Low triiodothyronine and survival in end-stage renal disease

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Plasma triiodothyronine (fT3) is a strong predictor of adverse clinical outcomes in various clinical conditions. Since fT3 in patients with end-stage renal diseases (ESRD) is frequently reduced and is associated with inflammation and cardiovascular damage, we prospectively tested the hypothesis that it predicts death in a cohort of 200 hemodialysis patients. Plasma fT3 was lower in ESRD patients ($P<0.001$) than in healthy subjects and in clinically euthyroid patients with normal renal function. During the follow-up 102 patients died. Patients who died had significantly lower plasma fT3 than those who survived ($P<0.001$) and in a Kaplan–Meyer analysis plasma fT3 was associated with death ($P<0.001$). On multivariate Cox's regression analyses, adjusting for a series of traditional and emerging risk factors including inflammation markers, patients with relatively higher plasma fT3 (hazard ratio (HR) (1 pg/ml increase in fT3)) had a 50% reduction in the risk of death (HR = 0.50, 95% CI: 0.35–0.72) as compared to those having relatively lower fT3 levels. Of note, plasma fT3 captured most of the predictive power of interleukin-6 (IL-6) because this latter variable emerged as a significant predictor of death only in a model excluding fT3. Low fT3 is an independent predictor of death in hemodialysis patients. These data lend support to the hypothesis that thyroid dysfunction is implicated in the high risk of the ESRD population.

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End-stage renal disease (ESRD) is a frequent cause of 'non-thyroidal illness (NTI),'[1,2] the definition now preferred to 'euthyroid sick syndrome' to denote altered thyroid hormones in the absence of underlying intrinsic thyroid disorder. Low free triiodothyronine (fT3), the biologically active form of thyroid hormone, is a major feature of this disturbance which is considered as a counter-regulatory response finalized at minimizing energy and protein wasting in acute and chronic stressful conditions. NTI is indeed commonly found in systemic illnesses such as acute and chronic infections, poorly controlled diabetes mellitus with ketoacidosis, myocardial infarction and severe myocardial ischemia, and virtually in any severe illness. Thyroid function is frequently altered in ESRD patients and about 1/4–1/5 of patients with ESRD display low fT3.[3,4] As also reflected by the new designation of the syndrome, non-NTI is now perceived as a condition less innocent than previously thought.[5] The pathogenesis of low T3 in NTI is complex and recent evidence indicates that inflammation plays a central role in this syndrome.[6–8] In a recent survey, we have shown that low fT3 is associated to inflammation and to cardiovascular damage in ESRD patients.[4] This observation suggests that low levels of this hormone may denote an unfavorable prognosis, a hypothesis in keeping with an extensive series of observations in patients with heart disease[9–11] and in various acute[12,13] and chronic diseases[14,15] indicating that low fT3 is one of the strongest markers of poor prognosis in these conditions. As a part of the original study design, we planned to prospectively test the hypothesis that fT3 predicts survival in ESRD patients. To this end, we undertook a follow-up study in the original cohort where the above-mentioned observations were made. The results of this study show that low fT3 is a strong and independent marker of death in dialysis patients thus implicating this alteration in the high mortality of ESRD.

RESULTS

The main demographic, somatometric, clinical, and biochemical characteristics of patients included in the study are detailed in Table 1. A total of 102 patients had had at least one cardiovascular event (myocardial infarction, electrocardiogram-documented anginal episodes, peripheral artery

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Table 1 | Main demographic, clinical, and biochemical data of dialysis patients

	Plasma fT3			
	I tertile (<2.9 pg/ml) (*n*=66)	II tertile (3.0–3.8 pg/ml) (*n*=66)	III tertile (>3.8 pg/ml) (*n*=68)	*P*-value for trend
Age (years)	67±12	60±14	55±16	**<0.001**
Male sex, *n* (%)	35 (53%)	30 (45%)	40 (59%)	0.50
Dialysis vintage (months)	38 (24–99)	50 (25–112)	39 (14–87)	0.27
Smokers, *n* (%)	18 (27%)	25 (39%)	28 (41%)	0.09
Diabetes, *n* (%)	19 (29%)	11 (17%)	5 (7%)	**0.001**
On antihypertensive treatment, *n* (%)	18 (27%)	22 (33%)	20 (29%)	0.79
EPO-independent patients, *n* (%)	27 (41%)	33 (50%)	35 (51%)	0.38
With previous CV events, *n* (%)	44 (67%)	34 (52%)	24 (35%)	**<0.001**
Systolic pressure (mm Hg)	141±28	144±24	134±24	0.11
Diastolic pressure (mm Hg)	73±13	79±14	75±12	0.17
Heart rate (beats/min)	78±11	77±8	79±11	0.54
Hemoglobin (g/l)	103±19	110±16	110±20	**0.03**
Albumin (g/l)	39±4	42±4	44±4	**<0.001**
Calcium* phosphate ($mmol^2/l^2$)	4.45±1.01	4.40±1.20	4.57±1.07	0.45
Homocysteine (μmol/l)	29 (20–43)	26 (21–38)	27 (17–48)	0.97
Cholesterol (mmol/l)	5.34±1.15	5.17±1.48	5.64±1.63	0.36
CRP (mg/l)	13.7 (4.3–25.9)	8.2 (3.4–19.1)	3.8 (3.4–9.5)	**<0.001**
IL-6 (pg/ml)	9.4 (4.6–15.1)	4.2 (2.6–6.3)	3.3 (2.2–6.1)	**<0.001**
ADMA (μmol/l)	2.23 (1.48–3.97)	2.18 (1.33–3.59)	2.52 (1.71–3.96)	0.54
fT4 (ng/100 ml)	1.2 (1.1–1.4)	1.2 (1.1–1.4)	1.1 (1.0–1.3)	0.13
TSH (mIU/l)	1.4 (0.8–1.9)	1.4 (1.0–2.1)	1.2 (1.0–1.3)	0.45

ADMA, asymmetric dimethylarginine; CRP, C-reactive protein; EPO, erythropoietin; fT4, free thyroxine; IL-6, interleukin-6; TSH, thyroid-stimulating hormone.
Data are expressed as mean±s.d., median and inter-quartile range or as percent frequency, as appropriate.
Values given in bold identify statistically significant differences.

disease, arrhythmia transient ischemic attacks, and stroke). All patients were clinically euthyroid.

Plasma fT3 was significantly ($P<0.001$) lower in ESRD patients (3.3±0.8 pg/ml) than in healthy subjects (3.7±1.0 pg/ml) and clinically euthyroid patients with normal renal function (3.6±0.8 pg/ml). Average plasma free thyroxine (fT4) in ESRD patients (1.23±0.25 ng/100 ml) was very similar to that found in healthy subjects (1.25±0.22 ng/100 ml). Fifteen ESRD patients (i.e. 7.5%) had thyroid-stimulating hormone (TSH) above the upper limit of the normal range (cutoff: 3 mIU/L). In Table 1 risk factors in dialysis patients are presented in relationship to fT3 tertiles. Patients in the first tertile (i.e., those with relatively lower plasma fT3 levels) were older, included a greater proportion of individuals with previous cardiovascular events and of diabetics, and displayed lower hemoglobin and serum albumin and higher serum interleukin-6 (IL-6) and C-reactive protein (CRP) when compared to those in other tertiles. The proportion of erythropoietin-independent patients was similar across fT3 tertiles (Table 1).

Table 2 | Causes of death in the study cohort

Causes of death	*n*
Cardiovascular	
Stroke	18
Heart failure	12
Myocardial infarction	17
Mesenteric infarction	5
Arrhythmia	4
Sudden death	8
Pulmonary embolism	3
Peripheral vascular disease	1
Other causes	
Cachexia	8
Sepsis/infection	11
Neoplasia	4
Hyperkalemia	3
Gastrointestinal hemorrage	3
Chronic obstructive pulmonary disease	1
Diabetes, hyperosmolar coma	1
Treatment withdrawal	1
Liver cirrhosis	1
Hemoptysis	1
Total	102

Thyroid hormones and survival

During the follow-up period, 102 patients died, 68 of them (i.e., 66% of total deaths) of cardiovascular complications (Table 2). Patients who died (3.1±0.7 pg/ml) had significantly lower plasma fT3 ($P<0.001$) than those who survived (3.7±0.8 pg/ml). Neither fT4 nor TSH were associated with death ($P=0.37$ and 0.23, respectively) and for this reason further analysis was restricted to fT3.

In a Kaplan–Meyer analysis fT3 tertiles were associated with death (log-rank test 25.3, $P<0.001$) (Figure 1) and an

association of similar strength was observed also in an univariate (unadjusted) Cox analysis with plasma fT3 as continuous variable (Table 3, Model 1). On multivariate Cox regression analysis, plasma fT3 remained a significant predictor of all-cause death (Table 3). Indeed, both in statistical models adjusting for age and sex (Model 2) and in fully adjusted models including potential confounders identified in Table 1 and univariate predictors of death (age, male sex, smoking, diabetes, previous cardiovascular events, systolic pressure, albumin, and asymmetric dimethylarginine (ADMA)) the strength of the association between plasma fT3 and death (Table 3, Model 3) remained strong and significant. In this analysis, patients with relatively higher plasma fT3 levels (1 pg/ml increase), had a fully adjusted relative risk for all-cause death by the 50% lower (HR: 0.50, 95% CI: 0.35–0.72; $P<0.001$) than that observed in those with relatively lower values. IL-6 failed to predict survival in the fully adjusted multivariate Cox's model (Table 3, Model 3). Interestingly, plasma fT3 captured most of the predictive power of IL-6 because this latter variable emerged as a significant predictor of death (HR (10 pg/ml increase in IL-6): 1.25, 95% CI: 1.01–1.54) only in a model excluding fT3. Accordingly, the prognostic overlapping of the two risk factors was of significant magnitude (21%).

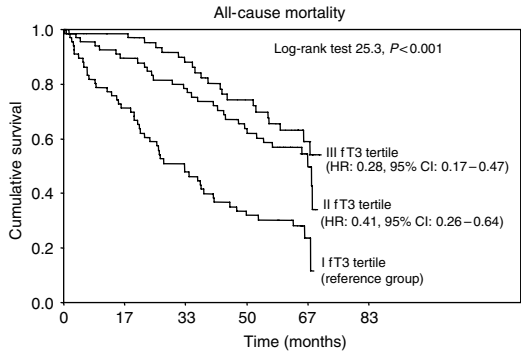

Figure 1 | Kaplan–Meier survival analysis of plasma fT3. Patients are grouped into three tertiles on the basis of individual values of plasma fT3. In parentheses we reported the HR of death (and the 95% CI) associated to each fT3 tertile.

DISCUSSION

This study shows that low fT3 is an independent predictor of death in hemodialysis patients. These data lend support to the hypothesis that thyroid dysfunction may be implicated in the high risk of the ESRD population.

Derangements in thyroid function in ESRD and in the study cohort

Thyroid hormone metabolism is disturbed at multiple critical steps in patients with chronic renal disease including iodine accumulation in the thyroid gland, protein binding and peripheral tissue metabolism (e.g., altered de-iodination), actual tissue concentration and availability.[2,3] It was hypothesized that subnormal free T3 in ESRD may be due to the accumulation of substances that inhibit binding of T3 to the solid-phase matrices. We found that fT3 but not fT4 was reduced in ESRD patients suggesting that low fT3 is unlikely to be an *in vitro* artifact because substances inhibiting binding are expected to affect fT4 to a greater extent than fT3. Thus, reduced fT3 seems to reflect a true selective T3 deficiency due to a defect in T4 to T3 conversion. It is important noting that reduced fT3 does not entail a condition of subclinical hypothyroidism because, as in a previous study,[16] we found that TSH and fT4 are in the normal range in the majority of patients with this alteration. However, low fT3 most likely may not be an innocent finding because it is a most consistent predictor of death in various diseases[9,11,12] and depressed fT3 is associated with inflammation and cardiovascular damage in ESRD.[4] In the present study, we have therefore tested the hypothesis that low fT3 predicts death in a well-characterized study cohort of ESRD patients.

Table 3 | Crude and adjusted relative risks of plasma fT3 for all-cause mortality

	All cause mortality relative risks (95% CI), *P*-values		
Variables (units of increase)	Model 1 (unadjusted)	Model 2 (age and sex adjusted)	Model 3 (fully adjusted)
Plasma fT3 (1 pg/ml)	0.45 (0.34–0.60), $P<0.001$	0.52 (0.39–0.69), $P<0.001$	0.50 (0.35–0.72), $P<0.001$
Age (1 year)	—	1.05 (1.03–1.07), $P<0.001$	1.06 (1.04–1.08), $P<0.001$
Male sex	—	1.97 (1.32–2.95), $P=0.001$	1.74 (1.03–2.93), $P=0.04$
Diabetes	—	—	1.66 (1.03–2.66), $P=0.04$
Previous CV events	—	—	1.76 (1.12–2.77), $P=0.01$
Hemoglobin (1 g/l)	—	—	1.01 (0.99–1.02), $P=0.10$
IL-6 (10 pg/ml)	—	—	1.03 (0.82–1.31), $P=0.79$
Smoking	—	—	1.47 (0.87–2.49), $P=0.15$
Systolic pressure (1 mm Hg)	—	—	1.00 (0.99–1.01), $P=0.94$
Albumin (1 g/l)	—	—	0.99 (0.94–1.04), $P=0.76$
ADMA (1 μmol/l)	—	—	1.24 (1.13–1.37), $P<0.001$

ADMA, asymmetric dimethylarginine; CRP, C-reactive protein; CV, cardiovascular; fT3, triiodothyronine; IL-6, interleukin-6.
Data are expressed as hazard ratio (95% CI) and *P*-value. Because of the collinearity between serum IL-6 and CRP, we included into the fully adjusted Cox model (Model 3) only serum IL-6. However, the inclusion of serum CRP instead of serum IL-6 did not affect the strength of the association between plasma fT3 and death (HR (1 pg/ml increase in plasma fT3): 0.51, 95% CI 0.36-0.71, $P<0.001$). IL-6 emerged as a significant predictor of death (HR (10 pg/ml increase): 1.25, 95% CI: 1.01–1.54, $P=0.04$) only in a model excluding fT3 (see text).

FT3 as a risk marker

FT3 is of crucial importance in adaptive mechanism(s) to starvation, stress, and severe illness. The reduction of fT3 and other thyroid hormones in severe illness has been interpreted in a teleological manner, that is, as an adaptive response aimed at sparing calories and protein. While this response does not seem to have detrimental effect in the short term, in the long term it signals, and probably contributes to cause[17] a high-risk situation. In intensive care patients it predicts 5 days mortality.[13] In patients with liver cirrhosis[15] or with severe pulmonary diseases[14] it is an indicator of poor prognosis and in patients with chronic heart failure it predicts death[9,11] and adds prognostic information to standard parameters of cardiac function including ejection fraction.[10] Furthermore, thyroid dysfunction is associated with a hypercoagulable status[18] and represents a risk factor for subclinical atherosclerosis in euthyroid hyperlipidemic patients.[19]

FT3 and survival in ESRD

The hypothesis that low fT3 is a risk factor for death has never been tested in patients with ESRD. In general, NTI in these patients is considered an innocent condition.[2] The cardiovascular system is very sensitive to thyroid hormone and not only clinical and subclinical hypothyroidism but also a low T3 syndrome is associated with changes in myocardial performance[10] and death[9] in patients with heart failure. By several analytical approaches we found that fT3 was a consistent predictor of death and the strength of this association was little modified by statistical adjustment for a series of traditional and non-traditional risk factors. Causality is a complex issue that cannot be resolved only on the basis of observational data. Statistical models are useful to generate interpretative hypotheses and it is an accepted concept that when two risk factors are in the same pathway one of them may loose predictive power.[20,21] FT3 was a highly significant predictor of death in a multivariate analysis including IL-6 while this cytokine predicted mortality only in a model excluding fT3. Such a statistical phenomenon suggests that inflammation and fT3 are in the same pathogenic pathway leading to death in ESRD patients (Figure 2) and that fT3 mediates part of the adverse effects of inflammation in these patients. Yet our interpretation should be merely considered as hypothesis generating and it remains to be specifically tested in experimental studies. One may wonder why IL-6 but not CRP or albumin or ADMA lost prediction power in the full model including fT3. IL-6 is considered a purer inflammation marker than CRP which reflects a larger array of biological phenomena than IL-6. For example, CRP seems to be directly – that is, independently of IL-6 – involved in the pathogenesis of arterial damage.[22] On the other hand albumin, an established inverse acute-phase reactant, reflects also the nutritional status. Furthermore, ADMA has complex effects on the cardiovascular system, that is, effects well beyond inflammation.[23] Thus, both on biological and statistical grounds it is not surprising that CRP, ADMA, and albumin turn out to be independent predictors of death.

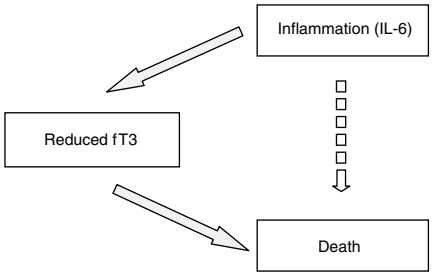

Figure 2 | Hypothetic chain of events leading to death. Reduced fT3 results from inflammation and determines death in ESRD patients.

Favorable effects of T3 administration were noted in an experimental model of myocardial infarction[24] and in a small series of patients with heart failure.[25] However, we still lack long-term studies testing the effect of T3 on mortality in patients with heart disease and generally in those NTI. D-Thyroxine administration in dialysis patients reduces the plasma concentration of lipoprotein(a),[26] that is, a lipoprotein very sensitive to inflammatory processes. However, near physiologic doses of T3 (50 μg/day) produce a negative nitrogen balance in these patients.[27] Although this effect may only reflect correction of hypothyroidism and can be prevented by increasing protein intake, caution is needed in studies exploring the effect of T3 in ESRD patients. The important observation that the low fT3 state of ESRD can be almost fully corrected by appropriate treatment of metabolic acidosis[28] opens an interesting perspective for intervention.

In summary, low fT3 is an independent predictor of death in hemodialysis patients. These data lend support to the hypothesis that thyroid dysfunction is implicated in the high risk of the ESRD population. Mechanistic studies and exploratory intervention trials in ESRD patients with low fT3 are at this stage needed to further investigate the nature of the association between fT3 and clinical outcomes unravelled by this study.

MATERIALS AND METHODS

The protocol conformed to the ethical guidelines of our institution, and informed consent was obtained from each participant.

Patients and controls

We studied 200 hemodialysis patients with ESRD (105 men and 95 women, aged 61 ± 15 years). This cohort represented all eligible patients being treated in two dialysis centers sharing the same practice patterns and serving the same metropolitan area during a calendar year and all incident patients who entered dialysis treatment in the same centers during the following 15 months. To be included in the study, patients had to be free of inter-current illnesses (infectious diseases, cardio-circulatory congestion, cancer, and any other diseases requiring hospitalization) and off drugs that may affect the plasma concentration of thyroid hormones. Eighteen patients were excluded from the study because they were taking β-blockers. Patients were being treated thrice weekly with standard

bicarbonate dialysis (138 mmol/l Na, 35 mmol/l HCO_3, 1.5 mmol/l K, 1.25 mmol/l Ca, and 0.75 mmol/l Mg) by cuprophane or semisynthetic membranes (dialysis filters surface area 1.1–1.7 m^2). Dry weight was targeted in each case to achieve a normotensive edema-free state. The average urea Kt/V in these patients was 1.20 ± 0.26. Seventy-one patients were habitual smokers (22 ± 16 cigarettes/day). A total of 107 patients were on treatment with erythropoietin. Sixty patients were on antihypertensive treatment (48 on mono-therapy with angiotensin-converting inhibitors, AT-1 antagonists, or calcium channel blockers and 12 on double or triple therapy with various combinations of these drugs). No patient was assuming lithium, amiodarone, or other drugs that may interfere with thyroid function and no patient had clinical evidence of hypothyroidism.

We formed two control groups: one composed of 31 healthy individuals (recruited from the clinical and laboratory staff and from a series of healthy senior members of an association that supports our institution) who were matched accurately (by 5 years categories) to patients for gender and age (15 men, 16 women, average age: 61 years). Furthermore, for fT3 measurement only, we formed an additional control group that comprised 262 clinically euthyroid individuals (average age: 55 years; range 20–85 years; 136 men and 126 women) who had normal renal function (serum creatinine < 1.2 mg/dl) and were referred consecutively to an internal medicine clinic for hypertension, gastrointestinal diseases, or osteoporosis.

Follow-up

After the initial assessment patients were followed up for an average time of 42 months (range 0.2–70 months). During the follow-up, fatal cardiovascular events (sudden death, mesenteric and myocardial infarction, electrocardiogram-documented arrhythmia, pulmonary embolism, heart failure and stroke, and other thrombotic events except arterio-venous thrombosis) and death of any causes were accurately recorded. Each event was reviewed and assigned an underlying cause by a panel of five physicians. As a part of the review process, all available medical information about each death was collected. This information always included study and hospitalization records. In the case of an out-of-hospital death, family members were interviewed by telephone to better ascertain the circumstances surrounding death.

Laboratory measurements

Blood sampling was performed between 0800 and 1000 mid-week, during the dialysis interval. Samples were taken into chilled ethylenediaminetetraacetic acid vacutainers, placed immediately on ice, and centrifuged within 30 min at $-4^{\circ}C$, and the plasma was stored at $-80^{\circ}C$ until assay. Cholesterol, albumin, calcium, phosphate, and hemoglobin measurements were made by standard methods in the routine clinical laboratory. FT3 and fT4 were measured by a commercially available RIA kits (RIA-coat fT3 and RIA-mat fT4 by Byk-Sangtek Diagnostica, Dietzenbach, Germany). In the fT3-RIA coat assay free T3 from serum samples competes with radioactive-labelled T3 for specific T3 antibodies which are covalently bound to the inner part of the test tubes. TSH was measured by a sensitive IRMA (IRMA-mat TSH, Byk-Sangtek Diagnostica). The intra-assay coefficient of variation of these hormones ranged from 2.8 to 4.7%; and the inter-assay coefficient of variation was from 6.5 to 7.1%. The upper limit of TSH of this assay is 3 mIU/l. The methods of measurement of plasma total homocysteine, CRP, plasma ADMA and serum IL-6 were reported elsewhere.[29–31] We specifically focused on IL-6 because this cytokine is the strongest predictor of death among inflammation markers.[31]

Statistical analysis

Data are reported as mean $\pm$ s.d., median and inter-quartile range or as percent frequency, as appropriate, and comparisons among groups were made by *P*-value for trend test.

The association between plasma fT3 and all-cause death was analyzed by the Kaplan–Meier method and by univariate and multivariate Cox regression analysis. As potential confounders for the association of fT3 with death we considered a series of traditional risk factors (age, sex, previous cardiovascular events, smoking, diabetes, arterial pressure, heart rate, antihypertensive treatment, and cholesterol), risk factors peculiar to ESRD (dialysis vintage, albumin, hemoglobin, calcium $\times$ phosphate, and homocysteine) and emerging risk factors as serum IL-6, serum CRP, and ADMA. The independent association between plasma fT3 and death was then analyzed in Cox models of various complexity: unadjusted, age and sex adjusted, and adjusted for covariates that were either associated (with $P < 0.05$) to plasma fT3 (see Table 1) or that resulted to be significantly related (with $P < 0.05$) with survival at univariate Cox regression analysis. The prognostic overlapping (degree of confounding) between fT3 and IL-6 was calculated by a standard method. By this method confounding is considered as statistically relevant when it exceeds 15%.[20]

Hazard ratios (HR) and their 95% CI were calculated with the use of the estimated regression coefficients and their s.e. in the Cox regression analysis. All calculations were carried out using a standard statistical package (SPSS for Windows Version 9.0.1, 11 March 1999).

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