Changes of nutritional status and the variations of serum indicators of patients with chronic kidney disease accompanied by hypothyroidism taking thyroid hormone replacement therapy as the therapeutic models

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A B S T R A C T

This study aimed to analyze the incidence of malnutrition in patients with chronic kidney disease (CKD) at stage III-IV accompanied by hypothyroidism and indicate the improvement in nutritional status and kidney disease of CKD patients after undergoing thyroid hormone replacement (THR) therapy as therapeutic models. The included 156 CKD patients in stage III-IV were divided into the CKD stage III group (CKD-III group) (n = 80) and CKD stage IV group (CKD-IV group) (n = 76), and the clinical indicators of all the patients were collected. Based on changes in thyroid function, the included patients were again divided into the following groups: subclinical hypothyroidism group (the experimental group, hereinafter referred to Y-group, n = 78) and non-subclinical hypothyroidism group (the control group, hereinafter referred to N-group, n = 78), in which the CKD-III group was divided into CKD-IIIN group (n = 38) and CKD-IIIY group (n = 42), and also the CKD-IV group was divided into CKD-IIVN group (n = 40) and CKD-IIVY group (n = 36). At the beginning, patients in the Y-group was orally given 25 µg/dL of levothyroxine; based on the progression of the disease, the dosage was regulated; the concentration of serum thyroid stimulating hormone (TSH) was assessed once per month, as well as changes in tri-iodothyronine (T3) and tetra-iodothyronine (T4). Estimated glomerular filtration rate (eGFR) in the CKD-IIIN group was significantly changed compared with that of the CKD-IIVY group after THR therapy. Comparison of nutrition-based indicators between the N-group and the Y-group showed that the serum albumin (ALB) level, the hemoglobin (HGB) level, and the grip strength of both the left and right hand were notably decreased (P < 0.05). After THR therapy, the indicators related to CKD patients were accompanied by subclinical hypothyroidism changes; the levels of ALB and HGB, as well as the grip strength of both the left and right hand were notably increased compared with before undergoing THR therapy (P < 0.05). In conclusion, malnutrition of chronic kidney disease caused by subclinical hypothyroidism could be partially recovered after THR therapy as therapeutic models.

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1. Introduction

Malnutrition is the primary cause of the decline in immune functions and the ability of physical activity, which is also closely associated with various infectious and non-infectious complications (Aldenbratt et al., 2017). Therefore, it is essential to regularly assess the nutritional status of patients with chronic kidney disease (CKD). Before CKD patients progress to end-stage renal disease (ESRD), the significance of treatment is to delay the progression of kidney disease and improve the patients’ life quality (Foley et al., 1998; Zhang et al., 2014). A study showed that the occurrence of atherosclerosis is closely related to the changes in thyroid stimulating hormone (TSH), and the recovery of thyroid function could improve the left ventricular diastolic and systolic functions (Gao et al., 2015). Thus, the early application of thyroid hormone replacement (THR) therapy as therapeutic models could satisfy clinical effects in different aspects. In addition, studies have
confirmed that in terms of reducing the incidence of cardio-cerebrovascular disease, the THR therapeutic model could diminish the level of blood lipids, protect the vascular endothelial cells, inhibit the expressions of a certain cytokine, and decrease the incidence of atherosclerosis (AS) (Huang et al., 2016; Shin et al., 2012; Dong et al., 2013). Therefore, it could provide a certain basis for the active treatment of CKD. The present study could further confirm the benefits of early treatment; meanwhile, it also explored the relationship among thyroid function, nutritional status, and kidney disease, thereby demonstrating the importance of protecting the patients’ residual renal function and active treatment of subclinical hypothyroidism (SH) to improve the patients’ nutritional status.

2. Materials and methods

2.1. Patients

A total of 156 non-dialysis patients with kidney disease who were admitted to Chongqing Traditional Chinese Medicine Hospital from September 2017 to January 2019 were included in this study. The clinical data and medical history of included patients were collected. The patients were divided into the CKD stage III group (the CKD-III group) (n = 80) and the CKD stage IV group (the CKD-IV group) (n = 76). Based on the progression of changes in thyroid function, the included patients were again divided into following groups: the subclinical hypothyroidism group (the control group, hereinafter referred to Y-group, n = 78) and the non-subclinical hypothyroidism group (the control group, hereinafter referred to N-group, n = 78), in which the CKD-III group was further divided into the CKD-III-N group (n = 38) and the CKD-III-Y group (n = 42), the CKD-IV group was further divided into the CKD-IV-N group (n = 40) and the CKD-IV-Y group (n = 36); thus, the experimental group was (CKD-IIIY + CKD-IVY) and the control group was (CKD-III-N + CKD-IV-N).

2.2. Baseline characteristics of patients

In this study, the height, weight, and grip strength of left and right hand of included patients were measured; the body mass index (BMI) was calculated (BMI < 18.5 kg/m² [malnutrition], BMI = 18.5–24 kg/m² [Normal], BMI = 24–27 kg/m² [overweight], and BMI > 27 kg/m² [obese]).

2.2.1. Assessment of serum-based indicators

The peripheral blood samples of the included patients were collected for the assessment of serum-based indicators, including serum albumin (ALB), hemoglobin (HGB), TSH, free triiodothyronine (FT3), free tetraiodothyronine (FT4), serum creatinine (Scr), and urea nitrogen; besides, based on the patients’ height and weight, their BMI was calculated; in accordance with the conditions, such as diet and sleep, the patients fulfilled Subjective Global Assessment (SGA) form (Table 1).

2.2.2. Glomerular filtration rate (GFR)

The normal estimated GFR (eGFR) ranged from 90 to 120 mL/min/1.73 m². According to the National Kidney Foundation (New York, NY, China), the CKD was divided into 5 stages based on the renal damages: stage I, the GFR > 90 mL/min/1.73 m²; stage II, GFR = 60–89 mL/min/1.73 m²; stage III, GFR = 30–59 mL/min/1.73 m²; stage IV, GFR = 15–29 mL/min/1.73 m²; stage V, GFR < 15 mL/min/1.73 m². Based on the Modification of Diet in Renal Disease (MDRD) equations, the Chinese modified eGFR equation was as follows: eGFR (mL/min/1.73 m²) = 186 × (Scr, mg/dl)−1.154 × (age)−0.203 × 0.742 (female).

2.2.3. Thyroid function

The thyroid function mainly included hormones secreted by following organs: the thyroid hormone (TH) (FT3 and FT4) secreted by the thyroid, and the TSH secreted by the pituitary gland. The recent changes in thyroid function could be indicated by the TH level. The TSH level could be stimulated by the TRH test and thus regulated (Huang et al., 2016). The hypothyroidism was divided into 4 stages: stage I, the TRH stimulation test was positive, i.e. the serum FT4 level was normal, the TSH level was at the maximum limit of normal ranges; stage II, the serum FT4 level was normal, i.e., the serum TSH level was 5–10 μU/mL; stage III, the serum FT4 was normal, i.e., the serum TSH > 10 μU/mL; stage IV, the serum FT4 level decreased, and the serum TSH level increased. The appropriate amount of levothyroxine was applied as the THR therapeutic model to the Y-group, the initial dosage was 25 μg/dl in accordance with heart disease history, age, weight, and other conditions, and therapeutic plans reached the overall TH dosage. The TH administered dose was recorded, and the detection of the thyroid was achieved by using the radio-immunoassay (RIA). The therapeutic objective was to recover the serum TSH and TH levels into the normal ranges. In accordance with the age, weight, disease conditions, and the patients’ identical difference, the dose of TH was regulated; the changes in concentrations of TSH were assessed monthly, as well as the levels of FT3 and FT4 until the therapeutic objective was achieved. After the therapeutic objective was successfully achieved, the hormone-based indicators were measured and detected every three months to observe the changes in the indicators described above after undergoing THR therapy as therapeutic models. The total duration of follow-up was 18 months. Since the indicators reached the therapeutic objectives, the assessment period was three months.

2.2.4. Statistical analysis

The data were expressed as mean ± standard deviation (SD); all the data were also analyzed by using SPSS 19.0 software (IBM, Armonk, NY, USA); the independent-samples t-test was used for

Table 1

Subjective global assessment form.

| Indicator | 1–2 points | 3–5 points | 6–7 points |
|-----------|------------|------------|------------|
| Weight changes (in the past 6 months) | Continuous weight loss > 10% | Continuous weight loss 5%–10% | No weight loss; or weight loss < 10%, which was improved in recent 1 month |
| Diet | Severe intake reduction or starvation | Continuous and serious gastrointestinal symptoms, over 2 weeks | Obvious intake reduction or liquid diet |
| Gastrointestinal symptoms | Slight or moderate gastrointestinal symptoms, <2 weeks | None |

Subjective Global Assessment (SGA) included four parts: the weight change, the diet, nutrition intake, and gastrointestinal symptoms. The assessment totally involved 28 points, among which 24–28 indicated normality; 15–23 indicated slight to moderate malnutrition; points < 15 indicated serious malnutrition.
making comparison among the groups. P < 0.05 was considered statistically significant.

3. Results

3.1. Analysis of nutritional status

As shown in Table 2, all the aforementioned stages of CKD were compared between Y-group and N-group, and the results showed that the proportion of patients with malnutrition in the Y-group was significantly increased (56.41% > 46.15%, P < 0.05), while the proportion of well-nourished patients was notably decreased (43.59% < 53.85%, P < 0.05).

3.2. Variations of serum TSH levels

The TH was complimented until the balance of hypothalamus-pituitary gland-thyroid was re-established. As shown in Table 3, after THR therapy, the serum TSH level was normal, and maintained in the normal range in the follow-up examinations; compared with the basement, there was significant difference (P < 0.01). The serum TSH level slightly changed in the N-group, compared with the Y-group (P < 0.05).

3.3. Variations before and after eGFR treatment

As presented in Table 4, after THR therapy, the eGFR level of CKD patients was improved compared with that before the therapeutic models.

3.4. Comparing nutrition-based indicators between the Y-group and the N-group

It could be inferred from Table 5 that the levels of ALB, HGB, and the grip strength of the left and right hand in Y-group were significantly decreased compared with the N-group (P < 0.05). However, the TSH levels in the Y-group were markedly increased compared with the N-group (P < 0.05).

As shown in Tables 5–7, there was no significant difference between indicators, including age, height, BMI, and TH dosage, and the degree of improvement in the thyroid function did not significantly change after the CKD-III and CKD-IV patients underwent THR therapy as therapeutic models. Besides, in terms of the improvement of eGFR, the degree of improvement did not remarkably change between the CKD-III group and the CKD-IV group; the improvement in CKD-III group was more obvious, therefore, it can be concluded that the subclinical hypothyroidism could be taken as the independent dangerous factor into account in the prediction and prognosis of renal function. In addition, the active detection

Table 2
The occurrence of malnutrition.

| Group   | Number of cases | Well-nourished | Malnutrition |
|---------|-----------------|----------------|--------------|
| Y-group | 78              | 34             | 44           |
| N-group | 78              | 42             | 36           |

Table 3
Variations of serum TSH levels in the Y-group during follow-up.

| TSH       | Basement | 6 M | 9 M | 12 M | 15 M | 18 M |
|-----------|----------|-----|-----|------|------|------|
| The CKD 3Y group | 6.91 ± 1.42 | 7.14 ± 1.27 | 7.26 ± 1.33 | 7.37 ± 1.61 | 7.51 ± 1.63 | 7.87 ± 1.58 |
| The CKD 4Y group | 6.72 ± 1.41 | 6.95 ± 1.23 | 7.58 ± 1.43 | 7.16 ± 1.46 | 7.29 ± 1.38 | 7.58 ± 1.71 |

Note: M, months.

Table 4
Variations of eGFR levels in the Y-group (CKD-IIIY + CKD-IVY) and the N-group (CKD-IIIN + CKD-IVN).

| TSH       | Basement | 6 M | 9 M | 12 M | 15 M | 18 M |
|-----------|----------|-----|-----|------|------|------|
| The Y-group | 56.8 ± 15.4 | 57.8 ± 14.8 | 58.2 ± 16.5 | 58.7 ± 18.6 | 57.9 ± 18.2 | 56.4 ± 16.1 |
| T          | 56.1 ± 16.3 | 52.4 ± 18.6 | 51.5 ± 17.3 | 50.9 ± 15.4 | 46.6 ± 18.5 | 44.8 ± 18.3 |

Note: M, months. The Y-group vs. the N-group, P < 0.001.
and treatment can be applied since the prone period of malnutrition, i.e. the CKD-III. Meanwhile, due to the obvious difference in nutritional status between the Y-group and the N-group, the thyroid dysfunction could aggravate the status of malnutrition. With the help of THR therapeutic model, the nutrition-based indicators in hypothyroidism patients were improved, therefore, the THR therapeutic model can be applied to the treatment of subclinical hypothyroidism for the CKD-III; for CKD patients, THR therapeutic model could diminish the occurrence of malnutrition; besides, the improvement of nutrition-based indicators was more notable in the CKD-III group than that in the CKD-IV group.

4. Discussion

The application of thyroid hormones on subclinical hypothyroidism therapies would protect the residual renal functions of CKD patients; conversely, the progression of the diseases would be accelerated (Chuang et al., 2016). During the therapeutic processes of CKD3 and CKD4 patients, the nutritional indicators including HGB, grip strength of the left and right hand, BMI, and SGA scores were improved compared with those measured before the application of the therapeutic model. Therefore, it was indicated that in terms of the CKD patients, the thyroid function was not the only dangerous factor which would affect the prognosis of kidney diseases. Besides, with the decrease of renal functions, the nutritional status would decrease correspondingly; especially when the CKD was accompanied by hypothyroidism, the nutritional status would further decrease. The incidence of hypothyroidism was in positive correlation with the decrease degree of the glomerular filtration rate (Kutlay et al., 2005; Lo et al., 2005). Due to the specificity of the clinical expressions of subclinical thyroid dysfunction, the occurrence rate of subclinical thyroid dysfunction increased with the decrease of eGFR levels (Singh et al., 2006). Research has shown that (Naseem et al., 2018): if the GFR > 90 mL/min/1.73 m², the incidence of SH would be 7%; if the GFR < 60 mL/min/1.73 m², the incidence would be 17.9%. Other research has indicated that (Afasar et al., 2017): the occurrence rate of hypothyroidism among patients with chronic diseases showed the trend of increase as the renal functions decreased; hypothyroidism was still regarded as an independent dangerous factor for CKD stage 3–4 patients. The early application of THR therapeutic model to the treatment of hypothyroidism would protect the nutritional status of kidney diseases. Meanwhile, it could also protect the residual renal functions; in terms of the acceleration of the progression of kidney diseases, the subclinical hypothyroidism would play a promotive role. The selection of therapeutic opportunities and the preventive treatments of diseases would improve the life quality of CKD patients.

The receptors of thyroid stimulating hormone (TSH) were widely distributed in the human body, which mainly regulated the secretion function of the thyroid (Woo et al., 2011; Gao et al., 2015). The lack of TSH would lead to the shrinkage of the thyroid gland and the inhibition of the synthesis level of gland hormones (Khan et al., 2013). The hyperfunction of TSH would lead to the hypertrophied thyroid gland and the hyperfunction of its secretion function (Eiland et al., 2012). TSH was of wide functions in the human body (Evans et al., 2011), and the primary cause was that the receptors of thyroid gland were widely distributed in the human body; through the combination with the receptors, the TSH would regulate the normal secretion function of thyroid follicles as well as the regulating functions of metabolism (Saleh et al., 2016). Therefore, the abnormal secretion of TSH would cause the corresponding malfunctions in systemic organs (Birk-Urovitz et al., 2017). The incidence and fatality rates of cardiovascular diseases were closely related to the early timely treatments (Kanajya et al., 2002). The research above has demonstrated that: the early applications of hormone replacement therapeutic model would lead to satisfied clinical effects in some aspects. The research of the paper has further demonstrated that the TH would not only relieve the symptoms of hypothyroidism but also reverse the accu-rate aggravation of potential chronic renal dysfunctions in hypothyroidism patients, as well as improving the nutritional status of the patients. The application of THR therapeutic model would improve the renal functions and nutritional status.

Various studies have shown that (Singh et al., 2016; Al-Mendalawi 2016): the cardiovascular functions as well as the blood lipid disorder were affected by the levels of TH, which also had the regulating effects on the abnormal metabolism of neurons and body fluids caused by hypothyroidism. Results of many studies have indicated that (Wada et al., 2011; Biondi and Cooper, 2008): if the TSH concentration of subclinical hypothyroidism patients exceeded 10 μIU/mL, the THR therapeutic model would benefit the thyroid dysfunction patients. The inappropriate dosages of TH replacement therapy were the most common cause of subclinical thyroid dysfunction. Therefore, the research in the paper excluded the patients with extremely high TSH concentrations during the process of case selection. Meanwhile, due to the potential risks of overtreatment, the paper also measured the TH levels, glomerular filtration rates, nutritional status, and cardiac functions on a regular basis to avoid the aggravation of cardiovascular diseases caused by overtreatment.

The occurrence of malnutrition among CKD patients was the result of multiple factors, in which the condition of hypothyroidism would affect the nutritional status of patients directly or indirectly. After the application of THR therapeutic model, nutritional indicators of CKD patients including the SGA nutrition scores, ALB, HGB, grip strength of the left and right hand, and BMI were all improved. In addition, the clinical application of THR therapeutic model would delay the progression of kidney diseases, particularly the CKD stage 3 and stage 4, which indicated that the early treatments were of more clinical values.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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