Int J Biol Med Res.2022 ;13(2):7445-7449

Contents lists available at BioMedSciDirect Publications

International Journal of Biological & Medical Research

Journal homepage: www.biomedscidirect.com

Original article

ASSESSMENT OF THYROID FUNCTION STATUS IN CHRONIC KIDNEY DISEASE

[a]P.SANGEETHA, [b]G. POONGODI

[a]*Assistant professor, Department Of Biochemistry, Govt Mohan Kumaramangalam Medical College, Salem*
[b]*Assistant professor, Department Of Biochemistry, Govt Dharmapuri Medical College, Dharmapuri*

ARTICLE INFO

Keywords:
Free T3
Free T4
TSH

ABSTRACT

Background : There is an increasing prevalence of Chronic Kidney Disease and their associated metabolic alterations, thyroid dysfunction being one among them.. This study was conducted to find whether thyroid hormone dysfunction differs significantly in CKD patients compared to patients with normal kidney function. Objective: To compare the thyroid hormone levels (Free T3, Free T4, TSH), urea, creatinine, total protein and albumin between CKD patients and healthy controls attending OPD of Nephrology Department in Government Mohan Kumaramangalam Medical College Hospital, Salem. Materials and methods: 50 healthy controls and 50 patients with Chronic Kidney Disease attending Nephrology OPD of Government Mohan Kumaramangalam Medical College Hospital,were selected. After obtaining their informed written consent, Fasting and random blood sample were analyzed for thyroid hormone levels and Serum urea, creatinine, total protein and albumin. Result : There was a significant reduction in free T3 levels in CKD patients when compared to the healthy individuals. The mean Free T3 levels were 51.68 ng/dl in the CKD patients and 67.84 ng/dl in healthy control. There was no significant correlation between Free T4 levels (1.07636ng/dl in the CKD patients,1.21492 ng/dl in healthy controls) and TSH levels (2.61096 µIU/ml in the CKD patients, 2.5076 µIU/ml in healthy controls) of CKD patients when compared to the healthy individuals. The mean serum concentrations of Total Protein and albumin was 5.992 gms% and 3.295 gms% in CKD Patients whereas the controls had higher serum concentration of both which were 7.188 mgs% and 4.5612 mgs% respectively. Conclusion: This study proves and provides evidence for the prevalence of hypothyroidism in patients with Chronic Kidney Disease, Making it important for clinicians to diagnose it and treat it early to avoid any complications due to thyroid dysfunction.

Introduction

Chronic Kidney Disease (CKD) is a disease spectrum characterized by progressive loss of renal function over a period of time. As per the National Kidney Foundation, it involves the presence of kidney damage or decreased level of function for 3 months or more [A]. In Chronic Kidney Disease (CKD), there occurs multiple abnormalities in thyroid hormone physiology including the state of chronic illness, malnutrition, negative nitrogen balance, and a multitude of other hormonal alterations [B].

Chronic Kidney Disease is a growing concern worldwide as it is associated with premature mortality, decreased quality of life and a very high cost of treatment [C]. Data from International Society of Nephrology's Kidney disease data center study reported a prevalence of chronic kidney disease to be 17% in India [D], making it an important public health problem. The number of Chronic Kidney Disease Patients has substantially increased in the past three decades due to an aging population with multiple comorbities. Its prevalence has even reached 35.8% in patients older than 64 years. [D1]

Alteration of various endocrinal systems including Calcitriol, Testosterone, Insulin like growth factor, erythropoietin etc has been observed in patients with Chronic Kidney Disease [E]. Among these, Endocrine abnormalities of thyroid hormone are one of the most common features.

Thyroid hormones are required forproper growth and development of the kidney and for the maintenance of fluid and electrolyte homeostasis. Whereas, kidney is an important target organ for the metabolism and elimination of these thyroid hormones. Hence any disturbance in kidney function results in an altered thyroid hormone physiology, making Thyroid dysfunction as unique characteristics in those individuals with advanced kidney diseases [F].

Also, thyroid diseases may occur more frequently in such patients than in the all inclusive community and may be under diagnosed due to limited clinical awareness in India [C]. These

* Corresponding Author : **Dr.Poongodi.G**
Email: poongodimowri@gmail.com
Mobile number: 9952499864

abnormalities in thyroid hormone levels can lead to further progression of Chronic Kidney Diseaseand causes serious adverse health outcomes such as cardiovascular diseases [G]. According to few studies, decreased active thyroid hormone levels are considered to be part of the deranged neuroendocrine and proinflammatory system that is associated with Congestive Heart Failure [H].

Chronic Kidney Disease is known to affect both hypothalamus-pituitary-thyroidal axis and thyroid hormone peripheral metabolism. Thyroid-stimulating hormone (TSH) levels may be normal or increased in chronic kidney disease, but with reduced Tri-iodothyronine levels(T3). Hence, an important interplay between thyroid hormone status and kidney function highlights the significance of understanding the correlation between them.

Chronic Kidney Disease is primarily assosiated with Hypothyroidism. Moreover, the diagnosis of hypothyroidism in this group of patients raises difficulties because of the typical signs and symptoms such as hypothermia, pallor and asthenia which are common in clinical picture of any of advanced kidney disease.

Early identification of thyroid hormone dysfunction among these patients will help in prevention of development of complications and improve the survival and quality of life of the patients. There is also a need to find whether thyroid hormone dysfunction differs significantly in Chronic Kidney Disease patients compared to patients with normal kidney function. However, there is limited evidence on the assessment of thyroid hormone status among the Chronic Kidney Disease patients in South Indian setting. Therefore this study is to assess the thyroid hormone status and biomarkers among the Chronic Kidney Disease patients and healthy controls

MATERIALS AND METHODS

This study was conducted in the Department of Biochemistry, Government Mohan Kumaramangalam Medical College Hospital, Salem .. The study population comprised of 50 Chronic Kidney Disease patients attending nephrology OPD of Government Mohan Kumaramangalam Medical College Hospital irrespective of the age and stage of disease and 50 Healthy controls with normal kidney function

Chronic Kidney Disease with essential hypertension/liver diseases/coronary artery disease/vasculitis/thyroid disorders on treatment/ other auto-immune disorders will be excluded.

Data collection was started after obtaining approval from Institutional Ethical Committee. All the selected subjects were interviewed after obtaining informed written consent. A thorough history was taken from the individuals enrolled in the study population.

For the study, 2 ml of 12 hours Fasting Venous Blood was collected under sterile conditions from the ante cubital vein. serum was separated after centrifugation at 3000 rpm for 10 minutes, alliquoted, and stored at -20°C for analysing thyroid hormone levels. 2 ml of random blood sample was collected and analyzed for serum urea, creatinine, total protein and albumin. Biochemical parameters such as Thyroid Stimulating Hormone [TSH], free triiodothyronine [FT3], free thyroxine [FT4] was analysed by using chemiluminescent immunoassay system in Cobas e411, Roche analyzer. Serum urea, creatinine, total protein and albumin was analysed by using BA400, Biosystem fully autoanalyzer in laboratory of the institute..

STATISTICAL ANALYSIS:

We entered data using MS EXCEL 2019 and analyzed using STATA version 14.0. We expressed the continuous variables such as age, serum urea, creatinine, T3, T4, TSH, total protein and albumin as median (IQR). We summarized the categorical variables such as gender as proportion. Independent T test was done to find the association between thyroid parameters (Free T3, Free T4, TSH), Total protein and Albumin of chronic kidney disease patients and healthy controls. However, TSH Parameter did not follow normal distribution and hence wilcoxan rank sum test was performed. P value less than 0.05 was considered statistically significant. We summarized the association by adjusted odds ratio (OR) with 95% confidence interval.

OBSERVATION AND RESULTS

Table 1. Demographic and clinical characteristics of the study participants (N=100)

Characteristic	CKD Patients	Control
Age, mean (SD) in years	45.0 (35.0 – 56.0)	45.0 (31.0 – 55.0)
Blood Urea, mean	124.48 mgs%	21.9948 mgs%
Serum Creatinine, mean	8.384 mgs%	0.8044 mgs%

Table 2. Association of Free T3, Free T4, TSH, Albumin and Total Protein with Chronic Kidney Disease and Healthy controls (N= 100)

Parameter	CKD Patients	Control	P value
Free T3	51.68 ng/dl	67.84 ng/dl	0.0053
Free T4	1.07636 ng/dl	1.21492 ng/dl	0.1306
TSH	2.61096 µIU/ml	2.5076 µIU/ml	0.8083
Albumin	3.295 gms%	4.5612 gms%	0.0000
Total Protein	5.992 gms%	7.188 gms%	0.0001

Serum free T3 concentration was less than the normal range in most of the CKD patients. The mean serum free T3 concentration of 51.68 ng/dl in the CKD patients was significantly lower than that of the control subjects 67.84 ng/dl.

The mean free T4 concentration was 1.07636ng/dl in the CKD patients and 1.21492 ng/dl in the healthy controls, which does not show a significant association.

Finally, there was no significant correlation between serum TSH concentration among patients with CKD and the healthy controls. The mean serum TSH concentration was 2.61096 µIU/ml in the CKD patients, and 2.5076 µIU/ml in the healthy controls.

The mean serum concentrations of Total Protein and albumin was 5.992 gms% and 3.295 gms% in CKD Patients whereas the controls had higher serum concentration of both which were 7.188 mgs% and 4.5612 mgs% respectively.

DISCUSSION

In this study, serum free T3 concentration was significantly lower than the normal range in the CKD patients in comparison with the controls. This is in accordance with the results of studies done by Singh et al, Gandham Rajeev et al, Rajagopal et al, Sang Heon et al.

The earliest and the most common thyroid function abnormality in Chronic Kidney Disease patients is a low T3 level, both total and free. Also known as a "Low T3 syndrome", it is the most common disturbance in CKD patients, while subclinical hypothyroidism is the most common thyroid disorder found in this group of patients. Several reasons can be attributed to this condition.Chronic metabolic acidosis and chronic protein malnutrition generally occurring in Chronic Kidney Disease, affects the iodothyronine deiodination as well as protein binding of T3. This in turn reduces the peripheral conversion of T4 to T3 and its protein binding[8].

A decrease in T3 is a manifestation of inflammation occurring in CKD patients. Inflammatory cytokines such as tumor necrosis factor (TNF) and interleukin (IL)-1 inhibit the expression of type 1 5′-deiodinase, which is responsible for peripheral conversion of T4 to T3. Thereby, decreasing the T3 levels[24]. Few studies also suggest that the decrease in t3 might be somewhat reversed once the inflammation is controlled. Also, there occurs an impaired renal handling of iodine which increases serum iodine levels, inturn causing a prolonged Wolff – Chaikoff effect [25]. According to it, Increase in total body inorganic iodine can potentially block thyroid hormone production.

Several studies have also shown that proinflammatory cytokines may inhibit T3 production. This can be explained by the fact that cytokine induced competition for limited amounts of co activators decreases hepatic type I iodothyronine 5-deiodinase expression, resulting in decrease T3 production. This is relevant because persistent inflammation and wasting are known to be common amongst CKD patients[8].

Previously Low T3 status of CKD was viewed as an adaptation that promotes energy saving. This is beneficial in cases of uremic wasting which can occur in cases of Chronic Kidney Disease. Conversely, it has been suggested that it might also be an indicator of maladaptation contributing to worsening of the disease.[26, 27]. Other disease processes e.g. liver disease, vasculitis and medications that reduce the peripheral conversion of T4 to T3 may also interfere with interpretation of the thyroid hormone profiles. Hence such patients were not recruited for the study.

In this study, there wasn't any significant correlation between Free T4 levels of patients with Chronic Kidney Disease when compared to the Controls.Whereas, Other studies like that of Rajagopal et al[17] reported a reduced Free T4 levels in CKD Patients.Major fraction of thyroxine hormones exists in protein bound state. But Patients with CKD have inhibitors which prevent binding of thyroid hormones to proteins. This can be explained by the impaired hormone binding to serum carrier proteins [6]. This reduction in serum protein binding of T4 is expected to affect total but not free, hormone levels. Hence, CKD patients might show reduced total t4 levels. This can also be due to the fact that the concentrations of major carrier proteins are usually normal in both CKD patients and controls. But, In CKD there are serum accumulations of many Uraemic toxins present that inhibit T4 binding to carrier proteins explaining low total T4 levels.

In contrast to this, in case of a CKD Patient on Dialysis, free T4 may be high due to the effect of heparin used in anticoagulation during hemodialysis, which inhibits T4 binding to its binding proteins[28].

In this study, there was no significant correlation between the serum concerntration of TSH between CKD patients and healthy controls.

However, The Serum concentration of thyroid-stimulating hormone (TSH) was found to be about normal or slightly increased in CKD Patients than the healthy controls despite a low serum T3 concentrations. Studies of Rajagopalan et al, Ramirez at al, also show similar findings.

This could be due to deregulation of hypothalamic-pituitary-thyroid axis. In Chronic Kidney Disease (CKD) patients, Uremia is prevalent because of which, the pituitary receptor response to TRH is blunted leading to a decrease in the production of TSH. The response in TSH release after stimulation with TRH (Thyrotropin Releasing Hormone) is sluggish because of the impaired renal clearance and prolonged half-life of TSH. [29]

Also according to few studies, both TSH circadian rhythm and TSH glycosylation are altered in CKD. The latter may compromise the TSH bioactivity. Both normal nuclear T3 levels and thyroid hormone receptor action in pituitary cells could explain normal serum TSH concentration.[30]

There is a significant reduction in Serum total protein and Albumin levels of CKD patients when compared to healthy controls. This could be due to several reasons like Albuminuria, liver damage, and a reduced production of the above-mentioned parameters. They may also decrease as a negative acute phase reactant or in response to inflammation.

Also, lower serum albumin levels may strongly and independently be associated with kidney function decline in elders.[31]

At the same time, a high protein intake must not be advised for a CKD patient as it may lead to increased intraglomerular pressure and glomerular hyperfiltration. This can cause damage to glomerular structure, further aggravating CKD. In Kidney, urea is filtered out of blood by glomerulli. The most frequently determined clinical indices for estimating renal function depends upon concentration of urea in the serum. Creatinine is a commonly used biomarker to measure kidney function. In CKD, an eventual reduction occurs in the excretion of creatinine by both the glomeruli and the tubules.

Serum Urea and Creatinine are the most widely accepted parameters to assess CKD. Hence, Increased Serum Urea (Condition called as Uremia) and high serum creatinine concentration is diagnosing of a renal disease. In CKD patients, the serum level elevation is because the kidney is unable to eliminate them.

Clinically, there is an increased prevalence of Goitre in patients with Chronic Kidney Disease. This is due to a significant reduction of the Glomerular Filtration Rate (GFR) leading to reduced clearance of Inorganic Iodides, causing a hypertrophic effect on Thyroid tissues. According to few studies, there is also a decreased clearance of goitrogenic substances like aryl acid, which can also be a contributing factor.[32]

CONCLUSION

Serum free T3 levels were significantly less in the chronic kidney disease patients when compared to the controls. There was no significant difference between both the groups with respect to free t4

and serum TSH levels. Total protein, albumin, were significantly reduced in CKD Patients. As the case group is of undialysed Chronic Kidney Disease patients, serum urea and creatinine were higher.

In Chronic Kidney Disease, abnormal Thyroid Hormone profile in Blood can occur without any underlying thyroid gland disorder. This study highlights the significant lowering of thyroid hormones in Chronic Kidney Disease Condition. Due to the persistence of uremic state, the symptoms pertaining to thyroid dysfunction are often masked, leaving it undiagnosed.

Hypothyroidism can cause Chronic Kidney Disease progression. Oxidative stress also contributes to hypertension that can further enhance disease progression. And the low serum T3 concerntrations in Chronic Kidney Disease patients has been documented to be connected with endothelial dysfunctions, atherosclerosis and cardiac abnormalities.Hence, this study shows the importance of regular screening for thyroid abnormalities and the need to diagnose it early in patients with Chronic Kidney Disease. Information obtained from this paper will help to increase clinical knowledge and enable clinicians to provide better management for their patients with Chronic Kidney Disease.

A common management technique opted is the thyroid hormone replacement in hypothyroid chronic kidney disease patients. Few observational studies have shown the recipient of exogenous thyroid hormone replacement were associated with decreased progression of chronic kidney disease. [33] But few studies have shown that attempts at T3 replacement have often resulted in negative nitrogen balance by increased muscle catabolism, implying the prudence in not correct the low state in Chronic Kidney Disease.

In extreme cases, where kidney transplant has to be undertaken, T3 values should to be evaluated. This is because, a low T3 levels prior to renal transplantation is found to be associated with post transplant risk of graft loss.[34]

Hence, further confirmatory studies could bring about effective management of hypothyroidism in Chronic Kidney Disease patients.

REFERENCES

1. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. Am j kidney Dis. 2002; 39 (2 Suppl): S1-S266.

2. Varughese S, Abraham G. Chronic Kidney Disease in India: A Clarion Call for Change. Clin J Am Soc Nephrol.2018;13(5):802-804. Doi;10.2215/CJN.09180817

3. Parameswaran S. Chronic kidney disease in India. Health Sci 2012;1:js001

4. Ene-lordache B, Perico N, Bikbov B, Carminati S, Remuzzi A, Perna A, Islam N, Bravo RF, Aleckovic-Halilovic M, Zou H, Zhang L, Gouda Z, Tchokhonelidze I, Abraham G, Mahdavi- Mazdeh M, Gallieni M, Codreanu I, Togtokh A, Sharma SK, Koirala P, Uprety S, Ulasi I, Remuzzi G : Chronic kidney disease and cardiovascular risk in six regions of the world (ISN- KDDC): A cross-sectional study. Lancet Glob Health 4: e307-e319,2016

5. Kuczera P, Adamczak M, Wiecek A. Endocrine Abnormalities in Patients with Chronic Kidney Disease. Pril (Makedon Akad Nauk Umet Odd Med Nauki). 2015;36(2):109-118.

6. Kaptein EM, Quion-Verde H, Chooljian CJ, Tang WW, Friedman PE, Rodriquez HJ & Massry SG. The thyroid in endstage renal disease. Medicine 1988 67 187–197.

7. James MT, Hemmelgarn BR, Tonlelli M. Early recognition and prevention of chronic kidney disease. Lancet. 2010;375(9722):1296–309

8. Carrero JJ, Qureshi AR, Axelsson J, et al. Clinical and biochemical implications of low thyroid hormone levels (total and free forms) in euthyroid patients with chronic kidney disease. J Intern Med. 2007;262(6):690-701. doi:10.1111/j.1365-2796.2007.01865.x

9. Cotoi L, Borcan F, Sporea I, et al. Thyroid Pathology in End-Stage Renal Disease PatientsonHemodialysis. Diagnostics (Basel). 2020;10(4):245.doi:10.3390/diagnostics10040245

10. J.C. Lo, G.M. Chertow, A.S. Go, C.Y. Hsu Increased prevalence of subclinical and clinical hypothyroidism in persons with chronic kidney disease Kidney Int., 67 (3) (2005), pp. 1047- 1052

11. Chonchol M, Lippi G, Salvagno G, Zoppini G, Muggeo M, Targher G. Prevalence of subclinical hypothyroidism in patients with chronic kidney disease. Clin J Am Soc Nephrol. 2008;3(5):1296-1300. doi:10.2215/CJN.00800208

12. 12.. Khatiwada S, Rajendra KC, Gautam S, Lamsal M, Baral N. Thyroid dysfunction and dyslipidemia in chronic kidney disease patients. BMC Endocr Disord. 2015;15:65

13. Zhang, Y et al. Thyroid hormone levels and incident chronic kidney disease in euthyroid individuals: The Kangbuk Samsung Health Study. International journal of epidemiology, 43(5), 1624-1632.

14. Hegedüs L. Thyroid size determined by ultrasound. Influence of physiological factors and non-thyroidal disease. Dan Med Bull. 1990;37(3):249-263.

15. 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

16. Rajeev G, Chickballapur Rayappa WD, Vijayalakshmi R, Swathi M, Kumar S. Evaluation of thyroid hormone levels in chronic kidney disease patients. Saudi J Kidney Dis Transpl 2015;26;90-3

17. Ramirez G, O'Neill W, Jr, Jubiz W, Bloomer HA. Thyroid dysfunction in uremia: Evidence for thyroid and hypophyseal abnormalities. Ann Intern Med. 1976;84:672–6

18. Rajagopalan B, Dolia PB, Arumalla 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

19. Sang Heon Song ET AL, The prevalence of low triiodothyronine according to the stage of chronic kidney disease in subjects with a normal thyroid-stimulating hormone, Nephrology Dialysis Transplantation, Volume 24, Issue 5, May 2009

20. Montenegro J, González O, Saracho R, Aguirre R, González O, Martínez I. Changes in renal function in primary hypothyroidism. Am J Kidney Dis. 1996;27(2):195-198. doi:10.1016/s0272-6386(96)90539-9

21. Pan B, Du X, Zhang H, Hua X, Wan X, Cao C. Relationships of chronic kidney disease and thyroid dysfunction in non dialysis patients: A Pilot study. Kidney Blood Press Res 2019;44:170–178

22. den Hollander JG, Wulkan RW, Mantel MJ, Berghout A. Correlation between severity of thyroid dysfunction and renal function. Clin Endocrinol (Oxf). 2005;62(4):423-427. doi:10.1111/j.1365-2265.2005.02236.

23. Welsem, M.E. & Lobatto, Sacha. (2007). Treatment of severe hypothyroidism in a patient with progressive renal failure leads to significant improvement of renal function. Clinical nephrology. 67. 391-3. 10.5414/CNP67391

24. Zoccali C, Tripepi 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.

25. Bando Y, Ushiogi Y, Okafuji K, Toya D, Tanaka N, Miura S. Non-autoimmune primary hypothyroidism in diabetic and non-diabetic chronic renal dysfunction. Exp Clin Endocrinol Diabetes 2002;110:408-15

26. Douyon L, Schteingart D.E. Effect of obesity and starvation on thyroid hormone, growth hormone, and cortisol secretion. Endocrinol Metab Clin North Am. 2002;31:173–89.

27. Vanhorebeek I, Langouche L, Van den Berghe G. Endocrine aspects of acute and prolonged critical illness. Nat Clin Pract Endocrinol Metab. 2006;2:20–31

28. Silverberg DS, Ulan RA, Fawcett DM, Dossetor JB, Grace M, Bettcher K. Effects of chronic hemodialysis on thyroid function in chronic renal failure. Can Med Assoc J. 1973 Aug; 109(4): 282–6

29. Weetman A.P, Weightman D.R, Scanlon M.F. Impaired dopaminergic control of thyroid stimulating hormone secretion in chronic renal failure. Clinical Endocrinology. 1981;15:4516

30. Wheatley T, Clark P.M, Clark J.D, et al. Abnormalities of thyrotrophin (TSH) evening rise and pulsatile release in haemodialysis patients: evidence for hypothalamic-pituitary changes in chronic renal failure. Clin Endocrinol (Oxf). 1989; 31:39–50.

31. Lang J, Kartz R, Ix JH et al. Association of serum albumin levels with kidney function decline and incident chronic kindey disease in elders. Nephrol Dial Transplant. 2018;33(6):986-992

32. V. S. Lim, V. S. Fang, A. I. Katz, and S. Refetoff, "Thyroid dysfunction in chronic renal failure. A study of the pituitary thyroid axis and peripheral turnover kinetics of thyroxine and triiodothyronine," Journal of Clinical Investigation, vol. 60, no. 3, pp. 522–534, 1977.V

33. Shin DH, Lee MJ, Kim SJ et al. Preservation of renal function by thyroid hormone replacement therapy in chronic kidney disease patients with subclinical hypothyroidism. The journal of clinical endocrinology and metabolism. 2012;97:27324-2740

V. S. Lim, V. S. Fang, A. I. Katz, and S. Refetoff, "Thyroid dysfunction in chronic renal failure. A study of the pituitary thyroid axis and peripheral turnover kinetics of thyroxine and triiodothyronine," Journal of Clinical Investigation, vol. 60, no. 3, pp. 522–534, 1977.