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Mini-Review

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Potential Interaction Between SARS-CoV-2 and Thyroid: A Review

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Abbreviations: ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; FT3, free triiodothyronine; FT4, free thyroxine; HLA, human leukocyte antigen; HPA, hypothalamic-pituitary-adrenal; HPT, hypothalamic-pituitary-thyroid; IL, interleukin; NEFA, nonesterified fatty acid; NTIS, nonthyroidal illness syndrome; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SAT, subacute thyroiditis; T3, 3,5,3′-triiodothyronine; T4, free thyroxine; TRH, TSH-releasing factor; TSH, thyrotropin; TT3, total 3,5,3′-triiodothyronine; TT4, total thyroxine

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Abstract

The novel coronavirus disease 2019 (COVID-19) produced by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is sweeping the world in a very short time. Although much has been learned about the clinical course, prognostic inflammatory markers, and disease complications of COVID-19, the potential interaction between SARS-CoV-2 and the thyroid is poorly understood. In contrast to SARS-CoV-1, limited available evidence indicates there is no pathological evidence of thyroid injury caused by SARS-CoV-2. However, subacute thyroiditis caused by SARS-CoV-2 has been reported for the first time. Thyroid dysfunction is common in patients with COVID-19 infection. By contrast, certain thyroid diseases may have a negative impact on the prevention and control of COVID-19. In addition, some anti–COVID-19 agents may cause thyroid injury or affect its metabolism. COVID-19 and thyroid disease may mutually aggravate the disease burden. Patients with SARS-CoV-2 infection should not ignore the effect on thyroid function, especially when there are obvious related symptoms. In addition, patients with thyroid diseases should follow specific management principles during the epidemic period.

Key Words: COVID-19, SARS-CoV-2, thyroid disease, metabolism, interaction

Coronaviruses are enveloped, nonsegmented, positive-sense, single-stranded RNA viruses. Until recently, only 2 beta coronaviruses, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus, have caused significant human morbidity and mortality (1, 2). However, with more than 76 million cases confirmed and approximately 1.7 million disease-related deaths in 222 countries/regions (as of December 22, 2020,

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11:13 PM GMT+8) (3), the World Health Organization declared the novel coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first isolated in Wuhan, China, as a "public health emergency of international concern."

Most patients affected by COVID-19 are asymptomatic or present with mild flu-like symptoms, whereas 14% of cases are severe and 5% are critical (4). The pathogenesis of COVID-19 involves SARS-CoV-2 entering the lung through the respiratory system and depositing in the lung parenchyma. Afterward, angiotensin-converting enzyme 2 (ACE2) on the surface of pneumocytes binds to the spike protein of the virus as a receptor and mediates its entry into host cells (5, 6). A study by Wrapp et al found that the binding ability of the SARS-CoV-2 spike protein to the ACE2 receptor was stronger than that of SARS-CoV-1 (7), which may explain why SARS-CoV-2 has caused a greater number of infections. In addition, viral RNA has also been detected in blood, stool, and urine samples of patients with COVID-19 (8), suggesting that SARS-CoV-2 can also interact with ACE2 expressed in other organs and lead to potential extrapulmonary spread and multiorgan involvement. In addition to the respiratory system, the marked tissue tropism of SARS-CoV-2 has also been detected in the cardiovascular, coagulative, gastrointestinal, and nervous systems (9). In fact, many endocrine organs, such as the pancreas, testis, ovary, adrenal gland, pituitary gland, and thyroid, have been found to express ACE2 (10, 11). ACE2 expression levels were found to be the highest in the testis, followed by the thyroid, and the lowest level was found in the hypothalamus (10, 11). The serum ACE level was positively correlated with 3,5,3′-triiodothyronine (T3) and thyroxine (T4) (12), suggesting it may be useful as a probe for exploring peripheral thyroid hormone action. In addition, one study by Rotondi and colleagues (13) demonstrates that the messenger RNA (mRNA) encoding for the ACE2 receptor is expressed in thyroid follicular cells, making thyroid a potential target for SARS-CoV-2 entry. SARS-CoV-2 infection may aggravate the original diseases in endocrine organs or induce new abnormalities. In turn, these endocrine diseases may worsen the adverse prognosis of COVID-19 (4, 9, 14, 15). Previous studies have indicated that the mortality rates of COVID-19 from different regions of the world vary greatly but have consistently shown that comorbidities, such as hypertension, chronic kidney disease, and type 2 diabetes, significantly increase the mortality of patients with SARS-CoV-2 (16-18).

Several reviews have described the impact of COVID-19 on the thyroid, including pathology, function, and disease, but most have not covered recently published studies with substantial contents and made a corresponding inference based only on the situation of the SARS era in 2003. Whether thyroid hormones or thyroid diseases in turn affect COVID-19 has not been mentioned. In addition, most studies have explored only the interaction between COVID-19 and the thyroid itself. Whether the medications used to treat COVID-19 will have additional effects on the thyroid gland is rarely reported. Therefore, in this report, we briefly review the potential interaction between COVID-19 and the thyroid gland, including thyroid pathology, thyroid function, and thyroid diseases. In addition, we explored the potential harmful effects of COVID-19 drugs on the thyroid.

Review

Effect of Severe Acute Respiratory Syndrome Coronavirus 2 on the Thyroid

Morphological and pathological changes

Postmortem examinations in patients who died of SARS-CoV-2 have been performed in several studies, reporting pathological changes in different organs including the thyroid gland (17-20). Interestingly, no abnormalities in morphology or significant damage in thyroid follicles were found, but only one mentioned lymphocytic infiltration in the interstitium (19). In addition, no SARS-CoV-2 was found in thyroid tissues by immunohistochemistry and polymerase chain reaction analysis. However, because the existing autoptic studies are still limited, not focused on thyroid disorders, and the thyroid function of these patients has not been described, more focused cytology/histology studies are needed to prove or disprove direct damage to the thyroid gland by SARS-CoV-2.

Previously, one study reported in detail the histopathological findings of the thyroid gland of SARS-infected patients during the outbreak of SARS-CoV-1 (22). The results showed that parafollicular cells and follicular epithelial cells were extensively damaged; epithelial cells were destroyed and fell off into the follicles, leading to the rupture of the follicles. However, there was no inflammatory infiltration or cell necrosis, which supports the hypothesis that extensive apoptosis leads to thyroid injury in SARS-CoV-1 infection. Overall, the differences in thyroid morphology results between SARS-CoV-1 and SARS-CoV-2 may suggest, on the other hand, that although SARS-CoV-2 causes a worse infection, its relative severity is lower than that of SARS-CoV-1. To be sure, the data on the effect of SARS-CoV-2 on thyroid structure are still insufficient.

Changes in thyroid function

Data on thyroid function affected by SARS-CoV-2 are controversial. A study by Chen et al compared the clinical characteristics of patients with COVID-19 in a deceased

group and a recovery group (23), finding that thyrotropin (TSH) and free 3,5,3′-triiodothyronine (FT3) concentrations were significantly lower in the deceased patients than in the recovered patients. The difference in the free thyroxine (FT4) levels was not statistically significant.

Another study by Chen et al analyzed thyroid function between patients with COVID-19 and healthy control individuals (23). During the follow-up period of 3 months after the diagnosis of COVID-19, 64% of the patients had abnormal thyroid function parameters. Of these patients, 56% had lower-than-normal TSH levels, which was a higher proportion than that in the healthy control group. The levels of serum TSH and total 3,5,3′-triiodothyronine (TT3) of the patients with COVID-19 were significantly lower than those of the healthy control group, while no significant difference in total thyroxine (TT4) was found between the 2 groups. In addition, in the subgroup analysis of patients with COVID-19 according to disease severity, the degree of the decrease in TSH and TT3 correlated positively with the severity of the disease: the more severe the COVID-19 infection was, the lower the TSH and TT3 levels. Similar results were also reported in 2 other studies (24, 25). Meanwhile, it is worth noting that the study by Muller and colleagues (24) also found a prevalence of thyrotoxicosis in 15.3% of COVID-19 patients compared with only 1.3% of controls. Notably, most patients with COVID-19 mentioned earlier did not receive thyroid hormone replacement therapy. After recovery from pneumonia, all thyroid hormone levels returned to within normal range. A study by Wei et al analyzed the thyroid function and pathological changes in patients infected with SARS-CoV-1 (21), and impaired thyroid function was found in patients with SARS; even after a few years, the serum TSH level of SARS patients was still lower than that of healthy controls, which suggests that SARS-CoV-1 may cause more severe thyroid function changes than SARS-CoV-2.

A retrospective study by Lania et al (26) found that the thyroid function evaluated at hospitalization correlated with some inflammatory parameters. This study included 287 noncritical patients hospitalized for COVID-19. Of all patients, 20.2% had thyrotoxicosis, and 5.2% had hypothyroidism. Moreover, the authors found the thyrotoxicosis was significantly associated with increased interleukin-6 (IL-6) levels, which indicates that COVID-19 may be associated with a high risk of thyrotoxicosis related to systemic immune activation induced by the SARS-CoV-2 infection.

The etiology and pathogenesis of thyroid dysfunction after COVID-19 have not been completely understood. One hypothesis is that there is a direct influence on the thyroid gland by SARS-CoV-2, which has been confirmed in the study of SARS-CoV-1. The thyroid gland is firmly attached to the wall of the trachea, which is invaded by the virus in advance. Therefore, there seems to be potential for the virus to invade the thyroid gland directly through the upper respiratory tract. One autopsy study of patients with SARS by Wei et al (21) showed obvious destruction of the follicular and parafollicular cells of the thyroid but not a reduction in thyroid follicular size, which may be responsible for reduced T3 and T4 levels. However, no significant abnormalities in thyroid follicular morphology were found in recent reports focused on postmortem examination of COVID-19 patients, and no SARS-CoV-2 was found in thyroid tissues by immunohistochemistry and polymerase chain reaction analysis (17-20). Although ACE2 is highly expressed in thyroid tissues (11), there may be other reasons preventing the virus from entering the thyroid follicular cells.

The second potential explanation could imply an underlying nonthyroidal illness syndrome (NTIS) caused by critical illness (27). Patients with NTIS are often characterized by normal or low serum TSH concentration and low T3 concentration, accompanied by a low concentration of T4 in more severe or prolonged illness (27, 28). A study by Khoo et al (29) detected that patients with COVID-19 had lower admission TSH and FT4 levels compared to those without COVID-19 after eliminating the potential interference of cortisol on TSH. Meanwhile, no overt thyrotoxicosis was found in any patients when using complete sets of FT4 and TSH measurements. Ten patients with COVID-19 in a study by Lui and colleagues (30) were found to have isolated low FT3, with normal TSH and FT4 levels, suggesting a possible NTIS; FT3 in the study showed a decreasing trend with worsening clinical severity of COVID-19. Similar results were also reported in patients with NTIS in other critical illnesses (31). Furthermore, an independent inverse correlation between erythrocyte sedimentation rate and FT3/FT4 ratio was also demonstrated in the Lui study (30), which suggested the potential effect of systemic inflammation on deiodinase activity.

The third hypothesis is that dysfunction of the hypothalamic-pituitary-thyroid (HPT) axis causes a diminished level of serum TSH in patients with SARS-CoV-2 (32). It has been reported that SARS-CoV-2 infection can affect the nervous system, usually affecting the cranial nerves of smell and taste (33). Leow et al (32) reported 4 SARS-CoV-1 survivors with biochemical hypothyroidism, 3 of whom had a central etiology, and 2 patients with central hypocortisolism who also presented with central hypothyroidism. Therefore, the authors suggested that SARS-CoV-1 affects the hypothalamus or pituitary gland and leads to HPT axis and hypothalamic-pituitary-adrenal axis dysfunction. In addition, Wei et al found that both the number and immunoreactive intensity of TSH-positive cells in the pituitary of SARS-CoV-1 patients decreased significantly compared with those in control individuals (34),

suggesting that the decrease in TSH levels may be related to changes in TSH-secreting cells in the pituitary. In addition, an autopsy study of patients with SARS-CoV-1 revealed that ACE2 was expressed in the hypothalamus and pituitary (35); edema and neuronal degeneration along with the SARS-CoV-1 genome have also been identified in the hypothalamus (32), suggesting that these regions may be potential targets of the virus. However, in this case (central hypothyroidism) we would expect accordingly low levels of TSH, FT3, and also FT4, whereas COVID-19 patients have unexpectedly normal/increased levels of FT4, which is the main limitation of this hypothesis. Additionally, there is still a lack of pathological evidence of SARS-CoV-2 invading the hypothalamus or pituitary cells, as well as information on other pituitary hormones in patients with SARS-CoV-2, especially in patients with abnormal thyroid function. Hence, more comprehensive data are needed to prove this hypothesis.

Last, except for the direct viral effect on thyroid or pituitary cells, another potential mechanism that cannot be ignored is the indirect effects of immune-mediated postviral inflammatory reaction caused by COVID-19 infection (21, 36). As we know, COVID-19 generally has 3 consecutive stages (37). The early stage is when the virus invades the respiratory tract, causing flu-like symptoms and possible development into viral pneumonia. The second stage is characterized by pulmonary inflammation and coagulation disorders, usually combined with innate immune activation and accompanied by triggering of proinflammatory responses, including cytokines IL-1β, IL-6, tumor necrosis factor α, and adaptive T-cell–mediated immune response (16, 37), while the postviral inflammatory reaction may be the inducing factor of thyroid dysfunction. Lania et al (26) also found that thyroid dysfunction was associated with a high level of IL-6 in patients with SARS-CoV-2 infection.

All together, thyroid dysfunction secondary to SARS-CoV-2 infection is likely a mixture of several mechanisms. It is also worth noting that the result of anti–COVID-19 drugs and the iodine load due to examination with computed tomography scan may also influence euthyroid status. However, most existing studies have not clarified this, and the effect of SARS-CoV-2 on thyroid function needs further study.

Thyroid disease

To date, 8 studies have reported subacute thyroiditis (SAT) associated with COVID-19, 7 of which were in the form of a case or case series report (38-44); the eighth was a retrospective controlled study with a large sample, and the description of SAT was brief and lacked the necessary data for analysis (24). Detailed clinical data of the 5 studies is listed in Table 1. The 10 patients were 9 women and 1 man, aged 18 to 68 years; 7 were Italian, and the other 3 patients were Burmese, Turkish, and Mexican, respectively. COVID-19 infection was confirmed in all of them by oropharyngeal swab examination or typical pulmonary characteristics of computed tomography scan. Notably, the symptoms of these patients with COVID-19 infection were not serious, all had only mild fever and upper respiratory symptoms, and no one had been treated in intensive care units. The time from diagnosis of COVID-19 infection to typical symptoms of SAT was from 5 to 42 days. The symptoms of SAT in all patients were classic, including fever, anterior neck pain, fatigue, tremors, anosmia, sweating, and palpitations. One patient in the study by Ippolito and colleagues may not have mentioned significant neck pain because of high-dose painkillers for previous back surgery (39). In addition to typical clinical symptoms, the diagnosis of SAT depends on general nonspecific laboratory and imaging examinations, for which a detailed description is shown in Table 1. However, 3 patients in a study by Muller et al who were finally diagnosed with SAT by thyroid ultrasound and scan did not present with obvious clinical symptoms; the laboratory indexes showed low or suppressed TSH concentrations with normal level of T3 and T4, which indicate the SAT may have overlapped with NTIS (24). Hence, because SAT may present with atypical symptoms and some symptoms may overlap with that of COVID-19, we suggest physicians be alert to the possibility of SAT during the COVID-19 pandemic. After diagnosis of SAT, most patients received treatment with corticosteroids, while one was given ibuprofen for severe neck pain. Clinical symptoms were relieved within a few days. In addition, the laboratory indexes of SAT returned to normal levels after 1 to 2 months, suggesting a good prognosis. Two patients were diagnosed with subclinical hypothyroidism at the last evaluation.

Although the benefit of glucocorticoids for the treatment of SAT is debated (45), it is undeniable that administration of glucocorticoids is beneficial for relieving symptoms quickly and significantly reducing the recurrence rate (47). The effectiveness of glucocorticoids in patients with COVID-19 has been demonstrated in several studies. Recently, a study by the RECOVERY Collaborative Group of Oxford University (47) found that the use of dexamethasone resulted in lower mortality among severe COVID-19 patients who were receiving either invasive mechanical ventilation or oxygen alone, which may be associated with the effect of glucocorticoids on modulating inflammation-mediated lung injury and thereby reducing progression to respiratory failure and death. Taken together, these results indicate that a small dose of glucocorticoids seems to be a more appropriate treatment option for SAT caused by SARS-CoV-2.

Table 1. Subacute thyroiditis patients' characteristics, symptoms, radiographic findings, laboratory findings, and treatment measures

Author, y	Country	No. of patients, sex	Symptoms of COVID-19	Time from symptom onset to recovery, d	Time from diagnosis of COVID-19 to SAT, d	Symptoms of SAT	Laboratory indexes	Imaging examination	Treatment of SAT	Time from diagnosis of SAT to recovery, d	Ref
Brancatella et al (2020)	Italy	18, F	Rhinorrhea, cough	14	15	Fever, palpitations, fatigue, neck pain	TSH(↓), FT4 (↑), FT3 (↑), TgAb(↑), Tg(–), TPOAb(–), TRAb(–), ESR(↑), CRP(↑), WBC(↑)	Ultrasound: multiple diffuse hypoechoic areas	Prednisone	40	(38)
Brancatella et al (2020)	Italy	38, F	Fever, rhinorrhea, anosmia, asthenia	4	16	Fever, asthenia, neck pain, anorexia	TSH(↓), FT4 (↑), FT3 (↑), TgAb(–), Tg(↑), TPOAb(–), TRAb(–), ESR(↑), CRP(↑)	Ultrasound: enlarged thyroid, multiple, diffuse hypoechoic areas, decreased vascularity	Prednisone	53	(42)
		29, F	Rhinorrhea	3	30	Neck pain, fever, palpitations, asthenia, sweating	TSH(↓), FT4 (↑), FT3 (↑), TgAb(↑), Tg(↑), TPOAb(–), TRAb(–), ESR(↑), CRP(↑)	Ultrasound: multiple diffuse hypoechoic areas, decreased vascularity. Thyroid scan: no uptake of Tc-99m	Prednisone	46 (asymptomatic with subclinical hypothyroidism)	
		29, F	Fever, cough, rhinorrhea, anosmia, diarrhea	14	36	Neck pain, palpitations, sweating	NA	Ultrasound: enlarged thyroid, multiple diffuse hypoechoic areas, decreased vascularity	Ibuprofen	47 (asymptomatic with subclinical hypothyroidism)	
		46, F	Fever, cough, rhinorrhea, anosmia, asthenia	6	20	Neck pain, fever, palpitations, asthenia, insomnia, anxiety, weight loss	TSH(↓), FT4 (↑), FT3 (↑), TRAb(–), CRP(↑)	Ultrasound: enlarged thyroid, multiple diffuse hypoechoic areas	Prednisone	44	

Table 1. Continued

Author, y	Country	No. of patients, sex	Symptoms of COVID-19	Time from symptom onset to recovery, d	Time from diagnosis of COVID-19 to SAT, d	Symptoms of SAT	Laboratory indexes	Imaging examination	Treatment of SAT	Time from diagnosis of SAT to recovery, d	Ref
Ippolito et al (2020)	Italy	68, F	Mild fever, cough, dyspnea	60	5	Palpitations, insomnia, agitation	TSH(↓), FT4 (↑), FT3 (↑), TgAb(–), Tg(↑), TPOAb(-), TRAb(-),	Ultrasound: enlarged hypoechoic thyroid, decreased vascularity. Thyroid scan: no uptake of Tc-99m	Methylprednisolone, prednisone	28	(39)
Asfuroglu Kalkan and Ates (2020)	Turkey	41, F	Fever	5	NA	Fever, neck pain	TSH(↓), FT4 (↑), FT3 (↑), TgAb(↑), TPOAb(–), ESR(↑), CRP(↑), WBC(↑)	Ultrasound: diffuse hypoechoic areas, decreased vascularity	Prednisolone	28	(40)
Ruggeri et al (2020)	Italy	43, F	Fever, rhinorrhea, cough, hoarseness	14	42	Fever, neck pain, fatigue, tremors, palpitations	TSH(↓), FT4 (↑), FT3 (↑), TgAb(–), Tg(↑), TPOAb(–), TRAb(–), ESR(↑), CRP(↑), WBC(↑)	Ultrasound: diffuse hypoechoic areas. Thyroid scan: reduced uptake of Tc-99m	Prednisone	28	(41)
Mattar et al (2020)	Singapore	34, M	Fever, cough, headache, anosmia.	NA	9	Fever, neck pain, tachycardia	TSH(↓), FT4 (↑), FT3 (↑), TPOAb(–), TRAb(–), CRP(↑), WBC(↑)	Ultrasound: enlarged hypoechoic thyroid, decreased vascularity.	Prednisolone, atenolol	70	(43)
Campos-Barrera et al (2020)	Mexico	37, F	Odynophagia, anosmia	NA	30	Neck pain, fatigue	TSH(↓), FT4 (↑), TT3 (↑), TgAb(–), TPOAb(–), TRAb(–), ESR(↑), CRP(↑), WBC(–)	Thyroid scan: no uptake of Tc-99m	–	–	(44)

Abbreviations: COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; F, female; FT3, free 3,3,5′-triiodothyronine; FT4, free thyroxine; NA, not available; SAT, subacute thyroiditis; Ref, reference; TgAb, thyroglobulin antibody; Tg, thyroglobulin; TPOAb, thyroid peroxidase antibody; TRAb, TSH receptor antibody; TSH, thyrotropin; WBC, white blood cell count.

The etiology and pathogenesis of SAT are not completely understood, but the disease is well known to follow a viral infection or a postviral inflammatory reaction, especially in genetically predisposed individuals (48, 49). Previous studies have shown that individuals carrying some human leukocyte antigen (HLA) haplotypes (such as HLA-Bw35, HLA-B67, HLA-B15/62, and HLA-Drw8) were susceptible to SAT (50, 51). The incidence of SAT often changes with the season and has a certain prevalence, especially during outbreaks of echovirus and coxsackievirus (48). Moreover, some other viruses that have shown evidence of being associated with SAT include Epstein-Barr virus, orthomyxovirus, hepatitis E, mumps, adenovirus, rubella, HIV, and cytomegalovirus (48). Although an autopsy study by Wei et al (21) showed obvious destruction of the follicular and parafollicular cells of the thyroid in patients with SARS, there was no report of coronavirus associated with SAT during the SARS-CoV-1 pandemic. In addition, a previous study demonstrated the presence of some other virus-like particles in the follicular epithelium of patients with SAT (48, 52), but as mentioned earlier, there is still no direct evidence of SARS-CoV-2 located in thyroid follicular cells (17-20). In addition, because the present huge interest in COVID-19 and limited cases could also lead to publication bias, this possibility should not be ignored.

According to these clinical findings (Fig. 1), thyroid dysfunction is common in patients with COVID-19 infection. Meanwhile, SARS-CoV-2 may be considered accountable for the onset of SAT, which highlights that SAT should be included as a complication triggered by SARS-CoV-2; during the COVID-19 pandemic, physicians should be alert to the possible connections between SARS-CoV-2 and thyroid dysfunction.

Effect of Thyroid on Coronavirus Disease 2019

Effect of thyroid diseases on coronavirus disease 2019

There is no evidence that patients with existing autoimmune thyroid disease, thyroid dysfunction, thyroid nodules, or cancer are more susceptible to contracting viral illnesses, including infection with SARS-CoV-2, or that they are at risk of developing more severe COVID-19 disease. Certain subsets of patients are likely to be at increased risk of developing severe coronavirus infection. Patients with thyroid ophthalmopathy usually receive glucocorticoid therapy and immunosuppressive therapy (53), which are considered to be extremely vulnerable and are highly likely

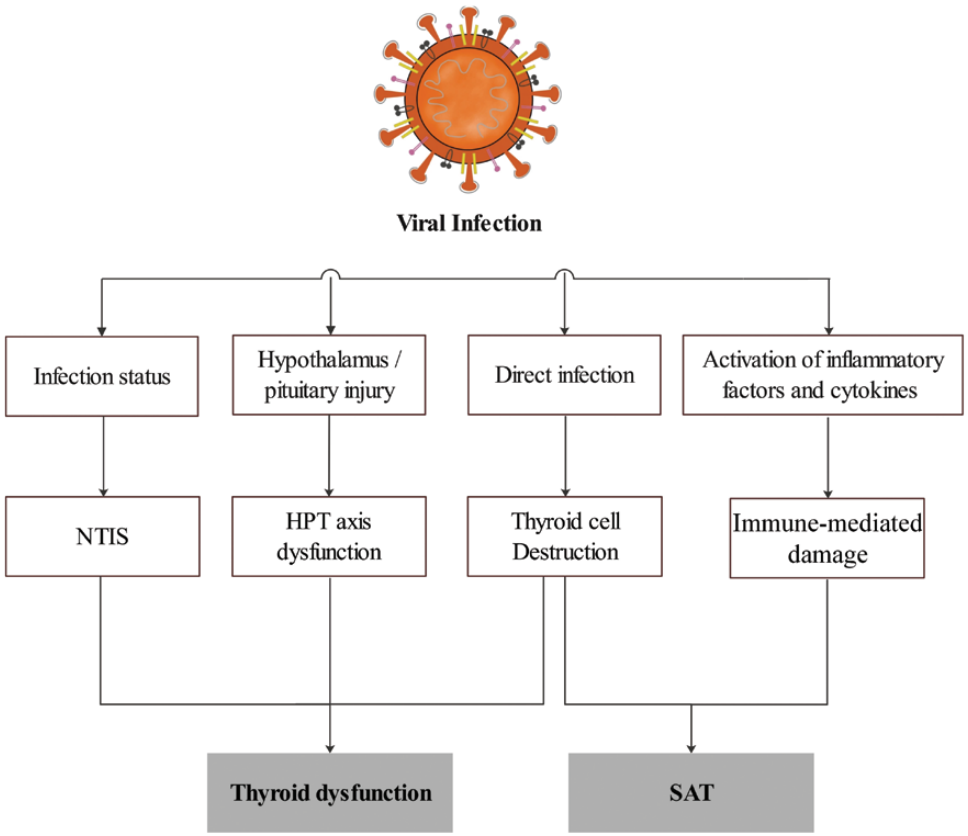

Figure 1. Potential mechanisms for effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections on thyroid. HPT, hypothalamic-pituitary-thyroid; NTIS, nonthyroidal illness syndrome; SAT, subacute thyroiditis.

to aggravate the disease once infected with COVID-19. Hence, one guideline suggested that these patients should self-isolate for at least 12 weeks (54). Moreover, it has been reported that conjunctivitis is a manifestation of COVID-19 (55), and SARS-CoV-2 mRNA can be detected in teardrops (56). Hence, patients with ophthalmopathy combined with COVID-19 may have a higher risk of infection transmission, especially when they have significant ocular soft-tissue involvement.

Patients with hyperthyroidism are not known to have an increased risk of COVID-19 infection, but there are 2 situations that may interact with COVID-19. COVID-19 often activates an excessive immune response. Therefore, it is strongly recommended that patients with thyroid dysfunction continue to take thyroid medications because of a higher risk of complications (such as thyroid storm). In addition, patients with thyrotoxicosis undergoing antithyroid drug treatment are at risk of developing neutropenia/agranulocytosis, albeit rarely, with a rate of 0.2% to 0.5% (57, 58). Symptoms of agranulocytosis (flu-like illness) may overlap with those of COVID-19, often making it difficult to differentiate one from the other clinically. Thus, it is recommended that patients on antithyroid drugs with symptoms suggestive of neutropenia immediately discontinue the drug and obtain an urgent full blood count to measure neutrophil count until symptoms have resolved (59).

3,5,3′-Triiodothyronine: a potential medication for severe coronavirus disease 2019?

A trial conducted by Pantos et al (60, 61) has been registered (ClinicalTrials.gov ID: NCT04348513) to investigate the efficacy and safety of intravenous high-dose T3 for critically ill patients with COVID-19.

Patients with severe/critical illness, such as sepsis, trauma, and myocardial infarction, may present with thyroid dysfunction secondary to NTIS or specific thyroid damage (direct, indirect, or both), and low circulating T3 has been proven to be associated with increased mortality (31). T3 does, however, have some potential mechanisms for the treatment of COVID-19, such as increasing the tolerance of cells to hypoxia by inhibiting p38 mitogen-activated protein kinase activation, promoting tissue repair by regulating Akt activity, and inhibiting lung fibrosis by improving epithelial mitochondrial function (62). The decreased and low concentration of T3 present in patients with severe extrathyroid diseases is a component of NITS, which is an adaptive phenomena to severity of infection, and this low T3 syndrome should not be treated with T3 in most patients. Therefore, in view of the lack of strong arguments, the effect of T3 in COVID-19 is questionable.

Effect of Anti–Coronavirus Disease 2019 Medications on the Thyroid

Medication therapy is an important measure for preventing and controlling COVID-19. Currently, there is no specific antiviral medication or vaccine approved for treating patients with suspected or confirmed COVID-19. The rapid progression of COVID-19 and the incomplete understanding of the disease have brought unprecedented challenges to health workers, researchers, and scientists. At present, more than 100 different drugs or experimental therapies have been used to treat COVID-19 (63, 64). Among them, some have been proven to be effective (47, 65, 66), some have no obvious effect on COVID-19 (67-69), and some still need to be further verified (70). In addition, whether these agents will affect the thyroid gland during anti–COVID-19 treatment is unclear. To the best of our knowledge, several drugs have been reported to have adverse effects on the thyroid gland in the treatment of other diseases. In the following section, we described the medications that may cause thyroid damage or affect its metabolism (Fig. 2).

Corticosteroids

Glucocorticoid is the most widely used and effective anti-inflammatory and immunosuppressant. An uncontrolled inflammatory state is frequent with COVID-19 and may contribute to multiorgan failure; diffuse alveolar damage with hyaline membranes were also found on pulmonary histological examination of patients with critical COVID-19. The effect of corticosteroids in controlling this exacerbated response has been proved in several high-quality published studies (71, 72). A study by the RECOVERY Collaborative Group in the United Kingdom (47) found that dexamethasone could increase survival rates among hospitalized patients who were receiving either invasive mechanical ventilation or oxygen alone for COVID-19 but not among those receiving no respiratory support. Hence, in the latest World Health Organization guideline on drugs for COVID-19 (73), systemic corticosteroids were recommended in patients with severe and critical COVID-19 but not in patients with nonsevere COVID-19.

It has long been known that glucocorticoids could affect serum TSH levels in humans. A study by Samuels and McDaniel (74, 75) demonstrated that the physiological dose of hydrocortisone plays an important role in the daily variation of serum TSH level, with lower levels in the morning and higher levels at night. Several other studies described acute inhibition of TSH secretion both in humans and rats that occurred after administration of pharmacological doses of glucocorticoid and rebounded after withdrawal of glucocorticoid (76, 77); similar results were also found in

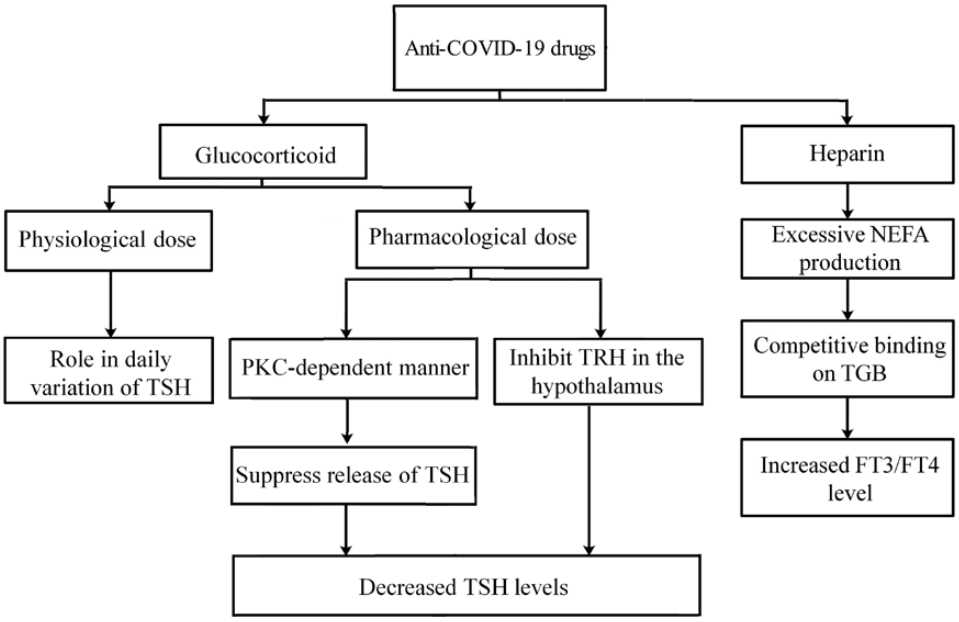

Figure 2. Potential mechanisms for effects of anti–novel coronavirus disease 2019 drugs on thyroid. NEFA, nonesterified fatty acid; PKC, protein kinase C;TGB, thyroxine-binding globulin.

patients with Cushing syndrome (78). However, the available evidence suggests that long-term high-dose glucocorticoids or Cushing syndrome cortisol excess does not seem to cause clinically evident central hypothyroidism requiring thyroid hormone replacement (77, 79). Therefore, the clinical application of glucocorticoid for normal thyroid function of noncritical patients usually does not evoke worry about the impact of treatment on thyroid function, but for patients with thyroid disease and critical COVID-19, glucocorticoid should be used cautiously.

The mechanism of the effect of glucocorticoid on TSH is still unclear. One possible explanation is that glucocorticoid can inhibit TSH-releasing factor (TRH) in the hypothalamus directly. John and colleagues (80) demonstrated that dexamethasone appears to suppress the release of TSH from thyrotropes in a protein kinase C–dependent manner through the protein annexin 1. Glucocorticoid receptors are found in the TRH neurons of male rats (81); additional direct evidence is that high-dose glucocorticoids could decrease TRH mRNA expression in the paraventricular nucleus of the human hypothalamus (82).

Low-molecular-weight heparin

As mentioned earlier, COVID-19 generally has 3 consecutive stages (37). In the second stage, which is characterized by pulmonary inflammation and coagulation disorders, activation of the coagulation cascade leading to severe hypercoagulability has been detected in these patients. In particular, disseminated intravascular coagulation can occur in critically patients (83). Hence, early anticoagulation such as heparin may reduce coagulopathy, microthrombus formation, and the risk of organ damage. The role of heparin in COVID-19 is supported by several retrospective studies (84-86), but its exact curative effect and appropriate effective dose should be proven in high-quality clinical trials.

The main effect of heparin on thyroid is interference with the measurement of serum free thyroid hormone, which was first reported in a study by Schatz et al (87). To verify this phenomenon, 9 healthy controls and 5 individuals with hypothyroidism were administered intravenous heparin, and a prompt (within 2-15 minutes) increase (up to 5-fold) in FT4 concentrations was found in this cohort. Previous studies (88, 89) have proven that this phenomenon is due to the significant increase of serum nonesterified fatty acid (NEFA) concentration induced by heparin-induced endothelial lipoprotein lipase activation. When the concentration of NEFA exceeds the normal serum-binding capacity, NEFA will directly compete for T4 and T3 binding sites on thyroxine-binding globulin. Therefore, patients treated with heparin should generally avoid having FT4 and FT3 measured. Meanwhile, when indicated, measurement of total thyroid hormone levels, together with TSH and thyroxine-binding globulin, can help confirm the patient's euthyroid status.

Limitations and Prospects

Like all reviews, ours has several limitations that warrant discussion. First, COVID-19 is a relatively new disease with limited access to public information. Although the number

of publications on COVID-19 histopathology is increasing almost every day, and although we have repeated our studies in the preparation of this report, we cannot rule out the possibility that we may not have included absolutely up-to-date publications. Second, the conclusion of the effect of SARS-CoV-2 on thyroid morphological and pathological changes has been gleaned mainly from several autopsy reports containing only a limited number of cases; more focused cytology/histology studies are needed to prove or disprove direct damage to the thyroid gland by SARS-CoV-2. Finally, as an increasing number of questions related to SARS-CoV-2 are being answered, the development and application of vaccines are the focus of current and future research. Up to December 21, 2020, a total of 236 vaccines are being studied, of which 39 have been in clinical trials (90). However, because most vaccines are currently in research or clinical trials, it is not known whether these vaccines will interact with the thyroid gland.

Conclusions

SARS-CoV-2 infection is a serious challenge facing the whole world that directly or indirectly involves multiple organs and multiple systems. In contrast to SARS-CoV-1, limited available evidence indicates there is no pathological evidence of thyroid injury caused by SARS-CoV-2. However, SAT caused by SARS-CoV-2 has been reported for the first time. In addition, thyroid dysfunction is also common in patients with COVID-19 infection. By contrast, certain thyroid diseases may have a negative impact on the prevention and control of COVID-19. In addition, some anti–COVID-19 agents may cause thyroid injury or affect its function, which has not been considered in previous reports. In addition, patients with thyroid disease should not only strengthen awareness of their own personal protection but also comply with professional medical consultation when necessary.

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