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Free triiodothyronine level correlates with statin responsiveness in acute myocardial infarction

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Abstract

Background Although thyroid hormone (TH) has important effects on lipid metabolism, the relationship between TH and statin responsiveness has never been investigated. We hypothesize that TH plays an important role in statin responsiveness in patients with acute myocardial infarction (AMI). **Methods** Consecutive 1091 hospitalized AMI patients in Fuwai hospital (Beijing, China) were enrolled into this current study. The study population was divided into three groups based on the intensity of statin treatment: low-intensity (n = 221), moderate-intensity (n = 712) and high-intensity (n = 158). Lipid levels were measured after statin therapy lasting for 10–14 days. The association between TH, lipid profile levels and achievement of low-density lipoprotein cholesterol (LDL-C) lowering goals was explored in patients with AMI on statin therapy. **Results** By general linear analysis, a significant linear trend between free triiodothyronine (FT3) and LDL-C level (linear coefficient r = –0.082, P = 0.001) and FT3 and total cholesterol (TC) level (r = –0.105, P = 0.031) was observed in the moderate-intensity statin group. A more apparent linear trend was detected in the high-intensity statin group (for LDL-C: r = –0.113, P = 0.005; for TC: r = –0.172, P = 0.029, respectively). However, no significant correlation was observed in the low-intensity statin group. Compared with the low-FT3 group (defined as FT3 < 1.79 pg/mL), the OR (95% CI) for attaining a LDL-C < 3.0mmol/L was found to be 2.217 (1.001–4.839) in the higher FT3 group (> 2.95 pg/mL). The OR (95% CI) for attaining the more intensive goal (LDL-C < 1.8mmol/L) was 2.836 (1.014–5.182). **Conclusions** Our study reveals that variation in FT3 levels is related to the cholesterol-lowering responsiveness of statins in AMI patients. These findings suggest that low FT3 may be a factor responsible for lack of LDL-C goal attainment and patients' poor responsiveness to statin treatment.

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Keywords: Acute myocardial infarction; Free triiodothyronine; Hypothyroid; Statin

1 Introduction

Treatment guidelines[1,2] recommend use of statins in acute myocardial infarction (AMI) based on a large number of randomized clinical trials[3–5] indicating that these inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase benefit patient outcomes. The most favorable and beneficial effects of statin therapy focus on reducing plasma low-density lipoprotein cholesterol (LDL-C), but the degree of lipid-lowering efficacy of statins differs. Attaining lipid-lowering goals is still a challenge in clinical practice in the era of statins,[6] and gaining understanding of potential influences on statin efficacy may provide additional benefits. Thyroid function significantly influence lipid metabolism, including the synthesis, mobilization, and degradation of lipids.[7] Although population-based studies exploring this association have been carried out, to our knowledge, no studies have directly illustrated the association between thyroid hormone (TH) and lipid levels in patients on statin therapy.

In AMI patients, especially those with left ventricular dysfunction, a transient but significant fall in circulating TH levels is common. Previous studies enrolling a limited number of patients indicated that low T3 levels correlated

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with high risk of subsequent mortality of AMI.[8,9] In parallel studies in animal models of AMI, TH was shown to facilitate the recovery of stunned myocardium and LV function.[10] Changes in plasma TH levels can result in a series of alterations of metabolic parameters related to cardiovascular disease risk.[11] Beyond the impact on adipocyte metabolism, THs influence the production of adipokines and are associated with insulin resistance.[12] Based on studies indicating that TH is a critical modulator of lipid metabolism, and taken together with the fact that TH levels can be significantly altered during AMI,[13] we hypothesized that down-regulated TH levels in AMI may exert negative effects on the efficacy of statin therapy.

In the present study, we aimed to clarify whether TH levels are associated with the lipid-lowering efficacy of statins in AMI. Our study may help to reveal a pathophysiological role of thyroid dysfunction in AMI and further characterize a potentially important risk factor. As it is well established that statins exhibit most of their LDL-C reducing effects within two weeks, study of AMI subjects with 10-14 days of hospitalization duration would appear to provide an appropriate model to address this question.

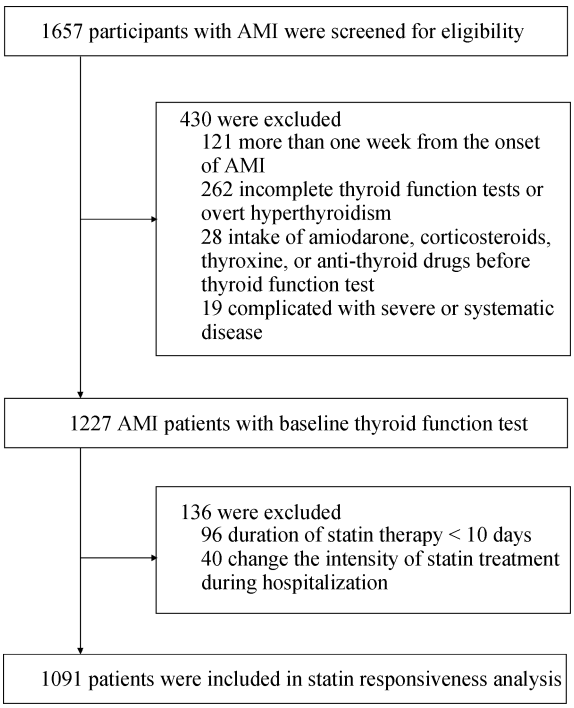

Figure 1. Study diagram showing number of patients available for baseline thyroid function test and statin responsiveness analysis. AMI: acute myocardial infarction.

2 Methods

2.1 Study group

A total of 1091 consecutive patients with the diagnosis of AMI were enrolled into the study. This population belongs to an initial AMI cohort which is shown in the flow chart (Figure 1). They were admitted to the Department of Cardiology of Fuwai Hospital for evaluation and treatment of AMI from January 2011 to December 2013. Diagnosis of AMI was established by tests of creatine kinase-MB and cardiac troponin I, in additional to typical electrocardiographic changes and/or characteristic chest pain.[14] Exclusion criteria were concomitant presence of situations as follows: overt hyperthyroidism; therapy with amiodarone, glucocorticoids, THs, or anti-thyroid drugs; interventional or surgical procedures performed within the last three months before hospitalization. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the ethics committee of Fuwai Hospital, China. All patients enrolled in the study provided informed consent.

2.2 Thyroid function test and biochemical assessments

Thyroid status was evaluated at the initial hospitalization and before patients were discharged. The median duration between hospital admission and second thyroid function test was 11 days. Twelve-hour-fasting blood samples were drawn and the serum levels of TH were measured using radioimmunoassay (Immulite 2000; Siemens, Germany) in the Nuclear Medicine Department of Fuwai Hospital. Enzymatic methods were used to measure serum levels of fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG), LDL-C, and high-density lipoprotein cholesterol (HDL-C) with Olympus reagents and automated spectrophotometry performed on an Olympus AU5400 system (Olympus Corporation, Tokyo, Japan). All measurements were performed at the clinical laboratory of Fuwai Hospital to minimize interassay variation.

The reference intervals of THs and other parameters in our laboratory are as follows: thyrotropin (TSH), 0.55–4.78 mIU/L; free triiodothyronine (FT3), 1.79–4.09 pg/mL; free thyroxine (FT4), 0.8–1.88 ng/dL; total triiodothyronine (TT3), 0.65–1.91 ng/mL; total thyroxine (TT4), 4.29–12.47 μg/dL; fasting plasma glucose (FPG), 3.9–6.3 mmol/L; TC, 3.6–6.2 mmol/L; LDL-C, 0.5–3.36 mmol/L; HDL-C, 0.8–1.5 mmol/L; TG, 0.4–1.8 mmol/L. Hypercholesterolemia was defined in accordance with the National Cholesterol Education Program Adult Treatment Panel III criteria (NCEP/ATPIII) as TC above 6.2 mmol/L.[15]

2.3 Statins dose regimens and statin intensity grading

Patients who were compliant with inclusion criteria were enrolled into this study and took statins once daily (before

bedtime) for 10–14 days: atorvastatin 10, 20, 40, or 80 mg; rosuvastatin 5, 10, or 20 mg; simvastatin 10, 20, 40, or 80 mg; fluvastatin 40 or 80 mg; pitavastatin 1, 2 or 4 mg; pravastatin 20, 40, or 80 mg. Based on the average LDL-C lowering efficacy observed in previous clinical studies, the degrees of statin treatment intensity are summarized into three ranking grades on the basis of previous studies and guidelines:[16,17] first, low intensity; second, moderate intensity; and third, high intensity. Detailed corresponding table of statin dosage and LDL-C lowering intensity grade are shown in Table 1S.

2.4 Statistical analysis

Statistical analysis was assessed with a SPSS statistical package 18.0 for Windows. All continuous variables are presented as mean ± SD and unpaired *t* tests were used to compare groups. Analysis of variance was used to compare means across multiple groups. Non-continuous and categorical variables are presented as frequencies or percentages and were compared using the χ^2 test. Pairwise comparison was performed using Tukey-Kramer test for continuous variables and χ^2 test for Bonferroni correction for categorical variables. To explore the relationship of TH with TC, LDL-C, HDL-C, and TG, we performed a general linear analysis in which TH was a categorical variable using SPSS version 18.0 (SPSS Inc., Chicago, IL). The relationships between parametric variables were assessed by Spearman's correlation analysis. In addition, the associations were adjusted for the potential confounding effects of gender, age, BMI, smoking status, glucose levels. Before the evaluation, all missing data were processed using the expectation-maximization algorithm available in the SPSS 18.0 software. A two-sided P value < 0.05 was considered statistically significant.

3 Results

3.1 Baseline clinical characteristics by categories of FT3 level

Table 1 shows the baseline clinical characteristics and TH levels of the study population. Patients with AMI were divided into five groups by the lower limit of normal value of FT3 and quartiles of FT3 levels within the normal range (< 1.79 pg/mL, n = 92; 1.80–2.42 pg/mL, n = 263; 2.43–2.67 pg/mL, n = 250; 2.68–2.95 pg/mL, n = 256; > 2.95 pg/mL, n = 251). Patients with FT3 < 1.79 pg/mL had the highest percentage of female and the lowest percentage of smokers. Significant differences were also detected with respect to age, left ventricular ejection fraction (LVEF), serum creatinine, TSH and percentage of diabetes mellitus.

Table 1. Baseline characteristics of study population according to the FT3 level.

	FT3 level, pg/mL					*P* value
	< 1.79 (*n* = 82)	1.80–2.42 (*n* = 260)	2.43–2.67 (*n* = 248)	2.68–2.95 (*n* = 252)	> 2.95 (*n* = 249)	
Age, yrs	63.11 ± 10.28	60.75 ± 11.03	56.91 ± 11.04	54.77 ± 10.39	54.66 ± 11.82	< 0.001
Male	52 (63.41%)	179 (68.85%)	207 (83.47%)	228 (90.48%)	230 (92.37%)	< 0.001
STEMI	53 (64.63%)	147 (56.54%)	153 (61.69%)	142 (56.35%)	136 (54.61%)	0.120
Smoking	36 (43.90%)	146 (56.15%)	153 (61.69%)	173 (68.65%)	197 (79.12%)	< 0.001
Hypertension	40 (48.78%)	124 (47.69%)	121 (48.79%)	105 (41.67%)	101 (40.56%)	0.162
DM	27 (32.93%)	76 (29.23%)	48 (19.35%)	46 (18.25%)	55 (22.09%)	0.007
Systolic BP, mmHg	119.85 ± 17.38	121.61 ± 19.00	123.25 ± 18.21	121.33 ± 18.29	120.34 ± 16.92	0.092
Diatolic BP, mmHg	67.39 ± 12.47	72.14 ± 12.7	76.56 ± 12.49	75.16 ± 10.91	76.10 ± 11.01	0.048
Killip Ⅲ-Ⅳ	7 (8.54%)	8 (3.07%)	8 (3.22%)	2 (1.56%)	6 (2.39%)	0.002
LVEF	51.72% ± 10.37%	53.12% ± 8.29%	55.16% ± 9.23%	57.54% ± 7.39%	57.38% ± 7.29%	0.001
Creatinine, μmol/L	91.23 ± 27.74	88.32 ± 25.48	83.14 ± 25.25	85.32 ± 17.23	83.92 ± 16.91	0.019
LDL-C, mmol/L	2.64 ± 0.83	2.64 ± 0.84	2.34 ± 0.91	2.51 ± 0.92	2.52 ± 0.91	0.579
HDL-C, mmol/L	1.01 ± 0.23	1.03 ± 0.28	1.04 ± 0.43	0.99 ± 0.38	0.98 ± 0.31	0.131
TC, mmol/L	4.62 ± 1.05	4.46 ± 1.02	4.32 ± 0.98	4.29 ± 0.80	4.24 ± 1.10	0.140
TG, mmol/L	1.63 ± 1.27	1.79 ± 1.17	1.69 ± 0.8	1.91 ± 1.09	1.77 ± 0.90	0.414
FPG, mmol/L	6.81 ± 2.91	6.98 ± 2.87	6.6 ± 2.73	6.57 ± 2.71	6.15 ± 2.28	0.022
Hs-CRP, μg/mL	8.26 ± 4.95	9.09 ± 4.39	7.74 ± 6.39	6.81 ± 4.78	5.19 ± 4.38	0.001
TSH, μIU/L	3.67 ± 10.31	2.95 ± 1.93	2.38 ± 5.18	2.19 ± 2.98	1.98 ± 1.29	0.017
FT4, pg/mL	1.05 ± 0.19	1.14 ± 0.21	1.15 ± 0.19	1.22 ± 0.29	1.26 ± 0.25	0.083

The data are presented as mean ± SD or *n* (%). BP: blood pressure; DM: diabetes mellitus; FPG: fasting plasma glucose; FT3: free triiodothyronine; FT4: free thyroxine; HDL-C: high-density lipoprotein cholesterol; Hs-CRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; TC: total cholesterol; TG: triglycerides; TSH: thyroid stimulating hormone; STEMI: ST segment elevation myocardial infarction.

No significant difference was found with regard to blood pressure and lipid profiles (including LDL-C, HDL-C, TC, and TG). The imbalance among these multiple confounding factors validated the necessity of the adjustment.

3.2 Correlation analysis between FT3 levels and serum lipid levels after statin treatment

As mentioned in methods section, LDL-C reducing efficacy differs among different kinds and dosages of statins, so we divided the AMI population into three groups based on the intensity of different kinds of statin treatment: low (n = 221), moderate (n = 712) and high (n = 158) intensity statin treatment group. As considerable inter-individual variation still exists in the lipid response to statin treatment beyond the dosage-effect of statin, we explored the relationship between TH levels and lipid levels after statin treatment lasting for 10–14 days.

As shown in Figure 2, levels of lipids (including TC, TG, LDL-C and HDL-C) do not show apparent trend across the categories of FT3. However, the correlation analysis performed in relation to intensity of statin showed something different: FT3 level correlates with TC and LDL-C in the moderate and high intensity statin groups. Spearman correlation analysis between FT3 and lipid levels is shown in Table 2. In the low-intensity statin group, no significant correlation was observed. But in moderate- and high-intensity

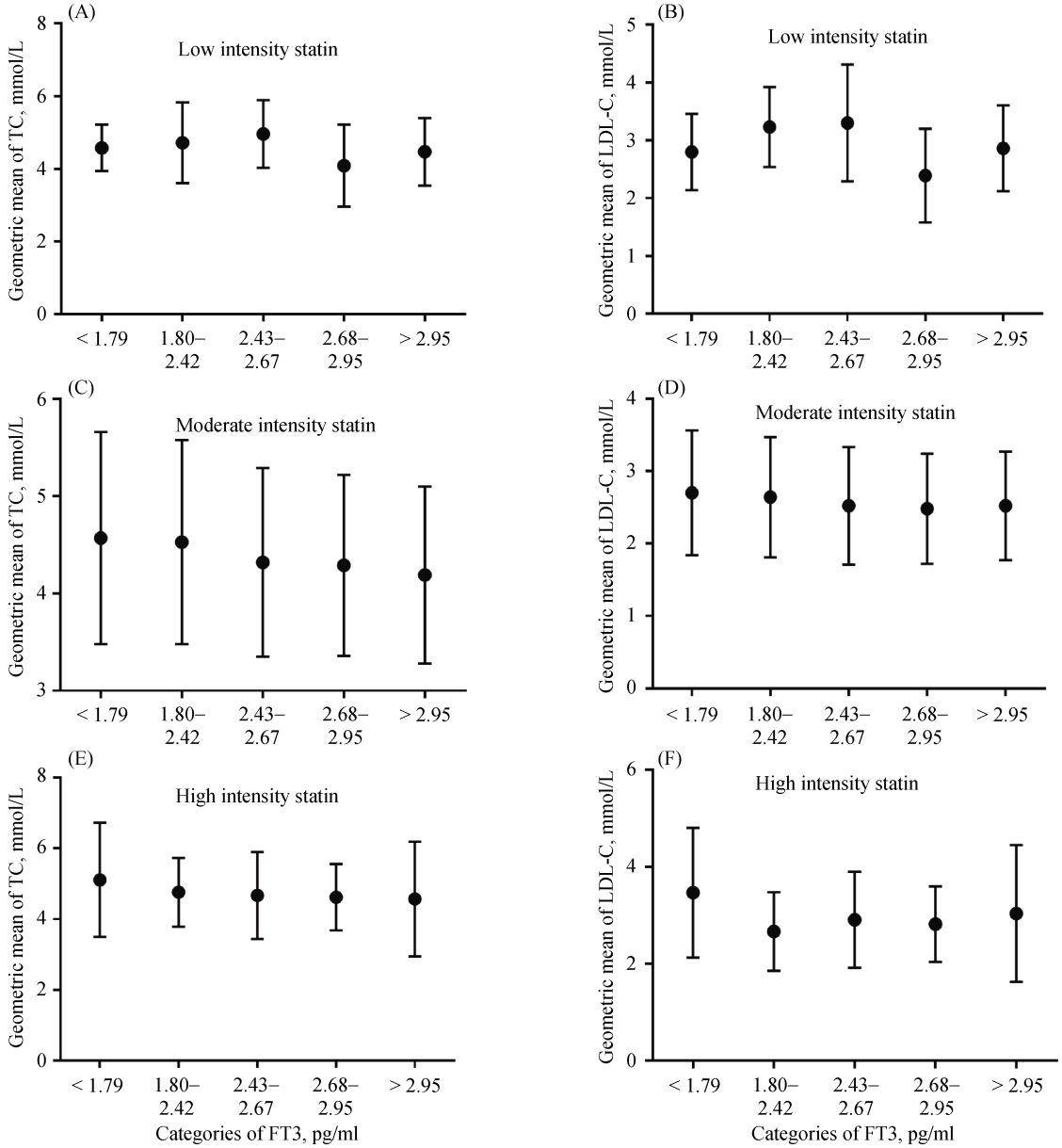

Figure 2. Correlation of FT3 levels with serum lipid levels response to different intensity grade of statins treatment. Geometric mean of TC and LDL-C in low- (A&B), moderate- (C & D); and high-intensity statin groups (E & F). FT3: free triiodothyronine; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol.

Table 2. Correlation analysis of TH levels and serum lipids levels.

	TG	TC	LDL-C	HDL-C
Low-intensity statins	r = –0.152, P = 0.015	r = –0.015, P = 0.816	r = 0.030, P = 0.637	r = 0.068, P = 0.284
Moderate-intensity statins	r = –0.021, P = 0.587	r = –0.124, P = 0.001	r = –0.153, P < 0.001	r = –0.061, P = 0.108
High-intensity statins	r = 0.096, P = 0.475	r = –0.160, P = 0.031	r = –0.149, P = 0.065	r = –0.168, P = 0.207

Values shown were adjusted for gender, age, BMI, smoking status. BMI: body mass index; FPG: fasting plasma glucose; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides; TH: thyroid hormone.

statin groups, FT3 showed significantly negative correlation with TC (r = –0.124, P = 0.001; r = –0.160, P = 0.031; respectively). FT3 also had a negative correlation with LDL-C level in the moderate-intensity statin group (r = –0.153, P < 0.001) and a slight negative trend in the high-intensity statin group (r = –0.149, P = 0.065). Other thyroid function parameters (TSH, FT4, TT4, and TT3) had no significant relationship with these lipid profiles.

In addition, general linear analysis was performed to further reveal the relationship between FT3 and lipid levels with adjustment for confounding factors. Table 3 shows the association between categories of FT3 and geometric means of serum lipids. A significant decrease in TC and LDL-C values with increasing levels of FT3 were found in the moderate- and high-intensity statin groups. These estimates were adjusted for gender, age, BMI, smoking status, and glucose levels. Table 3 shows a significant linear trend between FT3 and TC levels (linear coefficient = –0.105; P = 0.031) and FT3 and LDL-C levels (linear coefficient = –0.082; P = 0.001) in the moderate-intensity statin group. A more apparent linear trend was detected between FT3 and TC levels (linear coefficient = –0.172; P = 0.029) and FT3 and LDL-C levels (linear coefficient = –0.113; P = 0.005) in the high-intensity statin group. Thus, subjects with low FT3 levels had slightly higher adjusted TC and LDL-C levels compared with those with high FT3 levels (Figure 2). These results clearly indicate the significant negative correlation between FT3 and TC and LDL-C levels in the background of moderate- to high- intensity statin treatment.

FT4 and TSH levels were also compared, but no significant trend could be detected among FT4, TSH and any other type of lipid examined.

3.3 The relationship between FT3 levels and LDL-lowering goals

As a linear trend was only found in the moderate and high intensity statin group, we only calculated the percentage of LDL-lowering goals in these two groups. Since different LDL-lowering goals are recommended in guidelines, we chose the basic goal (European LDL-C goal, LDL-C < 3.0 mmol/L) and the intensive goal (LDL-C < 1.8 mmol/L, or reduction of LDL-C > 50%) to explore the influence of FT3 on statin responsiveness. As shown in Figure 3, the low-T3 group (defined as FT3 < 1.79 pg/mL) had the lowest percentage attaining the LDL-lowering goal, with gradual increasing trend in the other four increasingly higher FT3 categories within the normal range (for the basic goal: 62.26%, 68.70%, 82.26%, 81.76%, and 88.70%; for the intensive goal: 25.35%, 33.66%, 37.51%, 41.79%, and 43.55%).

The OR for attaining LDL-lowering goal adjusted by FT3 categories was calculated by logistic regression analysis. Compared with the low-T3 group (defined as FT3 < 1.79 pg/mL), the OR (95% CI) for attaining basic LDL-

Table 3. Geometric mean of serum lipids according to FT3 category in AMI subjects.

Categories of FT3	TG	TC	LDL-C	HDL-C
Low-intensity statin				
< 1.79, pg/mL	2.35 ± 0.57	4.58 ± 0.14	2.80 ± 0.16	0.96 ± 0.38
1.80–2.42, pg/mL	1.73 ± 0.65	4.72 ± 1.11	3.23 ± 0.69	0.84 ± 0.19
2.43–2.67, pg/mL	1.88 ± 0.42	4.96 ± 0.93	3.30 ± 1.01	1.09 ± 0.14
2.68–2.95, pg/mL	2.15 ± 1.05	4.09 ± 1.13	2.39 ± 0.81	1.29 ± 0.67
> 2.95, pg/mL	1.94 ± 0.64	4.47 ± 0.93	2.86 ± 0.74	0.99 ± 0.39
Linear Coeff	–0.007	0.014	–0.059	0.031
P for linear trend	0.257	0.921	0.114	0.219
Moderate-intensity statin				
< 1.79, pg/mL	1.62 ± 1.40	4.57 ± 1.09	2.70 ± 0.86	1.07 ± 0.36
1.80–2.42, pg/mL	1.82 ± 1.21	4.53 ± 1.05	2.64 ± 0.83	1.04 ± 0.25
2.43–2.67, pg/mL	1.64 ± 0.79	4.32 ± 0.97	2.52 ± 0.81	1.03 ± 0.28
2.68–2.95, pg/mL	1.94 ± 1.42	4.29 ± 0.93	2.48 ± 0.76	1.01 ± 0.25
> 2.95, pg/mL	1.75 ± 0.88	4.19 ± 0.91	2.52 ± 0.75	0.98 ± 0.24
Linear Coeff	0.009	–0.105	–0.082	0.041
P for linear trend	0.328	0.031	0.001	0.219
High-intensity statin				
< 1.79	1.63 ± 1.02	5.11 ± 1.61	3.47 ± 1.34	1.02 ± 0.25
1.80–2.42	1.50 ± 0.59	4.76 ± 0.97	2.67 ± 0.81	0.94 ± 0.21
2.43–2.67	1.79 ± 1.20	4.67 ± 1.23	2.91 ± 0.99	1.11 ± 0.32
2.68–2.95	1.74 ± 1.12	4.62 ± 0.94	2.82 ± 0.78	0.93 ± 0.20
> 2.95	1.66 ± 0.68	4.57 ± 1.62	3.04 ± 1.41	0.91 ± 0.29
Linear Coeff	–0.007	–0.172	–0.113	–0.005
P for linear trend	0.551	0.029	0.005	0.262

Values shown were adjusted for gender, age, BMI, smoking status, FPG. AMI: acute myocardial infarction; BMI: body mass index; FPG: fasting plasma glucose; FT3: free triiodothyronine; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides.

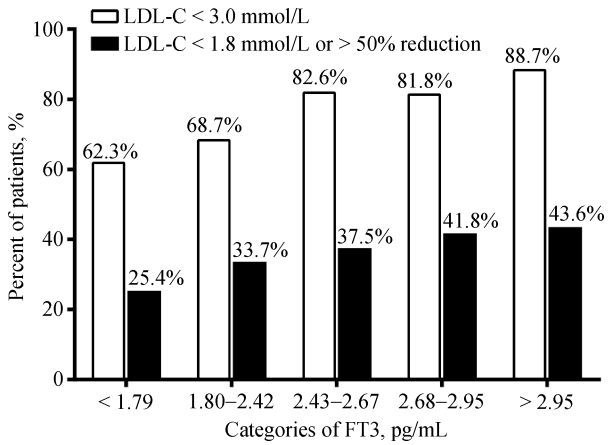

Figure 3. Percentages of patients who had LDL-C values below the basic goal (LDL-C < 3.0 mmol/L) and intensive goal (LDL-C < 1.8 mmol/L, or reduction of LDL-C > 50%) according to the categories of FT3. *N* = 82 for FT3 < 1.79 pg/mL group, *n* = 260 for FT3 within 1.80–2.42 pg/mL group, *n* = 248 for FT3 within 2.43–2.67 pg/mL group, *n* = 252 for FT3 within 2.68–2.95 pg/mL group and *n* = 249 for FT3 > 2.95 pg/mL group. FT3: free triiodothyronine; LDL-C: low-density lipoprotein cholesterol.

lowering goal were found to be 1.219 (0.501–4.225), 1.883 (1.081–3.005), 1.872 (1.042–3.776), and 2.217 (1.001–4.839) in the other four increasingly higher FT3 groups within normal range. For the intensive goal, the OR (95% CI) were found to be 1.386 (0.829–3.749), 1.518 (0.749–4.382), 2.334 (1.102–5.037), and 2.836 (1.014–5.182), respectively.

4 Discussion

In the present study, which includes a large volume of AMI patients, we explored the relationship between FT3 and serum lipid profiles response to statin treatment. Significant correlations were found between FT3 and TC levels and FT3 and LDL-C levels in the background of moderate-high intensity statin therapy. The percentage of attaining LDL goals increased with higher FT3 levels. Moreover, the relationship remained significant after further adjusting for traditional risk factors. The other parameters of thyroid function (including TSH, FT4, TT4 and TT3) didn't show any association with serum lipid levels after statin treatment. Our results clearly indicate the significant influence of FT3 on the cholesterol-lowering efficacy of statin treatment. To the best of our knowledge, this study is the first to address the contribution of TH levels to lipid parameters response to statin therapy.

One of the major findings in our study was that the influence of FT3 level on statin treatment exists in the moderate-high intensity statin regimen, but not in the low-intensity group. The LDL-lowering efficacy of statins is mainly by inhibiting HMG-CoA reductase activity, leading to decreases in hepatic cholesterol content and resulting in an up-regulation of hepatic LDL receptors. This procedure has apparent cross-talk with TH.[18–20] A previous study has shown that deficiency of T3 can result in significant decrease of the HMG-CoA reductase and T3 supplement can help restore the reductase activity,[21] suggesting an underlying mechanism for altered statin responsiveness related to FT3 levels. As considerable inter-individual variation exists in statin treatment, we have to take into account the individual variation of drug metabolism and disposition to attain the LDL-lowering goals in high-risk populations. The present study indicates that thyroid status might act as an important modulator in statin responsiveness, especially in high-risk patients who need intensive statin therapy.

Another interesting finding in the present study is that only FT3 levels, among the TH profiles, correlates with lipid levels. FT3 is the biologically active TH molecule, of which more than 80% is generated in peripheral tissues by 5'monodeiodination from T4. In both animal experiments and clinical observations, investigators have found that the down-regulation of T3 could happen immediately in the acute phase of AMI while levels of TSH and FT4 do not change significantly.[22] This may explain why the other thyroid function parameters did not correlate with serum lipid parameters response to statin treatment. Although changes in FT3 levels are partly transient and may recover after the acute phase in some patients, low FT3 level is associated with high mortality in AMI, suggesting that down-regulation of FT3 level is not only a physiological feedback response, but may also be involved in the progression of AMI.[8]

THs have variable effects on lipid metabolism. It has been consistently shown in experimental and clinical data that even mild thyroid dysfunction may lead to lipid metabolic abnormalities.[23] Additionally, TH receptors (TR) can act as an endocrine modulator of metabolic regulation and interact with other nuclear receptors.[24,25] Thyroid function not only regulates cholesterol synthesis, but is also involved in cholesterol degradation and mediates the activity of key enzymes.[26] The cholesterol-lowering effect of TH is mainly by regulating the expression of LDL-C receptors (LDLR) on hepatocytes and modulating the activity of cholesterol-α-monooxygenase.[27,28] Sequentially, it is not difficult to understand that LDL-C elimination was reduced in conditions of hypothyroidism.

Statins are the cornerstone of cholesterol lowering pharmacotherapy for the prevention and management of atherosclerotic cardiovascular disease (ASCVD). Emerging evidence has shown a consistent linear relationship between

LDL-C lowering effect response to a statin and the relative reduction in the risk of ASCVD outcomes.[29] Therefore, statin responsiveness becomes increasingly relevant, which is clearly exampled by an intravascular ultrasound study in patients with angiographic coronary artery disease.[30] In this study, non-responders or hypo-responders to a statin were at greater risk of progressive ASCVD. Some studies point out that early administration of a statin has beneficial effects on vascular system that are not directly related to their impact on lipid metabolism before primary interventional therapy in AMI patients.[31] Interesting findings have shown that restoration of TH signaling with T3 or TR-β selective agonists GC-1 and KB2115 are capable of markedly reducing serum cholesterol in mice devoid of functional LDLRs via inducing Cyp7a1 expression and stimulating the conversion and excretion of cholesterol as bile acids.[32, 33] Such a cholesterol-lowering effect is different from those of statins, which work primarily by inducing the expression of hepatic LDLR.

Despite the encouraging findings, our study has some limitations. The first one is that the statins treatment period (10–14 days) was relatively short compared with most previous studies of statin efficacy. However, it has been well established that most of the LDL-C reducing effects of statins occur within two weeks. Second, lipid level tests before statin treatment were only available in 55% of the initially evaluated patients, so the present study could not resolve the ambiguity due to the lack of changes in lipid level before and after statin treatment. Finally, the intensity grade of statin therapy may not completely represent the same efficacy of lowering-LDL, thus leading confounders in the correlation analysis. The role of TH levels and lipid profile response to a particular kind of statin needs to be further evaluated in a large population. Strengths of the present study include the well-characterized AMI cohort, complete information of lipid level and THs tests, and the exclusion of drug administration that might affect TH profiles.

In conclusion, we found a clear relationship between FT3 and serum lipid profile in response to statin treatment after AMI. Significant correlations were found between FT3 and TC levels and FT3 and LDL-C levels in the background of moderate-high intensity statin therapy. The relationship between FT3 and cholesterol-lowering efficacy of statin in AMI patients warrant further investigation.

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Table S1. High-, moderate-, and low-intensity of statin therapy (based on previous studies and our experience).

Atorvastatin	Rosuvastatin	Simvastatin	Fluvastatin	Pitavastatin	Pravastatin	Intensity grade
		10 mg	40 mg	1 mg	20 mg	Low
10 mg		20 mg	80 mg	2 mg	40 mg	Low
20 mg	5 mg	40 mg		4 mg	80 mg	Moderate
40 mg	10 mg	80 mg				High
80 mg	20 mg					High