

Mini-Review

COVID-19 and Thyroid Diseases: A Bidirectional Impact

Leonidas H. Duntas¹ and Jacqueline Jonklaas²

¹Evgenidion Hospital, Unit of Endocrinology, Diabetes, and Metabolism, University of Athens, Athens 11528, Greece; and ²Division of Endocrinology, Georgetown University, Washington, DC 20007, USA

ORCID numbers: 0000-0001-9133-4089 (L. H. Duntas); 0000-0002-2238-2666 (J. Jonklaas).

Abbreviations: ACE2, angiotensin-converting enzyme 2; AITD, autoimmune thyroid disease; ARDS, acute respiratory distress syndrome; FT3, free triiodothyronine; FT4, free thyroxine; GD, Graves' disease; GO, Graves ophthalmopathy; HICU, high intensity of care unit; IFN, interferon; IL-6, interleukin-6; LICU, low intensity of care unit; LT3, liothyronine; MMI, methimazole; NTI, nonthyroidal illness syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SAT, subacute thyroiditis; T3, triiodothyronine; T4, thyroxine; TNF, tumor necrosis factor; TSH, thyrotropin (thyroid-stimulating hormone).

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Abstract

Context: COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has become the most lethal and rapidly moving pandemic since the Spanish influenza of 1918-1920, is associated with thyroid diseases.

Methods: References were identified through searches of PubMed and MEDLINE for articles published from Jan 1, 2019 to February 19, 2021 by use of the MeSH terms "hypothyroidism", "hyperthyroidism", "thyroiditis", "thyroid cancer", "thyroid disease", in combination with the terms "coronavirus" and "COVID-19". Articles resulting from these searches and references cited in those articles were reviewed.

Results: Though preexisting autoimmune thyroid disease appears unlikely to render patients more vulnerable to COVID-19, some reports have documented relapse of Graves' disease (GD) or newly diagnosed GD about 1 month following SARS-CoV-2 infection. Investigations are ongoing to investigate molecular pathways permitting the virus to trigger GD or cause subacute thyroiditis (SAT). While COVID-19 is associated with non-thyroidal illness, it is not clear whether it also increases the risk of developing autoimmune hypothyroidism. The possibility that thyroid dysfunction may also increase susceptibility for COVID-19 infection deserves further investigation. Recent data illustrate the importance of thyroid hormone in protecting the lungs from injury, including that associated with COVID-19.

Conclusion: The interaction between the thyroid gland and COVID-19 is complex and bi-directional. COVID-19 infection is associated with triggering of GD and SAT, and possibly hypothyroidism. Until more is understood regarding the impact of coronavirus on the

thyroid gland, it seems advisable to monitor patients with COVID-19 for new thyroid disease or progression of preexisting thyroid disease.

Key Words: COVID-19, thyroid diseases, hyperthyroidism, subacute thyroiditis, autoimmune thyroiditis, non-thyroidal illness, hypothyroidism, thyroid cancer

COVID-19 is an infectious disease caused by a newly identified non-segmented single-stranded ribonucleic acid (RNA)- β coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is thought to have spread from infected animal species to humans, this leading in turn to person-to-person transmission [1]. COVID-19 has proven to be the most lethal and most rapidly moving pandemic since that of 1918, having caused 2 857 866 deaths as of April 8, 2021. In humans, it affects, inter alia, the respiratory, neurological, cardiovascular, and gastrointestinal systems. The virus is highly contagious, showing in some people high morbidity and mortality mainly due to severe acute respiratory syndrome (SARS) and exaggerated immune response (cytokine storm), leading to sepsis and death [2].

Although the disease affects all ages, the worst prognosis is seen in the elderly, in individuals with chronic underlying diseases—particularly obesity and diabetes mellitus—and reduced organ reserves, and in those with a particular genetic susceptibility to the virus, allowing it an easy entrance. COVID-19 has had a dramatic impact on daily life, profoundly affecting anxiety levels, the healthcare system, human activity and behavior, and the economy; all of which is proving exceedingly difficult for societies worldwide to cope with [3].

The spike proteins covering the coronavirus bind to angiotensin-converting enzyme 2 (ACE2) receptors, regulators of the renin-angiotensin-aldosterone system (RAAS), which are present on the epithelial surface of human cells. SARS-CoV-2 recruits a serine protease, TMPRSS2, which facilitates viral protein priming and cytoplasmic entry [4]. SARS-CoV-2 cell receptor (ACE2 receptor) genes are variably expressed in human organs, with the highest expression being in the small intestine, followed by the testis, heart, thyroid, kidney, and lungs, rendering these tissues particularly susceptible to infection [5]. The widespread expression of the ACE2 receptor and its variable density may explain the variety of symptoms and spectrum of organ failure occurring in patients with COVID-19 and other underlying diseases.

The fact that there is an abundance of ACE2 receptors in the thyroid parenchyma may expose the thyroid gland to SARS-CoV-2 infection. Awareness of the potential for resulting thyroid pathology allows the identification of vulnerable patient groups in a timely fashion so that therapeutic intervention and long-term monitoring can be implemented. Additionally, a patient's thyroid status may

have a direct impact on the course of COVID-19 due to the impact of thyroid hormone on multiple organs systems, including the cardiovascular and respiratory systems. In addition, given that thyroid abnormalities have been associated with disorders such as diabetes, obesity, kidney, dysfunction, and liver disease and that patients with these conditions are at increased risk for COVID-19 infection [6], it is possible that an underlying poorly controlled thyroid disorder may aggravate SARS-CoV-2 infection [7].

The aim of this mini-review is to summarize the current data regarding associations of COVID-19 with hyperthyroidism, with special focus on the potential impact of SARS-CoV-2 as a causal factor in the development of subacute thyroiditis (SAT) and as a trigger or perpetuator of Graves' disease (GD). Associations between COVID 19 and non-thyroidal illness and hypothyroidism will be explored. Moreover, the possibility will also be considered that thyroid dysfunction may be associated with worse COVID-19 outcomes. If this is the case, monitoring of thyroid status in COVID-19 patients, particularly those with preexisting thyroid disease, may be prudent.

Methods

References were identified through searches of PubMed and MEDLINE for articles published from Jan 1, 2019 to February 19, 2021 by use of the MeSH terms “*hypothyroidism*”, “*hyperthyroidism*”, “*thyroiditis*”, “*thyroid cancer*”, “*thyroid disease*”, in combination with the terms “*coronavirus*” and “*COVID-19*”. Articles resulting from these searches and references cited in those articles were reviewed. Relevant articles were also identified through searching authors' personal files. Preference was given to the most recent articles. A formal systematic review and grading of evidence was not undertaken. Greater emphasis was placed on high quality articles; however, given the fast pace at which knowledge regarding this topic is accruing, weight was also given to case reports and case series, due to their hypothesis-generating value.

Results

COVID-19 and the Immune System, and Subsequent Clinical Course

The immune profile of patients with COVID-19 has revealed that the disease causes severe lymphocyte

deficiencies, eg, lymphopenia, due to the exhaustion of cytotoxic T cells, and increased levels of proinflammatory monocytes [8]. The alveolar macrophages in the damaged pulmonary alveolar epithelial cells invaded by the virus generate viral nucleic acid, which stimulates the alveoli to secrete cytokines and chemokines, activating macrophages (macrophage activating syndrome) and dendritic cells. The cytokines, once overactivated, migrate to the inflammation site attracting more inflammatory cells and amplifying the inflammatory response [9]. Playing a major role in cytokine storm is the cytokine interleukin-6 (IL-6), which has both pro- and anti-inflammatory properties, this being dependent on the pathway of transduction: in the case of COVID-19, it is stimulated by tumor necrosis factor (TNF)- α and activates NF- κ B and is thought to be the culprit lesion inducing acute respiratory distress syndrome (ARDS) onset. High levels of IL-6 activate the coagulation system and increase vascular permeability, resulting in a rapid spread of the inflammation [10]: this often culminates in cytokine storm, which results in acute lung injury, the most severe form of the disease. The pathology shows diffuse alveolar damage, edema, and disseminated intravascular coagulation. Meanwhile, the endothelial cell damage activates coagulation and a status of hyperfibrinolysis that may cause clotting in small blood vessels [11].

It is noteworthy that even 2 months after recovery, the immune profile of recovered donors, when analyzed by multiparametric flow cytometry and compared to peripheral blood samples from active COVID-19 patients and control subjects, showed that the donors still had lower counts of granulocytes, CD4+ T cells, CD8+ T cells, and B cells, indicating that the duration of the immune disruption is of long rather than short duration [12].

However, while patients with autoimmunity might be considered to be at greater risk as regards morbidity and potentially mortality, any increased risk from COVID-19 infection among this group has not been supported by the existing data. In a small observational study including 10 patients with autoimmune inflammatory diseases, all were infected by SARS-CoV-2: 3 patients had a diagnosis of multiple sclerosis, 2 had rheumatoid arthritis, 4 had Hashimoto's thyroiditis, and 1 had psoriatic arthritis [13]. This group was compared with an age and gender matched group of 14 patients admitted to the hospital with COVID-19 but without any known autoimmune disease. No difference was observed regarding the course of the coronavirus infection and duration of hospitalization. The authors suggest that this might be an indication that the overall course of COVID-19 is not affected by the presence of an autoimmune inflammatory disease [13]. On the other hand, it should be borne in mind that the 4 patients with autoimmune diseases were receiving immune-modulatory

therapies (eg, interferon [IFN] α , anti-TNF- α , and anti-IL-6), and the 4 Hashimoto's thyroiditis patients were receiving levothyroxine treatment. Of note, 1 of the latter patients was receiving hydroxychloroquine, a treatment that could considerably have influenced the course of the infection. It therefore remains unclear whether patients with incompletely controlled autoimmune diseases or under immune-modulatory treatment may be at increased risk for a worse outcome of COVID-19.

With respect to organ damage caused by coronaviruses, Wei et al, investigating the effects of SARS-CoV on the thyroid in 2007, focused on the pattern of cellular and architectural alterations in follicular cells to detect any signs of viral proteins inducing cellular apoptosis as a pathogenetic factor of SARS-CoV infection [14]. To this end, the terminal deoxynucleotidyl transferase-mediated dUPT nick end-labeling (TUNEL) assay was used. As compared with normal thyroid glands, the thyroid glands of SARS-CoV-infected patients showed severe damage of the follicular cells with destruction of the follicular epithelium, exfoliation of epithelial cells, congested capillaries in the connective tissues between follicles, and fibrosis in the interconnective tissue [14]. If these morphological changes documented with SARS-CoV infection are also seen with SARS-CoV-2 infection, this may provide some explanation for the low serum levels of thyroxine (T4) and triiodothyronine (T3) found in patients with severe COVID-19.

COVID-19 and Hyperthyroidism

Generally speaking, patients with hyperthyroidism, of which GD is the most common form, and particularly those subjects being treated or with recurrent disease, are not considered to be at higher risk of contracting COVID-19 [15, 16]. However, patients with Graves' ophthalmopathy (GO) receiving steroid medication may, due to immunosuppression, theoretically be more prone to being infected. Future studies monitoring patients with active moderate-to-severe GO considered for treatment with teprotumumab, a human monoclonal antibody against the insulin-like growth factor type I receptor (IGF-IR) with a low side effects profile, in preference to treatment with steroids [17], may show whether treatment choice would have a differential impact on risks related to COVID-19 infection or progression.

One concern regarding patients recovering from GD or GO might be the finding that IFN- γ , TNF- α , and IL-6 cytokines [18], which are involved in the pathogenesis of both diseases, could potentially have a combined synergistic action in susceptible subjects, leading to recurrence of their disease and/or exacerbation of the virus infection. In line with these considerations are the recent, notable, *in vitro* findings that ACE2 is a human IFN-stimulated

gene in human airway epithelial cells, which knowledge advances our understanding of the mechanisms of viral infection. More specifically, the discovery suggests that SARS-CoV-2 may take advantage of species-specific IFN-driven upregulation of ACE2, a tissue-protective mediator during lung injury, thus leading to infection [19].

Moreover, a retrospective study investigating thyroid function in 287 consecutive patients affected by COVID-19 and hospitalized in non-intensive care units showed a higher incidence of hyperthyroidism and, inversely, correlation of thyrotropin (thyroid-stimulating hormone [TSH]) with IL-6 ($\rho = -0.41$; $P < 0.001$) and age [20]. Fifty-eight patients (20.2%) were found to have thyrotoxicosis, of whom 31 had overt disease, 15 (5.2%) had hypothyroidism, only 2 subjects had overt hypothyroidism, and 214 (74.6%) had normal thyroid function. The study investigated the hypothesis that SARS-CoV-2 might directly damage thyroid cells and that the cytokine storm associated with COVID-19 may induce thyroid dysfunction: the study results appear to support this hypothesis [20]. This was therefore the first study reporting that COVID-19 may indeed induce thyroid dysfunction. Due to concerns regarding administration of steroid therapy to these patients, the authors chose to follow-up the patients without specific treatment. Interestingly, thyroid function improved with improvement in infection-related symptoms, indicating that the impairment of thyroid function was induced by the virus due to high proinflammatory cytokine production. A recent prospective study of 125 patients with mild COVID-19 pneumonia compared with 125 individuals with severe COVID-19 pneumonia identified 12% of patients with severe pneumonia as having hyperthyroidism (6.4% overt and 5.6% subclinical). Hyperthyroidism was less frequent in the mildly ill group (1.6% overt and 4.8% subclinical). Thyrotoxicosis did not appear to adversely affect outcomes [21].

On the other hand, thyrotoxicosis left untreated can increase the risk for left ventricular hypertrophy and congestive heart failure [22]. Hyperthyroidism elevates circulating markers of endothelial dysfunction, including IL-6, IL-12, IL-18, fibrinogen, plasminogen activator inhibitor 1, von Willebrand factor, and vascular cell adhesion molecule-1, which were found to be significantly increased in patients with both overt and subclinical hyperthyroidism [23]. This may precipitate the hypercoagulable state which characterizes COVID-19 [24] and increase the incidence of cardiovascular complications. In addition, patients receiving antithyroid drug therapy, presenting even mild to moderate neutropenia, could be at risk for a worse outcome if they contract COVID-19, since their COVID-19 symptoms may be more severe due to immune derangement, this possibly aggravating the neutropenia and resulting in

cytokine storm cascade. The above speculations are, however, based on certain pathogenetic similarities between the 2 diseases, namely, the decrease of T-lymphocytes and of Treg cells and the increase of Th-17, as no studies are to date available regarding the progression of disease among patients with such conditions nor relating to their disease outcome. Another concern is treatment options with antithyroid drugs, including the titration regimen with the lowest possible dose of methimazole or the block + replace regimen. Firm recommendations are not easy to make in this instance, as the titration regimen is performed with a low dose of methimazole (MMI) in contrast to block + replace, which involves much higher MMI doses, together with levothyroxine administration, with, unavoidably, a higher incidence of side effects [25].

Recently, 2 Letters to the Editor were published each describing 2 cases, and thus documenting 4 patients with GD induced by COVID-19 [26, 27]. In the first letter, the authors reported 2 documented cases of concurrent presentation of SARS-CoV-2 infection and GD. A 47-year-old female with a 12-year history of GD and GO relapsed on concomitantly being infected with COVID-19 in May 2020. MMI treatment with 40 mg/daily quickly stabilized her thyroid status without complications. The second patient was a 61-year-old female with atrial fibrillation and GD since 2004. One month after being infected with COVID-19, she was admitted to the hospital with suspected heart infarction, which was ultimately not confirmed. Florid hyperthyroidism was diagnosed and treated with MMI 10 mg/daily for 3 months, thus achieving euthyroidism [26]. In the second letter, 2 female patients, 53 and 61 years old, were reported [27]. The first, whose GD had remained 30 years in remission, was infected with COVID-19 in April 2020 and had a relapse of GD a month later. The second, who had no history of thyroid disease, developed GD 2 months after COVID-19 infection, her entire immunological and thyroid hormone assessment being concordant with GD. She was successfully treated with methimazole 10 mg/day [27].

These cases presenting GD with a temporal sequence in relation to COVID-19 infection strongly suggest that GD may be triggered by SARS-CoV-2 infection. Viral infections (yersiniosis, HIV, hepatitis C) have been cited as major environmental factors implicated in the pathogenesis of autoimmune thyroid disease (AITD) [2, 28]. In addition, the hyperinflammatory state associated with severe SARS-CoV-2 infection could have triggered an immunological cascade with reactivation of GD, as has been described in other autoimmune disorders. It is of interest that whereas the hyperinflammation induced by SARS-CoV-2 is likely to be mainly mediated by Th-1 cytokines as well as IL-6, the pathogenesis of GD is apparently mediated by a Th-2

autoimmune response. This implies that the SARS-CoV-2 may trigger GD by altering the immune system in susceptible individuals.

Given that the ACE2 protein, which facilitates the host-cell entry of SARS-CoV-2 using the spike protein, may be differentially expressed in individuals with thyroid dysfunction [6], altered thyroid hormone synthesis may worsen SARS-CoV-2 infection. Manipulation of thyroid hormone levels in animal models can alter ACE receptor levels in the heart, illustrating the link between thyroid status and the renin-angiotensin-aldosterone system [29]. It thus appears that the thyroid gland and the viral infection, with its associated inflammatory-immune responses, are engaged in a complex interplay. The existing literature provides ample evidence that SARS-CoV-2 could target the thyroid gland and the entire hypothalamic-pituitary-thyroid axis, thereby inducing thyrotoxicosis, hypothyroidism, and non-thyroidal illness syndrome (NTI) [30, 31]. However, important questions remain, including whether this concerns a specific effect related to the viral load, what the role is of patients' susceptibility based on thyroid disease history, and whether thyroid dysfunction, by altering metabolism and the immune system, may facilitate SARS-CoV-2 infection and therefore influence severity and duration of disease.

Regular monitoring of thyroid function in patients with history of GD who are infected with COVID-19 is therefore advised [6]. Monitoring of thyroid function and periodic blood tests to prevent any deterioration of both conditions, while also bearing in mind the multilevel effects of thyroid hormone in several systems and other diseases, including diabetes and obesity, strongly point to the need for careful observation.

COVID-19 and Subacute and Atypical Thyroiditis

Muller et al [32] assessed the prevalence of thyrotoxicosis, suggestive of SAT, in 93 consecutive patients admitted to high intensity of care units (HICUs) because of COVID-19, in 101 patients admitted to HICUs not due to the infection, and in 52 patients with COVID-19, though with less severe symptoms, who were admitted to low intensity of care units (LICUs). The prevalence of SAT was estimated at 10% in the HICUs with COVID-19, as compared to 0.5% in the HICUs not due to COVID-19, which reflects the same rate as in the general population. TSH was lower in the HICU group with COVID-19 than in the LICU group with COVID-19 and HICUs without COVID-19. C-reactive protein was higher in HICU group that was COVID-19 positive, whereas free triiodothyronine (FT3) was not statistically significantly different among the groups. It is of interest that free thyroxine (FT4), elevated at admission, subsequently normalized, suggesting a combination of

thyrotoxicosis–non-thyroidal illness (NTI) due to a transient increase of thyroxine over some hours, which was identified as “thyroxine-thyrotoxicosis” [33].

Over the past year of the pandemic, several cases of SAT have been diagnosed together with COVID-19 infection. The first presentation was an 18-year-old woman who was admitted because of fever, neck pain radiating to the jaw, and palpitations occurring 15 days after a SARS-CoV-2-positive oropharyngeal swab. COVID-19 symptoms were mild and thyroid function and inflammatory markers normalized in 40 days [34]. Though the degree of change in thyroid function is likely to be related to the severity of COVID-19 infection, this case was reported together with that of a 37-year-old female with no thyroid disease history and who presented with SAT associated with a very mild presentation of COVID-19 [35]. The course was similarly mild and the infection was resolved in a few weeks. Another case describes a 43-year-old female who presented with moderate symptoms of SAT, following 6 weeks of being infected with COVID-19 [36]. She presented with persistent fever and neck pain accompanied by positive antibodies against SARS-CoV-2. Following adequate treatment with corticosteroids, the symptoms were resolved after 4 weeks. SAT in COVID-19 patients can sometimes be secondary to the “cytokine storm”, with IL-6 elevation inducing inflammatory or destructive thyroiditis, as observed during other viral infections that induce a thyrotoxicosis episode (ie, cytomegalovirus, enterovirus, and coxsackievirus) [16].

These above-mentioned cases underscore the importance of checking for SARS-CoV-2 infection in patients with SAT while also illustrating that young patients may develop mild forms of both COVID-19 and SAT without any sign of chronic thyroid disruption.

Non-Thyroidal Illness and Thyroid Function During COVID-19 Infection

It is well-recognized that there are a characteristic set of thyroid parameter abnormalities that accompany illness and hospitalization, and that the magnitude of these derangements reflects the severity of the illness. Illness associated with COVID-19 infection appears to be no exception, with low T3 and TSH levels being documented during the illness. In a retrospective study of 41 patients with COVID-19 infection, those with thyroid parameters compatible with NTI had evidence of greater disease severity, higher inflammatory markers, and worse outcomes than those without a NTI profile [37]. In another retrospective study of 50 patients with COVID-19 infection, TSH and T3 levels were significantly lower than the levels documented in non-COVID-infected patients with pneumonia and illness of a similar severity, and also significantly lower

than healthy controls [31]. In a cohort of patients admitted to hospital with suspected COVID-19, those with confirmed COVID-19 had lower TSH and FT4 values than those without COVID-19, but despite this, 86% of those with COVID-19 infection were euthyroid. Where values were available for patients with COVID-19, the TSH and FT4 values were lower upon hospital admission than the patient's outpatient baseline and recovered to above the values documented during hospitalization after discharge [38]. An additional study of 191 patients hospitalized with COVID-19 showed that 12 patients had low FT3 levels, 1 of whom also had a low TSH. In this group the COVID-19 infection was considered mild in 84.3%, moderate in 12.6%, and severe in 3.1% [39]. A recent retrospective study of patients with COVID-19 pneumonia compared with those with other causes of pneumonia showed that the COVID-19 group had significantly lower TSH values [40]. Both groups had lower TSH and T3 values compared with healthy controls. Patients with COVID-19 and with any abnormalities in TSH, T3, or T4 were more likely to have low lymphocyte counts and be categorized as having severe, rather than mild to moderate disease [40].

A recent prospective study of 144 individuals with COVID-19 followed serial TSH, FT4, and FT3 values during their hospitalization. The pattern of abnormalities observed were mostly low TSH values in 39%, accompanied by low FT3 in about half of these cases. The decrement in FT3 predicted mortality, whereas abnormalities were mostly reversed in survivors by the time of discharge [41]. Another prospective study of 250 patients with mild vs severe COVID-19 pneumonia showed that those who were critically ill had similar TSH values but lower FT3 and FT4 than those individuals who were less ill [21]. FT3 values were negatively correlated with length of hospital stay and C-reactive protein levels [21]. Also in hospitalized patients, another study tested the hypothesis that lymphopenia correlates with thyroid function abnormalities in patients with severe COVID-19 infections [42]. Patients with very low and high lymphocyte counts were investigated. Only T3 levels significantly correlated with lymphocyte counts ($\rho = 0.252$), and lower T3 concentrations were found in severely lymphopenic patients compared with nonlymphopenic patients. Moreover, severely lymphopenic patients with COVID-19 showed significantly decreased plasma concentrations of TSH, T4, FT4, and T3, compared to patients without lymphopenia, and significantly increased values of the inflammatory markers IL-6, C-reactive protein, and ferritin [42].

Thus, COVID-19 illness can be added to the list of conditions that are associated with NTI. A recent review of the thyroid complications of SARS compared with the thyroid complications of COVID-19 concluded that both

coronaviruses are associated with a NTI-like picture, with effects on the hypothalamus, pituitary, and thyroid gland all being seen [43].

The Relationship Between COVID-19-Related Lung Compromise and Thyroid Status

There may be some data that suggest a unique interaction between the lung compromise associated with COVID-19 and the thyroid. The lung is one of many organs that respond to thyroid hormone and the T3 receptor is present in alveolar type II cells. In these cells T3 increases the cell size and number, stimulates surfactant release, and increases the sodium, potassium-ATPase pump activity, increasing the ability of the cells to translocate fluid. Alveolar type II cells thus absorb alveolar edema fluid and are believed to be involved in the recovery process after lung injury is sustained in ARDS. Rats rendered hypothyroid by methimazole treatment are less able to clear fluid from their lungs [44], and fluid clearance is enhanced by liothyronine (LT3) administration [45]. Patients with lung fibrosis have high levels of type 2 deiodinase in their lungs [46], and reduced T3 levels in lung tissue could be hypothesized. Experimental LT3 administration, as an inhaled preparation that has been reformulated to achieve a neutral pH, has been shown to inhibit models of lung fibrosis in rats [46]. A preclinical safety trial was also conducted in rats [47]. Initially in a phase 1 study, inhalation of LT3 was shown to speed recovery from ARDS in 2 patients hospitalized with COVID-19 at the University of Minnesota [48]. LT3 is now being investigated in a phase 2 clinical trial (NCT 04115514) as a treatment for ARDS in humans, including that associated with COVID-19 [49]. These data illustrate the importance of thyroid hormone in protecting the lungs from injury, including that associated with COVID-19.

COVID-19 and the Development of Hypothyroidism

In contrast to the rapidly accumulating literature regarding thyrotoxicosis and thyroiditis associated with COVID-19 infection, there are relatively few studies addressing hypothyroidism associated with this infection (see Table 1). For example, in the THYRCOV study in which 20% of 287 patients hospitalized in a non-intensive care unit setting were documented to have thyrotoxicosis, only 5.2% had hypothyroidism with a TSH greater than 4.8 mIU/L [20]. Of the 15 patients with hypothyroidism, 2 cases were overt and 13 were subclinical. The hospital mortality was higher in those with TSH values above the reference range compared with those within the normal range, although hospital duration was not longer for those with the elevated

Table 1. Reports of the finding of hypothyroidism associated with COVID-19

Author, year	Type of study	Total number of patients with COVID-19	Number (%) of patients with hypothyroidism	Definition of Hypothyroidism (number overt)	Comments
Lania, 2020	Retrospective, single center	287	15 (5.2%)	TSH > 4.8 (2)	Mortality higher in those with hypothyroidism
Daraei, 2020	Retrospective, single center	390	21 (5.4%)	Not provided (not provided)	No effect of hypothyroidism on mortality
Muller, 2020	Single center, observational	126	7 (5.5%)	TSH > 4.3 (not provided)	7 of 78 (9%) ICU patients without COVID-19 developed hypothyroidism
Lui, 2020	Prospective, single center	191	1 (0.5%)	TSH > 4.8 (0)	Patient with TSH of 11 and TPO antibodies of 18,719
Tee, 2020	Case report	1	1	Not provided (1)	TSH 6.49, TPO antibodies > 2000
Dixit, 2020	Case report	1	1	TSH > 4.7 (1)	Myxedema coma, FT4 low, TPO antibodies 33 (normal < 20)
Gaven, 2021	Prospective, single center	250	4 (3%)	TSH > 4.2 (3)	No effect of hypothyroidism on mortality

TSH values [20]. A study of patients in Iran found that 5.4% of patients hospitalized for COVID-19 had hypothyroidism. This group of patients were mostly over 50 years of age and did not have higher mortality than the non-hypothyroid group [50]. In a study of those with mild vs severe COVID-19 pneumonia, none of those hospitalized with mild pneumonia had hypothyroidism, compared with 3.2% of those with severe pneumonia (2.4% overt; 0.8% subclinical) [21]. Hypothyroidism did not appear to affect outcomes.

In another study of 126 patients hospitalized with COVID-19, there were 14 patients (11%) who developed thyrotoxicosis compared with 1 out of 73 patients (1.3%) hospitalized in an intensive care unit without COVID-19 [32]. Seven of the 126 COVID-19-positive patients (5.5%) developed hypothyroidism, compared with 7 of the COVID-19-negative group (9%) [[32] see supplement]. Thus, this study suggests more comparable rates of the development of hypothyroidism in hospitalized patients with or without COVID-19 infection, compared with higher rates of hyperthyroidism in those with COVID-19, compared with those without COVID-19. Of all the patients who had any type of thyroid dysfunction, 8 patients had follow-up monitoring for a mean of 55 days after discharge and 2 were found to have confirmed hypothyroidism accompanied by thyroid sonography showing a picture suggestive of autoimmune thyroiditis. In a prospective study of hospitalized patients with COVID-19 in Hong Kong, most of those with abnormal thyroid function (13.1% of the group) had low TSH values, but 1 out of 191 patients (0.5%) had an elevated TSH of 11 mIU/L and elevated thyroid peroxidase antibodies (18 719 U/mL) [39].

Following discharge from hospital, the patient from the study in Hong Kong [39] continued to have hypothyroidism with a TSH of 10 mIU/L. There is a case report of an individual who reported symptoms consistent with hypothyroidism 7 days after the diagnosis of COVID-19 and was found to have mild hypothyroidism with a TSH value of 6.49 mIU/L and positive thyroid peroxidase antibodies (>2000 IU/mL) [51]. The authors hypothesize that Hashimoto's hypothyroidism may have developed as a result of cytokine storm [52]. However, there is no documentation of thyroid peroxidase antibodies prior to the infection so the sequence of events is unclear. A patient with dual diagnoses of myxedema coma and COVID-19 died from sudden cardiac arrest. Her diagnosis of hypothyroidism was made at the time of her hospitalization, but likely preceded her diagnosis of COVID-19 [53]. In summary, the predominate thyroid disorders seen with COVID-19 are hyperthyroidism and thyroiditis, with relatively few cases of hypothyroidism. There is insufficient data to determine if these cases of autoimmune hypothyroidism preceded the

COVID-19 or were triggered by the infection. However, the known association between COVID-19, the development of cytokine release syndrome, and the triggering of autoimmunity, supports the hypothesis of COVID-19 triggering autoimmune thyroid disease, including autoimmune hypothyroidism [16, 54]. A recent review of the thyroid complications of SARS compared with those of COVID-19, suggested that 7% of survivors of SARS had hypothyroidism [43].

Effect of Preexisting Thyroid Disease on the Prognosis of COVID-19

There are contradictory data regarding the impact that thyroid disease has upon the prognosis of COVID-19. For example, in a retrospective study of patients hospitalized in Iran that included 21 patients receiving levothyroxine treatment for hypothyroidism, hypothyroidism did not appear to affect mortality [50]. However, the number of patients with hypothyroidism were insufficient for a multivariable analysis. A retrospective study of 3703 patients hospitalized for COVID-19, including 251 with preexisting hypothyroidism, did not document any worse outcomes for the latter group, including risk of hospitalization, mechanical ventilation, or death [55].

In a study of 433 patients hospitalized with COVID-19 and categorized as having severe or nonsevere manifestations of COVID-19, a diagnosis of treated hypothyroidism (present in 43 patients [9.9%]) was significantly associated with having a severe form of COVID-19 [56]. Moreover, a meta-analysis of 8 studies was conducted that did not include the 3 prior studies. This analysis comprised 2169 patients who were categorized as having severe or nonsevere cases of COVID-19, the presence of preexisting thyroid disease was associated with an odds ratio of 2.48 (CI, 1.32-4.66) of having severe COVID-19 [57]. Unfortunately, excluded studies were not listed, although a clinically validated definition of severe COVID-19 was required for the studies that were included (the reference intended as reference 3 in this article is mis-cited and is intended to be Liu et al, 2020 [58]).

Most recently, in a population-based case control and cohort study from the Danish COVID-19 cohort, the risk of contracting SARS-CoV-2 as well as the prognosis of SARS-CoV-2 infection was assessed in patients with hypothyroidism and hyperthyroidism [59]. All individuals who tested negative ($n = 2\,400\,609$) or positive ($n = 28\,078$) between February and September 2020 in Denmark were included. These results suggest that treatment for thyroid disorders is not likely to increase the patient's risk of contracting SARS-CoV-2 infection or to compromise the clinical management of those who are already infected. On the other hand, the crude analysis shows an excess risk of

worse outcome of SARS-CoV-2 infection in patients treated for hypothyroidism and hyperthyroidism; however, these associations attenuate after adjustment for comorbidity, indicating that the latter may increase the risk rather than the thyroid disease per se. A multidisciplinary approach, individualized to the patient's clinical and serological features, together with long-term clinical monitoring, is advised to achieve optimal results. Patients with autoimmune disease receiving immunosuppressants may possibly have higher susceptibility to SARS-CoV-2 infection; however, suspension of ongoing therapy is generally contraindicated to avoid disease flares which could further increase the risk of COVID-19 infection [54].

It has been suggested that integrin $\alpha v \beta 3$, in addition to ACE2, may be required for internalization of coronaviruses [60]. Thyroid hormones in turn regulate the cellular uptake of integrins. Thus, it has been hypothesized that physiologic concentrations of T4 may be required for the actions of ACE2 and integrin $\alpha v \beta 3$ and internalization of the virus [60]. It has also been further hypothesized that lowering T4 levels may be a means of reducing viral uptake by cells. Further research may determine if there is a relationship with thyroid hormones and ability of SARS-CoV-2 to enter cells in humans, as appears to be the case in animal models [29], and if this might underlie the impact of thyroid disorders on the severity of COVID-19.

Interestingly, a recent prospective study studied the effect of preexisting thyroid nodules on the outcomes of patients hospitalized with COVID-19 pneumonia [21]. Thyroid nodules over 1 cm in size were found in 7% of those with mild illness and 26% of those with critical illness, with a statistically significant difference between the 2 groups ($P < 0.0001$). The authors speculated that worse outcome in patients with thyroid nodules could have been associated with hypoxia due to compression from the nodules or associated thyrotoxicosis. However, such theories need to be studied further as the critically ill group was also older than the mildly ill group [21].

Relationship Between COVID-19 and Thyroid Cancer

Although the current pandemic has clearly impacted the delivery of care for thyroid disorders, most especially thyroid cancer, little is known about either the effect of COVID-19 on the development or progression of thyroid cancer or about the susceptibility of individuals with thyroid cancer to infection or worse complications from COVID-19. With respect to the latter, administration of thyroid hormone, thyroid surgery, or use of radioactive iodine therapy are not known to increase susceptibility to or severity of COVID-19 infection.

Based on a meta-analysis, the prevalence of a cancer diagnosis in patients with COVID-19 was 2% [61], presumably with few of these patients having thyroid cancer specifically. Patients with a cancer diagnosis such as lung cancer may have a higher risk of severe events following COVID-19 [62], presumably in part due to their having undergone surgery or received chemotherapy. Two recent studies suggest worse outcomes from COVID-19 in patients with cancer. One study, which included 11 thyroid cancer patients among the 105 patients studied, showed that the patients with cancer had increased risk of severe COVID-19 related events [63], while another study showed increased mortality among those with cancer [64]. Lung cancer and another cancer metastatic to the lungs appeared to carry a worse prognosis [63]. It is reasonable to anticipate that patients with thyroid cancer who have received tyrosine kinase inhibitor therapy or external beam radiotherapy, have lung metastases, or who are older or have accompanying comorbidities may be at risk for greater complications of COVID-19.

Delay of Care for Thyroid Disorders During the COVID-19 Pandemic

The impact of the coronavirus pandemic upon the management of thyroid disorders has been extensively covered elsewhere [15, 65–67]. With respect to diagnosis and treatment of hypothyroidism, this is presumably the least impacted thyroid disorder and therapeutic goals to ensure euthyroidism continue to be important, with avoidance of unnecessary blood tests in order to limit exposure. The diagnosis and management of hyperthyroidism may be more affected by the pandemic due to reliance on radioisotopes for diagnosis and treatment, in addition to the need for laboratory testing for initial diagnostic and regular monitoring. The laboratory testing should continue as much as can be safely achieved, while the therapy may require more reliance on medical therapy, rather than therapy with radioactive iodine or surgery [15].

Diagnosis of thyroid cancer relies on ultrasonography, fine needle aspiration biopsy, and surgery, while treatment can comprise surgery, thyroid hormone therapy, radioiodine therapy, external beam radiotherapy, and targeted multikinase inhibitor therapy. The degree to which these can continue unaffected would be determined by the prevailing pandemic conditions and the individual patient's disease characteristics. This could encompass the entire spectrum from a low-risk thyroid cancer patient in whom temporary delay of diagnosis or therapy may have no impact on prognosis to cases of advanced or undifferentiated thyroid cancer where delay of therapy may be substantially detrimental to the patient, thus requiring a careful

consideration of the balance between benefits and risk [65–67]. Recent studies have shown that fewer thyroid biopsies were performed in 2020, compared with 2019 [68], and also that fewer thyroid nuclear medicine studies were performed [69]. The impact of a 3-month delay was estimated to have a 3% or less effect on 10-year thyroid cancer mortality risk in one modeling study [70].

Conclusions

Approximately 15% of patients with mild to moderate COVID-19 were observed to have thyroid dysfunction [39]. It is hypothesized that SARS-CoV-2 might directly impact upon thyroid morphology and function, thus possibly resulting in a worsening of preexisting AITD. In addition, COVID-19 may aggravate AITD through its effects on the immune system and may result in the development of cytokine storm. Nevertheless, it is still uncertain whether patients with autoimmune diseases are at increased risk for a worse outcome, although those receiving immune-modulatory treatment appear not to be at greater risk. The possibility that thyroid dysfunction may also increase susceptibility to COVID-19 infection deserves further investigation. While COVID-19 is associated with non-thyroidal illness, it is not clear whether it also increases the risk of the development of autoimmune hypothyroidism. Recent data illustrate the importance of thyroid hormone in protecting the lungs from injury, including that associated with COVID-19.

While thyroid function is not routinely assessed in the context of COVID-19 infection, more frequent thyroid function testing is considered to be reasonable. Patients who have GD coexisting with COVID-19, particularly during the acute stage of their autoimmune disease, or who are receiving long-term treatment with antithyroid drugs, should be carefully monitored, as aggravation of either or both diseases is possible. Because thyroid hormones play such a critical role in regulating multiple organ systems, thyroid hormone derangement, as for example, in those who have poorly controlled thyroid disease, may render these patients more vulnerable to COVID-19 infection and potentially predispose them to more severe disease.

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Additional Information

Correspondence: Leonidas H. Duntas, MD, Evgenidion Hospital, Unit of Endocrinology, Diabetes, and Metabolism, University of Athens, 20 Papadiamatopoulou Str., 11528 Athens, Greece. Email: leonidas@duntas.gr.

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