Pathologic dysregulation of the adrenal function can be caused by multiple etiologies, such as the inflammation of the adrenal gland (Alevriris et al. 2003). Immunostaining studies have revealed that ACE2R is expressed by zona fasciculate and zona reticularis. However, ACE2 expression has not been detected in the medulla. TMPRSS2 expression is detected in all three zones of the cortex (Li et al. 2020). Therefore, according to co-expression of ACE2R and TMPRSS2, the adrenal gland could be a potential target for SARS-CoV-2.

There are reports of adrenal infarction and adrenal hemorrhage in COVID-19 patients (Frankel et al. 2020, Kumar et al. 2020). Direct viral injury is the first possible theory for the involvement of the adrenal gland by SARS-CoV-2. Pathological studies of ten patients deceased from COVID-19 revealed similar histological changes with the pathology sections separated from lung tissue and infiltration of the CD3+CD8+ lymphocytes in the adrenal gland. Consistently, inflammation-related responses are also observed in immunohistochemistry studies (Zinserling et al. 2020). Another pathology that has been proposed for the adrenal damage in COVID-19 is thrombosis of the adrenal veins and corresponding adrenal infarction (Leyendecker et al. 2021). The highly vascularized structure of the adrenal gland increases its vulnerability to endothelitis. Endothelitis is an independent factor that can increase the risk of thrombosis. These mechanisms promote the thrombosis of the adrenal veins and adrenal infarction, which finally leads to adrenal degeneration, hemorrhage, and Waterhouse–Friderichsen syndrome. Another study on autopsies of five postmortem COVID-19 revealed small vessel necrosis mostly in the arterioles, subendothelial vacuolization, and apoptotic debris of adrenal vessels (Iuga et al. 2020). Autoantibodies produced against adrenocorticotropic hormone (ACTH)-like amino acids sequence coded by viral genome might contribute to the central AI in COVID-19 (Pal 2020). In severe
COVID-19 patients, catecholamines may act as a vasoconstriction trigger and cause adrenal vein thrombosis (Freire Santana et al. 2020). These processes are the main molecular and cellular mechanisms that can lead to adrenal damage in COVID-19. Clinically, adrenal involvement in COVID-19 can present with AI or Cushing’s syndrome (CS). Here, we aim to discuss the adrenal complications of COVID-19 in detail.

Adrenal insufficiency (AI)

AI is the clinical manifestation of inadequate production of glucocorticoids which can be accompanied by a deficiency of mineralocorticoids and androgens. It can result from primary adrenal damage or secondary to impaired function of the HP axis. The most important etiology of primary AI is autoimmune adrenalitis. Secondary AI could result from any process that involves the pituitary gland and interferes with corticotropin secretion. Tertiary AI results from a process that involves the hypothalamus and interferes with the secretion of corticotropin-releasing hormone (Álvarez-Troncoso et al. 2020). The clinical manifestation of AI is nonspecific. The most common symptom are fatigue, reduced muscle strength, anorexia, weight loss, nausea, vomiting, and gastric pain. The most common signs are skin hyperpigmentation, low blood pressure, postural hypotension, and dehydration. Hyponatremia and hyperkalemia are known biochemical findings in AI. For diagnosing AI, an early morning serum cortisol concentration lower than 80 nmol/L is useful which strongly suggests AI (30 µg/L) (Arlt & Allolio 2003). Several studies reported AI as a significant complication of COVID-19 (Mandal et al. 2021). In COVID-19, AI can present with various manifestations, including acute hypotensive episodes, vasopressor resistance hypotension, electrolyte disorder, adrenal hyperplasia, and seizure. In a study, it was reported that adrenal gland change may be associated with the SARS-CoV-2 virus in COVID-19 patients. Autopsy studies of 28 SARS-CoV-2 patients showed that adrenal lesions were mostly observed in severe COVID-19 patients. Interestingly, none of the cases presented with AI. These lesions are mild but they could result in a poor outcome. The major limitation of this study is the absence of viral detection in the adrenal gland. It could not be ruled out that other systemic or age-related diseases can be considered as an etiology of adrenal lesions (Freire Santana et al. 2020). Therefore, AI in patients with related signs and symptoms should be considered even months after infection with SARS-CoV-2. A case report of a patient who presented with hyponatremia and was diagnosed with AI and had asymptomatic COVID-19 5 months ago is an objective example (Perez et al. 2021).

AI can affect the prognosis of COVID-19 patients. The admission of cortisol level outside its normal range and a decrease in the amount of cortisol are predictors of poor prognosis in COVID-19. Tan et al. found that cortisol concentration of more than 744 nmol/L was associated with reduced median survival (Tan et al. 2020). Leyendecker et al. have shown that ICU admission and duration of ICU were significantly higher in the acute AI group vs the control group, but the mortality was the same in both groups (Leyendecker et al. 2021). Nevertheless, Dhillo et al. mentioned that an increased amount of cortisol was an independent predictor of acute death in COVID-19 patients (Tan et al. 2020). COVID-19 is a kind of stress that can increase the need for corticosteroids and prone the AI patient to critical illness-related corticosteroid insufficiency (CIRCI). A study detected 50.4% of COVID-19 ICU-admitted patients to have CIRCI. Supplementary replacement of corticosteroids in these patients improved the outcome of these patients (Sari et al. 2021).

The management of AI in COVID-19 is important. Arlt et al. discussed the management of the AI during COVID-19. They recommended that COVID-19 patients with primary adrenal insufficiency (PAI) use 20 mg hydrocortisone orally QD (daily). If the patients developed worsening symptoms, they proposed the following protocol: 100 mg hydrocortisone intramuscularly and 200 mg of it every 24 h/ 50 mg of it QD (Arlt et al. 2020).

Cushing’s syndrome (CS) and COVID-19

CS is a constellation of signs and symptoms resulting from excess glucocorticoids whether from endogenous or exogenous sources. Signs and symptoms of COVID-19 may be different in CS. Fever is one of the hallmarks of severe COVID-19 infection and is seen in most COVID-19 patients. Due to poor immune response in CS patients, limited febrile response in the acute phase of the disease is expectable (Pivonello et al. 2020). The severity of hypercortisolism in CS patients is associated with poor outcomes despite low inflammatory cytokines and lack of clinical presentation (Belaya et al. 2021). Patients with CS are susceptible to severe COVID-19 infection when infected with SARS-CoV-2. Reduced white B cell count and function, reduced CD4+ to CD8+ ratio, and reduced function of NK cells are mechanisms that make CS patients susceptible to severe infections, including COVID-19 (Aranda et al. 2017). Moreover, DM and hypertension are more common in CS patients, and both are considered poor prognostic factors in
COVID-19 patients. CS also increases pro-thrombotic status due to increased production of fibrinogen, factor VIII, and impaired fibrinolysis. This may result in multiorgan failure, thrombotic events in the body, and poor outcomes (van der Pas et al. 2013). SARS-CoV-2-induced hypokalemia can be more severe in CS due to the mineralocorticoid-like effect of corticosteroids (Somasundaram et al. 2020). To manage CS, cortisol-lowering therapy should be considered, including oral agents, such as ketoconazole, metyrapone, osilodostat, and parenteral agent like etomidate, until defining the main cause of CS in the patients (Newell-Price et al. 2020). Both COVID-19 and CS are associated with a hypercoagulable condition, and therefore, low-molecular-weight heparin use should be considered in CS patients infected with SARS-CoV-2 (Besharati et al. 2021).

Pancreatic complications of COVID-19

The pancreas is one of the retroperitoneal organs that plays a major physiologic role in the adjustment of blood glucose and digestion. It has two main parts, the exocrine (ductal) and the endocrine (islet) sections. Similar to the thyroid and adrenal glands, ACE2 and TMPRSS2 expression has been detected in the pancreas. Zhanguo et al. have demonstrated that the level of ACE2 expression in the pancreas is even more than respiratory tissue (Liu et al. 2020a). Nevertheless, there is controversy about the superiority of ACE2 expression by the exocrine or endocrine section of the pancreas. Some studies agreed on higher ACE2 expression by endocrine section; however, others believed that both exocrine and endocrine pancreas express ACE2 equally (Liu et al. 2020a). TMPRSS2 is mainly expressed in the exocrine section of the pancreas (Coate et al. 2020). Pancreas involvement in COVID-19 patients can present with acute pancreatitis, necrotizing pancreatitis, and dysregulation of the blood glucose hemostasis which can result in hyperglycemia.

The pancreatic injury may be confirmed by the presence of footprint of the SARS-CoV-2 (Wu et al. 2021) viral particles in the pancreas of the infected patients. The proposed mechanisms of pancreatic involvement in COVID-19 could be one or a mixture of the following: direct viral injury, systemic inflammatory-mediated damage, lipotoxicity, and drug-induced pancreatitis (Correia de Sá et al. 2021). Herein, we discuss every pancreatic complication of COVID-19 in detail.

Acute pancreatitis

Acute pancreatitis is an inflammation of the pancreas and surrounding tissue that needs urgent surgical/medical care. There are a variety of etiologies that can lead to acute pancreatitis, including gallstones, alcohol use, trauma, drug-induced pancreatitis, and viral infections. Mumps, hepatitis, coxsackie B virus, and cytomegalovirus (CMV) are viral etiologies that can cause acute pancreatitis. Based on the reports, SARS-CoV-2 infection can cause acute pancreatitis. Acute pancreatitis can present with typical abdominal pain with radiation to the back, increased serum lipase or amylase, and characteristic CT findings (Li et al. 2021).

Based on reports, acute pancreatitis could be the primary manifestation (Wang et al. 2020b) or the complication of COVID-19 (Hadi et al. 2020), which is referenced in Table 1. Alwaeli et al. reported a 30-year-old patient with typical signs and symptoms of COVID-19 who presented with epigastric pain with radiation to the back, nausea, vomiting, diarrhea, and ground-glass opacifications in radiologic findings. An abdominal CT scan revealed enhancement of the parenchyma, inflammation, and interstitial edema in the pancreas. The serum lipase and amylase levels were also increased. The PCR test for SARS-CoV-2 was detected positive. The patient was diagnosed with COVID-19 and was symptomatically treated in the ICU (Alwaeli et al. 2020). The prevalence of COVID-19-associated pancreatic injury was reported to be 17% by Wang et al. (Wang et al. 2020a) and 18% by Zhanguo et al (Ruggeri et al. 2021). Some critically ill COVID-19 patients may have elevated pancreatic enzyme levels; however, only 1.7% of them had definite pancreatitis. Therefore, pancreatic enzyme elevation is common in COVID-19 patients, and the elevation of amylase/lipase must not be considered as acute pancreatitis (Stephens et al. 2021). Moreover, hyperlipasemia may occur in absence of the pancreatitis. In this case, the higher serum lipase level is correlated with higher mortality, ICU admission, and elevated D-dimer (Ahmed et al. 2021). Therefore, in patients with nausea, vomiting, and abdominal pain, that are diagnosed with acute pancreatitis, it is better to rule out COVID-19 infection. The systemic inflammation that occurs in acute pancreatitis could worsen the ARDS, which can deteriorate the outcome of severe COVID-19 cases.

Necrotizing pancreatitis

Necrotizing pancreatitis is a life-threatening condition in which severe inflammation can progress to necrotic cell death of the pancreatic tissue. Necrotizing pancreatitis has been reported secondary to COVID-19 (Maalouf et al. 2021). Arbati et al. reported a 28-year-old man with ARDS and stabbing abdominal pain radiating to the back
<table>
<thead>
<tr>
<th>Complication</th>
<th>Symptoms</th>
<th>Laboratory findings</th>
<th>Imaging findings</th>
<th>Number of patients</th>
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<tr>
<td>Thyroid</td>
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| Subacute thyroiditis (SAT)         | Neck pain radiating to the jaw, Neck tenderness, Anorexia, Fever, Palpitation, Tachycardia, Fatigue, Sweating, Weight loss, Tremor | Increased T3, Increased T4, Reduced TSH, Negative anti-TPO Ab, Negative anti-TSH Ab, Negative anti-thyroglobulin Ab, Increased ESR and CRP | Heterogenic hypoechoic areas in thyroid sonography | 4 | All were new-onset  
1 (case report)  
1 (case report)  
1 (case report)  
1 (case report)  
1 (case report) |
|                                   |                                               |                                      |                                       |                    | Brancatella *et al.* 2020  
Chakraborty *et al.* 2020  
Campos-Barrera *et al.* 2021  
San Juan *et al.* 2020  
Ruano *et al.* 2021 |
| Non-thyroidal illness syndrome (NTIS) | N/A                                           | Reduced T3, Normal/reduced T4, Increased reverse T3 | N/A                                   | 10 out of 191  
3 had previous autoimmune thyroid pathology | Lui *et al.* 2021 |
| Hashimoto's thyroiditis            | Severe fatigue, Muscle weakness               | Increased TSH, Reduced free T4, Positive anti-TPO Ab | N/A                                   | 1 (case report)  
New-onset | Tee *et al.* 2020 |
| Silent thyroiditis                 | No neck pain, Weakness, Fatigue, Edema        | Increased T3, Increased T4, Reduced TSH, Positive anti-TPO Ab | N/A                                   | 1 (case report)  
New-onset | Chan *et al.* 2021 |
| Postpartum thyroiditis             | Fever, Generalized fatigue                    | Generalized fatigue, Normal thyroglobulin, Elevated anti-TG Ab | N/A                                   | 1 (case report)  
New-onset | Inaba & Aizawa 2021 |
| Graves' disease                    | Tachycardia, Weight loss, Heat intolerance, Palpitations, Tremor, Anxiousness, Fatigue, Ophthalmopathy, Dermopathy, Acropathy | Elevated free T3, Elevated free T4, Reduced T4, Positive anti-TSH receptor Ab | Hypoechoic areas, Increased vascularization | 1 (case report)  
New-onset  
2  
1 (case report)  
1 (case report)  
1 (case report) | Harris & Al Mushref 2021  
Mateu-Salat *et al.* 2020  
Lanzolla *et al.* 2021 |
| Adrenal                            | Fatigue, Muscle weakness, Anorexia, Weight loss, Nausea, Vomiting, Abdominal pain, Hypotension | Hyponatremia, Hypochloremia, Elevated CRP | Enlargement and haziness of peri-adrenal fat of adrenal gland | 1 (case report)  
New-onset  
1 (case report)  
1 (case report)  
1 (case report) | Katikar 2021  
Sánchez *et al.* 2022  
Hashim *et al.* 2021 |

(Continued)
## Table 1

<table>
<thead>
<tr>
<th>Complication</th>
<th>Symptoms</th>
<th>Imaging findings</th>
<th>Laboratory findings</th>
<th>Number of patients</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cushing's syndrome</td>
<td>Muscle weakness, Placidity, Pneumothorax,</td>
<td>Fat stranding, Edema of the peri-pancreatic tissue, Heterogenic pancreas density, Spleno-Renal space fluid accumulation</td>
<td>Elevated P50, Urine albumin, Elevated D-dimer</td>
<td>1 (case report)</td>
<td>Eagle et al. 2020</td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>Severe epigastric pain, Radiating to back, Nausea, Vomiting</td>
<td>Fat stranding, Edema of the peri-pancreatic tissue, Heterogenic pancreas density, Spleno-Renal space fluid accumulation</td>
<td>Elevated P50, Urine albumin, Elevated D-dimer</td>
<td>1 (case report)</td>
<td>Eagle et al. 2020</td>
</tr>
<tr>
<td>Necrotizing pancreatitis</td>
<td>Severe epigastric pain, Radiating to back, Nausea, Vomiting</td>
<td>Fat stranding, Edema of the peri-pancreatic tissue, Heterogenic pancreas density, Spleno-Renal space fluid accumulation</td>
<td>Elevated P50, Urine albumin, Elevated D-dimer</td>
<td>1 (case report)</td>
<td>Eagle et al. 2020</td>
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<tr>
<td>Impaired glucose tolerance and insulin resistance</td>
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</tbody>
</table>
Table 1  Continued.

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<tbody>
<tr>
<td>Hypovitaminosis D</td>
<td>Fatigue</td>
<td>Reduced serum vitamin D</td>
<td>N/A</td>
<td>612,601 (systematic review)</td>
<td>Petrelli et al. 2021</td>
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<tr>
<td></td>
<td>Generalized weakness</td>
<td>Reduced serum Ca</td>
<td></td>
<td>Decreased vitamin was associated with increased risk of infection and severity of COVID-19</td>
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<tr>
<td></td>
<td>Arthritis</td>
<td></td>
<td></td>
<td>999,179 (systematic review)</td>
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<td></td>
<td></td>
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<td></td>
<td>Low serum vitamin D was associated with poor outcome of COVID-19 infection.</td>
<td>Akbar et al. 2021</td>
</tr>
<tr>
<td>Reproductive system</td>
<td>Hypogonadism</td>
<td>Elevated LH</td>
<td>N/A</td>
<td>262</td>
<td>Kadihasanoglu et al. 2021</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No change in FSH</td>
<td></td>
<td>There was a reverse correlation between level of total testosterone and hospitalization.</td>
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<tr>
<td></td>
<td></td>
<td>Reduced testosterone</td>
<td></td>
<td>143</td>
<td>Moreno-Perez et al. 2022</td>
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<td></td>
<td></td>
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<td></td>
<td>Decreased level of serum testosterone was detected in 28.7% of the COVID-19 survivors</td>
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<td>55</td>
<td>Aboelnaga et al. 2021</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td>Testosterone deficiency was detected in about 51% of COVID-19 survivors.</td>
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</tr>
<tr>
<td>Epididymo-Orchitis</td>
<td>Abdominal/scrotal pain</td>
<td>Lymphocytopenia</td>
<td>Enlarged tests</td>
<td>1 (case report)</td>
<td>Kim et al. 2020</td>
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<tr>
<td></td>
<td></td>
<td>Increased CRP</td>
<td>The heterogeneous echogenicity of the tests</td>
<td>New-onset</td>
<td>Gagliardi et al. 2020</td>
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<tr>
<td></td>
<td></td>
<td>Increased IL-6</td>
<td></td>
<td>1 (case report)</td>
<td>Veyseh et al. 2020</td>
</tr>
<tr>
<td>Ovarian/testicular vein thrombosis</td>
<td>Abdominal pain</td>
<td>Increased D-dimer</td>
<td>Thrombosis of the ovarian/testicular vein in abdominopelvic CT angiography</td>
<td>New-onset</td>
<td></td>
</tr>
<tr>
<td>Impaired spermatogenesis</td>
<td>Possible infertility</td>
<td>Impaired semen analysis</td>
<td>N/A</td>
<td>23</td>
<td>Li et al. 2020</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(morphology and motility)</td>
<td></td>
<td>In 39% of COVID-19 inpatients, there was oligozoospermia and in 61%, there was increased number of seminal leukocytes. Also, decreased sperm concentration was detected.</td>
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<td>43</td>
<td>Gacci et al. 2021</td>
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<tr>
<td></td>
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<td></td>
<td>3 and 8 out of 43 patients were azoospermic and oligospermic, respectively.</td>
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</tr>
</thead>
<tbody>
<tr>
<td>Neuroendocrine system</td>
<td>Frontal headache, Nausea, Vomiting, Photophobia, Bilateral ptosis, Anisocoria and Ophthalmoplegia, Oculomotor nerve palsy, Declined visual acuity</td>
<td>Reduced thyroxin, Reduced cortisol</td>
<td>Necrosis of the pituitary gland</td>
<td>1 (case report)</td>
<td>Gianotti et al. 2021</td>
</tr>
<tr>
<td>Hypophysis apoplexy</td>
<td>Nocturia, Polyuria, Polydipsia</td>
<td>Increased serum osmolality, Decreased urine osmolality</td>
<td>Enlargement of the pituitary gland</td>
<td>1 (case report)</td>
<td>Misgar et al. 2021</td>
</tr>
<tr>
<td>Central diabetes insipidus (CDI)</td>
<td>Nocturia, Polyuria, Polydipsia</td>
<td>Reduced serum cortisol, Reduced serum ACTH eosinophilia</td>
<td>N/A</td>
<td>1 (case report)</td>
<td>Chua &amp; Chua 2021</td>
</tr>
<tr>
<td>Metabolic changes</td>
<td>New-onset persistent dyspepsia</td>
<td>N/A</td>
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<tr>
<td>Decreased adiponectin/</td>
<td>Reduced serum adiponectin, High serum leptin</td>
<td>N/A</td>
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<tr>
<td>Increased adipokines</td>
<td></td>
<td>N/A</td>
<td></td>
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</tr>
<tr>
<td>Electrolyte imbalance</td>
<td></td>
<td>N/A</td>
<td></td>
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</tr>
<tr>
<td>SIADH</td>
<td>Seizure, Encephalitis, Sinus bradycardia, Urinary retention</td>
<td>Hyponatremia</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>Seizure, Encephalitis, Sinus bradycardia, Urinary retention, Weakness, Impaired mental status</td>
<td>Hyponatremia, Increased serum Na⁺</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>Abdominal pain, Palpitation, Fatigue, Nausea, Vomiting</td>
<td>High serum K⁺ &gt; 5.1, Tall T waves in ECG, Sine P wave in ECG, Prolonged QT in ECG</td>
<td>N/A</td>
<td>136</td>
<td>Liu et al. 2021</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>Weakness, Constipation, Arrhythmia</td>
<td>Low serum K⁺ &lt; 3.5, Prolonged QT in ECG, Flattening of ST segment in ECG</td>
<td>N/A</td>
<td>108</td>
<td>Chen et al. 2020a</td>
</tr>
</tbody>
</table>

ACTH, adrenocorticotropic hormone; anti-TPO Ab, anti-thyroid peroxidase antibody; anti-TSH Ab, anti-thyroid-stimulating hormone antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FBS, fasting blood glucose; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; SIADH, syndrome of inappropriate anti-diuretic hormone secretion; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone; vitD, vitamin D3.
and nausea/vomiting to have heterogeneous pancreatic density, fat stranding, and fluid accumulation in the splenorenal space. The diagnosis of acute severe necrotizing pancreatitis was made, and the patient was successfully treated with supportive care in the ICU (Mohammadi Arbati & Molseghi 2021).

**Insulin resistance and impaired glucose tolerance**

DKA, hyperglycemia, and euglycemic ketosis are the most reported glucose-related disturbances in COVID-19. The uncontrolled blood glucose was first reported in hospitalized COVID-19 patients without previous diabetes and no glucocorticoid use (Yang et al. 2010). Another study showed that 46% of the 551 hospitalized COVID-19 patients were hyperglycemic. Interestingly, the authors reported that both hyperglycemic and normoglycemic patients had insulin resistance and abnormal cytokine profiles. These glycemic abnormalities also existed for 2 months after the recovery. Hypothetically, insulin resistance and new-onset hyperglycemia could result in hyper-stimulation of the beta cells of the pancreas. This may end in hypofunction of the β cells and diabetes (Montefusco et al. 2021). In another study, poor blood glucose control was associated with increased levels of inflammatory mediators, such as CRP, ferritin, and IL-6 (Katsiki & Ferrannini 2020). A study has shown that SARS-CoV-2 could enter and replicate in the endocrine and exocrine parts of the pancreas. Interestingly, the morphologic changes and impaired insulin secretion were also detected in *in vitro* studies (Müller et al. 2021). Hyperglycemia is not necessarily associated with new-onset diabetes. It could be associated with glucocorticoids used for COVID-19 patients. Moreover, the stress caused by cytokine storm can also increase blood glucose in a reactive process (Mantovani et al. 2020).

Studies showed that viruses could also trigger the initiation of insulin-dependent diabetes mellitus (IDDM). Since ACE2 expression has been observed in pancreatic β cells, direct pancreatic injury by SARS-CoV-2 could be considered as one of the mechanisms that trigger the IDDM (Chowdhury & Goswami 2020). Studies have also shown insulin resistance in COVID-19 patients (Seggelke et al. 2021). It could be explained by systemic inflammation, beta-cell failure, glucocorticoid use, and adipose tissue dysfunction. However, Reiterer et al showed that insulin resistance could be related to adipose tissue dysfunction, too. They detected the mRNA of the SARS-CoV-2 in adipose tissue (Reiterer et al. 2021). Adipose tissue produces adipokines that mediate several inflammatory markers and disrupt glucose homeostasis. Adiponectin is one of the adipokines that suppress TNF-α, IL-6 expression, and hepatic gluconeogenesis and stimulate glucose uptake in skeletal muscles. Interestingly, it was shown that adiponectin levels were 50–60% reduced in patients with severe COVID-19 compared to ICU control patients (Tan et al. 2021).

Current studies suggest that new-onset DM might be a complication of COVID-19 but it needs further study to confirm (Gadiparthi et al. 2020). However, the problem might not be limited to diabetes and hyperglycemia. Hollstein et al. reported a case of new-onset DKA in a 19-year-old male with the absence of the autoantibodies of type 1 DM (Hollstein et al. 2020). In another study, a 37-year-old patient who was newly diagnosed with DM was reported to present with deteriorated DKA after COVID-19 infection (Chee et al. 2020). Since glucocorticosteroids are used as an effective anti-inflammatory drug in severe COVID-19, it has been discussed receiving corticosteroids in diabetic patients can precipitate the progression of DKA. This study also proposed that the IL-6 level at admission could be a predictive factor for the development of DKA in COVID-19 (Mondal et al. 2021).

There is a bidirectional relationship between diabetes and COVID-19. COVID-19 may cause diabetes and impaired glucose control, and on the other hand, diabetic patients have a poor prognosis when infected with COVID-19 (Zhou et al. 2020b). Epidemiologic studies have demonstrated higher mortality in diabetics compared to non-diabetic patients (Novel Coronavirus Pneumonia Emergency Response Epidemiology Team Team 2020). A meta-analysis showed that the incidence of COVID-19 is almost equal between diabetic and non-diabetic patients; however, diabetic patients have a higher risk of progression to severe disease (Mantovani et al. 2020). Based on another study, fasting blood glucose higher than 7.78 mmol/L correlated with poor prognosis in COVID-19 patients (Song et al. 2021). Several mechanisms could explain the weak prognosis of the COVID-19 in diabetic patients. Increased pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-1 (Shanmugam et al. 2003), impaired antiviral immune response, facilitation of the entrance of the SARS-CoV-2 to the epithelial cells of the alveoli secondary to excretion of glucose, and increase in D-dimer level that induces coagulation cascade are the most important complications of the hyperglycemia (Sardu et al. 2020). A retrospective single-center study revealed that higher insulin requirement in COVID-19 pneumonitis is associated with the severity of the disease and respiratory failure (Lockhart et al. 2021).

Management of insulin resistance and impaired blood glucose in COVID-19 can improve the patient outcome.
It has been demonstrated that both hypoglycemia and hyperglycemia are correlated with worse outcomes in COVID-19, and therefore, strict monitoring of a patient’s blood glucose can improve the outcome (Longo et al. 2020). According to data, measurement of HbA1C on admission and continuous blood glucose monitoring are recommended in all COVID-19 patients admitted to the wards/ICU (Alahmad et al. 2020). Studies have shown that controlling the blood glucose level in hospitalized COVID-19 patients is associated with a better prognosis (Davis et al. 2021). Moreover, glucocorticosteroids that are commonly used in COVID-19 can exacerbate hyperglycemia. Therefore, choosing the appropriate anti-diabetic drug is an important clinical issue in COVID-19 patients. According to its immune-regulatory properties, insulin can be proposed as a candidate for controlling the glucose level in COVID-19 (Sun et al. 2021). In contrast, two retrospective studies showed that insulin treatment was associated with higher systemic inflammation and poor outcome in COVID-19 (Riahi et al. 2021, Yu et al. 2021). Other antidiabetic drugs, such as DPP4 and SGLT-2 inhibitors, have also shown promising effects in reducing the entrance of the virus to the host cell and secretion of pro-inflammatory cytokines, as well as controlling the blood glucose level (Mirabelli et al. 2020). Nevertheless, another study showed the harmful effect of DPP4 inhibitors in the progression of COVID-19 pneumonia (Elibol et al. 2021). Therefore, the application of anti-diabetic drugs to control the blood glucose level in COVID-19 must be done with caution and needs further investigations (Table 2).

Another issue that needs to be addressed is the dosage of insulin or antidiabetic drugs in patients with previous DM or insulin resistance. As mentioned above, hyperglycemia has been shown to deteriorate the outcome in severe COVID-19. Studies have recommended continuing the antidiabetic drugs and restricting blood glucose monitoring in DM patients (Sun et al. 2021). Moreover, studies have shown that in patients with previous DM who are infected with COVID-19, higher doses of insulin (e.g. 2.2 U/kg/day) could be required to control the blood glucose (Wu et al. 2020).

**COVID-19 effects on parathyroid hormone, calcium, and vitamin D metabolism**

Four parathyroid glands that are located at the back of the thyroid gland in the neck are considered important regulators of the calcium and phosphorous level in the body. The parathyroid gland senses the low calcium level and secretes parathormone (PTH), which regulates the calcium level by acting on bone, kidney, and intestine. PTH action in the intestine is dependent on vitamin D's existence. Therefore, alterations in serum PTH levels can affect the function of vitamin D (Van Slycke et al. 2021). There are limited studies about the ACE2 expression in parathyroid glands, but Hikmet et al. revealed the expression of ACE2 in parathyroid glands in their immunohistochemistry studies (Hikmet et al. 2020). Consistently, Jiang et al. also reported the expression of the ACE2 in the parathyroid glands by detecting the spike protein of SARS-CoV in acidophilic cells of the parathyroid glands in the autopsy of four SARS patients (He et al. 2006). Therefore, involvement of the parathyroid gland could be suspected in COVID-19. Hypoparathyroidism, alterations in serum calcium level and alterations of vitamin D are the most important endocrinologic effects of COVID-19 on parathyroid and its function.

**Hypoparathyroidism**

Elkattawy et al. reported a case of hypoparathyroidism in a COVID-19 patient based on the decline in the level of the PTH, increase in the phosphorous, and normal calcium level (Elkattawy et al. 2020). A similar case has been reported by Dianatfar et al. (2021). Both studies ruled out the possible etiologies for hypoparathyroidism and finally suggested that hypoparathyroidism and hyperphosphatemia could have occurred secondary to COVID-19 infection. There are limitations to these case reports. Since treatment with high-dose vitamin D can cause the same manifestations, the first limitation is the lack of data on the complete drug history of the admitted patient, which is commonly prescribed for COVID-19. The second is the prolonged hospitalization of the patient for about 2 months, which can be considered a reason for chronic stress and may have affected the levels of endocrine hormones. Although no other clear pathophysiology were identified to explain the hypoparathyroidism of this patient, COVID-19 cannot be considered the definite cause of hypoparathyroidism. Moreover, another explanation is the elevated pro-inflammatory cytokine profile that can suppress PTH secretion and could have contributed to hypocalcemia and hypophosphatemia (Fong & Khan 2012). In another study, primary hypoparathyroidism was reported to be decompensated after COVID-19 infection (Bonnet et al. 2021). Further studies are necessary to clarify the effect of COVID-19 infection on the function of the parathyroid glands.
Calcium

Calcium is one of the important electrolytes that participate in several signaling pathways in the body. Calcium has also been shown to play a critical role in the fusion and replication of viruses such as rubella, Ebola, human immunodeficiency virus-1, SARS-CoV, and Middle East respiratory syndrome coronavirus (Marazuela et al. 2020). Hypocalcemia is a common pathologic phenomenon that has been seen not only in COVID-19 but also in other viral infections, including the Ebola virus and SARS (Uyeki et al. 2016). Gustina et al. evaluated the prevalence of hypocalcemia in COVID-19 patients and showed that 82% of the included patients had hypocalcemia (Abobaker & Alzwi 2021). Consistently, another study demonstrated that 67% of severe COVID-19 patients had hypocalcemia (Liu et al. 2020b). Multiple mechanisms can explain COVID-19-induced hypocalcemia. Vitamin D deficiency,
hypoalbuminemia, increase in calcium influx due to the hypoxic injury, impaired intestinal absorption, inhibition of the PTH due to the rise in pro-inflammatory cytokines, and hypoparathyroidism caused by SARS-CoV-2 are the discussed mechanisms (Abobaker & Alzwi 2021). Thus, hypocalcemia could increase the rate of hospitalization, severity, and mortality rate and could serve as a prognostic factor in COVID-19 ICU patients (Martha et al. 2021).

Vitamin D

Vitamin D is a fat-soluble vitamin that regulates the metabolism of calcium and phosphorous. The important source of vitamin D in the body is the skin. In the lower layer of the epidermis, cholecalciferol, the precursor of the active vitamin D, is made from the 7-dehydrocholesterol by UV-B rays. Then, through two biochemical steps in the liver and kidney, it transforms into its active form, 1,25-hydroxycholecalciferol (1,25-vitamin D3). 1,25-vitamin D3 binds with its nuclear receptor and forms a complex that regulates the expression of 900 genes that are responsible for immune response and electrolyte metabolism (Panfili et al. 2021). Vitamin D has an important relationship with immunity and infectious diseases. A meta-analysis has detected the immunomodulatory effect of vitamin D and the relationship between vitamin D deficiency and a higher risk of community-acquired pneumonia (Zhou et al. 2019).

Activation of Toll-like receptors (TLRs) and increase in cathelicidin and β-defensin are coordinated by vitamin D. Its effect on the acquired immune system is via decreasing immunoglobulins and pro-inflammatory cytokines, including IFN-Y, TNF-α, IL-12, IL-17, IL-6, and IL-1B. It is also reported that vitamin D increases anti-inflammatory cytokines including IL-10, IL-5, and IL-4 (Zhang et al. 2012). Vitamin D also promotes anti-inflammatory effects by shifting immune response from T helper 1 to T helper 2 (Mahon et al. 2003).

Several studies have evaluated the relationship between serum vitamin D level and COVID-19 severity. Since the risk of severe infection in COVID-19 patients with vitamin D deficiency is increased, vitamin D could be used as a predictor of poor prognosis in COVID-19 (Carpanagno et al. 2021). Several systematic reviews have been executed to investigate the relationship between vitamin D and COVID-19. These studies mostly believe that a low level of vitamin D is related to an increased risk of infection, severity, and mortality of COVID-19. However, further studies are required to evaluate the benefits of vitamin D supplements in COVID-19 patients (Akbar et al. 2021). Interestingly, T regulatory cells that are known as a regulator of the immune cell activity and a key cell in inhibition of the cytokine storm progression were markedly lower in severe COVID-19 patients. Besides, some reports have also shown the promising effect of vitamin D supplementation on increasing the T-reg levels. The poor prognosis of the vitamin D-deficient COVID-19 patients could be related to increased serum pro-inflammatory cytokines, such as IL-6 and TNF-α. Vitamin D deficiency is also associated with increased thrombotic events that result in multiple organ injuries (Weir et al. 2020). The aforementioned data and the meta-analysis showed the potential role of vitamin D in ameliorating COVID-19 severity in hospitalized patients. The authors also mentioned that more randomized clinical trials were needed to confirm this (Shah et al. 2021). Nevertheless, some recent randomized clinical trials have shown no effect on reducing the intubation rate, in-hospital mortality, length of hospital stay, and outcome in patients that received high-dose vitamin D: (200,000 IU (Murai et al. 2021) and 300,000 IU (Güven & Gültekin 2021).

COVID-19 and neuroendocrinology

RAAS is a hormone-based system that regulates fluid balance and blood pressure. RAAS exerts its function through various mechanisms, such as regulation of vascular tone, circulating volume, sodium and water absorption, and collagen matrix turnover. Renin, angiotensin 2 (Ang2), and aldosterone are the main three hormones of RAAS. Over activation of RAAS is defined by elevated levels of Ang2 and aldosterone (Simko et al. 2021). Ang2 stimulates the production of inflammatory cytokines such as IL-1 and TNF-α. Aldosterone induces IL-6 secretion (Liao et al. 2020). Furthermore, inappropriate activation of RAAS was associated with pathologic conditions such as atherosclerosis, heart and kidney failure, and inflammatory damage such as acute respiratory distress syndrome (ARDS) (Simko et al. 2021). ACE2 is a physiologic regulator of RAAS which suppresses it by converting Ang1 and Ang2 to Ang(1–9) and Ang(1–7), respectively. ACE2/Ang2/AT1R pathway results in pro-inflammatory condition, oxidative stress, fibrosis, vasoconstriction, and inflammation. On the other hand, ACE2/Ang(1–9)/Ang(1–7)/Mas pathway promotes vasodilation and suppresses inflammation and fibrosis. SARS-CoV-2 binds to the membrane ACE2 receptor by its spike (S) protein and infects host cells. Therefore, endocytosis of spike/ACE2 complex leads to an increased level of soluble ACE2 (sACE2) and reduced activity of ACE2 which is accompanied by an elevated level of plasma Ang2 and aldosterone (Simko et al. 2021). Overactivation of the RAAS induces vascular endothelial damage and increases...
insulin resistance (Lisco et al. 2021). RAAS inhibitors (such as ACE inhibitors) application in COVID-19 patients is controversial because these drugs can increase ACE2 expression which can facilitate viral entry. So, it is expected that the severity of COVID-19 increases due to the elevated number of host cells infected by SARS-CoV-2. However, studies show that ACE inhibitors application not only has shown protective effects but also it was not relevant to increased risk of ICU admission (Speth 2020). The effects of ACE inhibitors on the promotion of COVID-19 are under investigation (Fig. 3 and Table 2).

ACE2 is slightly expressed by the pituitary gland, gonadotrope cells, and neural/glial cells (de Melo et al. 2021). Qiao et al. reported the expression of TMPRSS2 in human brain cell lines (Qiao et al. 2020). Two possible pathways could be considered for the neuroendocrine invasion of SARS-CoV-2. The first is anterograde transport of SARS-CoV-2 through the olfactory nerve and the second is through circumventricular organs (Butowt & Bilinska 2020). The pituitary gland is the main neuroendocrine target for the invasion of SARS-CoV-2. Moreover, neuroendocrine hormones, including prolactin, oxytocin, and melatonin, can potentially be used as adjuvant treatment options for COVID-19 which are mentioned in Table 2.

**Growth hormone (GH)**

GH decreases in both males and females, especially after the third decade of life. The level of the GH is higher in females than males, although the level of IGF-1, the mediator of the GH effects at the tissue level, is similar in both genders. Also, the production of GH is reduced in obese patients (Ciresi & Giordano 2017). On the other hand, it has been demonstrated that obese and elderly patients are at a higher risk of COVID-19 infection (Hussain et al. 2020). GH affects immune system function. GH exerts its anti-inflammatory roles by shifting macrophage maturation to the M2 subtype.

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**Figure 3**

The neuroendocrine system involvement in COVID-19. Created by Esmaeilzadeh et al. A full color version of this figure is available at https://doi.org/10.1530/JME-22-0036.
(Villares et al. 2013). Mauro Bozzola et al. showed that the level of IL-6 and TNF-α is higher in GH-deficient patients than in the control group and treatment with rhGH after 3 months reduced the inflammatory factors (Paganì et al. 2005). A low level of IGF-1 and IGFBP3 is associated with lethal ARDS. It is also shown that GH has a beneficial effect on tissue repairing in patients with lung volume reduction surgery (Felbinger et al. 1999). The level of GH is lower in male, obese patients, and elders, groups that are the most vulnerable to severe COVID-19 infection. This could propose a possible role of GH in preventing the progression of COVID-19 (Elkarow & Hamdy 2020). A recent study has shown that the IGF1 level in critically ill COVID-19 patients and non-survivors is lower than in non-critically ill patients and survivors (Ilias et al. 2021). Therefore, the low level of IGF1 is associated with poor outcomes in COVID-19 patients. This study had some significant limitations. The evaluation for medication use or conditions such as obesity, hepatic, or renal dysfunction which can affect IGF1 level was not considered. Considering the beneficial effect of these hormones on immune system and lung tissue repairing, hormone replacement therapy might be a conservative treatment in patient (Lubrano et al. 2020).

**Hypophysis apoplexy**

Pituitary apoplexy (PA) is defined as hemorrhagic or non-hemorrhagic necrosis of preexisting pituitary mass. There are several cases of PA secondary to COVID-19. An 84-year-old male presented with a drug history of aspirin and enoxaparin, due to a history of ischemic heart disease and atrial fibrillation, respectively. He presented with frontal headache, nausea, vomiting, photophobia, bilateral ptosis, anisocoria, and ophthalmoplegia 3 weeks after discharge. Notably, the secretion of hormones regulated by the anterior pituitary, including cortisol and thyroxin, was reduced. The diagnosis of PA was confirmed based on MRI. However, considering the existence of risk factors of anticoagulant treatment, the certain casualty between COVID-19 and PA is suspicious (Gianotti et al. 2021). Also, Kamel et al. reported a case of PA in a 55-year-old male COVID-19 patient with the presentation of oculomotor nerve palsy and declined visual acuity (Kamel et al. 2021).

**Central diabetes insipidus (CDI)**

A 60-year-old female was referred with nocturia, polyurea, and polydipsia 2 months after the diagnosis of COVID-19. Her laboratory findings, including serum and urine osmolality, were suggestive of CDI. The magnetic resonance imaging (MRI) study revealed thickening of the pituitary stalk and enlargement of the pituitary gland which implied infundibulo-neuro-hypophysis (Misgar et al. 2021). Another explanation for CDI can be the hypoxic encephalopathy induced by the hypoxic state of COVID-19 (Lisco et al. 2021). Therefore, neuroendocrine involvement in recovered COVID-19 patients should consider a long-term complication.

**Central hypocortisolism**

Chua et al. reported a 47-year-old male patient with recent COVID-19 in his convalescent phase to develop eosinophilia and dyspepsia. His 08:00 h serum cortisol and ACTH levels were reduced to 19 nmol/L and 7.1 ng/mL, respectively (Chua & Chua 2021). This study emphasizes the probability of late emergence of central hypocortisolism during or after the remission phase of COVID-19.

**COVID-19 metabolic complications**

DM and obesity are the most important endocrine dysfunctions that weaken the prognosis of COVID-19 patients. Moreover, metabolic dysfunction such as dyslipidemia and increased leptin are frequently observed in COVID-19 (Montefusco et al. 2021). Therefore, a precise understanding of metabolic dysfunction is necessary for COVID-19.

**Obesity and hyperlipidemia**

Obesity is a metabolic and systemic condition in which the accumulation of fat in the adipocytes results in hyperplasia and hypertrophy of the adipose tissue. The relationship between obesity and other comorbidities, including hypertension, stroke, atherosclerosis, cancers, and diabetes is well established. Ritter et al. showed that obese COVID-19 patients had higher mortality, severity, risk of infections, and also poor outcome (Ritter et al. 2020). The mechanism proposed for this is that the adipose tissue is not only a place for the accumulation of fat but also it is considered as an endocrine organ that plays important roles in the body by secreting a variety of hormones, proteins, and cytokines. Thus, attention is needed to investigate how obesity causes poor outcomes in COVID-19 patients. One possibility could be the ACE2 expression in adipocytes. Al-Benna et al. observed that ACE2 gene expression in visceral and subcutaneous adipose tissue is higher than in the lung. This could be explained by the poor outcome in obese COVID-19 patients (Al-Benna 2020). However, the studies
showed that obesity was correlated with a dysregulated immune response that results in chronic systemic inflammation, and it could predispose the obese COVID-19 patients resulting in ARDS and poor outcomes (Ritter et al. 2020). M1 macrophages, Th-1, B cells, neutrophils, and mast cells are higher than the M2 macrophages, Th-2, and regulatory T cells in obese patients. These conditions shift the immune responses from the anti-inflammatory situation to pro-inflammatory mechanisms. This pro-inflammatory condition is orchestrated by secretion of the IL-6, IFN-γ, IL-1β, MCP-1, and other pro-inflammatory adipokines that result in chronic and systemic inflammation (Louwen et al. 2018). Voort et al. found higher leptin levels in ventilated SARS-CoV-2 patients compared to a control group. It was concluded that excessive adipose tissue and higher leptin levels in obese COVID-19 patients may play a role in the development of respiratory failure and ARDS. The authors also proposed that these results may help scientists to find a better way to prevent obese patients from developing respiratory failure induced by COVID-19 (van der Voort et al. 2020). Leptin is one of the pro-inflammatory adipokines secreted by the adipose cells. However, adipose tissue can produce anti-inflammatory adipokines, such as adiponectin. Kears et al. evaluated the level of adiponectin in COVID-19 patients. They revealed that adiponectin level in the plasma of the COVID-19 patients with respiratory failure was significantly lower. Due to the anti-inflammatory, antioxidants, and insulin-sensitizing activity of the adiponectin, the authors proposed that increasing the levels of adiponectin in obese COVID-19 patients could ameliorate the prognosis of the obese COVID-19 patients (Kears et al. 2021). It seems that adipose tissue plays a major role in the immune-pathophysiology of the COVID-19; however, it needs further evaluation to confirm, and in the future, it may become a promising target for treatment in COVID-19 patients.

Concluding remarks and future prospects

Endocrinological complications of COVID-19 can significantly affect the prognosis and mortality of the patients. Understanding the pathophysiology of these complications can provide a rationale for timely diagnosis and management of the complications which can finally improve the outcome of the patients. Normal thyroid and adrenal function are necessary for body metabolism during stresses, such as COVID-19 infection. An underlying endocrinological disease can exacerbate COVID-19 severity (Baldelli et al., 2021, Esmaeilzadeh et al. 2021b). On the other hand, COVID-19 can alter the physiologic function of endocrinological organs. NTIS and AI are objective examples of this. Secondary to CIRCI or AI, the demand for glucocorticoids is increased in COVID-19 (Bellastella et al. 2020). As a viral infection, COVID-19 can also cause different types of thyroid inflammation, including SAT, ST, PT, HT, and GD (Khoo et al. 2021). Acute and necrotizing pancreatitis are two major complications of pancreas involvement by COVID-19 that can be lethal if not appropriately managed (de-Madaria et al. 2020). Hyperglycemia, caused by impaired glucose tolerance and insulin resistance, is commonly observed in hospitalized COVID-19 patients that can even progress to DKA/HHS, which are life-threatening conditions. Therefore, strict BS control and application of insulin or other glucose-lowering drugs must be considered, especially in ICU patients (Chen et al. 2020a).

Hypocalcemia, commonly induced by hypoparathyroidism and hypovitaminosis D, has been observed in COVID-19 patients. Therefore, treatment with calcium-D supplements might ameliorate hypocalcemia and vitamin D deficiency and are recommended in

Effects of COVID-19 on hepcidin metabolism

Hepcidin is a peptide hormone that is produced by the liver and regulates iron metabolism. Hepcidin reduces iron uptake and transport through inhibition of the ferroportin in hepatocytes, macrophages, and enterocytes. Studies have shown that the level of serum hepcidin is altered in COVID-19 patients. In a cohort study of 111 COVID-19 patients, the serum level of iron was decreased in 93.7% of the patients and the serum level of hepcidin was increased in 61.3% of the patients (Silvestri et al. 2021). In another study, Zhou et al. reported that increased serum levels of hepcidin and ferritin were associated with more severe outcomes in COVID-19 patients. Therefore, the levels of hepcidin and ferritin could be considered predictor marker for COVID-19 severity (Zhou et al. 2020a). Moreover, hepcidin inhibits ferroportin of macrophages that causes iron retention, macrophage activation, and ferritin secretion. These events result in hypoferremia. Hypoferremia impairs lymphocyte function and causes anemia. Furthermore, the macrophage activation leads to the production of the pro-inflammatory cytokines, including IL-6. Considerably, IL-6 also induces the production of hepcidin from hepatocyte which results in impaired function of the immune system (Girelli et al. 2021). Altogether, elevated serum levels of hepcidin and ferritin deteriorate the inflammation in COVID-19 which is associated with poor outcomes.
COVID-19 patients (Di Filippo et al. 2020). Alterations in sex hormone levels can present as hypogonadism; however, the effect of COVID-19 on fertility has not been elucidated, yet. One important issue that has recently been observed and requires more attention is pituitary apoplexy which can lead to critical subsequences and must be considered in symptomatic patients after COVID-19 infection (Gianotti et al. 2021). Metabolic disorders such as hyperlipidemia (HPL) and obesity are associated with poor prognosis. In COVID-19, the increase in leptin and decrease in adiponectin levels deteriorate the inflammatory condition and the prognosis (Cai et al. 2020). Electrolyte imbalance, presenting as hypokalemia, hyponatremia, hyperkalemia, and hypernatremia, is observed in COVID-19 patients and can exacerbate the patient’s clinical conditions and even lead to cardiac arrhythmia in COVID-19. To prevent this, fluid resuscitation and electrolyte management in COVID-19 patients is necessitated (Chen et al. 2020b). According to their anti-inflammatory effects, some endocrine hormones such as oxytocin, melatonin, prolactin, and testosterone are considered potential therapeutic options to reduce the severity of COVID-19 infections.

Since corticosteroids, including prednisolone and dexamethasone, are one of the mainstem therapies for COVID-19, the potential short- and long-term impact of corticosteroids, as anti-inflammatory drugs, should be addressed. Several studies have shown that corticosteroid therapy could reduce the mortality rate and need for mechanical ventilation in severe COVID-19 patients (Tlayjeh et al. 2020, Piniella-Ruiz et al. 2021). However, corticosteroid therapy might be associated with several side effects in different organs, including the adrenal gland. These adverse effects depend on dose, duration, and type of corticosteroid. Moreover, older age patients, comorbid conditions, usage of other immunosuppressive agents, and severity of underlying disease are other factors that could affect the incidence of these events (Miravitlles et al. 2021). Systemic corticosteroids administration increases the level of fasting glucose and insulin resistance which result in hyperglycemia or difficult glycemic control in the level of fasting glucose and insulin resistance which (2021). Systemic corticosteroids administration increases the level of fasting glucose and insulin resistance which could affect the incidence of these events (Miravitlles et al. 2021). Therefore, the administration of the appropriate dose and duration of corticosteroids should be considered to prevent any possible adverse effects.

In conclusion, current studies have demonstrated the importance of endocrinological complications in COVID-19. Further studies are required to determine the effect of these complications on COVID-19 prognosis and the efficacy of hormone-based interventions both in prophylaxis or treatment of COVID-19 (Table 2).

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