



The cytokine storm and thyroid hormone changes in COVID-19

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Abstract

Background COVID-19 is now a worldwide pandemic. Among the many extra-pulmonary manifestations of COVID-19, recent evidence suggested a possible occurrence of thyroid dysfunction.

Purpose The Aim of the present review is to summarize available studies regarding thyroid function alterations in patients with COVID-19 and to overview the possible physio-pathological explanations.

Conclusions The repercussions of the thyroid of COVID-19 seem to be related, in part, with the occurrence of a “cytokine storm” that would, in turn, induce a “non-thyroidal illness”. Some specific cytokines and chemokines appear to have a direct role on the hypothalamus–pituitary–thyroid axis. On the other hand, some authors have observed an increased incidence of a destructive thyroiditis, either subacute or painless, in patients with COVID-19. The hypothesis of a direct infection of the thyroid by SARS-Cov-2 stems from the observation that its receptor, ACE2, is strongly expressed in thyroid tissue. Lastly, it is highly probable that some pharmaceutical agents largely used for the treatment of COVID-19 can act as confounding factors in the laboratory evaluation of thyroid function parameters.

Keywords COVID-19 · Cytokine storm · Thyroid · ACE2 · Thyroiditis

Introduction

Ten months after the first report of pneumonias of unknown origin in Wuhan (China) [1], the Coronavirus Disease 2019 (COVID-19), caused by the respiratory syndrome coronavirus 2 (SARS-CoV-2), resulted in a world-spread pandemic. As of November 2020, the number of confirmed cases of COVID-19 has exceeded 35 million worldwide, with more than 1 million COVID-19-related fatalities. The epidemic has put public health systems under severe strain and lead to establishing various degrees of socio-economic lockdowns, both in the developing world and in western countries.

The clinical presentation of COVID-19 patients can vary remarkably, going from completely asymptomatic forms to extremely severe, multisystem clinical involvement. The most common presenting symptoms are due to lung and systemic involvement, and include fever, fatigue and dry cough that can rapidly evolve toward respiratory failure and acute respiratory distress syndrome (ARDS), requiring intensive care support. Less commonly, COVID-19 patients can present a variety of non-pulmonary manifestations, including neurological disorders (both central and peripheral), cardiac abnormalities (including heart failure and arrhythmias), renal failure, liver disease, rhabdomyolysis, coagulopathy and thrombosis [2]. Among the many extra-pulmonary manifestations, researchers have sought the possible occurrence of thyroid dysfunction. Up to now, very few studies have tackled this issue, and there is evidence of discrepancies among different clinical settings. Aim of the present review is to summarize available studies regarding thyroid function alterations in patients with COVID-19 and to overview the possible physio-pathological explanations.

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The cytokine storm induced by SARS-Cov-2 infection

The term “cytokine storm syndrome” describes a clinical syndrome that can occur in patients with severe COVID-19 disease, being characterized by a fulminant and often fatal hyper-cytokemia leading to multi-organ failure [3, 4]. The term was originally employed to describe the impressive activation of the immune system in the context of graft-versus-host disease [5]. Similar conditions were also described in other pathologic conditions, both infectious (i.e., avian H5N1 influenza virus infection [6] and SARS-Cov-1 infection) and non-infectious (i.e., leukemia patients receiving engineered T cell therapy). The widespread use of the term “cytokine storm” is probably due to its immediate meaning, which actually recalls the role of the immune system in producing an uncontrolled inflammatory response that is detrimental to host cells. Nevertheless, there is still no consensus regarding the exact definition of “cytokine storm”. In the case of COVID-19 disease, the cytokine storm could be the pathogenic process leading to ARDS, which characterizes the most severe cases [7, 8]. ARDS is a devastating event, with an estimated mortality of approximately 40%, defined as lung edema (not explained by cardiac failure or fluid overload) and acute onset of bilateral infiltrates, which result in severe hypoxemia [9, 10]. The exact physio-pathologic mechanisms underlying COVID-19 related cytokine storm are not fully understood; however, data from recent *in vitro* and *in vivo* studies and evidence coming from other coronaviruses (such as SARS and MERS) suggest an inflammatory vicious cycle that derives both from the direct cytotoxic effect of the virus on target cells and from the activation of immune cells. [11]. SARS-Cov-2, similarly to SARS-CoV and MERS-CoV viruses, uses the angiotensin-converting enzyme-related carboxypeptidase (ACE-2) receptor to infect target cells [12]. In addition to furin pre-cleavage, the cellular serine protease TMPRSS2 is also required to properly process the SARS- CoV-2 spike protein and facilitate host cell entry. When SARS-CoV-2 infects ACE-2-expressing cells, such as pneumocytes, the active replication and release of the virus can cause abrupt cell damage. This process is called pyroptosis, an abrupt inflammatory form of programmed cell death that leads to the subsequent release of intracellular molecules, including ATP, nucleic acids and damage-associated molecular patterns (PAMPs). These mediators are recognized by nearby endothelial and epithelial cells and alveolar macrophages, triggering the production of pro-inflammatory cytokines, in particular IL-1 β . Using a variety of pattern-recognition receptors (PRRs), alveolar epithelial cells and alveolar macrophages detect the released PAMPs,

such as viral RNA, and damage-associated molecular patterns (DAMPs), including ATP, DNA and protein oligomers. A wave of local inflammation ensues, involving increased secretion of the pro-inflammatory cytokines and chemokines (i.e., IL-6, IFN γ , MCP1 and CXCL-10) into the blood of affected patients. The secretion of such cytokines and chemokines attracts immune cells, notably monocytes and T lymphocytes, but not neutrophils, from the blood into the infected site. Pulmonary recruitment of immune cells from the blood and the infiltration of lymphocytes into the airways may explain the lymphopenia and increased neutrophil/lymphocyte ratio seen in around 80% of patients with SARS- CoV-2 infection. The ACE-2 is also present in many immune cells, such as macrophages, dendritic cells and monocytes [13, 14]. The direct SARS-Cov-2 infection of these cell subtypes results in their activation and secretion of inflammatory cytokines, such as interleukin-6 (IL-6) [15]. IL-6 is crucially involved in acute inflammation due to its role in regulating the acute phase response [16]. It is produced by almost all stromal cells and by B lymphocytes, T lymphocytes, macrophages, monocytes, dendritic cells, mast cells and other non-lymphocytic cells, such as fibroblasts, endothelial cells, keratinocytes, glomerular mesangial cells and tumor cells [17]. While in most cases, the infection is followed by an efficient defensive immunological response, in some patients the response is dysfunctional, causing a flood cytokines and chemokines in the serum and resulting in severe lung and even systemic damage. In this scenario, IL-6 exerts potent pro-inflammatory activities through binding to both its membrane receptor (mIL6-R) on immune cells and to a soluble receptor (sIL-6R). The activation of mIL6-R leads to pleiotropic effects on both the innate and acquired immune system. IL-6 binding to sIL-6R also forms a dimeric complex that can bind to the surface of any cell, including lung endothelial cells, resulting in the massive secretion of chemotactic molecules such as vascular endothelial growth (VEGF), monocyte chemoattractant protein-1 (MCP-1), CXCL8 and additional IL-6. This phenomenon attracts more immune cells in the infection site, causing an exponential escalation of the inflammatory process, commonly referred to as “cytokine storm”. Moreover, reduced E-cadherin expression and increased secretion of VEGF increase vascular permeability and leakage, which further contribute to the pathogenesis of ARDS [18]. In spite of the many cytokines, such as IL-1 β [19–23], IL-10 [7, 19–21, 24], TNF- α : [1, 19, 22, 23, 25–27] and IFN γ [19, 21, 26, 27], and chemokines, such as CXCL8: [7, 19, 21–23, 25, 28–31], CXCL9: [20, 22, 31, 32], CCL5 [24, 25, 30, 33, 34], CCL2 [1, 19, 22–25, 32, 35], CCL20: [24, 36], CCL3: [1, 19, 22–24, 35, 36] and CCL4 [19, 22, 35, 36] involved in the dysfunctional immunologic response in COVID-19 disease (which

Table 1 Summary of the cytokines and chemokines involved in COVID-19 pathogenesis

<i>Cytokines</i>	
IL-1 β	Increased in COVID-19 patients compared with controls [19]. Increased in patients with severe disease when compared with those with mild disease [20], increased in the acute phase of multisystem inflammatory syndrome in children (MIS-C) [21], increased release in bronchoalveolar lavage fluid [22], overexpressed mRNA by lung macrophages [22, 23]
IL-6	Increased in patients with severe disease when compared with those with mild disease [29, 37–39, 106]. Elevated in late stages of severe COVID-19 [33]. Correlated with disease severity [28, 41], predictor of mortality [42–44], higher in patients requiring ICU admission [41], correlated with RNAemia [101], increased release in bronchoalveolar lavage fluid [22], overexpressed mRNA by lung macrophages [22] and pneumocytes [27], increased in the acute phase of multisystem inflammatory syndrome in children (MIS-C) [21, 36]
IL-10	Increased in patients with severe disease when compared with those with mild disease [7, 20, 24], Increased in COVID-19 patients compared with controls [19], increased in the acute phase of multisystem inflammatory syndrome in children (MIS-C) [21]
TNF- α	Increased in COVID-19 patients compared with controls [19]. Increased in patients with severe disease when compared with those with mild disease [1, 25]. Up-regulation of the tumor necrosis factor-driven inflammatory response in PBMCs from COVID-19 patients [26], overexpressed mRNA by lung macrophages [22, 23] and pneumocytes [27]
IFN γ	Increased in COVID-19 patients compared with controls [19], Up-regulation of the IFN γ -driven inflammatory response in PBMCs from COVID-19 patients [26], increased in the acute phase of multisystem inflammatory syndrome in children (MIS-C) [21]. Lack of IFN response by lung macrophages [27]
<i>Chemokines</i>	
CXCL10 (IP10)	Increased in COVID-19 patients when compared with controls [32], Increased in patients with severe disease when compared with those with mild disease [1, 20, 24, 25, 46, 47], Correlated with disease severity [28], increased release in bronchoalveolar lavage fluid [35], overexpressed mRNA by lung macrophages [22, 23] and pneumocytes [27], predictor of mortality [24], overexpression in nasal swabs of COVID-19 patients [31]
CXCL8 (IL-8)	Correlated with disease severity [7, 25, 28, 29], Increased in COVID-19 patients compared with controls [19], increased release in bronchoalveolar lavage fluid [22], overexpressed mRNA by lung macrophages [23], increased in the acute phase of multisystem inflammatory syndrome in children (MIS-C) [21, 30], overexpression in nasal swabs of COVID-19 patients [31]
CXCL9 (MIG)	Increased in COVID-19 patients when compared with controls [32], Increased in patients with severe disease when compared with those with mild disease [20], overexpressed mRNA by lung macrophages [22], overexpression in nasal swabs of COVID-19 patients [31]
CCL5 (RANTES)	Increased in patients with severe disease when compared with those with mild disease [24, 25], predictor clinical outcome [33], increased in children with COVID-19 as compared with adults [30, 34]
CCL2 (MCP-1)	Increased in COVID-19 patients when compared with controls [32], increased in patients with severe disease when compared with those with mild disease [1, 24, 25], increased release in bronchoalveolar lavage fluid [35], increased in COVID-19 patients compared with controls [19], overexpressed mRNA by lung macrophages [22, 23]
CCL20 (MIP3 α)	Increased in patients with severe disease when compared with those with mild disease [24], increased in the acute phase of multisystem inflammatory syndrome in children (MIS-C) [36]
CCL3 (MIP1 α)	Increased in patients with severe disease when compared with those with mild disease [1, 24] increased release in bronchoalveolar lavage fluid [35], increased in COVID-19 patients compared with controls [19], overexpressed mRNA by lung macrophages [22, 23], increased in the acute phase of multisystem inflammatory syndrome in children (MIS-C) [36]
CCL4 (MIP1 β)	increased release in bronchoalveolar lavage fluid [35], Increased in COVID-19 patients compared with controls [19], overexpressed mRNA by lung macrophages [22], increased in the acute phase of multisystem inflammatory syndrome in children (MIS-C) [36]

are summarized in Table 1), the cytokine IL-6 [20–22, 27–29, 33, 36–45] and the chemokine CXCL10 [1, 20, 22–25, 27, 28, 31, 32, 35, 46, 47] have clearly emerged as recurrent markers of disease severity and poor outcome [38, 41, 42, 48].

Cytokines as the main mediators of the non-thyroidal illness (NTI) syndrome

Alterations in thyroid function parameters, which are

commonly referred to as “non thyroidal illness” (or sick euthyroid syndrome, or low T3 syndrome), can be detected in many severe clinical conditions, both acute (sepsis, trauma, acute myocardial infarction) and chronic (severe malnutrition, liver failure, end-stage renal disease requiring hemodialysis, cancer). The most typical alteration is a decrease in serum T3 level, that can be accompanied, or not, by a slight decrease in TSH level and, as the severity and length of the NTI syndrome increases, also in total T4 [49]. The magnitude of TSH and thyroid hormone changes is proportional to the severity of the underlying NTI and these alterations usually recede after the patient has recovered from the causative condition. The NTI syndrome appears to be an adaptive response to reduced tissue metabolism to preserve energy during systemic illnesses. In this scenario, deiodinases, a group of oxidoreductases that catalyze thyroid hormone activation and/or inactivation, creating a potent mechanism that tightly regulates plasma and intracellular levels of thyroid hormone, play a pivotal role in pathogenesis of the NTI syndrome. The activation of the pro- hormone T4 into the biologically active hormone T3 is catalyzed by type1 (D1) and type 2 (D2) deiodinases via outer-ring deiodination [50]. In contrast, type 3 deiodinase (D3) catalyzes the inactivation of both T4 and T3, by promoting the conversion of T4 to reverse T3 and the conversion of T3 to 3,3-T2, both biologically inactive. Thus, D3 contributes to thyroid hormone homeostasis protecting tissues from excess of thyroid hormones. D1 and D2 differ by their kinetic properties, substrate, specificity, and susceptibility to inhibitory drugs, as well as by their response to changes in the thyroid hormone status. While D2 is an exclusive outer-ring deiodinase, D1 promotes inner ring as well as outer-ring deiodination. The highest levels of D1 activity in humans are found in thyroid, liver, and kidney; while D2 is more widely expressed, being found in the pituitary, brain, thyroid, skin, skeletal, and heart muscles [51]. Reduced conversion of T4 to T3, and increased activity of D3 are typically observed in the NTI syndrome [52].

The NTI syndrome was consistently reported in patients admitted to intensive care units (ICU) [53, 54] and in patients with pneumonia [55]. Thus, it appears highly probable that patients experiencing severe COVID-19 disease requiring ICU admission could manifest this syndrome. Although the mechanisms underlying the NTI syndrome are multifactorial, circulating cytokines are considered as its main mediators, due to their multiple effects on the hypothalamic-pituitary thyroid axis, on circulating thyroid hormone binding proteins and on the peripheral metabolism of thyroid hormones [56]. In vitro and in vivo data demonstrating these effects are summarized in Table 2 for four main cytokines: IL-1 β [57–69], TNF- α [7, 57, 60, 70–77], IL-6 [74, 78–88] and IFN- γ [77, 89–99].

Although CXCL10 and other IFN-inducible chemokines have been thoroughly studied for their pivotal role in the pathogenesis and maintenance of autoimmune thyroid diseases [100], their role in thyroid function perturbation occurring in critically ill patients is probably negligible. As their name suggests, chemokines act as potent chemo-attractants towards cells that express their surface receptors, mainly belonging to the immune subset. For this reason, chemokines usually exert their action by attracting target cells via a chemical gradient into a specific site. This action is radically different from that of cytokines, which usually have pleiotropic and systemic effects on several cell types. Indeed, no in vitro study has ever highlighted alterations in thyroid hormone production or deiodinase activity after treatment with CXCL10.

Thyroid function alterations in patients with COVID-19 disease

Six main studies investigated thyroid function in hospitalized patients with Covid 19 disease. Several case reports were also published, mainly in outpatients suffering with subacute thyroiditis.

Chen et al. investigated thyroid function parameters in a group of 50 patients with unremarkable history of thyroid disease hospitalized for COVID-19 (15 mild, 23 severe and 12 critical cases). Two control groups were also investigated: 54 healthy subjects and 50 patients with non-COVID-19 pneumonia of similar severity. A low TSH was present in 56% of COVID-19 patients. COVID-19 patients were also found to have significantly lower serum TSH and total T3 levels as compared both with healthy subjects and with patients affected by non-COVID-19 pneumonia. Moreover, there was a significant association between a trend towards a reduction in serum TSH and total T3 levels and the disease severity. Serum total T4 levels were similar in the three groups. Although these findings were consistent with the development of an NTI syndrome in patients with severe COVID-19 disease, the fact that significant differences occurred between COVID-19 patients and patients with severe pneumonia suggested a specific role of SARS-Cov-2 infection in thyroid function alteration [101].

A completely different thyroid function picture was described by Lania et al. in Italy. These Authors investigated 287 consecutive COVID-19 patients (193 males and 183 females with a median age of 66 years) being hospitalized in a non-intensive care unit. No control group was enrolled. They found that 58 (20.2%) of these patients had serum TSH levels below the reference range, with 31 of them having laboratory evidence of overt thyrotoxicosis and 27 having normal serum FT3 and FT4 levels. Fifteen patients (5.2%) had laboratory data indicating hypothyroidism, which was

Table 2 Summary of the in vitro and in vivo effects of four main pro-inflammatory cytokines

	Evidence from in vitro data	Evidence from animal models	other interfering elements	Patients data
IL-1 beta	<p>↓ iodide uptake in FRTL-5 and in porcine thyroid cells [57–59]</p> <p>↓ T3 secretion in human thyrocytes [60], ↓ Tg mRNA expression in human thyrocytes [61, 97]</p> <p>↓ TPO mRNA in Graves' thyrocytes [63]</p> <p>↓ induction of DIO1 mRNA [64]</p> <p>↓ DIO1 activity in hepatocytes [65, 66]</p> <p>↓ TSH secretion in rat pituitary cells [69]</p>	<p>↓ TT4, TT3, TSH production in rats [67, 68]</p>		
TNF- α	<p>↓ iodide uptake in FRTL-5 and Thyroid cancer cells [Spizweg et al. 1999, 77], ↓ Tg synthesis in human thyrocytes [70]</p> <p>↓ T3 secretion in human thyrocytes [60], ↓ DIO1 activity [7, 71], ↓ basal and TSH-stimulated TPO and Tg gene expression in FRTL-5 cells and human normal thyroid cells [77]</p> <p>↓ TSH synthesis in rat pituitary cells [74]</p>	<p>↓ TSH, TT3, TT4</p> <p>↓ hypothalamic TRH synthesis, ↓ TSH glycosylation in mouse and rat models [57, 72]</p>	<p>↓ albumin production by rat hepatocytes(Perlmutter et al. 1986)</p>	<p>↓ serum T3 in cancer patients treated with recombinant human TNF-α (Feelders et al. 1999)</p>
IL-6	<p>↓ iodide uptake in FRTL-5 and thyroid cancer cells</p> <p>↓ Tg synthesis in human thyrocytes</p> <p>↓ T3 secretion in human thyrocytes [78, 79], ↑ proliferation in human thyrocytes, ↓ DIO1 mRNA [81]</p> <p>↓ DIO1 and DIO2 activity [81]</p> <p>↑ DIO3 activity [81]</p> <p>↓ basal and TSH-stimulated TPO and Tg gene expression in FRTL-5 cells and human normal thyroid cells [80]</p> <p>↑ expression of DIO2 in rat pituitary cells [74]</p>		<p>↓ hepatic synthesis of TBG, TTR, albumin [82, Ramadori et al. 1988)</p>	<p>Inverse correlation between IL-6 and FT3 levels [Bartalena et al. 1994] [Boelen et al. 1993, 1995; Davies et al. 1996; Friberg et al. 2002]</p> <p>Intravenous injection of IL-6 given to healthy humans causes a transient decrease in serum T3 and an increase in rT3 [88]</p>
IFN- γ	<p>↑ iodide uptake, ↓ thyroglobulin synthesis, ↓ basal and TSH-stimulated TPO and Tg gene expression in FRTL-5 cells and human normal thyroid cells ↓proliferation of human thyroid cells ↑ iodide uptake [89], ↓ Tg synthesis [90]</p> <p>↓ basal and TSH-stimulated TPO and Tg gene expression in FRTL-5 cells and human normal thyroid cells [90–94]</p> <p>↓ proliferation of human thyroid cells [95]</p> <p>↓ DIO-1 activity in FRTL-5 [77]</p>	<p>Severe hypothyroidism in transgenic mice expressing IFN-γ in thyroid cells due to down-regulation inhibition of the NIS gene [96]</p>		<p>No acute effect on circulating TSH, FT3, FT4 levels in critically ill patients after treatment with IFN-γ [98], higher risk of hypothyroidism in patients chronically treated [99]</p>

overt in 3 and subclinical in 13 of them. None of the patients complained of pain in the neck, while a new-onset atrial fibrillation was observed in 10 patients with overt thyrotoxicosis. Five thyrotoxic patients experienced a thromboembolic event (venous thromboembolism in 3 cases, ischemic stroke in 2 cases). No patient tested positive for thyroid autoantibodies. Eight thyrotoxic patients underwent thyroid ultrasound, showing signs of thyroid inflammation in 2 patients, small thyroid nodules in 3 patients and no significant alteration in the remaining 3 patients. In none of the them the classic ultrasound findings of subacute thyroiditis were described. In multivariate analysis, a significant inverse correlation between serum IL-6 and TSH levels was observed. In 7 thyrotoxic patients, thyroid function was longitudinally investigated for a short follow up (median 10 days). A progressive decrease in serum FT4 levels was detected, which was not influenced by methimazole treatment in 2 of them. Based on these findings the Authors hypothesized that their COVID-19 patients experienced a destructive, “silent” thyroiditis [102].

The hypothesis that the thyroid gland could be involved in COVID-19 disease stems from experiences in previous coronavirus pandemics (such as SARS and MERS) and from the potential susceptibility of thyroid cells to SARS-Cov-2 infection. Alterations of both thyroid function and structure were reported in patients affected by SARS-CoV-1. In autopsy specimens of 5 patients died of SARS, an extensive apoptotic process in follicular epithelium, causing exfoliation of epithelial cells into the follicle and alterations in follicular morphology were observed. No inflammatory infiltration was found in any specimen [103]. The same authors published a report regarding the immunohistochemical evaluation of pituitary histology on the same 5 patients, showing that the number and the staining intensity of TSH-expressing cells was remarkably reduced when compared with controls [104]. The anatomic location of the thyroid, which is contiguous to the upper airways, a main entrance site of corona viruses, further supports the hypothesis that the thyroid could be a direct target of SARS-CoV-2. As previously discussed, SARS-COV-2, similarly to the virus that caused SARS, uses the ACE-2 as its cellular entry receptor [105]. In this regard it is important to recall that a recent study demonstrated that ACE-2 is strongly expressed in follicular thyroid cells making them a potential target for SARS-COV-2 entry [106, 107]. In line with this *in vitro* data, several recent case reports described patients with SARS-Cov-2 infection being diagnosed with typical painful subacute thyroiditis [108–113]. It should be highlighted that these patients suffered with a mild (in 4 cases) or moderate (in 4 cases, requiring hospitalization) COVID-19 disease, but none of them experienced a cytokine storm or required ICU admission. Most of them were female patients (7 out

of 8) and their sign and symptoms of subacute thyroiditis occurred between 5 and 36 days (median 19) after the onset of COVID-19 disease. In all cases a TSH value below 0.1 $\mu\text{U/ml}$ at the onset of subacute thyroiditis was observed, while thyroid autoantibodies were undetectable in all cases.

A further study in hospitalized patients provides evidence for the occurrence of a destructive thyroiditis in patients with COVID-19. Muller et al. investigated thyroid function in 85 patients who were admitted to a high intensity care unit (HICU) in 2020 because of COVID-19. Non COVID-19 patients admitted to the same HICU in 2019 and COVID-19 patients admitted to a low-intensity care unit (LICU) in 2020 served as controls. They found that 13 (15%) of 85 patients admitted to the HICU for COVID-19 disease had thyrotoxicosis (defined as TSH < 0.28 mIU/L and/or FT4 > 21.9 pmol/L). As compared with this figure, one (1%) out of 78 non COVID-19 patients hospitalized in 2019 in the same HICU and one (2%) of 41 COVID-19 patients admitted to the LICU were thyrotoxic. Three patients (3.5%) in the COVID-19 group, as compared with 7 (9%) and 4 (9.8%) patients in the non-Covid HICU group and in the LICU group, respectively, were hypothyroid (defined as TSH > 4.30 mIU/L and/or FT4 < 10.3 pmol/L). COVID-19 patients hospitalized in the HICU had lower serum TSH and higher serum FT4 levels than patients in both control groups, while FT3 levels were similarly low in the three groups. In 8 thyrotoxic patients (1 patient with subclinical hypothyroidism, 1 patient with overt hypothyroidism, and 6 thyrotoxic patients) with COVID-19 disease a post-discharge follow-up was available: the 2 hypothyroid patients were still hypothyroid at the initial follow-up. One patient had positive AbTg and AbTPO, while the other had negative thyroid autoantibodies. Both patients had a marked diffuse hypoechoic pattern of the thyroid at ultrasound. The 6 patients with low or suppressed TSH concentrations or thyrotoxicosis at baseline had normal thyroid function and were negative for thyroid autoantibodies at follow-up; none reported neck pain ever. Thyroid ultrasound was performed in 5 of these patients: all of them had a diffuse mild hypoechoic pattern at thyroid ultrasound, while in 3 patients focal markedly hypoechoic areas, typical of subacute thyroiditis, were observed. Such areas corresponded to focal reduced Technetium-99 m uptake at single-photon emission Computed Tomography imaging, and the thyroid gland showed a general low to normal or reduced Technetium-99 m uptake. The authors described their finding as a combination of thyrotoxicosis (possibly due to a subacute thyroiditis) and NTI syndrome [113]. From a clinical point of view, the fact that some of the classic symptoms of subacute thyroiditis (such as asthenia, fever and neck pain) are shared by COVID-19 patients could suggest that, unless specifically searched for, the thyroid disease might be overlooked. Moreover, the frequent use of

corticosteroids such, as dexamethasone, in the therapy of patients with severe COVID-19 could abolish neck pain in those with concomitant subacute thyroiditis.

Compared with the previous studies of Lania et al. [102] and Muller et al. [113], Khoo et al. [114] recently reported different results. The authors described a cohort of 456 hospitalized patients from 3 hospitals in London with a clinical suspicion of COVID-19 in which both TSH and FT4 levels were routinely evaluated. In particular, the authors compared thyroid function parameters between the 334 patients with a confirmed diagnosis of COVID-19 and 122 patients without a COVID-19 diagnosis. Results showed that the vast majority (86.5%) of patients with COVID-19 were euthyroid, while only a minority were subclinical hypothyroid (5.1%) or overt hypothyroid (0.6%). Eight patients had a suspect of secondary hypothyroidism (2.4%). No patient received a diagnosis of neither subclinical nor overt thyrotoxicosis. The distribution of thyroid function alterations was similar between COVID-19 and non-COVID-19 patients. The authors observed slightly lower TSH and FT4 levels among COVID-19 patients when compared with the non-COVID-19 ones, even within the normal range. Moreover, lower TSH and FT4 levels were observed in patients with a fatal disease and in those admitted to ICU. A significant inverse relationship between C-reactive protein and cortisol levels and TSH levels was observed in COVID-19 patients. In a subset of patients where previous evaluations of TSH and FT4 levels were available, a slight reduction in both TSH and FT4 levels was observed in COVID-19 patients, but not in the non-COVID-19 ones. Lastly, among 55 patients in which an evaluation of thyroid function parameters before admission, at the moment of admission and after a median follow-up time of 79 days, was performed, results showed that thyroid function parameters returned to baseline levels after recovery of COVID-19. The authors concluded that in their cohort there was no suggestion of a COVID-19-related thyroiditis/thyrotoxicosis, but that their findings are more indicative of a NTI syndrome. Most importantly, all patients taking corticosteroids either at baseline or during COVID-19 were excluded from this study. One of the limitations of this study is the lack of measurements of thyroid autoantibodies and of FT3 or rT3. On the other hand, the study has the advantage of including patients in whom both TSH and FT4, irrespectively of TSH levels, were evaluated.

In another recent study from Hong Kong, Lui et al. [115] evaluated 191 COVID-19 patients admitted to a non-intensive care unit. Among enrolled patients, 11 cases showed reduced serum TSH levels with normal fT4 and fT3, but in none of them overt thyrotoxicosis was found. Three of these patients also had detectable levels of TSH receptor antibodies (TRAb), suggesting a diagnosis of Graves' disease. The authors highlighted that a higher SARS-CoV-2 load characterized patients with a reduced TSH. Moreover, an isolated

low serum fT3 level was detected in 12 other patients, who had higher acute-phase indexes (C-reactive protein levels, erythrocyte sedimentation rate and LDH) levels as compared with the rest of the cohort. Patients with low serum FT3 levels had a higher chance of clinical deterioration during the follow-up. The authors concluded that in their cohort two distinct groups of patients with COVID-19 related thyroid dysfunction could be identified: one characterized by subclinical thyrotoxicosis (mostly related with a thyroiditis process) and one characterized by a low T3 levels (probably due to a NTI syndrome).

In further study by Gao et al. [116], thyroid function parameters were evaluated in a cohort of 100 COVID-19 patients from Wuhan, and findings were compared between critical and non-critical patients. Results showed that TSH and FT3 levels, but not FT4 levels, were significantly lower in critically ill patients when compared with the non-critically ill ones. Moreover, FT3 levels at baseline, but not TSH or FT4, were independent predictors of mortality in this cohort of patients. An inverse correlation between C-reactive protein, TNF-alfa and IL-6 levels and TSH and FT3 levels was observed, while no correlation with FT4 was found. These data strongly suggest the occurrence of a NTI syndrome in this cohort of patients.

Lastly, some anecdotal case report described cases of severe hypothyroidism or Graves' thyrotoxicosis onset after COVID-19 [117, 118], but no systematic study has evaluated this issue so far.

Confounding factors: COVID-19 therapies

Among the increasing number of drugs that are or have been recommended for the treatment of COVID-19 patients, some do interfere with the hypothalamic-pituitary thyroid axis or with laboratory tests for the measurement of free thyroid hormones.

Glucocorticoids

The use of glucocorticoids in COVID-19 patients has been widely debated [119, 120]. In the early phases of the pandemic, many national guidelines either contraindicated or did not recommend glucocorticoid treatment [121]. However, in the clinical practice, almost 50% of COVID-19 patients have been treated with some form of glucocorticoid [122, 123]. Afterwards, a randomized clinical trial provided evidence that treatment with dexamethasone could reduce the 28-day mortality in COVID-19 patients receiving respiratory support, with no benefit (and possible harm) in those who do not require oxygen [124].

Glucocorticoids have long been known to affect serum TSH levels in humans [125, 126]. Even low doses of

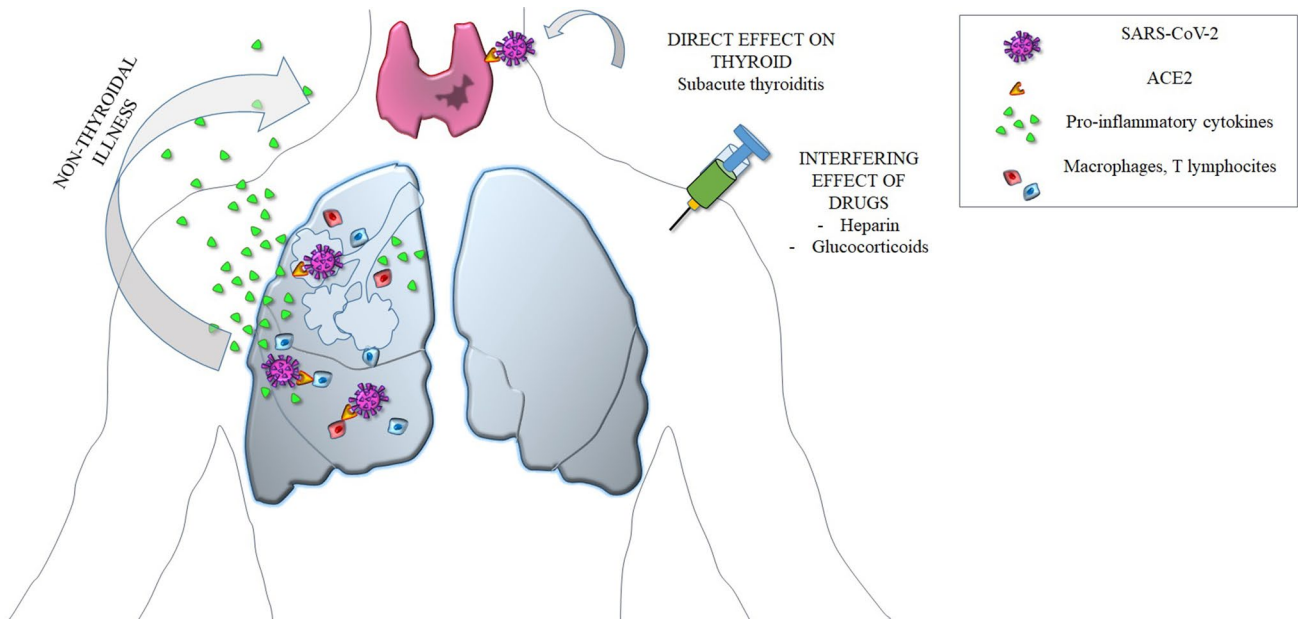


Fig. 1 Schematic representation of the possible mechanisms causing alterations in thyroid function parameters in patients with COVID-19

dexamethasone can lower serum TSH levels, while higher doses of prednisone are required to reach the same effect [126]. Glucocorticoids appear to suppress release of TSH through a direct inhibitory effect on pituitary thyrotrope cells [127] and an inhibition of TRH release in the hypothalamus [128, 129]. Moreover, glucocorticoids can interfere

with the production of active T3, through a direct induction of type 3 deiodinase and an increased conversion of T3 to reverse T3 [130]. Acute administration of glucocorticoids to humans or rats decreases the ratio of circulating T3 to T4, implying that these agents block T4 to T3 conversion. Recent studies in humans indicate that D3 activity is induced

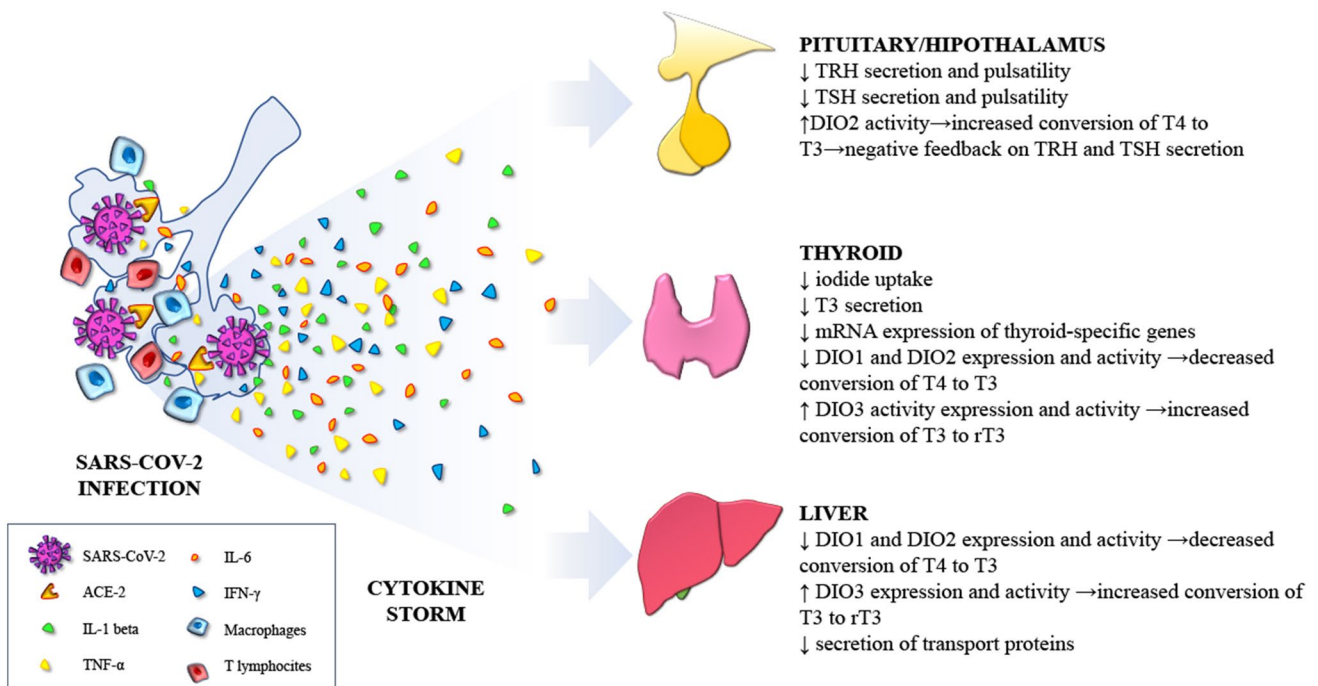


Fig. 2 Schematic representation of the mechanisms through which SARS-Cov-2 related cytokine storm can cause a Non-Thyroidal-Illness syndrome in COVID-19 patients

by dexamethasone, and the acute decrease in serum T₃ that follows a high dose of glucocorticoids may be due to an increase in D3-mediated T₃ clearance via 5 deiodination [131]. The resulting reduction in T₃ levels can mimic a NTI syndrome [132, 133] (Fig. 1).

Heparin

Heparin or low molecular weight heparin (LMWH) is increasingly prescribed in COVID-19 patients. An anti-thrombotic prophylaxis is mandatory in hospitalized and bedridden patients, who are also exposed to an increased pro-thrombotic risk directly related to COVID-19 disease. Moreover, heparin has potential beneficial non-anticoagulant effects, including reduction of endothelial leakage, neutralization of cytokines and chemokines, interference with leukocyte trafficking and with viral cellular entry [134] (Fig. 2).

Unfortunately, heparin is known to interfere in free thyroid hormone assays. Heparin liberates lipoprotein lipase from the vascular endothelium. As consequence, blood samples from heparin-treated patients have increased lipoprotein lipase activity, which persists *in vitro* and generates non-esterified fatty acids (NEFA) during sample storage or incubation. Free thyroid hormone assays, especially those with prolonged incubation periods, such as measurement by means of equilibrium dialysis, are most affected, since NEFA displace T₄ and T₃ from binding proteins, causing spuriously high values [135]. The effect is greater if samples are stored for a long time before the assay. Similar effects are seen with LMWH preparations [136]. Standard competitive free hormone assays are generally less affected by this phenomenon, since the incubation period is shorter and occurs at a temperature lower than 37 °C, but the interference cannot be completely excluded neither in this case. If the sample is stored for a long time the amount of NEFA in the samples constitutes an insuperable pre-clinical problem, that can be overcome only adding a non-toxic additive that can block the heparin-induced lipase at the moment of sample collection. If these laboratory alterations are suspected, the assay should be repeated at least 10 h after heparin withdrawal [136]. Moreover, total T₄ and total T₃ are likely to be more informative in this context [137].

Combined confounding factors

A study by Sapin et al. demonstrated how multiple inaccuracies of the hormonal thyroid profile can occur in critically ill patients submitted to multiple therapies. These authors evaluated serum FT₄ results obtained with 6 different commercial kits in 20 patients who had undergone bone marrow transplantations and who were previously euthyroid. Patients were treated with heparin and glucocorticoids, similarly to what happens in COVID-19 patients. Assay methods that

involved sample incubation at 37 °C (such as equilibrium dialysis) gave falsely high FT₄ values in 20–40% of patients, while analogue tracer methods, influenced by tracer binding to albumin, gave subnormal estimates of FT₄ in 20–30% of them, even if the values were closer to the reference range. By contrast, total T₄ was normal in the majority of these presumably euthyroid subjects. Interestingly, marked alterations in serum TSH were found, since half of the subjects had a suppressed serum TSH value. This change was probably attributable to glucocorticoid treatment. It is evident that in this context dosing artefacts in TSH and FT₄ could be falsely interpreted as a case of thyrotoxicosis [138].

Conclusions

Patients with severe COVID-19 disease may undergo the so-called cytokine storm. *In vitro* studies, experiments in animal models, and evidence in humans indicate that cytokines play an important role in the development of the NTI syndrome observed in critically ill patients. Several studies in hospitalized patients with COVID-19 disease indicate that the NTI syndrome is the most consistently observed alteration of thyroid function parameters. SARS-CoV-2 may also infect the thyroid producing a typical (painful) or, possibly, an atypical (painless) subacute thyroiditis. At present there is no evidence for a direct thyroid cytotoxic effect of cytokines on thyroid cells, at least in humans. Glucocorticoids and heparin, frequently administered to COVID-19 patients, may act as confounding factors due to their effect on the HPT axis (glucocorticoids) and to their interference (heparin) in the assays for free thyroid hormones.

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Compliance with ethical standards

Conflict of interest The authors have nothing to disclose.

Ethical Approval This study does not contain any study with human participants performed by any of the authors.

Informed consent For this type of study, consent is not required.

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