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Prevalence and Clinical Significance of Low T3 Syndrome in Non-Dialysis Patients with Chronic Kidney Disease

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Background: There are few data on the prevalence of low T3 (triiodothyronine) syndrome in patients with non-dialysis chronic kidney disease (CKD) and it is unclear whether low T3 can be used to predict the progression of CKD.

Material/Methods: We retrospectively studied 279 patients who had been definitively diagnosed with CKD, without needing maintenance dialysis. Thyroid function was analyzed in all enrolled subjects and the incidence of thyroid dysfunction (low T3 syndrome, low T4 syndrome, and subclinical hypothyroidism) in patients at different stages of CKD was determined.

Results: Glomerular filtration rate (GFR) of CKD patients was estimated as follows: 145 subjects (52%) had GFR <60 ml/min per 1.73 m²; 47 subjects (16.8%) had GFR between 30 and 59 ml/min per 1.73 m², and 98 subjects (35.1%) had GFR <30 ml/min per 1.73 m². Among all enrolled subjects, 4.7% (n=13) had subclinical hypothyroidism, 5.4% (n=15) had low T4 syndrome, and 47% (n=131) had low T3 syndrome. In 114 CKD patients in stages 3–5, serum T3 was positively related to protein metabolism (STP, PA, and ALB) and anemia indicators (Hb and RBC), and negatively related to inflammatory status (CRP and IL-6).

Conclusions: A high prevalence of low T3 syndrome was observed in CKD patients without dialysis, even in early stages (1 and 2). The increasing prevalence of low T3 as CKD progresses indicates its value as a predictor of worsening CKD. Furthermore, low T3 syndrome is closely associated with both malnutrition-inflammation complex syndrome (MICS) and anemia.

MeSH Keywords: **Anemia, Neonatal • Kidney Failure, Chronic • Renal Insufficiency, Chronic**

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Background

The 2002 guidelines for chronic kidney disease (CKD) represented an important shift towards its recognition as a worldwide public health problem [1,2]. The increased number of patients with early stage disease, the low quality of patients' lives and the poor outcomes of treatment emphasize the need for detection and reduction of risk factors for CKD. Recently, attention has been particularly focused on the thyroid dysfunction.

As a primary endocrine organ, thyroid plays an important role in kidney growth and function [3]. A variety of alterations in thyroid hormone levels and metabolism such as hypothyroidism and subclinical hypothyroidism have been reported in CKD patients [4–6]. Recently, much interest has been focused on euthyroid sick syndrome (ESS), which is characterized by decreased serum T3 and/or thyroxin (T4) levels, accompanied by increased reverse T3 (rT3) and no significant increase in thyroid-stimulating hormone (TSH) [7]. Low triiodothyronine (low T3 syndrome), the most common abnormality of ESS, occurs frequently in CKD patients [8] and has been reported to be a strong marker of adverse clinical outcomes in ESRD [9]. As early as 1977, Lim et al. [10] reported the prevalence of low triiodothyronine in ESRD was 80% in non-hemodialysis and 43% in hemodialysis patients, respectively. Notwithstanding intensive research on ESRD patients with or without dialysis, there are scarce data about the prevalence of low T3 in patients with early-stage CKD who are not on dialysis. In addition, it is unclear whether low T3 can be used to predict the progression of CKD.

We performed a cross-sectional study to investigate the prevalence of low T3 syndrome in CKD patients who were not undergoing dialysis, including a comprehensive analysis of the clinical significance of low T3 syndrome in CKD patients in all stages of disease, including stages 1 and 2.

Material and Methods

Ethics statement

This protocol conformed to the ethical guidelines of the Ethical Committee of Shanghai ninth people's hospital, and informed consent was obtained from each subject.

Study subjects

This study was performed retrospectively from June 2012 to May 2013. The diagnostic criteria for CKD were based on the Kidney Disease Outcome Initiative (K/DOQI) [11]. Glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation [eGFR

(ml/min/1.73 m²) = 1.86 × (Scr)^{-1.154} × (Age)^{-0.203} (×0.742 if female), where Scr indicate serum creatinine in mg/dl] [12]. A total of 279 CKD patients were enrolled after exclusion of subjects with primary thyroid diseases such as hypothyroidism, hyperthyroidism or thyroiditis, or who had taken drugs which might influence their thyroid function. Patients with hemodialysis, peritoneal dialysis, thrombotic diseases, septicemia, or myocardial infarction, and post-surgical patients, also were excluded.

Data collection

Initially, we recorded demographic information (name, sex, age, birthday, etc.), the presence of primary kidney disease and its complications, past history (such as acute and chronic infections or chronic diseases) of all enrolled subjects. Fasting blood samples were collected from the peripheral vein in the morning, and analyzed for indicators of renal function (creatinine, Cr; blood urea nitrogen, BUN; uric acid, UA), and for thyroid function (serum total T3 (TT3), free T3 (FT3), total T4 (TT4), free T4 (FT4), and thyroid stimulating hormone (TSH)). Routine urine samples were taken, and urinary protein assayed at 24 hours; kidney ultrasound was also performed to assist in evaluating the severity of illness. Thyroid function tests were performed using an electrochemiluminescence assay. The normal reference ranges for FT3, TT3, FT4, TT4 and TSH in our hospital's clinical laboratory were 2.5–3.9 pg/ml, 0.87–1.78 ng/ml, 0.58–1.64 ng/dl, 6.09–12.23 μg/dl, and 0.34–5.6 U/ml, respectively.

In the second phase of our research, we enrolled 114 patients in stages 3–5 of CKD using the definitions published by the National Kidney Foundation (stage 1, eGFR ≥90; stage 2, eGFR 60–89; stage 3, eGFR 30–59; stage 4, eGFR 15–29; stage 5, eGFR < 15 ml/min/1.73 m²). Subjects were classified into two groups according to their thyroid function, 76 with low T3 syndrome and 38 with normal thyroid function. Blood samples were collected from each group and analyzed for serum total protein (STP), albumin (Alb), pre-albumin (PAB), hemoglobin (Hb), hematocrit (HCT), red blood cell count (RBC), ferritin, serum iron, fasting blood glucose (FBG), glycosylated hemoglobin (HbA1C), total cholesterol (TC), triglyceride (TG), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), parathyroid hormone (PTH), serum calcium, serum phosphorus, serum magnesium, C-reactive protein (CRP), interleukin-6 (IL-6), and fibrinogen (Fg). Low T3 syndrome was characterized by a normal serum TSH level and low serum T3 level, excluding subjects who had been diagnosed with hypothyroidism, hyperthyroidism or thyroiditis.

Statistical analysis

Data analysis was performed using SPSS for Windows, version 17.0 (SPSS Inc., Chicago, IL, United States). The continuous variables were determined as to whether they were normally

Table 1. General characteristics of 279 enrolled subjects.

Parameter	Total
n	279
Age (years)	67.8±14.1
Male/female	149/130
Diabetes (+)/(-)	95/184
HBP (+)/(-)	199/80
History of CHD (+)/(-)	117/162
Chronic glomerulonephritis	134
Tubulopathy	56
Acute nephropylitis	18
Chronic interstitial nephritis	13
Arteriosclerosis	12
IgA nephropathy	11
Bilateral renal artery stenosis	6
CKD1 n (%)	63 (22.6)
CKD2 n (%)	71 (25.4)
CKD3 n (%)	47 (16.8)
CKD4 n (%)	31 (11.1)
ESRD n (%)	67 (24.0)

distributed using the Kolmogorov-Smirnov test. For data following non-normal distribution, results were expressed as median and range and were compared by Mann-Whitney U test. For data following normal distribution, results were expressed as mean ±SD and were compared by Student's t-test. Categorical data were analyzed using Pearson's Chi-square test or Fisher's exact test, where applicable. Degrees of association between continuous variables were evaluated with Pearson's

Table 2. Thyroid function in 279 enrolled subjects.

Variables	n	Reference range	±s	R	Range
FT3 (pg/mL)	279	2.5–3.9	2.82±1.42	1.38–16.93	15.55
TT3 (ng/mL)	279	0.87–1.78	0.95±0.49	0.30–4.90	4.60
FT4 (ng/dL)	279	0.58–1.64	10.5±5.2	6.0–55.0	49.0
TT4 (µg/dL)	279	6.09–12.23	91.0±25.9	45.9–268.3	222.4
TSH (µU/mL)	279	0.34–5.6	2.24±1.86	0.00–12.65	12.65

FT3 – free triiodothyronine; TT3 – total triiodothyronine; FT4 – free thyroxine I; TT4 – total thyroxine; TSH – thyroid stimulating hormone.

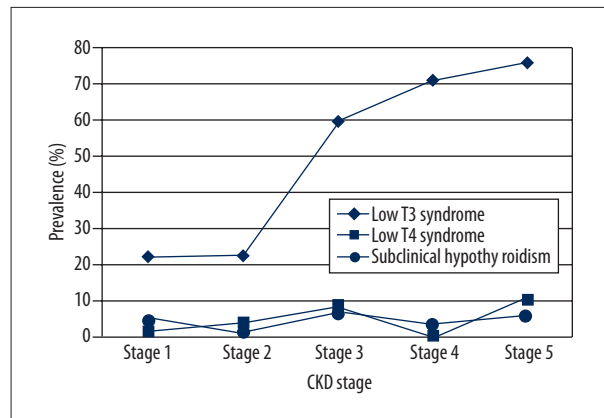


Figure 1. The prevalence of thyroid dysfunction in each CKD stage.

product-moment correlation test. A p value less than 0.05 was considered statistically significant.

Results

The prevalence of thyroid dysfunction in CKD

General characteristics of the subjects are summarized in Table 1. There were a total of 279 CKD subjects, 149 (53.4%) men and 130 (46.6%) women, with a mean age of 67.8±14.1 years, with 50.5 percent over 70 years of age. The most common etiology of CKD in our research was chronic glomerulonephritis, in 134 patients. Overall, GFR was estimated as <60 ml/min per 1.73 m² in 145 subjects (52%), between 30 and 59ml/min per 1.73 m² in 47 subjects (16.8%), and <30 ml/min per 1.73 m² in 98 subjects (35.1%); none of them required chronic dialysis therapy.

As shown in Table 2, the average serum thyroid function test results (TT3, FT3, TT4, FT4, and TSH) of all subjects were within their respective reference ranges although the ranges were broad. Among all patients, 4.7% (n=13) had subclinical

Table 3. Abnormal rate of thyroid function [n (%)] in each stage of CKD.

Variables		Stage 1	Stage 2	Stage 3	Stage 4	ESRD	P-value
FT3	Low	6 (9.5)	7 (9.8)	16 (34.0)	14 (45.2)	43 (64.2)	0.000*
	Normal	52 (82.5)	64 (90.2)	30 (63.8)	17 (54.8)	22 (32.8)	
	High	5 (7.9)	0	1 (2.3)	0	2 (3.0)	
TT3	Low	14 (22.2)	16 (22.5)	28 (59.6)	22 (71.0)	51 (76.1)	0.000*
	Normal	44 (68.9)	54 (76.1)	17 (36.2)	9 (29.0)	15 (23.9)	
	High	5 (7.9)	1 (1.4)	2 (4.3)	0	1 (1.5)	
FT4	Low	0	0	0	0	0	0.317*
	Normal	57 (90.5)	69 (97.2)	46 (97.9)	30 (96.8)	64 (95.5)	
	High	6 (9.5)	2 (2.8)	1 (2.1)	1 (3.2)	3 (4.5)	
TT4	Low	1 (1.6)	3 (4.2)	4 (8.5)	0	7 (10.4)	0.236*
	Normal	57 (90.5)	62 (87.3)	41 (87.2)	28 (90.3)	58 (86.6)	
	High	5 (7.9)	6 (8.5)	2 (4.3)	3 (9.7)	2 (3.0)	
TSH	Low	4 (6.3)	2 (2.8)	2 (4.5)	2 (6.7)	5 (7.5)	0.807*
	Normal	56 (88.9)	68 (95.8)	39 (88.6)	26 (86.7)	58 (86.6)	
	High	3 (4.8)	1 (1.4)	3 (6.8)	2 (3.7)	4 (6.0)	

The statistical method used for analysis was an exact probability test. According to the reference range of thyroid function, the value of each indicator (FT3, TT3, FT4, TT4, TSH) was classified as low, normal, or high.

hypothyroidism, 5.4% (n=15) had low T4 syndrome and 47% (n=131) had low T3 syndrome. Notably, the prevalence of low T3 syndrome increased as kidney function decreased, ranging from 22.2% for persons with CKD1 to 76.1% in persons with ESRD (Figure 1). By contrast, there was no significant change in serum TSH, TT4, or FT4 across the estimated GFR deciles (P=0.807, 0.236, and 0.317 respectively; Table 3).

The clinical significance of low T3 syndrome in patients with CKD

Given the high incidence of low T3 syndrome in patients with CKD stages 3–5, we collected 114 such patients from all enrolled subjects for detailed analysis. Subjects with low T3 or euthyroidism in each stage were randomly assigned in a 2: 1 ratio to study or control groups, respectively, to eliminate the impact of CKD stage. The baseline demographic and biochemical data of the two groups are shown in Table 4. Subjects with low T3 syndrome had significantly lower values of Alb, PA, Hb, RBC, Hct, CRP and IL-6 (P<0.05), while they did not differ from euthyroid subjects with regard to age, sex, renal function, FBG, HbA1C, TG, TC, or HLC-C (P>0.05). Notably, calcium-phosphorus product tended to be higher among subjects with low T3 syndrome, reaching statistical significance (P=0.01), while PTH, serum calcium, and serum phosphorus did not reach it (P>0.05).

Accordingly, we conducted correlation analysis to further explore the relationship between calcium-phosphorus metabolism and low T3 syndrome and found that there was no significant correlation.

We explored the relationship between serum T3 and energy metabolism, anemia, and inflammatory state using Pearson’s product-moment correlation. Within energy metabolism, there was a positive relationship between serum T3 and protein metabolism (TP=17.075×TT3+50.017, R²=0.2379; PA=0.0926×TT3+0.1483, R²=0.1318; Alb=13.787×TT3+23.166, R²=0.2839; Figure 2), while there was no correlation with glucose metabolism or lipid metabolism. With respect to anemia, there was a positive relationship between serum T3 and Hb, HCT, and RBC (Hb=38.979×TT3+67.815, R²=0.1735; RBC=1.4329×TT3+2.2281, R²=0.2475; HCT=0.1058×TT3+0.2197, R²=0.1564; Figure 3). Within the inflammatory state, there was a negative relationship between serum T3 and CRP (CRP=-26.042×TT3+37.468, R²=0.0856; Figure 4).

Discussion

In the present study, we found that CKD patients have a high incidence of thyroid dysfunction, within which low T3 syndrome

Table 4. Baseline demographic and biochemical characteristics of 114 subjects with stage 3–5 CKD.

Characteristics	Control group	Low T3 group	Test value	P-value
N	38	76		
Age (yr)	66.5±13.8	78.9±15.3	-1.168	0.250
Male, n (%)	25 (65.83)	44 (57.9)	0.661	0.416
FT3 (pg/ml)	2.76±0.24	2.25±0.28	9.617	0.000
TT3 (ng/ml)	1.05±0.18	0.63±0.15	13.060	0.000
FT4 (ng/dl)	0.92±0.18	1.04±0.25	-2.490	0.014
TT4 (µg/dl)	9.43±1.97	8.63±1.90	2.084	0.039
TSH (µU/ml)	2.11±1.34	2.56±0.26	-1.162	0.248
Scr (mmol/l)	391.47±150.55	405.26±167.28	-0.203	0.839
Alb (g/l)	37.34±4.95	32.07±6.75	4.680	0.000
PAB (g/l)	0.250±0.048	0.204±0.070	4.004	0.000
Hb(g/l)	109.94±18.66	91.58±22.81	4.128	0.000
TP (g/l)	67.26±8.42	61.21±8.66	3.529	0.001
Hct	0.34±0.05	0.28±0.06	4.095	0.000
RBC (×10 ¹² /L)	3.81±0.60	3.09±0.69	5.282	0.000
Ferroprotein (g/L)	146.75±15.65	189.41±17.81	-0.972	0.338
Serum iron (mol/L)	11.93±3.85	9.42±5.43	1.693	0.098
FBG (mmol/L)	5.85±2.17	5.82±1.93	0.076	0.939
HAb1c (%)	4.97±1.60	3.54±1.86	1.143	0.261
TG (mmol/L)	1.86±1.04	1.78±0.88	2.207	0.068
TC (mmol/L)	3.53±0.97	4.64±1.61	-2.530	0.043
HDL-C (mmol/L)	0.928±0.223	0.935±0.429	-0.130	0.897
CRP (M, mg/L)	4.1 (3.10~78.6)	18.85 (3.10~120.0)	Z=7.597	0.007
IL-6 (±s, ng/L)	8.7±4.3	17.7±6.4	t=4.552	0.000
Fg (±s, g/L)	3.59±1.17	4.01±1.50	t=-1.152	0.254

FT3 – free triiodothyronine; TT3 – total triiodothyronine; FT4 – free thyroxine I; TT4 – total thyroxine; TSH – thyroid stimulating hormone; Alb – albumin; PAB – pre-albumin; Hb – hemoglobin; TP – total protein; HCT – hematocrit; RBC – red blood cell; FBG – fasting blood glucose; HbA1c – glycosylated hemoglobin; TG – triglyceride; TC – total cholesterol; HDL-C – high density lipoprotein-cholesterol; CRP – C-reactive protein; IL-6 – interleukin-6; Fg – fibrinogen.

occurs most frequently. The prevalence of low T3 increases with increasing CKD stage, and serum T3 level is associated with severity of CKD. Moreover, we assembled a comprehensive panel of clinical data to explore the significance of low T3 syndrome with respect to energy metabolism, calcium-phosphorus metabolism, anemia, and inflammatory state. The results show that low T3 syndrome is positively related to protein-energy nutrition and anemia, and negatively related to

inflammation, but has no relationship with glucose metabolism, lipid metabolism, or calcium-phosphorus metabolism.

The incidence of thyroid dysfunction in patients with CKD

The interactions between kidney and thyroid functions have been known for many years. Thyroid hormones play an important role not only in the renal development but also the

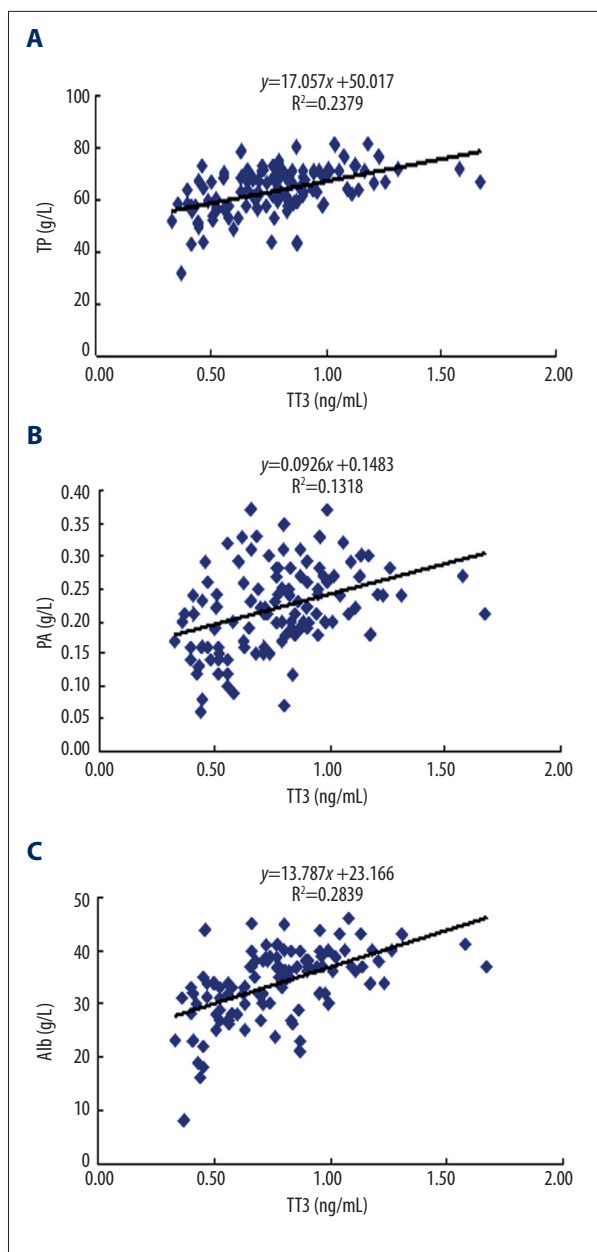


Figure 2. The correlation between TT3 and protein metabolism. TP – total protein (A); PA – pre-albumin (B); Alb – albumin (C); TT3 – total triiodothyronine. The statistical method used for analysis was Pearson's product-moment correlation.

renal physiology. Thyroid hormones influence protein synthesis and cell growth, which can accelerate the renal development and increase renal mass [13,14]. The effects on renal physiology include pre-renal and direct renal effects. Pre-renal effects are mediated by the influence of thyroid hormones on the cardiovascular system and the renal blood flow RBF. The direct renal effects are mediated by the effect of thyroid hormones on GFR, tubular secretory and re-absorptive processes,

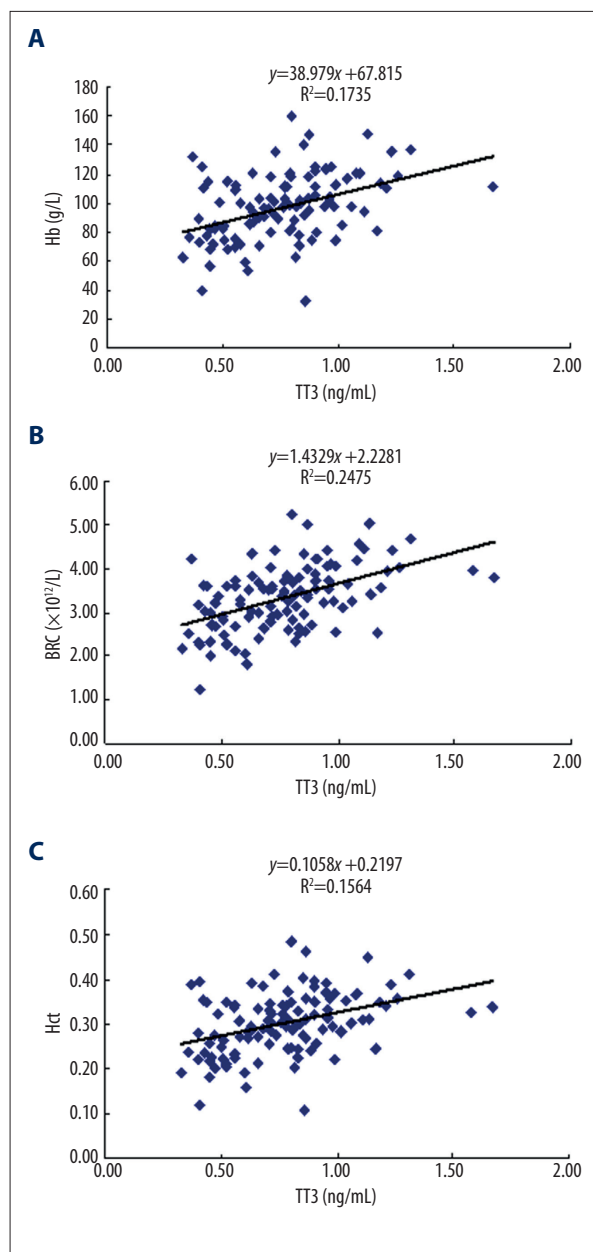


Figure 3. The correlation between TT3 and anemia related indicators. Hct – hematocrit (A); RBC – red blood cell count (B); Hb – hemoglobin (C); TT3 – total triiodothyronine. The statistical method used for analysis was Pearson's product-moment correlation.

and renal tubular physiology [15]. Thyroid dysfunction such as hypothyroidism and hyperthyroidism affects RBF, GFR, tubular function, electrolyte homeostasis, and kidney structure. Studies have observed the high incidence of thyroid dysfunction in patients with kidney disease such as acute kidney injury AKI, CKD with or without dialysis, kidney transplantation, several glomerulonephritis and so on.

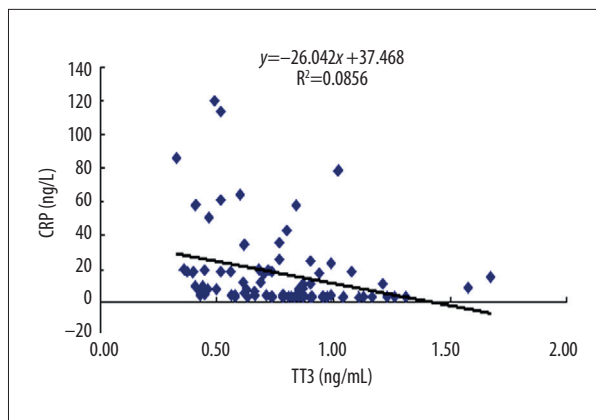


Figure 4. The correlation between TT3 and CRP. CRP C – reactive protein; TT3 – total triiodothyronine. The statistical method used for analysis was Pearson's product-moment correlation.

In CKD patients, dialytic or non-dialytic, previous literature shows [3–9] that common manifestations of thyroid dysfunction include hypothyroidism, subclinical hypothyroidism, and ESS. Hyperthyroidism is not usually associated with CKD but is known to accelerate it. However, a comparison of the prevalence in CKD patients of the above three kinds of thyroid dysfunctions has not been made. Some researchers [16] point out that low T3 level is the most common laboratory finding, followed by subclinical hypothyroidism. In the present study, we found that low T3 was more prevalent than either subclinical hypothyroidism or low T4 syndrome (47%, 4.7%, and 5.4%, respectively). Only the incidence of low T3 rose with CKD stage (Figure 1), which contrasts with another report based on cross-sectional data [6] from 3089 adult outpatients. This difference might be due to the lower sample number and higher age of subjects (50.5% >70 years of age) in our study, possibly producing selection bias.

The mechanism of thyroid dysfunction in relation to CKD has been studied extensively. In uremia, an ineffective clearance of abnormal serum constituents, inflammatory cytokines, iodide excretion, and an increase in nitrogen conservation have been clinically proven to affect the normal physiology and metabolism of thyroid hormones [15]. Some dialytic factors such as systemic acidosis, time on dialysis, markers of endothelial damage, and inflammation are also associated with low T3 levels [17]. Inflammatory cytokines such as tumor necrosis factor (TNF)- α and interleukin (IL)-1 inhibit the expression of type 1 5'-deiodinase, which is responsible for peripheral conversion of T4 to T3 [18]. In addition, impaired renal handling of iodine increases serum iodine levels, causing a prolonged Wolff-Chaikoff effect [19].

However, little is known regarding the etiology and specific mechanism of low T3 in patients with less severe CKD not

undergoing dialysis. In our study, while the prevalence of low T3 in CKD3 was lower than in CKD4 and 5, a total of 28 subjects (59.6%) had low T3 levels at an early stage (stage 3), suggesting that a significant decrease of T3 could be a remarkable finding when it occurs early in CKD. This is consistent with the report of Sang et al. [20], which presents the first evidence for the existence of a low T3 population among early stage CKD subjects in a euthyroid state. Despite any unresolved questions, our results, along with previously published data, will help increase awareness among clinicians in this field of the importance of thyroid dysfunction in their patients with CKD.

The clinical value of low T3 syndrome in CKD

Low T3 syndrome with malnutrition-inflammation complex syndrome (MICS)

MICS describes the combination of protein-energy malnutrition (PEM) and inflammation, both of which are common and occur concurrently in CKD patients, especially in ESRD. MICS is believed to be the main cause of erythropoietin hyporesponsiveness, and of a high rate of cardiovascular atherosclerotic disease, decreased quality of life, and increased mortality and hospitalization in dialysis patients [21]. Some researchers [22–24] have found that the origin of PEM appears to precede dialysis treatment, and it is engendered progressively as glomerular filtration rate (GFR) decreases to less than 55 mg/min. However, there is no consensus on its physiopathologic mechanism or on the right way to manage it. Knowledge of its possible causes and consequences is urgently required to improve clinical outcomes in CKD patients.

In a previous study, Yavuz et al. [25] found that MICS score, a sensitive tool for assessment of MICS in hemodialysis patients, was independently associated with FT3. Moreover, recent studies have shown that MICS is a strong risk factor for a poor prognosis in ESRD with low T3 levels [26]. In the present study, we found that T3 level was positively correlated to PEM indicators (low levels of serum albumin, pre-albumin, transferrin), and negatively correlated with inflammation-related indicators (CRP, IL-6, Fg). In practice, PEM and inflammation in CKD share diagnostic criteria such as assessment tools and measurements used to detect them as hypoalbuminemia [21]. With respect to thyroid dysfunction, experimental as well as clinical studies indicate that both PEM [27,28] and pro-inflammatory stimuli, in particular interleukin (IL) signaling [29,30], can reduce extrathyroidal conversion of T4 to T3. Both can interfere with the activity of the 5'-deiodinase system in different ways, resulting in decreased T3 production [31,32]. Consequently, we postulate that low T3 syndrome can be closely associated with MICS and might be a pathological condition and / or maladaptation in CKD patients with MICS.

Low T3 syndrome with anemia

Over 40% of patients with CKD are anemic. Despite the availability of erythropoiesis-stimulating proteins (ESPs) to stimulate RBC production, approximately 3/4 of patients initiating dialysis have hemoglobin lower than 11g/dL [33]. Several reports [34–36] have shown that hypothyroidism may contribute to ESP resistance in chronic hemodialysis patients and that early thyroxine administration can improve anemia significantly. Suspicion of a relationship between thyroid dysfunction and anemia with CKD should be considered. The effects of thyroid hormones on hematopoiesis have been documented, such as an increase in production of erythropoietin or hematopoietic factors by nonerythroid cells [37], regulating the intestinal absorption of folic acid and vitamin B12. Iron deficiency anemia is related to menorrhagia resulting from various hormonal imbalances and also malabsorption, which is seen in hypothyroidism [38].

As the first sign of hypothyroidism, anemia manifests in different ways. Erdogan Mehmet et al. [39] found that the frequency of anemia in subclinical hypothyroidism (39%) was as high as that in overt hypothyroidism (43%). However, to the best of our knowledge, no published study has researched the association between euthyroid sick syndrome and anemia, especially in CKD patients. In the present study, anemia prevalence was 84.2% in patients with low T3 syndrome and CKD, much higher than in the categories reported by Mehmet et al. Moreover, compared with euthyroid subjects, Hb, HCT and RBC were much lower in the low T3 group ($P<0.01$) and positively correlated to serum TT3 and FT3 levels ($P<0.01$), indicating that the lower the serum T3 level, the more serious anemia becomes. Taken together, these studies imply that the specific metabolic environment in CKD may induce anemia by influencing thyroid hormones. In any case, it is important to consider thyroid dysfunction, such as subclinical hypothyroidism or low T3 syndrome when unexplained anemia or refractory anemia occurs in CKD patients.

While euthyroid sick syndrome, especially the low T3 syndrome, is widely found in CKD patients, the low T3 levels (especially total T3 and not free T3) have been correlated with higher levels of markers of inflammation (CRP, IL-6, etc.), malnutrition (lower pre-albumin, IGF-1), increased endothelial dysfunction, poorer cardiac function, poor survival, and higher all-cause as well as cardiovascular mortality in some studies. The clinical

importance of this low T3 syndrome is still controversial. Some of these studies were underpowered to detect these associations or did not exclude confounders appropriately.

Limitations of T3 replacement therapy for CKD patients

The existence of a potential feedback mechanism between thyroid function and immune inflammatory factors in CKD patients indicate that maintenance of normal thyroid function might be important. However, it is still controversial whether CKD patients should be treated with thyroid hormone replacement. In several animal models, long-term L-T3 replacement has been proven to preserve the mitochondria and prevent ischemic cardiac remodeling [40,41]. The vast majority of research in therapy of patients with ESS failed to show clinical benefits [42–44]. We still need large-scale, multi-centered randomized controlled trials to clarify the need for thyroid hormone replacement in CKD and the specific therapy methods.

Our limitations

This study has several limitations that should be noted. The number of subjects was limited, with 50.5% over 70 years of age, which might have induced selection bias in this study. GFR was estimated using serum creatinine concentrations in the MDRD equation, which may be imprecise at higher GFR levels, albeit less so with the use of calibrated creatinine measurements. The cross-sectional design of the study also precludes the establishment of causal or temporal relationships among energy metabolism, anemia, inflammatory state, and low T3 syndrome.

Conclusions

A high prevalence of low T3 syndrome was observed in CKD patients not undergoing dialysis, even in early stages. The increasing prevalence of low T3 with CKD stage indicates that it is of predictive value for the severity of CKD in patients who are in the early stages of disease. Furthermore, low T3 syndrome is closely associated with both MICS and anemia.

Conflict of interest

The authors declare they have no conflict of interests.

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