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RESEARCH LETTER

Thyroid substitution may be a risk factor for Covid-19

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The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that causes coronavirus disease 2019 (COVID-19) uses angiotensin-converting enzyme 2 (ACE2) and type II transmembrane serine protease (TMPRSS2) as a gateway to enter the cells [1, 2]. Although host target cells with ACE2 and TMPRSS2 on their surface are particularly present in the lung, these two proteins are also highly expressed in the thyroid [3]. Moreover, viral absorption involving the integrin αvβ3 appears to be determined by thyroid hormone T4 levels (like the one in hormone replacement therapy (HRT)) [4]. Therefore, we aimed to investigate the relationship between patients under HRT and the occurrence of COVID-19.

We carried out a case–control study that included all adults patients ($n = 180$) with confirmed SARS-CoV-2 RT-PCR admitted in the University Hospital of Rennes between 16th March and 1st May 2020. For each case, two controls ($n = 360$) admitted 1 year before the cases were randomly matched (frequency matching) by age (10 years classes) and sex. All data were collected in accordance with the French legislation. For all patients included, information on body mass index (BMI) and thyroid medication at the hospital entrance were collected using electronic medical files (Dxcare® Medasys®). We used a logistic regression to study the risk of SARS-CoV-2 in relation with HRT, with a priori adjustment on age, sex, and BMI. Results are presented as odds ratios (OR) with their 95% confidence intervals. A p value < 0.05 is considered as significant. Analyses were conducted with SAS 9.4.

A total of 540 patients were included in this study and the results are shown in the Table 1. Mean age in the COVID-19 and control groups were 62.6 (±17.3) and 62.5 (±17.5), respectively. A male preponderance was observed both in the COVID-19 group (58.9%) and the control group (59.4%). BMI in the COVID-19 and control group were 28.3 (±5.48) and 25.7 (±5.4), respectively. Regarding hypothyroidism etiology, the majority of patients had chronic autoimmune thyroiditis (65% in the COVID-19 group and 60.9% for the control group), followed by hypothyroidism secondary to thyroidectomy (30% in the COVID-19 group and 34.7% in the control group), and amiodarone-induced hypothyroidism (5% in the COVID-19 group and 4.3% in the control group). The number of patients treated with HRT was significantly higher in the COVID-19 group than in the control group: 11.1% vs. 6.3%, respectively (OR = 2.60 [1.26–5.38] ($p = 0.01$)).

Our results suggest that patients undergoing HRT may be at a higher risk for COVID-19. The presence of ACE2 and TMPRSS2 at high levels in thyroid and the specific role of integrin αvβ3 in SARS-CoV-2 entrance may explain this association [5]. Accordingly, T4 has been shown to modulate the affinity of integrin for other proteins, and may support cellular virus internalization [4]. Moreover, T4 regulates the expression of a panel of cytokine genes, some of which are components of the "cytokine storm" of viral infections [4]. There is also an intimate relationship between levels of T3 and proinflammatory activities [6]. Explanation for the results observed in our study may be consequently the hormonal status or the effect of exogenous T4 supplementation since

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Table 1 Baseline characteristics of COVID-19 patients ($n = 180$) and matched controls ($n = 360$) and results of the multivariate logistic regression

	Covid-19 patients ($n = 180$)	Controls ($n = 360$)	OR [IC 95%]	p value
Age, means (±Sd)	62.6 (±17.3)	62.5 (±17.5)	1.00 [0.99–1.01]	0.90
Sex				
Female	74 (41.1%)	146 (40.6%)	Ref	
Male	106 (58.9%)	214 (59.4%)	1.02 [0.66–1.57]	0.92
Body mass index (BMI) means (±Sd)	28.3 (±5.48)	25.7 (±5.4)	1.09 [1.05–1.13]	0.001
Thyroid hormones				
No	160 (88.9%)	337 (93.6%)	Ref	
Yes	20 (11.1%)	23 (6.4%)	2.60 [1.26–5.38]	0.01

unfortunately no hormonal status was available in our data base.

Moreover, a recent study reported a significant reduction in T4 and TSH during the hospitalization of COVID-19 patients who had no thyroid disorder on admission [7]; these imbalances returning to normal after recovery. These findings support that patients under HRT are at higher risk of thyroid imbalances. In accordance with Speer and Somogyi prospective clinical studies might be interesting in order to analyze the thyroid function as a predictive factor for SARS-CoV-2 development and progression to respiratory failure [8]. Although our results need to be replicated with FT3, FT3/FT4, and TSH concentrations measurement, they deserve special attention for the patients under HRT during the current COVID-19 disease pandemic as suggested by Lui et al. [9].

More importantly, as many countries in the world are still facing a wave of the pandemic, it might be relevant to consider thyroid patients as a priority group in vaccination campaigns.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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