RESEARCH

Triiodothyronine (T3), inflammation and mortality risk in patients with acute myocardial infarction

Salman Razvi[1,2], Avais Jabbar[1,3], Arjola Bano[4], Lorna Ingoe[2], Peter Carey[5], Shahid Junejo[5], Honey Thomas[6], Caroline Addison[7], David Austin[8], John P Greenwood[9] and **Azfar G Zaman[1,3]**

[1]Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK
[2]Department of Endocrinology, Gateshead Health NHS Foundation Trust, Gateshead, UK
[3]Department of Cardiology, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
[4]Department of Cardiology, Institute of Social and Preventive Medicine, University of Bern, Bern University Hospital, Bern, Switzerland
[5]Departments of Endocrinology and Cardiology, South Tyneside and Sunderland NHS Foundation Trust, Sunderland, UK
[6]Department of Cardiology, Northumbria Healthcare NHS Foundation Trust, Cramlington, UK
[7]Department of Biochemistry, Gateshead Health NHS Foundation Trust, Gateshead, UK
[8]Department of Cardiology, South Tees Health NHS Foundation Trust, Middlesbrough, UK
[9]Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, UK

Correspondence should be addressed to S Razvi: salman.razvi@ncl.ac.uk

Abstract

Objectives: To study the relationship between serum-free T3 (FT3), C-reactive protein (CRP) and all-cause mortality in patients with acute myocardial infarction (AMI).
Design: Prospective multicentre longitudinal cohort study.
Methods: Between December 2014 and December 2016, thyroid function and CRP were analysed in AMI (both ST-elevation (STEMI) and non-ST-elevation) patients from the Thyroxine in Acute Myocardial Infarction study. The relationship of FT3 and CRP at baseline with all-cause mortality up to June 2020 was assessed. Mediation analysis was performed to evaluate if CRP mediated the relationship between FT3 and mortality.
Results: In 1919 AMI patients (29.2% women, mean (S.D.) age: 64.2 (12.1) years and 48.7% STEMI) followed over a median (interquartile range) period of 51 (46–58) months, there were 277 (14.4%) deaths. Overall, lower serum FT3 and higher CRP levels were associated with higher risk of mortality. When divided the patients into tertiles based on the levels of FT3 and CRP; the group with the lowest FT3 and highest CRP levels had a 2.5-fold increase in mortality risk (adjusted hazard ratio (95% CI) of 2.48 (1.82–3.16)) compared to the group with the highest FT3 and lowest CRP values. CRP mediated 9.8% (95% CI: 6.1–15.0%) of the relationship between FT3 and mortality.
Conclusions: In AMI patients, lower serum FT3 levels on admission are associated with a higher mortality risk, which is partly mediated by inflammation. Adequately designed trials to explore the potential benefits of T3 in AMI patients are required.

Key Words

- triiodothyronine
- inflammation
- mortality
- acute myocardial infarction

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Introduction

Cardiovascular diseases including acute myocardial infarction (AMI) are one of the leading causes of morbidity and mortality globally. Despite the improvements in patient outcomes, morbidity and mortality in AMI patients remain high (1). Therefore, additional strategies are required to further improve the prognosis and outcomes of AMI patients. Clinical and experimental data support an additional critical role for inflammation in the pathophysiology of plaque instability and thrombus formation (2). Biomarkers of inflammation such as C-reactive protein (CRP) are strong independent predictors of cardiovascular events (3).

The myocardium is sensitive to minor changes in thyroid function (4). Triiodothyronine (T3), the active thyroid hormone, has several important actions on the myocardial tissue and may be cardioprotective (5). Lower serum T3 levels in patients with cardiac diseases, including those with AMI, are associated with increased mortality risk (6, 7, 8, 9). However, the relationship between serum T3 and outcomes is complicated by the fact that both circulating and tissue T3 levels are downregulated by inflammation (6, 10). It is unclear whether changes in serum T3 levels and the subsequent higher post-AMI mortality are explained by the concomitant inflammatory process or whether T3 and inflammation have an additive and causal effect on mortality risk. We utilised data from an AMI cohort study to analyse the relationship between serum T3, CRP and mortality with the following specific objectives:

(1) To investigate the association of serum T3 with CRP and all-cause mortality.
(2) To investigate the association of combined serum T3 and CRP with all-cause mortality.
(3) To investigate if CRP mediates the association of serum T3 with all-cause mortality.

Methods

Participants

Patients from six acute cardiac centres in the North of England with both ST-elevation (STEMI) and non-ST-elevation (NSTEMI) AMI were recruited to the Thyroxine in Acute Myocardial Infarction (ThyrAMI-1) study (11). AMI was diagnosed as per standard criteria (12). The main purpose of the ThyrAMI-1 study was to identify patients with subclinical hypothyroidism who could be recruited into a randomised control trial of levothyroxine (LT4) or placebo. Between December 2014 and December 2016, AMI patients aged 18 years or more were invited to participate and all participants provided their written informed consent. Individuals on medications known to affect thyroid function such as amiodarone, lithium or anti-thyroid drugs were excluded, as were those with advanced malignancy, dementia or if informed consent could not be obtained. Patients with hypothyroidism treated with LT4 were included in the main analysis but were excluded in a sensitivity analysis. Ethical approval was obtained from the United Kingdom National Research Ethics Service (REF 14/NE/0151).

Measurements and outcomes

Demographic and clinical details of the participants were noted and biochemical parameters were measured on the first available admission sample. Left ventricular ejection fraction (LVEF) was assessed by transthoracic 2D echocardiography (using the biplane method using modified Simpson's rule) and the interval between the date of AMI and date of the scan was noted. Participants' survival status up to 15 June 2020 was evaluated by linking their National Health Service (NHS) number to NHS Summary Care Records (13).

Patient and public involvement

The trial management group was chaired by a member of the patient-led British Thyroid Foundation (BTF). In addition, members of the BTF helped design the participant information sheets. Additionally, results of the project continue to be disseminated to BTF members via their newsletter.

Laboratory assessments

Firstly, available serum samples were analysed on admission to the hospital (and prior to coronary angiography) for the majority of participants (>90%) and within 24 h for those whose initial sample quantity was inadequate. Peak troponin levels were analysed 6–12 h after admission. Thyroid function (thyrotrophin (TSH), free thyroxine (FT4) and free T3 (FT3)), peak high sensitivity (hs) cardiac troponin and creatinine were measured by either the Roche eCobas (Roche Diagnostics) at four sites or Advia-Centaur (Siemens Healthineers, UK) at two sites by the immunoassay method. CRP (hs) was similarly measured

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by the two platforms (Roche and Advia-Centaur) by the immunoturbidimetric method. Sites that used the Roche assay measured troponin T whereas sites that utilised the Advia-Centaur measured troponin I (Supplementary methods, see section on supplementary materials given at the end of this article). The reference ranges were applied uniformly *a priori* for these analytes: TSH 0.4–4.0 mU/L, FT4 9–25 pmol/L, FT3 3.0–7.0 pmol/L, creatinine 70–110 µmol/L, cardiac troponin T <14 ng/L, cardiac troponin I <40 ng/L and CRP <5.0 mg/L.

Statistical analyses

Continuous variables with a normal distribution are described with means and S.D., variables with a skewed distribution with median and quartiles, and categorical and discrete variables are presented as counts and percentages. Troponin T and I values were standardised, centred and combined to form a single variable termed standardised troponin (z-troponin) and z-troponin was utilised in all analyses. Continuous variables that were not normally distributed (such as TSH, z-troponin and CRP) were log-transformed prior to analysis. To assess the relationship between FT3 and CRP, various combinations of tertiles of FT3 and CRP were evaluated (Supplementary methods).

The association between FT3 and CRP was analysed by multivariable ordinary least square linear regression with restricted cubic splines (three knots) to account for the non-linearity of associations. Multicollinearity was assessed by variance inflation factor and was found to be low (<1.5) for all independent variables and the normal distribution of residuals of the regression model was analysed and confirmed by visual inspection.

The association between FT3 and all-cause mortality was evaluated using Cox proportional hazards multivariable analysis. Survival times were calculated from the date of the AMI till the date of death or date of being known to be alive. We used restricted cubic splines with three knots to account for the non-linearity of associations. In the main model, analyses were adjusted for age, sex, centre recruited from, ethnicity (White, South Asian, Black and others), smoking status (current, ex- or non-smoker), BMI, serum creatinine, z-troponin, CRP, type of AMI (STEMI or NSTEMI), LVEF adjusted for a time interval (in days) between the AMI date and the date of echocardiography, history of ischemic heart disease (yes/no), hypertension (yes/no), diabetes mellitus (yes/no), atrial fibrillation (yes/no) and hypothyroidism (yes/no). Covariates for the multivariable models were selected based on clinical relevance or if known to affect serum thyroid function parameters. Assay type was not used as an additional covariate in these analyses as centre from where the participant was recruited was already included. The proportionality assumption was tested using the Schoenfeld residuals for each individual variable. Furthermore, as CRP may not be a confounder but a mediator in the relationship between FT3 and mortality, two additional models were analysed. Firstly, we performed the Cox proportional hazards analysis adjusted for all the variables utilised in the main model except CRP. Second, we performed Cox proportional hazards multivariable analysis in which the separate variables of FT3 and CRP were replaced by the combination groups of FT3 and CRP. Statistical interaction between FT3 and various parameters based on biological plausibility were assessed. In order to assess the relationship between other thyroid function parameters and outcomes, we additionally evaluated the relationship between TSH and FT4 with CRP and all-cause mortality.

To deal with the missing data, multiple imputations were used. In addition, we performed mediation analysis (Supplementary Fig. 1), which evaluated whether the effect of FT3 on incident all-cause mortality was mediated by CRP. To ensure the validity and robustness of the results obtained, we investigated the relationship between FT3 levels and all-cause mortality by performing several sensitivity analyses. Details of analyses of missing data, mediation and sensitivity are provided in Supplementary methods.

The statistical software programmes SPSS v24.0 (Chic, Ill) and R (rms package, R project, Institute for Statistics and Mathematics, R Core Team, version 3.2.2 and mediation package, R project, R Core Team, version 3.6.2) were utilised for computing the analyses. A P value of <0.05 was deemed as indicating statistical significance.

Results

Patient demographics, clinical and biochemical parameters and comorbidities at baseline

The baseline characteristics of 1919 eligible participants are summarised in Table 1. The mean (S.D.) age of participants was 64.2 (12.1) years, 29.2% were women and 98.1% were White. Just less than half of the patients (48.7%) were diagnosed with STEMI. In addition, baseline demographic characteristics and biochemical parameters by various FT3 and CRP groups are provided in

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Table 1 Baseline characteristics of participants in the ThyrAMI-1 study.

Characteristic (n = 1919[a])	
Age, mean (±S.D.) (years)	64.2 ± 12.1
Females, *n* (%)	561 (29.2)
Ethnicity, *n* (%)	
White	1883 (98.1)
South Asian	23 (1.2)
Black	6 (0.3)
Others[b]	7 (0.4)
BMI, mean (±S.D.) (kg/m^2)	28.5 ± 5.5
Smoking status, *n* (%)	
Never smoked	707 (36.9)
Ex-smoker	614 (32.0)
Current smoker	596 (31.1)
STEMI, *n* (%)	935 (48.7)
Serum creatinine, mean (±S.D.) (μmol/L)	90.7 ± 41.1
Serum TSH, median (IQR) (mU/L)	2.0 (1.3–3.3)
Serum FT4, mean (±S.D.) (pmol/L)	16.3 ± 3.7
Serum FT3, mean (±S.D.) (pmol/L) (n = 1716)	4.7 ± 0.9
Peak cardiac troponin, median (IQR)	
Troponin T (ng/L) (n = 1348)	362 (104–1600)
Troponin I (ng/L) (n = 441)	8979 (1560–32908)
hsCRP, median (IQR) (mg/L) (n = 1648)	1.8 (1.0–8.6)
Left ventricular function	
LVEF, median (IQR) (%) (n = 1743)	54.0 (42.5–58.0)
Time interval between AMI and LVEF assessment, median (IQR) (days)	2 (1–5)
Pre-existing medical conditions, *n* (%)	
Ischemic heart disease	502 (26.2)
Hypertension	784 (40.9)
Type 2 diabetes mellitus	339 (17.7)
Atrial fibrillation	78 (4.1)
Hypothyroidism on LT4 therapy	113 (5.9)

[a]Unless otherwise stated. [b]Others comprised of people of Chinese, Middle Eastern and rest of ethnic groups not covered by the White, South Asian and Black categories.
FT3, free triiodothyronine; FT4, free thyroxine; hsCRP, high sensitivity C-reactive protein; IQR, interquartile range; LT4, levothyroxine; LVEF, left ventricular ejection fraction; STEMI, ST-elevation myocardial infarction; TSH, thyrotrophin.

Supplementary Fig. 2. Complete data for FT3, CRP, troponin and LVEF were available for 1716 (89.4%), 1687 (87.9%), 1789 (93.2%) and 1743 (90.8%) participants, respectively.

Relationship between FT3 levels and CRP at baseline

In the fully adjusted model, there was a significant negative non-linear relationship between serum FT3 levels and CRP (P < 0.0001; P for non-linearity 0.003) (Fig. 1). Visual inspection of the graph suggested that the slope of reduction in CRP was steeper when FT3 levels were ≤5.0 pmol/L. Therefore, the data were analysed separately by using an FT3 cut-off of ≤5.0 or >5.0 pmol/L. The relationship between FT3 and CRP in the two subgroups was different: for each unit (pmol/L) increase in FT3, there was a −5.28 (−6.27 to −4.29) mg/L, P < 0.0001 and −1.61 (−2.64 to −0.58) mg/L, P < 0.002, reduction in CRP, in those with baseline FT3 levels ≤5.0 and >5.0 pmol/L, respectively.

Relationship of baseline FT3 and CRP with all-cause mortality

The participants were followed over a median (interquartile range) period of 51 (46–58) months and 277 (14.4%) deaths were observed. In the main model, lower FT3 levels at baseline were associated with a higher risk of mortality in a non-linear manner (P < 0.0001, P for non-linearity 0.048) (Fig. 2). Visual inspection of the graph suggested that the slope of the relationship between the hazards of all-cause mortality and FT3 was steeper when FT3 was ≤5.0 pmol/L. When the data were analysed separately by baseline FT3 subgroups of ≤5.0 or >5.0 pmol/L, the negative linear relationship between baseline FT3 and all-cause mortality was only significant in the FT3 ≤5.0 pmol/L group with an adjusted hazard ratio of 0.81 (0.72–0.92), P < 0.0001. The baseline FT3 >5.0 pmol/L subgroup had no significant association with an adjusted hazard ratio of 0.94 (0.73–1.20), P = 0.16.

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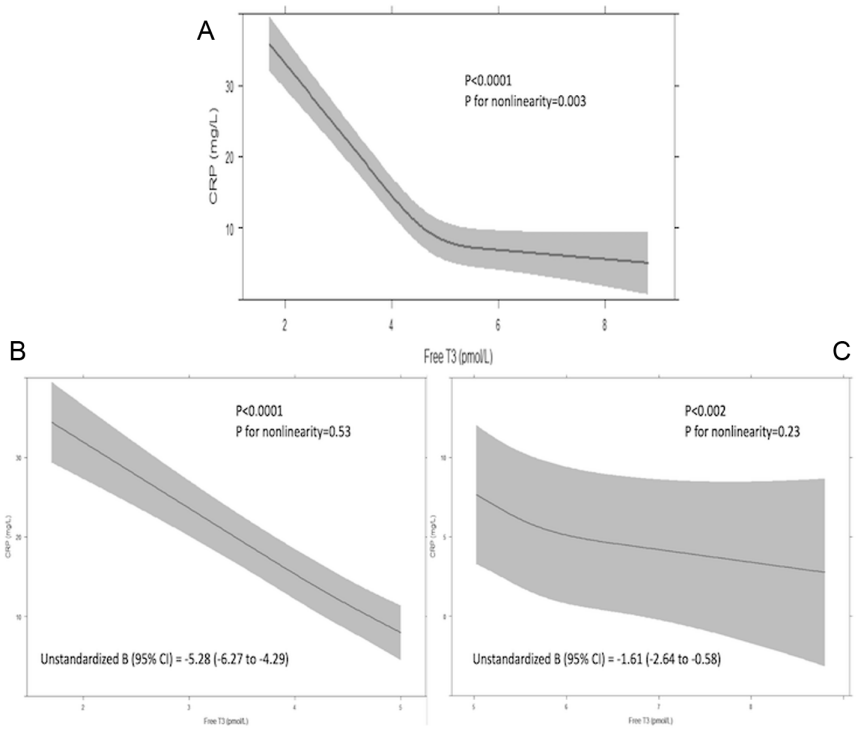

Figure 1
Cross-sectional association of baseline serum FT3 with CRP in all participants (A) and by baseline FT3 levels of ≤5.0 pmol/L (B) or >5.0 pmol/L (C). Association of CRP with FT3 levels at baseline using linear regression models with restricted cubic splines. The predicted means of CRP (blue line) with 95% CIs (grey area) were plotted against FT3, adjusted for age, sex, centre, ethnicity, BMI, smoking status, type of acute myocardial infarction (STEMI or NSTEMI), adjusted LVEF*, ischemic heart disease, type 2 diabetes mellitus, hypertension, atrial fibrillation, hypothyroidism, serum creatinine and z-troponin. The relationship between CRP and the two FT3 subgroups (≤5.0 or >5.0 pmol/L) was linear but different; steeper unstandardised B coefficient in the ≤5.0 pmol/L group (−5.28 (−6.27 to −4.29), P < 0.0001 than in the >5.0 pmol/L group (−1.61 (−2.64 to −0.58), P < 0.002, respectively. CRP, C-reactive protein; FT3, free triiodothyronine; LT4, levothyroxine; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction. *Adjusted for interval between the date of acute myocardial infarction and the date of echocardiogram.

Higher CRP levels at baseline were significantly associated with a higher risk of mortality overall in a non-linear manner (P < 0.0001; P for non-linearity <0.0001) (Supplementary Fig. 3). On visual inspection, the relationship between baseline CRP levels and subsequent mortality appeared to plateau after CRP levels of 12.5 mg/L. Therefore, the analysis was repeated by baseline CRP levels. This confirmed that hazard ratios were significant for the

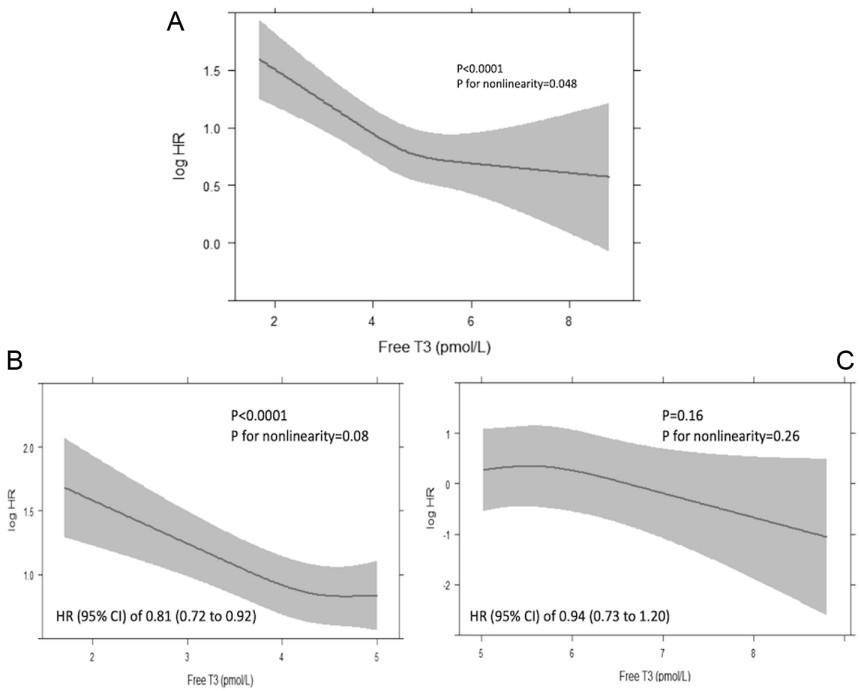

Figure 2
Relationship of baseline serum FT3 with all-cause mortality in all participants (A) and those with FT3 ≤5.0 pmol/L (B) or >5.0 pmol/L (C). Prospective association of FT3 at baseline with risk of all-cause mortality using Cox proportional hazards model with restricted cubic splines. The predicted log-relative hazards (blue line) with 95% CIs (grey area) were plotted against baseline serum FT3 levels, adjusted for age, sex, centre, ethnicity, BMI, smoking status, type of acute myocardial infarction (STEMI or NSTEMI), adjusted LVEF*, ischemic heart disease, type 2 diabetes mellitus, hypertension, atrial fibrillation, hypothyroidism, serum creatinine, z-troponin and CRP. When the data were analysed separately by baseline FT3 subgroups of ≤5.0 or >5.0 pmol/L, the negative linear relationship between baseline FT3 and all-cause mortality was only significant in the FT3 ≤5.0 pmol/L group with adjusted hazard ratio of 0.81 (0.72 to 0.92), P < 0.0001. The hazard ratio in the FT3 >5.0 pmol/L group was non-significant (0.94 (0.73–1.20), P = 0.16). CRP, C-reactive protein; FT3, free triiodothyronine; LT4, levothyroxine; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction. *Adjusted for interval between the date of acute myocardial infarction and the date of echocardiogram.

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CRP ≤12.5 mg/L group (1.05 (1.03–1.07), $P < 0.0001$) and not in the CRP >12.5 mg/L group (1.00 (0.99–1.00), $P = 0.34$).

Peak z-troponin levels independently predicted subsequent mortality in a linear manner (P for non-linearity 0.99) with an adjusted hazard ratio of 1.11 (1.05–1.18), $P < 0.0001$, for each unit increase in z-troponin (Supplementary Table 1). There was, however, a significant statistical interaction ($P < 0.0001$) between serum FT3 and z-troponin levels with regards to mortality. Thus, the relationship between FT3 and mortality was evaluated separately by the z-troponin tertile groups. This demonstrated that a significant inverse relationship between baseline FT3 levels and subsequent all-cause mortality only existed in those in the higher two z-troponin tertiles (Fig. 3).

In the first additional model analysis, when CRP was taken out of the model, the relationship between FT3 and all-cause mortality became somewhat stronger compared to the main model (hazard ratio (HR) of 0.75 (0.70–0.81)),

Variable	n	Events (%)	HR (95% CI)	p for interaction
Age quartiles, years				
<55	511	22 (4.3)	1.21 (0.66 to 2.23)	0.45
56 to 64	451	25 (5.5)	0.61 (0.30 to 1.23)	
65 to 73	485	52 (10.7)	0.53 (0.32 to 0.89)	
>73	472	177 (37.5)	0.82 (0.64 to 1.05)	
Gender				
Men	1358	188 (13.8)	0.75 (0.59 to 0.94)	0.65
Women	561	89 (15.9)	0.89 (0.62 to 1.28)	
Type of MI				
STEMI	935	91 (9.7)	0.65 (0.47 to 0.91)	0.34
NSTEMI	984	186 (18.9)	0.79 (0.69 to 1.04)	
z-troponin tertiles, units				
1st	598	84 (14.0)	1.17 (0.82 to 1.68)	0.01
2nd	594	110 (18.5)	0.69 (0.48 to 1.00)	
3rd	597	71 (11.9)	0.60 (0.44 to 0.83)	
LT4 use				
Users	113	30 (26.5)	1.41 (0.56 to 3.58)	0.65
Non-users	1806	247 (13.7)	0.77 (0.63 to 0.94)	
Assay				
Roche	1400	218 (15.6)	0.73 (0.57 to 0.92)	0.26
Centaur	519	59 (11.4)	0.67 (0.44 to 0.97)	
Complete case records	1687	250 (14.8)	0.78 (0.65 to 0.95)	N/A

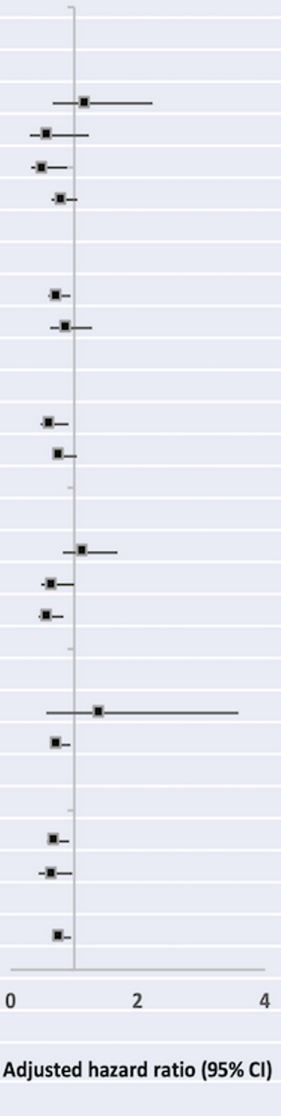

Figure 3
Sensitivity analysis for relationship between FT3 and all-cause mortality in various subgroups. Adjusted for age, sex, centre, ethnicity, BMI, smoking status, type of acute myocardial infarction (STEMI or NSTEMI), adjusted LVEF*, ischemic heart disease, type 2 diabetes mellitus, hypertension, atrial fibrillation, hypothyroidism, serum creatinine, CRP and z-troponin, except those who were compared in each analysis. *Adjusted for interval between the date of acute myocardial infarction and the date of echocardiogram. The P for interaction was calculated by the addition of the interaction term (independent variable × FT3) to the fully adjusted model above.

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suggesting that CRP partly confounded the association between FT3 and mortality. In the second additional analysis, the risk of mortality was evaluated by various FT3 and CRP tertile groups. This demonstrated that compared to patients in group E (high FT3 and low CRP) all other groups had higher adjusted mortality risk (P for trend <0.001) (Fig. 4). Patients in group A (low FT3 and high CRP) had a 2.4-fold risk of subsequent mortality than group E. Even patients in groups B (low FT3 and low CRP), C (medium FT3 and low, medium and high CRP) and D (high FT3 and high CRP) had an increased risk of subsequent mortality (hazard ratios between 1.42 and 1.52) compared to group E.

Mediation analysis between FT3, CRP and subsequent mortality

Log-transformed values of FT3 and CRP were used in this analysis to convert non-linear relationships. The association between serum FT3 concentrations and all-cause mortality was mediated by CRP levels. The average causal mediation, direct and total effects, representing the population averages, were significant (Table 2). The proportion (95% CIs) of the risk of higher mortality with FT3 that was mediated by the CRP pathway was 9.8% (6.1–15.0%), $P < 0.0001$.

Relationship between serum TSH and FT4 with CRP and all-cause mortality

There was no significant independent association between serum TSH levels ($P=0.11$) nor FT4 concentrations ($P=0.08$) with CRP levels at baseline, whereas the FT3/FT4 ratio was weakly associated ($P=0.04$) (Supplementary Table 2). Similarly, no significant relationship was observed between serum TSH and all-cause mortality ($P=0.91$). However, there was a significant positive association between FT4 levels ($P=0.008$) as well as the FT3/FT4 ratio ($P=0.0002$) with mortality (Supplementary Table 3).

Sensitivity analyses

There was no significant interaction between the various subgroups tested, except for tertile groups by z-troponin levels (Fig. 3). We also analysed if FT3 may mediate the relationship between CRP and all-cause mortality. This showed that the proportion (95% CIs) of mediation by FT3 in the CRP and all-cause mortality association was low: 0.11% (0.03–0.3%), $P=0.002$. After excluding the 174 (9.1%) participants who had their thyroid function assessed on a later sample but less than 24 h after admission, the relationship between serum FT3, CRP and all-cause mortality remained broadly similar (data not shown). As mediation analysis relies on a number of assumptions, sensitivity analyses were performed and confirmed that the mediation results were robust and not due to violation of these assumptions (Supplementary Figs 4 and 5).

Discussion

Our study shows that serum FT3 levels in AMI patients are inversely associated with mortality and this relationship

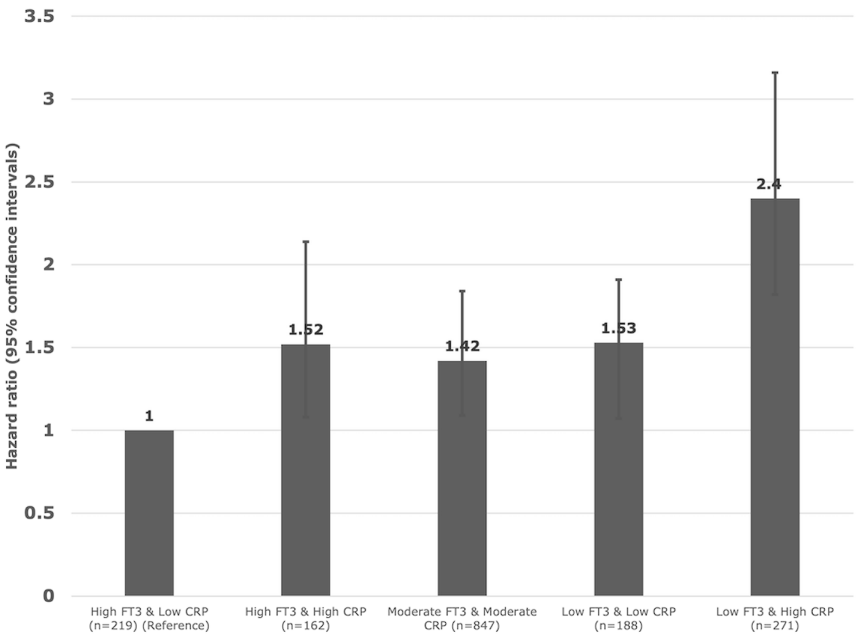

Figure 4
T3 and CRP levels and risk of mortality. Adjusted for age, sex, centre, ethnicity, BMI, smoking status, type of acute myocardial infarction (STEMI or NSTEMI), adjusted LVEF*, ischemic heart disease, type 2 diabetes mellitus, hypertension, atrial fibrillation, hypothyroidism, serum creatinine and z-troponin. The error bars represent the 95% CIs. FT3, free triiodothyronine; FT4, free thyroxine; hsCRP, high sensitivity C-reactive protein; LT4, levothyroxine; LVEF, left ventricular ejection fraction; STEMI, ST-elevation myocardial infarction; TSH, thyrotrophin. Definitions: high FT3>5.0 pmol/L, low CRP<1.0 mg/L, high CRP>6.0 mg/L, moderate CRP = 1.0–6.0 mg/L, moderate FT3 = 4.4–5.0 pmol/L, low FT3<4.4 pmol/L. *Adjusted for interval between the date of acute myocardial infarction and the date of echocardiogram.

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Table 2 Mediating the role of CRP in the association between free T3 levels and all-cause mortality in the ThyrAMI-1 cohort. All analyses were adjusted for age, sex, centre, ethnicity, BMI, smoking status, type of acute myocardial infarction (STEMI or NSTEMI), adjusted LVEF (adjusted for interval between the date of acute myocardial infarction and the date of echocardiogram), ischemic heart disease, type 2 diabetes mellitus, hypertension, atrial fibrillation, hypothyroidism on LT4 therapy, serum creatinine and z-troponin. Log-transformed values of FT3 and CRP were utilised in this analysis due to the non-linear relationships between FT3, CRP and all-cause mortality.

	Estimate (95% CIs)	***P* value**
Average causal mediation effect	−0.005 (−0.007 to 0.00)	<0.0001
Average direct effect	−0.05 (−0.07 to −0.03)	<0.0001
Total effect	−0.05 (−0.08 to −0.03)	<0.0001
Proportion mediated (%)	9.8 (6.1 to 15.0)	<0.0001

CRP, C-reactive protein; FT3, free triiodothyronine; LT4, levothyroxine; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.

is partly mediated via the inflammatory process. Our findings demonstrate that a combination of low FT3 levels and elevated CRP is associated with a higher mortality risk compared to either biomarker alone. Patients with the lowest FT3 and highest CRP levels had a 2.4-fold subsequent risk of mortality compared to those with the highest FT3 and lowest CRP concentrations.

Levels of circulating and tissue T3 levels are reduced in acute illness due to the downregulation of the activating deiodinase enzymes and upregulation of the inactivating deiodinase enzyme (14). This reduction in bioavailable thyroid hormone in the acutely affected tissue has been considered a protective mechanism by reducing metabolic demand (15). However, a number of observational studies have shown that lower serum T3 levels are associated with worse outcomes following AMI (16). Therefore, it is unclear whether the reduction in T3 levels is protective or maladaptive. The majority of the observational studies, however, have measured T3 levels a few days following the AMI when the inflammatory response following an AMI is at its peak (16). Our study, on the other hand, measured T3 levels as soon as possible after admission and thus reduced the impact of inflammation and non-thyroidal illness on thyroid function. Circulating T3 levels and markers of inflammation in AMI patients are negatively correlated (10). However, there is a paucity of data on the relation between low FT3, inflammation and subsequent mortality after acute AMI. Our analysis confirms that low T3 levels are associated with higher mortality but, importantly, also suggests that this association appears to be mediated, in part, by inflammation. Furthermore, even individuals with low markers of inflammation and low FT3 levels seem to be at a higher risk of death than those with high FT3 and low CRP.

There may be several possible explanations for the protective effect of T3 observed in AMI patients. Thyroid hormones, particularly T3, have considerable modulatory effects on myocardial tissue (5). In animal studies, T3 has been shown to be safe and cardioprotective in a post-infarct situation resulting in preservation of ventricular function and arrhythmia reduction (17). Alterations in T3 levels affect mitochondrial function and have been linked with ischemia-reperfusion injury (18). In patients with heart failure (19, 20) and those undergoing surgical revascularization (21, 22), T3 therapy has been shown to improve left ventricular function.

In animal models of AMI, T3 therapy may modulate the inflammatory process (23). In a randomised controlled trial T3 therapy was associated with a reduction in CRP levels in patients with heart failure (20). It is therefore plausible that the post-AMI reduction in circulating T3 is maladaptive and that T3 therapy may be beneficial. Treatment of subclinical hypothyroidism with LT4 therapy in patients with AMI does not improve LVEF (24). Importantly, a recent proof of principle trial of T3 in a small number of AMI patients has demonstrated safety and laid the foundations for subsequent larger adequately powered trials to be performed (25). Our data advances the literature and identifies a group of individuals who may potentially benefit from T3 therapy: AMI patients with low serum FT3, high CRP and larger infarcts (identified by high cardiac troponin release). The ideal dose, safety and efficacy of T3 will need to be tested in future therapeutic trials in this high-risk population.

Various therapies to reduce the inflammatory processes in managing cardiovascular disease have shown benefits. However, canakinumab has demonstrated clinical efficacy (26), but requires parenteral administration, increases infection risk, has an unknown long-term safety profile, and is expensive, whereas others (methotrexate and colchicine) have shown conflicting results (27, 28). T3 therapy has been available for decades as an oral preparation, is relatively inexpensive and its side-effect profile is well known. Appropriately designed trials are now needed to assess the safety and efficacy of T3 in patients with extensive AMI.

Our study has several strengths. Data were collected in a structured and prospective manner from a large group of participants with AMI from different hospitals. Multiple

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sensitivity analyses provided consistent findings. This analysis has several limitations. CRP data were not available for all participants and statistical imputation was utilised. However, multiple imputations of data is widely used and shown to be robust (29). Furthermore, sensitivity analysis performed after excluding the imputed data obtained similar results, confirming the reliability of the relationship. In addition, markers of cardiac damage (troponin I and T) were transformed and combined into a single unit. This statistical technique too is widely used, and sensitivity analysis confirmed the validity of the results (30). Despite the biological plausibility of our findings, the observational nature of our data precludes a definitive causal inference being drawn between the mediating role of CRP in the T3-mortality relationship. A source of selection bias could be that less unwell patients were recruited to this study. But, it is likely that this may actually underestimate the strength of the relationship between T3, CRP and mortality. Another limitation is the lack of subsequent thyroid function test data.

In conclusion, FT3 levels at the time of AMI are associated with mortality, and this relationship is partly mediated by the inflammatory process. Measuring FT3 and CRP levels in AMI patients may help in improving risk stratification in these individuals. Furthermore, this study provides data to support larger trials of T3 in AMI patients. Adequately powered randomised controlled trials are needed to investigate the effects of T3 therapy in AMI patients with low or low normal FT3 levels on clinical outcomes.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/ETJ-21-0085.

Declaration of interest

Dr Razvi has received speaker fees from Merck plc, Abbott India Pharmaceuticals Pvt. Ltd, and Berlin Chemie plc, manufacturers of levothyroxine. All other authors have no relevant disclosures.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contribution statement

Planning: Salman Razvi, Avais Jabbar, David Austin, John Greenwood, Azfar Zaman. Conduct: Salman Razvi, Avais Jabbar, Lorna Ingoe, Honey Thomas, Peter Carey, Shahid Junejo, David Austin, John Greenwood, Azfar Zaman. Reporting: Salman Razvi, Avais Jabbar, Arjola Bano. Overall responsibility and guarantor of content: Salman Razvi.

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