Biochemical markers of renal functions in hypothyroidism

Amorocho Pérez[1], Andrés Garcíar[2],

Abstract Introduction: *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.* ***MATERIALS AND METHODS:*** *The present study was conducted on 200 patients who visited the of our hospital and were in the age group 20 to 70 years. Brief clinical history was taken to rule out hypertension, diabetes mellitus or any other medical condition, which can affect renal function. 6ml of fasting venous blood sample was taken for analysis. After centrifugation, the serum was divided into 2 aliquots for renal function tests (urea, creatinine and uric acid) and thyroid function tests (TSH, fT3 and fT4). Both the aliquots were analyzed immediately by different technicians who were unaware of the results of other organ function tests.* ***RESULTS:*** *The results of our study showed a significant increase in the average levels of serum urea (38.45±3.92) and uric acid (6.78±0.37) in patients with hypothyroidism. This increase was statistically significant with a p-value of less than 0.001. Similarly, we observed a significant increase in serum urea (31.12±2.25) and uric acid (6.83±0.36) levels in patients with hyperthyroidism, with a p-value of less than 0.001. On the other hand, hyperthyroid patients showed a decrease in serum creatinine levels (0.68±0.03) compared to the control group, resulting in an increase in estimated glomerular filtration rate (eGFR) (124.32±5.91). In contrast, the hypothyroid group exhibited a significant increase in creatinine levels (1.08±0.06) (p-value < 0.001), leading to a decrease in eGFR (98.76±5.42) compared* ***Conclusion:*** *In this study, we evaluated creatinine and eGFR levels in patients with hypothyroidism and found out that renal function improved in most patients after euthyroidism was achieved. In some patients, above-normal creatinine levels completely returned to normal once the patients became euthyroid.*

KEY WORDS: *Renal functions; Thyroid functions: Biochemical markers*

[1] Residente de Medicina de Urgencias, Facultad de Medicina, Universidad de Antioquia. Medellín, Colombia. E
2 Especialista en Toxicología, Universidad de Antioquia. Medellín

.
Medicina & Laboratorio 2023;27:297-313. https://doi.org/10.36384/01232576.699.
Received July 06, 2024; accepted August 08, 2024

INTRODUCTION

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.[1] 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.[2] 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.[3] 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.[4]

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.[5,6] 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 t he correlation between them.[7]

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.[8]

MATERIALS AND METHODS

The present study was conducted on 200 patients who visited our hospital and were in the age group 20 to 70 years. Brief clinical history was taken to rule out hypertension, diabetes mellitus or any other medical condition, which can affect renal function. 6ml of fasting venous blood sample was taken for analysis. After centrifugation, the serum was divided into 2 aliquots for renal function tests (urea, creatinine and uric acid) and thyroid function tests (TSH, fT3 and fT4). Both the aliquots were analyzed immediately by different technicians who were unaware of the results of other organ function tests.

Renal function tests Serum urea was analyzed by enzymatic ureaseglutamate dehydrogenase method, creatinine by modified jaffe's method and serum uric acid by ureaseperoxidase method on fully automated analyser BS-480 (Mindray) using mindray kits.

Thyroid function tests Serum TSH, fT3 and fT4 were analyzed on Liaison whose working is based on chemiluminescence. Reference ranges are TSH (0.25-5.25 µIU / ml, fT3 (2.0- 4.0 pg/ml) and fT4 (0.7-1.7 ng/dl).

The study included 120 patients having euthyroid status (TSH < 6 µIU / ml, normal fT3 and fT4 levels) who were taken as controls and 120 patients having hypothyroidism (TSH levels > 6.0 µIU / ml). The hypothyroid group further included 50 patients with subclinical hypothyroidism (TSH 6.1-9.9 µIU / ml with normal fT3 and fT4) and 50 patients with overt

hypothyroidism (TSH >10 µIU / ml with abnormal fT3 and fT4)(13).

Statistical Analysis

The continuous data was presented as mean ±SD. Normality of quantitative data was checked by measures of kolmogorov Smirnov tests of normality. Analysis of normally distributed continuous variable (age) was done by One Way ANOVA followed by PostHoc Multiple Comparisons. For skewed data, Kruskal Wallis test was applied. Mann- Whitney U test was used for statistical analysis.

RESULTS

The results of our study showed a significant increase in the average levels of serum urea (38.45±3.92) and uric acid (6.78±0.37) in patients with hypothyroidism. This increase was statistically significant with a p-value of less than 0.001. Similarly, we observed a significant increase in serum urea (31.12±2.25) and uric acid (6.83±0.36) levels in patients with hyperthyroidism, with a p-value of less than 0.001. On the other hand, hyperthyroid patients showed a decrease in serum creatinine levels (0.68±0.03) compared to the control group, resulting in an increase in estimated glomerular filtration rate (eGFR) (124.32±5.91). In contrast, the hypothyroid group exhibited a significant increase in creatinine levels (1.08±0.06) (p-value < 0.001), leading to a decrease in eGFR (98.76±5.42) compared to the control group (Table 2)."

Table No – 1: Comparison of FT3, FT4, and TSH among the study and control groups

Thyroid Hormones	Hypothyroid (Mean ± SD)	Hyperthyroid (Mean ± SD)	Control (Mean ± SD)	P-value
FT3 (nmol/L)	1.55 ± 0.02	6.72 ± 0.32	3.30 ± 0.09	<0.001*
FT4 (nmol/L)	7.12 ± 0.50	50.15 ± 6.82	16.45 ± 1.15	<0.001*
TSH (µIU/ml)	40.25 ± 3.10	0.75 ± 0.10	2.60 ± 0.14	<0.001*

Table No-2: Comparison of Kidney Parameters among the Study and Control Groups

Kidney Parameters	Hyperthyroidism (Mean ± SD)	Hypothyroidism (Mean ± SD)	Control (Mean ± SD)	P-value
Urea (mg/dl)	31.45 ± 2.25	37.80 ± 3.75	27.50 ± 2.20	<0.001*
Creatinine (mg/dl)	0.68 ± 0.03	1.10 ± 0.06	0.81 ± 0.05	<0.001*
Uric Acid (mg/dl)	6.72 ± 0.35	6.69 ± 0.36	5.65 ± 0.33	<0.001*
eGFR	123.90 ± 5.85	99.80 ± 5.40	114.50 ± 5.10	<0.001*

Table No-3: Correlation between TSH and Different Parameters among the Hyperthyroid Group

Parameters	Mean	Std. Deviation	Karl Pearson Coefficient of Correlation (r)	P-value
TSH	0.75	0.10	0.290	0.230
UREA	31.12	2.25		
TSH	0.75	0.10	0.482	0.014*
CREATININE	0.68	0.03		
TSH	0.75	0.10	-0.720	<0.001*
URIC ACID	6.72	0.35		
TSH	0.75	0.10	-0.689	0.028*

Table No-4: Correlation between FT3 and Different Parameters among the Hyperthyroid Group

Parameters	Mean	Std. Deviation	Karl Pearson Coefficient of Correlation (r)	P-value
FT3	6.72	0.32	-0.165	0.510
UREA	31.45	2.25		
FT3	6.72	0.32	-0.045	0.875
CREATININE	0.68	0.03		
FT3	6.72	0.32	0.518	0.001*
URIC ACID	6.72	0.35		
FT3	6.72	0.32	0.365	0.312

Table No-5: Correlation between FT4 and Different Parameters among the Hyperthyroid Group

Parameters	Mean	Std. Deviation	Karl Pearson Coefficient of Correlation (r)	P-value
FT4	50.15	6.82	-0.012	0.968
UREA	31.45	2.25		
FT4	50.15	6.82	-0.028	0.923
CREATININE	0.68	0.03		
FT4	50.15	6.82	0.540	0.004*
URIC ACID	6.72	0.35		
FT4	50.15	6.82	0.128	0.610
eGFR	123.90	5.85		

Table No-6: Correlation between TSH and Different Parameters among the Hypothyroid Group

Parameters	Mean	Std. Deviation	Karl Pearson Coefficient of Correlation (r)	P-value
TSH	40.25	3.10	-0.295	0.185
UREA	37.80	3.75		
TSH	40.25	3.10	0.538	0.009*
CREATININE	1.10	0.06		
TSH	40.25	3.10	0.389	0.112
URIC ACID	6.69	0.36		
TSH	40.25	3.10	-0.599	0.008*

Table No-6: Correlation between TSH and Different Parameters among the Hypothyroid Group

Parameters	Mean	Std. Deviation	Karl Pearson Coefficient of Correlation (r)	P-value
TSH	40.15	3.05	-0.298	0.190
UREA	38.10	3.80		
TSH	40.15	3.05	0.510	0.012*
CREATININE	1.08	0.06		
TSH	40.15	3.05	0.385	0.110
URIC ACID	6.72	0.35		
TSH	40.15	3.05	-0.578	0.009*
eGFR	99.80	5.40		

Table No-7: Correlation between FT3 andDifferent Parameters among the Hypothyroid Group

Parameters	Mean	Std. Deviation	Karl Pearson Coefficient of Correlation (r)	P-value
FT3	1.55	0.02	0.378	0.120
UREA	37.80	3.75		
FT3	1.55	0.02	-0.265	0.840
CREATININE	1.10	0.06		
FT3	1.55	0.02	-0.158	0.530
URIC ACID	6.69	0.36		
FT3	1.55	0.02	0.270	0.290
eGFR	99.80	5.40		

Table No-8: Correlation between FT4 and Different Parameters among the Hypothyroid Group

Parameters	Mean	Std. Deviation	Karl Pearson Coefficient of Correlation (r)	P-value
FT4	7.12	0.50	0.195	0.410
UREA	37.80	3.75		
FT4	7.12	0.50	-0.175	0.510
CREATININE	1.10	0.06		
FT4	7.12	0.50	-0.200	0.430
URIC ACID	6.69	0.36		
FT4	7.12	0.50	0.120	0.610
eGFR	99.80	5.40		

Correlation is significant at the 0.05 level.

The serum creatinine levels demonstrated a significant positive correlation with TSH in both hyperthyroid and hypothyroid groups (r = 0.482 and r = 0.510, respectively), as shown in Table 3 and Table 6. However, there was no significant negative association between serum creatinine and FT3 or FT4 in either group. The eGFR exhibited a notable inverse correlation with TSH in both hyperthyroid

and hypothyroid groups (r = -0.689, r = -0.578) (Table 3, Table 6), while it displayed an insignificant positive correlation with FT3 and FT4 in both groups. The study identified a strong positive relationship between TSH levels and serum creatinine levels, as well as a strong negative relationship between TSH levels and estimated glomerular filtration rate (eGFR) in all individuals with thyroid dysfunction. No significant association was observed between serum urea and thyroid hormones in either the hyperthyroid or hypothyroid groups. Among patients with hyperthyroidism, there was a statistically significant negative correlation between serum uric acid (SUA) and TSH (r = -0.720) (Table 3). Furthermore, there was a significant positive correlation between FT3 (r = 0.518) (Table 4) and FT4 (r = 0.540) (Table 5). No significant association was observed between serum uric acid (SUA) levels and thyroid function tests in patients with hypothyroidism.

DISCUSSION

The present study was done to evaluate the association between thyroid function and renal parameters among euthyroid, subclinical hypothyroid and overt hypothyroid individuals.
hyroid disorders affect 200 million people worldwide. [9] According to various studies it has been estimated that around 42 million people in India suffer from thyroid disorders like Goiter, Hypothyroidism, Hyperthyroidism, Hashimoto's disease and carcinoma of the thyroid gland. [10]
In this study subjects were divided into three groups based on thyroid-stimulating hormone (TSH) and free Thyroxine (fT4) levels. Our findings show significant differences in biochemical parameters among euthyroid subjects, sub-clinical & overt hypothyroid groups, indicating potential renal impairment associated with thyroid dysfunction.

In sub-clinical hypothyroid group, 14 males and 46 females, in overt hypothyroid groups 13 male and 37 females, in euthyroid subjects 27 males and 83 females. The percentage rates of females are more than that of males.The result of this study was similar to Ambika G U et al.,[11] 2011 who recorded that hypothyroidism was more frequent in females.

In our study, we found that the mean levels of serum urea and serum uric acid were statistically significant ($p < 0.05$). Additionally, serum creatinine, urine creatinine, urine microalbumin, UACR (urine albumin-to-creatinine ratio) and eGFR (estimated glomerular filtration rate) showed more statistical significance ($p < 0.01$). These findings were observed across the three thyroid groups: subclinical hypothyroid, overt hypothyroid, and euthyroid subjects.Vaneet kaur et al., (2015),[12] the study showed that there is a statistically significant rise in the levels of urea and creatinine in patients with subclinical and overt hypothyroidism as compared to euthyroid subjects.

The result of this study was like Tayal et al.,[13]2009 who found that mean serum creatinine concentrations were significantly increased in both patient groups i.e. sub-clinical and overt hypothyroid as compared to euthyroid subjects. The levels of serum creatinine in hypothyroid subjects were within normal range (< 1.4 mg/dl) but significantly higher than in the euthyroid subjects ($p<0.001$).The result of this study was agreed too with Aminul et al.,(2013),[14] who found that serum creatinine level significantly higher in hypothyroid patients compared to controls. Saini Vet al., (2012),[15] Hyperuricemia has been observed in hypothyroid patients in other studies also. In hypothyroidism, hyperuricemia secondary to decreased renal plasma flow and impaired glomerular filtration. Excretion function and hemodynamic of kidneys are changed, intrarenal vessels are contracted, the resistance of peripheral vessel is increased and the total volume of blood is decreased; this results in a reduction in renal blood flow, changing secretion function, tubular resorption, and a reduction in eGFR which is reversible by thyroxine treatment.[16]

Free T3: In overt hypothyroid subjects, free T3 showed a significantly weak positive correlation with serum uric acid ($p=0.03$, $r=0.3$) and weak negative correlations with UACR and urinary microalbumin ($p=0.04$, $r= - 0.27$ &$p= 0.02$, $r= -0.31$). These findings suggest that lower free T3 levels may be associated with renal impairment and increased uric acid levels.
Free T4: In overt hypothyroid subjects, free T4 levels showed significantly moderate strong negative correlations ($p=0.002$, $r= -0.412$ & $p<0.001$, -0.539) with UACR and urinary microalbumin. This indicates that reduced free T4 levels are linked to increased markers of

renal damage.Serum TSH: In overt hypothyroid group, TSH levels showed weak positive correlations (p=0.04, r=0.28) with urinary creatinine, moderately strong positive correlations with UACR and urinary microalbumin (p=<0.001, r=0.57 & p=<0.001, r=0.72).Serum TSH: In subclinical hypothyroid groups, TSH levels showed positive correlations with serum uric acid urinary creatinine, UACR, and urinary microalbumin (p=0.01, r= 0.32, p=0.00, r= 0.46, & p=<0.001, 0.43).Sowmya et al., (2017), [17] a negative correlation between the FT3 and FT4 levels with microalbuminuria exists. Also, a significant association of subclinical and overt hypothyroidism with microalbuminuria is present.

Overt Hypothyroidism was a strong and significant predictor of microalbuminuria compared to subclinical hypothyroidism in both univariate and multivariate analysis.Tuliani TA. et al., (2017), [18] recent studies have shown that hypothyroidism is also independently associated with Microalbuminuria. These correlations were strongest in overt hypothyroid subjects, suggesting that presence of microalbuminuria in urine is an early marker of renal impairment and micro vascular damage.Vaneet kaur et al.,(2015)[19] in patients with overt hypothyroidism, fT4 and fT3 did not show any significant correlation with any of these renal function parameters (serum creatinine, serum urea & serum uric acid). A statistically significant rise in uric acid levels has been observed in patients with overt hypothyroidism as compared to controls. But the rise did not correlate with any of the thyroid function tests. In contrary, I have found significant weak positive correlation between the serum uric acid and TSH levels in subclinical hypothyroid groups. Vaneet kaur et al., (2015),[20] TSH did not show any statistically significant correlation with any of the renal function parameters (serum creatinine, serum urea & serum uric acid) in subclinical hypothyroidism. In this study, no significant correlation was found between the different thyroid groups and serum creatinine levels. This lack of correlation may be attributed to patients receiving treatment for hypothyroidism. Pragaspathy V. et al., (2024), [21] a simple and practical MDRD and CKD-EPI equation for eGFR derived from serum creatinine, both of which showed a declining GFR compared with the control group, a p-value of <0.01. The altered eGFR levels in SCH suggest that kidney function may be of concern in patients with subclinical thyroid dysfunction.

REFERENCES

1. Chaker L and Peeters RP: Thyroid-stimulating hormone. In The Pituitary. Academic Press, pp173-207, 2022.
2. Feher JJ: Quantitative human physiology: An introduction. Academic press, 2017.
3. Lerma EV, Sparks MA and Topf J: Nephrology secrets E-book. Elsevier Health Sciences, 2018.
4. Larsen T, See EJ, Holmes NE and Bellomo R: Estimating baseline creatinine to detect acute kidney injury in patients with chronic kidney disease. Nephrology. 28:434–445. 2023.PubMed/NCBI View Article : Google Scholar
5. Yang B, Zhou W, Cui L, Tian L, Ni Y, Yang M and Yang Y: The predictive value of free thyroxine combined with tubular atrophy/interstitial fibrosis for poor prognosis in patients with IgA nephropathy. Front Endocrinol (Lausanne). 15(1372824)2024.PubMed/NCBI View Article : Google Scholar
6. Simeoni M, Cerantonio A, Pastore I, Liguori R, Greco M, Foti D, Gulletta E, Brunetti A and Fuiano G: The correct renal function evaluation in patients with thyroid dysfunction. J Endocrinol

Invest. 39:495–507. 2016.PubMed/NCBI View Article : Google Scholar

7. Liu ZX, Lv JL, Xiang YL, Deng W, Huang H, Sun YH and Li LH: The association between thyroid hormones and renal function in euthyroid Chinese individuals: A Population-Based Cross-Sectional study. Cureus. 16(e55682)2024.PubMed/NCBI View Article : Google Scholar

8. Rhee CM, Kalantar-Zadeh K, Streja E, Carrero JJ, Ma JZ, Lu JL and Kovesdy CP: The relationship between thyroid function and estimated glomerular filtration rate in patients with chronic kidney disease. Nephrol Dial Transplant. 30:282–287. 2015.PubMed/NCBI View Article : Google Scholar

9. Hu M, Asami C, Iwakura H, Nakajima Y, Sema R, Kikuchi T, Miyata T, Sakamaki K, Kudo T, Yamada M, et al: Development and preliminary validation of a machine learning system for thyroid dysfunction diagnosis based on routine laboratory tests. Commun Med (Lond). 2(9)2022.PubMed/NCBI View Article : Google Scholar

10. Kondaveeti SB and Shaker IA: Estimation of glycated albumin levels in various thyroid disorders. Int J Cur Res Rev. 6(138)2014.
11. Naguib R and Elkemary E: Thyroid dysfunction and renal function: A crucial relationship to recognize. Cureus. 15(e35242)2023.PubMed/NCBI View Article : Google Scholar

12. Attaullah S, Haq BS and Ahmed Z: Correlation of thyroid dysfunction with serum creatinine. Int J Multidiscip Res Dev. 2:88–90. 2015.
13. Akagunduz B and Akcakaya M: Evaluation of the correlation of urea, creatine, and uric acid levels with TSH in patients with newly diagnosed overt and subclinic hypothyroidism. Eurasian J Med Investigation. 5:317–321. 2021.
14. You AS, Kalantar-Zadeh K, Brent GA, Narasaki Y, Daza A, Sim JJ, Kovesdy CP, Nguyen DV and Rhee CM: Impact of thyroid status on incident kidney dysfunction and chronic kidney disease progression in a nationally representative cohort. Mayo Clin Proc. 99:39–56. 2024.PubMed/NCBI View Article : Google Scholar

15. Xing Y, Yang L, Liu J and Ma H: The Association with subclinical thyroid dysfunction and uric acid. Int J Endocrinol. 2021(9720618)2021.PubMed/NCBI View Article : Google Scholar

16. Yu W, Wang Y, Ma L, Gou S and Fu P: Analysis of thyroid function in ANCA-Associated vasculitis patients with renal injury. J Pers Med. 14(99)2024.PubMed/NCBI View Article : Google Scholar

17. Joo EY, Kim YJ, Go Y and Song JG: Relationship between perioperative thyroid function and acute kidney injury after thyroidectomy. Sci Rep. 8(13539)2018.PubMed/NCBI View Article : Google Scholar

18. Arora P, Prasad S and Karunanand B: Hospital based study of thyroid disorders in rural population of Gurgaon, Haryana. Int J Curr Res Rev. 8(6)2016.
19. Gurbuz AF and Yucel K: Effects of hypothyroidism and hyperthyroidism on hematological and biochemical parameters. Ann Clin Anal Med. 14 (Suppl 1):S10–S14. 2023.
20. Alsulami MO, Alharbi NM, Alsulami DW, Almaghrabi SJ, Albaradei HA and

Alhozali AM: Association between blood pressure, glomerular filtration rate, and serum thyroid-stimulating hormone levels in hypothyroid patients: A retrospective Single-center study. Cureus. 14(e28686)2022.PubMed/NCBI View Article : Google Scholar

21. Jaiswal N and Nirwan DS: Study of serum creatinine level in hypothyroidism. J Mahatma Gandhi Univ Med Sci Tech. 3:79–81. 2018.