

Low-T3 Syndrome

A Strong Prognostic Predictor of Death in Patients With Heart Disease

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Background—Clinical and experimental data have suggested a potential negative impact of low-T3 state on the prognosis of cardiac diseases. The aim of the present prospective study was to assess the role of thyroid hormones in the prognosis of patient population with heart disease.

Methods and Results—A total of 573 consecutive cardiac patients underwent thyroid function profile evaluation. They were divided in two subgroups: group I, 173 patients with low T3, ie, with free T3 (fT3) <3.1 pmol/L, and group II, 400 patients with normal fT3 (≥ 3.1 pmol/L). We considered cumulative and cardiac death events. During the 1-year follow-up, there were 25 cumulative deaths in group I and 12 in group II (14.4% versus 3%, $P < 0.0001$); cardiac deaths were 13 in group I and 6 in group II (7.5% versus 1.5%, $P = 0.0006$). According to the Cox model, fT3 was the most important predictor of cumulative death (hazard ratio [HR] 3.582, $P < 0.0001$), followed by dyslipidemia (HR 2.955, $P = 0.023$), age (HR 1.051, $P < 0.005$), and left ventricular ejection fraction (HR 1.037, $P = 0.006$). At the logistic multivariate analysis, fT3 was the highest independent predictor of death (HR 0.395, $P = 0.003$). A prevalence of low fT3 levels was found in patients with NYHA class III-IV illness compared with patients with NYHA class I-II ($\chi^2 5.65$, $P = 0.019$).

Conclusions—Low-T3 syndrome is a strong predictor of death in cardiac patients and might be directly implicated in the poor prognosis of cardiac patients. (*Circulation*. 2003;107:708-713.)

Key Words: thyroid ■ heart diseases ■ prognosis

The cardiovascular system is one of the most important targets on which thyroid hormones act.^{1,2} More than 80% of the biologically active hormone triiodothyronine (T3) derives from peripheral conversion of prohormone thyroxine (T4) secreted by the thyroid gland.³ Clinical and experimental evidence has shown that T3 plays a major role in modulating heart rate and cardiac contractility as well as arterial peripheral resistance.^{1,2} T3 actions are carried out by binding with specific nuclear receptors that regulate responsive genes encoding for structural and functional cardiac proteins; direct, extranuclear, nontranscriptional effects have also been described.^{1,2}

A typical pattern of altered thyroid hormone metabolism characterized by low T3 circulating levels has been described in patients with acute myocardial infarction^{4,5} and heart failure⁶ and in adults and children after cardiopulmonary bypass.⁷⁻⁹ The principal pathophysiological mechanism underlying low circulating T3 is the reduced enzyme activity of 5' monodeiodinase responsible for converting T4 into T3 in peripheral tissues.^{10,11}

This low-T3 syndrome has commonly been interpreted by the medical community as an euthyroid sick syndrome, an adaptive compensatory and thus beneficial response that

decreases energy consumption in diseased states.¹⁰ This interpretation, however, has recently been questioned. Although clinical data documented the benefit gained from treating patients with synthetic thyroid hormones,¹²⁻²⁰ no studies have focused on documenting a direct link between low-T3 state and poor prognosis in cardiac patients.

To prospectively evaluate the impact of low circulating T3 on the prognosis of a large population of patients with heart disease, in January 1999 we systematically assessed thyroid hormone profile in patients admitted to our cardiology department.

Methods

Patients

Thyroid function profile was prospectively evaluated in all consecutive patients (n=1058) admitted to the cardiology department of the National Council Research Institute of Clinical Physiology (Pisa, Italy) from January 1, 1999, to January 1, 2000. The main initial exclusion criteria included clinical evidence of sepsis or cachexia or concomitant presence of any predominant severe systemic disease and absence of documented heart disease. A total of 208 patients were also excluded from the study, because of overt primary hypothyroidism (thyroid-stimulating hormone [TSH] level > 20 μ IU/mL and free T4 [fT4] < 7.7 pmol/L) in 4 patients, primary hyperthyroidism (free T3 [fT3] > 7.7 pmol/L or fT4 > 32.2 pmol/L with

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undetectable TSH levels) in 8 patients, and coronary revascularization (mostly percutaneous coronary angioplasty) or other major surgical procedures performed before ($n=135$) or within 6 months after the time of thyroid sampling ($n=61$). Therefore, the final population consisted of 573 consecutive patients with heart disease.

During hospitalization, all patients underwent conventional non-invasive and, if necessary, invasive diagnostic procedures for the characterization of heart disease and related risk factors according to the international guidelines. All of the data used in this study were collected at the time of hospitalization.

Thyroid Hormone Sampling

The thyroid function profile was assessed in all patients from 2 to 5 days after the admission. After rapid centrifugation of a venous sample, total T3 (TT3), fT3, total T4 (TT4), fT4, and TSH were all measured during the same morning by a completely automated AIA 600 system (Tosho Corporation). The reference intervals for our laboratory were as follows: TT3 1.23 to 2.60 nmol/L (80.0 to 170.0 ng/dL), TT4 58.4 to 155.8 nmol/L (4.5 to 12.0 $\mu\text{g/dL}$), fT3 3.1 to 6.5 pmol/L (2.0 to 4.2 pg/mL), fT4 9.2 to 24.0 pmol/L (7.1 to 18.5 pg/dL), and TSH 0.30 to 3.80 $\mu\text{IU/mL}$. The interassay coefficient for all determinations ranged between 8% for TSH and 9.7% for TT4.²¹ On the basis of fT3 values, patients were divided into two subgroups: group I, patients with low T3, ie, with fT3 below the lower limit of the reference interval (fT3 <3.1 pmol/L), and group II, patients with normal fT3 (≥ 3.1 pmol/L).

Follow-Up

Follow-up started from the day of thyroid hormone evaluation. Follow-up data were obtained from at least one of the following four sources: reviewing patient's hospital records, contacting patient's physician, interviewing the patient by phone with trained personnel, or periodically examining the patient in the outpatient clinic.²² The events considered were cardiac death and cumulative death (death from any natural cause). The cause of death was derived from medical records or death certificates. The definition of cardiac death required the documentation of significant arrhythmia or cardiac arrest or death attributable to congestive heart failure or myocardial infarction in the absence of any other precipitating factor. In case of death out of hospital not followed by autopsy, sudden unexpected death was classified as cardiac death. Deaths caused by accidents were excluded (follow-up censored at the time of death). In patients undergoing coronary revascularization after 6 months from the time of thyroid sampling, follow-up was censored at the time of revascularization and patients were considered alive at that time.

At our clinical unit, such follow-up, in accordance with the above criteria, started in 1982. Among a total of 8564 hospitalized patients, only 57 (0.6%) were lost at follow-up; follow-up was completed in 100% of the series of patients enrolled in the present study.

Statistical Analysis

Data are expressed as mean \pm SD. Groups were compared for categorical data or frequency of events using the χ^2 test (Yates correction) and for continuous variables using Student's *t* test. All tests were 2-sided, and $P < 0.05$ was considered statistically significant. Linear regression analysis by the least-square method was used to correlate different variables. Univariate and multivariate survival analyses were performed with the Cox proportional-hazards model and a dedicated statistical software (BMDP)²³ to establish the combined risk of cardiac-related death and all causes of death for the variables assessed. Continuous variables (age, left ventricular ejection fraction [LVEF], fT3, fT4, TT3, TT4, TSH, fT3/age ratio, and NYHA functional class) and dichotomized variables (sex, hypertension, diabetes, dyslipidemia, smoking, history of cardiac disease, obesity, history of acute or previous myocardial infarction, diagnosis of primary or postischemic dilated cardiomyopathy, documented myocardial ischemia, and medical treatment) were entered into the model with their individual values or according to the presence (yes) or absence (no) of the variable, respectively. An automatic stepwise selection procedure, using the maximum partial likelihood ratio χ^2

statistic (χ^2 test) to enter ($P \leq 0.05$ level) or remove ($P > 0.05$ level) a covariate into the model, was used. The data were also analyzed according to a modified stepwise procedure, in which the significant individual variables were included in the model in the same order in which they are usually considered by the cardiologist, entering fT3 after all of the other variables (age and sex, overall conventional cardiac risk factors, historic and clinical data, and fT3). Univariate logistic regression analysis was used to determine which variable might have predicted death. To adjust for several risk factors, multivariate logistic analysis was performed with all the variables found to be significant at the univariate analysis entering in a single step; SPSS 9 for Windows was used for regression analysis. The Pearson's product-moment correlation coefficient was used to evaluate the association among continuous variables.

Kaplan-Meier life table, estimating cardiac-related death and all causes of death, was used to summarize the follow-up experience in the patient population. Differences in survival curves were tested with the log-rank test (Mantel-Cox). $P < 0.05$ was considered statistically significant.

Results

Patients

Of the 573 patients, 101 had idiopathic and 17 had postischemic dilated cardiomyopathy, 91 had a previous myocardial infarction, 51 acute myocardial infarction, 189 documented myocardial ischemia, 60 arrhythmia, 11 valvular heart disease, 11 hypertrophic cardiomyopathy, and 42 other heart diseases including pericarditis, myocarditis, and hypertensive cardiomyopathy. Clinical characteristics of total patient population as well as low and normal T3 subgroups are summarized in Table 1. In the follow-up (11 ± 12 months), there were 19 cardiac deaths (10 in the first month) and 37 cumulative deaths (20 in the first month).

Thyroid Function Profile

The mean serum concentrations of TSH and thyroid hormones are summarized in Table 1. There were 173 patients (30% of total population) in group I and 400 patients in group II. fT3 and TT3 strongly correlated ($r=0.82$; $P < 0.0001$), so all results obtained with fT3 (see below) were confirmed by using TT3 values (<1.23 nmol/L for group I and ≥ 1.23 nmol/L for group II, respectively). Free T3 tended to slightly but significantly decrease with age ($r = -0.226$, $P < 0.001$). A statistical difference between the two groups was observed for TSH and TT4. Only 19.2% of patients assuming amiodarone (84 patients, 14.6% of total) had fT3 levels <3.1 pmol/L. The average fT3 value of the amiodarone subgroup was 2.34 ± 0.60 pmol/L, a value similar to that found among patients of group I (2.40 ± 0.66 pmol/L). Finally, patients of group I with low fT3 had slightly, but significantly, lower LVEF compared with patients with normal fT3 (Table 1). When considering all patients in the two groups, however, no correlation was found between fT3 serum concentrations and LVEF ($r=0.07$, $P = \text{NS}$). When taking into account the degree of heart failure (266 patients), low fT3 and normal fT3 were found in 15.7% versus 30% of patients with NYHA I-II and 84.3% versus 70% of patients with NYHA class III-IV, $\chi^2 = 5.65$, $P = 0.019$, respectively.

Low T3 and Mortality

Cumulative deaths were 25 in group I and 12 in group II (14.4% versus 3%, $P < 0.0001$); cardiac deaths were 13 in

TABLE 1. Clinical Characteristics of Study Population

	No.	%	Low T3 (n=173; 30%)	Normal T3 (n=400; 70%)	χ^2 Student's <i>t</i> Test	<i>P</i>
Sex, male/female	320/253	56/44	52%/48%	57.5%/42.5%	1.255	NS
Age, y, mean \pm SD	66 \pm 12		70 \pm 11	64 \pm 12	3.232	0.0012
History of CAD	181	31.6	31.2%	31.7%	0.001	NS
Smoker	204	35.6	26.6%	39.5%	8.226	0.0045
Diabetes	88	15.3	17.3%	14.5%	0.547	NS
Arterial hypertension	279	48.6	48.5%	48.7%	0.002	NS
Dyslipidemia	262	45.7	12.7%	23.2%	7.709	0.0057
Obesity	199	34.7	28.3%	37.5%	4.090	0.0447
Myocardial ischemia	189	33	19.6%	27.2%	3.327	NS
Acute myocardial infarction	51	8.9	12.7%	7.3%	3.803	NS
Previous myocardial infarction	91	15.8	21.3%	13.5%	5.049	0.0248
Idiopathic dilated cardiomyopathy	101	17.6	18.9%	17%	0.230	NS
Postischemic dilated cardiomyopathy	17	2.9	5.2%	2%	3.261	NS
Arrhythmias	60	10.2	8.6%	11.2%	0.604	NS
Valvular heart disease	11	1.9	1.2%	2.2%	0.297	NS
Hypertrophic cardiomyopathy	11	1.9	1.7%	2.2%	0.297	NS
β -Blockers	158	27.5	26%	28.2%	0.201	NS
Amiodarone	84	14.6	19.6%	12.5%	4.384	0.0385
ACE inhibitors	150	26.1	19%	29.2%	5.954	0.0163
LVEF, %, mean \pm SD	52.0 \pm 14		46.2 \pm 14.1	49.0 \pm 13.3	2.251	0.0251
TSH, μ IU/mL, mean \pm SD	1.99 \pm 2.39		2.39 \pm 3.14	1.81 \pm 1.96	2.680	0.0078
TT3, nmol/L, mean \pm SD	1.34 \pm 0.4		0.93 \pm 0.3	1.52 \pm 0.3	21.495	0.0001
TT4, nmol/L, mean \pm SD	112 \pm 48		104 \pm 73	116 \pm 31	2.720	0.0069
ft3, pmol/L, mean \pm SD	3.52 \pm 1.03		2.40 \pm 0.6	4.00 \pm 0.8	24.063	0.0001
ft4, pmol/L, mean \pm SD	17.0 \pm 5.2		16.6 \pm 5.7	17.2 \pm 5.3	0.965	NS
Follow-up, months, mean \pm SD	11 \pm 12		8 \pm 10	12 \pm 12

group I and 6 in group II (7.5% versus 1.5%, $P=0.0006$). Thirty-four (92%) of the cumulative deaths and 17 (89%) of the cardiac deaths were observed in patients with ischemic heart disease or with left ventricular dysfunction. In 33.3% of patients (one third) who had died, a second thyroid hormone profile was available before death, on the average 36 ± 44 days before death. In one third of patients who had died, the hormone profile was obtained outside the hospital. Free T3 serum levels were low in all cases, with a mean value similar to the basal one (ft3 2.01 ± 0.8 versus 2.08 ± 0.5 pmol/L, $P=NS$). Cumulative mortality was similar in patients receiving amiodarone and in patients not receiving treatment (6 of 84, 7%, versus 31 of 489, 6%, respectively, $P=NS$). By univariate analysis, ft3 was the strongest predictor of cumulative death (Table 2). By multivariate analysis, again ft3 was the strongest independent predictor of cumulative death (Table 3). When only cardiac death was considered, LVEF ($\chi^2=16.07$, $P<0.0001$) and dilated cardiomyopathy ($\chi^2=11.33$, $P=0.0008$) were the most important independent predictors at univariate analysis followed by ft3 ($\chi^2=8.87$, $P=0.003$) (Table 2). However, after dyslipidemia, ft3 was the most powerful predictor at multivariate analysis (Table 3).

When interactive procedure was used, ft3 added higher significant prediction of cumulative death after considering all of the other conventional variables (Figure 1). One year

and one month Kaplan-Meier survival curves for cumulative deaths in patients with low versus normal ft3 are shown in Figure 2. Differences in cumulative mortality were particularly evident in the first month of follow-up.

TABLE 2. Univariate Analysis of Predictor of 1-Year Mortality

Variables	χ^2	<i>P</i>
Cumulative death		
ft3	32.50	0.00001
Age	17.11	0.00001
ft3/Age ratio	13.55	0.0002
LVEF	13.04	0.0003
TT4	7.94	0.0048
Previous myocardial infarction	6.23	0.0126
Cardiac death		
ft3	8.87	0.0029
Age	5.94	0.01
ft3/Age ratio	6.14	0.01
LVEF	16.07	0.0001
Previous myocardial infarction	6.45	0.01
Dilated cardiomyopathy	11.33	0.0008

TABLE 3. Multivariate Analysis of Predictors of 1-Year Mortality

Variables	Hazard Ratio	Standard Error	95% CI	P
Cumulative death				
ft3	3.582	0.2784	2.0755 to 6.1815	0.0001
Age	1.051	0.0173	1.0154 to 1.0866	0.005
LVEF	1.037	0.0119	1.0132 to 1.0616	0.006
Dyslipidemia*	2.955	0.4460	1.2331 to 7.0841	0.023
Cardiac death				
FT3	2.359	0.3742	1.1329 to 4.9122	0.016
Age	1.047	0.0243	0.9984 to 1.0982	0.040
LVEF	1.069	0.0178	1.0329 to 1.1075	0.0001
Dyslipidemia*	4.236	0.5922	1.3272 to 13.5246	0.04

*Dichotomized variable.

Univariate and multivariate logistic analysis of data showed ft3 as the most potent and independent predictor of survival time, as highlighted by the higher absolute value for R and by the lower upper limit for the 95% confidence interval for the hazard ratio (see Table 4).

A good correlation was also observed between ft3 values and survival time of the patients who died (Figure 3).

When all 573 patients were subdivided according to low versus normal serum ft4 criteria (ie, ≥ 9.2 pmol/L and < 9.2 pmol/L), only 11 patients (1.9% of total) showed hormonal values below the lower limit of reference interval. Moreover, 1-year survival of patients with low versus normal TSH (cutoff, $0.3 \mu\text{IU/mL}$) was not statistically different between the 2 groups (TSH $\geq 0.3 \mu\text{IU/mL}$: 90.4%; $n=516$ versus TSH $< 0.3 \mu\text{IU/mL}$: 86.6%; $n=57$, $P=NS$).

Discussion

Low thyroid hormone concentrations, in particular low serum T3 concentrations, are a common finding in patients with

Interactive analysis of predictors of 1-year cumulative death

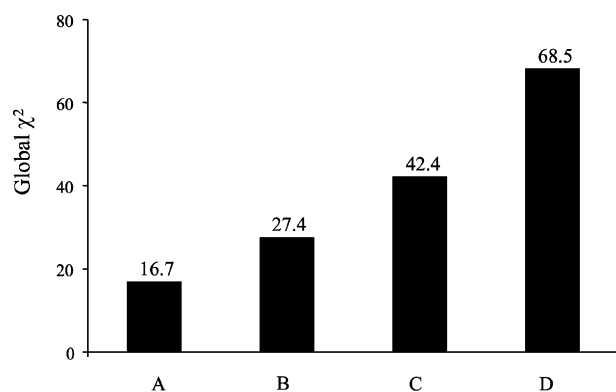


Figure 1. Interactive analysis of predictors of 1-year cumulative death. Global χ^2 values for the following variables: A (age and sex); B (age/sex and cardiac risk factors); C (age/sex, cardiac risk factors, and historical and clinical data); and D (age/sex, cardiac risk factors, historical and clinical data, and ft3).

Cumulative Death

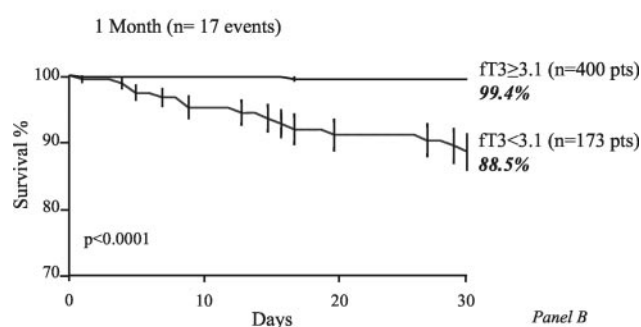
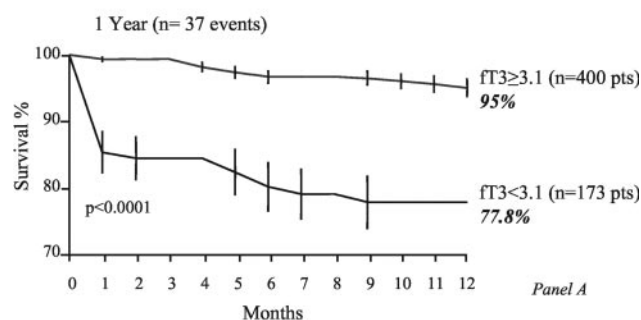


Figure 2. Kaplan-Meier survival curves of patients with low T3 (group I, $n=173$) versus those with normal T3 levels (group II, $n=400$). Events considered: 1-year (A) and 1-month (B) cumulative death.

nonthyroidal illnesses, including cardiac disorders. Its pathophysiological role is not well understood, although the common belief is in favor of an adaptive mechanism to preserve energy.^{1,10} Nonetheless, based on the knowledge of the fundamental actions of T3 on both the heart and vessels, a direct relationship between low circulating levels of T3 and adverse prognosis of cardiac patients has represented an attractive hypothesis in the last few years.² In this respect, it has been postulated that the low T3 state may produce a

TABLE 4. Univariate and Multivariate Logistic Regression*

Variables	Hazard Ratio	95% CI	P	R
Univariate regression				
ft3	0.248	0.145 to 0.425	< 0.0001	-0.294
LVEF	0.954	0.933 to 0.976	0.0001	-0.228
Age	1.066	1.030 to 1.104	0.003	0.200
Diabetes	2.174	1.012 to 4.669	0.046	0.085
TSH	1.126	1.024 to 1.238	0.015	0.120
Multivariate regression				
ft3	0.395	0.207 to 0.622	0.003	-0.217
LVEF	0.959	0.936 to 0.984	0.011	-0.177
Age	1.045	1.008 to 1.083	0.015	0.119

*Among all of the variables assessed (see Statistical Analysis), only the variables found to be significant reported in the Table.

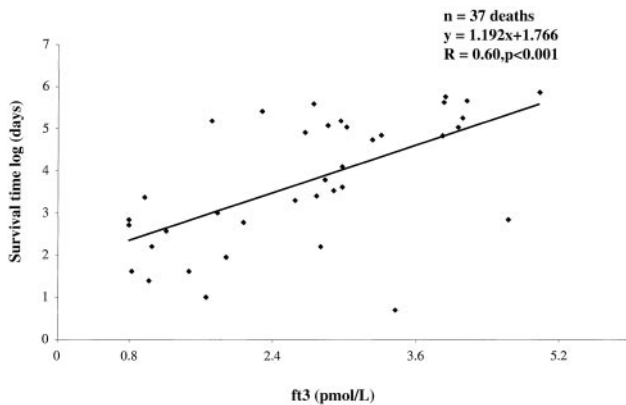


Figure 3. Correlation between ft3 serum concentrations and time of survival (days, logarithmic scale) in all cardiac patients (n=37) who died.

hypothyroid-like syndrome that contributes to the worsening or exacerbation of the intrinsic cardiac disease.^{1,24} The present study clearly shows the existence of a strong association between the reduction of biologically active T3 and mortality in a large population of cardiac hospitalized patients. Low T3 circulating levels were found in 30% of the studied population, a percentage that falls in the range of previously reported data on hospitalized patients for complex systemic diseases^{11,25–27} and remarkably similar to that recently observed by Ascheim and Hryniewicz²⁸ in a population of 132 cardiac outpatients. The Kaplan-Meier curves show the highly significant increase in the incidence of cardiac and cumulative deaths in patients with low T3 compared with patients with normal T3 levels. If one considers that the total mortality might represent the primary end point in clinical investigation, as recently proposed,²⁹ the relevance of the low T3 state as a strong, independent predictor of mortality in cardiac patients is even more emphasized by our results from univariate and multivariate logistic analysis as well as from interactive analysis (see Tables 2 through 4 and Figure 1) and from the good correlation we found between ft3 values and survival time of patients who died (Figure 3). It is noteworthy that both time-dependent and time-independent analyses revealed the fundamental role of T3 serum concentrations compared with the other parameters in predicting death.

The low T3 state could be at first interpreted as just a biological risk factor of cumulative and cardiovascular mortality and not as a direct causal factor contributing to the poor prognosis of cardiac patients. In regard to this important issue, some comments are necessary.

First, patients of both groups with low and normal ft3 values, respectively, did not differ in all the other conventional risk factors; a slightly higher prevalence of smoking, obesity, and dyslipidemia was indeed observed in group II, with normal ft3, compared with group I (see Table 1). Second, all patients were admitted to the same clinical unit in the same period of time and received care by the same medical staff using the same standard diagnostic and therapeutic decision-making procedures. Third, the strong relationship between low T3 and increased mortality was present

independently of the treatment with amiodarone, a drug known to reduce T4 peripheral conversion into T3 and thus T3 serum concentration. Actually, despite a slight but significant prevalence in patients receiving amiodarone observed in the group with low T3 (19.6% versus 12.5%, see Table 1), the mortality rate in these patients with low T3 levels did not differ from that of patients receiving amiodarone with normal T3. Fourth, clinical and experimental knowledge of the fundamental role of thyroid hormones, in particular of T3, in the cardiovascular homeostasis favors the hypothesis of a direct relationship between low T3 syndrome and mortality in patients with heart disease. In this respect, some beneficial effects of T3 treatment have been observed in patients submitted to cardiosurgery procedures,^{14,15,30} in patients with heart failure,^{16,20} and in animals after acute myocardial infarction.^{19,31} Moreover, experimental data support the hypothesis that cardiac gene expression and function are altered in animal³² and human³³ models of low T3 state.³² However, whether changes in thyroid hormone metabolism contribute to impairment of cardiac function remains to be determined; only the demonstration of beneficial effects on cardiovascular end points of long term T3 replacement in cardiac patients with low T3 state can answer this fundamental issue.

In conclusion, low T3 concentrations are a strong independent predictive marker of poor prognosis in cardiac patients and might represent a determinant factor directly implicated in the evolution and prognosis of these patients.

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