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COVID-19 infection and thyroid function

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ARTICLE INFO

Keywords:

COVID-19
Thyroid dysfunction
Thyroid function tests

ABSTRACT

Context: COVID-19 is a new viral infection affecting mainly the respiratory system with involvement of many other organs. Thyroid dysfunction has been described in COVID-19 but data are still unclear and conflicting on its frequency, severity and relationship with the outcome.

Patients and methods: We assessed thyroid function tests (TFT) in 50 patients admitted to our institution with confirmed COVID-19 infection. We excluded patients known to have thyroid diseases or taking drugs that may affect thyroid function. Serum free thyroxine (FT4), thyrotropin (TSH) and triiodothyronine (T3) were measured once or more during the first 10 days after admission. In about 50 % of the cases, a follow up TFT was obtained during the first year after discharge (at a median follow up of 6 months).

Results: We included 50 patients, 29 males (58 %) and 21 females (42 %). The median age was 47 years (range 25–89). Overall, TFTs were completely normal in all patients except for minor transient abnormalities in 5 patients (10 %) as follows: three patients had a mild transient elevated TSH, one had a mild transient suppressed TSH and one patient had a mildly low FT4 with normal TSH. There were no differences between the follow up TFTs obtained after discharge and TFTs obtained during admission in the acute phase.

Conclusion: In this study, thyroid dysfunction during acute COVID-19 infection was rare, mild and transient. However, the study might not be powered enough to detect an association between thyroid dysfunction and the severity of illness and further studies are needed to assess this issue. Late-onset thyroid dysfunction does not seem to occur in COVID-19 infection during the next year after discharge.

1. Introduction

SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), named also as COVID-19 is a new coronavirus infection with many gaps in our knowledge about its pathogenesis and clinical spectrum. This new pandemic started in the late 2019 in Wuhan, China and spread across the globe causing COVID-19 infection in >534 million of people and >6.3 million deaths (<https://www.worldometers.info/coronavirus/>, accessed on 03 June 2022). While the respiratory system reveals the major manifestations of COVID-19 infection, it has become clear over the last 2.5 years that COVID-19 is a systemic infection that involves many body organs. The thyroid gland is rich in angiotensin converting enzyme ACE2 receptor, the main route of entry of the virus to the cells. Various types of involvement of the thyroid gland in COVID-19 have been reported in a number of recent studies (Gorini et al., 2020; Brancatella et al., 2020a; Wang et al., 2020; Campi et al., 2021; Khatri et al., 2021; Laurino et al., 2021). However, in a recent large study which prospectively screened 334 COVID-19 patients

for thyroid function test abnormalities, the majority (86.6 %) were euthyroid (Khoo et al., 2021). In those with previous TFT in the year before admission, TSH and FT4 were found to be significantly lower during COVID-19 admission but in those patients who had follow up TFTs (55 patients), TSH and FT4 recovered to baseline levels (Khoo et al., 2021).

To assess the impact of COVID-19 infection on thyroid function in our patients, we performed thyroid function tests (TFT) during the acute phase of COVID-19 infection in 50 patients admitted to King Faisal Specialist Hospital & Research Centre (KFSHRC), Riyadh, Saudi Arabia during May 2020. In this report, we present our findings and briefly review the literature on COVID-19 and thyroid dysfunction.

2. Patients and methods

We included 50 consecutive adult patients (≥ 18 years of age) admitted for confirmed acute COVID-19 infection during 1–20 May 2020 (Fig. 1). All patients tested positive for COVID-19. We excluded patients who were known to have thyroid dysfunction or were on thyroid hormones, antithyroid drugs or drugs that may affect thyroid function such as glucocorticoids, amiodarone, anticonvulsants or biotin. The study was approved by the

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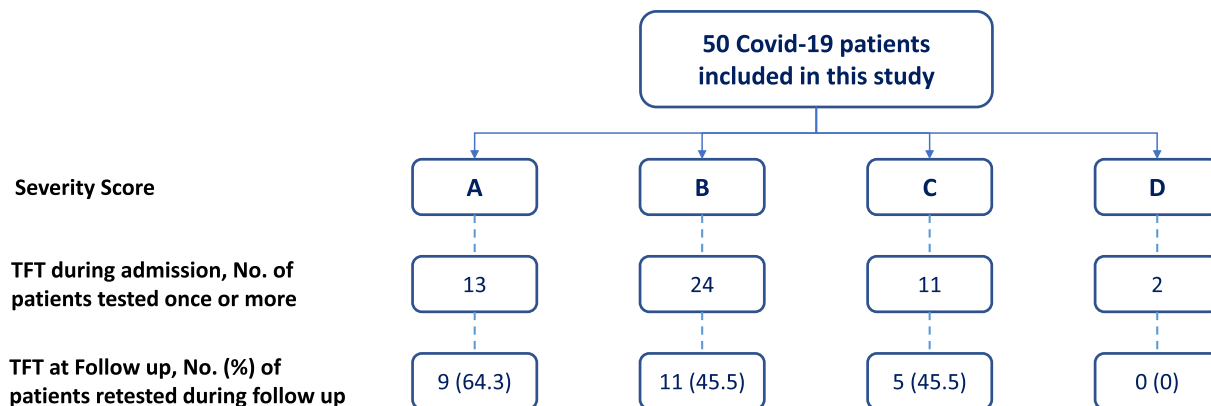


Fig. 1. A flow chart showing the total number of patients included and their distribution based on COVID-19 severity score and the number of those who had thyroid function testing during admission and those during the follow up.

Office of Research Affairs and the Institutional Review Board of the KFSHRC (RAC # 2201062). After obtaining an informed consent, we measured TFT including free T4 (FT4), total T3 (T3) and thyrotropin (TSH) on one or more days during admission (days 1, 2, 3, 4, 8 and/or 10). We used the KFSHRC COVID-19 scoring system to assess the illness severity. This severity score was based on guidelines from the WHO (WHO, n.d.) and Centers for Disease Control of North America (CDC) (Prevention CfDCCa, n.d.) as follows:

1. Asymptomatic (Stage A): Patients with positive COVID-19 test but no signs or symptoms of infection.
2. Mild Infection (Stage B): Patients with upper respiratory tract infection symptoms and other mild symptoms (including fever and gastrointestinal symptoms) without evidence of pneumonia.
3. Moderate Infection (Stage C): Patients with hypoxia with oxygen saturation <93 % at rest or presence of pneumonia on chest X-rays not requiring ICU admission.
4. Severe Infection (Stage D): Patients with pneumonia requiring ICU admission or any of the following:
 - a) Respiratory rate of >30 breaths/min
 - b) Arterial oxygen partial pressure to fractional inspiratory oxygen ratio (PaO₂/FiO₂) <300
 - c) More than 50 % lung involvement on imaging within 24–48 h
 - d) Critical respiratory failure requiring mechanical ventilation, septic shock or multiorgan dysfunction.

2.1. Laboratory testing

COVID-19 testing: For RNA extraction, we used Qiagen EZ1 Virus mini kit extraction (Qiagen, Hilden, Germany). For real-time polymerase chain reaction (RT PCR) amplification, we used Roche cobas® SARS-CoV-2 Qualitative assay on 6800 System (Roche Diagnostics Nederland B.V., Netherland). Serum TSH, FT4, and T3 were all measured by electrochemiluminescence assays on Cobas e 801 immunoassay analyzer (Roche Diagnostics GmbH, Mannheim, Germany).

2.2. Statistical analysis

Numerical values are expressed in median and range or interquartile range or mean ± SD and categorical values in rates and percentages. One-way analysis of variance (ANOVA) was used to compare hormonal levels between different COVID-19 severity of illness groups. Paired t-test was used to compare TFTs during admission with follow up TFTs after discharge. The Statistical Package for the Social Sciences (SPSS) version 21 (IBM, Chicago) was used for the analysis. A two-tailed P value < 0.05 was considered significant.

3. Results

3.1. Patients

The initial characteristics, TFTs and outcome for the whole group and by severity score are summarized in Table 1. We included 50 patients, 29 males (58 %) and 21 females (42 %). The median age was 47 years (range 25–89). The severity of illness was as follows: 13 (26 %) were in grade A, 24 (48 %) in grade B, 11 (22 %) in grade C and 2 (4 %) in grade D (Table 1). Thirty-seven patients (74 %) received Azithromycin and 31 (62 %) received Hydroxylchloroquine, 7 (14 %) received Tocilizumab and 2 (4 %) were in the WHO Solidarity trial. Six patients (12 %) needed ICU admission.

3.2. Thyroid function assessment

TFTs were done 78 times in these 50 patients during their hospital stay. The mean TSH was 2.29 mU/l (IQ range 1.1–3.1) (normal range 0.4–4.2 mU/l), median FT4 14.6 pmol/l (IQ range 11.6–16.1) (normal range 12–22) and the median T3 1.5 nmol/l (IQ range 1.2–1.8) (normal range 1.3–3.1 nmol/l) (Table 1). Overall, TFTs were completely normal in all patients except for minor transient abnormalities in 5 patients (10 %) summarized in Table 2. These include three patients who had mild transient elevated TSH, one had mild transient suppressed TSH and one patient had a mildly low FT4 with normal TSH (Table 2).

3.3. Thyroid function tests and the severity of illness

Using ANOVA, there were no significant differences in the TSH (F 1.15, P 0.34), FT4 (F 1.72, P 0.18) or T3 (F 1.93, P 0.14) levels among patients with different severity of illnesses using the above mentioned severity score (A, B, C, D) (Table 1). There were also no differences in TSH (F 1.2, P 0.27), FT4 (F 2.04, P 0.13), and T3 (F 2.87, P 0.099) between those patients that were treated in the general ward and those who needed ICU admission.

3.4. Outcome and follow up thyroid function tests after discharge

Of the 50 patients included in this study, 44 patients (88 %) were treated in the general ward and did not need ICU admission. They all recovered and were discharged home. Six patients (12 %) needed ICU admission; 4 (8 %) recovered and were finally discharged home while 2 (4 %) died due to acute respiratory distress syndrome (ARDS) and multiorgan failure.

Of the initial 50 patients, 25 (50 %) had follow up TFTs at a mean duration of 6.0 ± 2.6 months after discharge (Fig. 1). There were no significant differences between admission and the follow up levels of TSH (2.5 ± 1.8 mU/l vs. 3.3 ± 4.3 mU/l, P 0.48), FT4 (14.8 ± 2.2 mU/l

Table 1
Demographic, thyroid function tests and outcome of 50 COVID-19 patients with variable severity of illness.

Characteristic	Covid-19 severity score				
	All patients	A	B	C	D
Median age (range) years	47 (25–89)	45 (26–67)	49 (25–88)	49 (25–89)	57
Sex (M:F)	29:21	8:5	13:11	7:4	1:1
Severity, no. (%)	50 (100)	13 (26)	24 (48)	11 (22)	2 (4)
TFT at admission*					
TSH, median (range) mU/l	2.29 (1.1–3.1)	2.65 (1.17–5.0)	2.66 (0.0–7.36)	1.32 (0.45–3.5)	1.5 (0.35–2.69)
FT4, median (range) pmol/l	14.6 (11.9–16.1)	14.4 (10–18)	14.3 (10.9–17.70)	12.9 (12.3–16.0)	17.25 (15–19.5)
T3, median (range) nmol/l	1.5 (1.2–1.8)	1.65 (1.4–2.4)	1.7 (1.0–2.6)	1.5 (1.10–1.80)	1.35 (1.0–1.70)
Outcome, no (%)					
Discharged home, No ICU admission	44 (88)	13 (100)	23 (95.8)	7 (63.6)	1 (50)
Discharged home, ICU admission	4 (8)	0	1 (4.2)	3 (27.3)	0
Died	2 (4)	0	0	1 (9.1)	1 (50)
Total	50 (100)	13 (100)	24 (100)	11 (100)	2 (100)

* Normal ranges: TSH (0.4–4.2 Mu/l), FT4 (12–22 pmol/l), T3 (1.3–3.1 nmol/l).

vs. $14.13 \pm 14.13 \pm 4.3$ mU/l, $P 0.71$) and T3 (1.85 ± 0.13 nmol/l vs. 1.80 ± 1.02 nmol/l, $P 0.92$).

4. Discussion

There are many reports of thyroid dysfunction in patients with acute COVID-19 infection. Our study showed rare and mild changes in TFT. Only 10 % of cases had some minor abnormalities which frequently returned to normal over the next few days during admission. Our findings might be related to the selection of patients without known thyroid dysfunction prior to COVID-19 infection or might be due to the relatively small sample size. More likely is that thyroid dysfunction in COVID-19 is not common and frequently mild as this study and others (Khoo et al., 2021) have shown. One additional possibility is that thyroid dysfunction occurs later in the course of COVID-19 infection and evaluation for thyroid dysfunction was carried out early in this study. However, in our patients, follow up TFT in 50 % of patients were obtained at a median duration of 6 ± 2.6 months after discharge and were normal in all of them. Finally, the majority of our patients had mild to moderate severity COVID-19 infection and that may have been less likely associated with thyroid involvement.

Similar to our study, a study from China in which screening of 191 COVID-19 patients for abnormalities in thyroid function and thyroid autoimmunity at admission showed 13.1 % of them having mild abnormalities (Lui et al., 2020). In that study, lower TSH and free T3 were associated with more severe disease and low free T3 was associated with worse prognosis (Lui et al., 2020). In another study in which thyroid function abnormalities

Table 2
Demographic, clinical and laboratory data of five COVID-19 patients with abnormal thyroid function tests.

Patient	1	2	3	4	5
Age in years/sex	37/F	48/M	27/M	58/M	43/M
Severity score	A	A	B	B	C
WBC ($\times 10^3$ /cc)	6.93	4.13	7.50	4.9	4.68
Neutrophils (%)	65	56.7	58.6	62.3	41.3
Lymphocytes (%)	21.6	23.5	31.6	24.5	35.7
CRP mg/l (<1)	3.1	4.9	9.3	3.8	>300
Ferritin μ g/l (13–150)	32.5	330	106	124	277
D-dimer μ g/ml (0–50)	0.87	0.29	0.59	0.27	1.91
Baseline TFT					
Day of admission	1	1	1	1	2
TSH (0.4–4.2 mU/l)	4.67	3.36	7.36	6.98	0.041
FT4 (12–22 pmol/l)	15.1	10.5	14.6	13.0	23.1
T3 (1.3–3.1 nmol/l)	1.8	1.5	2.1	2.9	1.2
Follow up TFT					
Day of admission	5		2	2	
TSH (2)	3.84		4.65	5.5	
FT4 (2)	16.7		14.7	13	
T3 (2)	1.7		2.2	2.4	
Outcome	Recovery	Recovery	Recovery	Recovery	Recovery
Length of stay (days)	13	8	8	7	28

of 50 patients with recent COVID-19 infection were retrospectively reviewed and compared with normal control and patients with non-COVID19 pneumonia, 28 (56 %) of them had low TSH (Thyroid, 2021). TSH and total T3 were significantly lower in patients with COVID-19 infection than in control and patients with non-COVID-19 pneumonia. Low TSH and low total T3 correlated with the severity of the COVID-19 illness (Thyroid, 2021). In a study from England, all COVID-19 patients admitted to the hospital during a 6-week period were screened for thyroid function and compared with those admitted due to reasons other than COVID-19 (Khoo et al., 2021). They also compared thyroid function tests with previous results when available and with TFTs after recovery. The majority (86.6 %) of patients were euthyroid but TSH and FT4 were significantly lower in patients with COVID-19 than in non-COVID-19 patients and were also significantly lower than baseline levels (Khoo et al., 2021). At follow up, TSH returned to its baseline values. These changes are most likely due to non-thyroid sick syndrome (Khoo et al., 2021).

The pathophysiological mechanisms by which COVID-19 may affect thyroid gland (reviewed in Croce et al., 2021) include humoral effects related to the cytokine storm syndrome that leads to several effects on the hypothalamic pituitary thyroid axis, the thyroid hormone binding and the deiodinase function culminating in the well described non-thyroidal illness syndrome (Croce et al., 2021). However, there is no evidence of direct cytotoxic effect of cytokines on thyroid cells. On the other hand, COVID-19 may directly infect the thyroid and cause painful or painless thyroiditis. Finally, patients with COVID-19 infection frequently receive drugs that may alter TFT and confound their interpretation (Croce et al., 2021).

The main mechanism of entry of COVID-19 virus into cells is the attachment to the ACE2 and the transmembrane serine 2 (TMPRSS2) (Lam et al., 2020). These molecules are widely expressed in different tissues (Han et al., 2020; Lazartigues et al., 2020). Thyroid cells are rich in ACE2 (Rotondi et al., 2021) and this facilitates the entry of the virus into these cells with consequent direct injury or viral-induced immune-mediated injury (Gorini et al., 2020). The immune-mediated injury is triggered by several cells and cytokines including CD4+ and CD8+ T cells. T-helper 17 cells increase and T-regulatory 17:T-helper 17 ratio decrease. Several cytokines are increased including IL-6, IL2, IL-8, IL-17, IL-22, tumor necrosis factor, Interferon Gamma and alpha and colony stimulating factor. These cellular and humoral responses contribute to the severe inflammatory response called “cytokine storm” that is frequently associated with severe disease and acute respiratory distress syndrome (Swadling and Maini, 2020; Muyayalo et al., 2020; Moore and June, 2020; Zhang et al., 2020).

COVID-19 infection has been associated with different forms of thyroid dysfunction. Several case reports of subacute thyroiditis have been reported, occurring usually 2–7 weeks after the onset of COVID-19 infection and showing an excellent response to glucocorticoid therapy (Brancatella et al., 2020b; Campos-Barrera et al., 2020; Mattar et al., 2020; Asfuroglu Kalkan and Ates, 2020; Brancatella et al., 2020c; Chakraborty et al., 2020; Ippolito et al., 2020; Ruggeri et al., 2021). We have not seen any case of subacute thyroiditis in this study but that might be related to the

early presentation of those patients after the onset of symptoms. We have follow up data beyond the duration of admission in 50 % of patients and we did not see evidence of thyroiditis in any of them. However, we cannot exclude this possibility between the time of discharge and time of obtaining follow up TFTs with complete recovery of overt or silent thyroiditis. However, this possibility seems unlikely given the normal TFTs in all patients tested during follow up.

In addition to subacute thyroiditis, which is likely due to direct viral damage of the thyroid cells, chronic autoimmune (Hashimoto's type) thyroiditis with hypothyroidism has been described in patients infected recently with COVID-19 (Lui et al., 2020; Tee et al., 2021; Caron, 2020). Most of these cases had pre existing autoimmune markers and it is thought that COVID-19 triggered or reactivated autoimmune responses leading to further autoimmune-mediated damage and clinically overt hypothyroidism.

The euthyroid sick syndrome is not specific for COVID-19 infection but has been frequently reported in patients with this infection (Somasundaram et al., 2020; Henry et al., 2020). Patients with COVID-19 have high IL-6 levels (Henry et al., 2020) and this is implicated in the pathogenesis of euthyroid sick syndrome, also called, low T3 syndrome and nonthyroidal illness syndrome (Davies et al., 1996; Yamazaki et al., 1996).

Thyrotoxicosis was also reported to be common in COVID-19 infection. In a retrospective study of 287 patients admitted at a single center in Italy, 58 patients (20.2 %) had thyrotoxicosis, 15 patients (5.2 %) had hypothyroidism and 214 patients (74.6 %) had normal thyroid function tests. Thyrotoxicosis was associated with elevated levels of IL-6 (Lania et al., 2020).

All of these studies indicate inconsistent data and widely variable rates of thyroid dysfunction indicating the need for further studies to define the rates, type and course and outcome of thyroid dysfunction in COVID-19 infection and its impact the disease.

Although this study adds to the evolving knowledge of thyroid function in COVID-19, it has several pitfalls including the small sample size, heterogeneity in frequency and timing of TFT measurements, the small number of patients with severe disease, lack of data on ultrasound, thyroid scans, thyroid autoantibodies and lack of disease severity markers in the majority of patients. Although this was a prospective study with a specific protocol, it was undertaken at the early time of the COVID-19 pandemic (May 2020) and the study protocol could not be applied fully due to some logistic issues related to the anxiety and concern about safety of the staff and refusal of some patients of repeated testing. The majority of patients in this study had mild to moderate illness (disease severity score A and B) and only about a quarter of this cohort had severe disease. Therefore, it is not surprising that TFT abnormalities were rare. However, in general, the vast majority of patients with COVID-19 infection have relatively mild to moderate illness and the spectrum of patients included in our cohort is probably representative of the usual spectrum of COVID-19 infection in general. Considering all of these shortcomings, this study may not be adequately powered to detect an association between severity of COVID-19 and thyroid dysfunction and further studies are needed to assess this issue.

In summary, in this study TFTs were only rarely, transiently and mildly abnormal in COVID-19 infection. Whether these mild abnormalities are direct consequences of COVID-19 itself, manifestations of sick euthyroid syndrome or unrelated to the illness is unclear. There is no suggestion of correlation between the severity of the illness or outcome and thyroid function. There is also no suggestion of late-onset sequel of COVID-19 on thyroid function.

CRedit authorship contribution statement

Noha Mukhtar: Obtained consent, enrolled patients, obtained blood tests, collected data and supervised the study undertaking

Abdulmohsin Bakhsh: Obtained consent, enrolled patients, obtained blood tests, collected data

Nahlah Alreshidi: Obtained consent, enrolled patients, obtained blood tests and collected data

Abeer Aljomaiah: Obtained consent, enrolled patients, obtained blood tests and collected data

Hadeel Aljamei: Obtained consent, enrolled patients, obtained blood tests and collected data

Nada Alsudani: Obtained consent, enrolled patients, obtained blood tests and collected data

Tarek Elsayed: Obtained consent, enrolled patients, obtained blood tests and collected data

Roqayh Fadel: Obtained consent, enrolled patients, obtained blood tests and collected data

Eman Alqahtani: Obtained consent, enrolled patients, obtained blood tests and collected data

Ali S. Alzahrani: Conceived the research idea, designed the study, supervised the study conduct, analyzed the data and wrote the manuscript.

Data availability

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

We would like to thank the patients and their relatives for agreeing to enrol in this study and our colleagues who looked after these patients during their admission and helped us obtain consents and blood testing.

Funding

No specific funding was allocated for this study.

Peer Review Summary

Peer Review Summary and Supplementary data associated with this article can be found in the online version, at <https://doi.org/10.1016/j.endmts.2022.100122>.

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