



ORIGINAL: Assessment of Thyroid Function in COVID-19 Patients

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ABSTRACT

Introduction: Since the egression of the coronavirus 2019 (COVID-19) disease, more than 200 countries and areas around the world were affected. To the present, it is not clear whether COVID-19 has effects on thyroid function or not. The aim of the current study was to assess thyroid function in COVID-19 patients with history of thyroid disease and those without such a history and to find out the thyroid disturbance in both groups.

Material and Methods: The present study involved 86 COVID-19 affected patients admitted BioLab and the Balsam Hospital, Erbil/ Iraq between January and April 2021. Confirmation of COVID-19 infection all patients by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) of nasopharyngeal swabs. Thyroid hormones, and thyrotropin (TSH) level was analyzed and assessed.

Results: Most of the participants (88.4%) had normal T3 level, and there was no significant difference ($p = 0.069$) between those with normal T3, TPO and with no history of thyroid disease and those with such a history and/or high TPO. T4 levels of the participants with no history of thyroid disease and normal TPO did not differ significantly ($p = 0.725$) from those with a history of thyroid disease and/or high TPO. Regarding the level of TSH, there was significant difference ($p < 0.001$) between the two fore mentioned groups.

Conclusion: There is high prevalence of subclinical hypothyroidism in the COVID-19 patients with family history of thyroid disease and high TPO antibody level.

Introduction

The causative agent of coronavirus disease 2019 (COVID-19) is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). From December 2019, it has continued to spread worldwide. In patients with elevated risk factors and other comorbidities such as old age, male gender, chronic hypertension, and diabetes, COVID-19 infection induces both pulmonary and systemic infection, as well as multi-organ dysfunction (1, 2). The thyroid gland is one of

the endocrine glands which supposed to be mainly affected by coronaviruses due to high expression of the angiotensin-converting enzyme 2 (ACE2) receptor (3).

Clinical hypothyroidism (CH) is defined as a condition in which free T4 levels are below normal and TSH levels are above 10 mIU/L (4). Elevated TSH with normal free T4 levels is referred to as subclinical hypothyroidism (SCH) (5). In this case, an increase in anti-peroxidase (anti-TPO) coincides with an

increase in TSH (4, 6). Iodine insufficiency, thyroid destruction, and hypothalamic-pituitary diseases are among the other causes (7).

Several recent studies have identified the beginning of thyroid dysfunction in previously thyroid-healthy COVID-19 patients, as well as the possible negative effects of COVID-19 on patients with previously diagnosed thyroid diseases (8). A recent retrospective study included 50 COVID-19 patients in China found a noticeable decrease in TSH, and tri-iodothyronine (T3) of COVID-19 patients compared to non-COVID-19 group. The degree of decrease in TSH and T3 positively related with the severity of COVID-19. There was not any significant difference in the level of total thyroxine (TT4) of COVID-19 and non-COVID-19 patients (9).

Another study in Italy compared COVID-19 patients entered the intensive care units in 2020 with non-COVID-19 patients at the same unit in 2019. The subjects of the COVID-19 group had significantly lower TSH levels than that of the other group. Moreover, there is no significant difference in the levels of free T3. Thus, assessment of thyroid function is important in patients with COVID-19 as they may frequently experience thyrotoxicosis caused by a COVID-19 (10).

Lania et al. (2020) reported 5.2% of the patients in their study developed COVID-19-related primary hypothyroidism which was subclinical in 90% while overt in the rest. It is also evident that death in hypothyroid-COVID-19 patients higher than euthyroid patients with COVID-19 patients (11).

The enzyme thyroid peroxidase (TPO) adjusts the amount of thyroid hormone and thyrotropin receptor. Measurement of antibodies against TPO is essential in detecting auto-immune thyroid diseases (12). Clinical presentation of auto-immune thyroid diseases is either hyperthyroidism or hypothyroidism. According to the study of Prummel and Wiersinga (2005), women had higher level of thyroid antibodies than men (13). Annually, 2.1% of anti-TPO positive women with

normal thyrotropin levels develop hypothyroidism whereas only 18.6% and 3% of high TSH and low TSH group women develop hypothyroidism respectively. Sen et al. (2020), found that (15%) of the patients were anti-TPO antibody positive (sen2020). Since anti-TPO antibody present in 8-27% of the general population, the thyroid auto-immunity in COVID-19 patients is normal.

The aims of the current study were to evaluate the effects of COVID-19 on patients with/without history of thyroid disease and analyzing the relation of anti-TPO antibodies with thyroid dysfunction. This is the first study of its type conducted in Erbil/ Iraq in COVID-19 patients.

Methods

This cross-sectional study involved 86 COVID-19 pneumonia affected patients (adults < 30 years old) admitted BioLab and the Balsam Hospital, Erbil/ Iraq between January and April 2021. COVID-19 infection was confirmed in all patients by RT-PCR from nasopharyngeal swab. The T3, T4 and TSH hormones were assessed by an electrochemiluminescence assay (Roche Cobas® 6000's module e601 (Roche Diagnostics GmbH, Mannheim, Germany), whereas for assessing TPO levels, we used (Roche Cobas® e411) according to the manufacturer's recommendations. We also reported the characteristics of the patients including age, gender, preexisting thyroid disease, diabetes and blood pressure.

The reference ranges of T3, T4, and TSH were 1.3-3.1 nmol/ml, 66-181 nmol/L and 0.270-4.20 mIU/ml respectively. The normal ranges of TPO were 0-12 IU/ml. In the present study, determination of subclinical hypothyroidism was dependent on these reference ranges.

Statistical analysis

After entering data in Microsoft Excel Office, statistical analysis of the data carried out by using the Statistical Package for Social Sciences (SPSS, version 25). Chi square test of association was used to compare propor-

tions. Fisher's exact test was used when the expected frequency (value) was less than 5 of more than 20% of the cells of the table. A p value of ≤ 0.05 was considered as statistically significant.

Results

The total number of the participants was 86 COVID-19 affected patients. Their mean age \pm SD was (43.7 \pm 12.5) years, ranging from 22 to 74 years. The median was 41.5 years. The largest proportion of the sample (33.7%) were aged 30-39 years, and more than half (57%) were females. Around one quarter (24.4%) had history of thyroid disease. Only 5.8% and 9.3% of the participants had history of diabetes and hypertension respectively as in *Table 1*.

Table 1. Basic characteristics of the studied samples

Variable	No	%
Age	<30	8 9.3
	30-39	29 33.7
	40-49	22 25.6
	50-59	16 18.6
	≥ 60	11 12.6
Gender	Male	37 43.0
	Female	49 57.0
History of thyroid disease	Yes	21 24.4
	No	65 75.6
History of diabetes	Yes	5 5.8
	No	81 94.2
History of hypertension	Yes	8 9.3
	No	78 90.7
Total	86	100.0

It is evident in *Table 2* that the majority (88.4%) of the participants had normal T3 levels, and there was no significant difference between those with normal T3, TPO and with no history of thyroid disease and those with such a history and/or high TPO ($p=0.069$). It is worth to mention that three patients (7.7%) of those with no history of thyroid disease and normal TPO had high T3 level.

The pattern of T4 differs from that of T3. There was no significant difference between T4 level of the participants with no history of thyroid disease and normal TPO with those with history of thyroid disease and/or high TPO where it is clearly revealed that

96.5% of the samples had normal T4 level, and the difference was not significant ($p=0.725$).

Regarding the level of TSH, there was significant difference (<0.001) between the patients with high TSH, no history of thyroid disease and normal TPO (0.0%) and those with high TSH, history of thyroid disease and/or high TPO (34.0%).

Discussion

Thyroid hormones play a critical role in metabolism, growth, and development of the human body, hence any disruption in thyroid hormone levels could have serious clinical implications for immune response and human health. Individuals with a malfunctioning thyroid have been found to have a higher frequency of various comorbidities, putting them at a higher risk of viral infection. As a result, unregulated thyroid hormone may provide a significant danger of accelerating SARS-CoV-2 infection. Furthermore, in light of the current worldwide crisis caused by COVID-19, thyroid hormone monitoring may assist in the understanding of COVID-19 pathophysiology (14).

The coronavirus epidemic, which has affected millions of people around the world, has been declared a public health emergency. Individuals with comorbidities such as diabetes, heart disease, asthma, hypertension, and cancer are more vulnerable to infection and have higher morbidity and mortality rates (15). The research on hypothyroidism and thyroid disorders is still contradictory, with some studies indicating a connection (16) and others denying it (17).

The mean age \pm SD of the participants in the current study, was (43.7 \pm 12.5) years the largest proportion of the sample (33.7%) were aged 30-39 years, and more than half (57%) were females. About (24.4%) of the participants had history of thyroid disease. Only 5.8% and 9.3% of the participants had history of diabetes and hypertension respectively. This finding is consistent with that of (18), who found that 24 patients in their research had hypothyroidism. Out of these 21

Table 2. Thyroid function among those with or without history of thyroid disease

Variable	No History of thyroid and normal TPO		History of thyroid and/ or high TPO		Total		P-value	
	No	%	No	%	No	%		
T3	Low (<1.3)	5	12.8	1	2.1	6	7.0	0.069
	Normal (1.3-3.1)	31	79.5	45	95.7	76	88.4	
	High (>3.1)	3	7.7	1	2.1	4	4.7	
T4	Low (<66)	1	2.6	1	2.1	2	2.3	0.725
	Normal (66-181)	37	94.9	46	97.9	83	96.5	
	High (>181)	1	2.6	0	0.0	1	1.2	
TSH	Low	1	2.6	0	0.0	1	1.2	<0.001*
	Normal	38	97.4	31	66.0	69	80.2	
	High	0	0.0	16	34.0	16	18.6	

*By Fisher's exact test.

patients, 14 patients had diabetes (16), hypertension (19) and other comorbidities (15), the rest had hypothyroidism solely. COVID 19 positive hypothyroid patients had an average age of 44.9 years (18).

The findings of this investigation revealed a significant prevalence of subclinical hypothyroidism in those with a family history of thyroid disease, and/ or a high level of TPO antibodies in COVID-19 infected patients. People with a family history of thyroid disease and a high TPO level have obviously been more affected by COVID-19, more researches with larger number of participants may be needed. A few research has looked into the development of hypothyroidism during infection with COVID-19. Chen et al. (2021) discovered that 56 percent of COVID-19 infected patients had lower than normal TSH levels, which was statistically significant. They also discovered that the degree of TSH and TT3 reduction was associated to the severity of the disease. Dosi et al. (2020) discovered 2.7% of 365 COVID-19 patients had hypothyroidism. Hypothyroidism was also discovered to be the third most prevalent comorbidity among COVID 19 participants (18).

Several researches focused on the effects of this virus on numerous human organs due to its high infectivity and lethal outcomes. We sought to obtain a definitive conclusion despite the fact that experts in our region did not explore the effects of COVID-19 on patients with history of thyroid disease.

The majority of the participants in our study (88.4%) had normal T3 levels, and there was no significant difference ($p=0.069$) between those with normal T3, TPO, and no history of thyroid disease and those with such a history and/or high TPO. It's worth noting that three patients (7.7%) had elevated T3 despite having no history of thyroid illness and a normal TPO. There are five people with low T3 and no history of thyroid illness. This is similar to Wang et al., (2020)'s study who found 7 patients with lower-than-normal TSH and TT3 levels on admission, but normalized by Day 30 (20). Brancatella et al. (2020) recently published a case report of thyroiditis following SARS-CoV-2 infection, confirming thyroid dysfunction followed by a triphasic course of thyrotoxicosis, hypothyroidism, and euthyroidism (21).

The T4 levels of participants with no history of thyroid disease and normal TPO did not differ significantly ($p=0.725$) from those with a history of thyroid disease and/or high TPO. T4 levels were normal in 96.5 percent of the subjects.

Thyroid stimulating hormone (TSH) testing is frequently recognized as the most significant and sensitive test for hypothyroidism diagnosis. TSH is often regarded as the most important and sensitive test for hypothyroidism diagnosis. Primary hypothyroidism is characterized by a low serum T4 level and an accompanying increase in serum TSH. Normal serum T4 levels with minor to moderately elevated TSH levels and a normal FTI

characterize subclinical hypothyroidism (Romm, 2017).

There was significant difference (<0.001) in TSH levels between patients with high TSH, no history of thyroid disease, and normal TPO and those with high TSH, history of thyroid disease, and/or high TPO. TSH levels were normal in 80.2% of the subjects. This finding is in accordance with that of Chen et al., (2021), who found that TSH levels were normal in 44 percent to 94 percent of COVID-19 patients (9). In contrast to previous studies, low TSH levels were recorded in 15% to 56% of COVID-19 patients in connection with low or normal to high fT3 or fT4, but high TSH levels were only observed in up to 8% of patients with COVID-19, respectively (9, 11, 22–26). COVID-19 patients had considerably lower mean TSH readings than control groups in three investigations (9, 23, 25).

Chen et al., (2021) has found that COVID-19 patients' blood TSH levels were much lower in the severe and critical groups when compared to non-COVID19 pneumonia patients with similar degrees of severity suggests that COVID19 may have distinct effects on TSH secreting cells. These alterations could be due to a direct viral influence on pituitary cells, or its treatment contribute to hormonal alterations in the pituitary-endocrine axis feedback loops. SARS-CoV-2 is structurally and pathologically similar to SARS-CoV. As a result, they hypothesized that SARS-CoV-2 would likewise disrupt TSH-secreting cells.

Conclusion

There is high prevalence of subclinical hypothyroidism in the COVID-19 patients with family history of thyroid disease and/or high TPO antibody level. Therefore, larger studies with higher number of participants is needed to get better results.

Ethical standards statement

The current study was exerted in the Balsam Hospital, Erbil/ Iraq and it has been accepted by the research ethics committee.

Conflicts of interest

The authors declare that there is no conflict of interests.

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