FAVORABLE EFFECT OF LEVOTHYROXINE ON NUTRITIONAL STATUS OF PATIENTS WITH STAGE 3-4 CHRONIC KIDNEY DISEASE

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Abstract

The aim of this study was to analyze the incidence of malnutrition in patients with stage 3-4 chronic kidney disease (CKD) and primary subclinical hypothyroidism and the effect of levothyroxine for improving nutritional status and delaying kidney disease.

Patients and Methods. In the study were included 200 patients with stage 3-4 CKD: CKD3 stage group (n=100) and CKD4 stage group (n=100). These patients were further divided into: control group (non-treatment group) group a (n=65) and experiment group (treatment group) group b (n=135) according to their levothyroxine treatment. The CKD3 stage group is divided into c3 (n=35) and c3 (n=65), and CKD4 group is divided into c4 (n=30) and c4 (n=70) groups.

Results. Upon treatment of subclinical hypothyroidism with levothyroxine, nutritional indicators of patients are improved, and the weight, left and right-hand grip strength, hemoglobin (HB), serum albumin are higher compared to control. After levothyroxine treatment, eGFR in the treatment group increased with each time point, while in the control group it could be seen a significant decrease. This effect was more robust in the CKD3 group than in the CKD4 group. In conclusion, levothyroxine treatment can delay the progression of kidney diseases with more efficacy in stage 3 patients.

Key words: Chronic kidney disease, levothyroxine, nutritional status.

INTRODUCTION

Chronic kidney disease accounts for over 50% of all non-communicable deaths worldwide. Public health efforts are being made to achieve early prevention and effective treatment strategies against this disease, all over the world (1). The death by kidney disease ranks fifth to ninth among the most common causes of chronic diseases death, being named also silent killer (2, 3). Currently, in many cases, chronic kidney

disease is associated with primary hypothyroidism and with poor nutritional status, these conditions being closely interrelated (4). Studies showed that the rate of malnutrition is positively correlated with the decrease of glomerular filtration rate (GFR) that can also be found in chronic kidney disease when glomerular filtration rate is less than 60 mL/min (5). So it is extremely important to early identify the risk factors that can have a favorable effect on the development of early-stage chronic kidney disease (6).

Hypothyroidism is a relatively silent condition due to the lack of clinical manifestations, and can be easily ignored. High incidence rate of chronic kidney disease in patients with cardiovascular disease results in increased mortality rate (7). There is a clear relation between chronic kidney disease, cardiovascular disease and hypothyroidism demonstrated by epidemiological studies (8). Animal studies suggested that hypothyroidism leads to kidney dysfunction that implicates several mechanisms. These mechanisms are related with decreased cardiac output, alteration of intra-renal hemodynamics, decrease in renin-angiotensin-aldosterone production and activity and increase in tubule-glomerular feedback due to disturbances in chloride channel (9). The cardiovascular diseases are correlated with hypothyroidism or subclinical hypothyroidism and associated with the expression of saline alpha or other inflammatory markers (10). However, the proportion of people who are aware of this disease is low and the proportion of diagnosed patients that receive treatment is much lower. There is a global public health concern regarding patients that suffer from chronic cardiovascular disease and have not been diagnosed (11). Thyroid dysfunctions are also related to infertility (12) and sometimes these disturbances can be produced by exposure to multiple endocrine disruptors chemicals via food, water and commercial products (13-15). This infertility is often

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associated with women with polycystic ovaries and acne resistant to conventional classical treatment (16).

Improvement on nutritional status and quality of life though early diagnosis and treatment of disease remain a major goal (17). Previous studies have shown that abnormal cardiovascular function and blood lipid changes in patients, caused by thyroid dysfunction, can result in better clinical outcome after the treatment with levothyroxine. However, there is lack of consensus on whether applying thyroid hormones (TH) treatment of CKD can improve nutritional status. Malnutrition results in decreased immune function and physical activity capability in patients, and is closely related to various infectious and non-infectious complications. However, it has been implicated to several mechanisms including lack of protein energy intake, excessive loss of nutrients, and protein catabolism enhancement, with the latter being the most important. Regular and standardized assessments of the nutritional status in CKD patients are critical (18).

Recent studies have shown that early thyroid hormone replacement therapy can reduce the patient blood lipid, protect endothelial cells, and inhibit the expression of some cytokines and probability of atherosclerosis (19). It has a beneficial role in patients by reducing the death rate, so as to provide the basis for active treatment.

Based on all these information the aim of this study was to assess the effect of levothyroxine treatment on the nutritional status of patients with stage 3-4 chronic renal disease in order to clearly explain the correlation between thyroid function, nutritional status and kidney disease and the protective role of active treatment.

MATERIALS AND METHODS

Patients

A total of 200 non-dialysis patients admitted to the Department of Nephrology in The First People's Hospital of Fuyang from January 2016 to October 2016 were included in the study. The study had the approval of the Ethical Committee of The First People's Hospital of Fuyang and all the patients signed an informed consent for participating at the study.

Inclusion criteria: patients with stage 3-4 chronic kidney disease diagnosis according to the definition and staging of chronic kidney disease in the 2002 Kidney / Disease Outcomes Quality Initiative (K/DOQI): - the presence of abnormal blood or urine components or radiographic abnormalities, the

course of the disease should be over 3 months and the glomerular filtration rate should be between 15-60 mL/(min.1.73m²). Patients had TSH > 5mU/L.

Exclusion criteria: patients with acute exacerbation risk factors: uncontrolled hypertension; nephrotoxic drug; urinary tract infection; severe infection, hypercalcemia and severe hepatic insufficiency, patients with hypothyroidism caused by oral anti thyroid drugs, hypothyroidism caused by I¹³¹ radiotherapy, or hypothyroidism caused by pituitary surgery.

According to the above-mentioned renal function diagnostic criteria, a total of 200 patients were selected. The patients were divided into two groups: a control group that includes patients with normal thyroid function (n=65), that include 35 patients with CKD stage 3 and 30 patients with CKD stage 4 and a treatment group (n=135) that includes patients with subclinical hypothyroidism, 65 patients with CKD stage 3 and 70 patients with CKD stage 4. CKD stage 3 group was subdivided based on thyroid function into CKD stage 3 control group (3c, n=35) and CKD stage 3 treatment group (3e, n=65), and CKD stage 4 group was divided into CKD stage 4 control group (4c, n=30) and CKD stage 4 treatment group (4e, n=70). The patients in treatment group received the levothyroxine treatment. The patients in control group received placebo. In order to be able to clearly observe the incidence of different control group and experimental group patients, included in the study cohort of patients with history of simple were patients with CKD stage three, four, CKD3 associated with subclinical hypothyroidism and stage 4 chronic kidney disease (CKD) with subclinical hypothyroidism, not accompanied by other complications.

Research method

Data collection

A randomized controlled trial (RCT) was designed for this study.

Patient demographics and clinical data were obtained from patients' medical records and included height, weight, left and right hand grip strength, gender, complaints, medication, diet, sleep, and blood tests levels for serum albumin, hemoglobin, TSH, FT3, FT4, creatinine, and urea nitrogen. BMI was calculated according to the patient's height and weight, SGA nutrition was evaluated according to diet, sleep, and glomerular filtration rate of patients; $eGFR (mL/min/1.73m^2) = 175 * (Scr, mg/dL) - 1.154 * (age) - 0.203 * 0.742$ (female). Eventually, differences

in nutritional parameters between the subclinical hypothyroidism group (treatment group) and the non-subclinical hypothyroidism group (control group) were analyzed.

The treatment group received the moderate amount of levothyroxine for replacement therapy, with the initial dose being 25µg/d. Treatment was adjusted according to heart disease history, age, weight and other clinical features, in the view of complete dose replacement the earliest possible.

The utmost goal of treatment was to restore the levels of serum TSH and thyroid hormone to physiological levels. Serum TSH, FT3 and FT4 levels were detected every month for a period of 18 months. After reaching the desirable levels of markers, testing would be repeated every 3 months.

Test method

Serum Cr: unit of µmol/L, normal value of 32.0-115.0, and sensitivity of 0.1.

Serum TSH: unit of mIU/L, normal value of 0.35-5.50, and sensitivity of 0.01.

Serum urea nitrogen: unit of mmol/L, normal value of 2.86-8.20, and sensitivity of 0.01.

Serum albumin: unit of g/L, normal value of 35.0-55.0, and sensitivity of 0.1.

Hemoglobin: unit of g/L, normal value of 110-150, and sensitivity of 1.0.

The united standard is applied to accurately measure the height, weight, left and right hand grip strength, patients' BMI: BMI<18.5kg/m² (malnourished), BMI 18.5-25kg/m² (normal), BMI 25-29.9kg/m² (overweight), BMI>30kg/m² (obese). According to BMI<18.5kg/m², it is considered as malnourished.

Glomerular filtration rate was estimated according to the formula $GFR (mL/min/1.73 m^2) = 175 \times (Scr, mg/dL)^{-1.154} \times (age)^{-0.203} \times 0.742$ (female). According to the National Kidney Foundation, the CKD staging is as follows: stage 1 - $GFR > 90 mL/min/1.73m^2$; stage 2 - $GFR 60-89 mL/min/1.73m^2$; stage 3- $GFR 30-59 mL/min/1.73m^2$; stage 4 - $15-29 mL/min/1.73m^2$; stage 5 - $GFR < 15mL/min/1.73m^2$ or dialysis.

Statistical processing

Data were expressed as mean $\pm$ standard deviation ($\bar{x} \pm S$). All data were analyzed by SPSS19.0 statistical software. The independent sample t-test was used between the groups, statistical significance was estimated according to the results of the test.

Non-parametric samples were analyzed

using the Mann-Whitney test. The normality of the distribution of continuous values was assessed using the Shapiro-Wilk test for normality.

The $p < 0.05$ was considered statistically significant.

RESULTS

General Information

The general patient information is shown in Table 1. At the beginning of the study it was seen a statistical significant difference between the control and the treatment group regarding the age and sex of the patients, in the treatment group with subclinical hypothyroidism signs the age of the patients was higher compared with control ($P < 0.05$) (Table 1).

Comparison of nutritional markers between the groups

As shown in Table 1, plasma albumin levels (ALB) were significantly decreased in treatment group compared with control group along with the hemoglobin levels and left and right hand grip strength.

eGFR variations before and after treatment

Regarding the changes in eGFR levels in the two groups at different points after the treatment we observed that levothyroxine treatment determined an increase of eGFR values in patients with stage 3-4 chronic kidney disease in each time point. In control group it could be seen a decrease of eGFR with time that shows a continuous progression of the chronic kidney disease (Table 2).

Markers of nutritional status in patients with stage 3 chronic kidney disease

Levothyroxine treatment determined a significant increase in FT3 and FT4 levels and a significant decrease in TSH levels compared with control ($P < 0.001$) in patients with CKD stage 3. Also in the treatment group the ALB levels, left hand grip strength and right hand grip strength were significantly increased after the treatment compared with control (Table 3, Fig. 1).

There were 5 patients with complications in the third stage combined with hypothyroidism, which were eyelid edema, persistent hypertension and renal insufficiency. The results showed that the urine protein content of patients before and after treatment decreased.

Table 1. General information and nutritional indicators in control and treatment group

Observed indicators	Subclinical hypothyroidism (treatment group) (n=135)	Euthyroidism (control group) (n=65)	P
Age (year)	48±15	42±16**	0.01
Female (%)	53.33	54.84**	0.01
Total cholesterol (mmol/L)	5.7±2.2	5.1±2.2	0.072
Triglyceride (mmol/L)	2.3±1.7	2.1±1.2	0.396
Fasting blood glucose (mmol/L)	5.1±1.3	5.21±0.83	0.534
FT3 (pmol/L)	2.13±0.68	2.5±1.2**	0.006
FT4 (pmol/L)	11.9±2.8	12.6±2.9	0.103
TSH (μIU/mL)	8.6±2.1	2.2±1.3 **	<0.001
eGFR (mL/min/1.73m ²)	58.3±3.12	53.9±1.65	0.287
HGB (g/L)	98±15	110±17**	<0.001
ALB (g/L)	27.8±5.1	29.1±4.0	0.073
Blood pressure (mmHg)	141±5.1/104±3.2	146±4.6/110±2.9	0.010
Left hand grip strength (N)	142±60	182±84**	<0.001
Right hand grip strength (N)	160±61	196±82**	0.001
BMI(Kg/m ²)	21.0±2.8	20.5±3.2	0.261

Note: Compared with control group, *P < 0.05, **P < 0.01; The P-value for age and female was obtained by independent sample t-test. Other's P values were obtained by Mann-Whitney test. FT3:free triiodothyronine; FT4:free thyroxine; TSH:thyrotropin, thyroid stimulating hormone; eGFR: Glomerular filtration rate was estimated according to the formula $GFR (mL/min/1.73 m^2) = 175 \times (Scr, mg/dL) \cdot 1.154 \times (age) \cdot 0.203 \times 0.742$ (female). HGB: hemoglobin; ALB: albumin. BMI: Body Mass Index.

Table 2. Changes of eGFR values in the treatment and control group with time

eGFR(mL/min.1.73m ²)	Treatment group (n=135)	Control group (n=65)	P
Baseline	56.3±14.3	56.2±15.8	0.964
6 months	57.8±12.5	53.4±16.6*	0.038
9 months	58.4±15.5**	52.1±13.4**	0.005
12 months	59.8±18.8**	50.8±13.7**	0.001
15 months	58.4±17.4**	45.3±15.3**	<0.001
18 months	56.3±16.3**	44.9±17.3**	<0.001

The results are expressed as mean ± standard deviation.

Note: Compared with control group, **P < 0.01; eGFR: Glomerular filtration rate was estimated according to the formula $GFR (mL/min/1.73 m^2) = 175 \times (Scr, mg/dL) \cdot 1.154 \times (age) \cdot 0.203 \times 0.742$ (female).

Table 3. Indicators of stage 3 patients with chronic kidney disease in the treatment (3e) and control (3c) group

Observed indicators	Group 3c (n=35)	Group 3e (n=65)	P
FT3 (pmol/L)	3.11±0.56	4.09±0.79**	<0.001
FT4 (pmol/L)	9.4±2.1	13.6±1.89**	<0.001
TSH (μIU/mL)	11.53±3.59	4.62±2.83**	<0.001
eGFR (mL/min/1.73m ²)	42.4±6.3	48.9±8.5**	<0.001
HGB (g/L)	100.5±14.45	103.24±11.68	0.242
ALB (g/L)	28.41±5.18	32.53±5.93**	<0.002
Urine protein (mg) before treat	1.54±0.32	1.63±0.24**	<0.010
Urine protein(mg)after treat	0.50±0.19	0.61±0.12**	<0.01
Left hand grip strength (N)	143.13±59.74	191.34±53.76**	<0.001
Right hand grip strength (N)	172.51±42.35	202.51±12.74**	<0.001

Note: Compared with control group, **P < 0.01; P: The p-value is tested by Mann-Whitney test.

FT3:free triiodothyronine; FT4:free Thyroxine; TSH:thyrotropin; eGFR: Glomerular filtration rate was estimated according to the formula $GFR (mL/min/1.73 m^2) = 175 \times (Scr, mg/dL) \cdot 1.154 \times (age) \cdot 0.203 \times 0.742$ (female). HGB: hemoglobin; ALB: albumin. BMI: Body Mass Index.

Markers of nutritional status in patients with stage 4 chronic kidney disease

Levothyroxine treatment determined a significant increase in FT3 and FT4 levels and a significant decrease in TSH levels compared with control (P<0.001) in patients with CKD stage 4. Also

in the treatment group the ALB levels, HGB levels, left hand grip strength and right hand grip strength were significantly increased after the treatment compared with control (Table 4, Fig. 2).

The results showed that the urine protein content of patients before and after treatment

Figure 1. Indicators of stage 3 patients with chronic kidney disease in the experiment group and control group after the treatment.

Figure 2. Indicators of stage 4 patients with chronic kidney disease in the experiment group and control group after the treatment.

Table 4. Indicators of stage 4 patients with chronic kidney disease in the treatment (4e) and control group (4c)

Observed indicators	Group 4c (n=30)	Group 4e (n=70)	P
FT3 (pmol/L)	2.69±0.59	3.69±0.72**	<0.001
FT4 (pmol/L)	9.4±1.7	13.1±1.9**	<0.001
TSH (μIU/mL)	12.6±3.9	4.4±2.3**	<0.001
eGFR (mL/min/1.73m ²)	21.0±4.1	23.7±4.6**	0.007
HGB (g/L)	95.1±4.6	99.0±7.1**	0.007
ALB (g/L)	26.5±6.1	29.5±4.6**	0.008
Urine protein(mg)	2.2±0.24	<0.01	
Before treat	1.5±0.72**		
Urine protein(mg)	1.9±0.28	<0.01	
After treat	1.2±0.32**		
Left hand grip strength (N)	129±72	173±42**	<0.001
Right hand grip strength (N)	159±33	189±13**	<0.001

P:The p-value is tested by Mann-Whitney test.

Note: Compared with control group, **P < 0.01; FT3:free triiodothyronine;FT4:free thyroxine; TSH:thyrotropin; eGFR: Glomerular filtration rate was estimated according to the formula $GFR (mL/min/1.73m^2) = 175 \times (Scr, mg/dL)^{-1.154} \times (age)^{-0.203} \times 0.742$ (female). HGB: hemoglobin;ALB: albumin.BMI: Body Mass Index.

decreased. There were 15 patients with complications in the four stages of combined thyroid function reduction, which were bilateral blepharodema, persistent hypertension, renal insufficiency, bilateral lower limb edema, constipation, and sporadic atrial fibrillation.

In our study, the patients were chronically in the stage of chronic kidney disease, the body cannot give full play to the glomerular filtration and the renal tubule reabsorption function. As a result, some patients suffer from malnutrition, anorexia and other

diseases resulting in low levels of serum protein. There were 20 patients with malnutrition in the third stage of CKD, and 30 were malnourished in the fourth stage. Due to the occurrence of vomiting in some patients, there is no record of total protein intake and output. Univariable analyses were performed between continuous measurements and risk factors associated with CKD progression. Increasing BMI, WC and WHtR were significantly correlated with a minority of risk factors whereas WHR and CI were significantly correlated with multiple risk factors (Table 5).

Table 5. Univariable analysis between continuous measures and established risk factor for CKD progression

Dependent Variable	BMI		WC		WHtR		WHR		CI	
	Beta	Std. Error	Beta	Std. Error	Beta	Std. Error	Beta	Std. Error	Beta	Std. Error
eGFR(mL/min/1.73m ²)	-0.58	0.06	-0.08*	0.02	-12.55*	3.31	-18.54*	2.33	-14.414	2.54
SBP(mmHg)	0.02	0.08	0.05	0.02	4.12	4.74	10.45*	3.14	8.21*	3.12
Log UACR	0.003	0.006	0.015*	0.002	2.058*	0.354	3.124*	0.314	2.912*	0.214
Uric acid(mmol/L)	3.25*	0.31	2.18*	0.15	266.14	24.55	221.14*	21.56	214.36*	21.56
PWV	-0.051*	0.01	0.001	0.003	-0.745	0.514	2.123*	0.478	2.084*	0.412

*P<0.001. eGFR = estimated glomerular filtration rate; SBP = systolic blood pressure; UACR = urine albumin to creatinine ratio; PWV = pulse wave velocity; BMI = body mass index; WC = waist circumference; WHtR = waist-to-height ratio; WHR = waist-to-hip ratio; CI = conicity index.

This study shows that upon levothyroxine treatment, there is no significant improvement in the thyroid function in patients with no significant difference in age, height, body mass index, under the conditions of CKD3 stage and CKD4 stage. eGFR was improved after the levothyroxine treatment, especially in the CKD3 group where differences were statistically significant. Thus, it can be speculated that subclinical hypothyroidism can be used as an independent risk factor for renal function prognosis. Moreover, it is necessary to perform positive detection treatment from malnutrition prone period, namely chronic kidney disease stage 3. At the same time, nutritional status is significantly different among subclinical hypothyroidism and euthyroid patients. Thyroid dysfunction can lead to increased malnutrition. After levothyroxine treatment, nutrition evaluation index was improved in patients with hypothyroidism. As a result, applying levothyroxine treatment from the beginning of stage 3 chronic kidney disease can reduce the incidence of malnutrition in patients with chronic kidney disease, and especially in CKD3 group ($P<0.05$).

DISCUSSION

Nowadays, there is a rising trend in the incidence of chronic renal diseases, while the incidence of thyroid disease with chronic kidney disease is also increasing year by year (20). Thyroid, is closely influencing the kidney function (21). Substitutive treatment of subclinical hypothyroidism has a protective effect on the residual renal function of chronic kidney disease, which will impede the progression of the disease (22, 23). Our study showed that CKD stage 3 and CKD stage 4 patients after treatment had higher levels of hemoglobin, left and right hand grip strength, BMI compare to the untreated patients. Our study is in accordance with other studies results that showed that for CKD patients, thyroid dysfunction is a risk factor for prognosis. Other systems, as apelin/AJ system, FGF23-Klotho or association with malignant melanoma might

influence the progress of chronic kidney disease (24-26). Renal function decline will deteriorate the nutritional status, and the nutritional status of kidney disease will be further downgraded in the presence of hypothyroidism. The incidence of subclinical thyroid dysfunction is positively related to the decrease of eGFR and association with type 1 diabetes might further worsen the prognosis (27). A recent study demonstrated that when $GFR \geq 90 \text{ mL/min/1.73m}^2$, the incidence rate of SH was 7%, while when $GFR < 60 \text{ mL/min/1.73m}^2$, the incidence rate was 17.9% (28). In a survey carried out in the United States on nutrition and health, the incidence rate of stage 3 chronic kidney disease was 21% and stage 4 was 23.1%. The survey results showed that the incidence rate of hypothyroidism in patients with chronic disease showed an upward trend with decreasing renal function (29). Hypothyroidism, for CKD 3-4 stage patients, is still considered to be an independent risk factor. The effect on glomerular filtration rate has been demonstrated in patients with hypothyroidism in previous studies (30).

In patients with chronic kidney disease, malnutrition is caused by various factors (21). Hypothyroidism can affect the nutritional status of these patients either directly or through other mechanisms. Patients' health condition is closely related to the actual kidney function (32). Currently, many measures have been taken to improve the nutritional status of these patients, thus their nutrition has been ameliorated (33). The current study showed that renal function changes are closely related to the thyroid hormone treatment of subclinical hypothyroidism that is in accordance with other studies (34). Proper treatment is of great significance to the improvement of nutritional status (35). Here, we provide evidence that patients suffering from subclinical hypothyroidism, subjected to moderate levothyroxine replacement therapy, had improved levels of nutrition markers, including serum albumin, hemoglobin, left and right hand grip strength, and BMI.

Levothyroxine treatment can provide valuable input to clinical application, and replacement therapy can

delay the progression of renal disease (36). In addition, differences between stage 3 and stage 4 chronic kidney disease were compared, suggesting that early treatment is more effective which provides certain reference value for the timing of alternative treatment (37). Moreover, prognosis of CKD patients with hypothyroidism subjected to levothyroxine replacement therapy was evaluated (38). Through this study, it was shown that thyroid hormone replacement therapy improved eGFR levels in the CKD3 group and in the CKD4 group. The improvement of CKD3 group was significantly greater than that of CKD4 group, indicating that levothyroxine treatment can delay the progression of renal disease, and treatment can be more effective in stage 3 than in stage 4 patients. After levothyroxine replacement therapy of subclinical hypothyroidism, the nutrition markers of stage 3-4 chronic kidney disease patients were improved, and body mass index, left and right hand grip strength, hemoglobin (HB), serum albumin, and SGA scores were higher than those in prior treatment (39).

One of the limitations of this study is related to the small number of the patients, further studies should be done with higher cohorts in order to validate the results.

These findings can provide valuable input to the clinical treatment and the timing of levothyroxine replacement therapy in CKD patients.

Conflict of interest

The authors declare that they have no conflict of interest.

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