Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
2018, Vol. 46(10) 4061–4070

DOI: 10.1177/0300060518778190
journals.sagepub.com/home/imr
SAGE

The relationship between inflammatory factors, oxidative stress and DIO-1 concentration in patients with chronic renal failure accompanied with or without euthyroid sick syndrome

Shu-Lan Qin[1,*], Qi He[1,*], Ling Hu[1], Chun-Yan He[3], Li-Cheng Gao[1], Charlotte Aimee Young[4], Juan Chen[3], Cheng-Fang Jiang[3], Xiang-Feng Luo[1], Ying Zhou[1], Xia Sheng[1], Zhi-Hong Li[1], Mei-Ling Chen[1] and Gaosi Xu[2]

Abstract

Objective: To investigate the relationship between inflammatory factors, oxidative stress and type 1 deiodinase (DIO-1) concentration in patients with chronic renal failure (CRF) with or without euthyroid sick syndrome (ESS).

Methods: This study recruited patients with CRF and divided them into two groups: group 1 had low free triiodothyronine (FT3) levels; and group 2 had normal FT3 levels. Group 3 consisted of healthy volunteers. Serum levels of interleukin (IL)-6, IL-1β, tumour necrosis factor (TNF)-α, 8-isoprostane and DIO-1 were measured using enzyme-linked immunosorbent assays. Multiple regression analysis was used to analyse correlations between parameters.

[1]Department of Endocrinology, Third Affiliated Hospital, Nanchang University, Nanchang, Jiangxi Province, China
[2]Department of Nephrology, Second Affiliated Hospital, Nanchang University, Nanchang, Jiangxi Province, China
[3]Department of Experimental Centre, Jiangxi Health Vocational College, Nanchang, Jiangxi Province, China
[4]Department of Ophthalmology, University of California, San Francisco, CA, USA

*These authors contributed equally to this study.

Corresponding author:
Shu-Lan Qin, Department of Endocrinology, Third Affiliated Hospital, Nanchang University, 128 Xiang-Shan North Road, Dong-Hu District, 330008, Nanchang, China.
Email: qsl9995@aliyun.com

Results: Sixty patients were enrolled into each group and the groups were comparable in terms of vital signs, white blood cell count, free thyroxine and thyroid stimulating hormone concentrations. The serum DIO-1 concentration was significantly higher in group 2 than in groups 1 and 3. Multivariate regression analysis revealed that the DIO-1 concentration was inversely correlated with the TNF-α concentration.
Conclusions: Patients with CRF without ESS showed higher concentrations of DIO-1 than patients with ESS. The DIO-1 concentration was inversely correlated with the TNF-α concentration, which might indicate that the inflammatory response was milder in the patients with CRF without ESS than in those with ESS.

Keywords
Type I deiodinase, inflammatory factors, oxidative stress, chronic renal failure, euthyroid sick syndrome

Date received: 20 November 2017; accepted: 23 April 2018

Introduction

Chronic renal failure (CRF), a condition frequently attributed to uncontrolled diabetes mellitus and hypertension, has become an economic and public health burden both globally and locally.[1–4] Many studies have demonstrated that CRF is often accompanied by increased inflammatory markers, oxidative stress and thyroid function disorders.[5–9] In addition, patients with CRF often have nonthyroidal illness that frequently manifests with changes in serum thyroid hormone levels, which is known as euthyroid sick syndrome (ESS).[10,11] ESS, also known as nonthyroidal illness syndrome, refers to changes seen in thyroid function tests during episodes of critical illness.

In humans, peripheral thyroid hormone metabolism is mediated by three iodothyronine deiodinases, which are type I deiodinase (DIO-1), type II deiodinase (DIO-2) and type III deiodinase (DIO-3).[12,13] Much research has shown that DIO-2 and DIO-3 play a key role in the production of serum triiodothyronine (T3) from thyroxine (T4) and in the breakdown of the metabolite reverse triiodothyronine (rT3).[12–14] However, there has been no published research on DIO-1 and the relationship between inflammatory markers, oxidative stress and DIO-1 in patients with CRF with or without ESS.

Using clinical data and blood samples from patients with CRF with or without ESS, this study compared the concentrations of DIO-1, inflammatory markers and 8-isoprostane using enzyme-linked immunosorbent assays (ELISAs) in order to determine if there was a relationship between inflammatory markers, oxidative stress, DIO-1 and free T3 (FT3).

Patients and methods

Patient population

This study recruited consecutive patients with CRF in the Department of Nephrology, Second Affiliated Hospital, Nanchang University, Nanchang, China between October 2015 and October 2016. The inclusion criteria for the patients with

CRF were as follows: (i) age range of 40–80 years; (ii) renal failure was diagnosed by elevated levels of blood urea and serum creatinine and associated oliguria; (iii) no history of renal transplantation. A group of healthy volunteers was recruited through a routine community medical examination. Inclusion criteria for the healthy volunteers were as follows: (i) age range of 40–80 years; (ii) normal renal function tests; (iii) no history of diabetes mellitus, hypertension, or other chronic diseases; (iv) no history of renal transplantation. The exclusion criteria were as follows: (i) patients with tuberculosis or other systemic diseases; (ii) patients taking glucocorticoids or immunosuppressants; (iii) patients with injuries, clinical symptoms, or abnormal function of the heart, lung, or liver.

The patients with CRF were divided into two groups: group 1 (CRF with ESS) consisted of patients with low FT3 levels (< 2.3 pg/ml); and group 2 (CRF without ESS) consisted of patients with normal FT3 levels (2.3–4.2 pg/ml). Group 3 (control group) consisted of healthy volunteers.

All procedures performed in these studies involving human participants were undertaken in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Approval was obtained from the Institutional Ethics Committee of Third Affiliated Hospital, Nanchang University, Nanchang, China, before the commencement of the study (no: 15/NC/0243). Verbal informed consent for participation was obtained from all study participants including the healthy volunteers and patients.

Evaluation of demographic and clinical parameters

Prior to the measurement of clinical parameters, the date of birth/age and sex of each participant was recorded. Heart rate, respiration, blood pressure and body mass index were measured and recorded. Venous blood samples were collected on the morning after an 8–10 h overnight fast. The blood samples were stored at 4°C if not used immediately. The serum was collected by centrifugation at 1000 ***g*** for 5 min at 22°C using a Sigma 3-18K centrifuge (Sigma-Aldrich, St Louis, MO, USA). The concentration of serum lipids, albumin, creatinine, fasting blood glucose and uric acid were measured using reagents supplied by Yongchang (Shanghai, China). FT3, free T4 (FT4) and thyroid stimulating hormone (TSH) were measured using reagents supplied by Roche Diagnostics GmbH (Mannheim, Germany). All of the measurements were undertaken using routine methods in a clinical laboratory and recorded using equipment supplied by Olympus (Tokyo, Japan). A second venous blood sample was collected and mixed with 1% heparin to produce plasma. The concentration of plasma haemoglobin and the white blood cell count were measured using reagents from Baite (Nanchang, China) and recorded using equipment supplied by Sysmex (Tokyo, Japan).

Evaluation of DIO-1, inflammatory markers and 8-isoprostane

The concentrations of serum DIO-1 (USCN Life Sciences, Wuhan, China), 8-isoprostane (Cayman Chemical, Ann Arbor, MI, USA), interleukin (IL)-6, IL-1β and tumour necrosis factor (TNF)-α (RayBiotech, Norcross, GA, USA) were measured using ELISA kits according to manufacturers' instructions. The minimum detectable concentrations were 0.1 ng/ml for DIO-1, 0.1 pg/ml for 8-isoprostane, 1.0 pg/ml for IL-6, 1.0 pg/ml for IL-1β and 1.0 ng/ml for TNF-α. Intra- and inter-assay coefficients of variation for all ELISAs were $<10\%$ and $<15\%$,

respectively. The serum was collected from each patient as described above and added to each well of a microtitre plate and incubated for 2 h at 37°C. Each well was washed with the wash buffer provided by the manufacturer and incubated with 100 μl of enzyme-linked polyclonal antibodies for 2 h at 37°C. After four washes with the wash buffer provided by the manufacturer, the substrate solution provided by the manufacturer was added to each well. After incubation for 30 min at room temperature, the enzyme reaction was stopped by adding the stop buffer provided by the manufacturer and the intensity of each well was measured at 450 nm in a microplate reader (Bio-Rad, Hercules, CA, USA). The experiment was repeated in duplicate and the mean value used for statistical analysis.

Statistical analyses

All statistical analyses were performed using the SPSS® statistical package, version 17.0 (SPSS Inc., Chicago, IL, USA) for Windows®. Data are presented as mean ± SD unless otherwise indicated. Student's *t*-test was used to compare data between groups. Multivariate linear regression analysis was employed to determine the predictive value of quantitative parameters. A *P*-value < 0.05 was considered statistically significant.

Results

A total of 120 patients with CRF were enrolled in the study and were divided into two groups: group 1 (CRF with ESS) consisted of 60 patients with low FT3 levels (< 2.3 pg/ml) (40 males, 20 females; mean ± SD age 62.0 ± 12.4 years); and group 2 (CRF without ESS) consisted of 60 patients with normal FT3 levels (2.3–4.2 pg/ml) (43 males, 17 females; mean ± SD age 61.0 ± 12.0 years). Group 3 (control group) consisted of 60 healthy volunteers (25 males, 35 females; mean ± SD age 70.0 ± 6.1 years). The demographic and clinical characteristics of the study participants are presented in Table 1. There were no significant differences in age and sex distribution between groups 1 and 2. As a result of the 'rolling' method of recruitment of the healthy volunteers to group 3, there was a significant difference in the sex distribution and age between the patients in groups 1 and 2 and the control group ($P < 0.05$ for all comparisons). There were no significant differences between the three groups with regard to the basic vital signs, white blood cell count, FT4 and TSH.

The mean ± SD concentration of serum DIO-1 in group 2 was significantly higher than in group 1 (2.3 ± 0.2 ng/ml versus 1.4 ± 0.1 ng/ml, respectively; $P < 0.001$) and Group 3 (2.3 ± 0.2 ng/ml versus 1.3 ± 0.3 ng/ml, respectively; $P < 0.001$) (Figure 1). There was no significant difference in the concentration of DIO-1 between groups 1 and 3.

The mean ± SD concentration of serum IL-1β was significantly higher in groups 1 and 2 compared with the control group 3 ($P < 0.001$ and $P = 0.02$, respectively) (Figure 2). There was no significant difference in the concentration of IL-1β between groups 1 and 2. The mean ± SD concentration of serum TNF-α was significantly higher in groups 1 and 2 compared with the control group 3 ($P < 0.001$ and $P = 0.046$, respectively) (Figure 3). There was no significant difference in the concentration of TNF-α between groups 1 and 2. There were no significant differences between the three groups in terms of the mean ± SD concentration of serum IL-6 (Figure 4).

The mean ± SD concentration of serum 8-isoprostane was significantly higher in groups 1 and 2 compared with the control group 3 ($P < 0.01$ and $P < 0.05$, respectively) (Figure 5). There was no significant difference in the concentration of 8-isoprostane between groups 1 and 2.

Table 1. Demographic and clinical characteristics of two groups of patients with chronic renal failure (CRF) with and without euthyroid sick syndrome (ESS) and healthy control subjects.

Characteristic	Group 1 with ESS $n = 60$	Group 2 without ESS $n = 60$	Group 3 $n = 60$
Age, years	62.0 ± 12.4*	61.0 ± 12.0*	70.0 ± 6.1
Sex, male/female	40/20*	43/17*	25/35
Systolic blood pressure, mmHg	146.0 ± 22.5	143.4 ± 17.9	141.5 ± 17.6
Diastolic blood pressure, mmHg	78.6 ± 12.4	80.7 ± 11.6	77.0 ± 10.6
Heart rate, beats/min	79.4 ± 8.5	80.5 ± 7.4	79.3 ± 10.1
Respiratory, breaths/min	19.4 ± 0.8	19.3 ± 0.8	19.1 ± 1.2
Body mass index, kg/m^2	22.7± 2.0	23.3 ± 2.1	23.1 ± 3.2
TC, mmol/l	3.9 ± 1.3*	4.1 ± 1.1*	4.7 ± 1.0
Hb, g/l	77.8 ± 20.2*	87.4 ± 18.4*	131.9 ± 9.8
ALB, g/l	32.3 ± 4.5*†	34.9 ± 4.3*	46.8 ± 3.4
FBG, mmol/l	5.8 ± 2.4*	5.7 ± 1.6*	4.9 ± 1.1
CRE, μmol/l	657.8 ± 221.3*	643.8±161.5*	80.8± 10.5
WBC, 10^9/l	6.6 ± 3.0	6.4 ± 2.4	6.4 ± 1.1
Urea, mmol/l	19.0 ± 7.9*	18.9 ± 7.1*	5.6 ± 1.3
UA, μmol/l	443.2 ± 151.9*	452.2 ± 146.3*	288.6 ± 69.5
FT3, pg/ml	1.8 ± 0.4*†	2.6 ± 0.6*	3.4 ± 0.5
FT4, ng/dl	1.0 ± 0.3	1.1 ± 0.3	1.1 ± 0.2
TSH, μIU/l	3.2 ± 2.0	3.8 ± 1.5	2.3 ± 1.0

Data presented as mean ± SD or patient number.
Group 1, CRF patients with low free triiodothyronine levels; Group 2, CRF patients with normal triiodothyronine levels; Group 3, healthy control group.
*$P < 0.05$ group 1 or group 2 versus group 3; †$P < 0.05$ group 1 versus group 2; Student's t-test.
TC, total cholesterol; Hb, haemoglobin; ALB, albumin; FBG, fasting blood glucose; CRE, creatinine; WBC, white blood cell; UA, uric acid; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone.

Multivariate linear regression analysis demonstrated that the serum DIO-1 concentration was inversely correlated with TNF-α ($P < 0.001$), positively correlated with creatinine ($P < 0.0001$) and FT3 concentrations ($P < 0.0001$) (Table 2). There were no significant correlations between the concentrations of DIO-1, IL-1β and IL-6. Multivariate linear regression analysis demonstrated that serum 8-isoprostane concentration was not correlated with FT3 levels or DIO-1 concentration (Table 3).

Discussion

Chronic renal failure is a condition where there is a loss of kidney function over a period of months or years. It can be diagnosed by measuring serum creatinine levels, which are a degradative product of muscle protein. Creatinine levels are indicative of the glomerular filtration rate (GFR) and in CRF, the concentration of serum creatinine is increased, which indicates a lowered GFR.[15] There are five stages of CRF based on the GFR, with stage 5 (GFR < 15 ml/min/1.73m^2) also being known as end stage renal disease (ESRD).[16] CRF is a specifically severe clinical problem that has a significant socioeconomic impact worldwide.[17] The inflammatory response and oxidative stress are viewed as critical pathogenic factors in the initiation, development and progression of most renal diseases.[18–20]

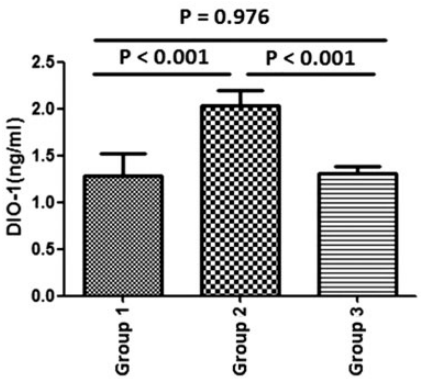

Figure 1. Serum type I deiodinase (DIO-1) concentrations in the two groups of patients with chronic renal failure (CRF) with and without euthyroid sick syndrome and healthy control subjects. Data presented as mean ± SD and compared using Student's *t*-test. Group 1, CRF patients with low free triiodothyronine levels; Group 2, CRF patients with normal triiodothyronine levels; Group 3, healthy control group.

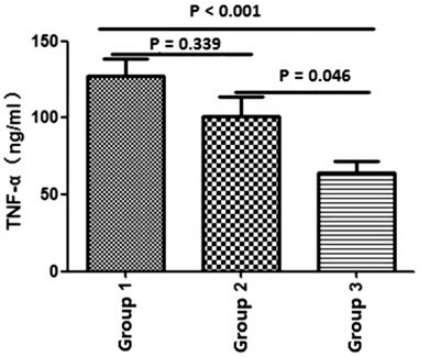

Figure 3. Serum tumour necrosis factor (TNF)-α concentrations in the two groups of patients with chronic renal failure (CRF) with and without euthyroid sick syndrome and healthy control subjects. Data presented as mean ± SD and compared using Student's *t*-test. Group 1, CRF patients with low free triiodothyronine levels; Group 2, CRF patients with normal triiodothyronine levels; Group 3, healthy control group.

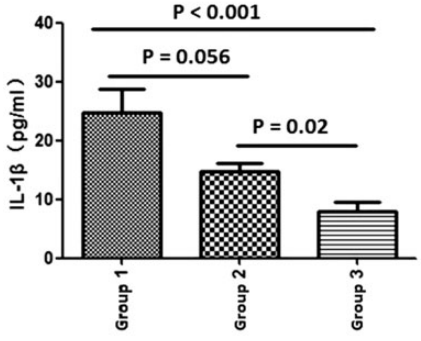

Figure 2. Serum interleukin (IL)-1β concentrations in the two groups of patients with chronic renal failure (CRF) with and without euthyroid sick syndrome and healthy control subjects. Data presented as mean ± SD and compared using Student's *t*-test. Group 1, CRF patients with low free triiodothyronine levels; Group 2, CRF patients with normal triiodothyronine levels; Group 3, healthy control group.

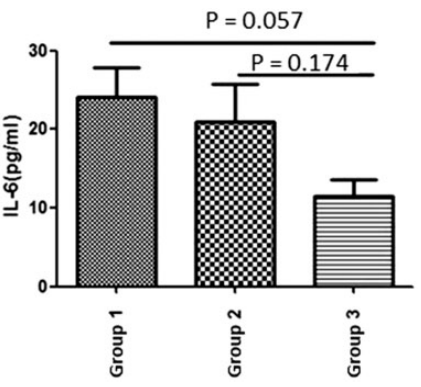

Figure 4. Serum interleukin (IL)-6 concentrations in the two groups of patients with chronic renal failure (CRF) with and without euthyroid sick syndrome and healthy control subjects. Data presented as mean ± SD and compared using Student's *t*-test. Group 1, CRF patients with low free triiodothyronine levels; Group 2, CRF patients with normal triiodothyronine levels; Group 3, healthy control group.

Thyroid dysfunction, such as ESS, occurs frequently in patients with CRF.[21,22] Whether the thyroid hormone abnormalities found in ESS patients are a physiological adaptation or a pathological change remains the subject of considerable debate. Until now, there has been little research that discusses the relationship

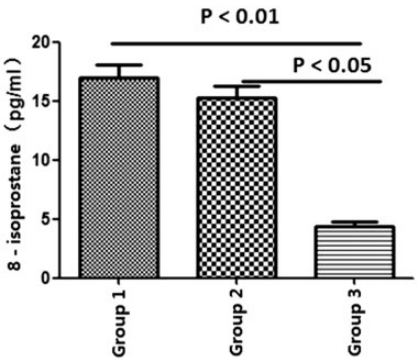

Figure 5. Serum 8-isoprostane concentrations in the two groups of patients with chronic renal failure (CRF) with and without euthyroid sick syndrome and healthy control subjects. Data presented as mean ± SD and compared using Student's *t*-test. Group 1, CRF patients with low free triiodothyronine levels; Group 2, CRF patients with normal triiodothyronine levels; Group 3, healthy control group.

between inflammatory factors, oxidative stress, plasma FT3 levels and DIO-1 concentration in patients with CRF.

The two groups of patients and the control group in this current study were considered comparable as there were no significant differences in their basic vital signs, white blood cell count, FT4 and TSH concentrations, despite there being significant differences in age and sex distribution due to the manner in which the healthy volunteers were recruited to the control group.

This current study found that the serum concentration of DIO-1 in patients with CRF without ESS was significantly higher than in patients with CRF with ESS and healthy control subjects. Changes in deiodinase expression have been postulated to play an important role in the altered

Table 2. Multivariate linear regression analysis of factors associated with the concentration of serum type I deiodinase (DIO-1) levels in patients with chronic renal failure with and without euthyroid sick syndrome ($n = 120$).

Model	B	SE	Beta coefficient	*t*	Statistical significance
Constant	−2.740	2.371		−1.156	NS
CRE	0.002	0.001	0.083	1.026	$P < 0.0001$
FT3	0.722	0.398	0.125	3.664	$P < 0.0001$
TNF-α	−0.01	0.003	−0.609	−3.356	$P < 0.001$

Dependent variable: DIO-1, $R^2 = 0.481$.
CRE, creatinine; FT3, free triiodothyronine; TNF-α, tumour necrosis factor-α; NS, not statistically significant ($P \geq 0.05$).

Table 3. Multivariate linear regression analysis of factors associated with the concentration of serum 8-isoprostane levels in patients with chronic renal failure with and without euthyroid sick syndrome ($n = 120$).

Model	B	SE	Beta coefficient	*t*	Statistical significance
Constant	13.484	10.713		1.259	NS
DIO-1	−0.576	0.358	−0.089	−1.608	NS
FT3	−0.975	0.946	−0.089	−1.031	NS
IL-1β	0.109	0.033	0.265	3.261	$P < 0.001$
TNF-α	0.042	0.013	0.41	3.154	$P = 0.002$

Dependent variable: 8-isoprostane, $R^2 = 0.413$.
DIO-1, type I deiodinase; CRE, creatinine; FT3, free triiodothyronine; IL-1β, interleukin-1β; TNF-α, tumour necrosis factor-α; NS, not statistically significant ($P \geq 0.05$).

circulating levels of thyroid hormones in ESS,[14,23] and low T3 syndrome is due to the inhibition of 5'-deiodinase.[23,24] DIO-1 is predominantly expressed in liver, kidney and thyroid and contributes to the FT3 production in euthyroid.[25,26] Previous research showed that DIO-1 catalysed the production of FT3 from T4 and inhibits the production of rT3.[27] Therefore, these current findings suggest that the reason why the patients with CRF without ESS can maintain normal concentrations of FT3 is due to the increased concentration of DIO-1. Further research is necessary to investigate the mechanism that triggers DIO-1 expression in patients with CRF without ESS. Research is also needed to investigate whether the thyroid hormone abnormalities found in patients with ESS are also the pathological changes observed in patients with CRF.

In recent years, several studies have shown an increase of inflammatory factors in patients with CRF and the levels of inflammatory factors are increased with the progression of renal failure.[28–30] Consistent with previous studies,[31,32] this current study found that the concentrations of serum IL-1β and TNF-α in patients with CRF were significantly higher compared with the healthy control subjects. Multivariate linear regression analysis demonstrated that the serum DIO-1 concentration was inversely correlated with the concentration of TNF-α and positively correlated with the concentrations of serum creatinine and FT3. Several investigators have reported that TNF-α plays an important role in the progression of CRF.[33,34] Furthermore, TNF-α is one of the most potent pro-inflammatory cytokines that is increased in the malnutrition, inflammation and atherosclerosis syndrome observed in patients with CRF.[35] As previously stated, this current study found that the serum DIO-1 concentration was inversely correlated with the concentration of TNF-α, which suggests that DIO-1 might inhibit the production of serum TNF-α. Future research is needed to investigate the mechanism by which DIO-1 could inhibit the production of TNF-α.

Some studies have shown that oxidative stress decreases the activity of deiodinase and oxidative stress was implicated as the key player in altering the levels of thyroid hormone in ESS.[36,37] In this current study, serum levels of 8-isoprostane, a marker of oxidative stress, was measured in patients with CRF with and without ESS. The concentration of serum 8-isoprostane was significantly higher in patients with CRF compared with the healthy control group. These current findings were consistent with previous research that showed that the progression of chronic kidney disease to advanced stages was associated with a significant increase in the generation of reactive oxygen species.[38] However, there was no significant difference in the serum 8-isoprostane levels between the CRF patients with ESS and without ESS in the current study, which suggests that ESS was not correlated with oxidative stress. The current study also found that the serum DIO-1 concentration was not associated with the serum 8-isoprostane concentration, which suggests that oxidative stress was not the reason for the elevated DIO-1 concentration.

In conclusion, patients with CRF showed an elevated inflammatory response and oxidative stress. Patients with CRF without ESS demonstrated a higher concentration of DIO-1 than patients with ESS and the concentration of DIO-1 was inversely correlated with the concentration of TNF-α, which might indicate that the inflammatory response was milder in patients with CRF without ESS than in those with ESS.

Declaration of conflicting interests

The authors declare that there are no conflicts of interest.

Funding

This research was supported by a grant from the Nanchang Science and Technology Bureau for the Promotion of Science (no. 2014SFZC009) and a grant from the Jiangxi Provincial Education Bureau for the Research of Science and Technology (no. GJJ151472).

ORCID iD

Shu-Lan Qin http://orcid.org/0000-0002-4987-2833

References

1. Qiu Z, Zheng K, Zhang H, et al. Physical exercise and patients with chronic renal failure: a meta-analysis. *Biomed Res Int* 2017; 2017: 7191826.
2. Liu ME, Qiu NC, Zha SL, et al. To assess the effects of parathyroidectomy (TPTX versus TPTX+AT) for Secondary Hyperparathyroidism in chronic renal failure: a systematic review and meta-analysis. *Int J Surg* 2017; 44: 353–362.
3. Pinto AR, da Silva NC and Pinato L. Analyses of melatonin, cytokines, and sleep in chronic renal failure. *Sleep Breath* 2016; 20: 339–344.
4. Lai J, Akindavyi G, Fu Q, et al. Research progress on the relationship between coronary artery calcification and chronic renal failure. *Chin Med J (Engl)* 2018; 131: 608–614.
5. Adler SM and Wartofsky L. The nonthyroidal illness syndrome. *Endocrinol Metab Clin North Am* 2007; 11: 657–672.
6. Rhee CM, Kalantar-Zadeh K, Streja E, et al. The relationship between thyroid function and estimated glomerular filtration rate in patients with chronic kidney disease. *Nephrol Dial Transplant* 2015; 30: 282–287
7. Tbahriti HF, Messaoudi A, Kaddous A, et al. The degree of chronic renal failure is associated with the rate of pro-inflammatory cytokines, hyperhomocysteinemia and with oxidative stress. *Ann Cardiol Angeiol (Paris)* 2014; 63: 135–139 [in French, English abstract].
8. Aziz MA, Majeed GH, Diab KS, et al. The association of oxidant-antioxidant status in patients with chronic renal failure. *Ren Fail* 2016; 38: 20–26.
9. Nomani H, Hagh-Nazari L, Aidy A, et al. Association between GSTM1, GSTT1, and GSTP1 variants and the risk of end stage renal disease. *Ren Fail* 2016; 38: 1455–1461.
10. Boelen A, Kwakkel J and Fliers E. Beyond low plasma T3: local thyroid hormone metabolism during inflammation and infection. *Endocr Rev* 2011; 32: 670–693.
11. Boonen E and Van den Berghe G. Endocrine responses to critical illness: novel insights and therapeutic implications. *J Clin Endocrinol Metab* 2014; 99: 1569–1582.
12. Peeters RP, Wouters PJ, Kaptein E, et al. Reduced activation and increased inactivation of thyroid hormone in tissues of critically ill patients. *J Clin Endocrinol Metab* 2003; 88: 3202–3211.
13. Bianco AC, Salvatore D, Gereben B, et al. Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodinases. *Endocr Rev* 2002; 23: 38–89.
14. Saito O, Saito T, Ueno K. et al. Comparison between serum free triiodothyronine levels and body fluid distribution in hemodialysis patients. *Clin Exp Nephrol* 2012; 16: 952–958.
15. Patel SS, Kimmel PL and Singh A. New clinical practice guidelines for chronic kidney disease: a framework for K/DOQI. *Semin Nephrol* 2002; 22: 449–458.
16. Inker LA, Astor BC, Fox CH, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis* 2014; 63: 713–735.
17. Hallan SI, Matsushita K, Sang Y, et al. Age and association of kidney measures with mortality and end-stage renal disease. *JAMA* 2012; 308: 2349–2360.

18. Zhong J, Yang HC and Fogo AB. A perspective on chronic kidney disease progression. *Am J Physiol Renal Physiol* 2017; 312: F375–F384.
19. Long Y and Nie J: Homocysteine in renal injury. *Kidney Dis (Basel)* 2016; 2: 80–87.
20. Gorin Y. The kidney: an organ in the front line of oxidative stress-associated pathologies. *Antioxid Redox Signal* 2016; 25: 639–641.
21. Zocalli C, Mallamaci F, Tripepi G, et al. Low triiodothyronine and survival in end-stage renal disease. *Kidney Int* 2006; 70: 523–528.
22. Enia G, Panuccio V, Cutrupi S, et al. Subclinical hypothyroidism is linked to micro-inflammation and predicts death in continuous ambulatory peritoneal dialysis. *Nephrol Dial Transplant* 2007; 22: 538–544.
23. Debaveye Y, Ellger B, Mebis L, et al. Regulation of tissue iodothyronine deiodinase activity in a model of prolonged critical illness. *Thyroid* 2008; 18: 551–560.
24. Kwakkel J, van Beeren HC, Ackermans MT, et al. Skeletal muscle deiodinase type 2 regulation during illness in mice. *J Endocrinol* 2009; 203: 263–270.
25. Liao XH, Di Cosmo C, Dumitrescu AM, et al. Distinct roles of deiodinases on the phenotype of Mct8 defect: a comparison of eight different mouse genotypes. *Endocrinology* 2011; 152: 1180–1191.
26. Wirth EK, Rijntjes E, Meyer F, et al. High T3, Low T4 Serum Levels in Mct8 Deficiency Are Not Caused by Increased Hepatic Conversion through Type I Deiodinase. *Eur Thyroid J* 2015; 4: 87–91.
27. Burman KD and Wartofsky L. Thyroid function in the intensive care unit setting. *Crit Care Clin* 2001; 17: 43–57.
28. Tbahriti HF, Meknassi D, Moussaoui R, et al. Inflammatory status in chronic renal failure: the role of homocysteinemia and pro-inflammatory cytokines. *World J Nephrol* 2013; 2: 31–37.
29. Yamashiro S, Kamohara H, Wang JM, et al. Phenotypic and functional change of cytokine-activated neutrophils: inflammatory neutrophils are heterogeneous and enhance adaptive immune responses. *J Leukoc Biol* 2001; 69: 698–704.
30. Malaponte G, Libra M, Bevelacqua Y, et al. Inflammatory status in patients with chronic renal failure: the role of PTX3 and pro-inflammatory cytokines. *Int J Mol Med* 2007; 20: 471–481.
31. Koriakova NN, Rozhdestvenskaia ED, Kazantseva SV, et al. Features of a cytokine profile in patients with chronic glomerulonephritis with progressive chronic renal failure. *Ter Arkh* 2006; 78: 14–17 [in Russian, English abstract].
32. Maksic D, Vasilijic S, Colic M, et al. Systemic and intraperitoneal proinflammatory cytokine profiles in patients on continuous ambulatory peritoneal dialysis. *Adv Perit Dial* 2009; 25: 50–55.
33. Sankaran D, Asderakis A, Ashraf S, et al. Cytokine gene polymorphisms predict acute graft rejection following renal transplantation. *Kidney Int* 1999; 56: 281–288.
34. Almroth G, Lönn J, Uhlin F, et al. Sclerostin, TNF-alpha and Interleukin-18 correlate and are together with klotho related to other growth factors and cytokines in haemodialysis patients. *Scand J Immunol* 2016; 83: 58–63.
35. Stenvinkel P, Heimbürger O, Lindholm B, et al. Are there two types of malnutrition in chronic renal failure? Evidence for relationships between malnutrition, inflammation and atherosclerosis (MIA syndrome). *Nephrol Dial Transplant* 2000; 15: 953–960.
36. Selvaraj N, Bobby Z and Sridhar MG. Is euthyroid sick syndrome a defensive mechanism against oxidative stress? *Med Hypotheses* 2008; 71: 404–405.
37. Singh PA, Bobby Z, Selvaraj N, et al. An evaluation of thyroid hormone status and oxidative stress in undialyzed chronic renal failure patients. *Indian J Physiol Pharmacol* 2006; 50: 279–284.
38. Modaresi A, Nafar M and Sahraei Z. Oxidative stress in chronic kidney disease. *Iran J Kidney Dis* 2015; 9: 165–179.