Sapporo Medical Journal
Volume 55, Issue 06, June 2021

Post COVID Thyroid Function Disturbance

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Abstract— Background: 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 has effects on thyroid function or not.**Object:**The target of the current revisionis to compare thyroid functionin COVIDcases with and without history of thyroid illness to find out the thyroid disturbance in both groups.**Methods:** The present study enrolled 86 COVIDaffected patients that alienated to groups with and without history of thyroidcases, beside comorbidities with diabetes or hypertension.Thyroid hormones [triiodothyronine (T3) and thyroxine (T4)],thyrotropin (TSH) and thyroid peroxidase (TPO) concentrationswere analyzed and assessed. **Results:**Most of the participants (88.4%) had normal T3 and TPO level, that there was no significant difference (p = 0.069) between groups of with and without history of thyroid disease and/or upraised of TPOantibody level.Also 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 was significant difference (p<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%).**Conclusions:**There is high prevalence of subclinical hypothyroidism in the COVID patients with family history of thyroid disorders and high TPO antibody levels.

Keywords: COVID, thyroid hormone, subclinical hypothyroidism, TSH, TPO.

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 (Chen et al., 2020, Marazuela et al., 2020). The thyroid gland is one of the endocrine glands which supposed to be mainly affected by coronaviruses due to promote expression of the angiotensin-converting enzyme 2 receptor (Wei et al., 2010).Clinical hypothyroidism is defined as a condition in which free T4 levels are below normal and TSH levels are above 10 mIU/L (Garber et al., 2012). Elevated TSH with normal free T4 levels is referred to as subclinical hypothyroidism (Budenhofer et al., 2013). In this case, an increase in anti-peroxidase (anti-TPO) coincides with an increase in TSH (Garber *et al.*, 2012, Kim and Park, 2014). Iodine insufficiency, thyroid destruction, and hypothalamic-pituitary diseases are among the other causes (Batistuzzo and Ribeiro, 2020).Latestinvestigation have identified the beginning of thyroid disturbance in previously thyroid-healthy COVID-19 cases, in addition to the possible negative effects of COVID-19 on cases with previously detected thyroid diseases (Rotondi*et al.*, 2021). A recent retrospective study included 50 COVID-19 patients in China found a noticeable decrease in TSH, and T3 of COVID-19 patients compared to non-COVID-19 group. The degree of decline in TSH and T3 positively linked with the severity of COVID-19. There was not any significant difference in the concentration of total thyroxine of COVID-19 and non COVID-19 patients(Chen et al., 2021b). 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 (Muller et al. 2020).Lania et al. (2020) reported 5.2% of the patients in their study developed COVID-19-related primary hypothyroidism which was subclinical in 90%. It is also evident that death in hypothyroidCOVID-19 patients higher than euthyroid patients with COVID-19 patients (Lania et al. 2020). The enzyme TPO adjusts the amount of thyroid hormone and thyrotropin receptor. Measurement of antibodies against TPO is essential in detecting auto-immune thyroid diseases (Jantikar, 2020). Clinical presentation of auto-immune thyroid diseases is either hyperthyroidism or hypothyroidism. According to the study women had higher levels of thyroid antibodies than men(Prummel and Wiersinga, 2005). Annually, 2.1% of anti-TPO positive women with normal thyrotropin levels develop hypothyroidism whereas only18.6% 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(Sen et al., 2020). Since anti-TPO antibody present in 8-27% of the general population, the thyroid autoimmunity in COVID-19 patients is normal. The aims of the current study were to estimate the effects of COVID on cases with/without history of thyroid disease and analyzing the relation of TPOwith thyroid dysfunction. This is the first study of its type conducted in Erbil/ Iraq in COVIDpatients.

Materials and Methods

This revision involved 86 COVID affected patients (adults<30 years old) admitted BioLab and the Balsam Hospital, Erbil/ Iraq between January and April 2021. COVID-19 infection was confirmedin eachparticipant 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 dependenton these reference ranges.

Statistical Analysis

After entering data in Microsoft Excel Office, statistical analysis of the data carried out by utilizing the Statistical Package for Social Sciences (SPSS, version 25). Chi square test of association was utilized to compare proportions. Fisher's exact test was used when the predictable frequency (value) was less than 5 of more than 20% of the cells of the table. A p value was reflected as statistically significant.

Results

The participant'stotal number was 86 COVID affected patients. Their mean age ± SD was (43.7 ± 12.5) years, with age rangingbetween 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).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 and TPO in those with no history of thyroid disease and those with such a history and/or high TPO (p =

0.069). It is value to statement that three patients (7.7%) of those with no history of thyroid disorder and normal TPO had high T3 level. The pattern of T4 differs from that of T3. There was no significant difference among T4 levels 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 was significant difference (p<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%).

Table 1: Basic characteristics of the revision studied samples.

	No.	(%)
Age		
< 30	8	(9.3)
30-39	29	(33.7)
40-49	22	(25.6)
50-59	16	(18.6)
≥60	11	(12.8)
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)

Table 2: Thyroid function among those with or without history of thyroid disease (by the Fisher's exact test)

	No History of thyroid and normal TPO		History of thyroid and/ or high TPO		Total		
	No.	**(%)**	**No.**	**(%)**	**No.**	**(%)**	**p**
T3							
Low (<1.3)	5	(12.8)	1	(2.1)	6	(7.0)	
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)	0.069
T4							

Low (<66)	1	(2.6)	1	(2.1)	2	(2.3)	
Normal (66-181)	37	(94.9)	46	(97.9)	83	(96.5)	
High (>181)	1	(2.6)	0	(0.0)	1	(1.2)	0.725
TSH							
Low	1	(2.6)	0	(0.0)	1	(1.2)	
Normal	38	(97.4)	31	(66.0)	69	(80.2)	
High	0	(0.0)	16	(34.0)	16	(18.6)	<0.001*

Discussion

Thyroid hormones play a critical part 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 (Kumari *et al.*, 2020).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 (Sanyaolu *et al.*, 2020). The research on hypothyroidism and thyroid disorders is still contradictory, with some studies indicating a connection (Hariyanto and Kurniawan, 2020) and others denying it (Dworakowska and Grossman, 2020).The mean age ± SD of the participants in the current study, was (43.7 ± 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(Table 1). This finding is consistent with that of (Bakshi and Kalidoss, 2021), who found that 24 patients in their research had hypothyroidism. Out of these 21 patients, 14 patients had diabetes (Hariyanto and Kurniawan, 2020), hypertension (Dosi *et al.*, 2020) and other comorbidities (Sanyaolu *et al.*, 2020), the rest had hypothyroidism solely. COVID 19 positive hypothyroid patients had an average age of 44.9 years(Bakshi and Kalidoss, 2021).The findings of this investigation revealed a significant prevalence of subclinical hypothyroidism in those with a family history of thyroid disease, and/ orelevated level of TPO antibodies in COVID infected patients. People with a family history of thyroid disease and increased TPO level have obviously been more affected by COVID, more researches with larger number of participants may be needed. Aninsufficientrevision 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 patientshad hypothyroidism.Hypothyroidism was also discovered to be the third most prevalent comorbidity among COVID 19 participants (Bakshi and Kalidoss, 2021).Researches focused on the effects of this virus on numerous human organs due to its high infectivity and lethal outcomes (Li *et al.*, 2020). 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(Table 2). 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 (Wang *et al.*, 2020).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(Brancatella*et al.*, 2020).The T4 levels of participants with no history of thyroid disease and normal TPO in the current inesigation 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 as shown in Table 2.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).Table 2 displays that there was a significant difference ($p<0.001$) in TSH concentrationsamongcases with elevated TSH, no history of thyroid disease, and normal TPO and those with increased TSH, history of thyroid disease, and/or improvedTPO. 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 cases (Chen *et al.*, 2021). In contrast to previous studies, reduced TSH levels were recorded in 15% to 56% of COVID-19 cases in connection with decreased or normal to increased fT3 or fT4, but improved TSH levels were only observed in up to 8% of patients with COVID-19, respectively (Chen *et al.*, 2021a, Gao *et al.*, 2021, Khoo *et al.*, 2021, Lania *et al.*, 2020, Lui *et al.*, 2021, Muller *et al.*, 2020, Zou *et al.*, 2020). COVID-19 patients had considerably lower mean TSH readings than control groups in three investigations (Chen *et al.*, 2021, Khoo*et al.*, 2021, Muller *et al.*, 2020).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 contributes to hormonal alterations in the pituitary-endocrine axis feedback loops.SARS-CoV-2 is structurally and pathologically similar to SARS-CoV-2. 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 patients with family history of thyroid disease and/or high TPO antibody level. Therefore, larger studies with higher number of participants are needed to get better results.

Acknowledgements

To BioLab and the Balsam Hospital in Erbil/ Iraq (for the all staffs including physicians and assistance) assist, which let us to collect samples.

Conflict of Interest

In this investigation, there are no conflicts.

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