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Cardiac effects of L-thyroxine administration in borderline hypothyroidism

Stefano Mariotti [a,*], Sandra Zoncu [b], Francesca Pigliaru [a], Claudia Putzu [a], Valentina M. Cambuli [a], Sara Vargiu [b], Martino Deidda [b], Giuseppe Mercuro [b]

[a] *Endocrinology, Department of Medical Sciences, University of Cagliari, Sardinia, Italy*
[b] *Department of Cardiovascular and Neurological Sciences, University of Cagliari, Sardinia, Italy*

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Abstract

Objective: To investigate the clinical relevance of L-thyroxine (L-T_4) substitution therapy in borderline hypothyroidism.
Design: To assess whether and to what extent administration of L-T_4 is able to modify systolic and diastolic function in patients with subclinical hypothyroidism and in subjects with autoimmune thyroiditis and normal serum TSH.
Methods: We studied 26 patients with classical Hashimoto's thyroiditis [18 with increased serum TSH (>3 mU/ml — Group A), and 8 with normal serum TSH (<3 mU/ml) — Group B]; a third group (C) included 13 healthy controls. All subjects underwent Pulsed Wave Tissue Doppler Imaging (PWTDI) to accurately quantify the global and regional left ventricular function.
Results: In both groups A and B we confirmed a significant impairment of systolic ejection ($p<0.001$ and $p<0.05$, respectively), a delay in diastolic relaxation ($p<0.001$ and $p<0.05$, respectively) and a decrease in the compliance to the ventricular filling ($p<0.05$). Administration of 50 μg/day of L-T_4 produced a progressive reduction of serum TSH (within the normal range) and normalization of all PWTDI parameters, which began after 6 months and finished after 12 months.
Conclusion: Our data confirm previous evidence that subclinical hypothyroidism is associated with a cardiac dysfunction, even when this is very mild (*i.e.* with serum TSH still comprised in the normal range), and show that these abnormalities are reversible with L-T_4 replacement therapy.

Keywords: Cardiac function; PWDTI; Hypothyroidism; L-thyroxine

1. Introduction

Subclinical hypothyroidism is a frequent condition defined by elevated TSH secretion in the presence of normal concentrations of circulating thyroid hormones [1–3]. It is associated with several mild cardiac abnormalities, such as impairment of left ventricular diastolic function at rest and of systolic function on effort [4–7]. In a recent study, we confirmed the presence of a diastolic dysfunction in patients with subclinical hypothyroidism and provided further evidence of impairment of systolic function in mild thyroid failure, also at rest [8]. Moreover, in the same investigation we demonstrated that a slight impairment in both systolic and diastolic function is also detectable in patients with euthyroid autoimmune thyroiditis and a serum TSH still comprised within the normal range [8]. Aim of the present study was to assess the effect of L-thyroxine (L-T_4) administration on cardiac function as compared to baseline in patients with borderline hypothyroidism. For this purpose, we used Pulsed Wave Tissue Doppler Imaging (PWTDI), an extremely sensitive technique in assessing the effects of subtle thyroid failure on heart contractility [8].

2. Subjects and methods

2.1. Study population

We studied 26 consecutive patients (25 females, 1 male) with Hashimoto's thyroiditis (for the diagnostic criteria, see

* Corresponding author. Endocrinology, Department of Medical Sciences, University of Cagliari, S.S. 554, bivio di Sestu, 09042 Monserrato (Cagliari), Sardinia, Italy. Tel.: +39 70 5109 6430; fax: +39 70 5109.
E-mail address: mariotti@pacs.unica.it (S. Mariotti).

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below [9,10]) seen at the outpatient Endocrinology Clinic of Cagliari University Hospital. Eighteen of them had subclinical hypothyroidism with increased (>3 μU/ml) serum TSH (5.69±2.16 μU/ml, range 3.51–10.7 μU/ml; Group A), and 8 had normal (<3 μU/ml) serum TSH (2.53±0.35 μU/ml, 1.43–2.89 μU/ml; Group B). Serum free-T_3 (FT_3) concentration was within the normal range in both groups. A third group included thirteen healthy age- and sex-matched euthyroid controls (12 females, 1 male), randomly selected from subjects evaluated in our outpatient Endocrinology Service with no clinical, echographic or laboratory evidence of thyroid dysfunction. Controls were studied only once, in order to obtain standard reference values for any cardiac parameter evaluated. None of the patients or control subjects was affected by cardiovascular risk factors, namely diabetes, hypertension, dyslipidemia and cigarette smoking. The basal features of patients and controls are reported in Table 1. No significant differences were observed among the groups in heart rate, blood pressure and serum FT_3 concentration. Mean serum free-T_4 (FT_4) concentration was significantly lower in patients belonging to Group A as compared to Group B and controls ($p<0.001$). Mean serum TSH was significantly increased in patients of Group A when compared to Group B ($p<0.01$). Although individual serum TSH concentration in patients of Group B was comprised within the normal range, the mean was significantly higher when compared with control subjects ($p<0.01$).

2.2. Study protocol

The Ethical Committee of our University approved the present study, and informed written consent was obtained from all subjects. Participants were familiarized with instrumentation and medical environment of echocardiographic laboratory before testing. All subjects underwent physical examination, a complete M-Mode, 2D, spectral- and color-Doppler and PWTDI study. Patients from groups A and B were studied at baseline and after 6 and 12 months of therapy with a fixed dose of L-T_4 (50 μg/die).

Table 1
Biophysical characteristics, cardiovascular measurements and hormonal data of patients and controls

	Patients		Controls ($n=13$)
	Group A	Group B	
	TSH>3 mU/l	TSH<3 mU/l	
	($n=18$)	($n=8$)	
Age (years)	42.0±8.9	39.0±10.0	39.0±8.2
Male/female	1/17	0/8	1/12
Weight (kg)	65.3±10.0	60±7.9	62.1±11.4
Height (cm)	158.8±5.2	162.2±5.2	162.6±10.5
BMI (kg/m2)	25.9±4.1	23.0±3.1	23.5±3.7
HR (bpm)	70.5±9.7	74.0±14.1	76.2±11.6
SBP (mmHg)	129.2±12.1	125.0±9.3	125.2±7.1
DBP (mmHg)	80.7±7.9	75.0±4.1	77.8±7.1
FT3 (pg/ml)	3.19±0.46	3.08±0.39	3.5±0.2
FT4 (pg/ml)	8.38±1.89*f	11.43±1.08	10.2±1.7
TSH (mUI/l)	5.69±2.16§#	2.53±0.35#	1.2±0.5

*$p<0.001$ *vs* Group B; $fp<0.001$ *vs* controls; §$p<0.01$ *vs* Group B; #$p<0.01$ *vs* controls.
BMI: body mass index; DBP: diastolic blood pressure; HR: heart rate; SBP: systolic blood pressure.

Table 2
Left ventricle morphological and functional 2D and Doppler echocardiographic indexes in patients and controls

	Baseline	L-T_4 50 μg 6 months	L-T_4 50 μg 12 months	Controls ($n=13$)
Group A (TSH>3 mU/l; n=18)				
LVMI (g/m^2)	81±11	88±14#	90±11# *	81±12
EF (%)	62±5	64±4	64±3	66±6
E_m (cm/s)	61±13*	64±13	67±13	70±10
A_m (cm/s)	59±10	63±14*	64±14*	53±11
E_m/A_m	1.0±0.2*	1.0±0.3*	1.1±0.3*	1.4±0.3
IVRT (ms)	87±11	82±8	81±6#	84±10
Group B (TSH<3 mU/l; n=8)				
LVMI (g/m2)	89±9	86±10	88±9	81±12
EF (%)	63±3	66±3	67±2	66±6
E_m (cm/s)	65±12	74±12	74±12	70±10
A_m (cm/s)	57±16	63±12	63±12	53±11
E_m/A_m	1.2±0.4	1.2±0.1	1.2±0.2	1.4±0.3
IVRT (ms)	88±10	84±10	82±5 #	84±10

*$p<0.05$, *vs* controls; #$p<0.05$ *vs* baseline.
A_m: mitral late diastolic peak velocity; EF: ejection fraction; E_m: mitral early diastolic peak velocity; IVRT: isovolumic relaxation time; LVMI: left ventricle mass index.

2.3. Doppler echocardiography

Recordings were performed by using a 2.5-MHz transducer. Left ventricular mass (LVM), LVM index (LVMI) and ejection fraction (EF) were calculated by conventional methods [11,12]. Pulsed Doppler transmitral flow velocities were recorded from 4-chamber apical view, with the sample volume placed at the level of the mitral valve leaflet tips. Early (E_m) and late (A_m) diastolic velocities of transmitral flow were measured and E_m/A_m ratio was derived. Isovolumic relaxation time (IVRT) was measured as the time interval between the end of systolic output flow and transmitral E_m wave onset, by placing the sample volume between the outflow tract and the mitral valve.

2.4. PWTDI

For this procedure we used an ultrasound system equipped with TDI capabilities (SSA-380A; Toshiba Corp., Tochigi, Japan). PWTDI mapping of systolic and diastolic velocities was assessed in the mitral annulus, with subjects in the left lateral decubitus position. By means of a 4-chamber apical view, a 3-mm sample volume was placed at level of both basal lateral and infero-septal mitral annulus, with the ultrasonic Doppler beam in a position as parallel as possible