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CLINICAL STUDY

Low plasma triiodothyronine levels in heart failure are associated with a reduced anabolic state and membrane damage

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Abstract

Background: Low plasma triiodothyronine (T_3) levels are considered a prognostic predictor of death in heart failure (HF) patients.
Aim: To study an association between plasma T_3 levels and several cardiac, neurohormonal, and metabolic markers of HF.
Methods: A total of 133 ambulatory HF patients (114 males; mean age 63.2 years) with left ventricular ejection fraction <40% were enrolled. TSH, total tetraiodothyronine (T_4) and T_3, N-terminal pro-brain natriuretic peptide (NT-proBNP), and other cardiac and metabolic parameters were measured. The lowest tertile of T_3 (group 1) was compared against the two upper ones (group 2).
Results: In simple logistic regression, the lowest T_3 tertile was associated with more advanced HF disease status: older (age: odds ratio (OR)=1.05; confidence interval (CI) 95% 1.01–1.09, $P=0.004$), lower functional capacity (walking test: OR=0.996; CI 95% 0.993–0.999, $P=0.008$), higher NT-proBNP (OR=1.64; CI 95% 1.19–2.27, $P=0.003$) and adiponectin levels (OR=1.07; CI 95% 1.02–1.11, $P=0.004$), lower DHEAS log-transformed (OR=0.50; CI 95% 0.31–0.80, $P=0.004$), and the presence of lower phase angle values as measured by body bioelectrical impedance analysis (OR=3.18; CI 95% 1.50–6.71, $P=0.04$) and worse renal function (OR=0.96; CI 95% 0.94–0.98, $P=0.003$). T_3 levels in the lowest tertile were independently associated with low phase angle values (OR=2.95, CI 95% 1.16–7.50, $P=0.02$) and the log transformation of DHEAS (OR=0.56; CI 95% 0.32–0.97, $P=0.04$).
Conclusion: We have demonstrated an association between plasma T_3 levels in the lower range and other deranged hormonal and metabolic parameters in HF patients.

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Introduction

Euthyroid sick syndrome and non-thyroidal illness syndrome are the terms currently used to define a condition characterized by an impairment of the hypothalamus–pituitary–thyroid axis present in most critically ill patients. A fall in serum triiodothyronine (T_3), also known as low T_3 syndrome, is one of the most common changes observed (1–3). This pathological process has been found to be present in about 30% of congestive heart failure (HF) patients. Those patients classified as New York Heart Association (NYHA) functional class III–IV (4) have shown a higher prevalence of low T_3 levels. Furthermore, the low T_3 syndrome in HF is considered a predictor of death (5, 6).

Several changes consistent with the downregulation of the thyroid hormone signaling system take place in the advanced failing heart and postinfarcted myocardium. This hypothyroid phenotype includes a lower expression of thyroid hormone receptor-α1 (TRα1 or THRA), sarcoplasmic reticulum calcium ATPase (SERCA2 or ATP2A2), and higher expression of β myosin genes (7–9). Although these changes in cardiac phenotype might be due to low circulating levels of thyroid hormones in HF, impaired thyroid hormone signaling might also result from the re-expression of deiodinase type 3 (D3), the local thyroid hormone inactivating enzyme, in cardiomyocytes (10, 11).

Reversal of this hypothyroid phenotype with physiological replacement of T_3 might prove beneficial as been shown in animal models of HF where left ventricular

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contractile performance was improved (12) or with ventricular ischemia where early long-term L-T_3 replacement has been shown to preserve the mitochondria and prevent ischemic cardiac remodeling (13). Moreover, studies of short-term T_3 replacement in patients undergoing coronary artery bypass surgery and in patients with advanced HF have also demonstrated a hemodynamic benefit with such therapy (14–16).

It can be argued that low T_3 levels present in HF might not just indicate disease progression but they might have a pathophysiological role. This might be explained by the direct effects of low T_3 levels in the cardiovascular system and/or through a possible interaction with catabolic and inflammatory parameters also present in HF (17). This is in line with the idea that the pathophysiological phenomenon behind HF initially involves a compensatory activation of hormonal, immunological, and proinflammatory systems. However, a later phase ensues where all of these compensatory responses eventually become maladaptive (18). The use of markers such as brain natriuretic peptide (BNP) (19) or adiponectin (20), which provide prognostic information of adverse outcome in HF, is well established. However, an interaction between T_3 levels and catabolic parameters present in HF still remains a matter of interest for further research.

In this study, we explored a possible association of low T_3 circulating levels with some of the hemodynamic, neurohormonal, and metabolic prognostic parameters present in congestive HF patients.

Materials and methods

Subjects

We prospectively included 151 consecutive ambulatory patients with systolic HF referred to our institute between May 2005 and March 2007 in the MIMICA study, designed to explain the relationship between metabolic and inflammatory markers and severity of disease (21). All patients had left ventricular ejection fraction (LVEF) $\leq$40% and were in a stable condition (not hospitalized because of decompensated HF, nor required a visit to emergency department or a raise of the diuretic dose) at least for 3 months prior to their inclusion in the study. After excluding overt hypothyroid and hyperthyroid patients, 133 patients remained to be included in the present analysis. Overt hypothyroidism was defined as TSH values $>$5.0 μIU/ml and total tetraiodothyronine (T_4) values $<$4.5 μg/dl. Overt hyperthyroidism was defined as TSH values $<$0.3 μIU/ml and T_4 values $>$13 μg/dl.

Blood sampling and analysis

Following a 12 h overnight fast, venous blood was obtained from the antecubital vein. Hematological parameters, urea, creatinine, glycemia, baseline insulin, liver, and cholesterol panels were determined. We measured high-sensitivity C-reactive protein (hsCRP), uric acid, leptin, adiponectin, albumin, cortisol and DHEAS, and N-terminal pro-BNP (NT-proBNP).

For determination of hsCRP, leptin, adiponectin, NT-proBNP, cortisol, and DHEAS, all the samples were processed in the same assay.

hsCRP was determined by Tina-quant CRP (Latex, Mannheim, Germany) high-sensitive immunoturbidimetric assay (Roche Diagnostics) in a Hitachi 917 autoanalyzer. The intra assay coefficient of variation (CV) was 0.43%.

Leptin was measured by IRMA (Active Human Leptin IRMA, Diagnostic System Laboratories, Inc., Webster, TX, USA). The intra assay CV of the assay at 3.0 ng/ml was 3.9% and at 12 ng/ml was 1.7%.

Adiponectin was determined by enzyme immunoassay (Quantikine Human Adiponectin/Acrp30 Immunoassay. R&D Systems, Inc., Minneapolis, MN, USA). The intra assay CV of the assay at 19.8 μg/ml was 2.5%.

NT-proBNP was determined by immunoassay (proBNP Elecsys Roche Diagnostics GmbH). The intra assay CV was 2.7%.

Plasmatic and urinary cortisol levels were evaluated by immunoassay (Access Cortisol, Beckman Coulter, Fullerton, CA, USA). The intra assay CV was 6.4% for plasmatic and 4% for urinary-free cortisol.

DHEAS was assessed by RIA (Coat-A-Count DHEAS-SO_4 Diagnostic Products Corporation, Los Angelas, CA, USA). The intra assay CV was below 5.3%.

TSH, T_3, and T_4 were determined by electrochemiluminescence immunoassay (Elecsys 1010-ROCHE Diagnostic). TSH reference values were 0.3–5.0 μIU/ml. Intra assay CV% was 2% and inter assay CV was 3.7% using a human serum sample with 0.9 μIU/ml (EP5-Modified protocol of National Committee of Clinical Laboratories Standards, NCCLS). Analytical sensitivity of the method was: 0.005 and functional sensitivity was 0.014 μIU/ml.

T_4 reference values were 4.5–13.0 μg/dl. Intra assay CV% was 2.9% and inter assay CV was 3.9% using a human serum sample with 9.0 μg/dl in six daily assays during 10 days (EP5-A, NCCLS).

T_3 reference values were 0.8–2.0 ng/ml. Intra assay CV% was 4.1% and inter assay CV was 4.9% using a human serum sample with 2.1 ng/ml in six daily assays during 10 days (EP5-A, NCCLS). Analytical sensitivity was 0.195 ng/ml.

In non-diabetic patients, insulin resistance was calculated by the homeostasis model assessment index for insulin resistance (HOMA-IR)=(fasting plasma glucose (mg/dl)$\times$fasting plasma insulin (μIU/ml))/(18$\times$22.5).

Echocardiography

The acquisition of echocardiographic data was performed using the Philips iE33 Ultrasound.

M-mode left ventricular dimensions were obtained from the parasternal long-axis view following the standard Echocardiography American guidelines, determining left ventricle diastolic and systolic diameters, interventricular septum, posterior wall, and aortic root. Left atrial area was traced in apical four-chamber view.

Ventricular function was performed in four-chamber apical view: the endocardial border was manually traced in end systole and end diastole and using the Simpson method (biplane), left ventricular end diastolic volume, left ventricular end systolic volume, and ejection fraction were assessed.

Six minutes walking test

Functional capacity was assessed with the 6 min walking test, performed in a flat straight 30 m corridor. The test was conducted under the control of an experienced physician who encouraged the patients to walk in the corridor at a higher rate from one extremity to the other as much time as possible. Patients were allowed to stop if necessary but were urged to resume the walk as soon as they recovered. Baseline and final heart rate and systolic blood pressure were recorded. The distance walked in 6 min (6MWD) is expressed in meters.

Bioelectrical impedance analysis

In every patient, body composition (muscle mass, fat mass content, and total, intra- and extracellular water) was assessed by body bioelectrical impedance analysis (BIA). All the tests were performed by the same skilled physician using a tetrapolar and multiple frequency equipment (four-channel bioimpedance meter BioScan MSR-916, Maltron International Ltd, Rayleigh, UK). BIA has been validated as a suitable method to determine body composition and is well correlated with dual-energy X-ray absorptiometry (22). The method is based on the resistance encountered through water and the body tissues during low-intensity electric current passage. The two electrodes are placed on the palm and wrist as well as the other two electrodes on the foot sole and ankle; all electrodes are placed on the right side of the body. In order to perform the test, the patient has to remain lying down on the supine position, in a fasted condition for the last 6 h and having avoided strenuous exercise within the last 12 h. Determination of phase angle, a marker of membrane damage, was also assessed (22). Low phase angle, a marker of membrane damage, was defined as <5.5 degrees in women or <6.5 degrees in men.

Protocol

All tests were carried out within 5 days of inclusion, at the Instituto Cardiovascular de Buenos Aires. The investigation complied with the principles outlined in the Declaration of Helsinki. The protocol was approved by the institutional ethics committee and signed informed consent was obtained from each participant.

In order to explore the relationship between low T_3 values and the baseline parameters, the population was divided into tertiles of T_3, and the lowest tertile (group 1) was compared against the two upper ones (group 2).

Statistical analysis

Categorical variables are presented as percentages and continuous variables as mean $\pm$ S.D. when their distribution was normal, or median and interquartile range when it was not.

Comparisons between the two groups were performed by Student's *t*-test (continuous variables) or χ^2 test (categorical variables). Simple and multiple logistic regressions were performed to define variables significantly associated with the lowest tertile of T_3. Logarithmic transformation was performed to achieve a normal distribution for skewed variables and to introduce them in the multivariable analysis.

Statistical analysis was performed with Stata 10 package (StataCorp, College Station, TX, USA).

Results

Baseline characteristics

Of the 133 patients, 114 (85.7%) were males and mean age was 63.2 ± 11.5 years; 9.7% were cigarette smokers, 24.8% diabetic, 54.9% had arterial

Table 1 Comparison of demographic parameters, clinical characteristics, heart failure disease status, and use of drugs between group 1 and group 2 patients.

	Group 1 $n=45$	**Group 2** $n=88$	***P* value**
Male sex (%)	88.8	81.8	0.29
Age (years)	67.2 ± 11.6	60.9 ± 11.8	0.002
Diabetes (%)	28.9	23.8	0.53
Hypertension (%)	46.6	55.6	0.32
Ischemic etiology (%)	62.2	48.8	0.14
NYHA III–IV (%)	35.5	22.7	0.11
Atrial fibrillation (%)	15.5%	6.8%	0.11
β-Blockers (%)	95.5%	89.8%	0.25
ACEI–ARB (%)	73.3%	85.2%	0.10
Amiodarone (%)	46.6%	31.8%	0.09
Diuretics (%)	93.3%	75%	0.01
Digitalis (%)	28.8%	19.3%	0.21
LVEF	28.2 ± 7.8	28.4 ± 7.7	0.90
6 min walking test (mts)	251 ± 132	320 ± 136	0.006
Resting metabolic rate (kcal)	1416 ± 208	1487 ± 244	0.09
Fat-free mass (%)	$70.6 \pm 7.4\%$	68.9 ± 7.9	0.22
Phase angle (degrees)	6.5 ± 2.2	7.2 ± 2.1	0.08
Low phase angle (%)	62.2	34.1	0.002

BMI, body mass index; NYHA III–IV, New York Heart Association functional class III–IV; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; LVEF, left ventricular ejection fraction.

Table 2 Comparison of biochemical values between group 1 and group 2 patients.

	Group 1 $n=45$	Group 2 $n=88$	*P* value
Hemoglobin (g/dl)	13.8±1.5	14.1±1.5	0.26
GFR (ml/min/1.73 m^2)	52±18	62±17	0.002
WBC count (1000/mm^3)	7.2±1.9	7.3±1.4	0.74
Na (meq/l)	140±4	141±3	0.16
K (meq/l)	4.7±0.4	4.7±0.4	0.63
HOMA-IR	2.3±1.5	3.1±2.5	0.09
Cholesterol (mg/dl)	188±41	199±60	0.32
Leptin (ng/ml)	9.5±6.8	9.7±6.1	0.86
Cortisol (μg/dl)	16.9±4.9	16.1±4.8	0.30
DHEAS (μg/dl)	40 (24–70)	63 (40–99)	0.003
hsCRP (mg/l)	2.7 (1.3–5.4)	2.7 (1.3–5.7)	0.96
NT-proBNP (pg/ml)	1350 (956–2676)	794 (235–1703)	0.0004
Adiponectin (μg/ml)	16.8±7.4	12.3±7.9	0.002
T_3 (ng/ml)	0.83±0.07	1.14±0.16	0.0001
T_4 (μg/dl)	8.6±1.8	7.9±1.3	0.028
TSH (μIU/ml)	2.6±2.3	3.3±2.5	0.12

GFR, glomerular filtration rate; WBC, white blood cell; HOMA-IR, homeostasis model assessment index for insulin resistance; hsCRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal pro-brain natriuretic peptide; T_3, triiodothyronine; T_4, total tetraiodothyronine.

hypertension, 50.4% had ischemic etiology, 42.8% had previous myocardial infarction, and 27.1% were classified as functional class NYHA III–IV. Mean LVEF was 28.3±7.9% and mean 6 min walking distance was 293±140 mts. The vast majority of the patients used β-blockers (90.2%) and angiotensin-converting enzyme inhibitor (ACEI) and an angiotensin receptor blocker (ARB), ACEI–ARB (80.4%). Approximately one-third of our patients (36.8%) were on amiodarone.

T_3 values ranged from 0.57 to 1.68 ng/ml. Mean T_3 value was 1.03±0.20 ng/ml.

Comparison of groups

The cutoff point between groups 1 and 2 was 0.95 ng/ml.

Tables 1 and 2 show the comparison of measured parameters between groups. Group 1 patients (low T_3 values) were significantly older, with higher use of diuretics, and a trend to be more symptomatic and more frequently treated with amiodarone. They presented with less than 6 min walking distance, worse renal function, lower levels of DHEAS, and higher NT-proBNP and adiponectin values. Their phase angle was lower, and the prevalence of low phase angle was higher. LVEF, left ventricular diameters and volumes, and E/A relation were not significantly different among tertiles.

In simple logistic regression (Table 3), the lowest T_3 tertile was associated with more advanced HF disease status: older, lower functional capacity, higher NT-proBNP and adiponectin levels, lower DHEAS log-transformed, and the presence of low phase angle values and worse renal function.

In multiple logistic regression (Table 3), the lowest tertile of T_3 was independently associated with low phase angle values (odds ratio (OR)=2.95, confidence interval (CI) 95% 1.16–7.50, $P=0.02$) and the log transformation of DHEAS (OR=0.58; CI 95% 0.37–0.92, $P=0.022$).

Discussion

In this study, we have shown for the first time that low T_3 levels, a strong indicator of poor prognosis in HF, are associated with lower BIA phase angle (a marker of membrane damage) and lower DHEAS (expression of diminished anabolic status). The association was independent of the influence of other recognized markers of HF such as age, weight loss, renal function, or muscle mass.

NT-proBNP also appeared related to lower T_3 levels, with significantly higher levels in group 1 patients. NT-proBNP levels are used for screening, diagnosis of acute HF, and to establish prognosis in HF. Higher levels imply a worse outcome (23). It has previously been shown that free T_3 is significantly related to NT-proBNP in patients with cardiovascular disease. Moreover, both parameters exert an independent and additively prognostic value for mortality in HF (24, 25). In agreement with these studies, as previously mentioned, we also

Table 3 Variables significantly associated with the lower T_3 tertile in univariate and multiple logistic regressions.

	Simple logistic regression			Multiple logistic regression		
Variables	OR	CI 95%	*P*	OR	CI 95%	*P*
Age (years)	1.05	1.01–1.09	0.004	0.98	0.93–1.03	0.51
Functional class III–IV	1.87	0.85–4.12	0.11	1.29	0.50–3.28	0.59
Amiodarone use	1.87	0.89–3.92	0.09	1.65	0.68–3.98	0.26
6 min walking test (mts)	0.996	0.993–0.999	0.008	0.999	0.995–1.003	0.72
GFR (ml/min/1.73 m^2)	0.96	0.94–0.98	0.003	0.97	0.95–1.00	0.15
DHEAS log value	0.50	0.31–0.80	0.004	0.56	0.32–0.97	0.04
NT-proBNP log value	1.64	1.19–2.27	0.003	1.09	0.72–1.64	0.68
Adiponectin (μg/ml)	1.07	1.02–1.11	0.004	1.03	0.97–1.09	0.26
Low phase angle	3.18	1.51–6.72	0.002	2.95	1.16–7.50	0.02

CI, confidence interval; OR, odds ratio; GFR, glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide.

found higher levels of NT-proBNP in patients with lower levels of T_3.

A novel association between low T_3 levels in HF and the adrenal steroid DHEAS was revealed in this study. It has previously been reported that plasma levels of DHEA are decreased in patients with HF (26) and that they can be used as a prognostic marker of bad outcome in HF (27). Although alternative explanations for the lower levels of this anabolic hormone in HF have been offered (28, 29), lower DHEAS levels in HF could also be interpreted in the light of a hypothyroid state. Lower DHEAS levels have previously been reported in hypothyroid women (30). It has been suggested that the lower concentrations of DHEA and DHEAS in hypothyroidism could be explained by decreased adrenal steroidogenesis (31). Moreover, an indirect regulation by thyroid hormones of human DHEA sulfotransferase family 1A member 2 (SULT2A1), the enzyme that catalyzes sulfonation of DHEA to DHEAS has been reported and could also be playing a role in lower DHEAS levels described in hypothyroidism (32). On the other hand, given that oxidative stress is present in hypothyroid patients (33), lower DHEAS levels found in our low T_3 patients could also be explained through a decrease in 17,20-lyase activity.

We evaluated body composition using whole-body BIA method and found that the chances of pertaining to the low T_3 group increased nearly three times when phase angle was low. A lower phase angle implies cell death or decreased cell integrity (34). With regard to HF, it has been described that bioimpedance phase angles are lower in patients with functional class NYHA III–IV compared with those with NYHA I–II (35). In agreement with our findings, a smaller phase angle after 6 months of follow-up was observed in HF patients who developed some alteration in the thyroid profile when compared with the rest of the cohort (36).

A limitation of our study is the high use of amiodarone found in the low T_3 group. Due to its big iodine load, amiodarone can decrease conversion of T_4 to T_3 yielding low serum T_3 levels. However, to discard its possible effects as a confounder, amiodarone use, together with other parameters such as age, that has been also reportedly associated with lower T_3 values, was adjusted within the multivariable analysis and was not independently related to low T_3 levels. Furthermore, our group of patients with the lowest T_3 levels was in a more advanced HF status and this is in line with authors that reported that concomitant amiodarone therapy does not have a relevant influence in the higher mortality rate found in HF patients with low T_3 (37).

On the other hand, the strengths of this study lie on the multiplicity of metabolic and neurohormonal parameters included. The reported findings are original and should be considered hypothesis generating.

In conclusion, we have found that low T_3 levels in HF patients are associated with several markers of illness. Lower anabolic activity and more severe membrane damage could partially explain a more advanced HF status among patients with low T_3 levels.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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