Letters to the Editors

Serum thyroxine levels are associated with increased systolic pulmonary arterial pressure in systemic sclerosis

Sirs,

Pulmonary arterial hypertension (PAH) represents one of the most frequent vascular complications and the most important cause of death in Systemic Sclerosis (SSc) (1). Thyroid disorders are associated with both PAH and SSc independently (2-3). We therefore aimed to evaluate the relationship between serum thyroid hormones and systolic pulmonary arterial pressure (sPAP) in SSc patients, compared to healthy controls.

In this cross-sectional study, we included 41 women affected by SSc (mean age 59±10 yr) and 36 age-matched healthy subjects, as controls. Subjects who have been already diagnosed with thyroid diseases, on therapy with L-thyroxine or drugs affecting thyroid function were excluded from the study. Also, exclusion criteria were pre-existing cardiovascular diseases and any comorbid autoimmune, infectious or inflammatory disease. The Ethics Committee approved the study and all subjects provided informed consent. In each subject, we measured serum TSH and free thyroxine (FT4) concentrations. sPAP was determined by echocardiography, based on the peak velocity of the velocity of tricuspid regurgitation (4, 5). Although PAH is diagnosed according to right heart catheterisation findings, non-invasive echocardiography represents an efficacious and validated screening tool for PAH evaluation (5). Based on recent evidences of the literature concerning sPAP values and related mortality (6), an estimated sPAP >36 mmHg at baseline echocardiography was chosen as the cut-off value in our cohort.

Demographic, clinical, and biochemical features of study cohort are summarised in Table I. Among SSc patients, 20/41 (48%) had sPAP values ≥36 mmHg. In these patients serum FT4 was significantly higher than in those with sPAP values <36 mmHg (12.3 ± 2.3 pm/L *vs* 10.7±1.3 pm/L; p=0.014). Moreover, a direct correlation was observed between sPAP values and FT4 serum levels both in SSc (n=41; r^2=0.24, p=0.0011) and in healthy controls (n=36; r^2=0.11, p=0.0425). After excluding SSc patients with sPAP values <36 mmHg, the correlation remained highly significant (r^2=0.543, p=0.0015). At final analysis, using the average FT4 serum levels (12.4 pmol/L) of SSc patients with sPAP ≥36 mmHg, we found a significant Relative Risk of 1.98 of having a sPAP value ≥36 mmHg for SSc patients with a FT4 serum concentration ≥12.4 pmol/L.

A long-established association exists between thyroid diseases and PAH. Approximately half of the patients with PAH have concomitant autoimmune thyroid diseases, Hashimoto's thyroiditis being the most frequent, and this strong association links both thyroid diseases and PAH to an immune system dysregulation (3). Also, SSc patients show an increased incidence of autoimmune thyroid diseases (2), and the association between skin thickness and serum TSH levels also supports a pathogenic role of thyroid hormones in SSc (7). Our present findings strongly suggest that, apart from the autoimmune link, thyroxine may have direct effects on pulmonary vascular function and integrity. Indeed, thyroxine can act on the pulmonary vasculature at several levels (8-10). Also, thyroxine can act on its specific membrane binding site, the extra-cellular domain of integrin αvβ3, stimulating proliferative pathways and disordered angiogenesis (10).

Our study shows that higher FT4 levels, even within normal ranges, seem to be associated to pulmonary hypertension in SSc patients, and the two parameters are significantly correlated. Thyroxine could represent a central modulator of vascular function and integrity in SSc-PAH. At the least in current practice, thyroid function should be tested as a part of the clinical profiling of SSc patients, since the diagnosis of thyroid dysfunction and the related therapies may confer risk for PAH in SSc patients, and therefore worsen prognosis. Systematic surveillance for thyroid dysfunction in SSc patients may prevent the haemodynamic exacerbation of PAH and right heart failure.

Table I. Demographic, clinical and biochemical characteristics of SSc patients and healthy controls.

	dcSSc	lcSSc	SSc (lcSSc+dcSSc)	Healthy controls	$p^{\#}$
n	16	25	41	36	
Age (yr)	57.5 ± 11.6	60.1 ± 9	59.1 ± 10.1	57.4 ± 10	0.758
RP duration (yr)	11.2 ± 7	10.7 ± 8.8	11 ± 8	-	
Disease Duration (yr)	7.3 ± 5.2	8.3 ± 8.1	8 ± 7	-	
mRSS	21 ± 11	9 ± 7	13 ± 9	-	
FT4	11.9 ± 2	11.5 ± 2.1	11.7 ± 2.0	12.3 ± 2	0.219
TSH	1.6 ± 1	1.3 ± 0.7	1.3 ± 0.7	1.5 ± 0.9	0.288
sPAP (mmHg)	33.4 ± 9.5	33.7 ± 10.3	33.6 ± 10	14.5 ± 6.9	<0.0001
ANA+ (%)	100	100	100	0	
ATA+ (%)	31	16	22	0	
ACA+ (%)	6	48	32	0	

Data are mean ± SD, except auto-antibodies (ANA, ATA, ACA) which are expressed as percentages of patients who tested positive for each antibody.
dcSSc: diffuse cutaneous systemic sclerosis; lcSSc: limited cutaneous systemic sclerosis; SSc: systemic sclerosis; RP: Raynaud's phenomenon; mRSS: modified Rodnan skin score; ANA: antinuclear antibodies; ACA: anticentromere antibodies; ATA: antitopoisomerase 1 antibodies. #SSc (dcSSc + lcSSc) versus controls.

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