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 (T3) levels are considered a prognostic predictor of death in heart failure (HF) patients.

Aim: To study an association between plasma T3 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 (T4) and T3, N-terminal pro-brain natriuretic peptide (NT-proBNP), and other cardiac and metabolic parameters were measured. The lowest tertile of T3 (group 1) was compared against the two upper ones (group 2).

Results: In simple logistic regression, the lowest T3 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). T3 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 T3 levels in the lower range and other deranged hormonal and metabolic parameters in HF patients.

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 (T3), also known as low T3 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 T3 levels. Furthermore, the low T3 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 T3 might prove beneficial as been shown in animal models of HF where left ventricular...
contractile performance was improved (12) or with ventricular ischemia has been shown to preserve the mitochondrial and prevent ischemic cardiac remodeling (13). Moreover, studies of short-term T3 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 T3 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 T3 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 T3 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 T3 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 mU/l and total triiodothyronine (T3) values <4.5 \( \mu \)g/dl. Overt hyperthyroidism was defined as TSH values <0.3 mU/l and T4 values >13 \( \mu \)g/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 immunossay (Quantikine Human Adiponectin/Acrp30 Immunoassay. R&D Systems, Inc., Minneapolis, MN, USA). The intra assay CV of the assay at 19.8 \( \mu \)g/ml was 2.5%.

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

Plasmatic and urinary cortisol levels were evaluated by immunossay (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-SO4 Diagnostic Products Corporation, Los Angeles, CA, USA). The intra assay CV was below 5.3%.

TSH, T3, and T4 were determined by electrochemiluminescence immunossay (Elecsys 1010-ROCHE Diagnostic). TSH reference values were 0.3–5.0 mU/ml. Intra assay CV% was 2% and inter assay CV was 3.7% using a human serum sample with 0.9 mU/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 mU/ml.

T3 reference values were 4.5–13.0 \( \mu \)g/dl. Intra assay CV% was 2.9% and inter assay CV was 3.9% using a human serum sample with 9.0 \( \mu \)g/dl in six daily assays during 10 days (EP5-A, NCCLS).

T4 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 (mU/ml)/(18 × 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 had 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 T3 values and the baseline parameters, the population was divided into tertiles of T3, 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 ± 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 χ² test (categorical variables). Simple and multiple logistic regressions were performed to define variables significantly associated with the lowest tertile of T3. 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 hypertension. The 6 min walking test was 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.

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

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

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.

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1</th>
<th>Group 2</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>13.8±1.5</td>
<td>14.1±1.5</td>
<td>0.26</td>
</tr>
<tr>
<td>GFR (ml/min/1.73 m²)</td>
<td>52±18</td>
<td>62±17</td>
<td>0.002</td>
</tr>
<tr>
<td>WBC count (1000/mm³)</td>
<td>7.2±1.9</td>
<td>7.3±1.4</td>
<td>0.74</td>
</tr>
<tr>
<td>Na (meq/l)</td>
<td>140±4</td>
<td>141±3</td>
<td>0.16</td>
</tr>
<tr>
<td>K (meq/l)</td>
<td>4.7±0.4</td>
<td>4.7±0.4</td>
<td>0.63</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.3±1.5</td>
<td>3.1±2.5</td>
<td>0.09</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>188±41</td>
<td>199±60</td>
<td>0.32</td>
</tr>
<tr>
<td>Leptin (ng/ml)</td>
<td>9.5±6.8</td>
<td>9.7±6.1</td>
<td>0.86</td>
</tr>
<tr>
<td>Cortisol (µg/dl)</td>
<td>16.9±4.9</td>
<td>16.1±4.8</td>
<td>0.30</td>
</tr>
<tr>
<td>DHEAS (µg/dl)</td>
<td>40 (24–70)</td>
<td>63 (40–99)</td>
<td>0.003</td>
</tr>
<tr>
<td>hsCRP (mg/l)</td>
<td>2.7 (1.3–5.4)</td>
<td>2.7 (1.3–5.7)</td>
<td>0.96</td>
</tr>
<tr>
<td>NT-proBNP (pg/ml)</td>
<td>1350 (956–2676)</td>
<td>794 (235–1703)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Adiponectin (µg/ml)</td>
<td>16.8±7.4</td>
<td>12.3±7.9</td>
<td>0.002</td>
</tr>
<tr>
<td>T₃ (ng/ml)</td>
<td>0.65±0.07</td>
<td>1.14±0.16</td>
<td>0.0001</td>
</tr>
<tr>
<td>T₄ (µg/dl)</td>
<td>8.6±1.8</td>
<td>7.9±1.3</td>
<td>0.028</td>
</tr>
<tr>
<td>TSH (µU/ml)</td>
<td>2.6±2.3</td>
<td>3.3±2.4</td>
<td>0.12</td>
</tr>
</tbody>
</table>

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; T₃, triiodothyronine; T₄, total tetraiodothyronine.

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 T₃ 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 T₃ 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 T₃ 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 T₃ levels, a strong indicator of poor prognosis in HF, are associated with lower BLA 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 T₃ 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 T₃ 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 T₃ tertile in univariate and multiple logistic regressions.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Simple logistic regression</th>
<th>Multiple logistic regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (CI 95%)</td>
<td>P</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.05 (1.01–1.09)</td>
<td>0.004</td>
</tr>
<tr>
<td>Functional class III–IV</td>
<td>1.87 (0.85–4.12)</td>
<td>0.11</td>
</tr>
<tr>
<td>Amiodarone use</td>
<td>1.87 (0.89–3.92)</td>
<td>0.09</td>
</tr>
<tr>
<td>6 min walking test (mts)</td>
<td>0.996 (0.993–0.999)</td>
<td>0.003</td>
</tr>
<tr>
<td>GFR (ml/min/1.73 m²)</td>
<td>0.96 (0.94–0.98)</td>
<td>0.033</td>
</tr>
<tr>
<td>DHEAS log value</td>
<td>0.50 (0.31–0.80)</td>
<td>0.004</td>
</tr>
<tr>
<td>NT-proBNP log value</td>
<td>1.64 (1.19–2.27)</td>
<td>0.003</td>
</tr>
<tr>
<td>Adiponectin (µg/ml)</td>
<td>1.07 (1.02–1.11)</td>
<td>0.004</td>
</tr>
<tr>
<td>Low phase angle</td>
<td>3.18 (1.51–6.72)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

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 T3.

A novel association between low T3 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 IA member 2 (SULT2A1), the enzyme that catalyzes sulfonation of DHEA to DHEAS has been reported and could also be playing a role in lower DHEA 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 T3 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 T3 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 T3 group. Due to its big iodine load, amiodarone can decrease conversion of T3 to T3 yielding low serum T3 levels. However, to discard the low T3 group increased nearly three times when the BIA method and found that the chances of pertaining to a small phase angle (35) compared with the rest of the cohort (36).

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In conclusion, we have found that low T3 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 T3 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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