THYROXIN AND THYROID-STIMULATING HORMONE CHANGES IN PATIENTS WITH COVID-19

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ABSTRACT

Objective: *Whether COVID-19 has any effect on thyroid function is still up for debate. The aim of this study was to assess thyroid function in COVID-19 patients.*

Materials and methods: *Clinical signs, laboratory results, and computed tomography scans of the chest of patients followed up in our hospital due to COVID-19 infection, who did not have a known history of thyroid disease, were analyzed retrospectively. Prior to the initiation of treatment for COVID-19 infection, a total of 131 patients who underwent thyroid function tests and 70 healthy volunteers were included in the study as the control group. Serum free thyroxine (fT4) and thyroid-stimulating hormone (TSH) levels of COVID-19 and control groups were measured and compared.*

Results: *When compared with the healthy control group, within the normal range, COVID-19 patients had a significantly lower TSH level and significantly higher fT4 level (p=0.001, p<0.001, respectively). When each group was compared with the control group in terms of clinical severity, it was found that TSH levels were significantly lower in the critical case group (p< 0.001), and fT4 levels were significantly higher in all levels of clinical severity of COVID-19 (mild to critical) (p<0.001, p<0.001, p=0.001, and p=0.006, respectively).*

Conclusion: *Although TSH and fT4 levels were within the normal range in COVID-19 infection, they changed significantly. This suggests that the changes in thyroid function tests in COVID-19 did not have any clinical significance, but caution should be exercised for the transition to thyrotoxicosis in patients with borderline thyroid function tests.*

Keywords: *COVID-19, severity, thyroxin, thyroid-stimulating hormone.*

DOI: 10.19193/0393-6384_2022_1_69

Received *March 15, 2021;* ***Accepted*** *October 20, 2021*

Introduction

The new type of coronavirus disease (COVID-19), which emerged due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a pandemic by the World Health Organization (WHO) on 2020 March 11, after it was seen all over the world[1, 2]. The main targets of SARS-CoV-2 were identified as the lungs and the immune system. However, it has also been reported rapidly that renal, cardiac, hepatic, neurological, and hematological complications due to COVID-19[3]. Although COVID-19 infection usually follows a mild clinical picture, when it follows a severe course, acute respiratory distress syndrome or multi-organ failure leading to death may be accompanied[4]. The number of studies in the literature on the effects of COVID-19 on thyroid function in humans is increasing gradually, and there is a growing comprehension of thyroid dysfunction and its pathophysiology. The two major factors used by the SARS-CoV-2 to infect the target cells are ACE2

and transmembrane protease serine 2 (TMPRSS2), which are expressed in the thyroid gland even more than in the respiratory system[5].

We performed a retrospective study with COVID-19 patients in a tertiary hospital. The aim of this study was to assess thyroid function in patients with COVID-19. Moreover, COVID-19 patients were compared with the healthy subjects in terms of thyroid function, and the association between thyroid function and disease severity was investigated.

Materials and methods

This study was designed as a retrospective, observational study. Prior to the initiation of the study, approval from the Clinical Research Ethics Committee of our institute was obtained, and the study was conducted according to the principles of the Declaration of Helsinki. Written informed consents of all patients were obtained before inclusion.

Medical records of patients admitted to our hospital and diagnosed with COVID-19 between June 2020 and November 2020 were analyzed retrospectively. COVID-19 diagnosis was verified based on the positive result obtained in the polymerase chain reaction (PCR) test of a sample collected using a nasopharyngeal swab stick. Those with a history of thyroid disease and/or under medical treatment due to this disease, those with chronic kidney disease, those who are pregnant, or those without thyroid function tests were excluded from the study. Patients whose thyroid function tests were performed before initiation of treatment (steroid and/or heparin, etc.) were included in the study. Clinical signs, laboratory results, and computed tomography (CT) scans of the chest were analyzed. Based on this analysis, all cases were classified into four groups according to their clinical severity: mild, moderate, severe, and critical[6]. Patients in mild case category had mild clinical symptoms and manifestations of pneumonia was not observed in chest CT scan. In moderate cases, patients had symptoms such as fever and respiratory tract symptoms, and manifestations of pneumonia could be observed in chest CT scan.

Patients with respiratory rate ≥30 breaths/min, oxygen saturation ≤93% at rest, arterial partial pressure of oxygen (PaO_2)/ fraction of inspired oxygen (FiO_2) ≤300 mmHg or more than 50% progression of the lesions on imaging within 24-48 hours were categorized as severe cases. Finally, patients with respiratory failure requiring mechanical ventilation, presence of shock and any other organ failure that required in the intensive care unit (ICU) were considered as critical cases[6]. Serum free thyroxine (fT4) and thyroid-stimulating hormone (TSH) levels of 131 patients were recorded at the time of their admission. Simultaneously, a total of 70 age-and sex-matched healthy participants, who visited the hospital for routine physical checkup were included in the control group.

Patients in the control group did not have thyroid disorders or health problems affecting thyroid function. TSH and fT4 levels of COVID-19 patients were analyzed and compared with healthy participants in the control groups. Serum concentrations of TSH and fT4 levels were measured using chemiluminescent microparticle immunoassay (Abbott, Architect i2000, Abbott Laboratories Diagnosis Division, IL, USA) with a reference range of 0.35-4.94 mIU/L and 0.7-1.48 ng/dL, respectively.

Statistical analysis

Statistical analyses were performed using the SPSS software version 20.0. The Kolmogorov–Smirnov (KS) test was used for the measurement data. Continuous variables with normal distribution are expressed as the mean±standard deviation, and continuous variables without normal distribution are expressed as medians. Chi-square (χ^2) test was used to analyze categorical variables. The level of significance was determined using the t-test for normally distributed values and the Mann-Whitney U test was used for non-normally distributed values. One-way ANOVA analysis of variance and Tukey's multiple comparison posthoc tests were used for comparison of qualitative variables among groups. Kruskal-Wallis was used for the non-normal distribution comparison of qualitative variables among groups. $P<0.05$ was set as the difference with the statistical significance.

Results

A total of 131 COVID patients and 70 healthy volunteers were included in the study. Of the COVID-19 patients included in the study, 70 (53.4%) were female, 61 (46.6%) were male, and their demographic, clinical and laboratory data were presented in Table 1. The age and sex distribution of COVID-19 patients were similar to that of the healthy control group (Table 2). When COVID-19 patients were grouped by the clinical severity of the disease; it was found that 22 (16.8%) were mild, 56 (42.7%) were moderate, 24 (18.3%) were severe

and 29 (22.1%) were critical cases (Table 1). When compared with the healthy control group, within the normal range, COVID-19 patients had a significantly lower TSH level and significantly higher fT4 level (p=0.001, p< 0.001, respectively) (Table 2). In order to assess whether this difference changed according to the clinical severity, each group was compared with the control group in terms of clinical severity. In this comparison, it was found that TSH levels were significantly lower in the critical case group (p<0.001), and fT4 levels were significantly higher in all levels of clinical severity of COVID-19 (mild to critical) (p<0.001, p<0.001, p=0.001, and p=0.006, respectively) (Table 3).

	COVID-19 patients
Age, year± SD	44.3±17.3
Sex female n (%) / male n (%)	70 (53.4)/61 (46.6)
Mıld n (%)	22 (16.8)
Moderate n (%)	56 (42.7)
Severe n (%)	24 (18.3)
Crıtıcal n (%)	29 (22.1)
Albumin(g/dl), mean± SD	3.93± 0.54
White blood cells (x 10^9/L), median (min-max)	5.09 (4.97-13.96)
Lymphocyte (x 10^9/L), mean± SD	1.38±0.78
Platelets (x 10^9/L), mean± SD	227.31±81.15
Lactate Dehydrogenase (U/L), median (min-max)	188.5 (117-557)
Creatine kinase (CK) (U/L), median (min-max)	82.5 (25-2314)
CK-MB (U/L), median (min-max)	16 (9-95)
Pro-B-type natriuretic peptides (ng/L), median (min-max)	32.6 (5-2011)
D-Dimer (μg/ml), median (min-max)	0.25 (0.2-17)
Ferritin (ng/ml), median (min-max)	102.5 (6.7-1087)
Fibrinogen (mg/dl), median (min-max)	313.5 (143-679)
C-reactive protein (mg/L), median (min-max)	4.1 (0.1- 278.5)
TSH (mIU/L), median (min-max)	1.81 (0.01-7.5)
freeT4 (ng/dl), median (min-max)	1.21±0.23

Table 1: Demographic, clinical, and laboratory data of COVID patients.

	COVID n=131	HEALTHY n=70	P
Age	44.3±17.3	46.9±1.2	0.23*
Sex female n (%)/male n (%)	70 (53.4)/61 (46.6)	48 (62.3)/29 (37.7)	0.21**
TSH (mIU/L) median (min-max)	1.81 (0.01-7.5)	2.2 (0.5-7.45)	**0.001*****
fT4 (ng/dl) mean± SD	1.21±0.23	0.94±0.38	**<0.001***

Table 2: Comparison between COVID patients and healthy control group in terms of demographics and thyroid function tests.
**Student's T-test, **Chi Square test, ***Mann-Whitney U test.*

	TSH median (min- max)	P*	fT4 mean ± SD	P**
Control n:70	2.2 (0.5-7.45)		0.94±0.38	
Mıld n:22	1.76 (0.2-4.72)	0.2	1.28±1.14	**<0.001**
Moderate n:56	1.88 (0.1-7.5)	0.42	1.21±0.22	**<0.001**
Severe n: 24	1.63 (0.17-5.18)	0.15	1.22±0.22	**0.001**
Crıtıcal n:29	0.62 (0.12-2.68)	**<0.001**	1.16±0.26	**0.006**

Table 3: Comparison between each COVID clinical severity group and the control group in terms of thyroid function tests.
*p*Mann-Whitney U test, p** Student's T-test.*

Discussion

In our study, we found that, within the reference range, TSH levels were low and T4 levels were high in COVID-19 patients compared to the healthy control group. When the changes in thyroid function tests were evaluated according to the clinical severity of COVID-19, we found that the T4 level was significantly high in all clinical cases compared to the control group.

Pre-clinical and clinical studies provide preclinical and case report level of evidence that the thyroid gland may be the target organ of COVID-19. Recently, it has been shown that COVID-19 can cause thyroid dysfunction in various clinical situations, and the suggested potential mechanisms are direct virus damage to the thyroid follicular cells, an indirect effect on the hypothalamus-pituitary gland axis, abnormal immune-inflammatory responses due to the secretion of cytokines and chemokines, and autoimmune reactions[7]. In addition, it was shown that ACE-2 receptors are expressed in the epithelial cells of the thyroid gland, and this functional receptor for SARS-CoV-2, making these cells a potential target for virus entry[8]. In addition to COVID-19-related thyroid disorders such as thyrotoxicosis (subacute thyroiditis, Graves' disease, thyroxine thyrotoxicosis) and hypothyroidism (primary or central), nonthyroidal illness syndrome (NTI) was also reported[9-11]. However, comparative studies with non-COVID patients revealed that it is not possible to explain these hormonal changes with NTI alone[9, 10]. Thyroid dysfunction (abnormal TSH and/or thyroid hormone levels) varies widely among available studies, but the most frequently reported abnormality was low TSH level with low, normal, or high free-T3 or T4[11-15]. Follicular cell damage shown in post-mortem studies suggests the direct effect of the virus on the thyroid cell or the effect of cytokine release due to inflammation as the cause

of low TSH[7]. In our study, when compared to the healthy control group, in COVID-19 patients, TSH level was low and T4 level was high, suggesting a tendency to thyrotoxicosis. This may be partially due to acute NTI, or SARS-CoV-2, which directly infects the thyroid gland. In case of acute stress in NTI, an increase in T4 levels was observed within a few hours, while TSH level could be found to be normal or high. It was not clear how long after the onset of symptoms patients were admitted to the hospital, and the T3 level specific for the diagnosis of NTI was not measured. However, hormonal changes (high T4 low TSH) exclude the diagnosis of NTI. This suggested that SARS-CoV2 may directly cause damage to the thyroid cell. We believe that this condition will be important for patients with borderline thyroid function values.

Correlation between thyroid hormone levels and clinical severity of COVID-19 has been reported in previous studies[9, 10, 16]. In our study, fT4 levels were found to be significantly higher than the control group from the beginning, regardless of the clinical severity of COVID-19 patients. In their study, Chen et al[9] found that the severity of the COVID-19 was negatively correlated with TSH and total fT3 levels but did not have a significant correlation with total fT4 levels. Similarly, Gao et al[16] reported significantly lower TSH and fT3 levels for the severe COVID-19 patients and a median value of TSH within normal range for most patients, while no difference was reported for fT4 levels. However, different results may have been obtained by these studies, since it is difficult to exclude hormonal changes due to steroid therapy affecting the pituitary-thyroid axis. Parallel to our findings, the study of Muller et al[10] on ICU patients with COVID-19 reported low or suppressed serum TSH with and without increase in free thyroxine concentrations, which suggested thyrotoxicosis. Lania et al[14] reported thyrotoxicosis in 20.2% of non-critically COVID-19 patients, which was possibly caused by SARS-CoV-2-related thyroiditis. Although fT4 and TSH values were within the normal range in our study, compared to the healthy control group, T4 level was significantly higher in all clinical severities (mild to critical) of COVID-19 and TSH levels were significantly lower only in the critical cases.

As is known, there is a lagging TSH response to changes in thyroid hormones. The time between the onset of the COVID-19 disease and the critical illness may have led to this outcome; studies that also take into account the onset of contact of patients can answer this question. Compared to the healthy control group, the elevated T4 observed in COVID-19 patients may create a risk for cardiovascular diseases in patients with borderline thyroid function tests. T4 elevation may promote the development of cardiovascular complications and arrhythmias defined in SARS-CoV-2 infection, and may cause poor outcomes. Therefore, based on the results of our study, we believe that thyroid function tests may be performed and evaluated before starting treatment in patients with COVID-19, especially for the patients in the critical category.

Limitation

The most important limitation was the retrospective design and the relatively small number of patients. Absence of an independent cohort of patients with pneumonia did not allow defining the true impact of COVID-19 on thyroid function.

Conclusion

Although TSH and fT4 levels were within the normal range in COVID-19 infection, they changed significantly. This shows us that the change in thyroid function tests in COVID-19 is not clinically significant, but caution should be exercised for the transition to thyrotoxicosis in patients with borderline thyroid function tests. Routine examination of thyroid hormone levels may be regarded in the admission of COVID-19 patients due to possible hormonal changes caused by SARS-CoV-2-related thyroid gland damage.

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Acknowledgements:
The authors thank all the nurses and healthcare professionals working in our hospital for their contributions.

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