American Journal of
Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Research Article

Effect of Vitamin D Status on Thyroid Dysfunction in Patients with COVID-19

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To Cite This Article: *Marika Gamkrelidze, Tamar Goderidze and Nato durglishvili and Manana Machitidze. Effect of Vitamin D Status on Thyroid Dysfunction in Patients with COVID-19. Am J Biomed Sci & Res. 2023 18(6) AJBSR.MS.ID.002534,* DOI: 10.34297/AJBSR.2023.18.002534

Received: May 15, 2023; **Published:** May 24, 2023

Abstract

Aim/objective: Our study aimed to explore thyroid function in covid-19 patients and its correlation with vitamin D deficiency.

Background: Several studies have found that abnormal thyroid function was standard in patients with COVID-9 and that thyroid stimulating hormone (TSH) suppression was associated with higher levels of markers of inflammation. On the other hand, there is evidence that vitamin D may modulate the secretion of TSH.

Methods: Thyroid function was assessed in 195 unvaccinated COVID-19 patients (the target group) who presented with complaints suggesting disease of the thyroid gland by measuring serum free thyroxine (FT4), TSH, and anti-thyroid peroxidase antibody (TPO-Ab), and by cervical ultrasonography; the results were corresponding to subacute thyroiditis (SAT). Vitamin D status was determined at the initial presentation by measuring serum D (25-OH) levels. The target group was divided into three subgroups: I subgroup 58 patients with severe vitamin D deficiency (<12.5 ng/ml), II subgroup: 65 patients with moderate vitamin D deficiency (12.5-20 ng/ml), and III subgroup: 72 patients with vitamin D insufficiency (20-30 ng/ml). In addition, serum C-reactive protein (CRP) was measured in all the patients. The control group included 15 healthy individuals. After one month of treatment with corticosteroids, all the patients recovered from the symptoms of SAT.

Results and Conclusions: In all three subgroups, the mean plasma TSH concentrations and FT4 concentrations were lower in COVID-19 patients compared to controls. Significant positive correlations were recorded between serum 25(OH)D and TSH, and negative correlations - between serum 25(OH)D and TF4 in the I and II subgroups. TPO-Ab was increased significantly in all three subgroups compared to controls, with a significant negative correlation with serum 25(OH)D in the I and II subgroups. Our study confirmed that low vitamin D levels could be associated with an increased risk of developing SAT in COVId-19 patients. However, it did not find a relationship between vitamin D deficiency and the severity of Covid-19 related thyrotoxicosis, nor it revealed that the severity of vitamin D deficiency affects the outcome of SAT in COVId-19 patients.

Keywords: COVID-19, Vitamin D, Thyroid stimulating hormone (TSH), Free thyroxine (FT4), Anti-thyroid peroxidase antibody (TPO-Ab), Subacute thyroiditis (SAT).

Introduction

SARS-COV-2 is a novel coronavirus responsible for the COVID-19 global world pandemic that began in late 2019. COVID-19 infection can range from asymptomatic or mild presentation to critical illness and death. Severe COVID-19 disease can be manifested by acute respiratory distress syndrome (ARDS) and multiple organ failure [1-5]. During the previous coronavirus outbreak with SARS-COV, some studies reported changes in thyroid function [6-8]. SARS-CoV-2 uses angiotensin-converting-enzyme 2 (ACE2) receptor to infect the host cells [9,10]. The mRNA encoding for the ACE-2 receptor is highly expressed in thyroid follicular cells, making them a potential target for SARS-COV-2 [11]. According to autopsy studies, the virus can enter any endocrine gland, including the pituitary gland, thyroid, parathyroids, adrenals, pancreas, and testis, and lead to transitory or definitive dysfunction [12,13].

Studies of thyroid dysfunction in patients with COVID-19 showed that the thyroid gland and the entire hypothalamic-pi-

tuitary-thyroid (HPT) axis could be damaged by SARS-CoV-2. COVID-19-related thyroid disorders could manifest as thyrotoxicosis, hypothyroidism, and non-thyroidal illness syndrome. Serum levels of thyroid-stimulating hormone (TSH), triiodothyronine (T3), and thyroxine (T4) have been significantly lower in patients with SARS-CoV compared with those in the control group, irrespective of phases (acute and convalescent) [6,7]. A positive correlation was found between the severity of SARS and a decrease in T3 levels [6]. Some studies have reported cases of COVID-19-related primary hypothyroidism [14] and found that in-hospital mortality was higher in hypothyroid patients with COVID-19 compared to COVID-19 patients with euthyroidism.

The underlying mechanism of COVID19related endocrine dysfunctions may be inflammation, vessel damage, necrosis, and autoimmune processes [12,13,15]. Several studies found that abnormal thyroid function (particularly hyperthyroidism) is standard in patients with COVID-9 and that TSH suppression is associated with higher levels of markers of inflammation [14,16]. Data from minimally invasive autopsies from SARS-CoV-2 patients reported no abnormalities in the thyroid follicular morphology but displayed lymphocytic infiltration in the interstitium [17]. Though in some studies, follicular epithelial cell disruption was also noted. *Wei, et al.* reported that autopsies of SARS cases revealed follicular epithelial damage in the thyroid gland, with large numbers of cells exfoliated into the follicle and undergoing apoptosis, which indicates the destructive effect of the virus on the thyroid gland [18]. The studies suggest that these changes result from cytolytic recognition by T cells of viral and cellular antigens in thyrocytes [19]. Some data suggest a higher risk of autoimmune disorders (including autoimmune thyroiditis and Graves' disease) after recovery of SARSCoV2 patients from the cytokine storm [12]. It was observed that patients with acute coronavirus infection presenting with thyrotoxicosis had statistically significantly higher levels of interleukin6 (IL6) [16]. *Chen, et al.* [20] described central hypothyroidism (low FT4 with inappropriately low/normal TSH) secondary to SARS-CoV-2 injury at the hypothalamus or pituitary level of the HPT axis [20].

COVID-19-related non-thyroidal illness (NTI) syndrome with a reduced level of T3 in serum with decreased or inappropriately normal TSH levels has been reported by several studies [14,16,21,22]. This condition may result from either a direct effect of the SARS virus on the cells of the pituitary gland or an indirect effect caused by the hyperactivation of circulating pro-inflammatory cytokines due to the SARS infection. The NTIS is thought to be an adaptive physiological mechanism instead of true thyroid dysfunction. In the prolonged phase of critical illness, the NTIS has been shown to be significantly correlated with mortality. [22].

Thyroid hormone levels were found to have prognostic value for predicting the severity of COVID-19 disease [23,24]. Chen et al. reported that low serum levels of FT3, FT4, and TSH in COVID-19 patients during admission were positively correlated with the severity of COVID-19 disease and in-hospital mortality among the patients [1,25]. Low TSH levels were an independent risk factor for mortality in COVID-19 presenting with NTI [26]. *Gao, et al.* [27] found that FT3 was remarkably lower in severely ill COVID-19 patients compared to non-severely ill cases, and it strongly correlated with mortality. However, other thyroid functional characteristics, including FT4, TSH, and FT3/FT4, were not significantly linked [27]. One meta-analysis studied COVID-19 in patients with pre-existing thyroid disease, concluding that the presence of thyroid disease was positively correlated with a more severe degree of COVID-19 infection [28].

Vitamin D deficiency is a global health problem prevalent in both developed and developing countries and is determined by low serum 25-hydroxy vitamin D (< 25 nmol/l) levels. Vitamin D has been proven to play an essential role in the modulation of inflammatory pathways and immune responses [29-31]. Low vitamin D levels are significantly correlated with the development of autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, type 1 diabetes mellitus, multiple sclerosis, and autoimmune thyroid diseases [32,33]. Vitamin D displays its effect via intracellular vitamin D receptors (VDR), which are expressed in monocytes/macrophages, T cells, B cells, natural killer cells (NK), and dendritic cells (DCs) [34]. It modulates the phagocytic activity of macrophages and NK cells [30] and induces the microbicidal activity of phagocytes [35]. Low levels of vitamin D are associated with an increase in inflammatory cytokines, TNF-alpha, and IL6 [36,37]. Vitamin D suppresses the differentiation and maturation of antigen presenting DCs. The inhibitory effect of vitamin D on DC maturation and differentiation is very similar to that of glucocorticoids [38-40]. It downregulates T helper type 1 cell (Th1 cell) immune responses by inhibiting the production of pro-inflammatory cytokines such as IL-12, IFN-γ, IL-6, IL-8 TNF-α, and IL-9, and it upregulates the production of type 2 anti-inflammatory cytokines such as IL-4, IL-5, and IL-10 [41-43]. Vitamin D enhances the maturation of Th2 cells and the activation of T regulatory cells [44]. Vitamin D inhibits B lymphocyte proliferation and differentiation [45]. Taken together, the overall effect of vitamin D is anti-inflammatory and helps to prevent autoimmune development.

The ligand for the nuclear vitamin D receptor (VDR) is expressed in many tissues, including benign and malignant thyroid tissue. Low vitamin D receptor expression in papillary thyroid cancer positively correlates with low serum vitamin D levels and disease aggressiveness [46]. Vitamin D protects human thyrocytes from programmed cell death via increased B-cell lymphoma 2 (Bcl-2) expression [47]. Both Hashimoto thyroiditis and Grave's disease have been found to be associated with lower vitamin D levels [47-49]. The findings of several studies suggest that vitamin D has a crucial role in regulating the thyroid-destroying autoimmune antibodies and the pituitary hormone TSH [50,51]. Though some studies revealed no significant association between vitamin D and autoimmune thyroiditis [52,53].

In a retrospective cohort study, low vitamin D status was associated with increased COVID-19 risk [54]. COVID-19 patients with acute respiratory failure showed a high prevalence of hypovita-

minosis D. Severe vitamin D deficiency could be a marker of poor prognosis in COVID-19 patients and is linked to significantly higher mortality risk [15]. Vitamin D deficiency has been associated with a significantly increased risk of pneumonia and an increase in thrombotic episodes, frequently observed in COVID-19 [55]. Some studies suggest that vitamin D supplementation could provide clinical benefits in disease progression in patients with COVID-19, irrespective of its serum levels at the time of the disease onset. However, more extensive clinical trials are needed to confirm this [56].

Methodology

In this study, we aimed to explore the characteristics of thyroid function in covid-19 patients and its possible correlation with vitamin D deficiency. The study included 195 unvaccinated COVID-19 patients (the target group) with complaints suggesting disease of the thyroid gland (the patients were referred to Contractor clinics of the University of Georgia hospital with fever (more than 38°C), fatigue, palpitations, and anterior neck pain). The patients were admitted to the hospital from February 2020 to February 2021. The patient's physical examination revealed a painful, tender, slightly enlarged thyroid gland. Thyroid function was assessed at hospital admittance by measuring free thyroxine (FT4), thyroid stimulating hormone (TSH), and anti-thyroid peroxidase antibody (TPO-Ab) by chemiluminescent assay (Immulite 1000®, Diagnostic Product Corporation, LA, CA, USA). Cervical ultrasonography was performed for each patient. Ultrasonic examination of the thyroid gland showed enlarged thyroid, multiple diffuse hypoechoic areas, and decreased vascularity. These changes were suggestive of subacute thyroiditis (SAT). Vitamin D status was determined at the initial presentation by measuring serum D (25-OH) levels utilizing the spectrophotometric method. Serum C-reactive protein (CRP) was also measured in all the patients.

We categorized the patients into three clinically relevant subgroups based on the serum 25(OH)D levels: I subgroup, 58 patients with severe vitamin D deficiency (<12.5ng/ml) (29.7% of the target group), II subgroup included 65 patients with moderate vitamin D deficiency (12.5-20ng/ml) (33.3% of the target group), and III subgroup included 72 patients with vitamin D insufficiency (20-30ng/ml) (36.9% of the target group). The control group included 15 healthy individuals. None of the participants had a history of thyroid disease or was on drugs affecting thyroid function at enrolment. None received glucocorticoids, dopamine/dobutamine, or iodinated contrasts before blood sampling for thyroid function tests. They were not on vitamin D supplements. The follow-up tests were conducted two weeks after the first presentation.

Data were analyzed using SPSS 25.0 for Windows. Parameters were tested for normality with the Shapiro-Wilk test. Pearson correlation tests estimated correlations. All tests were 2-tailed, and a p-value of less than 0.05 was considered significant.

Results

(Table 1) The mean plasma TSH and FT4 concentrations in all three subgroups were lower in COVID-19 patients than in controls. Significant positive correlations were recorded between serum 25(OH)D and TSH, and negative correlations - between serum 25(OH)D and TF4 in the I and II subgroups. TPO-Ab was increased significantly in all three subgroups compared to controls, with a significant negative correlation with serum 25(OH)D in the I and II subgroups (Figures 1,2).

Table 1: The clinical data of the groups are presented.

Table N 1	25(OH)D	TSH	FT4	CRP	TPO-Ab	P*
I subgroup n=58	10,45±1,71 ng/ml	0,22±0.08 uIU/ml	23,62±1,22 pmol/L	52,81±23,71 mmol/L	109,83±58,78 IU/ml	P<0.001
II subgroup n=65	16,03±1,93 ng/ml	0,45±0.06 uIU/ml	23,14±0,97 pmol/L	60,31±18,73 mmol/L	115,91±50,25 IU/ml	P<0.001
III subgroup n=72	25,67±2,58 ng/ml	0,65±0.23 uIU/ml	24,11±0,87 pmol/L	65,1±14,53 mmol/L	113,71±52,15 IU/ml	P<0.001
Control group n=15	36,4±3,58 ng/ml	2,78±1.03 uIU/ml	15,12±1,37 pmol/L	3,9±0,73 mmol/L	24,11±4,23 IU/ml	

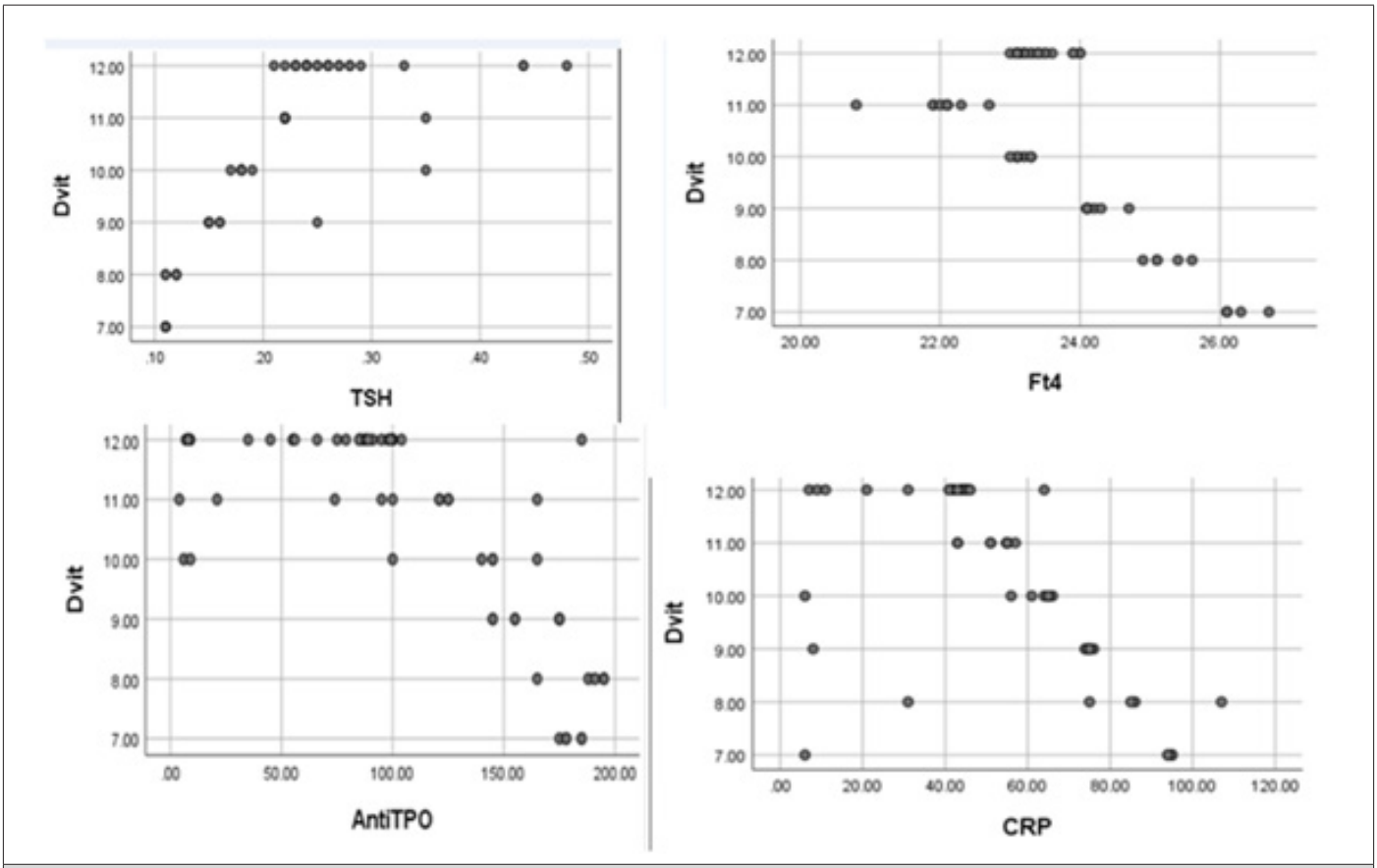

Figure 1: The first subgroup has correlations between the Vitamin D level and TSH, Ft4, TPO-Ab, and CRP.

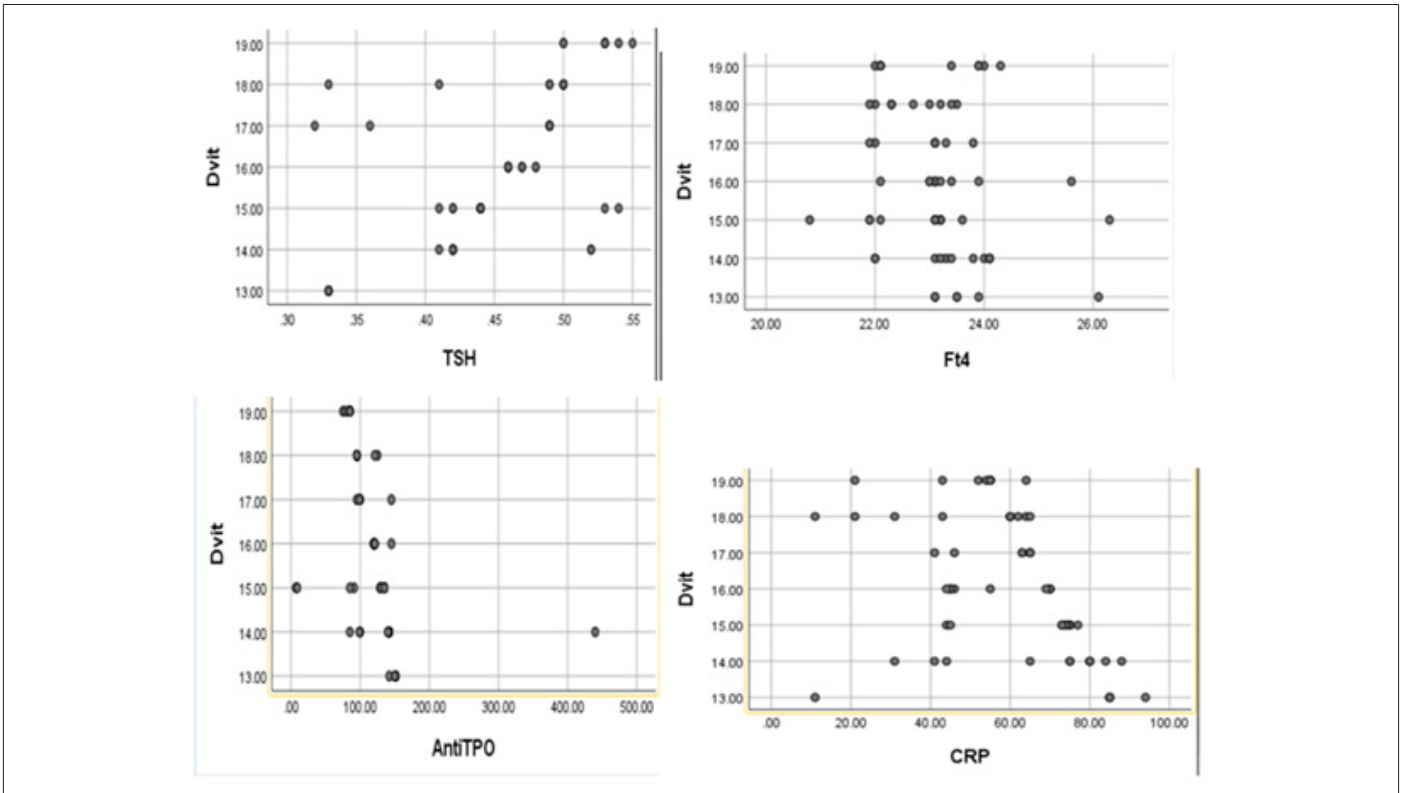

Figure 2: Correlations between the Vitamin D level and TSH, Ft4, TPO-Ab, and CRP in the second subgroup.

After the diagnosis of SAT, all the patients (except those with atypical thyroiditis) received corticosteroid treatment, while some were given ibuprofen for severe neck pain. After one month from the admittance, all the patients recovered from the symptoms.

Discussion

SARS-CoV-2 infection has been reported to have detrimental effects on multiple organ systems, including the hypothalamic-pituitary-thyroid (HPT) axis. Evidence suggests that thyroid function tests are altered during COVID-19, but the involved pathophysiological mechanisms still need to be clarified. Two mechanisms most likely might account for the changes in the thyroid gland observed in SARS-CoV-2 patients: An indirect effect via systemic inflammatory-immune responses to SARS-CoV-2 infection and a direct viral effect of SARS-CoV-2 virus.

SARS-CoV-2 could cause an increased immune response of T helper lymphocytes (Th1/Th17) that results in the activation of pro-inflammatory cytokines, including interleukins (IL1-IL6) and tumor necrosis factor α (TNFα). The release of large amounts of pro-inflammatory cytokines, described as cytokine storm syndrome, correlates with lung injury, multi-organ failure, and poor prognosis of severe COVID-19 cases. Increased immune responses of T helper lymphocytes and IL17-mediated cytokine signaling, associated with autoimmune thyroid disorders, have been detected in SARS-CoV-2 infections. [23]. Elevation of IL6 was detected in the acute phase, and it was significantly associated with thyrotoxicosis [48]. High IL6 is associated with low free triiodothyronine (FT3) [6].

Possible direct viral damage to the thyroid gland by the SARS-CoV-2 virus involves its interaction with ACE2 receptors. ACE2 is believed to play an essential role in the pathogenesis of coronavirus lung injury. SARS-CoV and SARS-CoV-2 use ACE2 receptors in the thyroid gland as well as in the kidneys, adrenal glands, adipose tissue, endothelium, pancreas, testes, ovaries, and human pituitary gland to invade the host cells [9,10,57]. SARS-CoV and SARS-CoV-2 use ACE2 receptors on thyroid cell membranes to enter the cell.

Chen et al. detected significantly lower TSH and TT3 in COVID-19 patients than in healthy control individuals and non-COVID-19 patients with pneumonia [58]. Moreover, the study found that the degree of the decrease in TSH and TT3 levels was positively correlated with the severity of the disease. TT4 level was not significantly different from the control group. After recovery without thyroid hormone replacement therapy, all the patients restored average values of thyroid hormones (TSH, FT3, FT4, TT3, and TT4).

Many studies reported subacute thyroiditis (SAT) associated with SARS-CoV-2 [59-62]. There have been reports of COVID-19-related SAT in patients who were not critically ill [63,64]. Also known as de Quervain thyroiditis, it is an inflammatory thyroid gland disease caused by a viral infection. It is typically characterized by three consecutive phases: 1. thyrotoxicosis during the first few months, 2. hypothyroidism for about three months, and 3. final restoration of euthyroidism [61]. SAT presents neck pain of varying degrees in the region of the thyroid gland, and a prodrome of generalized myalgias, low-grade fever, fatigue, and symptoms of upper respiratory inflammation characterizes it. In the initial phase, many patients present with clinical manifestations of mild to moderate thyrotoxicoses, such as tremors and palpitations [14]. The phase of thyrotoxicosis is usually followed by a phase of (transient) hypothyroidism with low free T4 and high thyroid stimulating hormone (TSH) levels. In most patients, euthyroid status is restored within 6-12 months. However, persistent hypothyroidism is observed in 10-15% of patients [65].

On SAT, thyrotoxicosis is caused by the release of preformed thyroid hormone into the circulation from the damaged thyroid follicular cells [66]. This causes transient thyrotoxicosis that most often self-resolves. Whether SAT represents a complication of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 is still unclear.

Suppressed serum TSH, with elevated free thyroxine concentrations in our target group patients with SAT, indicated thyrotoxicosis. Our results are consistent with the study of *Lania A, et al.* [16] reporting that thyrotoxicosis is common in patients with COVID-19 [16]. Thyrotoxicosis could result from SARS-CoV-2 directly infecting the thyroid gland. TSH suppression appears to be associated with the excessive release of inflammatory cytokines, including IL-6, characterizing COVID-19, as cytokines decrease TRH and TSH secretion [16,26]. Another potential mechanism might be a direct suppressing effect of SARS-CoV-2 on the hypothalamus and/or pituitary, similar to SARS-CoV-1 [8,18]. Thus, the results of the studies suggest that COVID-19, associated with systemic immune activation, may cause thyroid inflammation and result in hyperthyroidism. Though, we did not find lower TSH and higher FT4 plasma levels to be correlated with COVID-19 severity.

Most of the COVID-19 patients in our study had only mild-to-moderate fever and upper respiratory symptoms. However, nine patients (15,5%), eight patients (12%), and ten patients (13,9%) from the I, II, and III subgroups, respectively, were treated in intensive care units.

Neck pain was absent in 7 (12%), 5 (7.7%), and 9 (12.5%) patients in the I, II, and III subgroups, respectively. Therefore, their condition has been considered "atypical thyroiditis," which is mainly characterized by "T4 thyrotoxicosis" and which differs from the classic form of SAT by the absence of neck pain [51]). Though unlike *Muller, et al.* [51], we did not find a correlation between atypical thyroiditis and the illness severity in our study.

The time from diagnosis of COVID-19 infection to typical symptoms of SAT was 5 to 22 days. All the patients of the target group (except those with atypical thyroiditis) received treatment with corticosteroids, while some of them were given ibuprofen for severe neck pain. Clinical symptoms were mainly relieved within a few days. The laboratory indexes of SAT returned to normal levels after one month in all the patients, which indicated a good prognosis. These results corresponded with the outcomes of several previ-

ous studies that showed complete remission of SAT in most cases; the thyrotoxicosis was transient, self-limited, and did not require specific anti-thyroid drugs [14,67]. Corticosteroid treatment lasted one month for all the patients.

Anti-thyroid peroxidase antibody (TPO-Ab), which enhances pro-inflammatory cytokines, is a cause of autoimmune thyroid disease [68]. TPO-Ab positivity could be associated with severe COVID-19 pneumonia and a potential adverse prognostic factor for progression to severe respiratory failure (SRF) [69]. SARS-CoV-2 might trigger thyroid autoimmunity in the context of a generalized immune response. Thus, TPO-Ab positivity could indicate exaggerated immune system activation in COVID-19 patients and an increased risk of severe/complicated illness. It could also indicate SARS-CoV-2-induced thyroiditis with a transient anti-thyroid antibody rise. Some studies reported that serum 25(OH)D levels in euthyroid patients with Hashimoto's thyroiditis were inversely correlated with TPO-Ab levels. TPO-Ab levels were also significantly higher in vitamin D-deficient patients with Hashimoto's thyroiditis [67,70]. A study found the prevalence of TPO-Ab positivity in women with vitamin D deficiency and insufficiency compared to vitamin D-sufficient individuals. [17]. Though, other studies revealed no association between vitamin D deficiency and TPO-Ab positivity and proposed that Vitamin D deficiency does not increase the risk of autoimmune thyroid diseases [70-72]. In our study, TPO-Ab was significantly increased compared to the control group. It negatively correlated with vitamin D deficiency in the I and II subgroups.

There is evidence that vitamin D binds to specific binding sites and is uptaken by the thyrotrophin of the anterior pituitary, which indicates that vitamin D may modulate the secretion of TSH [73-75]. Studies have shown that a reciprocal relationship exists between serum TSH and vitamin D levels in hypothyroid subjects [46,76]. It was demonstrated that vitamin D supplementation among hypothyroid patients for 12 weeks improved serum TSH and calcium concentrations, but it did not change serum T3 and T4 levels [51].

In subacute thyroiditis patients, vitamin D levels were significantly lower than in the healthy control group. [77]. The same study revealed no relationship between vitamin D level and disease prognosis. However, it showed that vitamin D deficiency may increase the rate of respiratory tract infections (especially influenza, measles, adenovirus, and retroviruses) and SAT development. Administered vitamin D weekly in autoimmune thyroid disorders (AITD) significantly reduced TPOAb titers [70]. The study revealed no correlation between the severity of COVID-19 symptoms and vitamin D status.

Serum C-reactive protein (CRP) is a sensitive non-specific biomarker for inflammation; as an acute phase reactant, it has been found to be elevated in inflammatory thyroid disorders [65,78]. Acute phase reactants are valuable alternatives to erythrocyte sedimentation rate (ESR) due to significantly higher false positivity and false negativity associated with the latter [79]. Serum C-reactive protein concentration is a general non-specific marker of inflammation, subacute thyroiditis, and COVID-19 disease severity. Studies found significantly higher serum CRP levels amongst SAT patients than Graves' patients of similar age. CRP can be used as a diagnostic marker of SAT, especially when it may be confused with Graves' disease, another common cause of thyrotoxicosis. (Ibid). Our study revealed an inverse correlation between serum 25(OH) D levels and C-reactive protein (CRP), which is in harmony with the findings of other studies [80].

Conclusion

SAT could be considered an adaptive body response during acute illness or damage to the hypothalamic-pituitary-thyroid function caused by SARS-CoV-2. However, it becomes pathological if prolonged. Hence, there is a need to pay attention to thyroid function during the infection and follow-up period. Muller et al. suggest routine assessment of thyroid function in COVID-19 patients requiring high-intensity care, as they frequently present with thyrotoxicosis as a form of SARS-CoV-2-related SAT [80]. We did not find the presence of thyrotoxicosis on SAT to be correlated with the severity of Covid-19. However, there should be awareness of the potential development of thyroid dysfunction at SARS-CoV-2, which may be masked by the manifestation of Covid-19 symptoms by the respiratory system and by dexamethasone administration in the treatment of COVID-19 disease. Routine thyroid assays in hospitalized COVID-19 patients could be encouraged to detect thyroid dysfunction. The latter may develop in both the acute phase, during the infection, and the convalescence phase, post-COVID condition; therefore, thyroid function should be assessed again after recovery [81-96].

Our study confirmed that low vitamin D levels could be associated with an increased risk of developing SAT; The present study did not find a relationship between vitamin D deficiency and the severity of Covid-19 related thyrotoxicosis; nor it revealed that the severity of vitamin D deficiency affects the disease outcome in COVId-19 patients. More studies are needed to delineate further the pathophysiologic mechanisms of thyroid involvement in SARS-CoV-2 infection and the related role of vitamin D status. In addition, long-term studies of thyroid dysfunction in covid-19 patients would be informative.

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