

# Potential relationships between COVID-19 and the thyroid gland: an update

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[journals.sagepub.com/home/imr](https://journals.sagepub.com/home/imr)**Rania Naguib** 

## Abstract

In this review, I aim to provide a complete overview of recent advances in knowledge regarding severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2)-induced thyroid dysfunction. I discuss the findings regarding the role of SARS-CoV-2 in the development of thyroid dysfunction, including subacute thyroiditis, Graves' disease, non-thyroidal illness, thyrotoxicosis and Hashimoto's thyroiditis during and subsequent to coronavirus disease 2019 (COVID-19). The thyroid gland and the entire hypothalamic–pituitary–thyroid (HPT) axis may represent key targets of SARS-CoV-2. Thyroid dysfunction during and subsequent to COVID-19 has been documented in clinical studies and is usually reversible. Most of the thyroid disorders, including Graves' disease, euthyroid sick syndrome, Hashimoto's thyroiditis and subacute thyroiditis, have been documented as sequelae to COVID-19, and the SARS-CoV-2 virus has been implicated in the aetiology of each. COVID-19 has been suggested to trigger the activation of pre-existing thyroid disease or autoimmunity. Furthermore, patients with uncontrolled thyrotoxicosis are at risk of SARS-CoV-2 infection-related consequences. Because of the neutropenia caused by antithyroid medications, which may obscure the signs of COVID-19, this group of patients should receive special attention. It is suggested that thyroid dysfunction during COVID-19 is caused by direct infection of the thyroid or “cytokine storm”-mediated autoimmune effects on the thyroid.

## Keywords

Coronavirus disease 2019, thyroid, hyperthyroidism, thyroiditis, non-thyroidal illness, hypothyroidism, thyroid cancer

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Associate Professor of Medicine and Endocrinology,  
Department of Clinical Science, College of Medicine,  
Princess Nourah Bint Abdulrahman University, Riyadh,  
Saudi Arabia

### Corresponding author:

Rania Naguib, Associate Professor of Medicine and  
Endocrinology, Department of Clinical Science, College of  
Medicine, Princess Nourah Bint Abdulrahman University,  
Riyadh 11671, Saudi Arabia.

Email: [ranianaguib2000@yahoo.com](mailto:ranianaguib2000@yahoo.com)

## Introduction

Coronavirus disease 2019 (COVID-19) is a highly contagious disease caused by the



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severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a positive-sense, single-stranded, enveloped RNA virus in the beta-coronavirus family.<sup>1</sup> SARS-Cov-2 is phylogenetically related to SARS-CoV-1, the virus that causes severe acute respiratory syndrome (SARS). SARS-CoV-2, like SARS-CoV-1, infects human tissues by entering cells *via* the angiotensin-converting enzyme 2 (ACE2) receptor.<sup>2</sup> The histopathology of the thyroid gland of patients infected during the SARS-CoV-1 outbreak involved severe damage to the parafollicular cells and follicular epithelial cells, and destruction of epithelial cells, which were shed into the follicles, causing them to rupture. However, there was no inflammatory infiltration or cell necrosis, which is consistent with the hypothesis that SARS-CoV-1 infection causes thyroid injury by inducing extensive apoptosis. Overall, the differences in the thyroid pathology induced by SARS-CoV-1 and SARS-CoV-2 may imply that although SARS-CoV-2 causes a more severe infection, its effects on the thyroid are less severe than those of SARS-CoV-1.<sup>3</sup>

Most patients affected by COVID-19 are asymptomatic or present with mild influenza-like symptoms, but approximately 14% of patients present with severe symptoms and 5% are in a critical condition.<sup>3,4</sup> COVID-19 is caused by SARS-CoV-2 infection of the lung parenchyma. Then, the spike protein of the virus binds to angiotensin-converting enzyme 2 (ACE2) molecules on lung cell membranes, which mediate the intracellular entry of the virus.<sup>3-5</sup> Patients with COVID-19 have also been found to have viral RNA in their blood, stool and urine, which suggests that SARS-CoV-2 is able to bind to and interact with ACE2 expressed in other organs, permitting extrapulmonary dissemination.<sup>6</sup> In patients with risk factors such as old age, male sex, chronic hypertension, cardiovascular comorbidities and diabetes, SARS-CoV-2 infection

can cause both pulmonary and systemic inflammation, resulting in organ failure.<sup>2,7,8</sup> The variety of clinical manifestations and the multi-organ failure that characterise COVID-19 have been linked to both direct (caused by viral infection of target cells) and indirect (caused by abnormal immune-inflammatory responses to the virus, involving the coagulation, cytokine and complement systems) injury.<sup>2,9-13</sup>

The most common critical complications of COVID-19 are acute respiratory distress syndrome (ARDS) and respiratory failure, sepsis, acute cardiac injury and heart failure.<sup>7</sup> Tissue tropisms of SARS-CoV-2 to the cardiovascular, coagulative, gastrointestinal and nervous systems have also been reported.<sup>3</sup> Moreover, numerous endocrine organs, such as the pancreas, testes, ovary, adrenal gland, thyroid and pituitary gland, have been found to express ACE2, implying that these represent target tissues of SARS-CoV-2.<sup>14,15</sup> Infection with SARS-CoV-2 may aggravate existing diseases in endocrine organs or cause new abnormalities. In turn, such endocrine diseases may worsen the prognosis of COVID-19.<sup>3,5,16</sup>

Because ACE2 receptors are abundant in the thyroid parenchyma, the thyroid gland may be vulnerable to SARS-CoV-2 infection.<sup>17</sup> The serum concentration of ACE was found to be positively associated with those of 3,5,3'-triiodothyronine (T3) and thyroxine (T4), implying that it might represent a useful marker for the assessment of peripheral thyroid hormone function.<sup>3</sup> Furthermore, Rotondi and colleagues<sup>18</sup> identified ACE2 receptor mRNA expression in thyroid follicular cells, suggesting that the thyroid may be a potential target of SARS-CoV-2.<sup>3</sup> Thyroid hormones and immunomodulatory signalling molecules are involved in the complex interplay between the thyroid gland and viral infection. Viruses, along with the associated inflammatory and immune responses, may have significant effects on thyroid function.<sup>2</sup> Because

thyroid hormones affect multiple organ systems, including the cardiovascular and respiratory systems, thyroid status may have a direct effect on the course of COVID-19. Furthermore, given that thyroid abnormalities have been linked to disorders such as diabetes, obesity, kidney dysfunction and liver disease, and that patients with these conditions are more likely to contract COVID-19,<sup>19</sup> an underlying poorly-controlled thyroid disorder might exacerbate SARS-CoV-2 infection.<sup>17,20</sup>

Thyroid hormones influence both the innate and adaptive immune responses *via* genetic and non-genomic pathways. T4 and T3 increase the synthesis and release of cytokines that are components of the “cytokine storm” that can be induced by systemic viral infections. Furthermore, viral infections are environmental triggers for the development of subacute thyroiditis. Conversely, respiratory infections may trigger a thyroid storm in individuals with decompensated hyperthyroidism, which would increase the risk of infection-related mortality secondary to cardiovascular morbidity. It is also worth noting that T4 has been shown to activate human platelets, which could help provoke the pathological clotting that occurs during COVID-19 infection.<sup>2</sup> Thus, a better understanding of the pathophysiology of the thyroid gland during SARS CoV-2 infection may aid in the correct interpretation of thyroid function test anomalies and in the accurate assessment of thyroid function, especially in patients with severe forms of infection, facilitating more appropriate management.

In this review, I provide an update on knowledge of the relationship between COVID-19 infection and the thyroid gland.

## Review methods

Published studies were identified by searches using the MeSH terms “hypothalamic-pituitary-thyroid axis”, “hypothyroidism”,

“hyperthyroidism”, “thyroiditis”, “subacute thyroiditis”, “atypical thyroiditis”, “chronic thyroiditis”, “Hashimoto’s thyroiditis”, “Graves’ disease”, “thyroid illness” and “thyroid cancer”, with the terms “coronavirus”, “SARS-CoV-2” and “COVID-19” in the PubMed, MEDLINE, Google Scholar, EMBASE and Web of Science databases for publications published up to 14 December 2021. The articles identified using these searches, as well as the references listed in these articles, were reviewed. The most recently published articles were prioritised. Case reports, original articles, randomised controlled trials, reviews, and meta-analyses written in English were selected and analysed, and are discussed herein.

## Relationship between COVID-19 and the hypothalamic–pituitary–thyroid axis

An infection produced by SARS-CoV-2 has been reported to disrupt the nervous system by damaging the cranial nerves, resulting in the loss of smell and taste.<sup>21</sup> SARS genome sequences have been found in the cytoplasm of many neurons in the hypothalamus, and immunohistochemical analysis of adenohypophyses obtained during the autopsy of five patients with SARS revealed significant reductions in both the number and immunoreactivity of thyroid-stimulating hormone (TSH)-positive cells.<sup>2</sup> According to Ur *et al.*,<sup>22</sup> SARS-CoV-2 can propagate across nerve axons because high ACE2 expression causes a cytokine storm. High circulating concentrations of interleukin (IL)-6, IL-7, tumour necrosis factor (TNF)- $\alpha$ , the soluble version of the IL-2 receptor, and inflammatory chemokines have been detected during the cytokine storm generated by SARS-CoV-2.<sup>23</sup> SARS-CoV-2 has a substantial effect on TSH-secreting cells, resulting in lower

TSH concentrations and, as a result, a disruption of pituitary endocrine axis feedback loops. These effects on TSH-secreting cells may involve four different mechanisms: direct damage to the pituitary gland caused by SARS-CoV-2 (central TSH abnormalities caused by virus-related hypophysitis), indirect damage caused by pro-inflammatory cytokines and the cytokine storm, chronic stress caused by hypoxia, and the effects of specific classes of medication, such as glucocorticoids.<sup>21</sup> Chen *et al.* found that the serum concentrations of TSH and total T3 were considerably lower in patients with COVID-19 than in a control group.<sup>24</sup>

### **Relationships between COVID-19 and morphological and pathological changes in the thyroid gland**

The pathogenesis of the thyroid dysfunction that is induced by COVID-19 has not been characterised. One theory is that the virus has a direct effect on the thyroid gland. SARS-CoV-2 appears to have the ability to infect the gland by direct infiltration from the upper respiratory tract. Post-mortem examinations of individuals who died of COVID-19 have revealed pathological abnormalities in various organs, including the thyroid gland. However, surprisingly, no morphological abnormalities or severe damage to thyroid follicles have been discovered. Histological examination of the thyroid has revealed the absence of a lymphocytic infiltrate but the presence of extensive apoptosis, indicative of destructive thyroiditis, which may be the cause of the thyrotoxicosis.<sup>25,26</sup> In addition, despite ACE2 being highly expressed in the thyroid, SARS-CoV-2 has not been detected in thyroid tissues by either PCR or immunohistochemistry.<sup>27-29</sup> Thus, there may be factors that prevent the virus from infecting thyroid follicular cells.<sup>3,15</sup>

### **Relationship between COVID-19 and hypothyroidism**

Some previous studies have identified cases of COVID-19-related primary hypothyroidism.<sup>30-32</sup> Only 5.2% of 287 patients hospitalised in a non-intensive care setting were found to have hypothyroidism in the THYRCOV study.<sup>32</sup> The mortality rate of hospitalised patients was higher for those with TSH concentrations above the reference range than for those in the normal range, but the durations of hospitalisation were similar for the two groups. According to a study conducted in patients in Iran, 5.4% of those hospitalised because of COVID-19 had hypothyroidism. The majority of the participants were over 50 years old and did not have a higher mortality rate than the those without hypothyroidism.<sup>33</sup> In a study that compared patients with mild or severe COVID-19 pneumonia, none of those hospitalised with mild pneumonia had hypothyroidism, whereas 3.2% of those with severe pneumonia did have hypothyroidism (2.4% overt and 0.8% sub-clinical).<sup>34</sup> In addition, Tee *et al.*<sup>31</sup> described a case of overt primary hypothyroidism that occurred 7 days after the resolution of COVID-19, which was attributed to chronic autoimmune thyroiditis. Thus, primary hypothyroidism might develop during or after COVID-19.<sup>2</sup>

Abnormal endocrine findings at the hypothalamus or pituitary level of the HPT axis that are compatible with central hypothyroidism secondary to SARS-CoV-2 infection have been described in a few patients. Central hypothyroidism was identified in 2% to 6% of patients hospitalised for COVID-19 who had low free T4 and low or normal TSH concentrations by Chen *et al.* After recovery from COVID-19, these hormonal abnormalities disappeared, which implies that COVID-19 may have acute, transitory effects on the HPT axis.<sup>24</sup> The findings of this study suggest

that the incidences of hypothyroidism in patients hospitalised with or without COVID-19 are comparable. Of eight patients with thyroid dysfunction who were followed up for a mean of 55 days after discharge from hospital, hypothyroidism was confirmed in two, and thyroid ultrasonography revealed findings suggestive of autoimmune thyroiditis.<sup>30</sup> However, there are insufficient data to determine whether the autoimmune hypothyroidism preceded or was triggered by SARS-CoV-2 infection. Nevertheless, the known relationships between COVID-19, the development of cytokine release syndrome and the triggering of autoimmunity are consistent with the hypothesis that COVID-19 causes autoimmune thyroid disease, including autoimmune hypothyroidism.<sup>26,35</sup>

A prospective study of hospitalised COVID-19 patients conducted in Hong Kong showed that the majority of those with abnormal thyroid function (13.1% of the group) had low TSH concentrations, but only one of 191 participants (0.5%) had a high TSH concentration and a high thyroid peroxidase antibody titre.<sup>36</sup> This patient continued to be hypothyroid after being discharged from hospital. In a study of 433 patients hospitalised with COVID-19, hypothyroidism was present and being treated in 43 patients (9.9%), and this was significantly associated with severe COVID-19.<sup>37</sup> In addition, a recent study demonstrated that the in-hospital mortality of patients with hypothyroidism and COVID-19 is higher than that of euthyroid patients, which implies that hypothyroidism may have a negative effect on the outcome of COVID-19,<sup>32</sup> but another study showed that hypothyroidism did not have an effect on the outcome of the disease.<sup>17</sup> In a study by Gerwen *et al.*, patients with COVID-19 confirmed by the analysis of a nasopharyngeal swab were enrolled and data were collected from an electronic medical database.

Two hundred fifty-one (6.8%) of the 3703 patients with COVID-19 had pre-existing hypothyroidism, including those who had been diagnosed with hypothyroidism and those who were taking levothyroxine. The patients with hypothyroidism were more likely to be female (69% *vs.* 43%,  $p < 0.001$ ), of non-Hispanic white ethnicity (45% *vs.* 26%,  $p < 0.001$ ), and to have more than two comorbidities, such as overweight or obesity, arterial hypertension, and diabetes mellitus (68% *vs.* 53%  $p < 0.001$ ). However, in another study, pre-existing hypothyroidism was found to have no effect on the prognosis of COVID-19, including with respect to the risks of hospitalisation, mechanical ventilation, and death.<sup>38</sup>

In a retrospective study conducted in New York City,<sup>38</sup> the role of hypothyroidism as a putative risk factor for poor prognosis in patients with COVID-19 was explored further. There is some evidence of a specific relationship between COVID-19-related lung damage and the thyroid. The T3 receptor is expressed in alveolar type II cells, which is one of many cell types that respond to thyroid hormone. T3 increases the size and number of alveolar type II cells, stimulates surfactant release, and increases the activity of the sodium-potassium ATPase pump, which increases the ability of the cells to transfer fluid. As a result, alveolar type II cells can absorb alveolar oedema fluid and are thought to be involved in the recovery from ARDS-induced lung injury. This fluid clearance is improved by liothyronine (LT3) administration in rats rendered hypothyroid by methimazole therapy.<sup>17,39</sup> Patients with lung fibrosis express significant amounts of type 2 deiodinase in their lungs, which may be linked to a lower T3 concentration in lung tissue. Furthermore, experimental LT3 administration, in the form of an inhaled formula with a neutral pH, has been demonstrated to suppress

lung fibrosis in mice<sup>40</sup> and rats.<sup>41</sup> Finally, the inhalation of LT3 was demonstrated to accelerate the recovery from ARDS in two patients hospitalised with COVID-19 in a phase 1 trial conducted at the University of Minnesota, and in a phase 2 clinical trial (NCT 04115514), LT3 is being tested as a therapy for ARDS in humans, and particularly for that caused by COVID-19. These findings highlight the importance of thyroid hormones in the protection of the lungs from damage, including COVID-19-related injury.<sup>17</sup>

### **Relationship between COVID-19 and thyroiditis**

Subacute thyroiditis (SAT), also known as De Quervain thyroiditis, is a self-limiting thyroid disease that is induced by a viral or post-viral inflammatory process. Because neck pain is a defining feature of this condition, another term for it is “painful subacute thyroiditis”. The symptoms include a painful goitre, fever, palpitations, and exhaustion. A high circulating C-reactive protein (CRP) concentration and a high erythrocyte sedimentation rate (ESR), as well as localised hypoechogenicity in the thyroid gland, are typical findings in SAT. Thyroid damage and a thyrotoxicosis-induced reduction in TSH result in poor thyroidal uptake of radioiodine.<sup>42</sup> The clinical course of SAT usually consists of three phases: thyrotoxicosis for the first several months, hypothyroidism for approximately the next 3 months, and finally euthyroidism. Several studies have shown a relationship between COVID-19 infection and SAT.<sup>3,43–45</sup> The aetiology and pathogenesis of SAT have not been well characterised, but it is widely recognised that it is caused by a viral infection or a post-viral inflammatory response, particularly in genetically predisposed individuals.<sup>3</sup>

Viral infections may cause thyroid disease by liberating antigens secondary to necrosis or apoptosis, causing alterations to antigens or molecular mimicry, causing the secretion of pro-inflammatory cytokines and chemokines, and/or triggering aberrant human leukocyte antigen DR isotype (HLA-DR) expression and the activation of toll-like receptors (TLRs).<sup>2</sup> Individuals with certain HLA haplotypes, such as HLA-Bw35, HLA-B67, HLA-B15/62, and HLA-Drw8, have been demonstrated to be vulnerable to SAT.<sup>46</sup> A recent study also suggested that individuals with HLA-B\*35, HLA-B\*18:01, HLA-DRB1\*01, or HLA-C\*04:01 are predisposed to SAT.<sup>47</sup> A study of a large cohort of healthy Polish people and patients with SAT showed that HLA-B\*18:01 and HLA-DRB1\*01 are independent risk alleles for SAT. Furthermore, the HLA-B\*35 and HLA-C\*04:01 alleles have been shown to be markers of genetic susceptibility to SAT, whether they are present alone or together. Recent findings have led to serious questions regarding the negative predictive value of the absence of HLA-B\*35 in individuals with or at risk of SAT. In fact, a diagnosis of SAT or a susceptibility to SAT can be confirmed genetically on the basis of the presence of any of the four HLA alleles that have been identified to be SAT-related.<sup>48</sup>

It has been suggested that cytokines play a pathogenic role in the development of thyroiditis and thyroid autoimmune flare-ups.<sup>42</sup> Dormant autoimmune thyroid diseases, such as Hashimoto’s thyroiditis, may become clinically overt in patients with COVID-19 as a result of T helper (Th) 2-mediated autoantibody synthesis and Th1-mediated cellular immunity. Previous studies have shown that thyroiditis during COVID-19 may be caused by an increase in IL-6 secretion and/or cytotoxic effects of T-cells as part of a hyperinflammatory condition.<sup>30,32,49,50</sup> Owing to this

imbalance in the immune system, patients with thyroid autoimmune disorders may have more severe COVID-19 than otherwise healthy people, because of higher baseline serum concentrations of IL-6 and TNF- $\alpha$ . However, in predisposed patients, SARS-CoV-2 may disrupt immunotolerance, resulting in the development of immune-mediated thyroiditis, the exacerbation of a prior thyroid disease, or the recurrence of previous thyroid dysfunction.<sup>1,51</sup>

The incidence of SAT varies seasonally and tends to peak during echovirus and coxsackievirus outbreaks.<sup>3</sup> The clinical characteristics of thyroiditis during COVID-19 include a higher incidence in women, a high incidence of arrhythmias, such as atrial fibrillation, and a high incidence of silent (painless) thyroiditis.<sup>43</sup> Lymphocytopenia is a common haematological abnormality in SARS-CoV-2 infection, and this may reduce the lympho-plasmacytic infiltration of the thyroid gland and the associated pain in the anterior cervical region that occurs in some patients.<sup>30</sup> At the hormonal level, "T4 thyrotoxicosis" may be the result of thyroid cell lysis,<sup>26</sup> causing the release of pre-synthesised thyroid hormones, and a decrease in deiodinase activity, leading to a reduction in the T3 concentration. A hypoechoic, heterogeneous, non-vascularised thyroid gland can be identified on cervical ultrasonography.<sup>26,43,52</sup> In the study by Lania *et al.*,<sup>32</sup> more than one fifth of the patients who were hospitalised for COVID-19 but were not in intensive care units were found to have thyrotoxicosis but no neck pain, which most likely implies that they had painless (silent) thyroiditis, or more broadly, destructive thyroiditis without neck pain. The absence of neck pain and the presence of thyroid peroxidase antibodies are two key features of painless thyroiditis that help differentiate it from subacute thyroiditis.<sup>2</sup> The absence of neck pain associated with destructive

thyrotoxicosis may be attributed to the presence of leukopenia in COVID-19: the low lymphocyte count may preclude the formation of giant cells (congregates of lymphocytes, histiocytes, and colloid) in the thyroid, resulting in the absence of thyroid capsule stretching and consequent neck pain. Patients with thyroiditis subsequent to COVID-19 were followed up for a mean of 55 days, during which none experienced neck pain, and instead of lymphocytosis, they showed the lymphopenia that is typically associated with COVID-19.<sup>30</sup> Finally, one study led to the recommendation that patients with SAT should be tested for SARS-CoV-2 infection and showed that young people can develop mild forms of COVID-19 and SAT, without showing any signs of chronic thyroid dysfunction.<sup>17</sup>

## Relationship between COVID-19 and euthyroid sick syndrome

Euthyroid sick syndrome (ESS), also known as low T3 syndrome or non-thyroidal sickness syndrome, is characterised by abnormalities in the core components of the HPT axis, as well as variations in thyroid hormone metabolism in several target organs. ESS can manifest itself in a variety of acute and chronic systemic disorders, including cardiovascular, respiratory, and infectious diseases and cancer.<sup>53</sup> Low plasma T3, low or normal plasma T4, or high plasma reverse (rT3) concentrations in the presence of a normal or slightly low TSH concentration are the most common hormonal defects in ESS.<sup>2</sup> COVID-19 has also been reported to be associated with ESS.<sup>21</sup> Lui *et al.*<sup>36</sup> stated that ESS can be found in individuals with severe COVID-19 symptoms, as well as in those with mild or moderate symptoms who do not require critical care. Another retrospective study showed that there were lower TSH and T3 concentrations in 50 patients

with COVID-19 than in patients with pneumonia of other aetiologies who were similarly unwell or healthy controls.<sup>24</sup> Similarly, in a group of patients admitted to hospital with suspected COVID-19, those with confirmed COVID-19 had lower TSH and FT4 concentrations than those who did not have COVID-19.<sup>17</sup>

ESS is a severe systemic disease that occurs in two phases. In phase I, the acute phase, inhibition of the activity of deiodinase type I results in less conversion of T4 to T3, lower production of thyroid hormone-binding proteins, such as albumin and thyroid-binding globulin, a reduction in pulsatile TSH secretion, and greater metabolism of thyroid hormones. In phase II, the chronic phase, there are decreases in thyrotropin-releasing hormone (TRH) and TSH secretion, because of an increase in the secretion of IL-6, IL-18 and TNF- $\alpha$ .<sup>21,24,54</sup> ESS is thought to represent an adaptation that conserves energy under conditions of stress and macronutrient restriction, which characterise the early stages of systemic disease. However, it is associated with adverse outcomes, such as mortality, during protracted critical illness, when patients continue to require intensive medical care and parenteral nutrition. Indeed, patients in a critical condition who die have significantly lower plasma T4, T3, and TSH concentrations and higher plasma rT3 concentrations than survivors. Cytokines, which are generated during illness and affect the expression of a variety of genes involved in thyroid hormone metabolism, are thought to be a primary determinant of ESS.<sup>2</sup> In a retrospective study of 41 patients with COVID-19, those with thyroid parameters compatible with ESS had more severe disease, higher concentrations of pro-inflammatory substances, and worse outcomes than those without ESS.<sup>55</sup> A Low concentration of FT3 is frequently associated with, or predictive of, intractable COVID-19,<sup>42</sup> and the total T3 concentration has been shown

to be inversely associated with the severity of COVID-19.<sup>24</sup> Surprisingly, however, these hormonal abnormalities disappear with recovery from COVID-19, without the necessity for thyroid replacement therapy.<sup>24</sup>

### **Relationships of COVID-19 with thyrotoxicosis and Graves' disease**

Graves' disease is an autoimmune thyroid disease caused by antibodies that bind to the TSH receptor. Graves' disease can be induced or a relapse experienced when there is an autoimmune response, such as during COVID-19.<sup>8</sup> There is currently no evidence that individuals who have radioactive iodine (RAI) therapy or thyroidectomy are more susceptible to viral infection, including with SARS-CoV-2.<sup>21</sup> However, severe SARS-CoV-2 infection may induce a thyrotoxic storm in older individuals with poorly managed Graves' disease, increasing COVID-19-related mortality.<sup>26</sup> It is worth mentioning that Muller and colleagues<sup>30</sup> found thyrotoxicosis in 15.3% of patients with COVID-19, compared with only 1.3% of controls in their study, and another retrospective study of 287 non-critical COVID-19 patients by Lania *et al.*<sup>32</sup> showed that 20.2% had thyrotoxicosis, and that thyroid function assessed during hospitalisation was associated with the concentrations of several inflammatory markers. Furthermore, high IL-6 concentrations were shown to be closely associated with thyrotoxicosis, suggesting that COVID-19 may be linked to a high risk of thyrotoxicosis, because of systemic activation of the immune system in response to SARS-CoV-2 infection.

In individuals with COVID-19, Khoo *et al.*<sup>56</sup> found a slight temporary reduction in the circulating TSH concentration, which might also be interpreted as



hyperthyroidism, but ESS is probably the most likely explanation. A recent prospective study that compared 125 patients with mild COVID-19 pneumonia to 125 with severe COVID-19 pneumonia revealed that 13% of those with severe pneumonia had hyperthyroidism (6.4% overt and 5.6% subclinical), whereas the mild pneumonia group had a lower prevalence (1.6% overt and 4.8% subclinical). According to Liu *et al.*,<sup>36</sup> 14 (7%) of 191 COVID-19 patients showed features of thyrotoxicosis, including low TSH and/or high FT4 concentrations. It is also worth noting that 32% and 16% of COVID-19 patients with overt thyrotoxicosis experience atrial fibrillation and thromboembolic events, respectively. Furthermore, COVID-19 patients with thyrotoxicosis have a higher in-hospital mortality rate and stay in hospital longer than patients with COVID-19 but normal thyroid function. Thus, thyrotoxicosis appears to be clinically relevant in COVID-19, and has deleterious effects.<sup>32</sup>

Patients with thyrotoxicosis may be at a higher risk of infection-related complications, such as thyroid storm.<sup>57</sup> To reduce this risk, it is highly recommended that thyrotoxicosis should be well controlled.<sup>58</sup> Interestingly, thyroid function improves in parallel with improvements in COVID-19-related symptoms, implying that the virus causes the thyroid dysfunction by increasing the production of pro-inflammatory cytokines. Güven *et al.* showed that thyrotoxicosis does not have a negative effect on COVID-19 outcomes,<sup>34</sup> but if it is left untreated, it can lead to left ventricular hypertrophy and congestive heart failure, which might worsen the outcomes of COVID-19.<sup>59</sup> In individuals with either overt or subclinical hyperthyroidism, the circulating concentrations of markers of endothelial dysfunction, such as IL-6, IL-12, IL-18, fibrinogen, plasminogen activator-inhibitor 1, von Willebrand factor, and vascular cell adhesion

molecule-1, were found to be very high,<sup>60</sup> which might induce the hypercoagulability that is characteristic of COVID-19<sup>61</sup> and increase the risk of cardiovascular complications. It is also worth noting that T4 has been shown to activate human platelets, which could also help provoke the pathological clotting that occurs during COVID-19 infection.<sup>2</sup>

The treatment of thyrotoxicosis using thionamide medications is usually safe, but should be undertaken with caution because the signs and symptoms of COVID-19 are similar to those of anti-thyroid drug-induced agranulocytosis.<sup>42</sup> Thus, it is recommended that patients taking anti-thyroid drugs who experience symptoms suggestive of neutropenia should discontinue the drug immediately and undergo a full blood count urgently to assess their neutrophils.<sup>58</sup> Furthermore, patients taking anti-thyroid medication who have mild-to-moderate neutropenia may have a poorer prognosis if they contract COVID-19 because their COVID-19 symptoms may be exacerbated by the immunological defect, through a worsening of the neutropenia and the induction of a cytokine storm.<sup>17</sup> Certain subgroups of patients are predisposed to severe coronavirus-related disease. Patients with Graves' ophthalmopathy are typically treated using glucocorticoids and immunosuppressive medication, and they are therefore considered to be at particular risk of SARS-CoV-2 infection and of experiencing an exacerbation of their condition.<sup>62,63</sup> Conjunctival abnormalities linked to SARS-CoV-2 infection can delay the diagnosis of Graves' ophthalmopathy and put patients at risk of their condition worsening, including through the development of eye infections and a loss of vision.<sup>26</sup> This also explains why quarantine restrictions for these patients should be closely adhered to.<sup>62,63</sup>

A review of the literature suggests that there are currently insufficient data regarding the effect of COVID-19 on Graves' ophthalmopathy. However, a recent case report described the activation of Graves' ophthalmopathy 3 days following a second dose of a COVID-19 vaccine in a 50-year-old woman. The timing of this relative to her vaccination is consistent with the induction of an autoimmune or inflammatory syndrome.<sup>64</sup> Therefore, clinicians should remind patients to be aware of the symptoms and signs of thyroid-related eye disease and to seek appropriate medical and ophthalmic advice if these develop following COVID-19 vaccination.

### **Relationship between COVID-19 and thyroid cancer**

Despite the current pandemic having a clear impact on the delivery of care for patients with thyroid disorders, and particularly thyroid cancer, little is known regarding the effect of COVID-19 on the development or progression of thyroid cancer, or the susceptibility of people with thyroid cancer to infection or COVID-19-related complications.<sup>3,17</sup> Because patients with cancer may be at higher risk of serious consequences of SARS-CoV-2 infection,<sup>17,65</sup> perhaps at least in part because they have undergone surgery or chemotherapy, it is advisable to carefully evaluate patients with thyroid cancer, and especially those who are undergoing tyrosine kinase inhibitor therapy or external beam radiotherapy, have lung metastases, who are older, or who have accompanying comorbidities, to assess the risk of severe complications of COVID-19. Advanced thyroid malignancies can be treated with targeted medication, such as kinase inhibitors. Sorafenib, sunitinib and vandetanib, among other kinase inhibitors, have been employed in the treatment of disease caused by various viruses, including

coronaviruses, and their effectiveness as therapies for COVID-19 is now being investigated. However, because of the potential for adverse effects that could promote the progression of COVID-19, the management of certain anti-cancer therapies may be difficult during the pandemic.<sup>1</sup> There have been no studies published regarding the safety and efficacy of kinase inhibitors for the treatment of advanced thyroid cancers during the COVID-19 pandemic. Therefore, the commencement, continuation and discontinuation of these medications should be carefully tailored to each patient, perhaps through discussion within a multidisciplinary team to better assess the risk/benefit ratio.<sup>1,63</sup> Falcone *et al.* investigated one major concern, the influence of the pandemic on the emotional well-being and quality of life of patients with thyroid cancer, and found that it is generating significant emotional discomfort in this group of patients, regardless of the severity of their condition or their present healthcare needs. Specifically, women and patients under the age of 65 are the most likely to show high levels of psychological distress.<sup>66</sup>

### **Relationships between COVID-19 treatment and the thyroid gland**

COVID-19 is now being treated with a variety of medications, and various drugs have been documented to have negative effects on the thyroid gland.<sup>3</sup> Low-molecular weight heparin, corticosteroids and hydroxychloroquine have been used as treatments for COVID-19 and might have effects on the thyroid gland, either directly or after their metabolism.

#### ***Low-molecular weight heparin***

The pathogenesis of the COVID-19 coagulopathy is still uncharacterised; however, it is thought to involve a combination of localised pulmonary platelet consumption,

low-grade intravascular coagulation, thrombotic microangiopathy, endothelial dysfunction, and systemic inflammation.<sup>67</sup> The coagulopathy has been shown to be caused by both systemic inflammation and a SARS-CoV-2-specific mechanism that includes ACE2 inhibition, endothelial damage and dysfunction, and the induction of autoimmunity.<sup>68</sup> Therefore, early anticoagulation using heparin may help prevent the coagulopathy, microthrombus development, and organ damage. The results of several retrospective studies<sup>84–86</sup> are consistent with a role for heparin in the management of COVID-19.<sup>69–71</sup> The principal effect of heparin on the thyroid gland is to interfere with the measurement of serum free thyroid hormone concentrations. It has been reported that intravenous heparin administration results in a rapid (within 2 to 15 minutes) increase (up to five-fold) in FT4 concentration.<sup>3</sup> In addition, heparin-induced endothelial lipoprotein lipase activation causes a considerable increase in serum non-esterified fatty acid concentrations, and when these concentrations exceed their usual serum binding capacity, they directly compete for T4 and T3 binding sites on thyroxine-binding globulin. Because of this, patients who are taking heparin should not have their FT4 and FT3 concentrations measured. Instead, total thyroid hormone concentrations, as well as those of TSH and thyroxine-binding globulin, can be used to verify euthyroid status when necessary.<sup>1,3</sup> In addition to its anticoagulant effects, low-molecular weight heparin can directly inhibit viral entry into host cells, by interacting with SARS-CoV-2 spike proteins; inhibit heparanase activity, thereby limiting vascular leakage; reduce the effects of cytokines; and interfere with leukocyte trafficking.<sup>1,72</sup>

### **Corticosteroids**

The effects of glucocorticoids on serum TSH concentration in humans are well

known. A physiological dose of hydrocortisone influences the diurnal variation in serum TSH concentration, causing lower concentrations in the morning and higher concentrations at night.<sup>3</sup> Several other studies have shown that there is an acute reduction in TSH secretion in humans and rats following pharmacological glucocorticoid administration and that this recovers after glucocorticoid withdrawal. Comparable findings have also been made in individuals with Cushing's syndrome.<sup>3,73</sup> The mechanism of the effects of glucocorticoids on TSH remain unknown, but one theory is that glucocorticoids can directly suppress the release of TSH-releasing factor (TRH) in the hypothalamus. Furthermore, high-dose glucocorticoids have been shown to reduce TRH mRNA expression in the human hypothalamic paraventricular nucleus.<sup>1,3,21</sup> Corticosteroids have been shown to be beneficial in patients with COVID-19 and dexamethasone reduces mortality in patients with severe COVID-19 who are undergoing either invasive mechanical ventilation or oxygen administration alone.<sup>74</sup> This may be because the glucocorticoids reduce the inflammation-mediated lung injury, thereby preventing the progression of the disease to respiratory failure and death.<sup>3</sup> Most patients with SAT are treated with corticosteroids and their clinical symptoms resolve within a few days. Furthermore, after 1 to 2 months, the abnormalities in the laboratory parameters associated with SAT return to normal, which implies a favourable prognosis. Although the effectiveness of glucocorticoids for the treatment of SAT has been debated, it is clear that they are effective at relieving symptoms and that they greatly reduce the incidence of recurrence.<sup>74</sup> Taken together, these findings suggest that a low dose of glucocorticoids may be an effective therapy for SARS-CoV-2-induced SAT.

## **Hydroxychloroquine**

Hydroxychloroquine has been offered as a treatment option for some patients with COVID-19, either alone or as part of a combination therapy.<sup>75</sup> Because it may affect thyroxine metabolism, TSH concentration must be monitored to ensure that euthyroidism is maintained during such therapy.<sup>26</sup>

## **Conclusion**

The substantial advances in understanding of the pathophysiology of the thyroid dysfunction caused by SARS-CoV-2 infection have further characterised the link between viral infection and thyroid diseases, and novel findings continue to be made. Thyroid function can be disturbed during both the acute phase of an infection and during convalescence following COVID-19. Although some evidence suggests that thyroid dysfunction is caused by direct infection of the thyroid or a “cytokine storm”-mediated autoimmune effect on the thyroid, more research is needed at the molecular and clinical levels to facilitate better understanding of the diagnosis and treatment of thyroid diseases in patients during both phases. The data collected to date suggest that although the majority of patients are euthyroid, subacute thyroiditis, which can present atypically, without neck pain or lymphocytosis, ESS, and other thyroid autoimmune diseases can be present. The clinical significance of assessing thyroid function may therefore be primarily related to its reflection of more severe disease and the poorer prognosis of newly-developed COVID-19.

There is no scientific evidence that patients with poorly controlled thyroid disorders are more likely to contract COVID-19. However, those with uncontrolled thyroid dysfunction, and particularly those with thyrotoxicosis, are likely

to be at higher risk of infection-related comorbidities, for example a cytokine storm. Thus, this group of patients should be paid additional attention, given that neutropenia that can develop following anti-thyroid drugs, which can hide the symptoms of COVID-19. Furthermore, independent of any other underlying causes, patients with hyperthyroidism are likely to be at risk for poor outcomes, such as long hospital stays and mortality, as well as higher risks of severe and fatal COVID-19 disease.

There is also the possibility that thyroid dysfunction may be diagnosed erroneously in patients who are taking low-molecular weight heparin, corticosteroids or hydroxychloroquine as part of their COVID-19 management, because these medications can cause abrupt changes in thyroid hormone secretion and alter assay results. There have been few large, long-term studies, but the current evidence suggests that with conservative care, thyroid function returns to normal. Given the prevalence of thyroid dysfunction, thyroid function testing would be useful in patients admitted to the emergency room or intensive care unit, as well as during follow-up, to detect the onset of hypothyroidism in the context of a pituitary disorder and to diagnose thyrotoxicosis linked to inflammatory or destructive thyroiditis. Prospective studies should be conducted in the future to enhance our epidemiological and clinical understanding and to optimise the management of thyroid diseases in patients with COVID-19. The relationships between the thyroid gland and the new variants of SARS-CoV-2, such as Delta and Omicron, and any differences from those of the original SARS-CoV-2 strain should also be evaluated.


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## ORCID iD

Rania Naguib  <https://orcid.org/0000-0003-2176-7182>

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