Thyroid Hormone and Coronary Artery Disease: From Clinical Correlations to Prognostic Implications

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ABSTRACT

Background: Overt thyroid dysfunction, hypothyroidism in particular, may lead to coronary artery disease (CAD). Whether more subtle anomalies of thyroid hormone metabolism influence the progression of CAD remains a matter of speculation.

Hypothesis: The occurrence of CAD and long-term prognosis in patients without a history of either primary thyroid disease, myocardial infarction, or chronic heart failure is related to serum levels of biologically active free triiodothyronine (fT3).

Methods: The cohort consisted of 1047 clinically and biochemically euthyroid patients (median age 65.6 y and 69% male) who underwent coronary angiography in our institute for suspected CAD.

Results: Lower fT3 levels were predictive of both single-vessel ($p = 0.012$) and multivessel ($p = 0.009$) CAD. Through a multivariate logistic regression analysis, fT3 was still linked to the presence of CAD (hazard ratio [HR]: 0.48, 95% confidence interval [CI]: 0.34–0.68, $p < 0.001$). After a mean follow-up of 31 months, the survival rate was 95% and total mortality (log-rank 6.75, $p = 0.009$), as well as cardiac mortality (log-rank 8.26, $p = 0.004$), was greater among patients with low T3 (fT3<2.10 pg/mL) syndrome. At subsequent multivariate Cox regression analysis, the association between low T3 syndrome and survival was maintained (total mortality HR: 1.80, 95% CI: 1.05–3.10, $p = 0.034$; cardiac mortality HR: 2.58, 95% CI: 1.13–5.93, $p = 0.025$).

Conclusions: In this selected population, fT3 levels were inversely correlated to the presence of CAD and low T3 syndrome conferred an adverse prognosis, even after adjusting for traditional coronary risk factors.

Introduction

Triiodothyronine (T3), the biologically active form of thyroid hormone derived predominantly from the peripheral conversion of the precursor thyroxine (T4), exerts a wide range of functions in several organs, including the heart.[1] Abnormal thyroid hormone metabolism may lead to different forms of heart disease and hypothyroidism, in particular, is a well-known cause of accelerated coronary atherosclerosis.[1] In recent years, the consequences on the cardiovascular system of milder forms of thyroid dysfunction have been increasingly recognized. For example, low T3 syndrome, being characterized by reduced serum levels of both total and free (f) T3 with normal thyroid stimulating hormone (TSH) and fT4 levels, and once believed to be a beneficial adaptive mechanism under conditions of stress, has emerged as a strong prognostic determinant in chronic, systolic heart failure.[2,3] Increased mortality among patients with low T3 syndrome has also been observed in acute myocardial infarction,[4] a common precursor of chronic heart failure of ischemic origin. However, whether variations in fT3 levels, not only in the context of low T3 syndrome but also within the physiological range, are related to coronary artery disease (CAD) per se remains unclear. The primary aim of the study, therefore, was to examine the relationship between fT3 and the presence of CAD in a population free of primary thyroid disease and significant structural heart disease. A secondary aim was to analyze the impact of low T3 syndrome, also known as nonthyroidal illness syndrome and euthyroid sick syndrome, on long-term prognosis in this population.

Methods

Patients

The population under study was made up of 1047 Italian subjects with suspected CAD that had been admitted to our institute for coronary angiography. The following characteristics constituted the principal exclusion criteria:

(1) Abnormal serum levels of TSH or fT4,
(2) Reduced (<50%) left ventricular ejection fraction at echocardiography,
(3) Acute myocardial infarction at the moment of hospitalization,
(4) History of myocardial infarction or revascularization prior to hospitalization, and
(5) Therapy with amiodarone.

During hospitalization, all patients underwent coronary angiography. Each examination was reviewed by an expert interventional cardiologist and CAD was defined, by visual

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assessment, as a greater than 50% stenosis in at least 1 major vessel or principal side branch. Following discharge, patients were asked to participate in a follow-up program and annually received a brief questionnaire on symptoms, cardiovascular events, and intervening hospitalizations. Date and cause of death were obtained through certificates provided by local health authorities.

Thyroid Hormone Sampling

Serum TSH, fT3, and fT4 were measured after overnight fasting and prior to coronary angiography using an AIA 21 analyzer (Eurogenetics-Tosho, Turin, Italy). The reference intervals for our laboratory are: fT3: 2.1–4.2 pg/mL, fT4: 7.1–18.5 pg/mL, TSH: 0.3–3.8 μIU/mL. Because patients were clinically stable at the moment of hospitalization, none of them were receiving heparin, high dose diuretics or inotropic agents, which are all agents known to influence the accuracy of thyroid hormone sampling. In addition, because of the particular exclusion criteria applied, potential confounding by nonthyroidal illness, such as sepsis and cachexia, was minimized.

Statistical Analysis

Categorical variables are expressed as percentages. Non-normally and normally distributed continuous variables are expressed as median values, accompanied by their relative 25th and 75th values, and mean ± standard deviation, respectively. Comparisons between groups were made with a Student t test for independent samples, Mann-Whitney test, and the χ^2 test with Yates correction, where appropriate, whereas correlations were studied with Spearman's test. Variation in fT3 levels according to the severity of CAD was studied using a 1-way analysis of variance with subsequent Bonferroni post-hoc test. Multivariate logistic regression analysis was then performed to examine the association between thyroid hormone and the presence of CAD, after accounting for the following variables: age, gender, body mass index, family history of CAD, past or current smoker, arterial hypertension, hypercholesterolemia, diabetes mellitus, high-density lipoprotein cholesterol, C-reactive protein, and estimated glomerular filtration rate. Three different analyses were conducted so as to assess each component of thyroid function (fT3, fT4, and TSH) separately. With the variables which maintained statistical significance after multivariate analysis, probabilistic models for the prediction of CAD were constructed. Diagnostic accuracy of the models was determined through receiver operating characteristic curves and comparisons between curves were made with a Wilcoxon statistic.

Kaplan-Meier survival curves were constructed to examine the effect of low T3 syndrome on mortality, with differences in survival curves assessed through the log-rank test. Subsequently, multivariate Cox regression analysis was carried out adjusting for the following variables: age, gender, obesity, family history of CAD, past or current smoker, arterial hypertension, hypercholesterolemia, and diabetes mellitus. Statistical analyses were performed using SPSS v12 (SPSS, Inc., Chicago, IL) and a p value <0.05 was considered significant.

Results

Baseline Characteristics and Thyroid Function

Characteristics of the population on enrollment are shown in Table 1. A total of 43% of the patients did not have CAD, whereas 32% and 25% presented single-vessel and multivessel CAD, respectively. A total of 75% of the population had normal fT3 levels and the remaining 25% had low T3 syndrome; none of the patients had increased levels of fT3. The fT3 levels were significantly lower in the subgroup with, compared to that without, CAD. Thyroid stimulating hormone and fT4 levels, on the other hand, were similar in the 2 subgroups. In addition, the correlation between fT3 and CAD did not vary according to severity of disease; fT3 was lower in patients with both single-vessel (2.32 ± 0.42 pg/mL, $p = 0.012$) and multivessel CAD (2.31 ± 0.40 pg/mL, $p = 0.009$), but the difference in fT3 levels in these 2 groups was not statistically significant.

Among the coronary risk factors examined in our patients, only age ($R = -0.15, p < 0.001$), C-reactive protein ($R = -0.18$, $p < 0.001$), and glomerular filtration rate ($R = 0.22$, $p < 0.001$) were significantly, albeit weakly, correlated to fT3. However, after adjusting for these and other variables through multivariate logistic regression analysis, fT3 was still linked to CAD (see Table 2). Instead, TSH and fT4 did not emerge at multivariate analysis as significant predictors of CAD.

Among the patients with low T3 syndrome, the prevalence of CAD was significantly greater compared to that of the rest of the population (67% vs 56%, $p = 0.04$). When multivariate logistic regression was performed excluding patients with low T3 syndrome, fT3 remained a significant predictor of CAD, but with a higher hazard ratio (HR: 0.51, 95% confidence interval [CI]: 0.33–0.79, $p = 0.002$) compared to that obtained from the analysis on the entire population.

Two models for the prediction of CAD were then created; the first included the traditional coronary risk factors: male gender, advanced age, family history of CAD, hypercholesterolemia, and arterial hypertension, whereas the second included the same variables as well as fT3. By comparing receiver operator characteristic curves, a statistically significant difference between the 2 models was found (area under the curve [AUC] model without fT3: 0.72, 95% CI: 0.69–0.75, $p < 0.001$; AUC model with fT3: 0.74, 95% CI: 0.71–0.76, $p < 0.001$; $p = 0.031$ for difference between models), thus demonstrating that measurement of fT3, in addition to traditional risk factors, improves the diagnostic accuracy of CAD prediction.

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Table 1. Baseline Characteristics of Patients

	Overall (n = 1047)	CAD (n = 454)	CAD (n = 593)	*p* Value
Age (y)	65.6 (57.4–73.3)	64.0 (55.5–71.5)	67.1 (58.3–74.1)	<0.001
Gender (n, %)	723 (69%)	257 (57%)	466 (79%)	<0.001
Body mass index (kg/m²)	27.2 (24.6–29.8)	27.2 (24.7–30.3)	27.1 (24.5–29.4)	NS
Ejection fraction (%)	60 (56–60)	60 (56–60)	60 (55–60)	NS
Coronary risk factors				
Family history of CAD (n, %)	479 (46%)	186 (41%)	293 (49%)	0.08
Past or current smoker (n, %)	406 (39%)	160 (35%)	246 (41%)	0.04
Arterial hypertension (n, %)	656 (63%)	261 (57%)	395 (67%)	0.003
Hypercholesterolemia (n, %)	655 (63%)	238 (52%)	417 (70%)	<0.001
Diabetes mellitus (n, %)	187 (18%)	63 (14%)	124 (21%)	0.004
Laboratory analyses				
HDL cholesterol (mg/dL)	41 (35–49)	43 (36–52)	41 (35–48)	<0.001
C-reactive protein (mg/L)	2.2 (1.0–5.6)	1.8 (0.90–5.1)	2.4 (1.0–5.9)	0.002
Estimated GFR (mL/min/1.73 m²)	76.8 (65.7–87.6)	77.5 (67.2–89.2)	76.5 (64.8–87.3)	NS
TSH (μIu/mL)	1.53 (1.01–2.26)	1.56 (1.06–2.33)	1.50 (1.00–2.22)	NS
fT3 (pg/mL)	2.36 ± 0.43	2.41 ± 0.44	2.32 ± 0.41	0.001
fT4 (pg/mL)	11.3 (9.9–12.8)	11.3 (10.1–12.9)	11.3 (9.7–12.7)	NS
Discharge medical therapy				
Antiplatelet agents (n, %)	671 (64%)	209 (46%)	462 (78%)	<0.001
ACE inhibitors (n, %)	332 (40%)	150 (33%)	182 (31%)	NS
Lipid lowering drugs (n, %)	466 (45%)	130 (29%)	336 (57%)	<0.001
β-Blockers (n, %)	414 (40%)	96 (21%)	318 (54%)	<0.001
Calcium channel blockers (n, %)	166 (16%)	63 (14%)	103 (17%)	NS

Abbreviations: ACE, angiotensin-converting enzyme; CAD, coronary artery disease; fT3, free triiodothyronine; fT4, free thyroxine; GFR, glomerular filtration rate; TSH, thyroid stimulating hormone.

Follow-up Data

No subjects were lost to follow-up and total mortality after 31 months was 5%. Mortality was distributed evenly between patients with and without CAD, and the cause of death was secondary to heart disease in 40% of patients. A total of 43% of patients underwent myocardial revascularization, the majority of which occurred during initial hospitalization; fT3 levels were lower in revascularized patients (2.31 ± 0.42 pg/mL) compared to those treated medically (2.39 ± 0.43 pg/mL, $p = 0.001$). Following discharge, nonfatal myocardial infarction occurred in 2% of the population, exclusively among patients with CAD at baseline.

The fT3 levels were lower in patients who died compared to those still alive at the end of follow-up (2.15 ± 0.46 pg/mL vs 2.37 ± 0.42 pg/mL, $p < 0.001$). Kaplan-Meier survival curves stratified by thyroid function (see Figure) showed that total mortality was greater in patients with low T3 syndrome (log-rank 6.75, $p = 0.009$). When an additional analysis was performed excluding cases of noncardiac death, results did not change significantly; fT3 was lower among patients who died (2.09 ± 0.53 pg/mL vs 2.36 ± 0.42 pg/mL, $p = 0.02$) and low T3 syndrome continued to condition prognosis negatively (log-rank 8.26, $p = 0.004$). When Cox regression

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Table 2. Predictors of CAD at Multivariate Analysis

Clinical Variable	Hazard Ratio	95% CI	*p* Value
fT3	0.48	0.34–0.68	<0.001
Male gender	3.75	2.68–5.24	<0.001
Hypercholesterolemia	2.51	1.86–3.40	<0.001
Family history of CAD	1.62	1.21–2.18	0.001
Arterial hypertension	1.54	1.13–2.10	0.006
Age	1.04	1.02–1.05	<0.001
Diabetes mellitus	1.47	0.99–2.17	0.054
Body mass index (kg/m²)	0.99	0.97–1.01	NS
Past or current smoker	1.17	0.86–1.58	NS
HDL cholesterol	1.00	0.99–1.01	NS
C-reactive protein	0.98	0.94–1.03	NS
Estimated GFR	1.00	0.99–1.01	NS

Abbreviations: CAD, coronary artery disease; CI, confidence interval; fT3, free triiodothyronine; GFR, glomerular filtration rate; HDL, high-density lipoprotein.

analysis, adjusted for traditional coronary risk factors, was conducted subsequently, low T3 syndrome predicted both total mortality and cardiac mortality (see Table 3).

Discussion

The principal finding of our study is that, in the absence of primary thyroid disease and clinically evident heart disease, the occurrence of CAD is associated with lower serum levels of fT3. This was observed in the range of physiological values of fT3 as well as in the context of low T3 syndrome. Thyroid stimulating hormone and fT4, in contrast to fT3, were not linked to the presence of CAD in our population. A secondary finding of interest is the adverse impact of low T3 syndrome on total and cardiac survival, which is noteworthy in light of the limited number of deaths that occurred during follow-up.

Whereas hypothyroidism, both overt and subclinical, is a well-known risk factor for CAD, the effect of borderline abnormalities in thyroid function on the coronary circulation remains a matter of debate. To the best of our knowledge, only Auer et al[5] had previously examined the influence of physiological variations in fT3 on the prevalence of CAD. These authors observed, as in our study, that lower fT3 levels were predictive of CAD, but the population in their study was constituted by a relatively small group of patients whose characteristics were not well defined. In particular, the prevalence of myocardial infarction, both acute and remote, and that of myocardial revascularization was not specified. Perhaps more importantly, data regarding left ventricular systolic function were not provided, an important drawback in light of the well-known consequences of heart failure on the thyroid system.[2,3] Our study lends support to

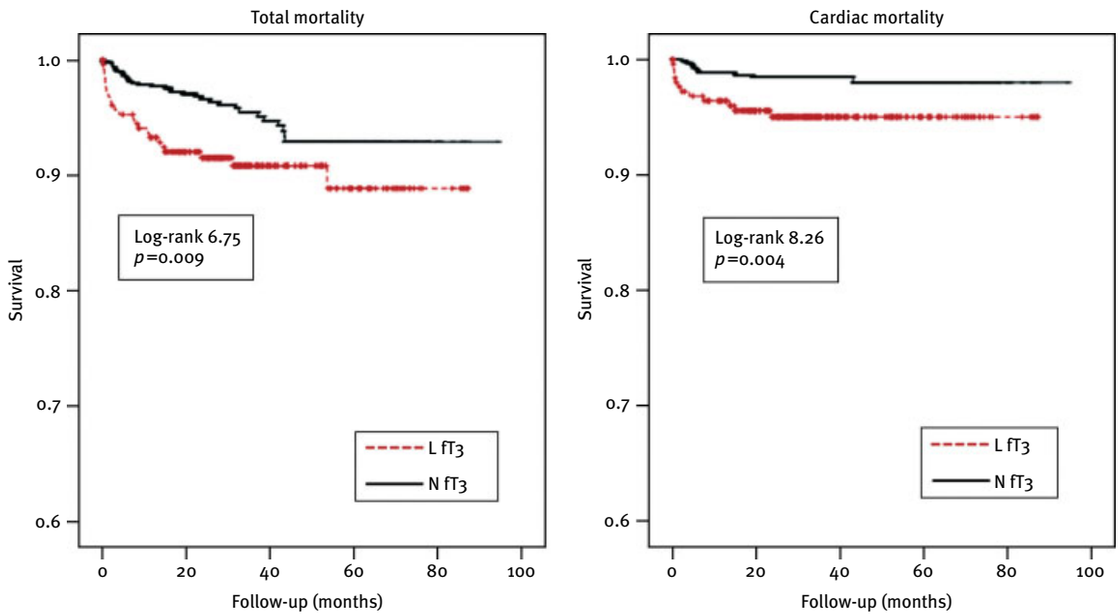

Figure 1. Kaplan-Meier survival curves for total and cardiac mortality stratified according to thyroid function. *Abbreviations*; N fT3, patients with normal fT3 levels; L fT3, patients with low T3 syndrome.

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Table 3. Significant Predictors of Total and Cardiac Mortality at Multivariate Analysis

	Total Mortality			Cardiac Mortality		
Clinical Variable	HR	95% CI	*p* Value	HR	95% CI	*p* Value
Low T3 syndrome	1.80	1.05–3.10	.034	2.58	1.13–5.93	0.025
Age	1.08	1.04–1.11	<.001	1.07	1.02–1.13	0.008
Diabetes mellitus	1.92	1.06–3.47	.031	1.69	0.65–4.38	NS

Abbreviation: NS, not significant; T3, triiodothyronine.

the theory advanced by Auer et al[5] in so far as we confirmed their results in a large cohort of patients in whom the impact of potential confounders was minimized by applying stringent exclusion criteria.

The reduction in fT3 levels observed in patients with CAD could be interpreted simply as a marker of disease rather than as an element contributing directly to disease progression. However, because fT3 represents the biologically active form of thyroid hormone, an isolated reduction in fT3 levels could constitute a model of abnormal thyroid hormone metabolism acting as a risk factor for CAD in a similar fashion to overt or subclinical hypothyroidism.[6] For example, the prevalence of risk factors, such as dyslipidemia and arterial hypertension, is greater in patients affected by hypothyroidism.[6] Hypothyroidism may also lead to endothelial dysfunction, hypercoagulability, impaired fibrinolysis, hyperhomocysteinemia, systemic inflammation, and platelet abnormalities.[6] Importantly, many of the aforementioned alterations are reversible upon normalization of thyroid function[7] and may be observed even in patients with physiological variations of TSH[8] and fT4.[9] Whether these same notions hold true for fT3 as well has not been established, but in our population the prevalence of hypercholesterolemia and arterial hypertension did not vary according to fT3 levels. However, we did not measure the other factors described above and, consequently, we cannot rule out their potential influence on our findings. Interestingly, at multivariate analysis fT3 emerged in addition to arterial hypertension and hypercholesterolemia, thus pointing to the potential existence of diverse mechanisms of action.

Clinical Implications

In recent years, several biomarkers, such as C-reactive protein and homocysteine, have acquired an important role in the risk stratification of patients with suspected CAD.[10] However, one should not overlook the importance of thyroid function which should always be assessed in patients at risk of CAD, to exclude not only secondary dyslipidemia, but also latent hyperthyroidism prior to coronary angiography. Furthermore, measurement of fT3, particularly if compared to that of other biomarkers, is simple, inexpensive, highly reproducible, may be performed in most laboratories, and is easy to interpret even by nonspecialists. Although the clinical utility of our findings may appear questionable in view of the modest differences in fT3 levels observed between patients with and without CAD, one should keep in mind that the fT3-CAD association, even after adjustment for confounding factors at multivariate analysis, was inverse and continuous: the lower the fT3 level, the greater the probability of CAD.

Limitations

Because measurements of fT3, fT4, and TSH were performed only once during initial hospitalization, we were not able to account for possible variations in thyroid function over time. In addition, we did not search for antithyroid antibodies, but in light of the exclusion criteria employed in our study, a high prevalence of these antibodies may be reasonably excluded. No significant variation in fT3 levels between single-vessel and multivessel CAD was noted, but coronary angiography provides a "lumenogram" and, as a result, it is not the ideal technique to quantify overall atherosclerotic burden. Finally, any statement regarding the causal role of fluctuations in fT3 levels on the progression of coronary atherosclerosis cannot be considered definitive on the basis of the present study due to its cross-sectional design. Only an appropriately designed, large-scale, longitudinal study, coupled with smaller studies aimed at investigating potential pathophysiological mechanisms, would be able to confirm such a hypothesis. However, considering that hypothyroidism increases the risk of CAD and that T3 therapy has proven benefits in diverse forms of heart disease,[11,12] any reduction in fT3 should not be viewed simply as an innocent bystander in cardiovascular disease.

Conclusions

In patients free of primary thyroid disease and significant structural heart disease, an inverse correlation exists between CAD and thyroid hormone, which extends across a wide spectrum of values of fT3. Moreover, low T3 syndrome, in which fT3 is markedly reduced, has an adverse impact on survival. For these reasons, thyroid function should always be evaluated in patients with suspected CAD.

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