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CLINICAL RESEARCH STUDY

Triiodothyronine levels for risk stratification of patients with chronic heart failure

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PURPOSE: We sought to explore the use of triiodothyronine (T_3) concentrations as an adjunct to clinical and functional parameters when estimating prognosis in patients with chronic heart failure.

METHODS: We enrolled 281 patients with postischemic (n = 153) or nonischemic (n = 128) dilated cardiomyopathy. Total and free T_3 concentrations, and traditional clinical and functional cardiac parameters, were measured 2 to 5 days after hospital admission. A multivariate model was utilized to predict all-cause and cardiac mortality.

RESULTS: All-cause mortality was 23% (n = 64) after a mean (±SD) of 12 ± 7 months of follow-up; 47 (73%) of the patients died from cardiac causes. The mean ejection fraction was lower in those patients who died than in those who survived (26% ± 8% vs. 31% ± 8%, $P < 0.001$), as were levels of total T_3 (1.0 ± 0.4 nmol/L vs. 1.3 ± 0.3 nmol/L, $P < 0.001$) and free T_3 (3.2 ± 1.4 pmol/L vs. 3.7 ± 1.0 pmol/L, $P < 0.001$). In a multivariate model, ejection fraction (odds ratio [OR] = 2.0 per 10% decrease; 95% confidence interval [CI]: 1.4 to 2.8 per 10% decrease; $P < 0.001$) and total T_3 level (OR = 0.3 per 1-nmol/L increase; 95% CI: 0.1 to 0.5 per 1-nmol/L increase; $P < 0.001$) were the only independent predictors of all-cause mortality. In an alternative model using free T_3 levels, ejection fraction (OR = 1.9; 95% CI: 1.4 to 2.7; $P < 0.001$) and free T_3 level (OR = 0.6 per 1 pmol/L; 95% CI: 0.5 to 0.8 per 1 pmol/L; $P < 0.02$) were associated with all-cause mortality. When we considered cardiac mortality alone, male sex (OR = 3.5; 95% CI: 1.7 to 13; $P < 0.04$), ejection fraction (OR = 1.7; 95% CI: 1.2 to 2.5; $P < 0.006$), and total T_3 level (OR = 0.3; 95% CI: 0.2 to 0.7; $P < 0.002$) were independent predictors with the multivariate model.

CONCLUSION: Low T_3 levels are an independent predictor of mortality in patients with chronic heart failure, adding prognostic information to conventional clinical and functional cardiac parameters.

Many models developed to predict prognosis in patients with heart failure incorporate neuroendocrine measurements with standard measures such as ejection fraction and severity of symptoms.[1-7] Thyroid function may be particularly helpful for assessing the evolution and prognosis of heart failure.[8] Thyroid hormones have cardiac and vascular effects,[9] and they also regulate biochemical reactions in most tissues. Altered thyroid hormone metabolism, characterized by low circulating levels of biologically active triiodothyronine (T_3), has been reported in patients following acute myocardial infarction,[10] with congestive heart failure,[11] and after cardiac surgery,[12,13] as well as in patients with other severe systemic diseases.[14]

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In an unselected sample of patients with cardiac diseases, we recently confirmed the negative prognostic value of a low T_3 concentration.[15] The primary goal of this study was to test whether measurement of T_3 concentration could be used as an additional prognostic tool, together with classic clinical and functional parameters, for risk stratification in a selected high-risk sample of patients with chronic dilated cardiomyopathy.

Methods

Sample

Between January 1998 and July 2001, we enrolled a total of 327 consecutive hospitalized patients with postischemic or nonischemic dilated cardiomyopathy. All patients had been treated medically for heart failure for at least 1 month. The study was approved by our institutional ethics review committee, and the investigation conformed to the principles outlined in the Declaration of Helsinki. Left ventricular ejection fraction was less than 45% and left ventricular end-diastolic diameter was greater than 56 mm in all patients. The reason for hospital treatment was either progressive deterioration of symptoms or evidence of worse cardiac function. Postischemic dilated cardiomyopathy was diagnosed by coronary artery disease found on angiography or by documented myocardial infarction; nonischemic dilated cardiomyopathy was diagnosed based on the absence of coronary artery disease on angiography. From our initial sample, we excluded 33 patients with clinical evidence of sepsis, cachexia, or other severe systemic disease. Six patients were excluded for overt hypothyroidism (thyroid-stimulating hormone [TSH] level >10 mIU/L and free thyroxine [T_4] level <7.7 pmol/L [6 pg/mL]), and 7 were excluded for hyperthyroidism (undetectable TSH level, and free T_3 level >7 pmol/L [4.5 pg/mL], or free T_4 level >30 pmol/L [23 pg/mL]). Thus, the final sample consisted of 281 patients; 118 (42%) were included in our previous study.[15] Left ventricular end-diastolic diameter was assessed by echocardiography and left ventricular ejection fraction by echocardiography or radionuclide ventriculography during the hospitalization. Obesity was defined as a body mass index >30 kg/m^2. All data used in this study were collected between 2 and 5 days after hospital admission.

Thyroid hormone measurements

The reference intervals for our laboratory were as follows: total T_3, 1.2 to 2.6 nmol/L (80 to 170 ng/dL); total T_4, 58 to 156 nmol/L (4.5 to 12 μg/dL); free T_3, 3.2 to 6.5 pmol/L (2 to 4.2 pg/mL); free T_4, 9.2 to 24 pmol/L (7.1 to 18.5 pg/mL); and TSH, 0.3 to 3.8 mIU/L.

Follow-up

Follow-up began when thyroid hormone levels were measured. Follow-up data were obtained from hospital records, contacts with family physicians, telephone interviews with the patients, and scheduled patient visits.[15] We ascertained all-cause and cardiac mortality from medical records or death certificates. Cardiac death required documentation of arrhythmia or cardiac arrest, death due to progressive heart failure, or myocardial infarction in the absence of a precipitating factor. Sudden unexpected death was classified as a cardiac death when it occurred outside the hospital and was not followed by an autopsy.

Statistical analysis

Statistical evaluation was preceded by a one-sample Kolmogorov-Smirnov test to ascertain the distribution of the continuous variables. Confidence intervals for categorical data were computed by the quadratic approximation to binomial distribution with continuity correction. Association between continuous variables was evaluated by the Pearson product-moment (Pearson r) or by the Spearman rank correlation coefficient (Spearman r), as appropriate. Groups were compared for categorical data or frequency of events using the chi-squared test, and for continuous variables using the Student t test or the Mann-Whitney U test, as appropriate. All tests were two-sided and $P<0.05$ was considered statistically significant. Analysis of variance and Bonferroni post hoc tests were used to assess the relation between total T_3 levels and New York Heart Association (NYHA) class. Continuous variables (age, ejection fraction, free T_3, free T_4, total T_3, total T_4, TSH, body mass index, left ventricular end-diastolic diameter, NYHA class) and dichotomized variables (sex, hypertension, obesity, diabetes, dyslipidemia, smoking, previous myocardial infarction, diagnosis of nonischemic or postischemic dilated cardiomyopathy, documented myocardial ischemia, medical treatment) were entered in the logistic regression model to identify univariate predictors of mortality or cardiac mortality. All variables with significant univariate associations ($P<0.05$) were included in multivariate models. Cumulative survival rates at 18 months were estimated, along with 95% confidence intervals; differences in survival curves were tested with the log-rank test. All analyses were performed using SPSS for Windows (version 10.05; SPSS Inc., Chicago, Illinois).

Result

Of the 281 patients, 128 (46%) had nonischemic dilated cardiomyopathy and 153 (54%) had postischemic dilated cardiomyopathy. During a mean ($\pm$SD) of 12 $\pm$ 7 months of follow-up, 64 patients (23%) died, including 47 (73%) of cardiac causes. Those who died were older and had worse cardiac function and lower T_3 levels, than those who survived during follow-up; they were also less likely to be dyslipidemic or obese (Table 1).

Table 1 Characteristics of the sample

Characteristic	Died during follow-up (n = 64)	Survived throughout follow-up (n = 217)	*P* value
	Number (%) or mean ± SD		
Male sex	53 (83)	154 (71)	0.08
Age (years)	70 ± 10	66 ± 11	0.01
History of smoking	33 (52)	97 (45)	0.40
Diabetes	15 (23)	45 (21)	0.87
Arterial hypertension	24 (38)	106 (49)	0.15
Dyslipidemia	21 (33)	111 (51)	0.01
Body mass index (kg/m^2)	26 ± 4	27 ± 5	0.14
Obesity (>30 kg/m^2)	10 (16)	22 (34)	0.009
Ischemic dilated cardiomyopathy	32 (50)	98 (45)	0.58
Beta-blocker use	17 (27)	21 (33)	0.45
Amiodarone use	20 (31)	85 (39)	0.31
ACE inhibitor use	22 (34)	104 (48)	0.07
Ejection fraction (%)	26 ± 8	31 ± 8	<0.001
Left ventricular end-diastolic diameter (mm)	64 ± 10	61 ± 9	0.02
TSH (mIU/L)	2.3 ± 2.6	1.9 ± 2.2	0.28
Total T_3 (nmol/L)*	1.0 ± 0.4	1.3 ± 0.3	<0.001
Total T_4 (nmol/L)*	104 ± 35	127 ± 67	0.10
Free T_3 (pmol/L)*	3.2 ± 1.4	3.7 ± 1.0	0.01
Free T_4 (pmol/L)*	18.2 ± 5.3	18.1 ± 5.0	0.83
NYHA class (I-IV)	2.9 ± 1.4	2.2 ± 1.7	0.003
Follow-up (months)	8.4 ± 7.3	13.6 ± 6.2	<0.001

ACE = angiotensin-converting enzyme; NYHA = New York Heart Association; T_3 = triiodothyronine; T_4 = thyroxine; TSH = thyroid-stimulating hormone.

*Conversion to conventional units is as follows: T_4, 1 nmol = 780 ng; T_3, 1 nmol = 651 ng.

In the total sample, there was a significant correlation between levels of total T_3 and free T_3 ($r = 0.79$, $P < 0.001$), but there was no correlation between total T_3 level and ejection fraction ($r = 0.009$, $P = 0.86$). There were weak correlations between body mass index and total T_3 level ($r = 0.13$, $P = 0.04$), and between NYHA class and total T_3 level ($r = 0.35$, $P = 0.03$).

Stratifying risk variables and mortality

In univariate models, age, NYHA class, ejection fraction, end-diastolic left ventricular diameter, and levels of free T_3 and total T_3 were associated with all-cause mortality (Table 2). In a multivariate analysis, only ejection fraction and total T_3 level were independent predictors. An alternative model showed that free T_3 level was also associated with all-cause mortality after adjustment for ejection fraction (when total T_3 level was not included in the model).

When we considered cardiac mortality, age, sex, ejection fraction, end-diastolic left ventricular diameter, and total T_3 levels were significant univariate predictors. Sex, ejection fraction, and total T_3 (or free T_3) level were the only independent multivariate predictors (Table 2).

Using cutoff values of 20% for left ventricular ejection fraction and a total T_3 level of 1.2 nmol/L (the lower limit of normal), we defined four subgroups of patients (Figure 1). The estimated survival of patients with an ejection fraction >20% and total T_3 level >1.2 nmol/L (90%; 95% confidence interval [CI]: 85% to 96%) was significantly greater than that in patients with an ejection fraction >20% and total T_3 level ≤1.2 pmol/L (73%; 95% CI: 63% to 83%; $P = 0.002$) and in patients with an ejection fraction ≤20% and total T_3 level ≤1.2 pmol/L (61%; 95% CI: 41% to 81%; $P < 0.001$). Survival of patients with an ejection fraction ≤20% and total T_3 level >1.2 pmol/L (83%; 95% CI: 69% to 98%) was significantly greater than that in patients with an ejection fraction ≤20% and total T_3 level ≤1.2 pmol/L (61%; 95% CI: 41% to 81%; $P = 0.02$).

Discussion

Our main finding is that T_3 levels are independent predictors of all-cause and cardiac mortality in patients with dilated cardiomyopathy, and add prognostic information to conventional clinical and functional cardiac parameters. Low T_3 levels had prognostic value even among patients with low ejection fractions. Because total and free T_3 levels are highly correlated, they cannot both be included in the same regression model. Thus, we were unable to determine which measurement is more useful.

Table 2 Factors associated with all-cause and cardiac mortality in univariate and multivariate logistic regression models

	All-cause mortality		Cardiac mortality	
Characteristic (units)	Odds ratio (95% confidence interval)	*P* value	Odds ratio (95% confidence interval)	*P* value
Univariate models				
Age (per 10 years)	1.5 (1.0–2.2)	0.02	1.7 (1.1–2.8)	0.01
Male sex	1.9 (0.9–4.0)	0.06	3.5 (1.3–9.3)	0.01
Ejection fraction (per 10%)	2.0 (1.3–2.7)	0.001	1.7 (1.2–2.4)	0.004
End-diastolic diameter (per 10 mm)	2.2 (1.5–3.2)	0.001	1.9 (1.3–2.9)	0.01
Total T_3 (per 1 nmol/L)	0.3 (0.1–0.5)	0.001	0.4 (0.2–0.7)	0.001
Free T_3 (per 1.0 pmol/L)	0.6 (0.5–0.9)	0.03	0.6 (0.5–0.8)	0.005
Obesity	0.4 (0.1–0.7)	0.006	0.5 (0.2–1.1)	0.08
NYHA (I–IV)	1.3 (1.1–1.6)	0.003	1.2 (0.9–1.5)	0.06
Multivariate model with total T_3				
Male sex			3.5 (1.7–13)	0.04
Total T_3 (per 1 nmol/L)	0.3 (0.1–0.5)	0.001	0.3 (0.2–0.7)	0.002
Ejection fraction (per 10%)	2.0 (1.4–2.8)	0.001	1.7 (1.2–2.5)	0.006
Multivariate model with free T_3				
Free T_3 (per 1.0 pmol/L)	0.6 (0.5–0.8)	0.02	0.6 (0.5–0.8)	0.005
Ejection fraction (per 10%)	1.9 (1.4–2.7)	0.001	1.9 (1.4–2.7)	0.001

NYHA = New York Heart Association; T_3 = triiodothyronine; T_4 = thyroxine.

The systemic actions of biologically active T_3, combined with evidence of its multisystem involvement in heart failure, provided the rationale for testing whether measuring T_3 levels would be useful in risk stratification. The effects of T_3 as a "whole body" marker, rather than a cardiac-specific marker, were reinforced by the absence

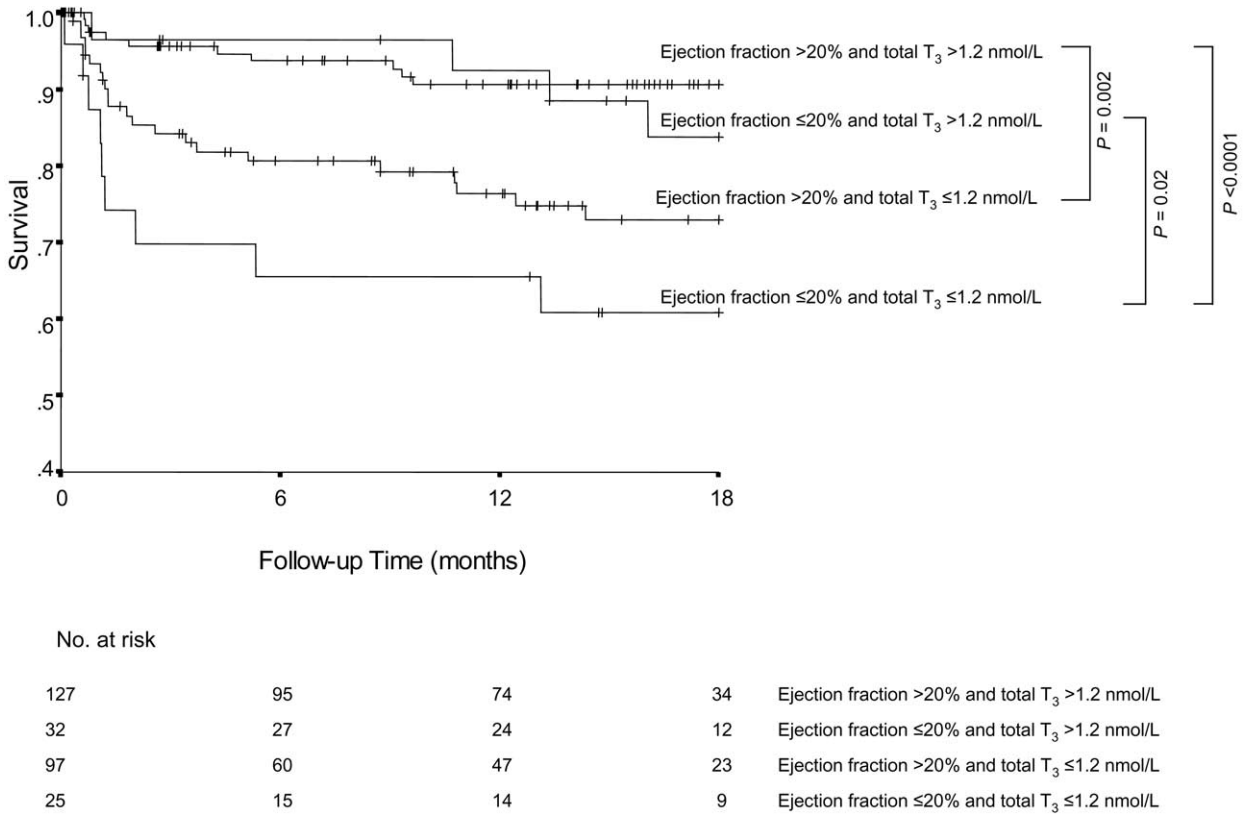

Figure 1 Kaplan-Meier 18-month survival curves in four subgroups identified according to the cutoff values of 20% for left ventricular ejection fraction and triiodothyronine (T_3) levels of 1.2 nmol/L.

of any direct correlation between T_3 level and ejection fraction.

Low T_3 levels may not be an adaptation to chronic illness that minimize catabolism;[8,10] accordingly, the high mortality of patients with very low T_3 levels is not surprising. Our results are also consistent with the adverse prognosis associated with increased peripheral production of biologically inactive reverse T_3 after acute myocardial infarction.[10] Indeed, altered thyroid metabolism may be implicated directly in the progression of heart failure.[9,16-23]

T_3 measurement offers a number of advantages—it is a simple, inexpensive, and reliable blood test that can be measured at most medical laboratories, unlike several other biohumoral markers like serum norepinephrine levels.[24,25]

In contrast with our previous study, in which the prognostic value of T_3 levels was demonstrated in moderately ill patients with various cardiac diseases,[15] the present results were obtained in patients who had been hospitalized for chronic heart failure. Thus, mortality was much higher than in our previous study, although similar to recent reports from similar samples.[26]

In conclusion, T_3 measurement is useful for risk stratification of patients with heart failure. Whether it adds prognostic value to measurements of natriuretic peptide levels remains to be determined. Further studies are needed to assess whether low T_3 levels are just prognostic markers or are implicated directly in the progression of heart failure.

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