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Original Scientific Paper

THYROID FUNCTION IN PATIENTS WITH COVID-19: A RETROSPECTIVE STUDY

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SUMMARY – The aim of this study was to assess whether COVID-19 affects thyroid function. The effect of COVID-19, which has involved the whole world in the last two years, on thyroid function is currently unknown. With the onset of the COVID-19 epidemic, 69,000 patients who presented to our hospital in the last 18 months and had the COVID-19 test were screened. Thyroid function tests of 500 patients with positive COVID-19 test and 1133 patients with negative COVID-19 test were compared. Hormone levels were expressed as mean ± standard deviation. The levels recorded in COVID-19 positive patients (thyroid-stimulating hormone (TSH) 2.54±14.54 μIU/mL, free triiodothyronine (fT3) 0.84±1.49 pg/mL, free thyroxine (fT4) 0.99±0.42 ng/dL, antithyroid peroxidase antibody (anti TPO) 140.04±276.55 IU/mL, and antithyroglobulin antibody (anti TG) 16.31±22.99 IU/mL) were compared with those measured in COVID-19 negative patients (TSH 1.90±8.22 μIU/mL, fT3 0.78±1.60 pg/mL, fT4 0.99±0.42 ng/dL, anti TPO 122.55±263.39 IU/mL, and anti TG 56.25±185.64 IU/mL). There was no significant difference between COVID-19 positive patients and COVID-19 negative cases in terms of thyroid function (TSH, p=0.66; fT3, p=0.24; fT4, p=0.93; anti TPO, p=0.52; and anti TG, p=0.39). For now, it may be some consolation for us that the coronavirus disease, which affects almost all body systems, does not seem to affect thyroid function.

Key words: *COVID-19; Thyroid-stimulating hormone (thyrotropin); Free triiodothyronine; Free thyroxine; Antithyroid peroxidase; Antithyroglobulin*

Introduction

The global COVİD-19 pandemic has affected all countries in the world[1].Thyroid hormones play an important role in the basic processes of life such as growth, development, energy, and metabolism[2]. For this reason, the relationship between COVID-19 and thyroid gland is a matter of curiosity. COVID-19 affects many organs and systems[2]. Thyroid gland may also be among the organs affected by COVID-19.

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Coronaviruses are single-stranded RNA viruses with spikes on their surface. Coronaviruses are divided into four genotypes, i.e. alpha coronaviruses, beta coronaviruses, gamma coronaviruses, and delta coronaviruses[3]. Beta coronaviruses are of zoonotic origin and are highly pathogenic to humans. Severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS) were previously known viral pathogens. They were causing severe respiratory infections. SARS-CoV-2 was a new coronavirus. It caused a pandemic. It has been called COVID-19 since it emerged in 2019[3].

The angiotensin-converting enzyme 2 (ACE2) is the receptor for cellular entry of COVID-19. The mRNA encoding ACE2 is expressed in thyroid follicle

cells. This may make the thyroid gland a potential target for COVID-19[4].

Materials and Methods

With the onset of the COVID-19 epidemic, 69,000 patients who came to our hospital in the last 18 months and had the COVID-19 test were screened. Thyroid function tests of 500 patients with positive COVID-19 test and 1133 patients with negative COVID-19 test were compared. The chemiluminescent microparticle immune assay (CMIA) was used on an Architect i2000SR (Abbott, USA) device. Age, gender, thyrotropin hormone (TSH, μIU/mL), free triiodothyronine (fT3, pg/mL), free thyroxine (fT4, ng/dL), antithyroid peroxidase antibody (anti TPO, IU/mL) and antithyroglobulin antibody (anti TG, IU/mL) levels were recorded in COVID-19 patients. Cases with overt thyroid disease, heart failure, liver failure, kidney failure, or malignancy were excluded. Approval for the study was obtained from the Ethics Committee of the University Medical School.

Statistics

Data were analyzed with Windows compatible SPSS version 22. The level of statistical significance was set at $p<0.05$. The compliance of data with normal distribution was determined with the Kolmogorov Smirnov test. For the variables that did not show normal distribution, Mann-Whitney U test was used on comparison of the two groups (COVID-19 positive and COVID-19 negative).

Results

The levels of TSH (2.54±14.54 μIU/mL), fT3 (0.84±1.49 pg/mL), fT4 (0.99±0.42 ng/dL), anti TPO (140.04±276.55 IU/mL), and anti TG (16.31±22.99 IU/mL) recorded in COVID-19 positive patients were compared with those found in COVID-19 negative patients (TSH 1.90±8.22μIU/mL; fT3 0.78±1.60 pg/mL; fT4 0.99±0.42 ng/dL; anti TPO 122.55±263.39 IU/mL; and anti TG 56.25±185.64 IU/mL). There was no significant difference between COVID-19 positive patients and COVID-19 negative cases in terms of thyroid functions (TSH, p=0.66; fT3, p=0.24; fT4, p=0.93; anti TPO, p=0.52; anti TG, p=0.39) (Table 1).

Discussion

The World Health Organization declared the COVID-19 epidemic as a pandemic in March 2020[2,5] because COVID-19 was spreading rapidly and uncontrollably, affecting all organs and systems of the body[2]. The first publication on the effect of COVID-19 on thyroid gland was a case of subacute thyroiditis. Subacute thyroiditis regressed within 2 weeks with prednisone treatment[2]. Mattar *et al.*[6], Brancatella *et al.*[7], Rugger *et al.*[8], Campos-Barrera *et al.*[9], Chakraborty *et al.*[10], Brancatella *et al.*[11], San Juan *et al.*[12], and Seyed Rasuli *et al.*[13] have reported cases of subacute thyroiditis caused by COVID-19 in the last 1.5 years. After steroid treatment, the patient thyroid function returned to normal. In a study conducted in China, TSH and fT3 levels were found to be low in proportion to the severity of the disease in patients with COVID-19[2,14]. This was consistent with the 'sick euthyroid syndrome'. Zou *et al.* showed that in patients with COVID-19 diagnosed with euthyroid sick syndrome, this condition was related to the severity of COVID-19[15]. Wang *et al.* detected common abnormalities in thyroid tests, especially in patients with severe COVID-19, and associated this with the euthyroid sick syndrome[16]. Malik *et al.* found low TSH and T3 in patients with COVID-19.

Table 1. Thyroid function in COVID-19 positive and negative patients

	COVID-19 positive Mean ± SD	COVID 19-negative Mean ± SD	p*
TSH (μIU/mL)	2.54±14.54	1.90±8.22	0.66
fT3 (pg/mL)	0.84±1.49	0.78±1.60	0.24
fT4 (ng/dL)	0.99±0.42	0.99±0.42	0.93
Anti TPO (IU/mL)	140.04±276.55	122.55±263.39	0.52
Anti TG (IU/mL)	16.31±22.99	56.25±185.64	0.39

SD = standard deviation; p*=Mann Whitney U test; TSH = thyroid-stimulating hormone; fT3 = free triiodothyronine; fT4 = free thyroxine; anti TPO = antithyroid peroxidase antibody; anti TG = antithyroglobulin antibody

Thyroid function returned to normal when all patients recovered from the coronavirus disease[17]. Baldelli *et al*. did a similar study. It was indicative of the euthyroid sick syndrome[18]. In a study conducted in England, thyrotoxicosis was not observed in any of the patients with COVID-19[19]. Although minor deviations were observed in thyroid function during the course of the disease, thyroid function returned to the initial level after recovery[19]. Mateu-Salat *et al*. presented 2 cases of Graves' disease occurring after COVID-19[20]. Lui *et al*. also drew attention to the increase in thyroid autoantibodies in patients with COVID-19, detected thyroid dysfunction in 15% of patients who had mild to moderate COVID-19[21]. They even emphasize that low fT3 is important in determining the prognosis[21]. Zhang *et al*. grouped patients with COVID-19 as those with and without thyroid dysfunction. They claimed that patients with COVID-19 with thyroid dysfunction had worse clinical outcomes[22]. Lang *et al*. found low TSH and fT3 in patients who died from COVID-19, and associated this with increased mortality[23]. A similar study was done by Gao *et al*. Free T3 was significantly lower in patients who had severe COVID-19 compared to those who did not have severe COVID-19. This was significant in predicting mortality[24]. Van Gerwen *et al*. showed that the course of COVID-19 was not adversely affected in patients previously diagnosed with hypothyroidism and receiving treatment[25]. In a study by Sen *et al.*, there was no difference in thyroid function tests of patients who had mild, moderate or severe COVID-19[26]. Clarke *et al*. showed that patients maintained their thyroid function 3 months after contracting COVID-19[27]. Conditions such as subacute thyroiditis and sick euthyroid syndrome are clinical manifestations that occur in times of stress, make the patient condition more complicated and worsened, and increase the severity of primary disease. Therefore, it is not surprising that we encounter it during the course of COVID-19. This does not show that COVID-19 has permanently damaged thyroid gland. To avoid such confusion, we did not include in our study patients who had COVID-19 severe enough to require intensive care. In our study, thyroid function tests of COVID-19 positive and negative cases were analyzed regardless of the severity of the disease. There was no significant difference in TSH, fT3, fT4, anti TPO, and anti TG values between the two groups.

Conclusions

It is known that coronaviruses, which are the cause of COVID-19, attach to ACE2 receptors, enter the cell, and reproduce in the cells they have entered. The status of the ACE2 receptor in thyroid gland is directly proportional to the condition that this gland is affected by infection. New studies are needed on this subject. Therefore, we believe that our study can shed some light on this research. For now, it may be some consolation for us that the coronavirus disease, which affects almost all systems of the body, does not seem to affect thyroid function.

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Sažetak

FUNKCIJA ŠTITNJAČE U BOLESNIKA S COVID-19: RETROSPEKTIVNO ISTRAŽIVANJE

M. Öztürk

Cilj istraživanja bio je procijeniti utječe li COVID-19 na funkciju štitne žlijezde. Zasad je nepoznat utjecaj što ga COVID-19, koji se proširio po čitavom svijetu u posljednje dvije godine, ima na funkciju štitnjače. Kad je nastupila epidemija COVID-19 probirom je obuhvaćeno 69.000 bolesnika koji su došli u našu bolnicu tijekom 18 mjeseci, a imali su COVID-19. Testovi rada štitnjače provedeni su u 500 bolesnika pozitivnih na COVID-19 i uspoređeni s onima u 1133 bolesnika negativnih na COVID-19. Razine hormona izražene su kao srednja vrijednost ± standardna devijacija. Razine zabilježene u bolesnika pozitivnih na COVID-19 (tireotropin (TSH) 2,54±14,54 μIU/mL, slobodni trijodtironin (fT3) 0,84±1,49 pg/mL, slobodni tiroksin (fT4) 0,99±0,42 ng/dL, protutijela na tireoidnu peroksidazu (anti TPO) 140,04±276,55 IU/mL i protutijela na tireoglobulin (anti TG) 16,31±22,99 IU/mL) uspoređene su s onima izmjerenima kod bolesnika negativnih na COVID-19 (TSH 1,90±8,22 μIU/mL, fT3 0,78±1,60 pg/mL, fT4 0,99±0,42 ng/dL, anti TPO 122,55±263,39 IU/mL i anti TG 56,25±185,64 IU/mL). Nije bilo značajne razlike između bolesnika pozitivnih i negativnih na COVID-19 u funkciji štitnjače (TSH, p=0,66; fT3, p=0,24; fT4, p=0,93; anti TPO, p=0,52; i anti TG, p=0,39). Zasad se možemo donekle utješiti da se čini kako koronavirusna bolest koja zahvaća gotovo sve sustave u organizmu ne utječe na funkciju štitne žlijezde.

Ključne riječi: *COVID-19; Tireotropin; Slobodni trijodtironin; Slobodni tiroksin; Tireoidna peroksidaza; Tireoglobulin*