Free Triiodothyronine in Hemodialysis Patients
Link With Malnutrition and Inflammation

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Keywords. hemodialysis, inflammation, malnutrition, triiodothyronine

Introduction. Free triiodothyronine (FT3) is a marker of comorbidity in end-stage renal disease and in many acute and chronic diseases. There is lack of data about the link between FT3 levels and malnutrition and inflammation in hemodialysis patients. The objective of the present study was to investigate the link between FT3 and malnutrition and inflammation in hemodialysis patients.
Materials and Methods. A total of 84 patients were included in the study (38 men and 46 women; mean age, 56.2 ± 14.8 years; hemodialysis duration, 95.72 ± 10.35 months). Serum FT3, free thyroxin, and thyroid-stimulating hormone concentrations were determined. Demographic data and laboratory values were evaluated. Patients' comorbidity status was determined using the Charlson Comorbidity Index (CCI), and malnutrition-inflammation status was determined by Malnutrition-Inflammation Score (MIS).
Results. Serum FT3 concentration inversely correlated with age (r = -0.328, P = .002), CCI (r = -0.591, P < .001), C-reactive protein (r = -0.299, P = .01), and MIS (r = -0.671, P < .001), and positively correlated with serum albumin (r = 0.389, P < .001). In multivariate linear regression analysis, FT3 was independently associated with MIS (β, -0.14; 95% confidence interval, -0.175 to 0.063, P = .003), adjusted for CCI, C-reactive protein level, serum albumin level, and MIS.
Conclusions. The results of this study indicate that FT3 is negatively correlated with inflammatory markers, namely C-reactive protein, and it is independently related with MIS in hemodialysis patients. Therefore, we suggest that FT3 can be accepted as an inflammatory marker in hemodialysis patients.

IJKD 2014;8:212-7
www.ijkd.org

Original Paper

INTRODUCTION

End-stage renal disease (ESRD) may affect thyroid functions in various ways by the low blood hormone level, effecting the peripheral hormone metabolism, reducing the binding to transport proteins, decreasing the tissue hormone quantity, and inducing the uptake of iodine by the thyroid gland.[1,2] This condition is associated with alterations in the concentrations of circulating thyroid hormones, usually a decrease in serum total and free triiodothyronine (FT3) concentrations.[3] Impaired immune response and persistent immune stimulation could have a role in low-grade systemic inflammation in ESRD patients. Although extensive studies have been done, the association with nonthyroidal illness and alterations in thyroid hormone levels has remained unknown. In one study, serum FT3 levels correlated with interleukin (IL)-6 and IL-10, and also IL-6 and IL-10 correlated in nonthyroidal illness.[4]

Free triiodothyronine is used as a euthyroid syndrome marker in various diseases. A decrease in FT3 level is observed in cases such as acute-chronic infections, ketoacidosis, inadequately controlled diabetes mellitus, myocardial infarction, and

myocardial ischemia.[5] Most patients with ESRD have reduced plasma levels of FT3, reflecting diminished conversion of T4 to T3 in the peripheral tissue.[6] It is postulated that ESRD may be associated with the concentrations of the thyroid hormone even in the absence of an intrinsic thyroid disorder.[6] A decreased FT3 concentration in ESRD patients is associated with systemic acidosis, duration of kidney failure, and markers of endothelial damage and inflammation. This condition may represent a compensatory mechanism to neutralize the thyroid dysfunction and to maintain the euthyroid status.[3]

Protein-energy malnutrition and inflammation are disorders that accompany and overlap each other in hemodialysis patients and malnutrition can lead to inflammation. As the evidence is inconclusive, the term *malnutrition inflammation syndrome* (MIS) is appropriate at present. The MIS is a comprehensive scoring system associated with prospective hospitalization and mortality. [7] An inflammatory process in ESRD is associated with the uremic milieu, an increased incidence of infections, and elevated levels of pro-inflammatory cytokines.[8] Many patients with ESRD have additional comorbidities that influence the patients' outcome.

There is lack of data about the relationship between plasma FT3 levels, malnutrition, and inflammation in hemodialysis patients. In this study, our aim was to explore the link between plasma FT3 levels and malnutrition and inflammation in hemodialysis patients.

MATERIALS AND METHODS

The study protocol was approved by a local research ethics committee. Patients who had been on hemodialysis for at least 6 months were enrolled. All of the patients were receiving hemodialysis with bicarbonate for 4 hours, 3 days a week, using semisynthetic membranes (dialysis filters surface area, 1.1 m^2 to 1.7 m^2) and with an average blood flow rate of 300 mL/min to 350 mL/min. None of the patients had a history of acute or chronic infection, cardiocirculatory congestion, malignancy, chronic inflammatory illness, or a history of hospitalization within the past 6 months. None of the patients were on medications that might interfere with the thyroid function, ie, lithium, amiodarone, or β-blockers. Dry weight was targeted in each case to achieve a normotensive edema-free state.

The following demographic and clinical parameters were evaluated: age, sex, comorbidity, etiology and duration of ESRD, presence of diabetes mellitus, hyperlipidemia (total cholesterol > 200 mg/dL), systolic and diastolic blood pressure, and body mass index. Blood sampling was performed at the outset of the inflammatory-infectious process and plasma FT3, thyroid-stimulating hormone, calcium, phosphorus, C-reactive protein (CRP), albumin, hemoglobin, iron, iron-binding capacity were measured following at least 8 hours of fasting. All blood samples were obtained between 8:00 AM and 10:00 AM during the midweek hemodialysis sessions. After 20 to 30 minutes of quiet resting in the semirecumbent position, the samples were taken into chilled ethylenediaminetetraacetic acid vacutainers, placed immediately on ice and centrifuged for 30 minutes at -4°C, and the plasma was stored at -80°C before the assay. Serum albumin, calcium, phosphate, CRP, hemoglobin, iron, and iron-binding capacity measurements were made by standard methods in the routine clinical laboratory. Free triiodothyronine was measured by a commercially available radioimmunoassay kit (Byk-Sangtek Diagnostica, Dietzenbach, Germany) and thyroid-stimulating hormone by a sensitive immunoradiometric assay (Byk-Sangtek Diagnostica, Dietzenbach, Germany).

Comorbidity was assessed by the modified version of Charlson Comorbidity Index (CCI; without the age and kidney disease components). The CCI, a composite score of multiple comorbid conditions, was developed and validated in the general population, which is a popular tool of assessing comorbidity and a strong predictor of outcome in ESRD patients.[9] Malnutrition and inflammation status was assessed by the Malnutrition Inflammation Score (MIS).

Statistical analysis was performed using the SPSS software (Statistical Package for the Social Sciences, version 19.0, SPSS Inc, Chicago, Ill, USA). Results were considered significant if the 2-tailed *P* value was less than .05. The normality of the distribution of data was evaluated by the Kolmogorov-Smirnov test with the Lilliefors correction. Data are expressed as mean ± standard deviation. Comparisons of the groups were assessed by means of the Student *t* test. For examination of correlations, the Pearson r coefficient was used. Multiple linear regression analysis was performed to detect the potential predictors of FT3 level in hemodialysis patients, and the included independent variables were age, CRP, serum albumin, CCI score, and MIS.

RESULTS

Overall, 84 hemodialysis patients with a mean age of 56.2 ± 14.8 years (range, 24 to 87 years), of whom 46 (54.8%) were males. The mean urea KT/V was 1.20 ± 0.26. None of the patients were smokers. A total of 45 patients were on treatment with erythropoietin. Forty patients were on antihypertensive treatment; 25 patients were on monotherapy with angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, or calcium channel blockers; and 15 patients were on double or triple therapy with various combinations of these drugs. The demographic and laboratory characteristics of the patients are shown in Table 1.

There was no significant difference between the men and the women in terms of age, ESRD duration, systolic and diastolic blood pressure, and body mass index. The prevalence of diabetes mellitus, hyperlipidemia and hypertension did not differ between the men and the women, either. The causes of ESRD were as follows: diabetic nephropathy (21 patients), hypertension (15 patients), chronic glomerulonephritis (13 patients), pyelonephritis (4 patients), amyloidosis (3 patient), solitary kidney (2 patients), and unknown (26 patients). There are no association between FT3 and cause of ESRD.

Table 1. Demographic and Laboratory Characteristics of the Hemodialysis Patients

Characteristic	Value*
Age, y	56.2 ± 14.76
Male sex	46 (54.8)
End-stage renal disease duration,, mo	97.72 ± 10.35
Systolic blood pressure, mm Hg	132.1 ± 22.0
Diastolic blood pressure, mm Hg	75.8 ± 9.5
Body mass index , kg/m^2	24.7 ± 3.0
Blood urea nitrogen, mmol/L	25.64 ± 6.66
Serum creatinine, µmol/L	923.78 ± 686.86
Serum sodium, mmol/L	136.88 ± 3.59
Serum potassium, mmol/L	6.80 ± 0.85
Serum albumin, g/L	39.95 ± 5.57
Serum ferritin, pmol/mL	1094.17 ± 760.90
Free triiodothyronine, pmol/L	0.033 ± 0.007
Thyroid-stimulating hormone, mIU/L	1.68 ± 1.15
Hemoglobin, g/L	10.51 ± 1.74
Malnutrition inflammation score	6.1 ± 1.6
Charlson Comorbidity Index score	4.3 ± 1.2

*Values are mean standard deviation, except for male sex variable, which is frequency (percentage).

None of the patients had clinical symptoms of thyroid dysfunction. Free triiodothyronine level was low (0.033 ± 0.007 pmol/mL). Thyroid-stimulating hormone (1.68 ± 1.15 µIU/mL) and FT4 levels were in normal range. In the women, FT3 was higher than that in the men (P = .03) and correlated with age (r = -0.425, P = .003), CCI score (r = -0.577, P < .001), MIS score (r = -0.673, P < .001), and serum albumin (r = 0.509, P < .001). In the men, FT3 correlated with serum CRP (r = -0.348, P = .04), MIS score (r = -0.653, P < .001), CCI score (r = -0.575, P < .001), hemoglobin level (r = 0.505, P = .01), and serum iron level (r = 0.411, P = .02; Table 2). Overall, FT3 significantly correlated with age (r = -0.328, P = .002; Figure 1), CCI score (r = -0.591, P < .001; Figure 2), CRP (r = -0.299; P = .01; Figure 3), MIS (r = -0.671, P < .001; Figure 4), and serum albumin (r = 0.389, P < .001; Figure 5). No correlation was observed between serum thyroid-stimulating hormone or FT4 and MIS scores.

All of the patients had FT3 results in the reference range (1.8 pg/mL to 4.2 pg/mL). Therefore, we divided patients into 3 groups according to their percentiles of FT3 (< 25th percentile, < 1.93 pg/

Table 2. Correlation of Plasma Free Triiodothyronine with Demographic and Laboratory Parameters and Malnutrition Inflammation Score in Female and Male Hemodialysis Patients

	Free Triiodothyronine			
	Women		Men	
Parameter	Correlation Coefficient	*P*	Correlation Coefficient	*P*
Age	-0.425	.003	-0.221	.18
Calcium	0.167	.27	0.005	.98
Phosphorus	-0.047	.76	0.001	> .99
C-reactive protein	-0.257	.1	-0.348	.004
Serum albumin	0.509	< .001	0.192	.26
Hemoglobin	-0.068	.66	0.505	.001
Iron	-0.011	.95	0.411	.02
Ferritin	-0.002	.99	-0.113	.53
Thyroid-stimulating hormone	0.125	.41	0.079	.64
Malnutrition Inflammation Score	-0.673	< .001	-0.653	< .001

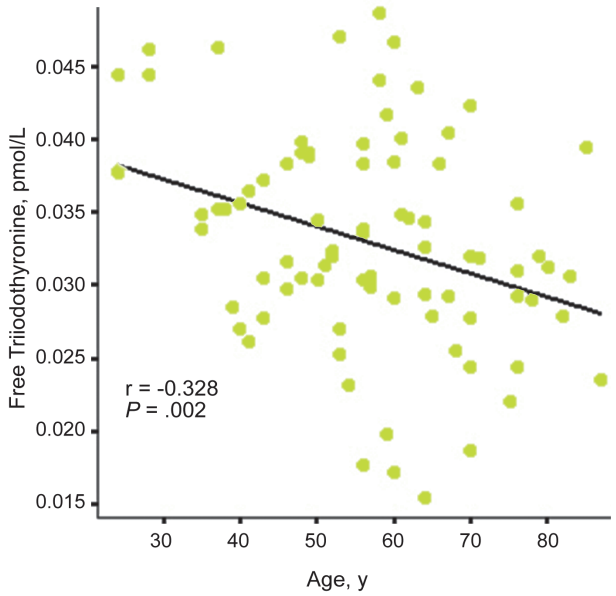

Figure 1. Correlation between plasma free triiodothyronine and age.

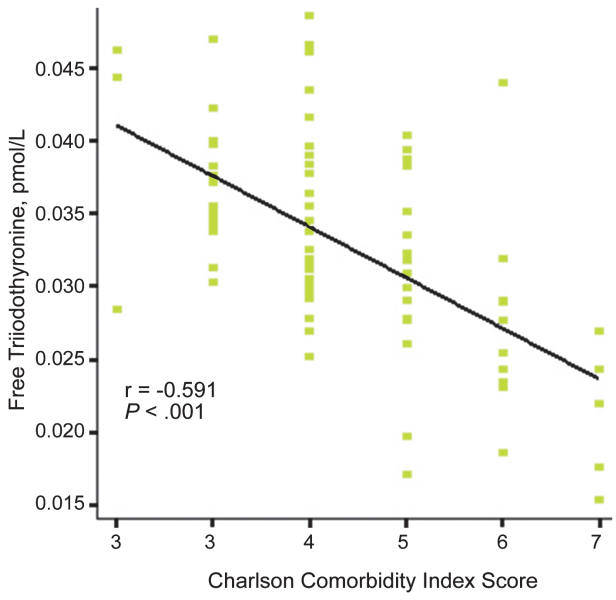

Figure 2. Correlation between plasma free triiodothyronine and Charlson Comorbidity Index score.

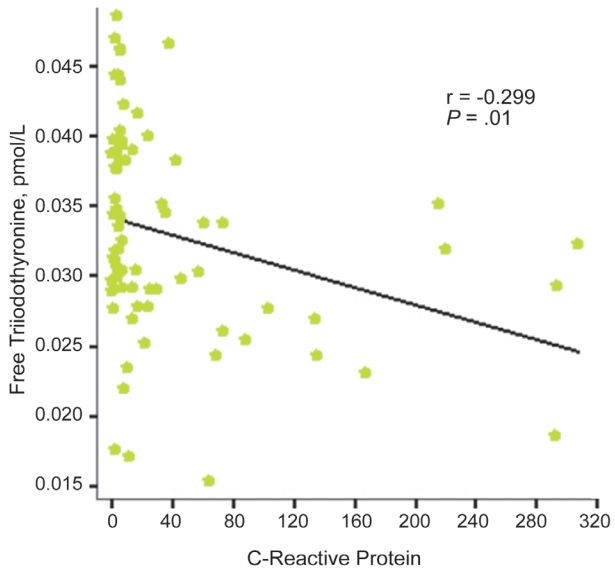

Figure 3. Correlation between plasma free triiodothyronine and C-reactive protein.

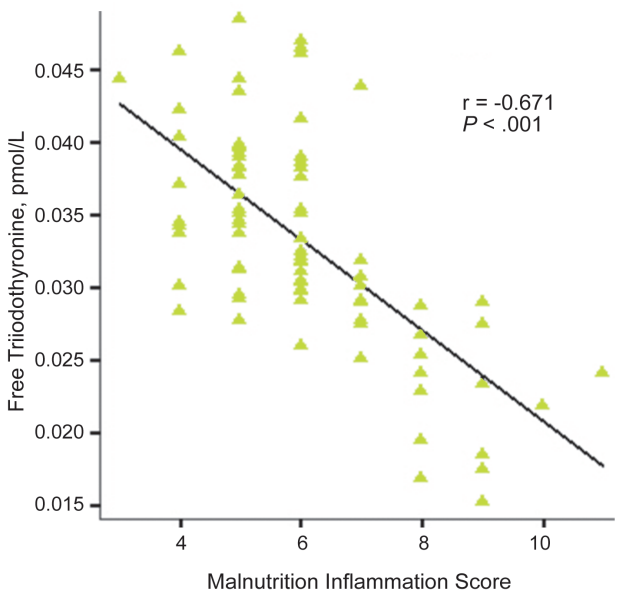

Figure 4. Correlation between plasma free triiodothyronine and Malnutrition Inflammation Score.

mL; 25 to 50th percentile, 1.93 pg/mL to 2.56 pg/mL; and > 75th percentile, > 2.56 pg/mL). From 75th to 25th percentile of FT3, the MIS significantly increased (*P* for trend = .001; data not shown).

In the multivariate linear regression analysis, FT3 was independently associated with MIS (β coefficient: -0.14, 95% confidence interval, -0.175 to 0.063; *P* = .003; Table 3), adjusted for age, CCI score, CRP, serum albumin, and MIS score.

DISCUSSION

This study demonstrated that thyroid function, as determined by plasma concentration of the FT3, was associated with MIS scores in stable hemodialysis patients. To our knowledge, this is the first study in the literature disclosing the link between FT3 and MIS score, which is a sensitive tool for assessment of MIS in ESRD patients.

End-stage renal disease patients frequently

Table 3. Multiple Linear Regression Model of Factors Affecting Plasma Free Triiodothyronine in Hemodialysis Patients

Variable	β	95% Confidence Interval	*P*
Constant	3.18	2.266 to 4.097	< .001
Age	-3.26	-0.009 to 0.003	.28
C-reactive protein	-8.10	-0.002 to 0.000	.21
Serum albumin	8.08	-0.085 to 0.247	.34
Charlson Comorbidity Index	-5.6	-0.237 to -0.051	.35
Malnutrition Inflammation Score	-0.14	-0.175 to 0.063	.003

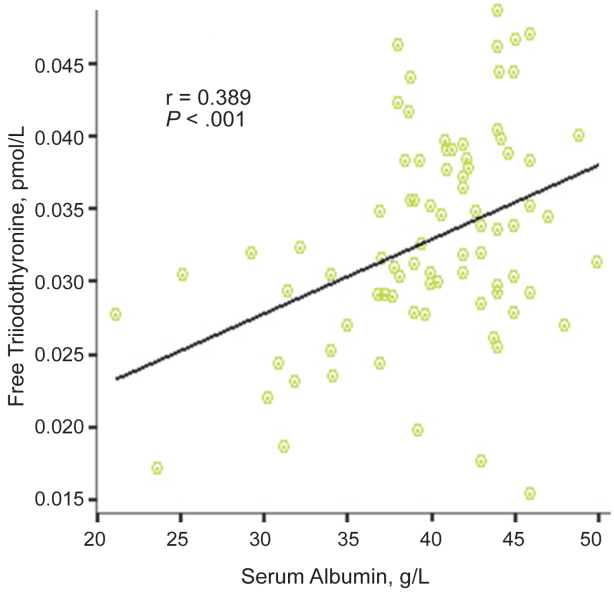

Figure 5. Correlation between plasma free triiodothyronine and serum albumin.

display alterations in thyroid function of various severities, ranging from the low-T3 syndrome to subclinical hypothyroidism. Furthermore, uremic patients have a variety of nonrenal, nonthyroidal disorders that affect thyroid hormone metabolism, such as diabetes mellitus, infections, and malnutrition, and they are often treated by drugs that interfere with thyroid function.[3] In our study, FT3 levels were lower in the women than the men on hemodialysis. We do not know the exact explanation for this finding. However, we speculate that a relatively increased ratio of adipose tissue to muscle mass may be affecting the peripheral thyroid hormone metabolism.

Recent studies have focused on alterations of serum FT3 concentrations in patients with ESRD. Inflammation is now emerging as one of the most important causes of deranged thyroid function associated with chronic or acute nonthyroidal illness. Free triiodothyronine has shown to be significantly associated with serum markers of inflammation and endothelial activation in patients with ESRD. Additionally, experimental as well as clinical studies indicate that the inflammatory cytokine network plays a central role in the genesis of the low T3 syndrome.[10] Thyroid function disturbances are associated with increased morbidity and mortality due to cardiovascular disease and related to endothelial dysfunction.[11] In view of the fact that cardiovascular disease is among the most common causes of mortality, alternative measures are needed to guide effective therapeutic approaches. In this respect, our results generate a new approach, in which MIS and thyroid dysfunction may be linked and this link may be readily assessed by MIS scale.

Nonthyroidal illness is a clinical syndrome characterized by a disturbance in thyroid function of increasing severity that may occur in various stressful conditions such as malnutrition, sepsis, surgery, myocardial infarction, and in fact in any severe illness.[12] Many patients with ESRD have additional comorbidities and malnutrition. A reduction in plasma FT3 level is the one of the earliest surrogate markers of thyroid dysfunction, and this reduction negatively correlates with the severity of illness and associated malnutrition. The association between inflammation markers and thyroid dysfunction in nonthyroidal illness has been investigated intensively. Furthermore, malnutrition and inflammation is a serious clinical problem in ESRD. These two are not just the markers of negative protein-energy balance, but are also risk factors for cardiovascular complications and high mortality in dialysis patients.[13]

High plasma IL-6 is an important feature of nonthyroidal illness and it is well established that in this syndrome, circulating IL-6 mirrors T3 levels. A causal involvement of IL-6 in nonthyroidal illness is suggested by the observation that chronic administration of this cytokine produces clear-cut suppression of plasma T3.[14] In our study, as

in the literature, FT3 negatively correlated with CCI and MIS scores, both in women and men. However, in the linear regression analysis, FT3 was independently associated with MIS score. We speculate that MIS may be more influential on thyroid dysfunction than associated comorbidity in hemodialysis patients.

In a study on the nonuremic population, serum CRP levels were established to be high in patients with clinical or subclinical hypothyroidism,[15] and in ESRD patients, FT3 index was lower than the controls.[16] In another study, FT4 was found to be negatively correlated with serum fibrinogen level and the authors suggested that the inflammatory events inducing the cardiovascular damage may be linked with downregulation in thyroid hormones.[17] In our study, supporting the previous data in the literature, FT3 level also negatively correlated with serum CRP level, which is a valuable parameter inflammation in hemodialysis patients.

The small number of patients was the first limitation in our study. The other limitation of our study was that thyroxine-binding globulin was not included in this study and FT3 measurement was checked one time.

CONCLUSIONS

Our study disclosed that plasma FT3 level was closely related with inflammatory response and MIS in hemodialysis patients. Therefore, we suggest that FT3 may be regarded as an inflammatory parameter in hemodialysis patients. Further studies are needed to reinforce our results.

CONFLICT OF INTEREST

None declared.

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Received June 2013
Revised August 2013
Accepted September 2013