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Original Article

Follow-up of congenital heart disease patients with subclinical hypothyroidism

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Abstract *Introduction:* Subclinical hypothyroidism or mild thyroid failure is a common problem in patients without known thyroid disease. *Methods:* Demographic and analytical data were collected in 309, of which 181 were male and 128 were female, congenital heart disease (CHD) patients. CHD patients with thyroid-stimulating hormone above 5.5 mIU/L were also followed up from an analytical point of view to determine changes in serum glucose, cholesterol, N-terminal pro b-type natriuretic peptide, and C-reactive protein concentrations. *Results:* Of the CHD patients, 35 (11.3%) showed thyroid-stimulating hormone concentration above 5.5 mIU/L. Of them, 27 were followed up during 2.4 ± 1.2 years – 10 were under thyroid hormone replacement treatment, and 17 were not. Of the 27 patients (25.9%), 7 with subclinical hypothyroidism had positive anti-thyroid peroxidase, and 3 of them (42.8%) with **positive** anti-thyroid peroxidase had Down syndrome. Down syndrome and hypoxaemic CHD patients showed higher thyroid-stimulating hormone concentrations than the rest of the congenital patients ($p < 0.001$). No significant differences were observed in serum thyroxine, creatinine, uric acid, lipids, C-reactive protein, or N-terminal pro b-type natriuretic peptide concentrations before and after the follow-up in those CHD patients with thyroid-stimulating hormone above 5.5 mIU/L whether or not they received levothyroxine therapy. *Conclusions:* CHD patients with subclinical hypothyroidism showed no significant changes in serum thyroxine, cholesterol, C-reactive protein, or N-terminal pro b-type natriuretic peptide concentrations whether or not they were treated with thyroid hormone replacement therapy.

Keywords: Subclinical hypothyroidism; follow-up; CHD

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SUBCLINICAL HYPOTHYROIDISM, ALSO CALLED MILD thyroid failure, is diagnosed when peripheral thyroid hormone levels are within normal reference laboratory range, but serum thyroid-stimulating hormone levels are elevated – mildly elevated if thyroid-stimulating hormone concentration is between 5.5 and 10 mU/L, and marked elevated if thyroid-stimulating hormone elevation is above 10 mU/L.[1,2] Although subclinical thyroid disease is common in the general population, screening and treatment recommendations are still controversial.[3]

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Although the natural history of subclinical hypothyroidism depends on the underlying cause and the population studied, little is known about congenital heart disease (CHD) patients.[4] The purpose of the study is to analyse the prevalence of under-recognised hypothyroidism and its metabolic impact, if any, on CHD patients whether or not they received levothyroxine therapy.

Methods

Data were collected on all consecutive clinically stable CHD patients observed in our Adolescent and Adult Congenital Heart Disease Unit of the Complejo Hospitalario Universitario Insular-Materno Infantil of Gran Canaria, between January, 2006 and January, 2013. All patients included in the study, or their

parents, gave informed consent for routine serum analytical determinations. The inclusion criteria specified patients older than 14 years with a structural CHD. Meanwhile, exclusion criteria were patients who had an active inflammatory disease, had undergone cardiac surgery during the previous 6 months with the intention of avoiding the sick euthyroid syndrome, or did not give prior authorisation for analytical extraction. In those patients with thyroid-stimulating hormone levels above 5.5 mIU/L, a new serum analytical extraction was requested, after seeking informed consent, to determine thyroid-stimulating hormone, thyroxine, cholesterol, creatinine, glucose, uric acid, N-terminal pro b-type natriuretic peptide, C-reactive protein, and anti-thyroid peroxidase and anti-thyroglobulin antibody concentrations.

CHD was verified by echocardiography, cardiovascular magnetic resonance, and/or cardiac catheterisation. Patients were classified into diagnostic groups according to the underlying cardiac anatomy. Patients with more than one defect were classified according to the prevalent lesion from a clinical and/or haemodynamic point of view. An additional clinical subgroup of CHD patients was created according to whether or not the patient had hypoxaemia, and patients were classified as hypoxaemic when basal oxygen haemoglobin saturation was $\leqslant 92\%$. Subclinical hypothyroidism was established as a serum thyroid-stimulating hormone $\geqslant 5.5$ mIU/L.[1,2] In those CHD patients who were under thyroid replacement hormonal treatment, thyroid-stimulating hormone level determination was obtained before the beginning of the medical treatment. All the patients were Caucasian, and the protocol of the study was approved by the hospital's Ethics Committee.

Body weight and height were measured with the patients wearing light clothes and barefoot. Body mass index was determined according to the equation: weight/height^2 in kg/m^2. Blood samples were collected for subsequent laboratory analysis after an overnight fast of at least 10 hours. Serum analytical determinations were obtained for thyroid-stimulating hormone (normal values: 0.34–5.6 mIU/L), serum glucose (70–110 mg/dl), creatinine (0.84–1.25 mg/dl), uric acid (2.6–6.0 mg/dl), total cholesterol (20–220 mg/dl), low-density lipoprotein cholesterol (10–155 mg/dl), high-density lipoprotein cholesterol (45–75 mg/dl), C-reactive protein (0–0.5 mg/dl), and N-terminal pro b-type natriuretic peptide (0–125 pg/ml) concentrations. In addition, thyroxine (0.6–1.6 ng/dl), anti-thyroid peroxidase (0–9 IU/ml), and anti-thyroglobulin (0–115 IU/ml) antibodies were measured in those CHD patients who had a thyroid-stimulating hormone level higher than 5.5 mIU/L. Serum creatinine, uric acid, cholesterol, and C-reactive protein were measured by spectrophotometry with an Olympus AU 2700 equipment (Olympus Diagnostic, Hamburg, Germany), N-terminal pro b-type natriuretic peptide levels were determined by immunoassay using the Siemens Stratus CS Acute Care Diagnostic System (Siemens Healthcare Diagnostics, Inc., Newark, Delaware, United States of America), thyroid-stimulating hormone, thyroxine, and anti-thyroid peroxidase antibody concentrations were calculated with an UniCel DXi 800 imunoassay system (Beckman Coulter, Brea, California, United States of America), and anti-thyroglobulin antibody levels were measured using a Cobas e411 analyser (Roche Diagnostics, Sussex, United Kingdom). The low-density lipoprotein-cholesterol (in mg/dl) was determined with the Friedewald formula (low-density lipoprotein = total cholesterol – [high-density lipoprotein + triglycerides/5]). The diagnosis of pulmonary arterial hypertension was made if there was a resting mean pulmonary artery pressure of $\geqslant 25$ mmHg. Pulmonary artery pressure was calculated invasively by means of cardiac catheterisation or non-invasively using Doppler echocardiography.[5] Indication to start hormone replacement therapy was taken by the primary care physician or the endocrinologist according to thyroid-stimulating hormone concentration but without an unique action criterion.

Quantitative variables were expressed as mean $\pm$ standard deviation or median and 5th and 95th (5; 95) percentiles. Qualitative variables were expressed as counts (percentages). Possible associations between categorical variables were evaluated using the Pearson χ^2-test or the Student's t-test for continuous data. The non-parametric Mann-Whitney U-test was used to compare two independent samples when the assumption of normality or homogeneity of variance was not met. A related-samples Wilcoxon test was used to determine the relationship between variables obtained at different times. Serum thyroid-stimulating hormone concentrations, in the different subgroups of age, were evaluated using a univariate general linear model adjusted for a p-value level of 0.05. Data analysis was carried out using SPSS 20.0 (SPSS, Chicago, Illinois, United States of America).

Results

Of a total of 559 CHD patients followed up in our unit, 309 patients, of which 181 were male and 128 female, with ages ranging from 14 to 80 years (median 23.9 years) fulfilled the inclusion criteria. Table 1 shows the most frequent types of CHDs and the number of patients who did not undergo surgery, were operated in childhood or in adulthood, who underwent percutaneous treatment, and those with congenital heart abnormalities that had associated arterial hypoxaemia or Down syndrome. Of the CHD patients, 35 (11.3%) showed thyroid-stimulating

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Table 1. Types of congenital abnormalities in CHD patients.

Types of congenital malformations	Patients	Not operated	Cardiac surgery in childhood*	Cardiac surgery in adulthood**	Percutaneous treatment***	PAH	Hypoxia	Down Sd.
Ventricular septal defect	47 (15.2)	36	9	2	0	3	4	7
Atrial septal defect	38 (12.3)	21	6	2	9	4	3	3
Coarctation of the aorta	30 (9.7)	0	28	0	2	0	0	0
Pulmonary stenosis	28 (9.1)	11	10	1	6	1	0	0
Aortic stenosis or bicuspide aorta	26 (8.4)	19	2	2	3	0	0	0
Tetralogy of Fallot	25 (8.1)	1	22	2	0	0	1	0
Atrioventricular septal defect	23 (7.4)	4	18	1	0	2	3	16
Transposition of the great arteries	22 (7.1)	6	15	0	1	0	4	0
Ductus	7 (2.3)	4	1	0	2	0	0	0
Double outlet right ventricle	7 (2.3)	1	5	1	0	0	5	0
Pulmonary atresia	6 (1.9)	0	6	0	0	2	5	0
Subaortic membrane	6 (1.9)	2	3	1	0	0	0	0
Univentricular heart	5 (1.6)	0	5	0	0	2	3	0
Other cardiopathies	39 (12.6)	25	11	3	0	2	4	1
Total	309 (100)	130	141	15	23	16	32	27

PAH = pulmonary arterial hypertension; Sd. = syndrome

*Childhood age group: birth to year 14

**Adulthood age group if older than 14 years old

***Percutaneous treatment as the most important intervention in correcting the congenital heart defect. Other cardiopathies include the following CHDs: mitral valve prolapse or mitral regurgitation (five patients), Eibstein anomaly (4 patients), anomalous pulmonary venous connection (3 patients), tricuspid atresia (3 patients), aortic regurgitation (3 patients), truncus arteriosus (2 patients), hypertrophic cardiomiopathy (2 patients), and other different congenital heart abnormalities (17 patients). Within the group of CHD patients with associated hypoxemia, there were also, besides those included in the table, two patients with triscuspid atresia, one patient with Ebstein anomaly, and one patient with pulmonary arteriovenous fistulae. In the group of patients with atrioventricular septal defect, 11 were complete and 12 were partial. All patients with complete atrioventricular septal defect had Down syndrome, of whom three had associated hypoxemia. In the subgroup of patients with transposition of the great arteries, 14 had dextro- or D-looped transposition of the great arteries, and 8 had Levo- or L-looped transposition of the great arteries. Of the patients, three with dextro transposition of the great arteries and one patient with levo transposition of the great arteries had associated hypoxemia

hormone concentration above 5.5 mIU/L, and 9 of them (25.7%) had thyroid-stimulating hormone concentrations higher than 10 mIU/L. No significant differences were obtained in serum thyroid-stimulating hormone concentrations in the different subgroups of age ($p = 0.77$) (Fig 1).

Table 2 shows demographic, clinical, and analytical data in CHD patients with thyroid-stimulating hormone levels below and above 5.5 mIU/L. Down syndrome and hypoxaemic CHD patients showed higher thyroid-stimulating hormone concentrations than the rest of the congenital patients ($p < 0.001$). Table 3 shows CHD patients with subclinical hypothyroidism, specifying those who had associated hypoxaemia, Down syndrome, amiodarone treatment, or positive antibody titres. No statistical significances were observed between hypoxaemic and non-hypoxaemic CHD patients in relation to the number of patients under amiodarone treatment ($p = 0.57$) or with Down syndrome ($p = 0.59$). Of the 35 patients with subclinical hypothyroidism, 27 were followed up during a mean follow-up period of 2.4 ± 1.2 years – 10 patients were under thyroid hormone replacement treatment, and 17 patients were not – and 8 patients were excluded from the follow-up – 2 patients died, 3 patients lived outside the island, and 3 patients did not give their consent to participate in the follow-up. Of the 17 patients with an initial thyroid-stimulating hormone concentration > 5.5 mlU/L and without thyroxine treatment, 8 (47%) patients returned to normal thyroid-stimulating hormone values. However, among patients with an initial thyroid-stimulating hormone concentration above 10 mlU/L, none of them returned to normal levels.

Tables 4 and 5 summarise laboratory test results from CHD patients, with and without thyroid hormone replacement therapy, respectively, at the beginning and at the end of the study. Table 6 shows the demographic and laboratory test results from the nine CHD patients with subclinical hypothyroidism and a thyroid-stimulating hormone $\geqslant 10$ mIU/L. None of the untreated patients developed signs of hypothyroidism during their follow-up, and none of the patients under thyroxine treatment developed adverse effects in relation to replacement therapy.

Discussion

Mild thyroid failure is a common biochemical finding in 3–8% of the general population, although prevalence varies depending on the characteristics of the

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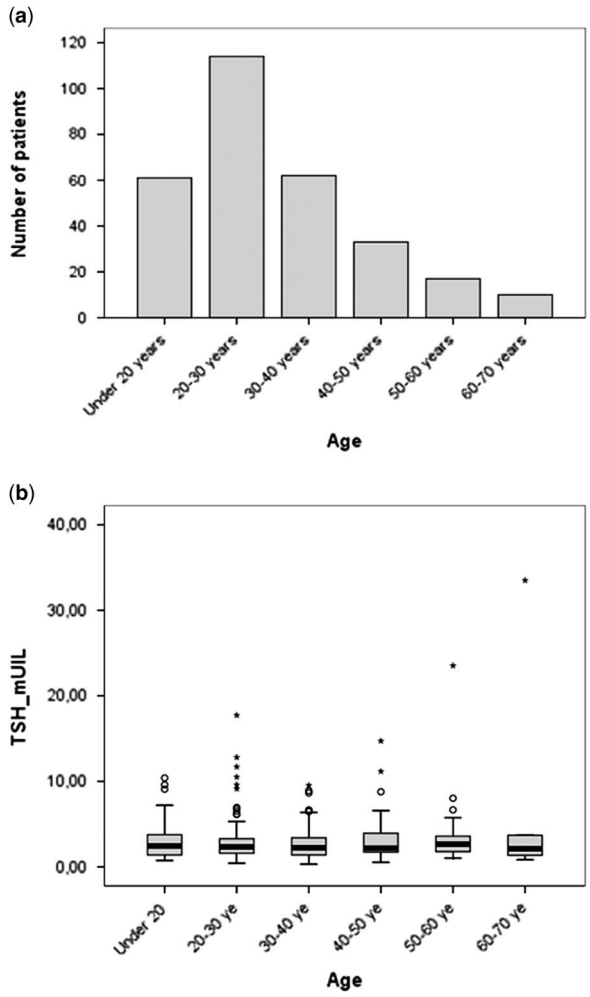

Figure 1.
*(**a** and **b**) Histogram showing the distribution of congenital heart disease patients by different age groups. Box-and-whisker diagram showing the distribution of thyroid-stimulating hormone (TSH) concentrations in the different age groups of CHD patients.*

populations studied and the upper limit set for thyroid-stimulating hormone measurements. However, we can state that subclinical hypothyroidism is especially high in populations with high iodine intake, older age groups, women, and Caucasians.[6]

The aetiology of subclinical hypothyroidism appears to be multifactorial, and autoimmune thyroiditis (Hashimoto's disease) and previous treatment for hyperthyroidism with radioactive iodine or surgery appear among the most common causes. However, other abnormalities such as radiotherapy to the head or neck, obesity, amiodarone treatment, or the existence of pulmonary arterial hypertension may favour its appearance. In relation to the latest, a significant percentage of patients with pulmonary arterial hypertension have concomitant thyroid dysfunction,[7] suggesting, hypothetically, that these patients had at some time experienced an autoimmune thyroiditis with participation of the immune system in the pathogenesis of pulmonary arterial hypertension.[8]

Autoimmune thyroiditis causes cellular damage and alters thyroid gland function by humoral and cell-mediated mechanisms. In fact, two antibodies, anti-thyroid peroxidase and anti-thyroglobulin, are mainly involved in this autoimmune response, increasing their concentrations over the years and can be associated with non-thyroid illnesses such as type 1 diabetes, rheumatoid arthritis, Addison's disease, pernicious anaemia, or when the patients have Down or Turner syndrome.[9,10]

It has been suggested that anti-thyroid peroxidase antibodies may be a risk factor for future thyroid dysfunction.[11] In this context, previous studies have shown an annual progression rate of subclinical to overt hypothyroidism of 2.6% if thyroid antibodies

Table 2. Demographic data and laboratory test results from CHD patients with thyroid-stimulating hormone < 5.5 mIU/L and < 5.5 mIU/L.

Variable	< 5.5 mIU/L (274)	≥ 5.5 mIU/L (35)	p
Age (years)	28.5 ± 14.9	30.3 ± 14.1	0.50
Gender (female)	106 (38.7)	22 (62.8)	0.01
Down syndrome	17 (6.2)	10 (28.6)	< 0.001
Hypoxemic CHD patients	20 (7.3)	13 (37.1)	< 0.001
Pulmonary arterial hypertension	11 (4)	5 (14.2)	0.01
Body mass index (kg/m^2)	24.3 ± 5.4	27.3 ± 6.5	0.006
Serum uric acid (mg/dl)	5.2 (3.3; 8.1)	5.7 (3.6; 9.8)	0.02
Serum glucose (mg/dl)	93 (80; 115)	93 (81; 125)	0.52
Serum creatinine (mg/dl)	0.9 (0.6; 1.2)	1.0 (0.8; 1.4)	0.18
Total cholesterol (mg/dl)	163 ± 35	164 ± 46	0.84
High-density lipoprotein cholesterol (mg/dl)	49 ± 11	48 ± 10	0.64
Low-density lipoprotein cholesterol (mg/dl)	95 ± 29	94 ± 36	0.85
Tryglicerides (mg/dl)	84 (43; 190)	87 (42; 291)	0.07
C-reactive protein (mg/dl	0.15 (0.0; 1.3)	0.26 (0.5; 1.6)	0.005

Patients included in the statistical analysis had 30 or more years. Quantitative variables are expressed as mean ± standard deviation or median and 5th and 95th (5; 95) percentiles; qualitative variables are expressed as percentages of total

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Table 3. Types of CHDs in CHD patients with thyroid-stimulating hormone concentration ⩾ 5.5 mIU/L.

Type of congenital malformations	Patients	Hypoxemia	Down syndrome	Amiodarone treatment	Anti-thyroid peroxidase antibodies*	Anti-thyroglobulin antibodies*	Hormone replacement therapy**
Atrial septal defect	3 (8.6)***	0	0	0	1	1	3
Ventricular septal defect	2 (5.7)	1	1	0	2	1	0
Ductus	3 (8.6)	0	0	0	1	0	1
Complete atrioventricular septal defect	7 (20.0)	3	7	0	2	0	2
Partial atrioventricular septal defect	1 (2.9)	0	1	0	0	0	1
Aortic stenosis	1 (2.9)	0	0	0	0	0	0
Coarctation of the aorta	2 (5.7)	0	0	0	0	0	0
D-Transposition of the great arteries	1 (2.9)	0	0	0	0	0	1
L-Transposition of the great arteries	1 (2.9)	0	0	1	0	0	0
Tetralogy of Fallot	1 (2.9)	1	0	0	0	0	0
Tricuspid atresia	1 (2.9)	1	0	0	0	0	0
Pulmonary atresia	3 (8.6)	2	0	0	0	0	0
Ebstein anomaly	1 (2.9)	1	0	0	0	0	0
Univentricular heart	2 (5.7)	1	0	1	0	0	1
Double outlet right ventricle	5 (14.3)	3	0	2	1	0	1
Aortic regurgitation	1 (2.9)	0	0	0	0	0	0
Total	35 (100)	13	9	4	7	2	10

*Number of patients with positive anti-thyroid peroxidase and/or anti-thyroglobulin antibodies. Antibody determination was performed in 27 of the 35 patients with subclinical hypothyroidism. Median and 5th and 95th (5; 95) percentiles of anti-thyroid peroxidase [1.4 (0.0; 720.3)] and anti-thyroglobulin [15.4 (0.0; 592.4)] antibody concentrations

**Patients under thyroid hormone replacement therapy (levothyroxine)

***Only one patient with atrial septal defect developed subclinical hypothyroidism in relation to a previous treatment for hyperthyroidism

Table 4. Laboratory test results from the 10 CHD patients with subclinical hypothyroidism and hormone replacement therapy.

Variable	Baseline	At follow-up	p
Serum thyroid-stimulating hormone (mIU/L)	12.2 (6.4; 33.5)	5.0 (2.1; 5.2)	0.008
Serum thyroxine (ng/dl)	1.0 ± 0.5	1.0 ± 0.2	0.65
Serum glucose (mg/dl)	99 (91; 212)	92 (80; 115)	0.12
Serum creatinine (mg/dl)	1.0 ± 0.1	0.9 ± 0.1	0.81
Serum uric acid (mg/dl)	5.5 (3.2; 7.0)	4.6 (3.9; 8.8)	0.10
Total cholesterol (mg/dl)	177 ± 50	174 ± 31	0.88
High-density lipoprotein cholesterol (mg/dl)	45 ± 17	47 ± 12	0.48
Low-density lipoprotein cholesterol (mg/dl)	105 ± 19	104 ± 18	1.00
Tryglicerides (mg/dl)	82 (47; 286)	92 (70; 218)	1.00
C-reactive protein (mg/dl)	0.1 (0.1; 1.4)	0.2 (0.0; 1.1)	0.91
N-terminal-pro-B-type natriuretic peptide (pg/ml)	94 (4; 657)	151 (41; 714)	0.08

Quantitative variables are expressed as mean ± standard deviation or median and 5th and 95th (5; 95) percentiles; qualitative variables are expressed as percentages of total. Thyroid replacement therapy treatment with oral levothryoxine (66.6 ± 38.6 μg every 24 hours)

were negative, but 4.3% if anti-thyroid peroxidase antibodies were present.[12] In our series, 7 of the 27 patients (25.9%) with subclinical hypothyroidism had positive anti-thyroid peroxidase, of whom 5 were under hormone replacement therapy, with no significant changes in thyroid-stimulating hormone concentrations during the follow-up, and 3 (42.8%) patients with positive anti-thyroid peroxidase had Down syndrome. Meanwhile, the remaining patients with Down syndrome had negative anti-thyroid peroxidase and anti-thyroglobulin antibodies. This may be because thyroid abnormalities in Down syndrome patients may be transient and related to inappropriate secretion of thyroid-stimulating hormone or thyroid insensitivity to thyroid-stimulating hormone, rather than to autoimmune thyroiditis.[10]

On the other hand, C-reactive protein is also known as a reliable marker of systemic inflammation and tissue damage. However, results of studies that investigated changes in C-reactive protein and thyroid dysfunction are contradictory. In this context, some authors have reported an increase in C-reactive protein concentrations in patients with subclinical hypothyroidism,[13] as seen in our series, whereas other authors have found no changes compared with control groups.[14] Nonetheless, what we could state was that treatment with thyroxine did not have any effect on C-reactive protein concentrations.

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Table 5. Laboratory test results from the 17 CHD patients with subclinical hypothyroidism and no hormone replacement therapy.

Variable	Baseline	At follow-up	p
Serum thyroid-stimulating hormone (mIU/L)	6.6 (5.1; 14.1)	5.9 (1.9; 16.1)	0.09
Serum thyroxine (ng/dl)	0.9 ± 1.2	1.0 ± 0.2	0.17
Serum glucose (mg/dl	91 (79; 127)	91 (71; 246)	0.03
Serum creatinine (mg/dl)	1.0 ± 0.2	1.0 ± 0.2	0.08
Serum uric acid (mg/dl)	5.7 (3.7; 9.9)	6.1 (3.8; 10.0)	0.61
Total cholesterol (mg/dl)	160 ± 53	164 ± 46	0.69
High-density lipoprotein-cholesterol (mg/dl)	46 ± 8	41 ± 9	0.02
Low-density lipoprotein-cholesterol (mg/dl)	84 ± 40	85 ± 35	0.50
Tryglicerides (mg/dl)	96 (40; 302)	89.0 (46; 603)	0.49
C-reactive protein (mg/dl)	0.3 (0.6; 1.9)	0.4 (0.2; 7.4)	0.72
N-terminal-pro-B-type natriuretic peptide (pg/ml)	383 (0; 9)	291 (13; 428)	0.80

Quantitative variables are expressed as mean ± standard deviation or median and 5th and 95th (5; 95) percentiles; qualitative variables are expressed as percentages of total. Ten out of 17 (58.8%) CHD patients persisted with thyroid-stimulating hormone concentrations above 5.5 mIU/L at the end of the follow-up

Table 6. Demographic and laboratory test results from the nine CHD patients with subclinical hypothyroidism and a TSH ⩾ 10 mIU/L.

Variables	TSH ⩾ 10 mIU/L		
Age (years)		37.1 ± 16.7	
Gender (female)		6 (67)	
Down syndrome		4 (44)	
Hypoxaemic CHD patients		2 (22)	
Pulmonary arterial hypertension		2 (22)	
Under hormone replacement treatment		7 (78)	
Follow-up (seven patients*)	**Baseline**	**At follow-up**	**p**
Serum thyroid-stimulating hormone (mIU/L)	14.7 (11.7; 33.5)	5.1 (2.5; 7.0)	0.01
Serum thyroxine (ng/dl)	0.7 ± 0.2	1.0 ± 0.2	0.65
Serum glucose (mg/dl)	97 (87; 107)	92 (79; 115)	0.35
Serum creatinine (mg/dl)	1.0 ± 0.1	1.0 ± 0.1	0.61
Serum uric acid (mg/dl)	5.6 (3.2; 6.8)	4.7 (3.9; 7.7)	0.20
Total cholesterol (mg/dl)	170 ± 51	165 ± 43	0.86
High-density lipoprotein cholesterol (mg/dl)	45 ± 13	45 ± 12	0.04
Low-density lipoprotein cholesterol (mg/dl)	95 ± 37	96 ± 31	0.85
Tryglicerides (mg/dl)	103 (47; 286)	97 (83; 218)	0.86
C-reactive protein (mg/dl)	0.1 (0.1; 1.5)	0.2 (0.0; 1.1)	0.49
N-terminal-pro-B-type natriuretic peptide (pg/ml)	63 (4; 129)	99 (41; 156)	0.14

TSH = thyroid-stimulating hormone

Quantitative variables are expressed as mean ± standard deviation or median and 5th and 95th (5; 95) percentiles; qualitative variables are expressed as percentages of total

*Of the patients, two were lost in the follow-up: one due to death and another because the patient lived outside the island. None of them were under amiodarone treatment. Thyroid replacement therapy treatment with oral levothryoxine was of 73.0 ± 12.4 μg every 24 hours. Mean follow-up of 2.2 ±0.9 years

With regard to hypoxaemia, the relationship between thyroid hormones and oxygen consumption has long been recognised. Moshang et al,[15] for example, showed that children with chronic hypoxia resulted in low serum thyroxine. The conclusions, reached by the authors, were that in chronically hypoxic patients there was a more rapid degradation of thyroxine to reverse triiodothyronine that would stimulate in those patients with an intact neuroendocrine feedback mechanism, thyroid-stimulating hormone production. Moreover, these authors stated that, as triiodothyronine (T3) and reverse triiodothyronine are largely extrathyroidal, serum thyroid abnormalities during hypoxia would be most likely due to alterations in extrathyroidal hormone metabolism.

Thyroid hormone also has multiple effects on the regulation of lipid synthesis, absorption, and metabolism, although the results on lipid concentrations are contradictory. We have previously reported that CHD patients have lower plasma cholesterol concentrations than the non-congenital ones.[16] However, some studies have shown that subclinical hypothyroidism can potentially contribute to a pro-atherogenic lipid profile, with effects being greater at higher thyroid-stimulating hormone

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levels.[17] On the contrary, other studies have not shown, as occurred in our series, any effect of subclinical hypothyroidism on these lipid measurements.[18] In relation to the benefit that entails treating subclinical hypothyroidism patients with synthetic thyroxine, Danese et al,[19] after a quantitative review of the literature in patients with mild thyroid failure, suggested that thyroxine therapy in individuals with mild thyroid dysfunction lowered mean serum total and low-density lipoprotein cholesterol concentrations, with the reduction in serum total cholesterol being larger in those patients with higher pretreatment cholesterol levels. Similarly, Meier et al[20] in a double-blind study showed that physiological levothyroxine replacement in patients with subclinical hypothyroidism had a beneficial effect on low-density lipoprotein cholesterol levels and clinical symptoms of hypothyroidism. However, Surks et al[21] in a scientific review considered that there was insufficient evidence to show benefits of levothyroxine therapy on lipid levels. In fact, clinical trials to date have not consistently shown a beneficial effect of levothyroxine treatment on serum lipid levels in subclinically hypothyroid patients[22] as also seen in our CHD patients. On the other hand, no significant differences were obtained in glucose concentrations between those patients under levothyroxine treatment, and no significant worsening on glycaemic control was observed between those patients with no hormone replacement therapy. On the contrary, other authors have showed a significant worsening of glucose levels at the follow-up supporting the role of subclinical hypothyroidism in glucose regulation.[23]

In conclusion, in CHD patients with subclinical hypothyroidism, most of whom had a thyroid-stimulating hormone concentration between 5 and 10 mIU/L, no changes were seen in serum thyroxine, glucose, cholesterol, or C-reactive protein concentrations before and after the follow-up regardless of whether they were or not under thyroid hormone replacement therapy. Although our small sample size, non-randomised design, can limit the result of our study we must consider a proper follow-up, especially in CHD patients with thyroid-stimulating hormone concentration above 10 mIU/L, with heart failure,[24] or at an increased risk for cardiovascular events.

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Conflicts of Interest

None.

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