Correlation of Thyroid Hormone Profile with Biochemical Markers of Renal Function in Patients with Undialyzed Chronic Kidney Disease

Swati Srivastava, Jitendra Rajput, Mayank Shrivastava, Ramesh Chandra, Mayank Gupta, Raman Sharma
Department of Medicine, SMS Medical College, Jaipur, Rajasthan, India

Abstract

Objective: The present study was conducted to evaluate the correlation of renal functions with thyroid hormone levels in patients with undialyzed chronic kidney disease (CKD). Literature shows significant alteration in thyroid hormone function tests in CKD patients who are receiving long-standing dialysis treatment. However, not much is described in those receiving conservative management without dialysis. Although CKD is associated with an increased prevalence of primary hypothyroidism, various studies on thyroid hormone status in uremic patients have reported conflicting results. Methodology: Thyroid hormone levels and biochemical markers of renal function were estimated in 30 undialyzed CKD patients and similar number of age- and sex-matched healthy controls, followed by statistical analysis and correlation. Results: Free triiodothyronine (FT3) and free thyroxine (FT4) were found to be significantly reduced ($P < 0.001$ for each) in undialyzed CKD patients whereas thyroid-stimulating hormone (TSH) levels showed statistically insignificant alteration in both groups. We also observed that urea and creatinine were negatively correlated whereas creatinine clearance was positively correlated with both FT3 and FT4 having high statistical (two tailed) significance with $P < 0.001$. Nonsignificant correlation was seen between blood urea and TSH ($r = 0.236, P = 0.069$), creatinine clearance, and TSH ($r = 0.206, P = 0.114$ Pearson’s correlation coefficient). There is just significant positive correlation between the serum creatinine values and TSH ($r = 0.248, P = 0.049$). Conclusions: Thyroid hormones were significantly decreased in undialyzed CKD patients as compared to healthy controls.

Keywords: Chronic kidney disease, renal function tests, thyroid hormones

INTRODUCTION

Thyroid hormones and renal functions have a multifaceted mutual interdependence. Thyroid hormones exert influence on water and electrolyte milieu in our body. Renal growth involves thyroid hormones making their contribution to renal physiology important. Decrease in iodothyronines is associated with reduced blood flow to kidneys and decreased glomerular filtration rate (GFR) along with alteration in tubular reabsorption resulting in decrease in water excretion. Conversely, thyrotoxicosis is found to cause polyuria following enhanced glomerular filtration and tubular reabsorption.

At the same time, kidneys not only contribute significantly to metabolism and removal of thyroid hormones from the body but also play important role in certain actions of these hormones. Therefore, the decline of kidney function is accompanied by changes in thyroid hormone levels.

The prevalence of subclinical hypothyroidism increases consistently with decline in GFR.

Renal disease, both acute and chronic, has been found to be associated with significant effects on the hypothalamus-pituitary-thyroid axis. Thyroid-stimulating hormone (TSH) levels may be normal or increased in chronic kidney disease (CKD) but with reduced response to thyrotropin releasing hormone (TRH). There is alteration in circadian rhythm and activity, suggesting abnormality at the level of hypophyses.

Address for correspondence: Dr. Swati Srivastava, A-1/76, Chitrakoot Scheme, Near Vaishali Nagar, Jaipur - 302 021, Rajasthan, India.
E-mail: swt_srivastava@yahoo.co.in

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Srivastava S, Rajput J, Shrivastava M, Chandra R, Gupta M, Sharma R. Correlation of thyroid hormone profile with biochemical markers of renal function in patients with undialyzed chronic kidney disease. Indian J Endocr Metab 2018;22:316-20.
Major fraction of thyroxine hormones exist in protein-bound state in blood which may be affected in CKD. Patients with CKD have inhibitors which prevent binding of thyroid hormones to proteins.\(^{[6]}\) Another aspect looking into the role of inflammation affecting the thyroid functions in patients with CKD is also generating interest recently. Hence, an important interplay between thyroid hormone status and kidney function highlights the significance of understanding the correlation between them.

Our study assessed thyroid hormone status in undialyzed CKD patients, comparing them with control group, to find the correlation between biochemical markers of renal function and thyroid hormone levels.

**Methodology**

We conducted a hospital-based case–control observational study in a tertiary care center in Northwestern part of India. After obtaining informed consent, thirty patients of age more than 14 years having established CKD and not on dialysis were included as cases. A similar number of age- and sex-matched healthy controls were taken as controls. Patients with known history of thyroid disorder, on drugs affecting thyroid function, pregnancy, and previous history of dialysis were excluded from the study. Ethical committee clearance was obtained before the study.

A thorough history was taken from the individuals enrolled in the study population. Blood sample taken after overnight fasting was analyzed for complete blood counts, blood glucose, blood urea, serum creatinine, serum calcium and phosphorus, liver function tests, serum proteins, serum electrolytes, complete urine analysis, and thyroid hormone levels (TSH, free triiodothyronine [FT3], free thyroxine [FT4]).

Biochemical parameters were analyzed in biochemistry laboratory, and thyroid hormones were estimated using chemiluminescent immunoassay system in Immulite 1000 Siemens machine in the immunoassay laboratory of the institute. Ultrasonography (USG) abdomen was done for evaluation of kidney size and corticomedullary differentiation.

Same number of age- and sex-matched healthy controls were evaluated for all above-mentioned investigations. Data were collected and statistically analyzed. GFR was calculated by Modification of Diet in Renal Disease Study formula.

**Statistical analysis**

All the data obtained were presented as mean ± standard deviation. Any differences in parameters between groups were tested for significance by two-tailed unpaired \(t\)-test. Comparisons were made between controls and cases groups. \(P = 0.05\) was considered to be statistically significant. Pearson’s correlation analysis was done to study any correlations between renal biochemistry and thyroid levels. All the statistical analyses were performed on SPSS for Microsoft Windows trial version 23 (SPSS inc., Chicago, IL,USA).

**Results**

The age and sex distribution in both the groups were comparable, and difference between groups was statistically insignificant. It was also observed that male patients were disproportionately larger in number (56.6%) as compared to females (43.3%).

Results in cases and control groups were as tabulated in Table 1. Mean FT3 was lesser in cases (1.4727 ± 0.3577) than controls (2.6613 ± 0.6155); the difference being statistically significant. Mean FT4 of cases was 0.9013 ± 0.1916, and in controls, it was 1.4263 ± 0.2594, there being less mean serum FT4 in cases as compared to controls and the difference between both the groups being significant. Mean serum TSH in cases was 1.8120 ± 1.0844, and in controls, it was 2.5233 ± 0.7447. There was higher mean serum TSH in controls as compared to cases, and the difference among both the groups was significant.

As the cases group consisted of undialyzed CKD patients, mean blood urea and mean serum creatinine of cases were significantly higher than those in controls. There was higher mean creatinine clearance in controls as compared to cases, and the difference among both the groups was significant. On USG, out of total cases, 63.33% had bilateral contracted kidneys and 36.67% had poor corticomedullary differentiation. All controls had normal USG findings.

Distribution of cases and controls according to FT3 range revealed that the levels of FT3 were significantly abnormal in 76.64% of the cases as compared to none in the controls. We also found significantly abnormal levels of FT4 in 70% of undialyzed CKD patients as compared to 13.34% of healthy controls, with mean FT4 in cases group being lower to control group, the difference being statistically significant (\(\chi^2 = 17.554\) with 1° of freedom; \(P = <0.001\)).

TSH was found abnormal in 26.66% of the cases as compared to 6.67% in the controls (\(\chi^2 = 3.0000\) with 1° of freedom; \(P = 0.083\)). Abnormal TSH values were not statistically significant in both groups.

**Correlation between thyroid hormone profile and markers of renal function**

There was moderate-to-strong inverse correlation between the blood urea and FT3 (\(r = −0.749, P < 0.01, R^2 = 0.56\)) as well as between the creatinine and serum FT3 (\(r = −0.692, P < 0.01, R^2 = 0.479\)). Significant moderately strong correlation was seen between creatinine clearance and FT3 (\(r = 0.686, P < 0.01, R^2 = 0.47\)) [Figure 1]. Correlation of FT4 with renal parameters also showed significant inverse moderately strong correlation between the blood urea values and serum FT4 (\(r = −0.723, P < 0.01, R^2 = 0.52\)) as well as serum creatinine and FT4 (\(r = −0.684, P < 0.01, R^2 = 0.459\)). Significant moderately strong correlation was observed between the creatinine clearance values and FT4 (\(r = 0.699, P < 0.01\)) using Pearson’s correlation coefficient [Figure 2]. The \(R^2 = 0.49\), it means 49% of the total variation in serum FT4 was explained by the linear relation with creatinine clearance.
Table 1: Observations

| Parameters          | Cases (n=30) | Controls (n=30) | Total (n=60) | P  |
|---------------------|--------------|----------------|--------------|----|
| Age (years)         | 31.60±8.76   | 30.77±8.23     | 31.18±8.44   | 0.706 |
| FT3 (pg/ml)         | 1.4727±0.3577| 2.6613±0.6155  | 2.0670±0.7799| <0.001 |
| FT4 (ng/dl)         | 0.9013±0.1916| 1.4263±0.2594  | 1.1638±0.3481| <0.001 |
| TSH (mIU/L)         | 1.8120±1.08449| 2.5233±0.74475 | 2.1677±0.98963| 0.004 |
| Blood urea (mg/dl)  | 69.53±24.15  | 30.07±6.63     | 49.80±26.54  | <0.001 |
| Serum creatinine (mg/dl) | 1.6367±0.30341 | 0.7653±0.13938 | 1.2010±0.49781 | <0.001 |
| Creatinine clearance| 45.27±10.6   | 110.4±26.90    | 77.83±38.59  | <0.001 |

SD: Standard deviation, TSH: Thyroid-stimulating hormone, FT3: Free triiodothyronine, FT4: Free thyroxine

No significant correlation was seen between the blood urea values and serum TSH ($r = 0.236, P = 0.069$) using Pearson’s correlation coefficient. The $R^2 = 0.056$, it means 5.6% of the total variation in serum TSH was explained by the linear relation with blood urea. There was just significant positive correlation between the serum creatinine values and serum TSH ($r = 0.248, P = 0.049, R^2 = 0.061$). Nonsignificant correlation between the creatinine clearance values and serum TSH was observed ($r = 0.206, P = 0.114, R^2 = 0.42$) [Figure 3].

Summarizing the results, there was significant inverse moderately strong correlation between the blood urea and free thyroid hormones as well as between serum creatinine and free thyroid hormones. There was no significant positive correlation between the blood urea values and TSH, with just significant positive correlation between the serum creatinine and TSH. We observed significant moderately strong correlation between the creatinine clearance values and FT3 and FT4 with no significant correlation with TSH.

**DISCUSSION**

Many alterations in thyroid functions have been reported in association with CKD patients. We conducted a case–control observational study to correlate thyroid hormones status in undialyzed CKD patients and healthy controls. In our study, patients only on conservative management were studied. This is because thyroid profile undergoes changes due to dialysis independent of that due to CKD. Dialysis also changes the previous serum status of thyroid hormone in the patients with renal failure.

The levels of FT3 and FT4 in our study were significantly abnormal (lower) in undialyzed CKD patients as compared to healthy controls. Free thyroid hormone levels significantly decreased with rising blood urea, serum creatinine, and declining creatinine clearance. Nonsignificant correlation occurred between the blood urea values and creatinine clearance with TSH. There was just significant positive correlation between the serum creatinine values and TSH.

Various patterns of alteration of thyroid profile in CKD patients have been reported in literature. Singh et al. evaluated thyroid hormones status and oxidative stress in 20 undialyzed CKD patients and 20 controls. They observed a significant decrease in the levels of T3, T4, total protein, and albumin levels in patients with kidney disease as compared to control. A study was conducted by Haria and Lunia in 2013 to evaluate the thyroid hormones status in patients with CKD. They observed decreased total thyroid hormone and FT3 levels in 74% CKD patients whereas TSH, FT4 were similar to controls. Mehta et al. in 1991 conducted a study to evaluate total free thyroid hormone levels in chronic renal failure. They found that significant decrease in TT3, FT4, and FT3 levels was associated with increasing renal damage. Rajagopalan et al. in 2013 found significant reduction in T3 and T4 with unchanged TSH in patients with CKD as compared to controls. They also found a significant negative correlation of blood urea and serum creatinine with thyroid hormones.

In a study from Nepal, the authors found abnormal thyroid function in patients with CKD. They found subclinical hypothyroidism to be significantly associated with CKD and also association of CKD progression to thyroid function abnormalities.

In a pioneering study, Ramirez et al. compared two groups of patients with renal failure not on dialysis and those on dialysis with normal individuals. They observed significantly reduced T3 in both renal failure groups when compared to normal individuals. However, the reduction in T4 was statistically significant only in hemodialysis group. These findings were not associated with decrease in thyroid binding globulin in nonhemodialysis renal failure group suggesting pathophysiology independent of binding proteins.

Our study found no significant alterations in mean TSH level in CKD patients as compared to controls. The mean TSH levels were comparable to controls for the various ranges of GFR. TSH levels did not show any correlation with the severity of renal failure. This is consistent with the results obtained by Ramirez et al. and Lim. Ramirez et al. observed impaired response of thyrotropin to its releasing hormone indicating abnormality in hypothalamic-pituitary axis in patients with CKD. The uremic patients had probably a defective pituitary response highlighting the role of pituitary in contributing to ineffective negative feedback mechanism. However, contrary to this, Joseph et al. demonstrated high TSH in the presence of low thyroid hormones. They observed thyrotropin levels rising with degree of renal insufficiency, favoring a normal thyroid hypophyseal feedback loop.

Srivastava, et al.: Thyroid profile in undialyzed CKD patients
glycosylation may be affected along with reduced response to its releasing hormone, TRH.\[^{[14]}\] Furthermore, reduced thyroid hormone response to TSH has been demonstrated low.\[^{[7,12]}\]

Role of inflammation has been studied in disorders such as malnutrition, sepsis, chronic renal disorders, and myocardial infarction producing condition of stress and leading to thyroid disturbances.\[^{[15]}\] Effect of cytokines and interleukins has been considered an important cause contributing to these changes. Zoccali \textit{et al}. correlated inflammatory markers interleukin 6 (IL6), C reactive protein (CRP), and endothelial adhesion molecules with FT3 in patients on hemodialysis. They postulated a decrease in FT3 as a manifestation of inflammation occurring in CKD patients which might be somewhat reversed once the inflammation is controlled.\[^{[15]}\]

Inflammatory cytokines such as tumor necrosis factor (TNF) \(\alpha\) and IL6 have been found to have inverse relationship to T3.\[^{[15,16]}\]

Another study evaluated the contribution of inflammation and thyroid function as risk factors for acute kidney injury (AKI). They evaluated if thyroid hormone levels and CRP had any influence on cystatin C, a renal biomarker. Although CRP was found to have association with AKI, predictive value was not established. Furthermore, they did not find predictive value of thyroid function tests for AKI in these patients.\[^{[17]}\] Contrary to these findings, another study observed positive association of subclinical hypothyroidism with CKD in patients with type 2 diabetes mellitus concluding the possibility of thyroid dysfunction posing as a risk factor for CKD.\[^{[18]}\] Association of low thyroid hormones with high levels of high-sensitivity CRP and IL6 may contribute to impaired cardiovascular function and overall survival, highlighting their clinical significance in chronic kidney disorders.

Nonthyroidal illnesses producing low thyroid hormones, FT3 in particular, have been recognized by many. This active form of thyroid hormone if reduced may contribute to decreasing protein loss and balancing energy homeostasis. Thyroid dysfunction in CKD involving alteration in thyroid hormone metabolism and peripheral deiodination has been evaluated. Defect in deiodinase enzyme activity peripherally converting T4 to T3 causes reduced levels of T3.\[^{[9]}\] Inactivation of T4 and T3 by conversion to reverse T3 and T2, respectively, involves selenium-dependent iodothyronine deiodinase. Alteration in selenoprotein homeostasis in CKD patients affecting thyroid hormone profile has been studied by Reinhardt \textit{et al}.\[^{[19]}\] Selenoprotein P is the major selenium transport protein representing the selenium status in the body. They observed that in patients with chronic renal disease, selenoprotein P had negative correlation with T4 levels, both total and free hormones. However, they did not find association of selenoprotein P with T3 and thyrotropin. They did not find any association between thyroid hormone status and selenoprotein P concentration in patients on chronic hemodialysis.

A distinct aspect looking into the common autoimmune etiology in patients having autoimmune thyroid diseases and glomerulonephritis is under review. Membranous, membranoproliferative, and other forms of glomerulonephritis have been associated with autoimmune thyroid disorders. The pathophysiology involves megalin, a thyrotropin-dependent glycoprotein.\[^{[20]}\] Its role in immunopathogenesis of glomerular injury and glomerular deposition of immune complexes is hypothesized.
Iodine excretion is also impaired in CKD, leading to its excess with resultant reduced uptake secondary to Wolff–Chaikoff effect.\(^{[14]}\) This iodine metabolism defect may also result in hypothyroidism. Furthermore, role of low T3 in renal transplant patients with pretransplantation thyroid hormone status contributing to the results of transplantation is also generating interest.\(^{[21]}\)

**Conclusions**

Abnormal thyroid hormone profile in blood without any underlying disorder of thyroid gland can occur in chronic renal disorders, causing difficulty and errors in their interpretation. Our data highlight that CKD leads to significant lowering of free thyroid hormone levels, with reduction correlating with the severity of renal disease. This projects the importance of thyroid hormone estimation along with exercising adequate care in interpretation of their results in patients with CKDs. Further larger studies evaluating the clinical significance of thyroid hormones status in CKD patients would enhance our understanding in the subject.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Iglesias P, Diez JJ. Thyroid dysfunction and kidney disease. Eur J Endocrinol 2009;160:503-15.
2. Brent GA, Weetman AP. Hypothyroidism and thyroiditis. In: Williams Textbook of Endocrinology, Melmed S, Polonsky KS, Reed Larsen P, Kroneberg HM. 13th ed, Elsevier Publications; India, 2016. p. 416-48.
3. Davies TF, Laurberg P, Bahn RS. Hyperthyroid disorders. In: Williams Textbook of Endocrinology, Melmed S, Polonsky KS, Reed Larsen P, Kroneberg HM. 13th ed, Elsevier Publications; India, 2016. p.369-415.
4. Gattineni J, Sas D, Dagan A, Dwarkanath V, Baum M. Effect of thyroid hormone on the postnatal renal expression of NHE3. Am J Physiol Renal Physiol 2008;294:F198-204.
5. Lo JC, Chertow GM, Go AS, Hsu CY. Increased prevalence of subclinical and clinical hypothyroidism in persons with chronic kidney disease. Kidney Int 2005;67:1047-52.
6. Lim VS. Thyroid function in patients with chronic renal failure. Am J Kidney Dis 2001;38:S80-4.
7. Singh PA, Bobby Z, Selvaraj N, Vinayagamoorthi R. An evaluation of thyroid hormone status and oxidative stress in undialyzed chronic renal failure patients. Indian J Physiol Pharmacol 2006;50:279-84.
8. Haria J, Lunia M. Sick euthyroid syndrome in chronic kidney disease. J Evol Med Dent Sci 2013;2:8267-73.
9. Mehta HJ, Joseph LJ, Desai KB, Mehta MN, Samuel AM, Almeida AF, et al. Study to evaluate total and free thyroid hormone levels in chronic renal failure. J Postgrad Med 1991;37:79-83.
10. Rajagopalan B, Dolia PB, Arunalla VK, Seshadri Reddy V. Renal function markers and thyroid hormone status in undialysed chronic kidney disease. Al Ameen J Med Sci 2013;6:70-4.
11. Khatriwada S, Rajendra KC, Gautam S, Lamsal M, Baral N. Thyroid dysfunction and dyslipidemia in chronic kidney disease patients. BMC Endocr Disord 2015;15:65.
12. Ramirez G, O’Neill W Jr., Juhiz W, Bloomer HA. Thyroid dysfunction in uremia: Evidence for thyroid and hypophyseal abnormalities. Ann Intern Med 1976;84:672-6.
13. Joseph LJ, Desai KB, Mehta HJ, Mehta MN, Almeida AF, Acharya VN, et al. Measurement of serum thyrotropin levels using sensitive immunoradiometricassays in patients with chronic renal failure: Alterations suggesting an intact pituitary thyroid axis. Thyroidology 1993;5:35-9.
14. Kaptein EM. Thyroid hormone metabolism and thyroid diseases in chronic renal failure. Endor Rev 1996;17:45-63.
15. Zoccali C, Tripedi G, Cutrupi S, Pizzini P, Mallamaci F. Low triiodothyronine: A new facet of inflammation in end-stage renal disease. J Am Soc Nephrol 2005;16:2789-95.
16. van der Poll T, Romijn JA, Wiersinga WM, Sauerwein HP. Tumor necrosis factor: A putative mediator of the sick euthyroid syndrome in man. J Clin Endocrinol Metab 1990;71:1567-72.
17. Schanz M, Pannes D, Dippon J, Wasser C, Alcersch MD, Kimmel M, et al. The influence of thyroid function, inflammation, and obesity on risk prediction of acute kidney injury by cystatin C in the emergency department. Kidney Blood Press Res 2016;41:604-13.
18. Zhou JB, Li HB, Zhu XR, Song HL, Zhao YY, Yang JK, et al. Subclinical hypothyroidism and the risk of chronic kidney disease in T2D subjects: A case-control and dose-response analysis. Medicine (Baltimore) 2017;96:6519.
19. Reinhardt W, Dolf S, Benson S, Broecker-Preuß M, Behrendt S, Hög A, et al. Chronic kidney disease distinctly affects relationship between selenoprotein P status and serum thyroid hormone parameters. Thyroid 2015;25:1091-6.
20. Illies F, Wingen AM, Bald M, Hoyer PF. Autoimmune thyroiditis in association with membranous nephropathy. J Pediatr Endocrinol Metab 2004;17:99-104.
21. Rotondi M, Netti GS, Rosati A, Mazzinghi B, Magri F, Ronconi E, et al. Pretransplant serum FT3 levels in kidney graft recipients are useful for identifying patients with higher risk for graft failure. Clin Endocrinol (Oxf) 2008;68:220-5.