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COVID-19 Alter Thyroid Function Tests During the Acute Phase

Covıd-19 Akut Dönemde Tiroid Fonksiyon Testlerini Bozuyor

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ABSTRACT

Objective: This study aims to evaluate thyroid function tests in patients diagnosed with COVID-19, previously normal thyroid function.

Materials and Methods: This research was conducted using the data of patients who visited COVID-19 outpatient clinics for the first time and had normal thyroid function in their medical history. All patients were divided into two groups based on their age and gender. Group I consisted of patients whose PCR test was positive for the first time, while Group II (control group) consisted of patients whose test was negative. The study examined the TSH (thyroid-stimulating hormone), fT3 (free triiodothyronine), fT4 (free thyroxine), albumin, and total protein (TP) test parameters of all patients in both groups and compared the results. Statistical significance was assessed using SPSS 20.0, and a *p*-value of less than 0.05 was considered significant.

Results: The study included 1360 patients, with 356 in Group I and 1004 in Group II. In Group I, TSH levels were low, but fT3 and fT4 levels were significantly high. Additionally, albumin and TP values were significantly lower in Group I. A moderate positive correlation was found between albumin and fT3 levels, as well as between albumin and TP levels, in Group I. There was no statistically significant difference in age or gender distribution between the groups

Conclusions: There is a significant increase in thyroid function tests when COVID-19 infection is first diagnosed. However, detailed pathophysiological studies are needed to reveal the underlying reasons for this increase.

Keywords: Albumin, COVID-19, thyroid-stimulating hormone, thyroxine, total protein, triiodothyronine

ÖZ

Amaç: Bu çalışmada, geçmişte tiroid fonksiyonu normal olan COVID-19 tanısı almış hastalarda tiroid fonksiyon testlerinin değerlendirilmesi amaçlanmıştır.

Materyal ve Metot: Bu araştırma, COVID-19 polikliniklerine ilk kez başvuran ve tıbbi geçmişinde normal tiroid fonksiyonu olan hastaların verileri kullanılarak yürütülmüştür. Tüm hastalar yaş ve cinsiyetlerine göre iki gruba ayrılmıştır. Grup I, PCR testi ilk kez pozitif çıkan hastalardan oluşurken, Grup II (kontrol grubu) testi negatif çıkan hastalardan oluşmuştur. Çalışmada, her iki gruptaki tüm hastaların TSH (tiroid uyarıcı hormon), sT3 (serbest triiyodotironin), sT4 (serbest tiroksin), albumin ve toplam protein (TP) test parametreleri incelenmiş ve sonuçlar aralarında karşılaştırılmıştır. İstatistiksel anlamlılık SPSS 20.0 kullanılarak değerlendirilmiş ve 0,05'ten küçük p değeri anlamlı kabul edilmiştir.

Bulgular: Çalışmaya 1360 hasta dahil edilmiş olup, Grup I'de 356 ve Grup II'de 1004 hasta yer almıştır. Grup I'de TSH düzeyleri düşüktü, ancak sT3 ve sT4 düzeyleri anlamlı derecede yüksekti. Ek olarak, albümin ve TP değerleri Grup I'de anlamlı derecede düşüktü. Grup I'de albümin ve sT3 düzeyleri arasında ve albümin ve TP düzeyleri arasında orta düzeyde pozitif korelasyon bulundu. Gruplar arasında yaş veya cinsiyet dağılımında istatistiksel olarak anlamlı bir fark yoktu.

Sonuç: COVID-19 enfeksiyonu ilk teşhis edildiğinde tiroid fonksiyon testlerinde anlamlı bir artış vardır. Ancak, bu artışın altında yatan nedenleri ortaya çıkarmak için ayrıntılı patofizyolojik çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Albümin, COVID-19, tiroid stimüle edici hormon, tiroksin, total protein, triiyodotironin

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INTRODUCTION

The COVID-19 infection, caused by the highly contagious SARS-CoV-2 virus, first emerged in Wuhan, China, in 2019, leading to a global pandemic in 2020.[1] It has been reported that the increase in mortality among COVID-19 patients is associated with various disorders triggered by the infection.[2] In fact, some researchers have described COVID-19 as "the most significant public health threat worldwide this century".[3] Studies indicate that long-term COVID-19 can affect multiple organs and cause over 200 symptoms. It is estimated that at least 65 million people worldwide suffer from this condition.[4] However, the lack of a complete consensus on its treatment and the numerous mysteries surrounding its pathogenesis raise critical questions about COVID-19. Many scientific studies have been conducted on COVID-19; further detailed research is needed to investigate the relationship between COVID-19 infection and thyroid function. The SARS-CoV-2 virus penetrates the cells using the angiotensin-converting enzyme 2 (ACE 2) receptor, including cells in the thyroid gland. Consequently, there is a link between SARS-CoV-2 infection and various thyroid disorders, as reported.[5]

Thyroid hormones are among the most important hormones involved in regulating metabolism and significantly affect all cells in the body. The thyroid gland produces, stores, and releases T3 and T4 hormones into the bloodstream as needed. Hypothyroidism occurs due to insufficient thyroid hormone secretion, whereas hyperthyroidism is marked by high T3 and T4 levels along with low serum TSH levels.[6] Increased thyroid hormone synthesis can occur due to excessive secretion of pre-synthesized thyroid hormones or extreme thyroid hormone concentration in tissues caused by endogenous or exogenous extrathyroidal sources.[7] Commonly used tests for thyroid function include TSH, fT3, and fT4. Additionally, albumin and total protein (TP) levels, which play a role in thyroid hormone transport, should not be overlooked.

This study aimed to investigate differences in thyroid tests during the acute phase of COVID-19 in patients admitted to outpatient clinics. The study examined the relationship between COVID-19 and thyroid hormones during the acute period, taking into account albumin, total protein (TP), age, and gender. The findings are expected to provide new insights for clinicians.

MATERIALS AND METHODS

Ethics Committee Approval: This study was conducted upon approval from the Sakarya University Faculty of Medicine Ethics Committee (Date: 04.03.2022, decision no: 112789). All authors declare to follow and obey the Helsinki Declaration criteria.

Study Design: In addition, this study was carried out with the permission and approval of the Ministry of Health of the Republic of Türkiye and in accordance with the scientific research criteria of the ministry. The research was conducted between March 11, 2020, and February 28, 2022, using the automation system of a training and research hospital. Participants included individuals who applied to COVID-19 outpatient clinics for the first time and had normal thyroid function in their medical history. Patients under the age of 18, patients with a history of thyroid disease, those under treatment that could affect thyroid hormone levels, and patients on steroid therapy were excluded. The patients were divided into two distinct groups: the patient group (Group I) consisted of those with a positive PCR test, and the control group (Group II) consisted of those with a negative PCR test. The study examined TSH (thyroid-stimulating hormone), fT3 (free triiodothyronine), fT4 (free thyroxine), albumin, and TP test parameters for all individuals in both groups. Age and gender were also recorded, and all data were compared between the groups.

Molecular Testing for SARS-CoV-2: Both nasopharynx and oropharynx swab samples were collected from patients using a Dacron swab. Immediately after collection, the samples were retained in a viral transport medium, stored at 2-8°C, and delivered to the molecular microbiology laboratory for analysis. The samples were transported in compliance with cold chain protocols and infection control measures. Upon arrival at the microbiology laboratory, the samples were processed in a level 3 bio-safe negative-pressure room. Total nucleic acid isolation was performed using the Bio-Speedy® Viral Nucleic Acid Isolation Kit (Bioeksen, Türkiye). The Bio-Speedy® COVID-19 RT-qPCR Detection Kit (Bioeksen, Türkiye) was used for RT-PCR analysis. PCR amplification data and the test results were evaluated consistently with the manufacturer's recommendations.

Biochemical Analysis: Blood samples for biochemical and hormone tests were drawn during outpatient clinic admission. Hormone tests were performed using the Architect i2000 SR (Abbott, USA) device. Albumin and TP tests were conducted on Beckman Coulter AU 5800 (Koto-Ku, Tokyo, Japan) fully automated analyzers. The normal range for Thyroid Stimulating Hormone (TSH) is 0.35-5.5 μIU/mL, with a precision of ≤2.4% CV and a sensitivity of ≤0.0025 μIU/mL. Free T3 (fT3) falls within a normal range of 2.3-4.2 ng/L, has a precision of ≤5.3% CV, and a sensitivity of ≤1.0 ng/L. Free T4 (fT4) has a reference range of 0.89-1.76 ng/L, a precision of

≤4.6% CV, and a sensitivity of ≤0.4 ng/dL. Total Protein (TP) is typically within 66-83 g/L, with a precision of ≤0.5% CV and a sensitivity of 0.77 g/L. Albumin levels normally range from 35-52 g/L, with a precision of ≤0.58% CV and a sensitivity of 0.07 g/L.

Statistical Analysis: SPSS 20.0 was used for all analyses. A power analysis was carried out using G*Power 3.1 software to determine whether the sample size was adequate to detect statistically significant differences between the two independent groups (Group I/study group, Group II/control group) in thyroid function parameters. Since the smallest effect size between the two groups was obtained as d = 0.26, the study hypothesised that there would be a small effect size between the two groups with d = 0.26, and it was determined that a total of at least 624 people should be studied, with at least 312 people in each group at a power of 90% and a 5% error level. However, since this study has a cross-sectional design, the minimum value calculated was taken into account in order to increase the generalizability of the study and the maximum number that could be reached in the relevant data range was aimed for. Thus, 1360 people were included in the study. The distribution of continuous variables was assessed using visual and statistical methods. Normally distributed variables are presented as mean ± standard deviation, while non-normally distributed variables are shown as median and interquartile range (1st and 3rd quartiles). Categorical variables are expressed as percentages and numbers. The chi-square test was used to compare categorical variables between the case and control groups. The Student's t-test was used for normally distributed variables, and the Mann-Whitney U test was used for non-normally distributed variables. Spearman correlation analysis was performed for continuous variables, and box plots were used for visual representation. A p-value of <0.05 was considered statistically significant.

RESULTS

In Group I, TSH levels were low, while fT3 and fT4 levels were high (Figure 1).

The mean values of the thyroid function tests were presented in Table 1, and the comparative results among these hormones were statistically significant (p<0.001 for TSH, p=0.007 for fT3, and p<0.001 for fT4). Additionally, albumin and TP values were significantly lower in Group I (p<0.001 for both). In Group I, a low negative correlation was detected between fT3, TP levels, and age.

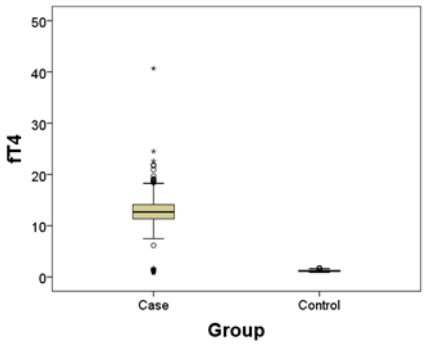

Figure 1. Box plot graph of fT4 levels in the case and control groups.

Table 1. Comparison of TSH, fT3, fT4, TP, and albumin levels for Group I and Group II.

Parameters		Group I (*n*=356)	Group II n(*n*=1004)	p
Sex	Male	206 (57.9)	529 (52.7)	0.092[a]
	Female	150 (42.1)	475 (47.3)	
Age, Average ± SD		64.12±17.07	59.28 ± 11.67	0.061[b]
TSH, Median (1^{st}Q-3^{rd}Q)		0.82 (0.35-1.50)	1.65 (1.09-2.59)	**0.001**[c]
fT3, Median (1^{st}Q-3^{rd}Q)		3.27 (2.42-4.29)	3.12 (2.86-3.40)	**0.007**[c]
fT4, Median (1^{st}Q-3^{rd}Q)		12.68 (11.32-14.13)	1.18 (1.07-1.29)	**0.001**[c]
Albumin, Median (1^{st}Q-3^{rd}Q)		32.70 (28.15-37.15)	42.50 (40.20-44.70)	**0.001**[c]
Total Protein, Median (1^{st}Q-3^{rd}Q)		63.00 (57.90-68.00)	71.80 (69.20-76.70)	**0.001**[c]

[a]: Pearson Ki kare test; [b]: Student t test; [c]: Mann-Whitney U test; SD: Standard Deviation; Q: Quartile.

Conversely, a moderate positive correlation was found between albumin levels and both fT3 and TP levels (Table 2). There was also a weak negative correlation between albumin and age, as well as between fT3 and age. A low positive correlation was observed between albumin and both fT3 and TP levels.

In Group II, a high positive correlation was found between albumin levels and both fT3 (r=0.308, p<0.001) and TP levels (r=0.473, p<0.001), as shown in Table 3.

Table 2. Correlations of age, TSH, fT3, fT4, Albumin, and TP in Group I.

Parameters	Tests	Age	TSH	fT3	fT4	Albumin	TP
Age	***r***	1	0.023	-0.358 [a]	-0.075	-0.491 [a]	-0.281 [a]
	p		0.668	**0.001**	0.156	**0.001**	**0.001**
TSH	***r***	0.023	1	0.060	-0.153**	0.052	0.036
	p	0.668		0.256	0.004	0.325	0.506
fT3	***r***	-.358**	0.060	1	0.392**	0.539 [a]	-0.347 [a]
	p	**0.001**	0.256		**0.001**	**0.001**	**0.001**
fT4	***r***	-0.075	-0.153**	0.392 [a]	1	0.049	0.121
	p	0.156	**0.004**	**0.001**		0.363	0.023
Albumin	***r***	-.491**	0.052	0.539 [a]	0.049	1	-0.701 [a]
	p	**0.001**	0.325	**0.001**	0.363		**0.001**
Total Protein	***r***	-.281**	0.036	0.347 [a]	0.121	0.701 [a]	1
	p	**0.001**	0.506	**0.001**	0.023	**0.001**	

[a]**:** p<0.001.

Table 3. Correlation of age, TSH, fT3, fT4, Albumin, and TP in Group II.

Parameters	Tests	Age	TSH	fT3	fT4	Albumin	TP
Age	***r***	1	0.004	-0.382[a]	-0.014	-0.367 [a]	-0.193 [a]
	p		0.908	**0.001**	0.661	**0.001**	**0.001**
TSH	***r***	0.004	1	-0.040	-0.120 [a]	-0.055	0.035
	p	0.908		0.210	**0.001**	0.079	0.272
fT3	***r***	-0.382 [a]	-0.040	1	0.144 [a]	0.308 [a]	0.058
	p	**0.001**	0.210		**0.001**	**0.001**	0.067
fT4	***r***	-0.014	-0.120 [a]	0.144 [a]	1	0.119 [a]	0.105 [a]
	p	0.661	**0.001**	**0.001**		**0.001**	**0.001**
Albumin	***r***	-0.367 [a]	-0.055	0.308 [a]	0.119 [a]	1	0.473 [a]
	p	**0.001**	0.079	**0.001**	**0.001**		**0.001**
Total Protein	***r***	-0.193 [a]	0.035	0.058	0.105 [a]	0.473 [a]	1
	p	**0.001**	0.272	0.067	**0.001**	**0.001**	

[a]: p<0.001.

DISCUSSION AND CONCLUSION

It is well-known that COVID-19 primarily affects the lungs.[8] However, ongoing research is exploring how the virus impacts other medical conditions, including thyroid function. Thyroid hormones possess a highly vital role in regulating essential bodily functions such as growth, development, metabolism, and energy supply.[9] Therefore, routine checks for TSH, fT3, and fT4 levels are essential when assessing thyroid gland function. Additionally, albumin and total protein measurements should be considered when studying thyroid hormones. This research suggests that these measurements are necessary to evaluate thyroid function accurately.

COVID-19 can cause transient or permanent changes in thyroid function, and non-thyroidal illness syndrome has been frequently reported. After the acute infection period, some patients have suffered subacute thyroiditis and thyroid hormone imbalances, which in turn cause long-term complications. Immune system responses and ongoing inflammation are blamed for such complications.[4]

A study of 146 COVID-19 patients in the intensive care unit with normal thyroid levels found that thyroid hormone levels decreased slightly in those who recovered, but the decrease was more significant in those who died.[10] The study suggested that a severe decrease in thyroid hormones could serve as a prognostic parameter for COVID-19 patients. However, other studies indicate that hypothyroidism is observed in COVID-19 patients in later stages. In contrast, our findings suggest that hormone levels tend to

increase during the acute phase of COVID-19, possibly due to systemic and metabolic processes. We believe this represents a temporary period of thyrotoxicosis. If the patient does not respond to treatment and progresses to a severe stage, thyroid tissue damage may occur, leading to a noteworthy decline in hormone levels. In another study involving 48 SARS patients, significant decreases in serum T3, T4, and TSH levels were observed. Specifically, serum T3 and T4 levels decreased by 94% and 46%, respectively. During recovery, T3 and T4 levels were 90% and 38%, respectively. The decrease in T3 levels was particularly correlated with disease severity.[11,12]

A retrospective analysis of 274 COVID-19 patients in intermediate and critical conditions found that 113 patients died, while 161 recovered. T3 serum levels were significantly lower in those who died compared to those who recovered (0.7 mIU/mL vs. 2.8 pmol/L, respectively). However, the difference in T4 levels between the two groups (15.8 pmol/L for those who died and 18.3 pmol/L for those who recovered) was not significant.[13] Another retrospective study of hospitalized SARS-CoV-2-infected patients with previously unknown thyroid diseases found that 56% (28/50) of patients had significantly lower TSH levels.[14] Additionally, serum T3, T4, and TSH levels in SARS patients were considerably lower compared to controls during both the progression and recovery periods of the disease.[15] However, in COVID-19 patients, T4 and T3 levels increase while TSH levels decrease.[16] Our study found that COVID-19 patients had low TSH levels, while fT3 and fT4 levels were elevated.

Studies have shown that low serum albumin levels are associated with poor prognosis in COVID-19 patients and are among the specific biomarkers of severe infection.[17] Low serum albumin levels were also observed in COVID-19 patients in another study.[18] Serum albumin levels are among the test parameters examined in COVID-19 studies. Our study, along with others, revealed that albumin levels are low in COVID-19 patients. For example, a study on the C-reactive protein to albumin ratio in severe COVID-19 patients suggested that this ratio could be an essential biomarker for risk stratification and clinical follow-up.[19] Our findings, consistent with previous studies, suggest that low albumin levels may be a biomarker of COVID-19 severity.

In conclusion, there is a significant increase in thyroid function tests in patients who are admitted to outpatient clinics with suspected COVID-19 and test positive on PCR. This increase may be due to a sudden metabolic response, but more detailed studies are needed to uncover the underlying pathophysiological mechanisms. The findings of this study were derived from data collected exclusively from patients at a single hospital. More significant and comprehensive conclusions could be achieved through a meta-analysis that synthesizes data from this and similar studies.

Ethics Committee Approval: This study was conducted upon approval from the Sakarya University Faculty of Medicine Ethics Committee (Date: 04.03.2022, decision no: 112789). All authors declare to follow and obey the Helsinki Declaration criteria.

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