ORIGINAL PAPER

doi: 10.5455/medarh.2022.76.12-16
MED ARCH. 2022 FEB; 76(1): 12-16
RECEIVED: FEB 02, 2022
ACCEPTED: FEB 25, 2022

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Hypothyroidism and Subclinical Hypothyroidism as a Consequence of COVID-19 Infection

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ABSTRACT

Background: Hypothyroidism occurs as a consequence of chronic autoimmune inflammation of the thyroid gland, which occurs due to the reduced function in the secretion of hormones FT3 and FT4 and requires replacement therapy for life. CoV-19 infection has shown many complications in all organic systems, during the acute phase of infection and in the post COVID period. **Objectives:** The aim of the study was a) to compare the frequency of patient visits for hypothyroidism and the average dose of levothyroxine in the SANASA polyclinic in the year before COVID pandemic, in the early 2019, with the frequency of patient visits during COVID infection in 2020 and 2021; b) to determine the incidence of hypothyroidism after the COVID 19 infection, the time of onset of hypothyroidism after acute phase of the disease, and the average dose of levothyroxine; and c) to monitor the incidence of subclinical hypothyroidism, which did not require substitution, before and after COVID 19 infection. **Methods:** In the SANASA polyclinic from the 2019 database we found 58 patients, at the age between 18-70 years, 53 women and 2 men with hypothyroidism and 2 female and 1 male patients with subclinical hypothyroidism. In 2020 there were a total of 89 patients, 73 women and 4 men with hypothyroidism, and 9 women and 3 men with subclinical hypothyroidism. In the 2021 there were 101 patients, 86 women and 7 men with hypothyroidism and 7 female and 1 male patients with subclinical hypothyroidism. **Results:** There was a significant difference in the number of patients with hypothyroidism and subclinical hypothyroidism during 2020 and 2021 in relation to 2019. The average dose of levothyroxine per patient did not differ statistically, comparing all three years, as well as comparing those who were ill, compared to patients who did not have COVID-19. There were diagnoses of post COVID subclinical hypothyroidism in 2020, as in 2021, with an average time of diagnosis of 2 months after infection for clinical hypothyroidism and 8 weeks for subclinical hypothyroidism. **Conclusion:** CoV-19 infection adversely affects thyroid tissue causing clinical hypothyroidism, requiring levothyroxine substitution as well as subclinical hypothyroidism which should be monitored.

Keywords: hypothyroidism, subclinical hypothyroidism, CoV-19 infection, levothyroxine.

1. BACKGROUND

Hypothyroidism is a chronic thyroid disease that requires lifetime replacement therapy due to reduced function in the secretion of T3 and T4 hormones. Primary hypothyroidism is due to changes of autoimmune nature in the thyroid gland, most often due to Hashimoto's thyroiditis, with a lack of hormones T3 and T4, especially their active free fractions FT3 and FT4, and TSH from the pituitary gland being consecutively high, with increased antibodies, especially AntiTPO (1). The link between COVID-19 and various autoimmune diseases affecting the thyroid gland and other systems in the body is still the subject of research. One of the possible mechanisms by which COVID-19 could trigger certain autoimmune disorders is the molecular mimicry with activation of immune pathways (2). Primary injury to the thyroid gland itself may play a key role in the pathogenesis of thyroid disorders in COVID-19 patients, too. Subacute thyroiditis, autoimmune thyroiditis and the atypical form of thyroiditis are complications of COVID-19. Thyroid hormone dysfunction affects the outcome by increasing mortality in critical illnesses like acute respiratory distress syndrome, which is a leading complication in COVID-19. Angiotensin-converting enzyme 2 is a membrane-bound enzyme, which is also expressed in the thyroid gland and the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) uses it for docking, entering as well as replication (3).

2. OBJECTIVE

The aims of the study were a) to compare the frequency of patient visits for hypothyroidism and the average dose of levothyroxine in the SANASA polyclinic in the year before COVID, in the early 2019 and during the COVID infection in 2020 and 2021; b) to determine the incidence of hypothyroidism after COVID 19 infection, the time of onset of hypothyroidism after the acute phase of the disease, and the average dose of levothyroxine; and c) to monitor the incidence of subclinical hypothyroidism, which did not require substitution, before and after the COVID-19 infection.

3. PATIENTS AND METHODS

Participants

The study was designed as a retrospective-prospective, and was conducted at the SANASA Polyclinic, with the consent of the director of the polyclinic and with the patients consent, in the period of January 2019 to December 2021. The study included 248 patients, 230 women and 18 men diagnosed with primary hypothyroidism and subclinical hypothyroidism, at the age between 18-70 years.

Procedure

Blood samples were taken from the cubital vein from all of the subjects, 248 of them, according to the standard procedure of blood collection, on an empty stomach (without any therapy before blood collection) at the SANASA polyclinic. Thyroid hormones FT3, FT4 and TSH and antibody-AntiTPO were determined. Patients who included levothyroxine replacement therapy underwent control of FT3, FT4, TSH after 8 weeks, due to levothyroxine dose titration.

Research methods

After the results of FT3, FT4, TSH, AntiTPO were obtained, the doctor talked with the patient, examined him, interpreted the results and determined the therapy. We extracted, from the anamnesis, the data on the duration of hypothyroidism and the doses of levothyroxine. For newly diagnosed hypothyroidism in 2020 and 2021 we asked if the patients had a CoV-19 infection. For those who had recovered from CoV-19 infection, we asked for the time period from overcoming the infection to diagnosing hypothyroidism and subclinical hypothyroidism.

Statistical analysis

SPSS17.0 for Windows statistical program was used to create statistical calculations. Arithmetic mean, standard deviation and t-test for small unpaired samples were used.

4. RESULTS

In the SANASA polyclinic, from the 2019 database, we found 58 patients with clinical and subclinical hypothyroidism. There were 53 women, average age of 55 years (+/- 4-8), and 2 men average age of 38 years (+/- 2-3) with hypothyroidism. There were 2 women at the age of 65 years (+/- 1-2) and 1 male patient at the age of 68 years with subclinical hypothyroidism (Table 1). Out of a total of 53 women, 7 of them were diagnosed with newly discovered hypothyroidism, and 46 of them with previous hypothyroidism, with an average dose of 125 micrograms in levothyroxine therapy. (+/- 25-50), and 2 men, with previously diagnosed hypothyroidism, at average levothyroxine dose 112.5 micrograms. (+12.5) (Table 2). Three cases of new found subclinical hypothyroidism were diagnosed, which did not require therapy, 2 women at the age of 30 (+/- 2) and one man at the age of 46 (Table 2).

There were a total of 89 patients with clinical and subclinical hypothyroidism in 2020. There were 73 women, average age of 47 (+/- 6-10) years and 4 men average age of 36 years (+/- 2-4) with hypothyroidism ($p < 0.001$) compared to 2019. Of the 73 women, there were 31 with newly diagnosed hypothyroidism ($p < 0.001$) compared with 2019, and 19 of them overcame CoV-19 infection (Table 1). The time of hypothyroidism detection after CoV-19 infection was 2 to 5 months, the average of 3 months (+/- 1-2) (Table 3). The average dose of levothyroxine was 125 micrograms. (+/- 25-50) and there was no statistically significant difference for those women who did not and who overcame CoV-19 infection, $p = 0.22$ (Table 2). Of the 4 men in total, 3 of them had newly diagnosed hypothyroidism and previous CoV-19 infection. The time of the hypothyroidism detection was, on average, 2 months (+/- 1) (Table 2). The average dose of levothyroxine was 100 (+/- 25) micrograms and did not differ significantly from those who did not have CoV-19 infection, $p = 0.02$ (Table 3). There were 9 newly diagnosed women, at average age of 35 years (+/- 3-8), who overcame CoV-19 infection and got subclinical hypothyroidism (Table 1). The time to diagnose subclinical hypothyroidism was on average 10 weeks (+/- 2) (Table 2). There were 3 men with subclinical hypothyroidism, at average age of 31 (+/- 1-2), with CoV-19 infection, and the time of diagnosis subclinical hypothyroidism was 8 (+/- 2-4) weeks and did not require levothyroxine substitution, but did require monitoring.

In 2021, there were total of 101 patients, 86 women, in the middle-age of 39 (+/- 4-8) and 7 men in the middle-age of 36 (+/- 4-6) with hypothyroidism, and there was a significant difference compared to 2020 ($p < 0.002$). At the group of 86 women, 37 of them had newly diagnosed hypothyroidism, which was a significantly higher number than in 2020 ($p < 0.002$) (Table 1). 24 of them had CoV-19 infection and the time of detection of hypothyroidism after CoV-19 infection was from 8 weeks to 6 months, on average of 3 months (+/- 1-2) (Table 2). The average dose of levothyroxine was 125 (+/- 25-50) micrograms, and there was no statistically significant difference in dose, for those who did not and who had CoV-19 infection ($p = 0.02$) (Table 3). At the group of 7 men, 5 of them were with newly diagnosed hypothyroidism and had a previous CoV-19 infection. The time of hypothyroidism detection was 2 months on average (+/- 1). The mean dose of levothyroxine was 125 (+/- 25) micrograms and there was not statistically significant difference compared to those without CoV-19, ($p = 0.02$). There were 7 women with subclinical hypothyroidism, in the 32 middle-age of (+/- 2-6), and 6 of them had CoV-19 infection. There was 1 man at the age of 29,

Diagnosis	2019.	2020.	p	2021.	p
Patients with hypothyroidism	55	77	P<0.001	93	P<0.002
Newly diagnosed hypothyroidism	7	35	P<0.001	44	P<0.002
Newly diagnosed hypothyroidism- post Cov-19	/	21	/	29	P<0,01
Patients with subclinical hypothyroidism	3	11	P<0.01	8	P=0.02
Newly diagnosed subclinical hypothyroidism	3	11	P<0.01	7	P=0.03
Newly diagnosed subclinical hypothyroidism- post Cov-19	/	11	/	7	P=0.03

Table 1. Number of patients with post COVID newly diagnosed subclinical and clinical hypothyroidism, by age

Time of diagnosis	2020.		2021.	
Gender	women	men	women	men
Post Cov-19 hypothyroidism	3 months (+/-1-2)	2 months (+/-1)	3 months (+/-1-2)	2 months (+/-1)
Post CoV-19 subclinical hypothyroidism	10 weeks (+/-2)	8 weeks (+/-2-4)	8 weeks (+/-2)	weeks

Table 2. Average time to diagnosis of clinical hypothyroidism, and subclinical hypothyroidism after CoV-19 infection

Dose of Levothyroxine (micrograms)	2019.		2020.		p	2021.		p
Gender	women	men	women	men		women	men	
Hypothyroidism	125 (+/-25-50)	112.5 (+/-12,5	125 (+/-25-50)	100 (+/-25)	P=0.22	125 (+/-25-50)	125 (+/-25)	P=0.24
Newly diagnosed hypothyroidism	125 (+/-25-50)	112,5 (+/-12.5-25)	125 (+/-12.5-25)	125 (+/-12.5-25)	P=0.22	125 (+/-25-50)	125 (+/-25)	P=0.22
Newly diagnosed hypothyroidism- post Cov-19	/	/	125 (+/-25-25)	125 (+/-12.5-25)	/	125 (+/-25-50)	125 (+/-25)	P=0.20

Table 3. Average dose of levothyroxine in clinical hypothyroidism, and newly diagnosed post CoV-19 hypothyroidism by age

with a diagnosis of subclinical hypothyroidism 6 weeks after CoV-19 infection. The time after CoV-19 infection and diagnosis of subclinical hypothyroidism was 8 (+/-2) weeks. All patients with subclinical hypothyroidism did not require levothyroxine substitution, but did require a follow-up (Table 3).

The total number of patients with clinical hypothyroidism in 2020 and 2021 was significantly higher than in 2019, (p <0.001), as well as the number of newly diagnosed hypothyroidism (p <0.001), partly because more patients decided to go to private clinics due to the epidemiological situation, and partly due to the CoV-19 infection and post-covid19 hypothyroidism. Patients with hypothyroidism in 2020 (women at average age of 47 years) and in 2021 (women at average age of 39 years) were younger than patients in 2019 (women at average age of 55 years). There were younger patients with subclinical hypothyroidism in 2020 (women with an average age of 35 years, men with an average age of 31 years) and 2021 (women at average age of 32 years, men at average age of 29 years) compared to 2019 (women at average age of 30 years, one male patient at the age of 46 years). The average TSH values of 12.5 (+/- 2.5-8.5) in patients who had CoV-19 infection did not differ significantly from the TSH values of 11.9 (+/- 2.0-9.5) of those who did not have CoV-19 infection. It was similar with the values of FT3, FT4 and AntiTPO (Table 1).

5. DISCUSSION

Data on the relationship between COVID-19 and thyroid have been emerging, and rapidly increasing since March 2020. The thyroid gland and the virus infection with its associated inflammatory-immune responses are known to be engaged in complex interplay. SARS-CoV-2 uses ACE2 combined with the transmembrane protease serine 2 (TMPRSS2) as the key molecular complex to infect the host cells. Interestingly, ACE2 and TMPRSS2 expression levels are high in the thyroid gland and more than in the lungs. The thyroid gland and the entire hypothalamic-pituitary-thyroid (HPT) axis could be relevant targets of damage by SARS-CoV-2. Specifically, COVID-19-related thyroid disorders include thyrotoxicosis, hypothyroidism, as well as nonthyroidal illness syndrome (4).

SARS-CoV-2 may induce thyroid dysfunction that is usually reversible, including subclinical and atypical thyroiditis. Patients with baseline thyroid diseases are not at higher risk of contracting or transmitting SARS-CoV-2, and baseline thyroid dysfunction does not foster a worse progression of COVID-19. However, it is unclear whether low levels of free triiodothyronine, observed in seriously ill patients with COVID-19, may worsen the disease's clinical progression and, consequently, whether the triiodothyronine supplementation could be a tool for reducing this burden. Glucocorticoids and heparin may affect thyroid hormone secretion and measurement respectively, leading to possible misdiagnosis of thyroid dysfunction in severe cases of COVID-19 (5).

In patients who were not previously diagnosed with any thyroid conditions, the scenario of COVID-19-related anomalies of the hypothalamus-pituitary-thyroid axes may include either: A process of central thyroid stimulating hormone (TSH) disturbances via virus-related hypophysitis; an atypical type of subacute thyroiditis which is connected to the virus spread or to excessive cytokine production including a destructive

process with irreversible damage of the gland or low T3 (triiodothyronine) syndrome (so called non-thyroid illness syndrome) which is not specifically related to the COVID-19 infection, but which is associated with a very severe illness status (6).

During the 2019 coronavirus disease pandemic (COVID-19), several papers reported endocrine and metabolic conditions that may be considered risk factors for new coronavirus infection (SARS-CoV-2) (7). Doctors know that several viruses can cause subacute thyroiditis (de Quervain thyroiditis) and clusters of this disease have been reported during the outbreak of a viral infection (8). De Quervain thyroiditis is thought to be of viral origin, with possible pathogens including the mumps virus, cytomegalovirus, enterovirus, and Coxsackie virus. Clinically, the condition is characterized by thyrotoxicosis with severe pain in the front of the neck (8).

The possible localization of SARS-CoV-2 at the level of the thyroid gland cannot be ruled out, given that previous studies have shown the presence of some viral particles in the follicular epithelium of patients with subacute thyroiditis (8). The thyroid gland is strictly connected to the structures of the upper respiratory tract, which is attacked by this virus at an early stage of infection. Thyrotoxicosis can worsen cardiovascular conditions, leading to tachyarrhythmias in some cases. To date, we know that some patients with COVID-19 mention ear pain (which can be a symptom of subacute thyroiditis), and one of the most common cardiovascular complications in these patients is tachyarrhythmia. A rapid assessment of free thyroid hormones and TSH would allow for early diagnosis and appropriate therapy, and help avoid more serious complications. While subacute thyroiditis often occurs a few weeks after a viral infection of the upper respiratory tract, it can be a late complication of SARS-CoV-2 infection. Thyroid function should also be monitored during follow-up of patients with acute COVID-19 infection. The data published so far have not considered the possibility of direct aggression of this virus on the adrenal gland in previously healthy subjects (9, 10). Timely screening of pituitary-adrenal axis function and identification of this condition could allow for adequate replacement therapy avoiding severe shock (11). In the presence of subacute thyroiditis or adrenal insufficiency, the corticosteroid therapy should be used to interrupt the release of large amounts of thyroid hormone and improve adrenal function, thus preventing clinical deterioration in these patients.

New evidence suggests that SARS-CoV-2 may act as a trigger for subacute thyroiditis (SAT). The link between COVID-19 and various autoimmune diseases affecting the thyroid gland and other systems in the body is still the subject of research (12-16). Three cases of autoimmune thyroid disease such as deep hypothyroidism, Graves' disease and subacute thyroiditis 6 weeks and 8 weeks after COVID-19 infection were identified. The time relationship between COVID-19 infection and the manifestations of autoimmune thyroid disease in the patients described here raises the question of the combined effects of COVID-19 on the immune system and the thyroid gland. All three patients were positive for COVID-19 infection prior to the diagnosis. The first patient was 38 years old, who developed hypothyroidism 6 weeks after COVID-19 infection, which was confirmed by laboratory findings: TSH 136 mIU/L (range 0.34–5.6), free T4 level 0.2 ng/dL (range 0.93–1.7). The second patient was 33 years old, who developed Graves' disease 8 weeks after COVID-19 infection, with TSH <0.01 mIU/L (ref. range 0.4–4.5), free T4 2.1 ng/dl (ref. range 0.8–1.8), total T3 216 ng/dl (ref. range 76–181), elevated TSI 309 (normal <140). The patient reacted positively to methimazole 10 mg in a few weeks. The third patient was a 41 year old healthy woman, who developed subacute thyroiditis 6 weeks after COVID-19 infection, with TSH 0.01 mIU/L and free T4 1.9 ng/dL. Three weeks later, she developed hypothyroidism, with a TSH of 67.04 mIU/L and a free T4 of 0.4 ng/dl. The temporal relationship between COVID-19 infections in the patients described here raises the question of the possible effects of COVID-19 on the immune system and thyroid gland (17, 18 and 19). In the 21 published work of subacute thyroiditis associated with SARS-CoV-2 infection, the mean age of patients was 40.0 ± 11.3 years with a higher prevalence in women (71.4%). The mean number of days between the onset of COVID-19 disease and the onset of SAT symptoms was 25.2 ± 10.1. Five patients had continuous COVID-19, while the infection receded in 16 patients before the onset of SAT symptoms. Temperature and neck pain were the most common ailments (81%). 94% of patients reported some type of hyperthyroidism symptoms, while laboratory findings in all patients (100%) confirmed this, with low TSH and high T3 and/or T4. Inflammatory markers were elevated in all cases reported by SE and CRP. All 21 cases (100%) had an ultrasound finding indicating SAT. Steroids and anti-inflammatory drugs were the mainstay of treatment, and all patients reported withdrawal symptoms; however, 5 patients (23.8%) were reported to have hypothyroid disease during follow-up. Extensive studies are needed to better understand the underlying pathogenic mechanisms, but current evidence suggests that health professionals must recognize the possibility of SAT in both current and completed COVID-19 infection to optimize treatment and care for patients (20). Based on the pathophysiology of SARS-CoV-2 pituitary-thyroid infection and review of recent articles, we suggest routine assessment of acute-stage thyroid function for patients with COVID-19 requiring high levels of intensive care, as they often develop concomitant thyrotoxicosis due to subacute thyroiditis associated with SARS-CoV-2, as well as during convalescence, to diagnose and adjust levothyroxine replacement therapy in patients with primary or central hypothyroidism. Given the still-present COVID-19 pandemic, future prospective studies are needed to increase epidemiological and clinical knowledge and optimize the treatment of thyroid disorders in patients with COVID-19 (21). We were interested in whether this increase in the number of thyroid diseases was associated with CoV-19 infection in our popu-

lation? In our work with patients during 2020, we have noticed an increase in newly diagnosed hypothyroidism and subclinical hypothyroidism. As CoV-19 infection continued in 2021 we planned to monitor the incidence of subclinical and clinical hypothyroidism, as well as the time of onset of the disease after CoV-19 infection with a dose of levothyroxine.

6. CONCLUSION

Based on a retrospective-prospective study we conducted over three years at the SANASA polyclinic, we came to the following conclusions: In 2020 and 2021, the total number of patients with hypothyroidism as well as the number of patients with subclinical hypothyroidism was higher than in 2019. Post CoV-19 infection hypothyroidism and subclinical hypothyroidism were significant in newly diagnosed cases. The average dose of levothyroxine replacement therapy did not differ significantly in post covid hypothyroidism compared to levothyroxine doses in patients who did not have CoV-19 infection. The time after COVID-19 infection and the diagnosis of hypothyroidism was average 3 months for women and 2 months for men, and for subclinical hypothyroidism the average time was 8-10 weeks for women and 6-8 weeks for men. After our research, we suggested to all patients who overcame the covid infection to control the hormonal status of the thyroid gland 2-3 months after the infection.

- **Patient Consent Form**: All participants were informed about subject of the study.
- **Author's Contribution**: A.B. gave substantial contributions to the conception or design of the work in acquisition, analysis, or interpretation of data for the work. Dž.H. had a part in article preparing for drafting or revising it critically for important intellectual content. A.Š. gave final approval of the original research and made substantial contribution in monitoring of the data compilation and evaluation of results.
- **Conflicts of interest**: There are no conflicts of interest.
- **Financial support and sponsorship**: None.

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