CLINICAL STUDY

The impact of low triiodothyronine levels on mortality is mediated by malnutrition and cardiac dysfunction in incident hemodialysis patients

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Abstract

Objective: Little is known about the impact of low triiodothyronine (T₃) levels on mortality in end-stage renal disease (ESRD) patients starting hemodialysis (HD) and whether this impact is mediated by malnutrition, inflammation, or cardiac dysfunction.

Design and methods: A prospective cohort of 471 incident HD patients from 36 dialysis centers within the Clinical Research Center for ESRD in Korea was selected for this study. Based on the median value of T₃, patients were divided into 'higher' and 'lower' groups, and all-cause and cardiovascular (CV) mortality rates were compared. In addition, associations between T₃ levels and various nutritional, inflammatory, and echocardiographic parameters were determined.

Results: Compared with those in the 'higher' T₃ group, albumin, cholesterol, and triglyceride levels, lean body mass estimated by creatinine kinetics (LBM-Cr), and normalized protein catabolic rate (nPCR) were significantly lower in patients with 'lower' T₃ levels. The 'lower' T₃ group also had a higher left ventricular mass index (LVMI) and a lower ejection fraction (EF). Furthermore, correlation analysis revealed significant associations between T₃ levels and nutritional and echocardiographic parameters. All-cause and CV mortality rates were significantly higher in patients with 'lower' T₃ levels than in the 'higher' T₃ group (113.4 vs 18.2 events per 1000 patient-years, $P < 0.001$, and 49.8 vs 9.1 events per 1000 patient-years, $P = 0.001$, respectively). The Kaplan–Meier analysis also showed significantly worse cumulative survival rates in the 'lower' T₃ group ($P < 0.001$). In the Cox regression analysis, low T₃ was an independent predictor of all-cause mortality even after adjusting for traditional risk factors (hazard ratio = 3.76, $P = 0.021$). However, the significant impact of low T₃ on all-cause mortality disappeared when LBM-Cr, nPCR, LVMI, or EF were incorporated into the models.

Conclusion: Low T₃ has an impact on all-cause mortality in incident HD patients, partly via malnutrition and cardiac dysfunction.

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Introduction

Thyroid hormone has numerous effects on the kidney, playing an important role in renal development and growth as well as in sodium and water homeostasis. Renal plasma flow (RPF) and glomerular filtration rate (GFR) are also influenced by thyroid hormone. As a result, reductions in RPF and GFR, an increase in serum creatinine concentrations, and hyponatremia are frequently observed in primary hypothyroidism patients, and these renal derangements can be nearly normalized by thyroid hormone replacement therapy (1, 2, 3).

Conversely, the kidney is involved in the metabolism and excretion of thyroid hormone; thus, renal failure can lead to significant changes in thyroid function. Goiter, thyroid nodules, reduced total and free

3,5,3'-triiodo-L-thyronine (fT₃) and thyroxine (T₄) levels, and subclinical hypothyroidism are not uncommon in patients with chronic kidney disease (CKD). Among these abnormalities, reduced serum T₃ concentration (low T₃) is the most frequently observed alteration of thyroid hormone in CKD patients (1, 4). A recent study has shown that there is a significant correlation between serum T₃ levels and estimated GFR (eGFR) and that the prevalence of low T₃ gradually increases with worsening CKD stage (5). In addition, some previous studies have demonstrated that up to 70% of stage 5 CKD patients have low T₃ (6). This alteration in CKD patients has mainly been attributed to impaired TSH response to thyrotropin-releasing hormone and decreased peripheral biosynthesis of T₃ from T₄ due to uremia and has been considered to be merely

an adaptive process to preserve energy (1, 7). Recently, however, low T_3 has also been suggested to be associated with metabolic acidosis, systemic inflammation, endothelial dysfunction, atherosclerosis, and cardiomyopathy in patients with end-stage renal disease (ESRD) (8, 9, 10, 11, 12).

Accumulating evidence has indicated that low T_3 is associated with clinical outcomes in patients with various chronic diseases, including congestive heart failure, respiratory failure, and liver cirrhosis (13, 14, 15, 16). Since low T_3 is the most common disturbance of thyroid hormone levels in ESRD patients, the adverse impact of low T_3 on patient survival has been widely explored in patients on maintenance hemodialysis (HD) and peritoneal dialysis (PD) (17, 18). Furthermore, low pre-transplant serum fT_3 levels have been revealed to be a significant predictor of subsequent graft failure in kidney transplant recipients (19). In spite of a large number of previous investigations on the prognostic value of low T_3 for all-cause and cardiovascular (CV) mortality in ESRD patients, the majority of the study subjects were prevalent HD or PD patients and echocardiographic findings were not included in the analysis in most of these studies. In addition, compared with fT_3 concentrations, total T_3 levels were more commonly determined in many hospitals and were less influenced by the way of measurement or medications such as heparin (20, 21, 22), but clinical outcomes were more frequently defined based on serum or plasma fT_3 concentrations than on total T_3 concentrations.

Therefore, in this study, we determined whether low serum total T_3 levels were a significant predictor of mortality in Korean incident HD patients from the Clinical Research Center for ESRD (CRC for ESRD) cohort. Moreover, the associations between T_3 concentrations and metabolic acidosis, systemic inflammation, malnutrition, and echocardiographic parameters were investigated in these patients.

Subjects and methods

Subjects

Initial recruitment for this prospective observational multi-center study involved all ESRD patients starting HD between August 1, 2008, and October 31, 2012, at 36 centers of the CRC for ESRD in Korea. Within 7 days of the initial dialysis, the patients provided written informed consent and were enrolled into the study cohort. Among these patients, we excluded those who were aged <18 years, had a history of PD or kidney transplantation prior to HD, were on thyroid hormone replacement or suppressive therapy due to overt thyroid disease, were on medications affecting thyroid hormone levels, such as amiodarone, glucocorticoids, and lithium, had underlying active malignancy, or died within 3 months of the commencement of HD.

Patients who had insufficient baseline data, including thyroid function test results, were also excluded from the study. Ultimately, a total of 471 incident HD patients were included in the final analysis.

This study was carried out in accordance with the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board at each participating center.

Data collection

Demographic and clinical data were recorded at the time of study entry, including age, gender, BMI calculated as weight/height², primary renal disease, comorbidities, and medications. Coronary arterial disease (CAD) was defined as a history of angioplasty, coronary artery bypass grafts, myocardial infarction, or angina, while peripheral arterial disease (PAD) was defined as a history of claudication, ischemic limb loss and/or ulceration, or peripheral revascularization procedure. The composite of CAD, congestive heart failure of any cause ischemic, valvular disease related or amyloid deposition related to uremia, and arrhythmia was designated as cardiac disease, while the composite of cardiac disease, PAD, and cerebrovascular disease, transient ischemic attack, ischemia/infarction, or bleeding as cardiovascular disease (CVD). Laboratory data were measured using pre-dialysis fasting blood samples collected on the day of a mid-week dialysis session, when the patients were considered to be clinically stable and to be in euvoletic state. These laboratory data included data on hemoglobin (Hb), white blood cell (WBC) count, blood urea nitrogen, creatinine, calcium, phosphorus, intact parathyroid hormone, albumin, total cholesterol, triglyceride, alkaline phosphatase, HbA1c, sodium, potassium, bicarbonate, serum iron, ferritin, N-terminal pro-B-type natriuretic peptide (NT-proBNP), cardiac troponin T (cTnT), and high-sensitivity C-reactive protein (hs-CRP) levels. During follow-up, these data were measured every 3 months according to the K/DOQI guideline (<http://www.kidney.org>, June 26, 2013). eGFR was calculated using the four-variable Modification of Diet in Renal Disease (MDRD) Study and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Study equation (23). In addition, 24-h urine sample collection was executed to determine 24-h urinary protein, urea, and creatinine excretion. Nutritional status was also evaluated using subjective global assessment (SGA) score (24), lean body mass estimated by creatinine kinetics (LBM-Cr) (25), and normalized protein catabolic rate (nPCR) (26). Thyroid function test was performed 3 months after the initiation of HD and annually thereafter based on the consideration of the economic issue and the opinion of the clinician who participated in this prospective observational study. Serum T_3 , free T_4 (fT_4), and TSH levels were determined using a chemiluminescent microparticle immunoassay on the Architect-i2000SR analyzer (Abbott Laboratories),

and the reference ranges were 0.58–1.59 ng/ml, 0.70–1.48 ng/dl, and 0.35–4.94 μ IU/ml respectively. Since there was an extremely wide variation in the biochemical data at 0 month due to diverse patients' conditions to start HD, we used the laboratory data collected at 3 months after HD commencement, when correction of uremia, anemia, and acidosis was considered to be sufficiently achieved.

Echocardiography was performed on a non-dialysis day, close to the time of discharge, based on the imaging protocol recommended by the American Society of Echocardiography. Left atrial dimension (LAD) was assessed at end-ventricular systole at the level of the aortic valve according to the leading-edge-to-leading-edge convention. Left ventricular (LV) mass was determined using the method described by Steiber *et al.* (24), and the LV mass index (LVMI) was calculated by dividing LV mass by body surface area. LV systolic function was defined by LV ejection fraction (LVEF) using a modified biplane Simpson method from the apical two-chamber and four-chamber views. Multiple reproducibility, inter-reader reliability, intra-reader reliability, and reader drift analyses were performed at a core echocardiography laboratory (Kyungpook National University, Daegu, Korea) on a random sample of 3% of the entire cohort each year. The intra-class correlation coefficients for the echocardiographic measures were 0.773 for LAD, 0.745 for LVMI, and 0.842 for LVEF.

Outcome measures

For this study, data on all mortality events were retrieved from the database and carefully reviewed. The primary and secondary endpoints were all-cause mortality and CV mortality respectively. CV mortality was considered death from myocardial infarction or ischemia, congestive heart failure, pulmonary edema, cerebral hemorrhage, or cerebrovascular disorder.

Statistical analysis

Statistical analysis was performed using SPSS for Windows, version 18.0 (SPSS, Inc.). Continuous variables are expressed as mean $\pm$ s.d. or median (interquartile range) and categorical variables as a number (percentage). Normality of the distribution was ascertained using the Shapiro–Wilk test. The patients were dichotomized into 'higher' and 'lower' T₃ groups based on the median values of serum T₃ concentrations. Patient demographics, clinical characteristics, and laboratory findings were compared between the two groups using Student's *t*-test or Mann–Whitney *U* test for continuous variables and the χ^2 test for categorical variables. Because of the log-normal distributions of NT-proBNP, cTnT, and hs-CRP concentrations, natural log values (Ln) were used in the analysis. The associations of serum T₃ levels with other variables

were determined using Pearson's correlation analysis. A multivariate linear regression analysis was conducted to identify the independent determinants of T₃ concentrations.

Cumulative survival curves for all-cause and CV mortality were created using the Kaplan–Meier method, and between-group survival was compared using a log-rank test. The independent prognostic power of serum T₃ levels for mortality was ascertained using multivariate Cox proportional-hazards regression analysis, which included only the variables of *P* values <0.10 in the univariate analysis. The positive predictive value of T₃ concentrations for mortality was also analyzed using the receiver operating characteristic (ROC) curve analysis with calculated area under the ROC curve (AUC). *P* values <0.05 were considered statistically significant.

Results

Baseline characteristics

The baseline demographic and clinical characteristics of the patients are given in Table 1. The mean age was 56.9 ± 14.9 years and 57.3% of the patients were male. The most common cause of ESRD was diabetes (DM, 53.3%), followed by hypertension (14.4%). The median values of serum T₃, fT₄, and TSH concentrations were 0.8 ng/ml, 1.1 ng/dl, and 1.9 μ IU/ml respectively.

The demographic and clinical characteristics were compared between the dichotomized two groups based on the median levels of T₃ (0.8 ng/ml). The mean age, the proportion of female patients, and modified Charlson comorbidity index (CCI) were significantly higher in the 'lower' T₃ group than in the 'higher' T₃ group (*P* < 0.05 or < 0.01). In addition, CVDs were significantly more prevalent in the 'lower' T₃ group (*P* = 0.015). There was no significant difference in medication history between the two groups, except for the use of clopidogrel, which was prescribed more frequently in the 'lower' T₃ group than in the 'higher' T₃ group (*P* < 0.048).

With regard to the laboratory and echocardiographic findings, patients with 'lower' T₃ levels demonstrated blood glucose and serum uric acid levels that were significantly higher, while Hb, serum albumin, total cholesterol, triglyceride, and bicarbonate concentrations were significantly lower than those of the 'higher' T₃ group (*P* < 0.05–*P* < 0.001). However, there were no differences in serum calcium, phosphorus, NT-proBNP, cTnT, and hs-CRP levels and eGFR between the two groups. The proportion of malnourished patients assessed by SGA was significantly higher (*P* = 0.02) and LBM-Cr and nPCR were significantly lower in the 'lower' T₃ group than in the 'higher' T₃ group (*P* < 0.05). Among 379 patients (192 in the 'lower' T₃ group and 187 in the 'higher' T₃ group) who

Table 1 Baseline demographic and clinical characteristics of the study subjects.

Variables	Total (n=471)	T ₃ <0.8 ng/ml (n=228)	T ₃ ≥0.8 ng/ml (n=243)	P
Age (years)	56.85±14.94	58.63±14.96	55.19±14.76	0.012
Sex (male)	270 (57.3%)	116 (50.9%)	154 (63.4%)	0.006
BMI (kg/m ²)	23.14±3.69	22.71±3.89	23.55±3.48	0.065
Systolic BP (mmHg)	143.0±23.4	142.7±22.2	143.3±24.5	0.814
Diastolic BP (mmHg)	77.6±14.0	76.7±14.3	78.5±13.6	0.159
Smoking status				0.049
Current smoker	54 (11.5%)	30 (13.2%)	24 (9.9%)	
Ex-smoker	138 (29.3%)	55 (24.1%)	83 (34.2%)	
Non-smoker	279 (59.2%)	143 (62.7%)	136 (56.0%)	
Primary cause of renal disease				0.636
Diabetes	251 (53.3%)	128 (56.1%)	123 (50.6%)	
Hypertension	68 (14.4%)	35 (15.4%)	33 (13.6%)	
Chronic GN	69 (14.6%)	29 (12.7%)	40 (16.5%)	
Others ^a	50 (10.6%)	22 (9.6%)	28 (11.5%)	
Unknown	33 (7.0%)	15 (6.6%)	18 (7.4%)	
Comorbid disease				
Chronic lung disease	47 (10.0%)	25 (11.0%)	22 (9.1%)	0.497
Coronary arterial disease	72 (15.3%)	40 (17.5%)	32 (13.2%)	0.186
Peripheral arterial disease	47 (10.0%)	27 (11.8%)	20 (8.2%)	0.195
Cerebrovascular disease	62 (13.2%)	36 (15.8%)	26 (10.7%)	0.103
Congestive heart failure	73 (15.5%)	42 (18.4%)	31 (12.8%)	0.093
Arrhythmia	13 (2.8%)	7 (3.1%)	6 (2.5%)	0.690
Diabetes	260 (55.2%)	131 (57.5%)	129 (53.1%)	0.366
Connective tissue disease	50 (10.6%)	24 (10.5%)	26 (10.7%)	0.941
Ulcer	42 (8.9%)	21 (9.2%)	21 (8.6%)	0.827
Liver disease	47 (10.0%)	19 (8.3%)	26 (10.7%)	0.383
Cardiac disease ^b	121 (25.7%)	68 (29.8%)	53 (21.8%)	0.047
CVD ^c	172 (36.5%)	96 (42.1%)	76 (31.3%)	0.015
Modified CCI	5.16±2.45	5.44±2.52	4.90±2.36	0.017
Medications				
RAS blockers	241 (51.2%)	123 (53.9%)	118 (48.6%)	0.242
CCB	268 (56.9%)	127 (55.7%)	141 (58.0%)	0.611
Beta blocker	251 (53.3%)	114 (50.0%)	137 (56.4%)	0.166
Aspirin	106 (22.5%)	58 (25.4%)	48 (19.8%)	0.140
Clopidogrel	34 (7.2%)	22 (9.6%)	12 (4.9%)	0.048
Vitamin D	64 (13.6%)	35 (15.4%)	29 (11.9%)	0.280
ESA	159 (33.8%)	69 (30.3%)	90 (37.0%)	0.120

BP, blood pressure; GN, glomerulonephritis; CVD, cardiovascular disease; CCI, Charlson comorbidity index; RAS, renin-angiotensin system; CCB, calcium channel blocker; ESA, erythropoietin-stimulating agent.

^aOther causes of renal failure include polycystic kidney disease, interstitial nephritis, acquired obstructive uropathy, chronic pyelonephritis, reflux nephropathy, and amyloidosis.

^bComposite of coronary arterial disease, congestive heart failure, and arrhythmia.

^cComposite of coronary arterial disease, congestive heart failure, arrhythmia, peripheral arterial disease, and cerebrovascular disease.

underwent echocardiography, the 'lower' T₃ group had a significantly higher LVMI ($P=0.002$) and a lower LVEF ($P=0.012$) than the 'higher' T₃ group (Table 2).

Associations of T₃ levels with malnutrition and inflammation markers and echocardiographic findings

Pearson's correlation analysis revealed that serum T₃ concentrations had significant inverse correlations with age ($r=-0.156$, $P=0.001$), serum glucose levels ($r=-0.180$, $P<0.001$), WBC counts ($r=-0.114$, $P=0.016$), and Ln hs-CRP ($r=-0.150$, $P=0.003$). In contrast, there were significant positive associations between serum T₃ concentrations and serum bicarbonate ($r=0.234$, $P<0.001$), albumin ($r=0.354$, $P<0.001$), total cholesterol ($r=0.179$, $P=0.001$), and triglyceride ($r=0.193$, $P<0.001$) levels, LBM-Cr

($r=0.174$, $P=0.003$), and nPCR ($r=0.223$, $P<0.001$). Furthermore, serum T₃ concentrations had a significant inverse correlation with LVMI ($r=-0.157$, $P=0.002$) and a significant positive relationship with LVEF ($r=0.168$, $P=0.001$) (Table 3 and Fig. 1).

Furthermore, a significant association of serum T₃ levels with serum albumin ($r=0.244$, $P=0.002$) and bicarbonate ($r=0.348$, $P<0.001$) concentrations still persisted in 163 patients even at 12 months (Supplementary Figure 1, see section on supplementary data given at the end of this article).

Determinants of serum T₃ levels

The multivariate linear regression analysis, including variables with P values <0.1 in the univariate analysis, demonstrated that age, serum albumin, bicarbonate, triglyceride, and hs-CRP concentrations, and nPCR

Table 2 Laboratory and echocardiographic findings of the study subjects.

Variables	Total (n=471)	T ₃ <0.8 ng/ml (n=228)	T ₃ ≥0.8 ng/ml (n=243)	P
Laboratory data at 3 months				
Hemoglobin (g/dl)	10.84 ± 1.41	10.58 ± 1.32	11.01 ± 1.45	0.001
WBC (/μl)	5883.4 ± 2996.4	5911.4 ± 3040.1	5282.5 ± 3106.5	0.032
Calcium (mg/dl)	8.67 ± 0.81	8.69 ± 0.87	8.63 ± 0.76	0.731
Phosphorus (mg/dl)	4.70 ± 1.44	4.71 ± 1.43	4.70 ± 1.45	0.909
Uric acid (mg/dl)	6.91 ± 1.96	7.10 ± 1.93	6.74 ± 1.98	0.043
iPTH (pg/ml)	182.59 ± 54.27	180.45 ± 47.18	184.57 ± 60.93	0.789
Glucose (mg/dl)	124.17 ± 44.24	137.77 ± 55.46	111.58 ± 40.73	0.003
HbA1c (%)	6.10 ± 1.41	6.14 ± 1.50	6.06 ± 1.29	0.453
Protein (g/dl)	6.64 ± 0.73	6.49 ± 0.71	6.76 ± 0.73	<0.001
Albumin (g/dl)	3.76 ± 0.52	3.61 ± 0.52	3.89 ± 0.47	<0.001
BUN (mg/dl)	54.89 ± 21.38	56.56 ± 19.64	53.27 ± 22.92	0.258
Creatinine (mg/dl)	7.75 ± 3.16	7.84 ± 3.19	7.67 ± 2.98	0.293
GFR-MDRD (ml/min per 1.73 m ²)	6.92 ± 3.71	6.86 ± 2.94	6.99 ± 4.38	0.187
GFR-EPI (ml/min per 1.73 m ²)	7.14 ± 3.74	7.04 ± 2.95	7.23 ± 4.42	0.218
Total cholesterol (mg/dl)	153.20 ± 36.69	147.05 ± 37.40	158.99 ± 35.71	0.019
Triglyceride (mg/dl)	126.01 ± 46.49	116.77 ± 41.84	134.12 ± 54.70	0.012
Sodium (mmol/l)	138.11 ± 4.17	137.83 ± 4.77	138.35 ± 3.50	0.067
Potassium (mmol/l)	4.73 ± 0.83	4.74 ± 0.79	4.72 ± 0.87	0.726
Bicarbonate (mmol/l)	22.47 ± 4.41	21.80 ± 4.39	23.12 ± 4.35	0.007
hs-CRP (mg/dl)	0.14 (0.04–0.55)	0.16 (0.04–0.74)	0.13 (0.04–0.50)	0.167
NT-proBNP (pg/ml)	7377.0 (2074.0–26 328.0)	8613.0 (2124.0–29 821.5)	5385.5 (1940.3–18 780.0)	0.107
cTnT (ng/ml)	0.054 (0.028–0.113)	0.060 (0.030–0.126)	0.047 (0.026–0.093)	0.110
T ₃ (ng/ml)	0.80 ± 0.28	0.58 ± 0.16	1.00 ± 0.19	<0.001
Free T ₄ (ng/dl)	1.10 ± 0.26	1.08 ± 0.24	1.12 ± 0.28	0.084
TSH (μIU/ml)	1.90 (1.24–3.32)	1.90 (1.20–3.29)	1.94 (1.24–3.35)	0.899
24-h urine study				
Urea (mg/dl)	247.6 (158.9–451.7)	238.0 (158.1–353.0)	261.5 (163.8–970.0)	0.129
Creatinine (mg/dl)	68.2 (42.6–181.4)	64.6 (39.3–114.9)	76.9 (44.9–327.2)	0.017
Protein (mg/day)	922.4 (349.2–2109.1)	772.2 (348.4–1767.4)	1056.0 (353.7–2461.7)	0.124
Urine volume (ml/day)	780.0 (460.0–1100.0)	700.0 (400.0–1022.5)	800.0 (490.0–1150.0)	0.118
Nutritional markers				
SGA > 1 (malnutrition)	147 (31.2%)	83 (36.4%)	64 (26.3%)	0.020
LBM-Cr	44.89 ± 6.08	44.20 ± 6.05	45.72 ± 6.05	0.033
nPCR	0.94 ± 0.39	0.86 ± 0.34	1.05 ± 0.46	0.021
nPCR ≥ 1.0	118 (25.1%)	52 (22.8%)	66 (27.2%)	0.007
Baseline echocardiographic parameters				
LAD (cm)	4.30 ± 0.74	4.28 ± 0.74	4.33 ± 0.74	0.476
LVMI (g/m ²)	144.05 ± 49.91	151.71 ± 56.54	136.04 ± 40.52	0.002
LVEF (%)	58.66 ± 11.31	57.22 ± 12.44	60.13 ± 9.83	0.012

WBC, white blood cell; iPTH, intact parathyroid hormone; BUN, blood urea nitrogen; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; EPI, Chronic Kidney Disease Epidemiology Collaboration equation; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal pro-B-type natriuretic peptide; cTnT, cardiac troponin T; SGA, subjective global assessment; LBM-Cr, lean body mass estimated by creatinine kinetics; nPCR, normalized protein catabolic rate; LAD, left atrial diameter; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction.

were significant independent determinants of serum T₃ levels (Table 4).

Clinical outcomes according to serum T₃ concentrations

During a mean follow-up duration of 24.2 ± 17.7 months, 49 patients (10.4%) died. Among them, 22 patients (44.9%) died from CV causes and 12 (24.5%) from infection. All-cause, CV, and infection-related mortality rates were significantly higher in patients with 'lower' T₃ levels than in the 'higher' T₃ group (all-cause mortality: 113.4 vs 18.2 events per 1000 patient-years, *P* < 0.001; CV mortality: 49.8 vs 9.1 events per 1000 patient-years, *P* = 0.001; and infection-related mortality: 27.7 vs 4.5 events per 1000 patient-years, *P* = 0.014) (Table 5). The Kaplan–Meier analysis

also indicated that the 'lower' T₃ group had significantly worse all-cause and CV cumulative survival rates compared with the 'higher' T₃ group (*P* < 0.001 and *P* = 0.001 respectively) (Fig. 2). Overall hospitalization rates, as well as composite death and hospitalization rates, were also significantly higher in patients with 'lower' T₃ levels than in the 'higher' T₃ group (Table 5).

On the other hand, serum T₃ levels provided significant positive predictive values for all-cause mortality before (AUC = 0.674, *P* = 0.005) and even after adjusting for BMI, smoking status, modified CCI, aspirin and clopidogrel usage, serum HbA1c, albumin, and potassium concentrations, eGFR by CKD-EPI, Ln hs-CRP, and SGA score (AUC = 0.878, *P* < 0.001) (Fig. 3). There was also a significant positive predictive value of T₃ levels for CV death (AUC = 0.702, *P* = 0.007) (data not shown).

Table 3 Correlations of serum T₃ levels with various nutritional, inflammatory, and echocardiographic variables.

Variables	T ₃ (ng/ml)	
	<i>r</i>	<i>P</i>
Age (years)	−0.156	0.001
Sex (male)	−0.162	<0.001
Glucose	−0.180	<0.001
HbA1c (%)	−0.042	0.432
Bicarbonate (mmol/l)	0.234	<0.001
Nutritional markers		
BMI (kg/m ²)	0.076	0.104
Albumin (g/dl)	0.354	<0.001
Total cholesterol	0.179	0.001
Triglyceride	0.193	<0.001
LBM-Cr	0.174	0.003
nPCR	0.223	<0.001
Inflammatory markers		
White blood cell (/ μ l)	−0.114	0.016
Ln hs-CRP	−0.150	0.003
Echocardiographic parameters		
LAD (cm)	0.001	0.978
LVMI (g/m ²)	−0.157	0.002
LVEF (%)	0.168	0.001

LBM-Cr, lean body mass estimated by creatinine kinetics; nPCR, normalized protein catabolic rate; Ln hs-CRP, log-transformed high-sensitivity C-reactive protein; LAD, left atrial diameter; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction.

Low T₃ as a predictor of all-cause mortality

The univariate Cox proportional-hazards regression analysis revealed that BMI, smoking, modified CCI, aspirin and clopidogrel usage, eGFR by CKD-EPI, serum HbA1c, albumin, and potassium concentrations, Ln hs-CRP, LBM-Cr, nPCR <1.0, LVMI, LVEF, and low T₃ were significant risk factors for all-cause mortality (Supplementary Table 1, see section on supplementary data given at the end of this article). In multivariate

Cox models, low T₃ remained as a significant independent predictor of all-cause mortality (hazard ratio (HR)=3.758, 95% CI=1.055–13.382, *P*=0.021), even after adjusting for BMI, smoking status, modified CCI, aspirin and clopidogrel usage, eGFR by CKD-EPI, serum HbA1c, albumin, and potassium levels, Ln hs-CRP, and SGA score. However, when LBM-Cr, nPCR, LVMI, or LVEF were included in the successive models for further adjustment, the significant impact of low T₃ on all-cause mortality disappeared (Table 6).

In another analysis, we divided the patients into 'subnormal' and 'normal' T₃ groups based on the lowest normal value of T₃ (0.58 ng/ml) and determined the impact of 'subnormal' T₃ on the clinical outcome. Similarly, 'subnormal' T₃ was a significant risk factor for all-cause mortality (HR=5.943, 95% CI=1.442–24.492, *P*=0.014), but its statistical power disappeared when LBM-Cr, nPCR, LVMI, or LVEF were further incorporated into the models (Supplementary Tables 2 and 3, see section on supplementary data given at the end of this article).

Furthermore, low T₃ was not a significant independent predictor of CV mortality after adjusting for smoking status, DM, underlying CVDs, eGFR by CKD-EPI, serum albumin and potassium concentrations, Ln hs-CRP, and SGA score (HR=2.735, 95% CI=0.917–11.395, *P*=0.086) (data not shown).

Discussion

Thyroid hormone abnormalities are common in CKD patients. Among these, low T₃ is the most frequently observed alteration of thyroid hormone in patients with CKD. Recently, accumulating evidence has indicated that low T₃ may act as a prognostic factor for adverse clinical outcomes in prevalent ESRD patients rather

Figure 1 The correlation of serum T₃ levels with various nutritional, inflammatory, and echocardiographic variables. Serum T₃ concentrations had significant positive associations with (a) serum albumin levels, (b) LBM-Cr, (c) nPCR, and (d) LVEF, while there were significant inverse correlations of T₃ with (e) LVMI and (f) Ln hs-CRP. LBM-Cr, lean body mass estimated by creatinine kinetics; nPCR, normalized protein catabolic rate; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; Ln hs-CRP, log-transformed high-sensitivity C-reactive protein.

Table 4 Determinants of serum T₃ concentrations.

Variables	T ₃	
	Regression coefficient	P
Age (years)	−0.003	0.017
Sex (male vs female)	0.025	0.448
Underlying cardiovascular disease	0.027	0.424
Hemoglobin (g/dl)	0.009	0.489
Glucose (mg/dl)	−0.022	0.749
Albumin (g/dl)	0.068	0.047
Total cholesterol (mg/dl)	0.003	0.983
Triglyceride (mg/dl)	0.179	0.013
Bicarbonate (mmol/l)	0.010	0.006
SGA > 1 (vs SGA ≤ 1)	−0.033	0.354
nPCR ≥ 1.0 (vs nPCR < 1.0)	0.107	0.001
hs-CRP ≥ 5 mg/dl (vs hs-CRP < 5 mg/dl)	−0.192	0.019

SGA, subjective global assessment; nPCR, normalized protein catabolic rate; hs-CRP, high-sensitivity C-reactive protein.

than as an innocent bystander (17, 18). In this study, we demonstrated that low T₃ is a significant independent risk factor for all-cause mortality in incident HD patients. Moreover, it seems that the impact of low T₃ on mortality may be due, in part, to malnutrition and cardiac dysfunction.

Low T₃ has been reported to be present in up to 70% of patients with ESRD (5, 6). It has been proposed that multiple mechanisms contribute to this high prevalence of low T₃, including systemic inflammation, malnutrition, and metabolic acidosis (8, 9). Zoccali *et al.* (17) showed that fT₃ was a significant independent predictor of mortality even after adjusting for a series of traditional and non-traditional risk factors including interleukin-6 (IL6) in a multivariate analysis, but that this inflammatory cytokine predicted mortality only in a model excluding fT₃. These findings suggest that fT₃ and inflammation are involved in the same pathogenic pathway leading to death in ESRD patients and that fT₃ mediates part of the adverse effects of inflammation in

these patients. Moreover, similar findings have been demonstrated in prevalent PD patients (18). We also found that plasma T₃ levels were significantly associated with hs-CRP concentrations and that hs-CRP was a significant independent determinant of T₃. In contrast to a majority of previous studies, however, there was no difference in hs-CRP levels between the 'lower' and 'higher' T₃ groups in the present study. It is surmised that this discrepancy may partly be due to differing ethnicities and dialysis duration (prevalent vs incident). Further investigation, including various inflammatory markers in a large, ethnically homogenous incident HD patient cohort, will be needed to confirm whether the impact of T₃ levels on mortality is independent or associated with inflammation.

It is well known that T₃ increases cardiac output by affecting tissue oxygen consumption, vascular resistance, blood volume, cardiac contractility, and heart rate (28, 29). Therefore, low T₃, even in the normal range, has been suggested to be associated with various CVDs in ESRD patients, which has been clarified by several previous studies (12, 17, 30, 31). In their study, Zoccali *et al.* (12) showed that LV systolic function was depressed and LVMI was increased in the first fT₃ quartile of 234 prevalent dialysis patients when compared with patients in other quartiles. In another recent, cross-sectional study, across decreasing fT₃ tertiles, carotid-femoral pulse wave velocity (c-f PWV) and carotid artery-intima media thickness (CA-IMT) measured by Doppler ultrasonography were found to be incrementally higher in 137 maintenance HD patients. Furthermore, fT₃ concentrations have been demonstrated to be significantly associated with c-f PWV and CA-IMT, indicating that fT₃ levels are negatively associated with carotid atherosclerosis and arterial stiffness (30). The present study also found that in the 'lower' T₃ group, LVEF was significantly lower, whereas LVMI was significantly higher, which was in concordance with previous observations. In addition,

Table 5 Comparisons of clinical outcomes according to serum T₃ levels.

	T ₃ < 0.8 ng/ml (n = 228)		T ₃ ≥ 0.8 ng/ml (n = 243)		P
	n (%)	Rates (per 1000 patient-years)	n (%)	Rates (per 1000 patient-years)	
Mortality					
All-cause	41 (18.0%)	113.36	8 (3.3%)	18.15	< 0.001
CV	18 (7.9%)	49.77	4 (1.6%)	9.08	0.001
Infection	10 (4.4%)	27.65	2 (0.8%)	4.54	0.014
Hospitalization					
All-cause	102 (44.7%)	282.07	75 (30.9%)	170.16	0.002
CV	35 (15.4%)	96.77	24 (9.9%)	54.45	0.073
Infection	29 (12.7%)	80.18	14 (5.8%)	31.76	0.009
Composite ^a					
All-cause	132 (57.9%)	364.96	79 (32.5%)	179.24	< 0.001
CV	48 (21.1%)	132.71	24 (9.9%)	54.45	0.001
Infection	33 (14.5%)	91.24	14 (5.8%)	31.76	0.002

CV, cardiovascular.

^aComposite: composite death and hospitalization.

Figure 2 Kaplan-Meier plots for all-cause and cardiovascular survival. Compared with patients with 'higher' T_3 , the 'lower' T_3 group showed significantly worse (a) all-cause and (b) cardiovascular cumulative survival rates.

serum T_3 concentrations had a significant inverse correlation with LVMI and a significant positive relationship with LVEF. Even though a multivariate Cox hazards regression analysis revealed that low T_3 was a significant risk factor for mortality after adjusting for traditional risk factors, the independent predictive value of low T_3 for mortality disappeared when LVEF and/or LVMI were included in a multivariate Cox model. These findings suggest that the association between T_3 levels and all-cause mortality is largely mediated by cardiac dysfunction. Similarly, cardiac abnormalities, low LVEF and high LVMI had a significant impact on all-cause mortality only when T_3 levels were excluded from the multivariate analysis (data not shown), suggesting that the relationship between cardiac dysfunction and mortality was mediated by T_3 .

A recent study by Ozen *et al.* (6) has shown that ftT_3 is a significant predictor of mortality in adjusted Cox regression models including albumin or hs-CRP levels, but that the significance is less when compared with that of a crude Cox model. Moreover, further adjustment for both albumin and hs-CRP levels made the impact of ftT_3 levels on mortality disappear. These findings suggest that ftT_3 is a strong and inverse mortality predictor, in part explained by its underlying association with nutritional

state and inflammation. In this study, we included for the first time not only albumin levels but also the SGA score, LBM-Cr, and nPCR to determine the relationship between T_3 and nutritional status and demonstrated that T_3 levels were significantly associated with nutritional parameters in incident HD patients. Furthermore, T_3 was a significant independent predictor of all-cause mortality in a traditional risk factors-adjusted Cox model. However, the relationship became insignificant when nutritional parameters were included in the multivariate Cox hazards regression analysis. Similarly, the impact of nutritional parameters on mortality was no longer significant when T_3 was included in the Cox model (data not shown). Taken together, the prognostic power of T_3 and nutrition seem to be interrelated.

Several aspects of the methods and scope of this study may limit the interpretation of research outcomes. First, since the study subjects were all Korean incident HD

Figure 3 Receiver operating characteristic curves of T_3 for all-cause mortality. Serum T_3 concentrations provided significant positive predictive values for all-cause mortality (a) in an unadjusted model (AUC=0.674) and (b) in a model adjusted for BMI, smoking status, modified CCI, aspirin and clopidogrel usage, serum HbA1c, albumin, and potassium concentrations, eGFR by CKD-EPI, Ln hs-CRP, and SGA score (AUC=0.878). CCI, Charlson comorbidity index; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; Ln hs-CRP, log-transformed high-sensitivity C-reactive protein; SGA, subjective global assessment.

Table 6 Multivariate Cox proportional-hazards regression analysis for all-cause mortality.

	Serum T_3		
	HR	95% CI	P
Model 1	3.758	1.055–13.382	0.021
Model 2	7.715	0.976–60.987	0.053
Model 3	7.692	0.973–60.816	0.052
Model 4	6.860	0.839–56.096	0.072
Model 5	8.008	0.971–66.046	0.053

Model 1: adjusted for BMI, smoking status, modified Charlson comorbidity index, aspirin and clopidogrel usage, glomerular filtration rate estimated by Chronic Kidney Disease Epidemiology Collaboration equation, serum HbA1c, albumin, and potassium concentrations, log-transformed high-sensitivity C-reactive protein, and subjective global assessment score; Model 2: Model 1 + lean body mass estimated by creatinine kinetics; Model 3: Model 1 + normalized protein catabolic rate ≥ 1.0 (vs < 1.0); Model 4: Model 1 + left ventricular mass index; Model 5: Model 1 + left ventricular ejection fraction.

patients, the association between T_3 levels and mortality may not be generalized to other populations. Second, we focused on studying the effect of T_3 levels in this study, while previous investigations have found that both low T_3 and fT_3 levels are independent risk factors for mortality in prevalent dialysis patients (6, 17, 18, 32). In incident dialysis patients, however, only T_3 , but not fT_3 , levels were associated with worse all-cause and CV mortality after adjustment for confounding factors (31). This may be attributed to a lower technical specificity of fT_3 measurement by RIA (20), especially for the stored samples (21), and a smaller influence of heparin on T_3 than on fT_3 (22, 33). In addition, T_3 levels are determined as a total form rather than as a free form in most hospitals in Korea due to the financial benefits and convenience. Based on these findings, we considered T_3 as a more stable and reliable factor, and used T_3 rather than fT_3 for the analysis. Third, more than half of our study population, mostly having CV complications, were taking beta blockers. Patients with renal failure, especially those on dialysis treatment, have a considerably high prevalence of CV complications due to uremic toxin, volume overload, chronic inflammation, oxidative stress, and abnormal bone metabolism (34). In fact, 87% of the patients had hypertension and 36.5% of the patients had underlying CV complications in this study. Even though beta blockers are known to affect serum T_3 concentrations, we inferred that excluding these patients would result in selection bias. Moreover, the proportion of patients on beta blockers was not different between the 'lower' and 'higher' T_3 groups, and beta blocker usage was not significantly associated with serum T_3 concentrations in the correlation analysis ($r=0.062$, $P=0.180$). Furthermore, in the linear regression analysis, beta blocker usage was not a significant determinant of serum T_3 concentrations ($R=0.043$, $P=0.093$). Fourth, there was a disparity in the timing of laboratory measurements and echocardiography. As has been mentioned above, since there was an extremely wide variation in the biochemical data

at 0 month due to diverse patients' conditions to start HD, we used the laboratory data collected at 3 months after HD commencement, when correction of uremia, anemia, and acidosis was considered to be sufficiently achieved. On the other hand, based on the results of previous studies demonstrating that LVMI, LVEF, and fractional shortening are improved after long-term HD of 12–36 months (35, 36), correction of malnutrition, anemia, acidosis, and thyroid hormone might influence the cardiac function at 3 months. However, no studies have yet shown significant changes in echocardiographic findings within 3 months of short-term dialysis. In this study, echocardiography was carried out not at the start of dialysis but close to the time of discharge, when patients were considered to be in euvolemic state. In fact, the mean interval between dialysis commencement and echocardiography was 19.7 days in our patients. In addition, since most incident HD patients had to undergo maintenance HD at private clinics in Korea and to pay an additional fee of \$300–350 for echocardiography, it was not easy to perform echocardiography at outpatient clinics after 3 months of initial dialysis. Therefore, we inevitably used 3-month laboratory data and baseline (about 3 weeks after the start of HD) echocardiographic parameters. Fifth, since only 3-month laboratory data were included in the analysis, it was difficult to determine the impact of the change in T_3 levels on patients' clinical outcomes. Meuwese *et al.* (32) assessed the association between baseline and trimestral variation in T_3 levels and mortality in 210 prevalent HD patients and found that not only basal low T_3 but also persistently low T_3 was significantly associated with increased mortality risk, especially due to CV causes. While the HRs for all-cause and CV mortality were higher in patients with persistently low T_3 than in patients with low basal T_3 , there was still a significant association of low basal T_3 with mortality. Sixth, all-cause and especially CV mortality rates in this study were relatively low. A small number of events may limit the power of statistical analyses in identifying the independent predictors of all-cause and especially CV mortality. Finally, the follow-up duration was relatively short and thus a sufficient number of patients could not be recruited for a longitudinal study. Since this prospective observation cohort study is still ongoing, the long-term association between T_3 levels and mortality can be elucidated in the future. Despite these limitations, to our knowledge, this study is the first to investigate the association of T_3 levels with echocardiographic findings and various nutritional parameters, including albumin levels, SGA score, LBM-Cr, and nPCR, and their impact on all-cause and CV mortality in a large, ethnically homogenous incident HD patient cohort.

In conclusion, low T_3 is a significant independent risk factor for all-cause mortality in incident HD patients, and its impact on mortality may be attributed, in part, to malnutrition and cardiac dysfunction.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-13-0540>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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