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RESEARCH LETTER

Thyroid hormone treatment and SARS-CoV-2 infection

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It has recently been reported that the incidence of COVID-19 might be higher in people who are on thyroid hormone substitution treatment (THS) with levothyroxine [1]. The significance of such an association is obvious, given that levothyroxine is one of the most prescribed medications worldwide (currently the second most prescribed drug in the USA) [2]. Based on experimental evidence from animal models of coronavirus disease, it has been speculated that thyroid hormones propagate cellular internalization and replication of SARS-Cov-2 through interaction with plasma membrane integrins [3].

We examined the prevalence of THS in a cohort of hospitalized patients with COVID-19 and compared it with that of controls. We also examined whether there was an association of levothyroxine treatment with in-hospital mortality in the same cohort of hospitalized COVID-19 patients.

The COVID-19 cohort consisted of 170 consecutive admissions (median age 62.7 years, 57.6% male) to the COVID-19 Unit of the Department of Internal Medicine of a tertiary general hospital in Athens, Greece. The control group consisted of 170 randomly selected, age- and sex-matched non-COVID patients who had been admitted to the same hospital department during the year preceding the study. All data were fully anonymized and collected according to Greek legislation.

The results are summarized in Table 1. There was no statistically significant difference in the percentage of patients who were on levothyroxine between the COVID-19 and the control group (18.2% versus 16.5%, $p = 0.67$). Patients with COVID-19 who were on levothyroxine had a lower case fatality rate compared to those who were not on THS treatment although the difference was of marginal statistical significance (6.6% versus 20,9%, $p = 0.06$). Multivariate logistic regression analysis using death as dependent variable and age, sex and THS as independent variables showed that COVID-19 patients receiving levothyroxine had a lower risk of in-hospital death (Adjusted Odds Ratio 0.23 (95% confidence interval 0.05–1.17)).

Our results are at variance with those reported recently by a French group (Bacle et al.) who found that the percentage of hospitalized COVID-19 patients taking levothyroxine was almost double that of controls (11.1% versus 6.3%) [1]. The authors concluded that patients on THS might be at increased risk of contracting COVID-19. Although our sample size would not permit detection of small increases in COVID-19 hazard associated with THS, our study had sufficient statistical power (>80%) to detect an increase of the magnitude seen in the study by Bacle et al. However, it should be noted that the prevalence of THS in our control group was much higher compared to the control group of Bacle et al. (16.5% versus 6.3%, $p < 0.001$). There is evidence that THS is overused in the Greek population and it has been argued that up to 60% of subjects who receive levothyroxine have no thyroid disease [4]. Supposing that this also applies to the patients of our study, our results are more likely to reflect the impact of levothyroxine rather than that of thyroid disease on COVID-19 hazard.

In keeping with our results, population based studies utilizing insurance data and health system records have shown that being on THS is not a risk factor for acquiring SARS-CoV-2 infection [5–7]. Our finding of lower mortality in COVID-19 patients receiving levothyroxine, if confirmed in larger studies may lead to new therapeutic opportunities. There is experimental evidence that thyroid hormones play a lung-protective role by promoting alveolar fluid clearance and inhibiting fibrosis [8, 9]. Both alveolar fluid accumulation and pulmonary interstitial fibrosis are important drivers of mortality and morbidity in SARS-CoV-2 infection. Moreover, the non-thyroidal illness syndrome, characterized by decreased peripheral levels of thyroid hormones combined with lack of a reciprocal increase in

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Table 1 Frequency of levothyroxine (T4) treatment in COVID-19 patients and controls, and mortality of COVID-19 patients according to whether they were on levothyroxine.

	N	Mean age (Range)	On T4 *N* (%)	Mortality of COVID-19 on T4 (%)	Mortality of COVID-19 not on T4 (%)	
COVID-19 patients	170	62.3 (21–90)	31 (18.2)	6.5	20.9	$p = 0.06$
Male	98	60.9 (21–90)	8 (8.2)	0.0	21.1	$p = 0.35$
Female	72	64.1 (37–90)	23 (31.9)	8.7	20.4	$p = 0.21$
CONTROL patients	170	62.3 (23–90)	28 (16.5)			
Male	98	61.0 (23–90)	8 (8.2)			
Female	72	64.1 (37–90)	20 (27.8)			

TSH is often seen in COVID-19 patients and has been associated with adverse prognosis [10–13]. Against this background, the results of a clinical trial of inhaled triiodothyronine in patients with acute respiratory distress syndrome (ARDS) including COVID-ARDS are awaited with interest [14, 15].

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Ethics approval This is a retrospective observational study involving statistical analysis of fully anonymized patient data. Ethical approval was waived by our institution's Research and Ethics Committees.

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