

Thyroid Function Disorders in Patients with Chronic Kidney Disease

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Abstract

Background: Various thyroid functional test abnormalities are commonly observed in chronic kidney disease (CKD) due to alterations in thyroid hormone synthesis, metabolism, and regulation. **Objectives:** The study aims at investigating the prevalence of thyroid function disorders in patients with CKD and its association with the degree of renal failure. **Methods:** A cross-sectional study was performed on patients with CKD, at the Nephrology unit, Hawler Teaching Hospital, Erbil, Iraq from 1 July 2020 to 31 December 2020. Demographic features such as age, sex, and body mass index (BMI) were recorded; blood tests were done, including serum-free triiodothyronine (FT3), free thyroxine (FT4), thyrotropin (TSH), and creatinine. The CKD-EPI (epidemiological) equation was used to estimate glomerular filtration rate (eGFR). The participants were classified according to their thyroid function, age, BMI, and eGFR. The association of thyroid dysfunction with gender, age, BMI, and eGFR was studied. **Results:** A total of 104 patients with CKD enrolled in the current study: Half of them were on conservative treatment, and the other half were on a chronic hemodialysis (HD) program. Fifty four (51.9%) of them were male, mean age was 53.99 ± 14.59 years, mean BMI was $25.19 \pm 3.14 \text{ kg/m}^2$, and most of them (63.5%) were overweight. According to eGFR classification, most of the participants (70.2%) were at stage 5 CKD, 20.2% at stage 4, and 9.6% at stage 3. From the study population, it was observed that 34 out of 104 (32.7%) participants presented with thyroid function disorders. Among them, 22 (21.2%) patients presented with subclinical hypothyroidism, seven (6.7%) had overt hypothyroidism, three (2.9%) hyperthyroidism, and two (1.9%) subclinical hyperthyroidism. Hypothyroidism (clinical and subclinical) was positively associated with increasing age and advanced CKD. **Conclusion:** Thyroid function disorders are common among patients with CKD. Hypothyroidism, the most prevalent one, was positively associated with increasing age, low eGFR, and in patients on HD therapy.

Keywords: Chronic kidney disease, eGFR, hemodialysis, hypothyroidism, thyroid dysfunction

INTRODUCTION

CKD represents a worldwide public health problem, with a global prevalence of 9.1%.^[1] It is defined as abnormalities of kidney structure or function present for more than three months, with implications for health.^[2] CKD increases the risk of all-cause mortality, cardiovascular disease, and progression to end-stage renal disease (ESRD).^[3] Thus, identifying the risk factors for CKD or a decrease in eGFR may help in understanding the mechanism of CKD and provide new strategies for its prevention.^[4]

Thyroid hormones play an important role in kidney development and physiology, through their actions on growth, renal blood flow, and maintenance of kidney homeostasis.^[5,6] Several lines of epidemiological evidence

and clinical trial data have investigated the effects of thyroid hormones on renal function decline.^[7] Thyroid dysfunctions have an important effect on renal function, as well as cardiovascular alterations.^[8] On the other hand, CKD can lead to changes in thyroid function, through non-thyroidal illness, metabolic acidosis, altered hormonal catabolism, diminished peripheral conversion, hormonal removal during HD therapy, and increased iodine store in the thyroid gland.^[9,10]

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Submission: 28-10-2021 **Accepted:** 19-11-2021 **Published:** 20-Apr-2022

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How to cite this article: Sinjari HY, Ibrahim JM. Thyroid function disorders in patients with chronic kidney disease. Med J Babylon 2022;19:76-80.

Access this article online

Quick Response Code:



Website:
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DOI:
10.4103/MJBL.MJBL_93_21

A growing body of cross-sectional studies have linked overt and subclinical hypothyroidism to a lower eGFR and an increased prevalence of CKD.^[7,11,12] Longitudinal studies have presented conflicting results, linking kidney function decline to low or high thyroid function.^[10,13] The coexistence of hypothyroidism and renal dysfunction in patients has prompted investigation into the effects of thyroid hormone replacement therapy on CKD.^[14] Interestingly, there is evidence that a reduction of the eGFR may be improved after thyroid hormone substitution therapy.^[6,15] However, most evidence regarding the association between thyroid and kidney function has been based on cross-sectional studies and included mostly patients with CKD or thyroid dysfunction.^[16] Due to the nature of the cross-sectional study and the conflicting results of prospective studies, the causality between TSH and eGFR should be further confirmed.^[1,6] The study aims at investigating the prevalence of thyroid function disorders in patients with CKD and its association with the degree of renal failure, as the identification of these patients could contribute to correct diagnosis and treatment.

PATIENTS AND METHODS

This cross-sectional study was conducted in the Nephrology unit in Hawler Teaching Hospital, Erbil, Iraq from July 1, 2020 to December 31, 2020. The study was approved by the scientific and ethical committee of the College of Medicine, HMU, in accordance with the Helsinki's declaration guideline for the involvement of humans in research. All participants gave their written and informed consent. A sample of patients with confirmed CKD defined on the basis of the National Kidney Foundation guidelines of having an eGFR $<60 \text{ mL/min/1.732 m}^2$ for more than three months^[2] were enrolled in this study, unless they met any of the following exclusion criteria: less than 18 years of age, those with known thyroid problems, a personal or family history of organ-specific autoimmune diseases such as insulin-dependent diabetes mellitus, seriously ill patients, and a history of intake of medications such as amiodarone and steroids. Out of the 114 patients who met the inclusion criteria, 104 enrolled in the study and the remaining dropped out because of their unwillingness or missing data. All participants underwent a detailed history and proper physical examination. For each participant, the following data were recorded: age, gender, BMI: kg/m^2 , duration of HD, and medication use during the treatment course. Regarding their age, the participants were divided into four groups as follows: 18–29, 30–49, 50–69, and 70–89 years. The patients were classified according to their BMI kg/m^2 into five groups as follows: underweight (BMI < 18.5), normal (18.5–24.9), overweight (25–29.9), obese (30–39.9), and morbid obese (≥ 40).^[17] The venous blood was drawn in the morning after an overnight fast for lab tests; serum creatinine was assayed on KENZA 450 TX/KENZA 450 ISE Automated Biochemistry Analyzer (France).^[18] GFR was

estimated by using the CKD Epidemiology Collaboration 2009 equation^[19] and reduced kidney function was defined as eGFR $<60 \text{ mL/min/1.73 m}^2$, corresponding to stage 3–5 CKD, stage 3 (30–59), stage 4 (15–29), and stage 5 (<15).^[2] Thyroid hormones were measured by using Vidas and mini Vidas from Biomerieux-France; mini Vidas is a compact automate immunoassay system based on the Enzyme-Linked Fluorescent Assay principles.^[18] Thyroid dysfunction was considered if patients' thyroid hormones fall outside the reference range: free T3 (FT3) (4.0–8.3 pmol/L), free T4 (FT4) (9.0–20.0 pmol/L), and thyrotropin (TSH) (0.25–5 mIU/L); overt hypothyroidism was defined as TSH $>5 \text{ mIU/L}$ and FT3 < 4.0 and FT4 $< 9.0 \text{ pmol/L}$; subclinical hypothyroidism was considered if TSH $>5 \text{ mIU/L}$ and FT3 and FT4 were within the reference range; subclinical hyperthyroidism was defined if TSH $<0.25 \text{ mIU/L}$ and FT3 and FT4 were within the reference range; and overt hyperthyroidism was considered if TSH $<0.25 \text{ mIU/L}$ and FT3 $> 8.3 \text{ pmol/L}$ and FT4 $> 20 \text{ pmol/L}$.^[20] Low T3 syndrome was defined as FT3 $< 4 \text{ pmol/L}$ and if TSH and FT4 were within the reference range.^[5]

Ethical approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients verbal and analytical approval before sample was taken. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee according to the document number 222 (including the number and the date in 25/3/2020) to get this approval.

Statistical analysis

Continuous variables were presented as mean and standard deviation (SD), and categorical variables were presented as frequency and percentage. One-way ANOVA test was used for continuous variables, and Chi-square test was used for categorical variables to compare proportions. Generated data were entered into MS excel and analyzed with the Statistical Package for Social Sciences version 24 (SPSS, IBM company, USA). A p value of <0.05 was considered significant.

RESULTS

A total of 104 patients (51.9% males and 48.1% females) with CKD enrolled in this study. Their mean age was 53.99 ± 14.59 years, mean BMI was $25.19 \pm 3.14 \text{ kg/m}^2$, and most of them (59.6%) were overweight. Half of the participants were on a chronic HD program with a mean duration of 4.7 ± 3.56 years, and the other half were on conservative treatment at a different stage of CKD. Most of the participants (70.2%) were at stage 5 of CKD and were either on HD or on conservative treatment. Among the study sample, 70 (67.3%) patients were euthyroid. Hypothyroidism (subclinical and overt) is the most common thyroid disorder

detected in 27.9% of participants. Low T3 syndrome (low FT3 with normal FT4 and TSH) was observed in 14.4% patients with CKD [Table 1].

The current study revealed a significant association between hypothyroidism and gender, as overt hypothyroidism (85.7%) was mainly detected in females, whereas subclinical hypothyroidism (68.2%) was mostly seen in males

($P = 0.032$). Participants with hypothyroidism were more likely to be older ($P = 0.002$), had a lower mean eGFR ($P = 0.023$), or were on HD treatment ($P = 0.002$). There was a nonsignificant association between TSH categories and BMI classifications ($P = 0.205$) [Table 2].

DISCUSSION

The patients with CKD may be at a higher risk for thyroid dysfunction via several mechanisms such as iodine retention, metabolic acidosis, mineral deficiency (e.g. selenium), protein losses, alterations in regulation of the hypothalamic-pituitary-thyroid axis, and changes in the metabolism, degradation, and excretion of thyroid hormones.^[6,8]

In the current study, our main target was to evaluate the prevalence of and risk factors for thyroid disease among patients with CKD, as many cases of thyroid dysfunction, particularly hypothyroidism, may remain latent or undiagnosed in advanced CKD due to symptom overlap with uremia (e.g. cold intolerance, fatigue, decreased cognition) and coexisting comorbidities.^[8] Further, there is evidence that exogenous thyroid hormone therapy may lead to a significant improvement in renal function in hypothyroid patients with CKD.^[15] Most of our patients were euthyroid (67.3%); however, subclinical and overt hypothyroidism is quite frequent among them, 21.2% and 6.7% respectively, which is much higher than that reported in the general population, 0.3% to 3.7%.^[21] Our findings cannot be attributed exclusively to CKD, as we have no data regarding their basic thyroid autoimmunity

Table 1: Characteristics of the study population

Characteristics	No./SD or %
Gender (M/F)	54/50
Age (years)	53.99 ± 14.59
BMI (kg/m ²)	25.19 ± 3.14
eGFR (mL/min/1.73m ²)	13.88 ± 11.55
Hemodialysis patients	52 (50%)
Patients with CKD on conservative treatment	52 (50%)
Hemodialysis duration (years)	4.7 ± 3.56
Creatinine (mg/dl)	5.92 ± 3.31
TSH (mIU/L)	3.76 ± 3.61
FT4 (pmol/L)	12.83 ± 3.22
FT3 (pmol/L)	5.35 ± 1.98
Subclinical hypothyroidism	22 (21.2%)
Overt hypothyroidism	7 (6.7%)
Overt hyperthyroidism	3 (2.9%)
Subclinical hyperthyroidism	2 (1.9%)
Low T3 syndrome (low FT3 alone)	15 (14.4%)

BMI = body mass index, TSH = thyrotropin, eGFR = estimated glomerular filtration rate

Table 2: Association between TSH categories and gender, BMI, eGFR, and CKD state

Variables	Normal	Subclinical hypothyroidism	Hypothyroidism	Hyperthyroidism	Subclinical hyperthyroidism	P Value
Gender						
Male	36 (51.4%)	15 (68.2%)	1 (14.3%)	1 (33.3%)	1 (50%)	0.032
Female	34 (48.6%)	7 (31.8%)	6 (85.7%)	2 (66.7%)	1 (50%)	
Age						
(18–29 years)	25 (35.7%)	2 (9.09%)	0 (0%)	0 (0%)	0 (0%)	0.002
(30–49 years)	20 (28.5%)	2 (9.09%)	0 (0%)	1 (33.3%)	1 (50%)	
(50–69 years)	15 (21.4%)	6 (27.2%)	3 (42.9%)	1 (33.3%)	1 (50%)	
(70–89 years)	10 (14.2%)	12 (54.5%)	4 (57.1%)	1 (33.3%)	0 (0%)	
BMI						
Underweight	0 (0%)	0 (0%)	0 (0%)	1 (33.3%)	0 (0%)	0.205
Normal	24 (34.3%)	5 (22.7%)	2 (28.6%)	1 (33.3%)	1 (50%)	
Overweight	44 (62.9%)	16 (72.7%)	2 (28.6%)	1 (33.3%)	1 (50%)	
Obese	2 (2.8%)	1 (4.6%)	3 (42.8%)	0 (0%)	0 (0%)	
CKD stage						
Stage 3	8 (11.4%)	1 (4.5%)	1 (14.3%)	1 (33.3%)	0 (0%)	0.023
Stage 4	18 (25.7%)	2 (9%)	1 (14.3%)	0 (0%)	0 (0%)	
Stage 5+ 5D*	44 (62.8%)	19 (86.3%)	5 (71.4%)	2 (66.7%)	2 (100%)	
CKD State						
Dialysis (5-D)	29 (41.4%)	15 (68.2%)	4 (57.1%)	2 (66.7%)	2 (100%)	0.002
Conservative	41 (58.6%)	7 (31.8%)	3 (42.9%)	1 (33.3%)	0 (0%)	
Total	70 (100%)	22 (100%)	7 (100%)	3 (100%)	2 (100%)	

*Including all patients with Stage 5 CKD, on conservative or on HD therapy

and iodine status; however, they are in concordance with the results shown by several cross-sectional and epidemiological studies, for instance a study performed in the United States on a large, nationally representative cohort of veterans with CKD by Rhee *et al.*,^[7] and an epidemiologic study that has largely been conducted within European-based cohorts,^[22] in addition to a large body of cross-sectional studies performed in different countries.^[18,23-25]

This study revealed an increasing trend for TSH levels and/ or risk of hypothyroidism across CKD stages 3–5, including those receiving HD therapy, with an inverse association with eGFR. This finding clearly indicates that more severe CKD will be associated with more complications, including thyroid disorders, which was consistent with the results demonstrated by many epidemiological and cross-sectional studies.^[7,22,25-27] In the largest U.S.-based study, Lo *et al.*^[6] observed a high prevalence of hypothyroidism with incrementally lower categories of eGFR among the Third National Health and Nutrition Examination Survey.

Our data revealed a female predominance of overt hypothyroidism, with similar results reported in the literature.^[24,27] However, subclinical hypothyroidism was more prevalent among male patients. Such an association was not observed in a number of studies,^[18,25,28] which may reflect that hypothyroidism is derived from CKD rather than due to gender differences.

Our observation, as expected, that hypothyroid patients tended to be older, is in agreement with previous reports, including a large observational study conducted on U.S. veterans.^[7] However, this is not the rule, as some studies revealed no age-related changes in TSH.^[18,25]

The present study showed no increase in the prevalence of hypothyroidism among participants with higher BMI, in disagreement with a study by Cotoi *et al.*,^[27] who reported that an increase of BMI raises the risk of developing thyroid disease. Our relatively small size sample may not be enough to demonstrate such an association.

In the current study, overt and subclinical hyperthyroidism was found in 2.9% and 1.9% patients with CKD, similar to previous studies.^[18,27] The prevalence of hyperthyroidism in patients with CKD is similar as in the case of the general population; thus, CKD is not directly associated with hyperthyroidism.^[10]

Low FT3 level (in euthyroid patients) is the most frequently observed biochemical thyroid alteration in CKD^[5] that is related to a higher risk of cardiovascular disease and all-cause mortality^[12] caused by the diminished peripheral deiodination of T4-to-T3, and it is associated with chronic metabolic acidosis, non-thyroidal illness, malnutrition, and inflammatory markers.^[10,12] However, our data exhibited low T3 syndrome in 15% of participants, and this was

lower than most, but not all, previous reports,^[5,10,25,27] which could be due to our exclusion of seriously ill patients.

Study limitations

There are many factors that may lead to thyroid dysfunction had not been studied like; first, the prevalence of thyroid autoimmunity status in the study population. Second, the iodine status of the participants, as excess iodine nutrition or iodine deficiency in our region may contribute to thyroid disorders. Third, patients with non-thyroidal illness were not identified.

CONCLUSION

Thyroid function disorders are common among patients with CKD. Hypothyroidism, the most prevalent one, was positively associated with increasing age, low eGFR, and in patients on HD therapy. We recommend regular checkups of thyroid function profile in the case of patients with CKD, as the early identification of thyroid disorders would help in better management of these patients.

Acknowledgment

The authors would like to thank the staff of the Nephrology unit and the laboratory for their unreserved support and also the patients who participated in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

None.

Author contributions

All the authors were involved in drafting the article, data collection, statistical analysis, article writing, and critical review. All the authors approved the final version of the article to be submitted for publication.

REFERENCES

1. GBD Chronic Kidney Collaboration. Global, regional, and national burden of chronic kidney disease, 1990–2017: A systemic analysis for the Global Burden of Disease study 2017. *Lancet* 2020;395:709-33.
2. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation and treatment of CKD-MBD. *Kidney Int Suppl* 2017;7:1-59.
3. Afsar B, Yilmaz MI, Siriopol D, Unal HU, Saglam M, Karaman M, *et al.* Thyroid function and cardiovascular events in chronic kidney disease patients. *J Nephrol* 2017;30:235-42.
4. Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, *et al.*; American Thyroid Association Task Force on Thyroid Hormone Replacement. Guidelines for the treatment of hypothyroidism: Prepared by the American Thyroid Association task force on thyroid hormone replacement. *Thyroid* 2014;24:1670-751.
5. Basu G, Mohapatra A. Interactions between thyroid disorders and kidney disease. *Indian J Endocrinol Metab* 2012;16:204-13.

6. Rhee CM. The interaction between thyroid and kidney disease: An overview of the evidence. *Curr Opin Endocrinol Diabetes Obes* 2016;23:407-15.
7. Rhee CM, Kalantar-Zadeh K, Streja E, Carrero JJ, Ma JZ, Lu JL, *et al.* The relationship between thyroid function and estimated glomerular filtration rate in patients with chronic kidney disease. *Nephrol Dial Transplant* 2015;30:282-7.
8. Rhee CM, Brent GA, Kovesdy CP, Soldin OP, Nguyen D, Budoff MJ, *et al.* Thyroid functional disease: An under-recognized cardiovascular risk factor in kidney disease patients. *Nephrol Dial Transplant* 2015;30:724-37.
9. Farag, SES. Functional and morphological thyroid disorders in hemodialysis patient. *J Thyroid Disord Ther* 2013;2:2-5.
10. Mohamedali M, Reddy Maddika S, Vyas A, Iyer V, Cheriya P. Thyroid disorders and chronic kidney disease. *Int J Nephrol* 2018; 2014:1-6.
11. Piexoto EJF, Bittencourt MS, Goulart AS, Santos IS, Oliveira SM, Ladeira RM, *et al.* Thyrotropin levels are associated with chronic kidney disease among healthy subjects in cross-sectional analysis of the Brazilian Longitudinal study of adult health. *Clinic Exper Neph* 2017;21:1035-43.
12. Iglesias P, Bajo MA, Selgas R, Díez JJ. Thyroid dysfunction and kidney disease: An update. *Rev Endocr Metab Disord* 2017;18:131-44.
13. Zhang Y, Chang Y, Ryu S, Cho J, Lee WY, Rhee EJ, *et al.* Thyroid hormone levels and incident chronic kidney disease in euthyroid individuals: The Kangbuk Samsung health study. *Int J Epidemiol* 2014;43:1624-32.
14. Remarks about the Study on Evaluation of Thyroid Hormone Levels in Chronic Kidney Disease Patients; 2018. Available from: <https://search.proquest.com/openview/pq-ogscholar@cbl=2035639>. [Last accessed on].
15. Shin DH, Lee MJ, Lee HS, Oh HJ, Ko KI, Kim CH, *et al.* Thyroid hormone replacement therapy attenuates the decline of renal function in chronic kidney disease patients with subclinical hypothyroidism. *Thyroid* 2013;23:654-61.
16. Chaker L, Sedaghat S, Hoorn EJ, Elzen WP, Gussekloo J, Hofman A, *et al.* The association of thyroid function and the risk of kidney function decline: A population-based cohort study. *Eur J Endocrinol* 2016;175:653-60.
17. Weir CB, Jan A. BMI Classification Percentile and Cut Off Points. Treasure Island, FL: StatPearls Publishing; 2021.
18. Khatawada S, Rajendra KC, Gautam S, Lamsal M, Baral N. Thyroid dysfunction and dyslipidemia in chronic kidney disease patients. *BMC Endocr Disord* 2015;15:65.
19. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, *et al.*; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150:604-12.
20. John PW. Managing thyroid disease in general practice. *Med J Aust* 2016;205:179-84.
21. Taylor PN, Albrecht D, Scholz A, Gutierrez-Buey G, Lazarus JH, Dayan CM, *et al.* Global epidemiology of hyperthyroidism and hypothyroidism. *Nat Rev Endocrinol* 2018;14:301-16.
22. Asvold BO, Bjørø T, Vatten LJ. Association of thyroid function with estimated glomerular filtration rate in a population-based study: The HUNT study. *Eur J Endocrinol* 2011;164:101-5.
23. Allawi AA. Prevalence of hypothyroidism in chronic kidney disease among sample of Iraqi patients. *J Fac Med* 2013;55:97-101.
24. Pakfetrat M, Dabbaghmanesh MH, Karimi Z, Rasekhi A, Malekmakan L, Hossein Nikoo M. Prevalence of hypothyroidism and thyroid nodule in chronic hemodialysis Iranian patients. *Hemodial Int* 2017;21:84-9.
25. Yuasa R, Ohashi Y, Saito A, Tsuboi K, Shishido S, Sakai K. Prevalence of hypothyroidism in Japanese chronic kidney disease patients. *Ren Fail* 2020;42:572-9.
26. Rhee CM, You AS, Nguyen DV, Brunelli SM, Budoff MJ, Streja E, *et al.* Thyroid status and mortality in a prospective hemodialysis cohort. *J Clin Endocrinol Metab* 2017;102:1568-77.
27. Cotoi L, Borcan F, Sporea I, Amzar D, Schiller O, Schiller A, *et al.* Thyroid pathology in end-stage renal disease patients on hemodialysis. *Diagnostics*. 2020;10:245.
28. Bashkin A, Abu Saleh W, Shehadeh M, Even L, Ronen O. Subclinical hypothyroidism or isolated high TSH in hospitalized patients with chronic heart-failure and chronic renal-failure. *Sci Rep* 2021;11:10976.