Journal of Cardiology 72 (2018) 215–219

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Low T3 syndrome improves risk prediction of in-hospital cardiovascular death in patients with acute myocardial infarction

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ARTICLE INFO

Article history:
Received 18 November 2017
Received in revised form 19 January 2018
Accepted 2 February 2018
Available online 23 March 2018

Keywords:
Low T3 syndrome
In-hospital cardiovascular death
Acute myocardial infarction
TIMI risk score

ABSTRACT

Background: Low triiodothyronine (T3) syndrome (LT3S) is frequently seen in patients with acute myocardial infarction (AMI). We examined the association between LT3S and severity of myocardial injury and determined whether LT3S adds predictive value over thrombolysis in myocardial infarction (TIMI) risk score for in-hospital cardiovascular (CV) death.

Methods: Of 2459 AMI patients, 529 pairs of euthyroid and LT3S individuals with similar baseline characteristics were identified using 1:1 propensity score matching. LT3S was defined as free T3 (fT3) <2.36 pg/mL, normal values of thyroid-stimulating hormone and free thyroxin. Primary outcome was in-hospital CV death. Receiver operating characteristic curves were generated to assess the predictive effects of fT3, TIMI risk score, and TIMI-LT3S risk score on in-hospital CV death.

Results: LT3S was found in 23.3% of patients with AMI. The peak values of cardiac troponin I in ng/mL and N-terminal pro-brain natriuretic peptide in ng/mL were significantly higher in LT3S: 6.6 (1.3–19.6) *vs.* 3.5 (0.8–12.1), $p < 0.001$ and 3625 (1046–12,776) *vs.* 2158 (774–6759), $p < 0.001$. Patients with LT3S had significantly higher rate of in-hospital CV death than those without (4.7% *vs.* 1.7%, $p = 0.005$). Lower levels of fT3 yielded an area under the curve (AUC) of 0.741 for predicting CV death. LT3S, when added to the TIMI risk score, significantly increased AUC for in-hospital CV death than TIMI risk score alone (0.775 *vs.* 0.738, $p = 0.005$).

Conclusions: LT3S was associated with more severe myocardial injury and increased in-hospital CV mortality in patients with AMI. Furthermore, it improved risk prediction of in-hospital CV death post-AMI when it was added to the TIMI risk score.

Introduction

Thyroid hormone levels are often altered in response to acute myocardial infarction (AMI) in the absence of pre-existing thyroid disease [1]. The most common alteration of thyroid function, known as low triiodothyronine (T3) syndrome (LT3S), is characterized by decreased levels of serum T3, normal levels of thyroid-stimulating hormone (TSH) and thyroxin (T4) [2]. T3, in the form of free T3 (fT3) as biologically active thyroid hormone, has been considered to have multiple effects on the cardiovascular system, including upregulating effective contractile function, decreasing systemic vascular resistance, as well as improving endothelial function and promoting angiogenesis [3–6], thus, the decrease in T3 may lead to less cardiovascular protection in patients with AMI. Indeed, prior studies have shown that LT3S is associated with poor outcomes in patients with heart disease [7–9]. However, whether LT3S can improve risk prediction of in-hospital outcomes in patients with AMI has not been evaluated. The current study aimed to examine the association between LT3S and severity of myocardial injury and to determine whether LT3S adds predictive value over thrombolysis in myocardial infarction (TIMI) risk score for in-hospital cardiovascular (CV) death given that TIMI risk score is a widely accepted risk assessment model for short-term outcome in patients with AMI [10,11].

Methods

As shown in Fig. 1, a total of 2745 patients aged >18 years who were admitted to Beijing Friendship Hospital between January

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https://doi.org/10.1016/j.jjcc.2018.02.013
0914-5087/

Fig. 1. Study population and selection. AMI, acute myocardial infarction; T3, triiodothyronine.

2013 and February 2017 with a confirmed AMI diagnosis were considered for enrollment into the study. AMI diagnosis was based on (a) symptoms consistent with acute coronary syndrome, (b) increased serial cardiac troponin profile consistent with acute injury, and (c) typical electrocardiographic changes or significant angiographic coronary stenosis [12]. Two hundred eighty-six patients were excluded because they had known thyroid diseases, or were treated with amiodarone, dopamine, or corticosteroids before hospital admission, considering these drugs would affect the thyroid hormone levels [13,14]. The study protocol was developed following the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institution's human research committee.

The demographic data, laboratory data, and echocardiographic results were collected at admission and during hospitalization for AMI. All patients had blood samples collected within 24 h of presentation and tested for thyroid hormone, glucose, lipids, high-sensitivity C-reactive protein (hsCRP), erythrocyte sedimentation rate (ESR), fibrinogen, albumin, alanine aminotransferase, and creatinine by a certified laboratory at our institution. The reference ranges of thyroid hormone were: TSH (0.51–4.85 μIU/mL), fT3 (2.36–3.7 pg/mL), fT4 (free T4, 0.71–1.2 ng/dL). Patients were divided based on thyroid hormone profile: euthyroid group – with normal values of TSH, fT3, and fT4 and LT3S group – with fT3 <2.36 pg/mL, normal values of TSH and fT4. For each patient, the TIMI risk scores for STEMI and NSTEMI population were respectively calculated at admission [10,11]. TIMI-LT3S risk score was calculated as the arithmetic sum of the TIMI risk score and thyroid status score (euthyroid = 0, LT3S = 1).

The peak values of cardiac troponin I (cTnI) and N-terminal pro-brain natriuretic peptide (NTproBNP) after serial measurements were used as indicators of myocardial injury. The normal range of cTnI was 0–0.03 ng/mL. Echocardiography was performed on the second day of hospitalization using a VIVID 7 (General Electric Medical Systems, Horten, Norway). In-hospital outcomes were collected and confirmed by medical records. Primary outcome was in-hospital CV death. Secondary outcomes included the severity of myocardial injury, length of stay and in-hospital major adverse cardiac events (MACE) which was defined as a composite of CV death, re-infarction, and stroke.

Propensity score matching was performed to assemble euthyroid and LT3S cohorts with similar baseline characteristics due to significant differences found between the 2 groups (Table 1). Propensity score was calculated with the use of a multivariable logistic regression model with LT3S (dichotomized as yes or no) as the dependent variable. Baseline characteristics and cardiovascular risk factors were entered into the model as co-variables to control for possible confounders [including age, gender, body mass index (BMI), hypertension, diabetes mellitus, dyslipidemia, smoking status, and classification of AMI]. Matching was performed in a 1–1 ratio without replacement, with caliper width of 0.2 times the standard deviation of the logit of the propensity scores. Propensity score matching identified 529 paired individuals from each cohort: 34.2% of euthyroid and 92.3% of LT3S (Fig. 1). After matching, there were no significant differences between the baseline variables between the 2 groups (Table 1).

Demographic and biochemical characteristics of the study population with and without LT3S were compared using the Mann–Whitney *U*-test for continuous variables and the Chi-square test for categorical variables. Receiver operating characteristics (ROC) curves were generated to demonstrate the ability of fT3, TIMI risk score, and TIMI-LT3S risk score to predict in-hospital CV death. Area under the curve (AUC) and cut-off value of fT3 were calculated. Comparison between ROC curves was done using the Delong method provided by MedCalc software program (Ostend, Belgium). All other analyses were performed with the use of SPSS 22.0 (Chicago, IL, USA). A value of $p < 0.05$ was considered statistically significant.

Results

Among a total of 2459 patients enrolled in the study, 574 (23.3%) were found to have LT3S at the time of admission for AMI.

Table 1
Baseline characteristics of euthyroid and LT3S cohorts before and after propensity score matching.

Clinical variables	Before match			After match		
	Euthyroid (n = 1548)	LT3S (n = 574)	p	Euthyroid (n = 529)	LT3S (n = 529)	p
Age, years	62 (54–73)	74 (61–81)	<0.001	70 (61–79)	71 (60–79)	0.329
Male sex, %	77.1	58.7	<0.001	64.5	62.4	0.483
BMI, kg/m^2	25.7 (23.4–27.8)	24.6 (22.1–27.0)	<0.001	24.7 (22.8–26.9)	24.6 (22.6–27.1)	0.575
Hypertension, %	64.0	68.7	0.047	65.4	68.8	0.239
DM, %	32.4	39.3	0.003	38.2	38.9	0.801
Dyslipidemia, %	43.7	41.8	0.431	41.6	41.8	0.950
Smoker, %	65.2	49.4	<0.001	54.4	51.6	0.234
STEMI, %	45.2	50.2	0.042	50.7	49.0	0.580

Values are median (interquartile range) unless otherwise indicated.
BMI, body mass index; DM, diabetes mellitus; LT3S, low triiodothyronine syndrome; STEMI, ST elevation myocardial infarction.

As shown in Table 2, within the propensity score-matched cohorts, the LT3S group had lower TSH, fT3, fT4, total T3, total T4 levels, and higher fasting glucose levels, while other glucose parameters including glycated albumin and glycosylated hemoglobin were similar between the 2 groups. The LT3S cohorts had lower total cholesterol, triglyceride, and low-density lipoprotein cholesterol levels. They were more likely to have lower red blood cell counts and albumin and higher serum creatinine levels. There were no significant differences in platelet or serum alanine transaminase levels between the 2 groups. Interestingly, the LT3S cohorts also had higher concentrations of inflammatory markers including white blood cell counts, hsCRP, ESR, and fibrinogen. As Table 3 shows, angiographic and procedural characteristics were similar between patients with and without LT3S, except for more use of intra-aortic balloon pumping in patients with LT3S.

Outcomes in euthyroid and LT3S cohorts after propensity score matching are presented in Table 4. The peak values of cTnI and NTproBNP were significantly higher in LT3S. No significant difference was observed in the post-percutaneous coronary intervention left ventricular ejection fraction. Subjects with LT3S had increased length of hospital stay compared with those without. Noteworthy, LT3S cohorts showed a significantly higher rate of in-hospital CV death than euthyroid cohorts (4.7% *vs.* 1.7%, p = 0.005) although the difference in MACE did not reach statistical significance (8.1% *vs.* 5.9%, p = 0.15).

Table 2
Laboratory parameters in euthyroid and LT3S cohorts in propensity score-matched participants.

	Euthyroid (n = 529)	LT3S (n = 529)	p
TSH, μIU/mL	1.4 (0.9–2.1)	1.2 (0.7–2.0)	<0.001
fT3, pg/mL	2.6 (2.5–2.8)	2.2 (2.0–2.3)	<0.001
fT4, ng/dL	0.94 (0.83–1.11)	0.88 (0.79–1.01)	<0.001
TT3, ng/dL	76.4 (68.9–87.0)	60.8 (52.8–69.8)	<0.001
TT4, ng/mL	84.6 (73.6–94.7)	78.4 (68.2–89.2)	<0.001
Fasting glucose, mmol/L	5.7 (4.9–7.6)	6.1 (5.0–8.0)	0.031
GA, %	15.0 (13.3–18.3)	15.4 (13.6–18.5)	0.104
HbA1C, %	6.0 (5.6–6.9)	6.0 (5.6–7.0)	0.530
TC, mmol/L	4.4 (3.7–5.0)	4.2 (3.5–4.8)	0.005
TG, mmol/L	1.33 (1.01–1.89)	1.25 (0.89–1.75)	0.019
HDL-C, mmol/L	1.04 (0.91–1.24)	1.05 (0.88–1.23)	0.491
LDL-C, mmol/L	2.5 (2.0–3.0)	2.4 (1.9–2.9)	0.006
WBC, $\times 10^9$/L	7.4 (6.0–9.0)	7.9 (6.3–9.9)	0.004
RBC, $\times 10^9$/L	4.1 (3.8–4.6)	3.9 (3.5–4.4)	<0.001
Platelet, $\times 10^9$/L	209 (172–253)	204 (168–254)	0.294
hsCRP, mg/dL	5.7 (2.0–13.1)	13.0 (3.6–25.1)	<0.001
ESR, mm/h	14 (7–28)	20 (11–34)	<0.001
Fibrinogen, g/L	3.0 (2.5–3.7)	3.2 (2.6–4.0)	0.008
Albumin, g/L	38.3 (35.5–41.2)	37.1 (33.5–39.6)	<0.001
ALT, U/L	21.0 (15.0–31.0)	21.0 (15.0–32.0)	0.590
Creatinine, μmol/L	79.0 (67.7–95.0)	85.0 (70.5–110.1)	<0.001

Values are median (interquartile range).
ALT, alanine aminotransferase; ESR, erythrocyte sedimentation rate; fT3, free triiodothyronine; fT4, free thyroxin; GA, glycated albumin; HbA1C, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; LT3S, low triiodothyronine syndrome; RBC, red blood cell count; TC, total cholesterol; TG, total triglyceride; TSH, thyroid-stimulating hormone; TT3, total triiodothyronine; TT4, total thyroxin; WBC, white blood cell count.

Table 3
Clinical and procedural characteristics in euthyroid and LT3S cohorts in propensity score matched participants.

	Euthyroid (n = 529)	LT3S (n = 529)	p
Prior myocardial infarction, %	14.7	12.5	0.282
Prior PCI, %	13.4	14.0	0.789
Prior CABG, %	3.4	1.9	0.125
Time to treatment, min	240 (90–660)	235 (70–660)	0.235
Primary CAG, %	61.6	68.0	0.125
Door to balloon time, min	86 (70–151)	83 (66–150)	0.146
Target vessel			
LAD as IRA, %	45.0	43.9	0.521
Multi-vessel disease, %	82.1	81.3	0.772
Pre-procedural TIMI 3 flow, %	51.5	45.7	0.119
Post-procedural TIMI 3 flow, %	98.0	96.7	0.266
IABP use, %	0.8	3.2	0.004
Stent rate, %	88.3	91.8	0.101
Stent number ≥ 2, %	32.7	30.8	0.509
Total stent length, mm	38 (28–66)	38 (29–69)	0.289
Successful PCI rate, %	96.6	95.1	0.242
Complete revascularization rate, %	91.9	90.7	0.533
TIMI risk score	4 (3–5)	4 (3–6)	0.124

Values are median (interquartile range) unless otherwise indicated.
CABG, coronary artery bypass graft surgery; CAG, coronary arteriography; IABP, intra-aortic balloon pumping; IRA, infarct-related artery; LAD, left anterior descending coronary artery; LT3S, low triiodothyronine syndrome; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

Table 4
Clinical outcomes in euthyroid and LT3S cohorts in propensity score matched participants.

	Euthyroid (n = 529)	LT3S (n = 529)	p
cTnI, ng/mL	3.5 (0.8–12.1)	6.6 (1.3–19.6)	<0.001
NTproBNP, pg/mL	2158 (774–6759)	3625 (1046–12776)	<0.001
LVEF < 50%, n (%)	192 (36.3)	186 (35.2)	0.700
Length of stay, day	8 (6–10)	9 (7–11)	0.001
MACE[a], n (%)	31 (5.9)	43 (8.1)	0.148
In-hospital cardiovascular death, n (%)	9 (1.7)	25 (4.7)	0.005
Re-infarction, n (%)	16 (3.0)	14 (2.6)	0.711
Stroke, n (%)	8 (1.5)	5 (0.9)	0.402

Values are median (interquartile range) unless otherwise indicated.
cTnI, cardiac troponin I; NTproBNP, N-terminal pro-brain natriuretic peptide; LT3S, low triiodothyronine syndrome; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events.
[a] MACE was defined as a composite of cardiovascular death, re-infarction, and stroke. There were 2 patients in the euthyroid group and 1 patient in the LT3S group having both re-infarction and in-hospital cardiovascular death.

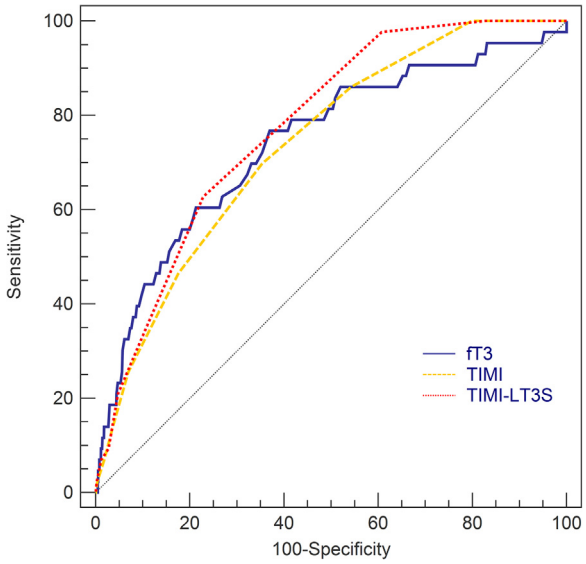

Fig. 2. Receiver-operator characteristic curves of fT3, TIMI risk score, and TIMI-LT3S risk score to predict in-hospital cardiovascular death in patients with AMI. AUC for lower levels of fT3 was 0.741 (95% CI, 0.722–0.760). AUC for TIMI risk score was 0.738 (95% CI, 0.718–0.757) and it increased to 0.775 (95% CI, 0.756–0.792) when including LT3S. The difference in AUCs between TIMI risk score and TIMI-LT3S was statistically significant, $p = 0.0019$. AMI, acute myocardial infarction; AUC, area under the curve; fT3, free triiodothyronine; LT3S, low triiodothyronine syndrome; TIMI, thrombolysis in myocardial infarction.

For prediction of in-hospital CV death in patients with AMI, the ROC curve of fT3, TIMI risk score, and TIMI-LT3S risk score are displayed in Fig. 2. Lower levels of fT3 yielded an AUC of 0.741 (95% CI, 0.722–0.760). The cut-off value of 2.415 pg/mL had a sensitivity of 76.7% and specificity of 63.0% for predicting in-hospital CV death. AUC for the TIMI risk score was 0.738 (95% CI, 0.718–0.757) and was significantly increased to 0.775 (95% CI, 0.756–0.792) when adding LT3S to the TIMI risk model ($p = 0.0019$).

Discussion

Our study found that patients with LT3S had more severe myocardial injury, increased inflammatory markers, longer length of hospital stay, and higher rates of in-hospital CV death, compared with those with normal T3. Furthermore, the study showed that adding LT3S to the TIMI risk score significantly improved risk prediction of in-hospital CV death in patients with AMI.

The prevalence of LT3S among patients with AMI is 23.3% in this study, which has been reported to be 5–35% in the literature [1,15,16]. The wide range could be attributed to different patient populations. During the acute coronary event, factors that seem to be associated with development of LT3S include older age, female, lower BMI, history of hypertension, and diabetes mellitus. There have been conflicting results about the correlation between T3 levels and myocardial damage [17–19]. In this study, we found higher peak cTnI and NTproBNP levels indicating more severe myocardial injury in the LT3S group.

Our study showed that patients with LT3S had higher levels of plasma inflammatory markers including white blood cell counts, hsCRP, ESR, and fibrinogen. It has been reported that interferon-α can cause disturbances in thyroid hormone metabolism in healthy volunteers [20]. About 85% of T4 is primarily secreted by the thyroid gland and then converted to T3 by the enzyme 5′-monodeiodinase in liver, kidneys, and skeletal muscles. Inflammatory cytokines have been reported to lower the 5′-monodeiodinase activity [21], which support the hypothesis that LT3S may be developed as response to the increased inflammatory state during AMI.

The increased rate of in-hospital CV death in post-AMI patients with LT3S found in our study is consistent with previous reports [1,16,22]. ROC showed AUC of 0.741 with lower levels of fT3 for in-hospital CV death. Moreover, we demonstrated that adding LT3S significantly improved AUC of 0.738 with the TIMI risk score alone to AUC of 0.775 with inclusion of LT3S in the risk prediction. However, it cannot be determined if the decrease in fT3 is directly responsible for the increased cardiovascular death. Because patients with LT3S also had more extensive myocardial damage and higher serum creatinine levels, which likely attributed to the increased mortality.

The decrease in fT3 was thought to be an adaptive response to acute diseases by decreasing catabolism and conserving energy expenditure [10]. Supplementation of T3 has not been proven to be effective in improving outcomes among patients with noncardiac illnesses-induced LT3S [23]. However, the effect of T3 replacement in patients with AMI [9,24] remains to be further investigated.

Several limitations in our study should be taken into account: (1) Patients were from a single center. (2) The outcome data were limited to in-hospital events. (3) Thyroid hormone measurements were performed only at admission for AMI. It is not known if asymptomatic LT3S was existing and if fT3 would change post-AMI. (4) The number of in-hospital CV deaths ($n = 34$) limited our statistical capability to correct for all risk variables included in the TIMI risk score in this analysis. (5) Details such as the classification of coronary lesions could not be precisely evaluated based on the retrospectively collected data. Further prospective multi-center studies with larger sample size and follow-up assessment of thyroid hormone are needed to confirm our findings.

Conclusions

LT3S was associated with more severe myocardial injury, longer hospitalization, and increased in-hospital cardiovascular mortality in patients with AMI. In addition, LT3S improved risk prediction of in-hospital CV death when it was added to the TIMI risk score. The TIMI-LT3S risk score may provide a better risk stratification for increased risk of in-hospital CV death.

Conflict of interest

The authors declare that there is no conflict of interest.

Acknowledgements

This research was supported by Research Foundation of Beijing Friendship Hospital, Capital Medical University (No. YYQDKT2016-10), National Natural Science Foundation of China (No. 81670315), and Beijing Natural Science Foundation (No. 7172059).

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