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Review Article

The Impact of COVID-19 (SARS-CoV-2) Virus Infection on the Endocrine System: A Review Study

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Abstract

The global coronavirus disease 2019 (COVID-19) pandemic is rapidly growing, and high mortality rates are reported in this regard. Coronaviruses are known to cause multi-organ system damage. Few data are available on the impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on different endocrine glands. As angiotensin-converting enzyme-2 (ACE2) receptor is extensively expressed in the endocrine organs, and thus several important questions have arisen regarding whether the function of the endocrine organ changes in COVID-19 disease and patients with the SARS-CoV-2 infection develop endocrine disorders. Databases including PubMed, Web of Sciences, Scopus, and Google Scholar were searched for studies published from 1996 to February 15, 2021. New-onset diabetes mellitus has been reported by different studies at rates ranging from 5.8% to 35%. Hypercortisolism in admission time could predict disease severity. Tissues from the hypothalamus and the pituitary gland in animals are rich in ACE2, and some endocrinopathy may be secondary. Thyroiditis and thyrotoxicosis have also been recognized in the COVID-19 infection. Hypocalcemia and vitamin D deficiency may be correlated with disproportionate parathormone levels. Patients with decreased serum calcium levels had worse clinical variables and higher incidences of complications such as septic shock. Men are more susceptible to hypogonadism, and differences in the COVID-19 infection and mortality rates between males and females are due to the differential effects of estradiol and testosterone on the immune system. Considering that different glands have the ACE2 receptor, the coronavirus may be able to alter their function. Hence, this review mainly focused on COVID-19-associated endocrinopathy.

Keywords: Coronavirus disease 2019, Pancreas, Adrenal, Thyroid, Sexual gonad

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Introduction

The coronavirus 2019-nCoV (COVID-19) pandemic is rapidly growing around the world due to its highly contagious nature and has led to a high mortality rate during this outbreak (1).

It is well established that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) uses angiotensin-converting enzyme 2 (ACE) as a receptor to enter host cells (2, 3). ACE2 is expressed in different endocrine tissues (4). Thus, several important questions arise in this regard. Does the function of the endocrine organ change in COVID-19? Moreover, do patients with SARS-CoV-2 infection develop endocrine disorders?

According to the existing studies, it seems coronaviruses are known to cause the signs and symptoms of multi-organ system damage (1).

This review focuses on possible changes in various glands and endocrinopathy caused by a coronavirus, as well as the medical precautions required in concomitant endocrine disorders in patients affected with COVID-19.

Materials and Methods

In this review, several electronic databases were searched, including PubMed, Web of Science, Scopus, EMBASE, Cochrane Library, and Google Scholar for relevant studies published from 1996 to February 15, 2021. The search was conducted using the combinations of relevant medical subject headings terms as coronavirus disease 2019, SARS-CoV-2, 2019 novel coronavirus, COVID-19 virus, hormones, endocrine systems, diabetes mellitus, pituitary, thyroid, gonadal steroid hormones, and sex steroid hormones. The search was limited only to English articles including abstracts.

Diabetes

New-onset Diabetes Mellitus

The occurrence of diabetes in 15% of 1099 Chinese people with SARS-CoV-2 is documented in previous research (5). In addition, the United States reported a rate of 11% of diabetes in COVID-19 patients (6). Moreover, one study (7) reported the prevalence of diabetes of 8.2% in 1590 hospitalized patients with SARS-CoV-2 in China with a median age of 48.9, but these rates were higher in severe patients compared to non-severe ones (34.6% vs. 14.3%). It seems that the rate of diabetes in subjects with SARS-CoV-2 is related to age, kind of study population, the severity of illness, and likely type of diabetes (8). Nonetheless, diabetes may be an important risk factor affecting the clinical severity of SARS-CoV-2 and subsequently the risk of death (9-13).

Moreover, in a Chinese retrospective analysis, COVID-19 patients with diabetes had more severe pneumonia, high levels of inflammatory and coagulation factors, and fewer lymphocytes, but a higher level of neutrophil (10). Considering the mentioned information, the possible mechanisms increasing the risk of developing severe coronavirus can be divided into several categories, including high affinity and binding of the virus to its receptor, the immune system disorders and inflammation reaction abnormality in diabetic people, decreased virus clearance, and inappropriate functions of the lungs in these patients, as well as comorbidities and complications that are associated with diabetes and COVID-19 (14-16).

High mortality of COVID-19 patients with diabetes may be due to the overexpression of the furin protease enzyme in diabetic people (17). The furin is a cellular endoprotease that proteolytically activates many proprotein substrates such as growth factors, receptors, extracellular matrix proteins, and pathogenic factors. Fernandez et al showed a high concentration of plasma furin in diabetics, reporting that more circulating furin can be a compensatory response to increase the synthesis of active insulin receptors because of the role of furin in the maturation of insulin receptors (17). During the SARS-CoV-2 infection, furin cleaves the S1/S2 furin-like cleavage site in the spike (S) protein of the virus and facilitates viral entry into the target cells after the binding of the spike glycoprotein of the virus to ACE2 on the host cell surface (15). In turn, elevated furin can predominantly start and promote the infection in diabetes individuals with COVID-19. It may enhance viral load in the target sites that have more furin, including lungs, kidneys, and atherosclerotic plaques, resulting in lethal complications such as acute respiratory distress syndrome, acute kidney injury, and cardiovascular disease by plaque instability (15). Additionally, furin is completely necessary for the blood coagulation process and blood hemostasis (18), thus it is assumed that the enhancement of furin in diabetic patients with SARC-CoV-2 may accelerate the rate of mortality in these people by blood clots. Furthermore, the increased expression of ACE2 during diabetes in the lung, kidney, heart, and pancreas may be another reason for more affinity cellular binding and extensive virus entry (19-21). It is speculated that diabetic patients, because of higher affinity to SARC-CoV-2, may be exposed to further increased risk of the virus.

Impairing the adaptive immune response to the virus and enhancing the inflammatory reaction of the innate immune system can exacerbate adverse effects in diabetic patients with the SARS-CoV-2 infection (22). The dysregulation of the immune system during hyperglycemia and diabetes mellitus has been documented by some studies (23, 24). Defects in the adaptive immune system can blunt the anti-viral interferon-γ response of T lymphocytes by elevated production of advanced glycation end-products and diminished count of T lymphocytes in diabetic conditions (16). Further, less count of T lymphocytes and more leukocytes and neutrophils were observed in patients with severe COVID-19 with diabetes in comparison with non-diabetic ones (10, 11, 25). Therefore, reduced antiviral activity may increase the severity of infections in diabetic individuals with COVID-19.

On the other hand, delay in the initiation of adaptive immunity can induce abnormality in inflammatory reactions such as high production of interleukin-6 (IL-6), IL-2, IL-8, and tumor necrosis factor alpha in diabetic people, probably triggering cytokine storms (16). Then, it is assumed that inflammatory reactions are more severe in patients with severe COVID-19 and diabetes (11, 25). Accordingly, these patients are at an increased risk of uncontrolled inflammations and adverse outcomes.

Low lung function has been known in diabetes people. Furthermore, some animal and human studies identified alveolar-capillary micro-angiopathy and interstitial fibrosis in diabetic cases that can affect pulmonary diffusion function (26-28). Therefore, they may be at increased susceptibility and risk for viral infections such as SARS-CoV-2. In addition, a recent finding reported that the clearance of SARS-CoV-2 is prolonged in the respiratory system of diabetic people (29). Consistent with these reports, the symptoms of cough and dyspnea were non-significantly higher in diabetes patients with severe COVID-19 (11).

The weak prognosis and mortal effects of diabetes on COVID-19 can mainly be related to comorbidities and/or complications that are associated with diabetes, including hypertension, cardiovascular disease, chronic kidney disease, and thrombophilia (11, 30). Similar to diabetes, all these comorbidities are mostly prevalent in COVID-19 (30). The large numbers of the diabetic population have asymptomatic coronary artery disease. Hence, if affected by SARS-CoV-2, these people are more prone to undesirable consequences such as acute

coronary syndrome, heart failure, and arrhythmia because of the hyper-inflammatory process and intensive coagulation responses (30). Likewise, it seems that the down-regulation of circulating microRNA-146a (miR-146a) in patients suffering from comorbidities such as diabetes, hypertension, and obesity may contribute to severe COVID-19 because miR-146a is able to modulate excessive inflammatory responses to the virus in the recipient cell (31).

The Effect of COVID-19 on the Pancreas and the Development of Acute Hyperglycemia

Recent studies suggest that there may be a two-way link between diabetes and COVID-19 (14, 32-35). According to one report, ACE2 is one of the important physiological regulators in inflammation and glucose homeostasis and is expressed in the pancreas (8). It has been specified that the expression of ACE2 in the pancreas of normal people is slightly more than lungs, as the first target organ of the virus. Additionally, it is expressed in the glands of the exocrine and endocrine in the pancreas (33, 34). It is thought that SARS-CoV-2 may combine with ACE2 in the pancreas to enter cells and result in pancreatic injury when it is circulating into the blood. Consistent with this hypothesis, a retrospective study at Wuhan reported the signs of pancreatic injury such as the elevated level of amylase and lipase, which was 1.85% in mild and approximately 17% in severe COVID-19 ones (33). Moreover, pancreatic lesions were constructed in 7.46% of severe COVID-19 patients, mostly including the focal enlargement of the tissue or dilatation of the pancreatic duct, although pancreatic damages were mild (33, 34). Similarly, the systemic inflammatory response in severe COVID-19 patients might create mild damage to the pancreas (34). Thus, it is suggested that damage to the islets and endocrine parts of the pancreas by SARS-CoV-2 may alter glucose metabolism and may complicate the pathophysiology of pre-existent diabetes or create new-onset diabetes in non-diabetic people, leading to the impairment of insulin secretion in ß-cell and intensification of insulin resistance (33-35). The findings of a retrospective study in two hospitals at Wuhan showed that fasting blood glucose ≥7.0 mmol/L at admission in patients with COVID-19 without a former diagnosis of diabetes could be an independent predictor for mortality (36). Furthermore, some studies demonstrated hyperglycemia following COVID-19 even in people without any previous history of diabetes (32, 36-38). Interestingly, the high prevalence of fasting glycaemia and first appearance diabetes were reported among patients with the SARS (39). SARS in 2003 was caused by another coronavirus, which is closely similar to SARC-CoV-2 and uses ACE2 to enter to host cells (40). Yang et al followed cases who experienced hyperglycemia during the hospitalization by SARS-CoV. This 3-years-follow-up determined that the damage of the pancreas and diabetes was transient because diabetes was only continued in two of 20 diabetic-SARS-CoV patients after 3 years (39).

The short- and long-term diabetic effects of SARS-CoV-2 are not determined yet. Hence, a comprehensive follow-up is required for understanding the development of COVID-19-related diabetes.

COVID-19-Associated Adrenal Disorder

Various physiological stresses increase the serum cortisol level by activating the hypothalamic-pituitary-adrenal (HPA) axis. It also reduces cortisol metabolism and cortisol-binding globulin, enhancing cortisol bioactivity. Plasma cortisol elevation due to the body's stress response is crucial for inducing adjustable changes in the immune system, metabolism, and cardiovascular function (41). The physiologic cortisol requirements might unbalance in conditions of organic and/or psychological changes such as the COVID-19 pandemic (42). The proper response of the HP axis determines the body's function in the face of diseases, and an increased or decreased response can increase the mortality rate (43).

So far, there have been scarce data about adrenal changes in SARS-CoV-2 patients, Tan et al measured the baseline serum cortisol within 48 hours of admission in COVID-19 suspected infected patients with no signs of adrenal insufficiency or glucocorticoid treatment. The median cortisol concentration was 22.43 µg/dL [the interquartile range (IQR) 16.53-30.19] in COVID-19 patients versus 18.81 µg/dL [IQR 13.7-24.79] in the patient group who did not have COVID-19 (P<0.0001). The elevation of serum cortisol was the prognosticative of acute mortality. The patients with a cortisol level ≤ 26.97 µg/dL had a median survival longer than those who had a cortisol level >26.97 µg/dL. Based on the results of a study, doubling cortisol levels increased the hazard of mortality by 42%. (41). High cortisol levels at admission time are probably correlated with the severity of systemic disease and less survival among patients with severe COVID-19. In this cohort study, they did not clearly observe adrenal insufficiency in the acute phase of the COVID-19 infection. The serum cortisol is a marker of the severity of illness, and it is also a better marker compared to C-reactive protein (CRP), D-dimer, and the neutrophil-to-leukocyte ratio for the severity and mortality rate of the COVID-19 infection (41).

In another study on intensive care unit (ICU) COVID-19 positive (confirmed by clinical and radiological characteristics) and ICU non-COVID-19 patients, the median amount of serum cortisol on the first day of ICU admission was 21.84 µg/dL (18.22-30.11) and 16.47 µg/dL (13.73-19.13), respectively, which was significantly different between the two groups (the patients on mechanical ventilation were excluded from analysis). In COVID-19 patients, other laboratory tests such as CRP,

creatinine, D-dimer, aspartate aminotransferase, and neutrophil-to-leukocyte ratio were higher than in non-COVID-19 ICU patients, highlighting further severity of the disease in SARS-CoV-2, ICU patients (43). This could be due to the direct attack of the virus on adrenal glands, and inflammatory cytokines probably activate the HPA axis (44). Second, the news of a pandemic causes severe stress on people, and the fear of death increases cortisol more (43, 45). The researchers stated that the lowest and highest amounts of cortisol were observed in non-COVID-19 living patients and dead COVID-19 patients in two COVID-19 and non-COVID-19 patient groups. In the multivariate logistic regression analysis, compared to other laboratory tests, only the amount of cortisol was statistically significant. The cortisol cutoff point was 31 µg/dL; thus it could be a marker to find patients at risk of death to attract more attention to these patients (43).

In another small sample-size study, only 28 COVID-19 positive patients, most of whom were afflicted with asymptomatic or mild disease, had cortisol, adrenocorticotropic hormone (ACTH), and dehydroepiandrosterone sulfate (DHEAS) levels that were measured in the 24-48 hours of the hospital admission time. The median of cortisol, ACTH, and DHEAS was 7.1 µg/dL [1.12-21.27], 18.5 ng/L [4-38], and 3 µmol/L [0.27-11], respectively. These tests were repeated several times in the coming days in 20 patients. Cortisol decreased in 7 patients and adrenal insufficiency was diagnosed in these cases accordingly. One and two patients had one-time hypoglycemia and hypotension, which are two important signs of adrenal insufficiency. Cortisol and ACTH decreased to the least level of their concentration, but DHEAS was in a normal range in the repeated following days. The authors concluded that their patients developed secondary adrenal insufficiency. This study had two limitations. An extremely small sample size was included in this study, and most patients were asymptomatic or had mild COVID-19 characteristics. The authors concluded that secondary adrenal insufficiency may have happened (44), but it needs more investigational in-vitro studies, animal models, and clinical trials. COVID-19-induced adrenal hemorrhage has been reported in several clinical cases that occasionally lead to adrenal insufficiency (46-47), and in a case series of an autopsy, it has been observed in patients who died from COVID-19, adrenal micro-infarction, and adrenal lesions (48, 49). Therefore, hypoadrenalism can be fatal in some patients (50).

Adrenal insufficiency diagnosis depends on the amount of blood protein. If blood albumin is normal (≥ 2.5 g/dL), serum cortisol less than 10 µg/dL is considered adrenal insufficiency. A cortisol level of more than 15 µg/dL is normal. Nevertheless, if the blood albumin is <2.5 gr/dL, the serum cortisol level less than 8 µg/dL is considered adrenal insufficiency, and over 11 µg/dL is normal. A cosyntropin stimulation test is necessary for diagnosing adrenal insufficiency between the minimum and normal levels, (51). The previous section explained that cortisol levels were related to albumin concentration, but most studies measured cortisol without measuring albumin. More detailed, longer, and complete studies are needed to investigate the chronic effects of SARS-CoV-2 on the adrenal glands. Studying patients who survived from SARS-CoV with no previous endocrine disorders revealed that they had transient hypocortisolism after recovery. Nearly 40% of the patients had hypocortisolism three months after recovery, and 83.3% of them had secondary hypocortisolism and low ACTH levels. Moreover, most of these patients had taken no exogenous glucocorticoids drugs at the time of illness. Orthostatic hypotension was the most prevalent symptom among the recovered patients (52). Although hypotension is highly common in COVID-19 patients, some studies have shown acute adrenal insufficiency, which needs more investigation.

Steroid Hormone and ACE2

ACE2 is a well-established protective arms' component of the renin-angiotensin-aldosterone system (RAAS) that prevents ACE/angiotensin II (ANG II) pressor effects and tissue remodeling action (53). Prescribing mineralocorticoid receptor (MR) antagonists in patients with hypertension and cardiovascular diseases may cause up-regulating ACE2 expression in target cells (54). Steroid hormone receptors determine the components of the RAAS and may have determined different severity levels in COVID-19 between men and women and in patients with pre-existing endocrine-related disorders. The receptor for aldosterone was identified in many tissues such as the cardiovascular system, cardio-myocytes, and vessel wall not necessarily involved in the control of the blood volume in the kidney. The prescribed angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and MR antagonist drugs in many diseases can elevate ACE2 expression, resulting in sensitivity to viral infections and/or viral loads (55).

A large-scale study in Italy reported that the use of ACE inhibitors and ARBs was more frequent among patients with SARS-CoV-2; however, there was no evidence indicating that using ACE inhibitors or ARBs affect the risk of COVID-19, and new recent information represented that patients who continue taking ACEi/ARB medication have a lower risk of all-cause mortality (56).

There are local tissue RAASs in many peripheral organs having autocrine, paracrine, and intracrine effects that differ from those of the circulating RAAS. Therefore, steroids may be effective on the COVID-19 infection by acting on the RAAS (55).

Concomitant COVID-19 and Adrenal Disease

Addison

Based on our current literature, insufficient data exist confirming that patients with adrenal insufficiency are

at increased risk of COVID-19 infection, and they are probably more prone to greater risk of complications because of the potential for the adrenal crisis that can be triggered by the infection (57).

Impaired natural immunity and the dysfunction of neutrophils and natural killer cells are among the leading causes of increased mortality and increased probable risk of the coronavirus in these patients. Likewise, the lack of a proper increase in the dose of hydrocortisone at the onset of the infection is probably one of the reasons for the higher mortality rate and medical complications in these patients (57). In patients with adrenal insufficiency and the symptoms of COVID-19, the dose of glucocorticoid drugs should be at least doubled to avoid an adrenal crisis. Therefore, the "sick days" rule should be established in the cases of suspected COVID-19 with the slightest symptoms (42).

Cushing's Syndrome

Cushing's disease patients and patients who use supra-physiologic doses of steroid drugs could be at a higher risk of the COVID-19 infection due to the potential immunosuppressive action of steroids, and because of probable adrenal insufficiency, patients should take more caution (42).

High-dose and chronic use of corticosteroids can lead to the onset of diabetes. In people who have recently been diagnosed with diabetes, chronic use of corticosteroids results in a 94% higher risk of hospitalization due to diabetes complications. Complications such as high blood sugar and changes in lipid and bone metabolism lead to severe consequences in patients with diabetes (58).

Glucocorticoids Drugs

Regardless of serum cortisol levels, glucocorticoid drugs are used in many critical diseases such as viral infections, including respiratory syncytial virus, and influenza, as well as Middle East respiratory coronavirus and SARS. However, their benefits are not highly clear and their use in COVID-19 is debatable (59). Although routine use of glucocorticoids is not recommended by the World Health Organization (WHO), these drugs are applied in COVID-19 cases due to the presumption of cytokine storm caused by the virus that can be averted by the use of glucocorticoids (59).

In the study by Young et al, prescribing dexamethasone (6 mg/d, once daily for up to 10 days) in COVID-19 patients to usual care demonstrated that mortality reduced to one-fifth and one-fourth in patients receiving oxygen alone and mechanical ventilation, respectively. However, there was no advantage in patients who did not need oxygen (55).

In a meta-analysis study on 7737 patients, 36% of patients received glucocorticoid drugs in addition to standard treatments. Mortality rate and the need for mechanical ventilation were significantly reduced in these patients, and superinfection with corticosteroid was not observed in these cases. It seems that these drugs are effective only when the COVID-19 is moderate or severe. Moreover, their proper use in the stage of hyper-inflammation, which is usually the second week after the onset of symptoms, should be taken into consideration (60).

During the infection, rising circulating glucocorticoid concentrations is crucial for survival. In different diseases such as hypovolemic shock due to the infection and cytokine storm diseases, inadequate corticosteroid production could be fatal, but the dose range is highly important. Prescribing the right dose at the right time can be critical as well. High levels of glucocorticoids are immunosuppressive and can increase the risk of fatal infection consequences (55).

Hypothalamus and pituitary

According to some studies, there is a connection between the SARS-CoV-2 infection and a wide range of neurological signs and symptoms such as headaches, dizziness, nausea, loss of consciousness, seizures, encephalitis, and the like (61-64). Hypothalamus and pituitary (HP) tissues are rich in ACE2 in animals (34, 65, 66). Furthermore, changed levels for several hormones in the postmortem human pituitary tissue and some survivors of the SARS-CoV infection have long-term neuroendocrine deficits that strongly support the opinion of the hypothalamus as a target of the viral infection (5, 67-69).

Intriguingly, dysfunctional hypothalamic neural networks could be the major risk factors for severe COVID-19 (5, 67, 69). Coronavirus can affect any organ during the viraemic phase, because some forms of endocrine disorders, including hypophysitis, thyroiditis, and adrenalitis have viral etiologies (70, 71).

Hypothalamus controls a broad spectrum of physiological processes such as differentiation and control of pituitary gland hormone production, energy homeostasis, and fluid homeostasis/osmoregulation. The hypothalamus is directly connected to other parts of the central nervous system involved in functions affected in COVID-19 patients (e.g., several brainstem nuclei that control fluid homeostasis, cardiac function, and respiration). It is also associated with regions involved in the perception of odor and taste, including the olfactory bulbs and presumptive vomer nasal neurons, along with piriform cortices, the insula, amygdala, and thalamus (72-74).

Some studies demonstrated the detection of neuronal degeneration and brain edema, along with the SARS genome in the hypothalamus 40, 41, 52).

Similarly, Leow et al reported the biochemical evidence of HP involvement in SARS (52). The survivors of SARS had evidence of central hypocortisolism and central hypothyroidism. Hypophysitis or a direct hypothalamic injury could have caused a state of HP dysfunction; nonetheless, considering that SARS-CoV-2 has a high

frequency of neurological symptoms, it can be assumed that SARS-CoV-2 may also affect the HP directly or by immune-mediated hypophysitis (75).

Hypothalamus releases corticotropin-releasing hormone (CRH), which induces a systemic response to stress. Further, it triggers neuro-endocrinological pathways, including the activation of the HPA axis, sympathetic nervous system, and angiotensin, and finally releases stress hormones such as corticosteroids, catecholamines, glucagon, growth hormones, and renin (76). This function of these hormones, along with stress-induced cytokines causes an acute-phase response and the activation of acute-phase proteins, which are considered important inflammation mediators (77). In addition, both stress and inflammation are mediated by the CRH. An inflammatory or stress response can evoke cytokines that cross similar somatosensory pathways to signal the brain (77).

Incessant and repeated acute or chronic stress can cause chronic inflammatory changes in the brain and other organs. Previous research showed that psychological stress increases the risk of acute upper respiratory tract infections (77). These repeated stressful events and uncontrolled inflammatory responses increase vulnerability to get respiratory tract infections (78).

SARS-CoV could enter the brain via an ACE2 receptor located in the olfactory bulb (79) and lead to anosmia and ageusia. These symptoms could be related to a local or central pathology such as damage to the hypothalamus leading to hormonal deficiencies (80).

Both subunits (S1 and S2) of the SARS-CoV are known to bind to ACE2 receptors, leading to its down-regulation and causing further reductions in ACE2 cell surface expression, thus increasing AII production. On the HP tissue, decreased ACE2 cell surface expression results in the hyperactivity of the ACE–AII–AT1R axis in the hypothalamus, where ACE2 receptor levels are normally low, making it more sensitive to dysfunction and leading to partial or total loss of smelling sense, which has been reported as one of the first symptoms of the COVID-19 infection (81-83).

Thyroid and Coronavirus

Studies demonstrated that the presence of ACE2 and transmembrane protease, serine 2 (TMPRSS2) in thyroid follicular cells is more considerable compared to the lungs (84-87). In accordance with these issues, thyroiditis (88) and thyrotoxicosis have been recognized during the COVID-19 infection (86, 89, 90). Neck pain and swelling of the thyroid gland develop after an upper respiratory tract viral infection (91). Data on thyroid problems during the COVID-19 pandemic are scarce. However, some studies demonstrated that the complex effects of this new type of virus share many similarities with the other strain of the coronavirus, namely, SARS-CoV (92). One recent study has reported that the serum level of thyroid-stimulating hormone (TSH) and total triiodothyronine (T3) significantly decreased by the coronavirus infection in 50 Chinese patients with no previous history of thyroid diseases. The prevalence of thyrotoxicosis was investigated in 93 Italian individuals with COVID-19 and it was found that 14 patients had thyroid dysfunction while most of them were men (93). In accordance with this observation, the findings of other studies addressing endocrine disorders among 287 patients indicated a higher incidence (20.2%) of thyrotoxicosis due to the inflammation of the thyroid (89, 94). It is known that systemic inflammation or immune activation induced by the COVID-19 infection has provoked thyrotoxicosis by elevated IL-6. Han et al concluded that serum IL-6 levels could be an indicator of disease severity caused by the coronavirus so that the level of IL-6 was higher when the disease was more severe (95).

It should be noted that two main possible mechanisms by which the pandemic situation can lead to thyroid dysfunction, include directly and indirectly effects (94); this virus can attack the pituitary-thyroid axis, leading to direct cellular destruction with apoptosis (86).

The indirect insult of the coronavirus refers to the hyperactivity of the immune response, including Th1/Th17 that induce the release of pro-inflammatory cytokines during cytokine storm complication. Accordingly, inflammatory thyroiditis was observed during viral infections (96). The elevation of the concentration of ILs, especially IL-6, causes the impairment of thyroid hormone transport proteins and pituitary cell TSH secretion, leading to a decrease in free T3, T4, and TSH concentrations, and this pathological condition is called 'euthyroid sick syndrome' (89, 94).

Autoimmune thyroid disorders such as Graves' disease, and infrequently, chronic autoimmune thyroiditis are rarely associated with cytokine storm and immune function imbalance. However, primary hypothyroidism may develop after cytokine storm and autoimmune thyroiditis induced by the SARS-CoV-2 infection (84, 89). The viral infection stimulates acquired and innate immunity, and the thyroid tissue could be the target of the immune cells such as T-cells. Finally, this gland is damaged through hyper-inflammatory syndrome and cytokine storm induced by the immune system during this pandemic (97).

It should be noted that management considerations of patients with underlying hypothyroidism and primary hypothyroidism during the viral infection are strongly recommended since thyroid dysfunction is etiologically related to infection with COVID-19. In addition, extra caution is required for patients on anti-thyroid drugs (92). Patients suffer from short- and long-term thyroid problems caused by the virus, thus they should be screened for a long time after the infection (87).

Generally, based on the impact of the SARS-CoV-2 infection and thyroid diseases on each other and the potential risk of viral complications, thyroid function and the pituitary-thyroid axis should be assessed in clinical therapy. However, the pathophysiology of the SARS-CoV-2 infection in the pituitary-thyroid axis provides ample scopes for future investigation.

Parathyroid

Nonetheless, there is no clear evidence demonstrating that primary hyper/hypoparathyroidism is a risk factor for COVID-19. It seems that patients with the chronic renal disorder and parathyroid dysfunction may be at risk for COVID-19. Parathyroid hormone is important in calcium regulation, and intracellular calcium signaling is necessary for the replication of some viruses and their intracellular functions (92, 98).

Previous studies represented that SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) use calcium ions for their function. Removing intracellular and/or extracellular Ca^{2+} caused the suppression of viral entry for SARS-CoV and partial reduction of the viral fusion of MERS-CoV (99-101).

It is known that the cytoplasmic domain of SARS-CoV-1 binds calcium in vitro, causing a change in its protein conformation. However, the mechanism of calcium signaling in the COVID-19 is yet unknown. According to one study, there is no correlation between ACE2 expression, viral attacks, inflammation of the parathyroid glands, or changes in parathyroid hormone or calcium homeostasis and coronavirus infections. However, hypocalcemia has been detected in patients infected with the coronavirus (102). Hypocalcemia is common laboratory data in patients. The main causes of hypocalcemia consist of decreased dietary intake, the elevation of parathyroid hormone (PTH), vitamin D (VD) deficiency, hypo-proteinemia, hypomagnesemia, and drug interactions. Serum calcium levels less than 2.0 mmol/L are usually connected with worse clinical situations in severely ill patients (103-105).

The incidence of hypocalcemia and VD deficiency was reported to be extremely high in patients with COVID-19. Hypocalcaemia may be due to PTH imbalanced and VD deficiency, as well as hypo-albuminemia and impaired intestinal absorption of calcium and hypoxic tissue damage with a subsequent increase in calcium influx drug interactions. The lower amount of calcium levels in the blood results in worse clinical variables and a higher incidence of septic shock (105-106).

Tachypnea in patients with COVID-19 leads to respiratory alkalosis. Chronic respiratory alkalosis increases the resistance of renal PTH receptors, leading to hypo-calcemia and hyper-phosphatemia. Therefore, COVID-19 could affect the function of parathyroid glands directly through the invasion of parathyroid gland tissues by SARS-CoV-2 and indirectly secondary to its effect on the respiratory system (106).

Effects of SARS-CoV-2 on Gonads and the Reproductive System

The testis is one of the important organs with a high level of ACE2 expression (107). According to scRNA-seq data, it was revealed that Leydig, Sertoli, and spermatogonia cells have high levels of ACE2. The expression of ACE2 is 3-fold higher in Leydig and Sertoli cells compared to spermatogonia cells (108). This is because the expression of ACE2 is extremely high in the testes, making them a viral reservoir in males and may play a role in the maintenance of the virus. The clearance of the virus results in more delays in males compared to females (109). TMPRSS2 has an impact on ACE2 and SARS-CoV-2 spike (S) protein, facilitating the SARS-CoV-2 entry into the cells (110). TMPRSS2 is mainly detected in Sertoli cells (111), spermatogonia, and spermatids, while ACE2 is widely expressed in spermatogonia, Sertoli, and Leydig cells (108). The expression of both ACE2 and TMPRSS2 is mediated by testosterone (T) (112). This could be one reason for the etiology of an increased rate of COVID-19 in men. The rates of the COVID-19 infection and mortality in males and females differ due to estradiol (E2) and T differential effects on the immune system. T reduces the immune response, while E increases it (113).

SARS-CoV-2 triggers inflammatory responses and may disrupt blood-testis-barrier and can easily enter the testis (114). The relationship between COVID-19 and male reproductive hormones has been reported in different studies. Given that the basal T level may be affected by different factors, the T: luteinizing hormone (LH) ratio seems a better parameter for evaluating the functions of the testes. It was shown that the level of serum LH significantly increased, while T: LH and follicle-stimulating hormone (FSH): LH ratios decreased in COVID-19 patients compared to healthy age-matched controls (115). They also found that the T: LH ratio had a negative relationship with the severity of COVID-19, while having a positive relationship with the anti-Müllerian hormone. Thus, they hypothesized that following COVID-19, similar to the early stage of hypogonadism, the impairment in T production in testis leads to the elevation of LH, because of feedback between gonad and pituitary, and results in a normal T level, while the T: LH ratio represents a decrease. In addition, they concluded that prolactin (PRL) significantly increased in men with COVID-19. It is well known that PRL suppresses the gonadotropins secreted by pituitary glands. However, it seems that the level of Leydig cell damage is more than suppression by PRL, leading to an increase in the LH secretion. The level of FSH, serum E2, and T: E2 ratios were the same between patients and controls. Inhibin B, which is secreted from Sertoli cells, is the most important hormone that controls

the secretion of FSH. It seems that damage to Sertoli cells is less compared to Leydig cells in COVID-19. The normal serum E2 level also demonstrates that androgen aromatization does not impair following COVID-19. Nevertheless, it should be noted that most cases in this study (88%) were mild and moderate patients. It could be suggested that men with COVID-19 should be considered as a case of hypogonadism, and hypogonadism treatment is suggested in this regard (115). Rastrelli et al evaluated 31 patients with COVID-19 and found that the serum T and dihydrotestosterone (DHT) levels decreased in most severe cases, implying that lower baseline levels of total T (TT) and calculated free T are the risk factors of poor prognosis and mortality. They introduced a threshold of TT < 5 nmol/L or calculated free T < 100 pmol/L for the prediction of poor prognosis (116), indicating that a low T level in COVID-19 patients may promote cytokine storm since T seems to have an essential role in the systemic suppression of pro-inflammatory cytokines (117). Likewise, Ma et al investigated sex hormones in 119 COVID-19 patients and 273 control men and reported that T levels were the same in both groups, but a higher serum LH and a lower serum T: LH ratio were detected in patients compared to controls (118). They also found that serum FSH, E2, and the T: E2 ratio had no changes in patient groups. Accordingly, they proposed that the cause of the LH increase is multifactorial. A Turkish study also confirmed T reductions after COVID-19 (119). Schroeder et al retrospectively evaluated the sex hormones of male (n=35) and female (n=10) patients admitted to the ICU and demonstrated that most males had low levels of T (68.6%) and DHT (48.6%). A low level of DHT is hypothesized to be related to a low level of T, as a precursor. Nevertheless, most females (60%) had a high level of T but the DHT was normal. Both genders had a high level of E2 (45.7% in males and 40% in females), which was related to obesity and a high level of aromatase. The majority of patients (68.6% of males and 90% of females) had a normal level of sex hormone-binding globulin. In addition, 62.8% of males and all the females had a normal level of LH. Only 11.4% of males and 40% of females represented a high level of FSH. In male patients, the T level was negatively correlated with IL-2 and interferon-gamma, and the E2 level had a positive correlation with IL-6. In contrast, in females, T was positively correlated with inflammatory cytokines, implying that low and high levels of T in males and females have an association with inflammatory cytokines in a sex-dependent response (120). It has been shown that T has an immune-modulatory role in the differentiation of T-lymphocytes (121). The androgen receptor is expressed in many cells, including immune cells in both males and females, and its function mainly relies on the levels of androgens such as T and DHT (120). It seems that the severity of the T reduction is dependent on the severity of the infection (122).

Several mechanisms have been proposed for the possible effects of SARS-CoV-2 on testis function. Elevated body temperature, which may occur during COVID-19, may impair spermatogenesis. Scrotal discomfort was reported by patients, suggesting that orchitis, as a clinical manifestation, may occur in the acute phase of COVID-19 (123, 124). Cytokines released during COVID-19 may damage testicular cells as well. It seems that COVID-19 induces primary hypogonadism by impairing Leydig cells. Additionally, inflammatory and immunologic reactions are responsible for virus-mediated testicular damage (115), suggesting that testicular damage and T level reduction are due to immune reaction rather than the effect of the virus on the HP-testis axis (125). The viral infection may also induce testicle atrophy via the hyalinization of seminiferous tubules induced by lymphocyte infiltration in the testis (126). It is hypothesized that ACE2 on Leydig cells may change local micro-vascular flow and vessel permeability and induce inflammation (127). In addition, several mechanisms have been proposed for the cause of reducing LH during COVID-19 (128). Oxidative stress (OS) induced by COVID-19 increased the cortisol level, leading to a decrease in the LH level and thus the T level. The reduced T level in COVID-19 patients may be due to increasing age or some metabolic diseases such as type II diabetes or cytokine storm (120, 129-130).

Spermatozoa may trigger apoptosis and mitochondria generate reactive oxygen species (ROS), leading to OS (131). Leukocytes may also phagocyte spermatozoa, leading to increasing ROS locally (132). Further, OS can be induced by the proinflammatory cytokines released in COVID-19 (133).

Most studies reported that the RNA of the SARS-CoV-2 virus is not detected in the semen of patients with active or resolving infection (124, 134-137). However, in a study on 38 patients, it was revealed that 15.8% of patients had SARS-CoV-2 viral RNA in their semen (138). There are controversial results in this regard in the literature. The phase that the semen is obtained is an important factor since the virus may not be present in the semen of patients in the recovery period.

There are controversial data regarding the effects of COVID-19 on sperm parameters. It was shown that sperm concentration, total sperm count, progressive, and total motility were significantly lower in moderate-infected patients compared to mild-infected or controls (135). Similarly, Holtmann et al demonstrated the negative effect of SARS-CoV-2 on the sperm concentration, total sperm count, and the total number of progressive motility in patients with moderate symptoms (123). Koç and Keseroğlu also found that semen volume, sperm motility, and sperm morphology were decreased with COVID-19 (119). Nevertheless, the long effects of SARS-CoV-2 on sperm parameters are unlikely to happen. The angiotensin system has a physiological role in human

sperm function and prevention of apoptosis, but it makes the sperm more susceptible to SARS-CoV-2. The spike protein on SARS-CoV-2 binds to ACE2 and thereby affects the phosphatidylinositol 3-kinase/AKT pathway, increasing apoptosis and impairing sperm survival (114). It is suggested that proteases from the TMPRSS-family can cleave ACE2 and the viral spike proteins (S1 and S2) that promote the fusion of the virus and sperm and transform the sperm cell into a viral vector (114). It seems that SARS-CoV-2 has no long-term effects on the male reproductive system, and the risk of the infection of the embryo derived from the infected sperm is low. The adverse effect of COVID-19 on sperm DNA integrity was also reported in a case report (139). It was found that the detrimental effects of the COVID infection on semen parameters and sperm DNA damage are associated with OS (140). The severity and duration of the COVID infection can predict damage (141). Most studies have different limitations, including low sample size, inter-patient variations, and poor study design (114). Large studies with a focus on semen parameters before and after COVID-19 are necessary to understand the impact of COVID-19 on semen analysis.

Limited studies are available on the effects of COVID-19 on the female gonad and reproductive system. Along with TMPRSS2, SARS-CoV-2 used the cathepsins, CTSB, and CTSL to enter the cells as an alternative method (123). The co-expression of protease TMPRSS2 or cathepsin B/L (CTSB/L) is needed for the activation of ACE2 and thereby entering the SARS-CoV-2 into the cells. In females, the level of ACE2 expression was extremely low in the ovary in less than 5% in the stroma and perivascular cells of the ovarian cortex. In addition, theTMPRSS2 was not found in the ovary, and the co-expression of ACE2/CTSB or ACE2/CTSL was not observed in the ovary, suggesting that SARS-CoV-2 may not enter ovarian cells and impair oogenesis (142). Although animal studies have indicated high expression of ACE2 in the ovarian tissue (143), the level of ACE2 expression was extensively low in the fallopian tubes, myometrium, and breast in COVID-19 patients (142). The expression level of TMPRSS2 is low in the oocytes in comparison with ACE2, implying that TMPRSS2 may be a limiting factor for the infection of the oocyte. Oocytes in the antral follicles are more prone to SARS-CoV-2 because 62% of them express both ACE2 and TMPRSS2. Nevertheless, cumulus cells surrounding the oocytes express low levels of ACE2 and TMPRSS2 and are suggested to be physical barriers to the infection (144).

Conclusion

Some studies have reported the prevalence of diabetes after the COVID-19 infection in people without any previous history of diabetes, which diabetes may be an important risk factor that affects the clinical severity of SARS-CoV-2 and subsequently the risk of death. These patients need more attention accordingly. Since getting the COVID-19 infection includes extensive stress and blood cortisol increases; furthermore, more increases in cortisol are related to the severity and mortality of the disease. Patients with adrenal insufficiency are likely to need higher doses of medications. Acute adrenal insufficiency has not been extensively studied after the COVID-19 infection and requires short- and long-term investigations. In Cushing's disease, high-dose and chronic use of corticosteroids can lead to the onset of diabetes, thus patients are at a higher risk of the COVID-19 infection and should take more caution. Thyroid dysfunction such as thyrotoxicosis and thyroiditis, due to the inflammation of the thyroid in patients with no previous history of thyroid diseases, was reported as well. The extremely high incidence of hypocalcemia and VD deficiency in patients with COVID-19 may be due to PTH imbalanced and VD deficiency. SARS-CoV-2 triggers inflammatory responses and may disrupt blood-testis-barrier and can easily enter the testis. Therefore, more short- and long-term studies are required to evaluate the certain effects of the SARS-CoV-2 virus on the endocrine glands.

Authors' Contribution

All authors contributed to the study design, data collection, writing, and preparation of this study.

Conflict of Interest Disclosures

The authors declare no conflict of interests.

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