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Araştırma Makalesi / Research Article

Assessment of Thyroid Function Tests in Patients with COVID-19 Infection and Their Relationship with Euthyroid Sick Syndrome

COVID-19 Enfeksiyonlu Hastalarda Tiroid Fonksiyon Testlerinin Değerlendirilmesi ve Hasta Ötiroid Sendromu ile İlişkisi

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Abstract

Aim: Thyroid functions are affected by many factors functions such as some infections and drugs. This study aimed to investigate how the thyroid function tests were affected after COVID-19 infection and their relationship with euthyroid sick syndrome.
Material and Method: Our study was designed as a retrospective and case-control study. The participants consisted of two groups as the control and patient groups. Thyroid function tests (TFT), hemogram and routine biochemistry of the groups were assessed. In addition, the tests of the patient group within the last 6 months before the infection were assessed. The patients' symptoms, presence of a chronic disease, smoking history, and clinical status during COVID-19 infection were recorded.
Results: A total of 473 people were included in the study. Of the participants, 54.5% were female. The white blood count (WBC), hemoglobin (HGB), platelet (PLT), and neutrophil (NEU) counts were higher in the patient group. Lymphocyte (LY) and mean platelet volume (MPV) counts were similar. Tyroid stimulating hormone (TSH) and triiodothyronine (T3) values of the patients were higher compared with the control group. The thyroxine (T4) level was similar in the two groups.TSH, T3 and T4 levels of the patient group before COVID-19 were higher than the results just after the quarantine process after COVID-19 infection.
Conclusion: Thyroid dysfunction develops in COVID-19 patients within the course of the disease. This condition can be partially explained with the euthyroid sick syndrome. It is also possible with the thyroid gland being the direct or indirect target of the virus.

Keywords: COVID-19, thyroid dysfunction, euthyroid sick syndrome

Öz

Amaç: Tiroid fonksiyon testleri bazı enfeksiyonlar ve ilaçlar gibi birçok faktörden etkilenir. Bu çalışma, COVID-19 enfeksiyonu sonrası tiroid fonksiyon testlerinin nasıl etkilendiğini ve hasta ötiroid sendromu ile ilişkisini araştırmayı amaçlamıştır.
Materyal ve Metot: Çalışmamız retrospektif ve vaka kontrol çalışması olarak planlandı. Katılımcılar kontrol ve hasta grubu olarak iki gruptan oluşmuştur. Grupların tiroid fonksiyon testleri (TFT), hemogram ve rutin biyokimyası değerlendirildi. Ayrıca hasta grubunun enfeksiyondan önceki son 6 ay içindeki testleri değerlendirildi. Hastaların semptomları, kronik hastalık varlığı, sigara içme öyküsü ve COVID-19 enfeksiyonu sırasındaki klinik durumları kaydedildi.
Bulgular: Çalışmaya toplam 473 kişi dahil edildi. Katılımcıların %54.5'i kadınd. Hasta grubunda beyaz kan sayımı (WBC), hemoglobin (HGB), trombosit (PLT) ve nötrofil (NEU) sayıları daha yüksekti. Lenfosit (LY) ve ortalama trombosit hacmi (MPV) sayıları benzerdi. Hastaların tiroid uyarıcı hormon (TSH) ve triiyodotironin (T3) değerleri kontrol grubuna göre daha yüksekti. Tiroksin (T4) düzeyi iki grupta benzerdi. Hasta grubunun COVID-19 öncesi TSH, T3 ve T4 düzeyleri, COVID-19 enfeksiyonu sonrası karantina sürecinin hemen sonrasındaki sonuçlara göre daha yüksekti.
Sonuç: COVID-19 hastalarında hastalığın seyri içerisinde tiroid disfonksiyonu gelişir. Bu durum kısmen hasta ötiroid sendromu ile açıklanabilir. Tiroid bezinin virüsün doğrudan veya dolaylı hedefi olması da mümkündür.

Anahtar Kelimeler: COVID-19, tiroid disfonksiyonu, hasta ötiroid sendromu

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INTRODUCTION

Thyroid functions are affected by several functions such as some infections and drugs (1). Some viruses such as mumps, influenza, coxsackie, ebstein barr virus, adenovirus, and human immunodeficiency virus cause thyroiditis and change the production of thyroid hormones (2). Various thyroid diseases can develop in the early and late periods after the virus infections. The inflammation of thyroid gland, which is known as subacute thyroiditis, can develop in the early period, in other words, a few weeks after the virus infection. They can also cause the dysfunction of the immune system in the late period after months and favor the development of autoimmune thyroid diseases (3). Euthyroid sick syndrome is defined as the abnormal findings in the thyroid hormones without a thyroid disease (4). It is known that the thyroid dysfunction is associated with the severity of the underlying disease and that low thyroid hormone levels are associated with poor prognosis in several diseases (5,6,7).

The coronavirus disease-19 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a pandemic disease that rapidly spreads all over the world and affects millions of people (8). It was declared a pandemic by the World Health Organization on the 11th of March 2020 and caused millions of people to be infected and die (9,10,11). COVID-19 has serious and complicated effects of the various human organs and systems (12). After entering the body, COVID-19 can cause damage by binding to the receptors in several tissues and organs including the thyroid gland and thyroid dysfunctions can develop (13). The patients who have had COVID-19 infection can have low TSH and T4 compared with the normal people (14) and hyperthyroidism (15) and subacute thyroiditis (16) due to thyroid gland damage can be seen in blood as well. This study aimed to reveal how the thyroid function tests were affected after COVID-19 infection and investigate the relationship with the euthyroid sick syndrome.

MATERIAL AND METHOD

This study was performed in the Family Medicine Outpatient Clinic of Incesu State Hospital. A total of 885 participants between the 25th of October, 2020 and 25th of November, 2020 were included in the study. Our study was designed as a retrospective and case-control study. The participants consisted of two groups as the control and patient groups. The control group consisted of the participants who were admitted to the outpatient clinic within the date of study, who were not infected with COVID-19, who had no chronic diseases, and who got the tests stated below. The patient group consisted of the participants who were diagnosed with COVID-19 and admitted to the outpatient clinic after the quarantine process. The patient group's tests within the last six months before the infection and within 14 days after the end of the quarantine process were assessed. The tests performed were the TFTs, CBC and routine biochemistry. The patients' symptoms, presence of a chronic disease, smoking history, and clinical conditions during COVID-19 infection were recorded.

Inclusion Criteria for the Study

The inclusion criteria for the control group were not having been infected with COVID-19, not having a chronic disease and having gotten the TFT, hemogram and routine biochemistry. For the patient group, the criteria were having been infected with COVID-19, having gotten the mentioned tests within the last six months before the infection at the latest, and having gotten the mentioned tests again within the 14 days after the infection at the latest.

Exclusion Criteria for the Study

The exclusion criteria were being under the age of 18, having had hypothyroidism and/or hyperthyroidism before, using a medication that could affect the thyroid functions, and having an autoimmune disease.

Statistical Analysis

For the continuous variables that were among the features focused on, descriptive statistics-mean, standard deviation, and minimum and maximum values- were calculated and categorical variables were expressed in counts and percentiles. Whether the numerical data of the variables were normally distributed or not was determined with one sample Kolmogorov-Smirnov test. Chi-square test was used to determine the relationship between the groups and categorical variables. Student-t test was used in comparison of normally distributed numerical data for independent two groups and Mann Whitney U test was used in non-normally distributed two groups. The Wilcoxon test was used in paired groups that were not normally distributed. SPSS 21.0 software program was used for calculations. Statistical significance level in the calculations was accepted as 5%.

Ethics Approval

The institutional approval for the study was obtained from Kayseri Local Health Authority and the ethics approval was obtained from the Non-Interventional Research Ethics Committee of Nuh Naci Yazgan University (Committee Number: 2020/24, Date: 07.12.2020).

RESULTS

A total of 473 individuals were included in the study. While the study group consisted of 259 individuals there were 214 individuals in the control group. Of the participants, 54.5% were female, 40.8% were housewives and 75.5% were married. The rate of the participants with at least one chronic disease was 18.4%. Of the participants, 12.3% had diabetes mellitus, 12.9% had hypertension, 7.4% had cardiovascular disease, 8% had chronic pulmonary disease, and 0.4% had malignancy. While 3.8% of the patient group was hospitalized 3% had pneumonia. Of the participants, 9.9% were smoking. The patient and control groups were similar in terms of age and gender (p: 0.125, p: 0.52). There was no difference between the groups in terms of marital status and occupation (p: 0.158, p: 0.102) (Table

1). WBC, hemoglobin, platelet count, and neutrophil count were higher in the patient group (p: 0.047, p:0.005, p<0.001, p:0.50). Lymphocyte and MPV counts were similar (p: 0.217, p:0.975).

In the patient group, T4 value of 8 patients (3.1%) (1 had low and 7 had high values), T3 value of 12 patients (4.7%) (10 had low and 2 had high values) and TSH value of 12 patients (4.7%) (5 had low and 7 had high values) were not in the reference rage.

TSH and T3 values of the patients were higher compared with the control group (p:0.011, p<0.001). T4 level was similar in the patient and control groups (p: 0.107) (Table 2). TSH, T3 and T4 levels of the patient group before COVID-19 were higher than the results just after the quarantine process after COVID-19 infection (p<0.001, p<0.001, p<0.001) (Table 3).

Table 1. Demographic Data of the Patient and Control Groups

		Patient n(%)	Control n(%)	P
Gender	Male	127(49)	86(40.2)	0.054
	Female	132(51)	149(59.8)	
Age		44(18-87)	51(18-91)	0.125
Occupation	Officer	26(10)	36(16.8)	0.102
	Housewife	106(40.9)	87(40.7)	
	Employee	48(18.5)	46(21.5)	
	Retired	39(15.1)	20(9.3)	
	Student	28(10.8)	19(8.9)	
	Self-employed	12(4.6)	6(2.8)	
Marital Status	Married	203(78.4)	154(72)	0.158
	Single	56(21.2)	60(28)	
Smoking	Yes	26(10)	21(9.8)	0.531
	No	233(90)	193(90.2)	

Table 2. Comparison of CBC and TFTs of the Patient and Control Groups

	Patient Median(min-max)	Control Median(min-max)	p
WBC	7.23(1.03-19.03)	6.9(4.03-17)	0.047
HGB	14.3(7.3-19.9)	14(9.8-19.9)	0.007
PLT	258(88-979)	227(130-351)	<0.001
NEUTROHIL	3.58(1.18-7.98)	3.97(1.07-10.76)	0.05
LYMPHOCYTE	2.5(1.29-4.26)	2.68(1.05-5.86)	0.217
MPV	9.4(0.26-11.1)	9.4(1.1-12.6)	0.975
TSH	1.64(0.06-9.1)	1.88(0.35-4.93)	0.011
T3	2.97(0.67-4.94)	3.18(1.72-4.78)	<0.001
T4	1.06(0.70-4.15)	0.88(0.7-1.47)	0.077

Table 3. Comparison of the Pre-Quarantine and Post-Quarantine TFT Values of the Patient Group

	Pre-Quarantine	Post-Quarantine	P
TSH	1.87(0.28-10.7)	1.52(0.06-6.2)	<0.001
T3	3.32(1.01-4.52)	3.01(1.01-4.32)	<0.001
T4	1.13(0.65-3.24)	1.05(0.74-3.19)	<0.001

DISCUSSION

COVID-19 is an infectious disease that has caused a pandemic worldwide. The pathophysiology of COVID-19, a new type of disease with high contagiousness and mortality, is not fully known. A series of studies have reported that COVID-19 has severe and complex effects on respiratory, digestive, circulatory, and urogenital system (12). Although it has been revealed in some studies that COVID-19 causes thyroid diseases such as subacute thyroiditis and hyperthyroidism its pathophysiology is not clearly known (17).

We found that the participants who had COVID-19 before had lower T3 and TSH levels compared with the control group. T4 levels were not significantly different. In the patient group, T4 of 0.4%, T3 of 3.9% and TSH level of 1.9% were under the reference range. In the study by Chen et al., low TSH and T3 levels were detected in the patient group. There was no difference between the two groups in terms of T4 level. In addition, the degree of the decreases in the TSH and T3 levels revealed a positive correlation with the severity of the disease (18). Lania et al. revealed that TSH value was under the reference value in 20% of the patients who had COVID-19 and that more than half of them experienced apparent thyrotoxicosis (15). Similarly, Müller et al. proved in their study on the patients hospitalized at intensive care unit that the patients had findings compatible with thyrotoxicosis (19). In the study on patients developing pneumonia in China, severe patients had lower TSH and T3 levels compared with mild patients and the dead patients had also lower TSH and T3 levels compared with those surviving (20). Although the effect of COVID-19 seems different in terms of thyroid function tests it is obvious that the disease affects the thyroid hormone release.

COVID-19 is associated with the increased inflammation. SARS-CoV-2 nucleic acid has been seen in respiratory tract, salivary, stool, and breast milk and it has been determined that it reveals a wide distribution. This may be because of the cytokine effect triggered by the virus. This condition is revealed as the cause in inflammatory conditions (21). The increased cytokine profile such as IL-2, IL-6, IL-7, INF-, and TNF-α have been associated with the severity of disease and mortality rate (22, 23). In addition, the increased leukocyte, neutrophil and platelet level and reduced lymphocyte level are the other inflammatory changes that have been detected in the group with thyroid dysfunction. It has been reported that thyroid dysfunction is related to the altered inflammatory process (13). We found that leukocyte, neutrophil and platelet level of the patients increased while lymphocyte level was stable, which is consistent with the findings in literature.

The thyroid sick syndrome is one of the conditions developing after the infection. Its common causes are mainly severe infections, liver and renal failure, severe diabetic complications, malignancy and malnutrition, and burn and trauma (24). It generally occurs as reduced plasma T3 level or low/normal T4 and TSH levels (25).

The thyroid function tests can differ before and after the COVID-19 infection. In a patient who had no thyroid disease history, low TSH level and increased T3 level were detected after the disease (26). Moreover, low TSH and T4 level was detected in a Chinese patient (27). In their study, Khoo et al. reported that most of the COVID-19 patients were euthyroidic, but they observed mild decreases in TSH and T4 compared with the pre-infection values (14). In our study, post-disease TSH, T4 and T3 values of the patients were low compared with the pre-disease values in parallel with the euthyroid sick syndrome.

Limitations of the Study

Our study has various limitations. It is a single center study and has a sample size with a limited number. In addition, the study was retrospectively performed and the severity of the disease could not be assessed. Therefore, the correlation between the severity of the disease and thyroid function tests could not be assessed.

CONCLUSION

In conclusion, the present study has revealed that euthyroid sick syndrome, hypothyroidism and hyperthyroidism can occur in COVID-19 patients. Thyroid dysfunction develops within the course of the disease. While this can partiallybe explained by the non-thyroid disease syndrome it is also possible that thyroid gland can be the direct target of SARS-CoV-2 virus.

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Conflict of Interest: *The authors declare that they have no competing interest.*

Ethical approval: *The institutional approval for the study was obtained from Kayseri Local Health Authority and the ethics approval was obtained from the Non-Interventional Research Ethics Committee of Nuh Naci Yazgan University (Committee Number: 2020/24, Date: 07.12.2020). .*

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