Value of Low Triiodothyronine and Subclinical Myocardial Injury for Clinical Outcomes in Chest Pain

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Abstract: *Background:* Low triiodothyronine (T3) levels and subclinical myocardial injury may be associated with adverse cardiac and cerebrovascular (CCV) events in individuals without clinically apparent coronary heart disease (CHD). The aim of this study was to determine the associations of a low T3 level and subclinical myocardial injury with the development of adverse CCV events in individuals without clinically apparent CHD. *Methods:* T3 and high-sensitivity cardiac troponin T (hs-cTnT) levels were analyzed in 250 patients with chest pain free of CHD and heart failure. The primary end point was the composite of sudden cardiac death, ischemic stroke, newly developed atrial fibrillation, pericardial effusion and thrombosis. *Results:* Throughout a mean follow-up of 15.6 months, the primary end point happened in 17 patients (6.8%). Kaplan-Meier analysis disclosed a notably higher overall occurrence rate in patients with hs-cTnT levels ≥0.014 ng/mL and in patients with T3 <60 ng/dL. An exaggerated hazard was observed in patients with combined high hs-cTnT and low T3 levels. After adjustment, the hazard ratio for overall events in patients with high hs-cTnT/low T3 versus normal hs-cTnT/T3 was 11.72 (95% confidence interval, 2.83–48.57; $P = 0.001$). *Conclusions:* In patients with chest pain without clinically obvious CHD, high hs-cTnT combined with low T3 was associated with adverse cardiac/CCV events and was an independent predictor of overall events even after adjustment. These data suggest the importance of systemic factors, such as low T3 syndrome, in the development of adverse cardiac/CCV events beyond advancing clinical atherosclerotic coronary disease in patients with chest pain.

Key Indexing Terms: Triiodothyronine; Troponin; Death; Stroke; Atrial fibrillation. **[Am J Med Sci 2015;350(5):393–397.]**

Thyroid hormones play a vital role in the physiological aspects of the cardiovascular systems, one of their primary targets, in healthy subjects.[1,2] Indeed, several studies provide evidence of a connection between altered thyroid circumstances and the development and progression of cardiac disease.[3] Appropriate cardiovascular function depends on thyroid hormone homeostasis. Bioactive triiodothyronine (T3) is a potent controller of the inotropic and lusitropic properties of the heart through its effects on myosin isoforms and calcium-managing proteins.[2,4] Low T3 syndrome is defined as low levels of circulating T3 in individuals with normal or slightly decreased thyrotropin (TSH) and thyroxine (T4) concentrations.

Among several biomarkers recently recognized for their ability to noninvasively detect subclinical myocardial injury,[5] cardiac troponin T (cTnT) has been known to be independently associated with coronary heart disease (CHD).[6,7] Therefore, cTnT is a recommended biomarker for use in the detection of myocardial infarction (MI) and in acute coronary syndromes.[8] Indeed, several authors have proposed that somewhat elevated troponin values may designate subclinical cardiac injury and that high-sensitivity cTnT (hs-cTnT) may presently permit the detection of early phases of myocardial damage masked in the past.[9,10] Kim et al[11] previously reported that T3 levels were inversely associated with hs-cTnT levels in patients with no clinically evident CHD. However, no information is available regarding the impact of a low T3 level and subclinical myocardial injury on long-term clinical outcomes.

The aim of current investigation was to determine the associations of a low T3 level and subclinical myocardial injury with the occurrence of adverse cardiac and cerebrovascular (CCV) events in individuals without clinically apparent CHD.

METHODS

Subjects

A total of 365 consecutive patients with chest pain who underwent TSH, free thyroxine (FT4), T3 and hs-cTnT measurements in the emergency department or outpatient department of the cardiovascular center of the Chosun University Hospital between November 2011 and January 2012 were included in current investigation with endorsement from the Chosun University Hospital Research Ethics Committee 2014-05-003. Patients who were diagnosed with overt hyperthyroidism or CHD were excluded. Therefore, 250 patients were included in this analysis.

Blood Collection and Measurement of Biomarkers

Venous blood samples were obtained in K2-EDTA–coated tubes (Becton Dickinson Vacutainer Systems, Franklin Lakes, NJ) and serum-separator blood-drawing tubes. TSH, T3 and FT4 concentrations were determined by the immunoradiometric assay and radioimmunoassay using RIA-gnost FT4, TSH and T3 kits (CISbio International, Cedex, France). The tests were executed within 2 hours after sample collection (normal range: TSH, 0.25–4 mIU/L; FT4, 0.7–1.8 ng/dL; T3, 60–190 ng/dL). The levels of hs-cTnT were measured using the Cobas 6000 (Roche Diagnostics, Penzberg, Germany) with a lower limit of detection of 0.003 ng/mL within 2 hours after sample collection.

Outcomes

Clinical information was gained from outpatient records or telephone interviews. The primary end point was a composite of sudden cardiac death (SCD), ischemic stroke, newly

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developed atrial fibrillation (AF), pericardial effusion and thrombosis. SCD was defined as death by terminal rhythm disorders verified on electrocardiography (ECG), death observed by a witness within 1 hour of cardiac symptoms onset, or unexpected death, presumably or possibly of cardiac origin. Ischemic stroke was defined as a neurologic deficit lasting longer than 24 hours. Cerebral computed tomography or magnetic resonance imaging was available in all patients with ischemic stroke.

Statistical Analysis

All values are expressed as mean ± standard deviation or as number (percentages). Baseline characteristics were compared between groups using 1-way analysis of variance for continuous variables and the χ^2 test for noncontinuous variables. Event-free survival curves were constructed using the Kaplan-Meier method, and outcomes were compared using the log-rank test.

Independent predictors of overall events were analyzed using Cox proportional hazards regression. Baseline clinical, biochemical and angiographic data with a P value of <0.05 were entered into a forward stepwise multivariate Cox proportional hazards model. Statistical analyses were carried out using SPSS 12.0 (SPSS, Inc, Chicago, IL), and a P value of <0.05 was considered statistically significant.

RESULTS

Baseline Biomarker Values

Mean TSH, T3, FT4 and hs-cTnT levels in the overall population were 5.97 ± 15.0 mIU/L (median, 1.92 mIU/L; interquartile range [IQR], 1.02–3.31 mIU/L), 84.9 ± 36.1 (median, 81.7 ng/dL; IQR, 58.1–110.0 ng/dL), 1.18 ± 0.42 ng/dL (median, 1.15 ng/dL; IQR, 0.98–1.38 ng/dL) and 0.013 ± 0.021 ng/mL (median, 0.003 ng/mL; IQR, 0.003–0.017 ng/dL), respectively. In total, 115 subjects (46%) had quantifiable levels (>0.003 ng/mL) of hs-cTnT. Overall, 28% of participants had high hs-cTnT levels (≥0.014 ng/mL).

Clinical Characteristics

The mean age of patient was 60.2 years, and 42.4% were male (Table 1). Patients were stratified into 4 groups according to cutoff values of 0.014 ng/mL for hs-cTnT and 60 ng/dL for T3: normal hs-cTnT/T3, normal hs-cTnT/low T3, high hs-cTnT/normal T3 and high hs-cTnT/low T3. Baseline clinical characteristics and biochemical data on the basis of combined

TABLE 1. Baseline characteristics and biochemical data on the basis of combined hs-cTnT and T3

Characteristics	Total (N = 250)	Normal hs-cTnT/ T3 (n = 150)	Normal hs-cTnT/low T3 (n = 30)	High hs-cTnT/normal T3 (n = 37)	High hs-cTnT/low T3 (n = 33)	*P*
Age (yr)	60.2 ± 16.5	55.7 ± 15.8	61.6 ± 14.5	66.5 ± 12.9	72.5 ± 16.9	<0.001
Men	42.4%	46.7%	33.3%	40.5%	33.3%	0.349
Hypertension	35.2%	32.0%	23.3%	45.9%	48.5%	0.073
LVH[a]	13.2%	10.0%	3.3%	32.4%	15.2%	0.001
Diabetes	26.0%	21.3%	30.0%	35.1%	33.3%	0.215
Smoker[b]	20.8%	24.0%	16.7%	21.6%	9.1%	0.261
TSH (mIU/L)	5.97 ± 15.0	3.29 ± 8.1	7.98 ± 8.5	6.36 ± 16.1	3.96 ± 12.28	0.082
Free T4 (ng/dL)	1.18 ± 0.4	1.20 ± 0.4	0.92 ± 0.6	1.27 ± 0.5	1.21 ± 0.5	0.003
T3 (ng/dL)	84.9 ± 36.1	102.9 ± 28.8	44.2 ± 11.2	86.1 ± 24.9	38.8 ± 13.2	<0.001
hs-cTnT (ng/mL)	0.013 ± 0.021	0.004 ± 0.002	0.005 ± 0.002	0.032 ± 0.018	0.052 ± 0.020	<0.001
eGFR (mL/min per 1.73 m^2)[c]	71.2 ± 20.5	73.4 ± 14.5	75.2 ± 20.6	66.4 ± 28.2	62.8 ± 29.6	0.014
LDL-C (mg/dL)	105.5 ± 31.4	107.4 ± 33.5	71.7 ± 28.7	109.6 ± 21.4	112.2 ± 17.4	<0.001
HDL-C (mg/dL)	47.0 ± 12.4	48.8 ± 12.5	42.2 ± 11.8	44.8 ± 11.5	42.9 ± 12.2	0.041
CCB	10.4%	7.3%	10.0%	16.2%	18.2%	0.171
RAAS blocker	18.4%	16.7%	6.7%	32.4%	21.2%	0.044
Diuretics	5.6%	6.7%	0.0%	2.7%	9.1%	0.327
Beta blocker	9.2%	8.7%	10.0%	10.8%	9.1%	0.979
OHA	12.0%	12.0%	20.0%	10.8%	6.1%	0.396
Insulin	1.2%	0.0%	3.3%	5.4%	0.0%	0.031
Statin	12.4%	10.7%	13.3%	18.9%	12.1%	0.596
Warfarin	2.4%	2.0%	0.0%	5.4%	3.0%	0.508
SBP (mm Hg)	117 ± 12.7	117 ± 11.8	116 ± 12.0	120 ± 15.1	118 ± 14.2	0.543
DBP (mm Hg)	72 ± 8.8	72 ± 8.8	71 ± 6.5	74 ± 9.5	74 ± 9.6	0.501

Cutoff level of hs-cTnT and T3; 0.014 and 60 ng/dL, respectively.

[a] LVH calculated by electrocardiographic Cornell criteria.

[b] "Smoker" means active smokers and exsmokers in whom smoking is stopped less than 1 year before enrollment.

[c] eGFR was calculated using the modification of diet in renal disease formula: GFR = $186.3 \times (\text{serum creatinine})^{-1.54} \times (\text{age})^{-0.203} \times (0.742$ if female).

CCB, calcium channel blocker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; hs-cTnT, high-sensitivity cardiac troponin T; LDL-C, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; OHA, oral hypoglycemic agent; RAAS, renin angiotensin aldosterone system; SBP, systolic blood pressure; T3, triiodothyronine; T4, thyroxin; TSH, thyroid-stimulating hormone.