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Research Article

The COVID-19 Infection Impact on the Values of Thyroid Hormones

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ABSTRACT

The COVID-19 pandemic has proven an important test in the ability of the scientific medical world to effectively understand, describe and manage pathophysiology processes when dealing with aggressions from newly emerged pathogens. As time progresses, more and more studies are published reflecting the systemic impact of what was originally thought to be a respiratory infection. It appears that COVID-19 can directly affect the cardiovascular system, the gastrointestinal system (including the liver and the pancreas), the renal system, and the nervous and musculoskeletal systems. Furthermore, due to the abundance of ACE2 and TMPRSS2 receptors in the thyroid, required for the internalization of the virus, it seems likely that SARS-CoV-2 may affect the thyroid directly, as well as in the context of an increased systemic inflammatory response.

Keywords: COVID-19; Infection; Thyroid hormones; Pathophysiology

INTRODUCTION

Thyroid damage has been associated with acute conditions and several viral infections, among which, Hepatitis C Virus (HCV) occupies an important place [1-3]. HCV chronic infection is associated with a multitude of extra hepatic manifestations, either by inflammatory or autoimmune mechanisms [4-7] or even by direct infection of other organs, such as the thyroid. In fact, thyroid involvement is considered as the most frequent endocrine disorder associated with HCV chronic infection; Mechanisms responsible for thyroid damage are thyroid destruction induced by an increased inflammatory response resulting in autoimmune thyroiditis [8] or by direct HCV infection [9].

Important similarities between HCV and COVID 19 have been studied. Both viruses originally thought to have specific target-organs have proven to be systemic infections. The resemblance between the two viruses originates at a genomic lever, both being single-strained RNA viruses. Furthermore, exacerbation of the immune response, particularly from T helper 2 lymphocytes has been associated with HCV infection and the previous SARS infections, inducing immune-mediated tissue damage, also suspected in COVID-19 [10]. On a molecular level, both HCV and SARS-CoV-2 use ion channels (viroporins) as entry pathways into the cells; these viruses have structurally similar proteins, p7 and E, that bind to viroporins [11]. One of the most important ion channel impairments in both these infections is the damage of chloride channels, essential for several physiologic processes such as neuronal excitation, muscle contraction and trans-epithelial fluid transportation [12]. In the ongoing SARS-CoV-2 pandemic, hypochloremia has been associated with the diagnosis of COVID-19 and with increased illness severity [13].

MATERIALS AND METHODS

This study aims to determine the effects of COVID-19 infection on thyroid diseases associated with HCV chronic hepatitis. The

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study was approved by the local ethics committee. We routinely monitor patients with chronic HCV infection for every 6 months even after obtaining sustained virologic response after direct acting antiviral therapy, in accordance to current guidelines [14]. From April 2020 to October 2020, we performed a prospective observational study on patients with cured HCV infection and documented thyroid disease that became infected with SARS CoV-2.

Inclusion criteria for the current study were:

- History of HCV chronic hepatitis, with undetectable HCV-RNA at three months, after direct- acting antiviral therapy (either ombitasvir/ paritaprevir/ritonavir and dasabuvir or ledipasvir/ sofosbuvir);
- Documented thyroid disease (autoimmune thyroiditis, hyperthyroidism or hypothyroidism) with antibody and hormonal determination within 6 months before COVID-19 infection;
- Documented COVID-19 infection cured within a month before the first visit.

The exclusion criteria were:

- History of thyroid cancer associated to HCV chronic infection;
- Hepatitis B virus or HIV co-infection;
- Changes in thyroid substitution therapy or anti-thyroid drugs within 6 months of the first visit;
- Decompensated cirrhosis, solid or hematological neoplasia.

Demographic and medical data were retrieved from electronic source documents. Evaluation at one and three months after COVID-19 infection included serum determination of anti-thyroid antibodies, Anti-Thyroglobulin (anti-TG) and Anti-Thyroid Peroxidase (ATPO), Thyroid-Stimulating Hormone (TSH), free Thyroxin (fT4), free Triiodothyronine (fT3), and evaluation of thyroid medication, with dose adjustment if required. TSH, fT3, fT4 and anti-TG antibodies were determined using electro chemiluminescence assays (normal values between 0.27 and 4.2 μUI/mL for TSH, between 2.2 and 4.4 pg/ml for fT3, between 12 and 22 pmol/l for fT4 and less than 115 IU/ml for anti-TG) while ATPO were determined using chemiluminescence with micro particles (normal values less than 34 IU/ml).

Data was evaluated using statistical software SPSS. Numerical values were expressed as mean ± standard deviation. ANOVA test was performed in order to compare values at the three visits of evaluation, considering statistical significance at a p-value less than 0.05.

Within our study group, patients with evidence of thyroid hormone impairment were defined as either having hypothyroidism or hyperthyroidism (regardless of the underlying mechanism and regardless of the presence/absence of autoimmune antibodies), while all patients referred to as having "autoimmune thyroiditis" had euthyroidism. We only use the term autoimmune thyroiditis, if the patient had normal thyroid hormones and could not be classified in any of the two subgroups (hypothyroidism or hyperthyroidism).

RESULTS AND DISCUSSION

A total of 42 patients were included in the study, with a mean age of 52.67 years, female patients representing 64.28%. Baseline characteristics of the study group are presented in Table 1. Out of the 42 patients, 7 patients were receiving medication for thyroid disease: 5 patients with hypothyroidism were receiving levothyroxine (mean dose of 55.4 mcg daily) and 2 patients with hyperthyroidism were receiving methimazole (mean dose of 7.5 mg daily).

Study group	Baseline characteristics
Mean age	52.67 ± 21.08 years
Gender distribution	Female: 27 patients
	Male: 15 patients
Mean time-lapse after SVR	14.6 ± 7.2 months
Degree of liver fibrosis	F0-F2: 11 patients
	F3: 19 patients
	F4: 12 patients
Type of thyroid disease	Autoimmune thyroiditis: 37 patients
	Hyperthyroidism: 2 patients
	Hypothyroidism: 5 patients
ATPO (N<34 IU/ml)	With autoimmune thyroiditis (37 patients): 982.1 ± 426.6
	Without autoimmune thyroiditis (7 patients): 18.4 ± 7.2
Anti-TG (N<115 IU/ml)	With autoimmune thyroiditis (37 patients): 324.2 ± 132.21
	Without autoimmune thyroiditis (7 patients): 65.9 ± 21.7
TSH (N: 0.27-4.2 μUI/mL)	Euthyroidism: 3.87 ± 1.16
	Hypothyroidism (under levothyroxine): 2.14 ± 0.81
	Hyperthyroidism (under methimazole): 3.27 ± 1.03
fT3 (N: 2.2-4.4 pg/ml)	Euthyroidism: 2.11 ± 1.62
	Hypothyroidism (under levothyroxine): 3.91 ± 0.62
	Hyperthyroidism (under methimazole): 2.57 ± 1.31
fT4	Euthyroidism: 15.92 ± 3.53

(N: 12-22 pmol/l)	Hypothyroidism (under levothyroxine): 18.13 ± 6.22	
	Hyperthyroidism (under methimazole): 16.46 ± 3.13	

Table 1: Baseline characteristics of the study group.

36 patients had mild COVID-19 infection, while 6 patients had a moderate form of infection. The most frequent symptoms were: myalgia (34/42 patients), fatigue (31/42 patients), fever (25/42 patients), headache (21/42 patients) and digestive symptoms (23/42 patients).

At one month follow-up, we found an increase in anti-thyroid antibodies, in patients with autoimmune thyroiditis as well as patients with baseline normal values of antibodies. In patients with autoimmune thyroiditis, mean values of ATPO were 1187.7 ± 285 IU/ml (*versus* 982.1 ± 426.6 IU/ml at baseline, p=0.02) and mean values of anti-TG were 563.2 ± 193.1 IU/ml (*versus* 324.2 ± 132.21 IU/ml at baseline, p=0.01). In patients without autoimmune thyroiditis, ATPO levels increased to 123.7 ± 32.8 IU/ml (*versus* 18.4 ± 7.2 IU/ml at baseline, p<0.01) and anti-TG values increased to 134.8 ± 42.2 IU/ml (*versus* 65.9 ± 21.7 IU/ml at baseline, p=0.03). Furthermore, we found a significant decrease in TSH, fT3 and fT4 levels in patients with euthyroidism. The results are presented in Table 2. Treatment was discontinued in 2 patients receiving levothyroxine and one patient receiving methimazole.

Antibodies	Diseases	Baseline	One month	p value	Three months	p value
TSH (μ UI/mL)	Euthyroidism	3.87 ± 1.16	2.19 ± 1.12	0.02	2.28 ± 0.69	0.4
	Hypothyroidism	2.14 ± 0.81	1.56 ± 0.7	na	2.12 ± 0.43	na
	Hyperthyroidism	3.27 ± 1.03	2.67 ± 1.14	na	2.81 ± 0.92	na
fT3 (pg/ml)	Euthyroidism	2.11 ± 1.62	1.71 ± 0.46	0.04	1.92 ± 0.34	0.3
	Hypothyroidism	3.91 ± 0.62	3.12 ± 0.74	na	3.44 ± 0.68	na
	Hyperthyroidism	2.57 ± 1.31	2.09 ± 0.45	na	2.24 ± 0.18	na
fT4 (pmol/l)	Euthyroidism	15.92 ± 3.53	9.22 ± 2.18	0.01	11.57 ± 2.91	0.05
	Hypothyroidism	18.13 ± 6.22	13.48 ± 3.53	na	15.54 ± 4.45	na
	Hyperthyroidism	16.46 ± 3.13	12.17 ± 2.95	na	14.88 ± 2.79	na

Note: na=statistical analysis was not performed due to the low number of patients (2 patients with hyperthyroidism and 5 patients with hypothryoidism)

Table 2: Evolution of TSH, FT3 and FT4 in patients with euthyroidism and dysthyroidism after COVID-19 infection.

At 3 months follow-up, we noted a significant decrease in ATPO levels (84.13 ± 25.12 IU/ml *versus* 123.7 ± 32.8 IU/ml, p=0.02, in patients without autoimmune thyroiditis and 843 ± 205 IU/ml *versus* 1187.7 ± 285 IU/ml, p=0.01, in patients with autoimmune thyroiditis). Anti-TG levels were significantly lower in patients with autoimmune thyroiditis (408 ± 113.2 IU/ml *versus* 563.2 ± 193.1 IU/ml, p=0.01) and in patients without autoimmune thyroiditis (86.21 ± 18.48 IU/ml *versus* 134.8 ± 42.2 IU/ml, p=0.03). We also noted an increase in TSH, FT3 and FT3 levels, without statistical significance, except FT4 levels in patients with euthyroidism. Patients receiving levothyroxine or methimazole did not require dose adjustment or drug discontinuation. Also, the patients that discontinued medication (with either levothyroxine or methimazole) did not require any treatment restoration within three months of follow-up.

The present study shows that COVID-19 infection influences the thyroid function and the presence and levels of anti-thyroid antibodies in patients with pre-existent conditions associated with HCV chronic infection. It is a well-known fact that there is a thyroid response associated with systemic inflammation; a "low triiodothyronine" syndrome has been described in association with sepsis, potentially accompanied by low levels of T4 [15]. Moreover, septic shock may induce hypophyseal hypo perfusion, causing central hypothyroidism [16]. It has also been shown that decreased baseline thyroid function is associated with a poor prognosis in patients with sepsis or septic shock, independent of other prognostic factors [17]. Sepsis induced thyroid dysfunction appears to be a transient condition and may represent an adaptive mechanism, in order to protect the thyroid from cellular death caused by systemic inflammatory response syndrome. Furthermore, there are several pro-inflammatory cytokines (IL1β, IL6 and TNF-α) that have inhibitory effects on the thyroid function [18]. These mechanisms partially explain the results of our study, particularly the decrease in TSH, fT3 and fT4 levels shortly after COVID-19 infection.

Recent articles have tackled the varieties of thyroid disease associated with COVID-19 infection, regardless of a preexistent thyroid dysfunction or HCV infection. In a case series, it has been suggested that COVID-19 may induce sub-acute thyroiditis, developing as late as 36 days after COVID-19 typical symptoms [19]. The four patients report presented with thyrotoxicosis and received low-dose steroid therapy. Incidence of thyroiditis in intensive-care unit patients has also been evaluated in a prospective study comparing COVID-19 infected to non-infected patients [20]. This study also presents a high incidence of thyrotoxicosis in the COVID-19 subgroup without underlying thyroid disease. Another large single center retrospective study found a high incidence of thyroid dysfunction in 278 patients admitted to non-intensive care units for COVID-19 infection: Thyrotoxicosis in 20.2% and hypothyroidism in 5.2% [21]. On

the other hand, a retrospective study on 50 patients with COVID-19 infection without previous thyroid disease found low levels of TSH and total triiodothyronine, which normalized after the infection resolution [22]. Furthermore, a large multicenter trial including 621 patients reports lower values of TSH and FT4 in COVID-19 infected patients than in non-infected patients. Interestingly, none of the patients in this study presented overt thyrotoxicosis. [23]. A recent systematic review found a prevalence of thyroid dysfunction ranging from 13%-64% in total number of 1237 patients [24].

Inconclusive data also emerge when studying the impact of COVID-19 on patients with a history of thyroid illness. A report of two cases presents the recurrence of Graves' disease during infection, both after more than 2 years of stable thyroid function without medication [25]. An article regarding the relationship between thyroid cancer and COVID-19 shows an increased prevalence of the infection in this subgroup of patients [26]. The presence of thyroid cancer appears not to be an additional risk factor for mortality in COVID-19 [27].

To our knowledge, none of the articles published analyze the impact of COVID-19 on patients with HCV- induced thyroid disease, although this is a frequently encountered condition. A systematic review published in 2016 showed an increased prevalence of high anti-TG and ATPO antibodies and a 3 fold risk of hypothyroidism in patients with HCV chronic infection [28]. Modern interferon free therapies in HCV infection, associated with high cure rates and few adverse reactions, are expected to reduce the rate and severity of HCV extra hepatic manifestations [29,30]. It appears that HCV- associated thyroid disorders may persist after all oral antiviral therapy but less frequent and severe than after the classical interferon-based regimens [31-35].

Our study reveals that COVID-19 infection has a significant impact on the values of thyroid hormones and antibodies and may lead to medication adjustments in patients with known thyroid illness. However, the study has several limitations:

- Absence of patients with severe COVID-19 infection,
- Insufficient data regarding corticoid therapy received during infection and a small number of patients,
- Not permitting sufficient correlations to the stage of liver disease.

Our findings regarding COVID-19 consequences among HCV-infected patients with preexistent thyroid dysfunction are comparable with those described by other recent studies (that included patients without known HCV-induced thyroidal dysfunction) [19-24].

CONCLUSION

In conclusion, we highly recommend monitoring thyroid hormones and antibodies during COVID-19 infection in all patients, as uncovering the mechanisms responsible for thyroid disease may contribute to the better evaluation and management of these patients. Nevertheless, even during world medical crises such as the one we are enduring, it is important to keep in mind that patients require medical attention for a multitude of reasons and diseases, and medical care and monitoring should not be discontinued.

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