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Evaluation of Thyroid Status in Hospitalized Patients with COVID-19

Nasser Mikhail MD*, Soma Wali MD

Endocrinology Division, Department of Medicine, Olive-View UCLA Hospital, David-Geffen-UCLA Medical School, CA, USA.

1. Abstract

Background: Preliminary data suggest that thyroid dysfunction may commonly occur in association with coronavirus disease-2019 (COVID-19).

Objective: To clarify the significance of abnormal thyroid tests in patients with COVID-19 admitted to the hospital.

Methods: PUBMED search of English literature until September 22, 2020. Since there is lack of randomized trials, case reports, retrospective studies, and National guidelines are reviewed.

Results: Retrospective studies suggest that 7%-60% of patients with COVID-19 admitted to the hospital display thyroid hormone alterations typical of non-thyroidal illness (NTI). The extent of thyroid hormone changes correlates with severity of COVID-19. In NTI, thyroid hormones normalize with recovery of COVID-19 without specific treatment. Measurement of thyroid hormones in admitted COVID-19 patients without symptoms or signs suggestive of abnormal thyroid function may lead to unnecessary further investigations and increase cost. In addition, routine measurement of thyroid hormones can create confusion in interpretation of results. Other new onset thyroid diseases are rarely reported in admitted COVID-19 patients. Only 4 well-documented cases of subacute thyroiditis were reported in association with infection with COVID-19.

Conclusions: Alterations of thyroid hormones due to NTI are common in hospitalized patients with COVID-19 and return to normal spontaneously with recovery without thyroid-directed therapy. Routine measurement of thyroid hormones is not indicated in patients who do not have pertinent thyroid symptoms or signs.

2. Keywords: Thyroid; COVID-19; Non-thyroidal illness; Thyroiditis; Measurement; Treatment.

3. Running Title: Thyroid in COVID-19

4. Introduction

In critically patients, irrespective of the underlying cause of illness, there are characteristic thyroid hormone changes that generally correlate with the underlying disease severity [1,2].

These thyroid hormone alterations are collectively known as NTI or euthyroid sickness [1,2].

The commonest and earliest thyroid hormone change in NTI is the drop of levels of triiodothyronine (T3), hence non-thyroidal illness is also called the low T3 syndrome [1,4].

The reason of low T3 is the inhibition of conversion of thyroxine (T4) to the more active T3 by the enzyme type 1 deiodinase [1,2].

***Corresponding author:** Nasser Mikhail MD, Endocrinology Division, Department of Medicine, Olive-View UCLA Hospital, David-Geffen-UCLA Medical School, CA, USA, E-mail: nmikhail@dhs.lacounty.gov

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There is also mild suppression of thyrotropin or thyroid stimulating hormone (TSH) in the beginning of illness, and typically TSH rises and even becomes slightly elevated during recovery. In NTI, plasma levels of T4 are either low-normal or frankly low [1,2]. It has been shown that reduction in circulating levels of T3 and T4 correlate inversely with mortality i.e, the lower the levels of thyroid hormones, the higher the mortality [1,2]. The mechanisms of NTI are not fully understood. There is still debate whether NTI represents an adaptive or mal-adaptive response to severe systemic illness [1,2]. Indeed, the few randomized trials of thyroid hormone treatment to patients with NTI did not generally show any significant clinical benefit [2]. Furthermore, normalization of thyroid hormones occurs spontaneously after resolution of critical illness. Therefore, most experts do not recommend thyroid hormone therapy in NTI.

4.1. Non-thyroidal illness in patients with COVID-19

The few available retrospective studies suggest that admitted patients with COVID-19 exhibit thyroid hormone changes similar to those observed in NTI [3-6].

Overview and main findings of these studies are summarized in Table 1.

Table 1: Retrospective studies of admitted patients with COVID-19 with thyroid abnormalities consistent with non-thyroidal illness.

Study	**Chen et al [5]**	**Wang et al [6]**	**Li et al [3]**	**Sun et al [4]**
Study groups	COVID-19 (n=50), non-COVID-19 pneumonia (n=50), healthy controls (n=54)	COVID-19 (n=84), non-COVID pneumonia (n=91), healthy controls (n=807)	COVID-19 (n=40), healthy controls (n=57)	COVID-19 (n=336)
Patients' characteristics	Moderate COVID-19 n= 15, severe n=23, critical n=12	Mean age of COVID-19 patients was 57 years, 63% men. Severe COVID-19 n= 63	All patients had non-severe COVID-19	Severe/critical cases n=26
Thyroid hormone results	1. 56% of COVID-19 patients had subnormal TSH 2.TSH and TT3 were significantly lower in COVID-19 patients vs the 2 other 2 groups 3. Similar TT4 in the 3 groups.	1. 60% of COVID-19 patients had subnormal TSH, or TT3, or TT4 2. TSH lower in COVID-19 vs the 2 other groups	1. TSH and free T3 were lower in COVID-19 patients vs controls, but remained within normal range.	Severe/critical cases have significantly lower TT3, free T3, free T4 compared with non-severe cases.
Correlation of thyroid hormones with COVID-19 severity	The degree of decreases in TSH and TT3 positively correlated with severity of COVID-19.	Abnormal TSH and TT3 more common in severe COVID-19 vs mild/moderate COVID-19 (74% vs 24%, respectively, P <0.001)	Not reported	Lower TT3, free T3, and free T4 in severe cases
Correlation of thyroid hormone results with cytokines and inflammatory markers	Not reported	Cytokine levels are similar to healthy controls. C-reactive protein significantly higher in COVID-19 patients vs controls.	Not reported	Not reported
Follow-up of thyroid hormones	Returned to normal after recovery	Returned to normal after recovery 30-day post admission	Not reported	Not reported

		(follow-up in 7 patients).		
Any thyroid specific therapy	None	None	None	None
Comment	62% of patients received methylprednisolone that may lower TSH	No difference in thyroid antibodies between groups.	-	-

TSH; thyroid stimulating hormone

TT3; total tri-iodothyronine

TT4; total thyroxine

In 40 patients admitted with non-severe COVID-19, Li et al [3] compared several laboratory results with age-and sex-matched 57 healthy control subjects. They found that (mean ± SD) circulating levels of free T3 were significantly lower than control subjects, 4.57 pmol/L ± 0.8 pmol/L and 5.29 pmol/L ± 0.9 pmol/L, respectively; P<0.0001 [3]. Likewise, corresponding plasma levels of TSH were slightly but significantly lower in patients with COVID-19 than in control individuals, 2.13 µIU/ml ± 0.9 µIU/ml and 2.75 µIU/ml ± 1.3 µIU/ml, respectively; P<0.017 [3]. However, free T3 and TSH values remained within the normal range in COVID-19 patients likely reflecting their non-severe COVID-19 [3]. Unfortunately, T4 levels were not measured in this study [3]. In another retrospective study from China, Sun et al [4] described a series of 336 patients with COVID-19 admitted to the hospital, of whom 26 patients (7.7%) had severe/critical COVID-19 (definition was not provided). These workers found that plasma levels of total T3, free T3 and free T4 were significantly lower in patients with severe/critical disease compared with subjects with non-severe disease (actual levels of hormones were not provided) [4]. In a third retrospective Chinese study, Chen et al [5] found that 56% (28 of 50) of patients with COVID-19 admitted to the hospital had subnormal TSH levels. In addition, they found that levels of TSH and total T3 were significantly lower than a control group of healthy subjects and another control group of non-COVID-19 pneumonia [5]. Moreover, the degree of decreases of TSH and total T3 correlated positively with severity of COVID-19 [5]. Similar findings were reported by Wang et al [6]. Importantly, the latter 2 studies demonstrated that thyroid hormone abnormalities normalized after recovery from COVID-19 without any thyroid-directed therapy, as expected in NTI [5,6]. In addition to its retrospective design, one limitation of the study of Chen et al [5] was the fact that 62% (31 of 50) of their patients received methylprednisolone 57.3 mg/d (equivalent to approximately 60 mg prednisone/d). This relatively high dose of glucocorticoids is known to suppress TSH secretion from the pituitary [7]. This may explain, at least in part, why Chen et al [5] observed that TSH levels in patients with COVID-19 were significantly lower than patients with non-COVID-19 pneumonia despite comparable disease severity. Nevertheless, a direct inhibitory effect of COVID-19 on TSH secretion by pituitary gland could not be excluded. Indeed, Wei et al [8] demonstrated damage of TSH-secreting cells in autopsies of patients dying from severe acute respiratory syndrome (SARS) caused by another coronavirus closely related to the virus causing COVID-19.

Taken together, available studies suggest that patients with COVID-19 admitted to the hospital exhibit thyroid hormone changes that closely mimic those occurring in NTI.

4.2. Subacute thyroiditis in admitted patients with COVID-19

Subacute thyroiditis (also called de Quervain thyroiditis) is a painful form of thyroiditis associated with low-grade fever, sore throat and fatigue [9]. Classically, it has 3 stages: initial thyrotoxic stage of 3-6 weeks due to destructive thyroiditis, followed by

mild hypothyroidism lasting up to 6 months, then most patients return to euthyroidism within 12 months [9]. Approximately 5%-15% develop permanent hypothyroidism [9]. Etiology of subacute thyroiditis is likely viral and unlikely autoimmune since only 25% of patients have antithyroid antibodies in low titers [9]. Only 4 well-documented cases of subacute thyroiditis were reported in relation to COVID-19 [10-13] (table 2).

Table 2: Reported cases of subacute thyroiditis in admitted COVID-19 patients.

Study	Ippolito et al [10]	Asfuroglu and Ates [11]	Brancatella et al [12]	Ruggeri et al [13]
Patient's characteristics	69 year-old woman	41 year-old Caucasian woman	18 year-old woman	43 year-old woman
Clinical presentation	Palpitations, insomnia, agitation (no neck pain)	Neck pain and tenderness on exam, normal sized-thyroid, fever 38.5 C	Neck pain radiating to the jaw, fever 37.5 C , palpitations	Fever 37.5 C, neck pain, tremors, palpitations
Timing of thyroiditis in relation to COVID-19	Day 5 after hospitalization for COVID-19	COVID-19 diagnosed same time of thyroiditis	15 days after diagnosis of COVID-19	Approximately 6 weeks after diagnosis of COVID-19
Thyroid antibodies	Anti-TPO, anti-TSH-R, and anti-Tg antibodies were undetectable	Not reported	Anti-TPO, anti-TSH-R were undetectable, but anti-Tg antibodies were 120.2 IU/ml (N <30)	Anti-TPO, anti-TSH-R, and anti-Tg were undetectable
Treatment	Methylprednisolone 40 mg IV for 3 days, then 25 mg prednisone/d orally then gradual tapering over 4 weeks	Prednisolone 16 mg/d then tapering over 4 weeks	Prednisone 25 mg/d then tapering. Symptoms resolved within 1 week.	Prednisone 25 mg/d followed by tapering
Outcome	Recovery after 10 days of treatment	Marked improvement on prednisolone and hospital discharge	Spontaneous recovery after 4 days	Recovery after 4 weeks
Other tests	Increase Tg 187 ug/L (N=3.5-77).	Increased ESR134 mm/h, C-reactive protein 101 mg/dl	Tg 5.6 ug/L (normal range not reported)	Tg 188 pg/ml (N 0-40)
Thyroid nuclear scan	No thyroid uptake in Tc 99-scan	Not reported	Not reported	Markedly reduced uptake in Tc 99-scan
Thyroid ultrasound	Enlarged hypoechoic thyroid, mg/L (N < 1 decreased vascularity and 3 cm thyroid nodule (known from before)	Decrease vascularity, heterogeneous parenchyma	Multiple hypoechoic areas	Diffusely enlarged and hypoechogenic thyroid

All cases had suppressed TSH and elevated T4 and/or T3 levels

Anti-TPO; anti-thyroid peroxidase antibodies

Anti-TSH-R; anti-TSH receptor antibodies

Anti-Tg; anti-thyroglobulin antibodies

Tg; thyroglobulin

ESR; erythrocyte sedimentation rate

All patients were successfully treated with glucocorticoids Although the mechanisms of thyroiditis associated with COVID-19 are not fully understood, it is known that subacute thyroiditis can occur in conjunction or more frequently few weeks after viral infection [14]. Thus, there are 2 potential mechanisms whereby thyroiditis occurs in COVID-19. The first mechanism may be related to the activation of immune system and inflammatory markers during the course of COVID-19. Such

activation may trigger thyroiditis by yet unknown mechanism. In the meantime, the virus causing COVID-19, the severe acute respiratory syndrome coronavirus-2 (SARS-Cov-2), uses angiotensin-converting enzyme 2 (ACE2) as receptor to enter host cells [15]. These receptors have widespread distribution in the human body [16]. In fact, Li et al [16] have demonstrated that ACE2 expression levels were highly present in the human thyroid tissue. Thus, a second mechanism of COVID-19 associated thyroiditis may be direct invasion of thyroid tissue by SARS-Cov-2 causing destructive thyroiditis. Indeed, in severe acute respiratory syndrome (SARS) caused a related coronavirus (SARS-Cov-1), thyroid gland was affected by extensive injury of follicular and parafollicular cells [17].

4.3. Autoimmune hypothyroidism in COVID-19

To the best of the author's knowledge, only one well-documented case of autoimmune (Hashimoto's) hypothyroidism was reported in a patient with COVID-19. Thus, Tee et al [18] described a Chinese 45-year-old Chinese man who was diagnosed with primary hypothyroidism 7 days after the onset of mild COVID-19. Thyroid peroxidase antibodies were elevated consistent with autoimmune etiology of primary hypothyroidism [18].

4.4. Clinical implications of thyroid abnormalities in patients hospitalized with COVID-19

Based on the available data, the authors recommend against routine screening of thyroid function in hospitalized patients with COVID-19 due to the following reasons.

First, the common prevalence of NTI, a condition that resolve spontaneously after recovery and for which no treatment has shown significant clinical benefit.

Second, interpretation of thyroid function in NTI may be sometimes challenging.

Table 3 displays different laboratory and clinical features that help distinguish between NTI and other thyroid diseases.

Table 3: Hormonal and features of different types of thyroid diseases.

	Non-thyroidal illness	**Subclinical thyroid disease**	**Central (secondary) hypothyroidism**	**Subacute thyroiditis**	**Hyperthyroidim**	**Primary hypothyroidism**
Setting	Criticallly ill patients	Relatively healthy outpatients	History of pituitary tumor or hypophysectomy in some patients	May uncommonly complicate COVID-19	Outpatient or in patient	Outpatient or in patient
Thyroid hormone pattern	Very low T3, TSH: low, but detectable. T4: Low-normal or low.	Subclinical hypothyroidism: low-normal T4, elevated TSH. Subclinical hyperthyroidism: subnormal or undetectable TSH, normal T3 and T4	Low T4, and subnormal or inappropriately normal TSH	Elevated T3 or/and T4, and undetectable TSH	Elevated T3 or/and T4, and undetectable TSH	Subnormal T4 and elevated TSH
Other tests	Negative thyroid antibodies	Anti-TPO and anti-Tg antibodies commonly elevated in subclinical hypothyroidism	Negative thyroid antibodies. Commonly associated with central adrenal insufficiency	Markedly elevated Tg, ESR, C-reactive protein	Elevated TSH-receptor antibodies in Graves' disease	Anti-TPO and anti-Tg antibodies commonly elevated
Physical exam	Physical signs are inconsistent	Normal in vast majority of cases.	No specific signs	Neck pain, tender	Painless goiter, possible thyroid bruit,	Painless goiter may be

	with thyroid dysfunction e.g. tachycardia in presence of subnormal T3 and T4.			goiter, low-grade fever, tachycardia.	tachycardia, tremors, proptosis	present, bradycardia
Imaging studies	Not useful	Thyroid scan in subclinical hyperthyroidism	MRI of sella turcica	Decreased or no uptake of radio-iodine or Tc-99 in thyroid scan	Increase uptake of radio-iodine or Tc-99 in thyroid scan	Thyroid ultrasound if there is goiter

TSH; Thyroid stimulating horome
T4; thyroxine
T3; Tri-iododothyronine
TG; Thyroglobulin
Anti-TPO; anti-peroxidase antibodies
ESR; erythocyte sedimendation rate

In the author's experience, thyroid hormones in NTI change every day or every other day in parallel to the gravity of underlying illness. Thus, repeat thyroid hormone testing may help clarify the diagnosis. Third, a recent retrospective study in non-COVID-19 patients found that there was low yield in testing inpatients for thyroid disorders. In addition, such strategy caused significant expense to the health care system [19]. Fourth, our recommendation is in agreement with guidelines of American Thyroid Association and American Association of Clinical Endocrinologists. These guidelines emphasized that TSH measurement should be done only if there is an index of suspicion for thyroid dysfunction [20]. On the other hand, thyroid hormones should be assessed in hospitalized patients with COVID-19 having any symptoms or signs that might be suggestive of thyroid dysfunction (e.g. unexplained tachycardia or bradycardia, any kind of arrhythmia, heart failure), or clinical picture suggestive of thyroiditis (e.g neck pain, unexplained fever). It should be emphasized that NTI may occur on top of other thyroid diseases. In these cases, endocrinology consultation may be necessary for proper diagnosis and management.

5. Conclusions and Current Directions

Preliminary data suggest that prevalence of NTI in hospitalized patients with COVID-19 ranges from 7% to 60%, depending on definition of thyroid hormone abnormalities, and the underlying severity of COVID-19. Smaller number of patients with COVID-19 develop subacute thyroiditis likely triggered by the causative virus of COVID-19, SARS-Cov-2. Evaluation of thyroid function in hospitalized patients with COVID-19 is indicated in case of presence of any pertinent symptoms or signs. Otherwise, universal measurements of thyroid hormones in hospitalized patients with COVID-19 may sometimes lead to unnecessary investigations or treatment. Clearly, this recommendation may change if there is convincing evidence showing that thyroid hormone treatment in NTI will be associated with clinical benefit. Indeed, studies are underway to evaluate the efficacy and safety of T3 therapy in critically ill patients with COVID-19 [21].

6. References

1. Van den Berghe G. Non-thyroidal illness in the ICU: a syndrome with different faces. Thyroid. 2014; 24: 1456-1465.
2. Fliers E, Bianco AC, Langouche L, Boelen A. Thyroid function in critically ill patients. Lancet Diabetes Endocrinol. 2015; 3: 816-825.
3. Li T, Wang L, Wang H, et al. Characteristics of laboratory indexes in COVID-19 patients with non-severe symptoms in Hefei City, China: diagnostic

value in organ injuries. Eur J Clin Microbiol Infect Dis. 2020; 1-9.

4. Sun L, Song F, Shi N, et al. Combination of four clinical indicators predicts the severe/critical symptom of patients infected COVID-19. J Clin Virol. 2020; 128: 104431.

5. Chen M, Zhou W, Xu W. Thyroid Function Analysis in 50 Patients with COVID-19: A Retrospective Study. Thyroid. 2020; 10.

6. Wang W, Su X, Ding Y, et al. Thyroid function abnormalities in COVID-19 patients. MedRxiv. 2020.

7. Haugen BR. Drugs that suppress TSH or cause central hypothyroidism. Best Pract Res Clin Endocrinol Metab. 2009; 23: 793-800.

8. Wei L, Sun S, Zhang J, et al. Endocrine cells of the adenohypophysis in severe acute respiratory syndrome (SARS). Biochem Cell Biol. 2010; 88: 723-730.

9. Samuels MH. Subacute, silent, and postpartum thyroiditis. Med Clin North Am 2012; 96 (2): 223-233.

10. Ippolito S, Dentali F, Tanda ML. SARS-CoV-2: a potential trigger for subacute thyroiditis? Insights from a case report. J Endocrinol Invest. 2020; 43: 1171-1172.

11. Asfuroglu Kalkan E, Ates I. A case of subacute thyroiditis associated with Covid-19infection. J Endocrinol Invest. 2020; 43: 1173-1174.

12. Brancatella A, Ricci D, Viola N, Sgrò D, Santini F, Latrofa F. Subacute Thyroiditis After Sars-COV-2 Infection. J Clin Endocrinol Metab. 2020; 105: 2367-2370.

13. Ruggeri RM, Campennì A, Siracusa M, Frazzetto G, Gullo D. Subacute thyroiditis in a patient infected with SARS-COV-2: an endocrine complication linked to the COVID-19 pandemic. Hormones (Athens). 2020; 1-3.

14. Desailloud R, Hober D. Viruses and thyroiditis: an update. Virol J 2009; 6: 1-14.

15. Vaduganathan M, Vardeny O, Michel T, et al. Renin-Angiotensin-Aldosterone system inhibitors in patients with Covid-19. N Engl J Med. 2020; 382: 1653-1659.

16. Li M, Li L, Zhang Y, Wang X. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. Inf Dis Poverty. 2020; 9: 45.

17. Wei L, Sun S, Xu CH, et al. Pathology of the thyroid in severe acute respiratory syndrome. Human Pathol. 2007; 38: 95-102.

18. Tee LY, Hajanto S, Rosario BH. COVID-19 complicated by Hashimoto's thyroiditis. Singapore Med J. 2020; 10.

19. Dogra P, Paudel R, Panthi S, et al. Low yield of thyroid-function tests in adult hospitalized patients-A retrospective analysis. Internation J Gen Med. 2020; 13: 343-349.

20. Gharib H, Guttler RB, Tourtelot JB, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. Endocr Pract. 2002; 8: 457-469.

21. Pantos C, Tseti I, Mourouzis I. Use of triiodothyronine to treat critically COVID-19 patients: a new clinical trial. Crit Care. 2020; 24: 209.

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