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Original Research Article

Clinical Importance of Evaluation of Thyroid Function Status in Patients with Chronic Kidney Disease

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ABSTRACT

Introduction: The incidence of thyroid disorders has been found to increase with increase in the severity of renal failure. This study was carried out for evaluation of thyroid function status in patients of chronic renal failure.

Methods: This case-control study was carried out at a tertiary care center. 50 cases of chronic kidney disease and 50 healthy controls were enrolled for the study. Routine laboratory investigations including blood urea and serum creatinine were done. Levels of free T3, free T4 and TSH were measured.

Results: The levels of free T3 and free T4 were found to be significantly lower in patients with chronic kidney disease in comparison with healthy controls ($p < 0.001$, $p < 0.001$). On other hand, there was no significant difference in levels of TSH among the two groups ($p= 0.34$). There was strong negative correlation between the levels of serum creatinine and free T3 ($r = -0.63$, $p = 0.00$), and also between the levels of serum creatinine and free T4 ($r = -0.49$, $p =0.00$). Blood uea also showed a significant correlation with free T3 ($r = -0.52$, $p = 0.00$), and with free T4 ($r= -0.38$, $p = 0.00$). The levels of TSH showed insignificant relation with changes in blood urea and serum creatinine.

Conclusion: This study showed that with deterioration in functional capacity of kidneys, thyroid hormone levels in circulation undergo a significant change. So evaluation of thyroid function status should be regarded as an important part of treatment in patients of chronic renal failure to achieve best results.

Keywords: Chronic Kidney Disease, Proteinuria, Subclinical Thyroid Disorders, Primary Hypothyroidism.

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INTRODUCTION

Patients with end stage renal disease display a variety of endocrine disturbances, of which the most common are diabetes mellitus and thyroid disorders.[1] An epidemiological study[2] suggested that chronic kidney disease (CKD) is associated with a higher prevalence of primary hypothyroidism, both overt and subclinical. The study showed prevalence of subclinical hypothyroidism of 7% in patients with estimated GFR (Glomerular filtration rate) $\geq$ 90 ml/min per 1.73 sq.m. In this study, prevalence of subclinical hypothyroidism was found to be 17.9% in patients with estimated GFR (Glomerular filtration rate) < 60 ml/min per 1.73 sq.m. Hence, prevalence of hypothyroidism was found to be increased with fall in glomerular filtration rate (GFR).

The interactions between kidney and thyroid functions have been known for years. The kidneys play an important role in metabolism, transport, degradation and excretion of thyroid hormones.[3] So impaired kidney function leads to disturbed thyroid physiology. This includes disturbance in thyroid hormone production, distribution and excretion.[4] Mostly, these thyroid disorders associated with CKD are subclinical. At same time, thyroid hormone has been known to play a very vital role in growth, development and functional capability of kidneys.[5] The children with congenital hypothyroidism have a higher prevalence of congenital renal anomalies.[6] This fact supports that thyroid hormones play an important role in development of kidneys during early embryogenesis. It has been well known that hypothyroidism decreases, while the hyperthyroidism increases the kidney-to-weight ratio by a not fully understood mechanism.[7]

In view of the variability of thyroid function status in patients with CKD, this prospective study was done to establish a correlation, if any between thyroid dysfunction and severity of renal disease.

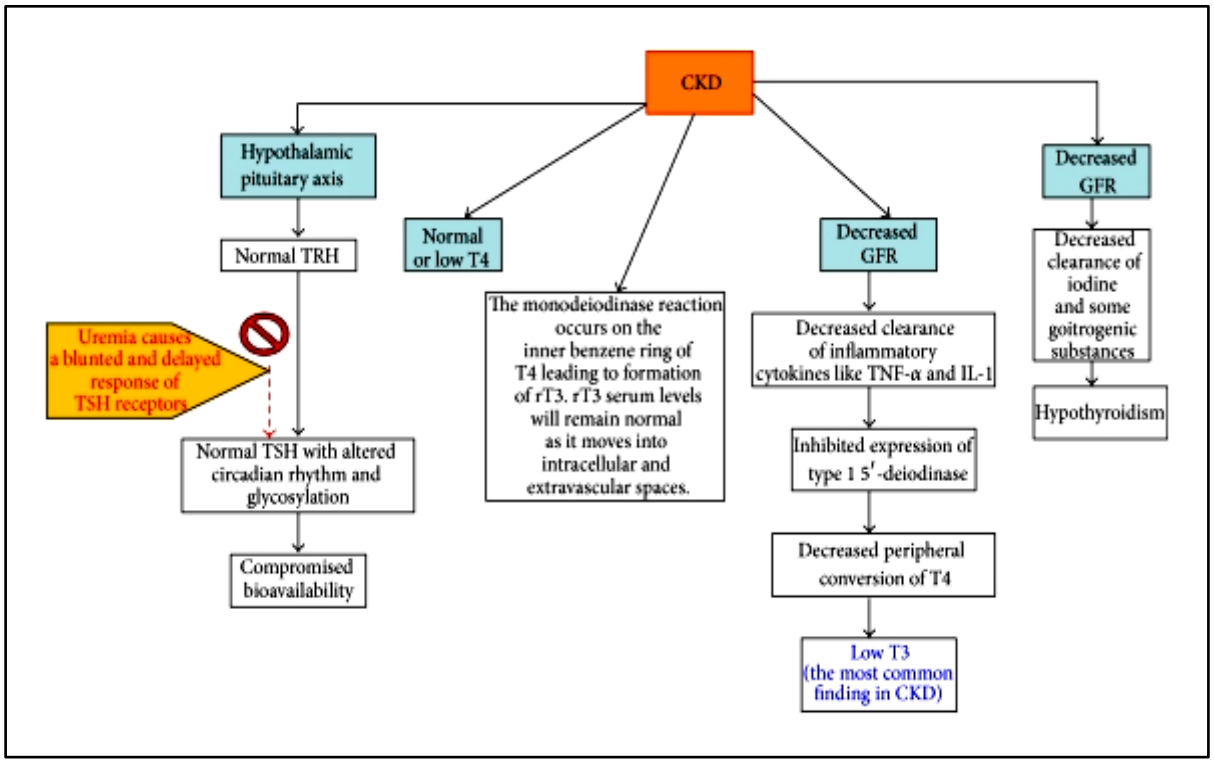


Figure 1: Pathogenesis of effects of chronic kidney disease (CKD) on thyroid function parameters

MATERIALS AND METHODS

It was a prospective case-control study. The study was carried out in GGS Medical College Faridkot. 50 cases of CKD and 50 healthy controls were enrolled for the study. Both the groups were age and sex-matched. Patients with diabetes mellitus, chronic liver failure, auto-immune diseases and those on steroid therapy were excluded from the study. Patients with previous history of thyroid disorders prior to the onset of renal disease were also excluded from the study.

The diagnosis of CKD was established on the basis of clinical profile and biochemical tests which included blood urea, serum creatinine and creatinine clearance calculated from Cockgraft Gault formula.[8]

For evaluation of thyroid status, a detailed clinical history of the subject was taken on a pre-designed proforma. Examination was done which included measurement of body weight, body mass index, pulse rate and palpation for enlarged thyroid gland. Then each patient was evaluated for hypothyroidism or hyperthyroidism by separate questionnaires.[9,10] Summed scores of plus 20 or above in either the hypothyroidism questionnaire or hyperthyroidism questionnaire indicated a high probability of thyroid dysfunction.

Blood sampling and lab investigations:

After 12 hours overnight fasting, around 4 ml of drawn from the study subjects by venepuncture. Blood samples were centrifuged at 3000 rpm for 15 minutes, and serum was obtained. The following investigations were done on serum for each patient and control:

1. Serum free tri-iodothyronine(fT3)
2. Serum free thyroxine(fT4)
3. Serum thyroid stimulating hormone(TSH)

These hormones were measured on Beckman Coulter Access-2 chemiluminescence machine. Measurement is based on the principle of competitive binding immunoenzymatic assay.[11]

Reference ranges for these thyroid hormones are[11]:

Free T3 (2.5-3.9 pg/ml)

Free T4 (0.61-1.12 ng/dl)

TSH (0.35- 5.5 mIU/L)

Routine blood investigations included blood urea, serum creatinine, uric acid, electrolytes, fasting blood sugar and liver function tests. Blood sugar and liver function tests were done to exclude the patients with diabetes mellitus and chronic liver failure. Statistical analysis was done using SPSS version 17 software. All the data obtained was presented as mean ± S.D. All the important parameters were compared in Group A (patients with chronic kidney disease) and Group B(healthy controls), and p value was calculated. A p value < 0.001 was considered to be statistically significant.

Zulewski's Hypothyroidism clinical score.	
CHARACTERISTICS	
Symptoms	
Diminished Sweating	12
Hoarseness	07
Paraesthesia	14
Dry skin	21
Constipation	14
Impairment of hearing	02
Weight increase	18
Physical signs	
Slow movements	13
Delayed ankle reflex	16
Coarse skin	14
Periorbital puffiness	15
Cold skin	14
Women <55 years	10

RESULTS

The mean values of blood urea, serum creatinine, creatinine clearance and thyroid hormones have been depicted in Table 1. Comparisons were made for thyroid hormone status between the cases with chronic kidney disease and healthy controls. It was found that both free T3 and free T4 were significantly reduced in patients with chronic kidney disease as compared to healthy controls (p=0.00,p=0.00). On other hand, TSH levels remained to be unchanged in patients group compared to controls (p=0.34). Correlation analysis was performed between renal function and thyroid function parameters. It has been depicted in table 2. The levels of free T3 and free T4 were found to be negatively correlated to the levels of blood urea and serum creatinine. It was found that values of free T3 (rather than values of free T4) had stronger negative correlation with levels of serum creatinine (rather than levels of blood urea). With increase in serum creatinine in chronic kidney disease patients, there was corresponding fall in serum free T3. The TSH values did not show any significant change with changes in the levels of blood urea or serum creatinine.

Table 1: Comparison of important parameters in the two study groups (parameters expressed as Mean ± 1 S.D.)

Parameter	CKD cases	Healthy controls	p value*
Blood urea (mg %)	91.3 ± 18.6	28.2 ±5.3	<0.001
Serum creatinine (mg %)	9.19 ± 1.40	0.89 ± 0.25	<0.001
Creatinine clearance (using CG formula in ml/min)	86.9 ± 14.1	119.4 ± 3.2	<0.001
Free T3 (pg/ml)	1.78 ± 0.45	3.02 ± 0.39	<0.001
Free T4 (ng/dl)	0.61 ± 0.18	0.99 ± 0.12	<0.001
TSH (µlU/ml)	2.99 ± 0.35	2.83 ± 0.31	0.34
Age (in years)	52.5 ± 5.4	52.3 ± 5.8	0.56

* p value < 0.001: Highly Significant

Table 2: Correlation analysis between renal function parameters and thyroid function parameters

Variable	Correlation	Free T3	Free T4	TSH
Urea (mg%)	r value	-0.52	-0.38	-0.19
	p value	0.00**	0.00**	0.04*
Creatinine (mg%)	r value	-0.63	-0.49	0.005
	p value	0.00**	0.00**	0.96
Creatinine clearance (ml/min)	r value	0.63	0.45	-0.06
	p value	0.00**	0.00**	0.46

r value = Pearson's correlation coefficient, p value denotes level of significance, *p value < 0.001: Highly Significant

Figure 2: Scatter plot showing correlation between free T3 and serum creatinine in patients with CKD

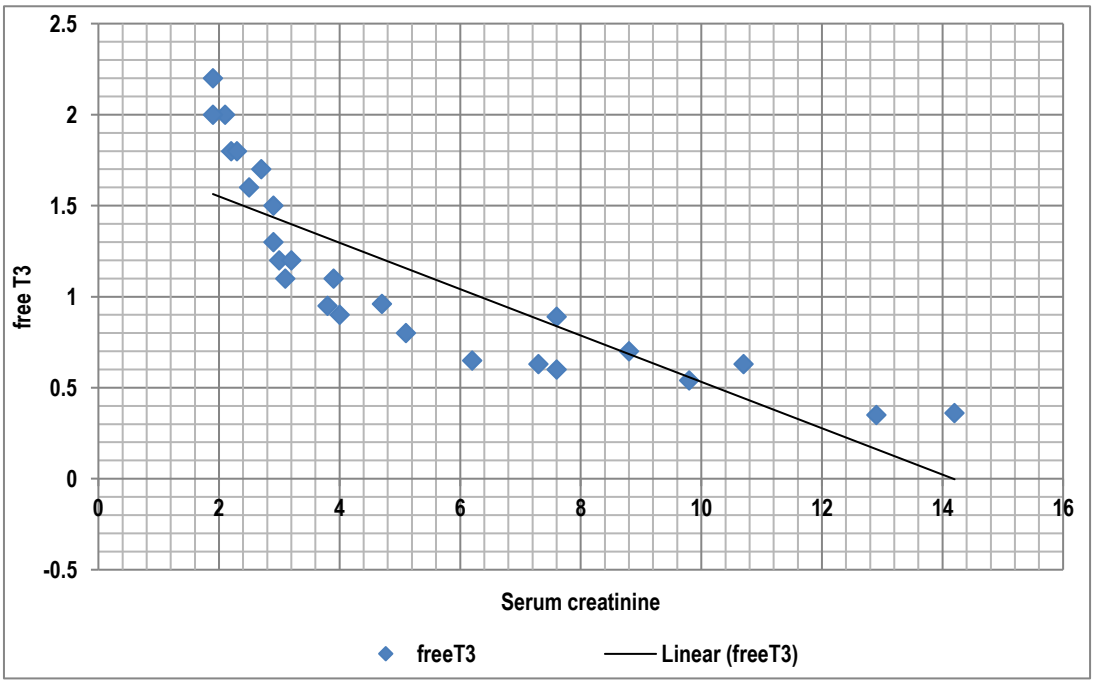


Figure 3: Scatter plot showing correlation between free T4 and serum creatinine in patients with CKD

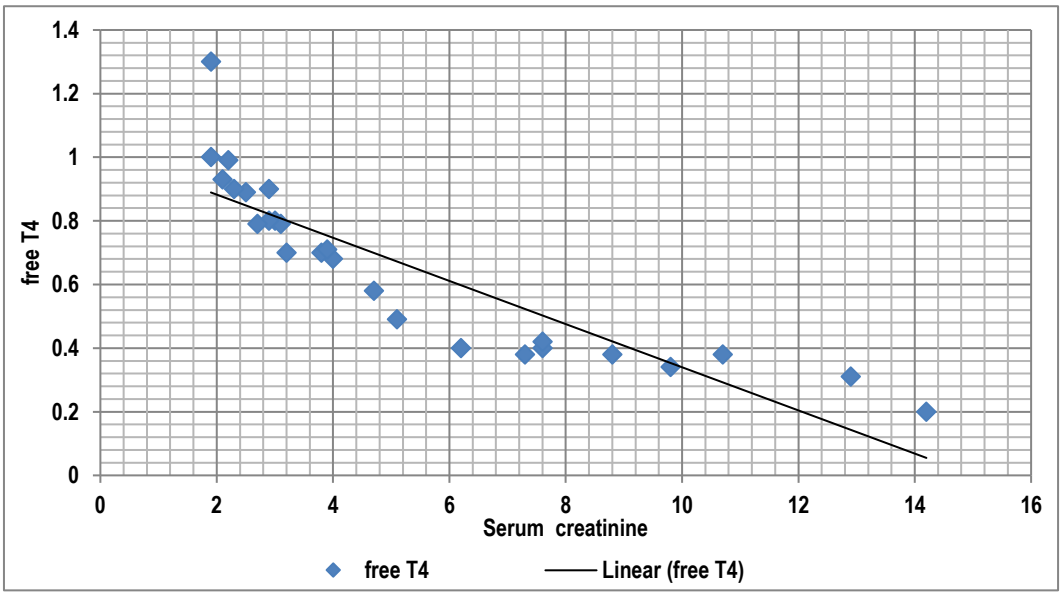


Figure 4: Scatter plot showing correlation between free T3 and blood urea in patients with CKD

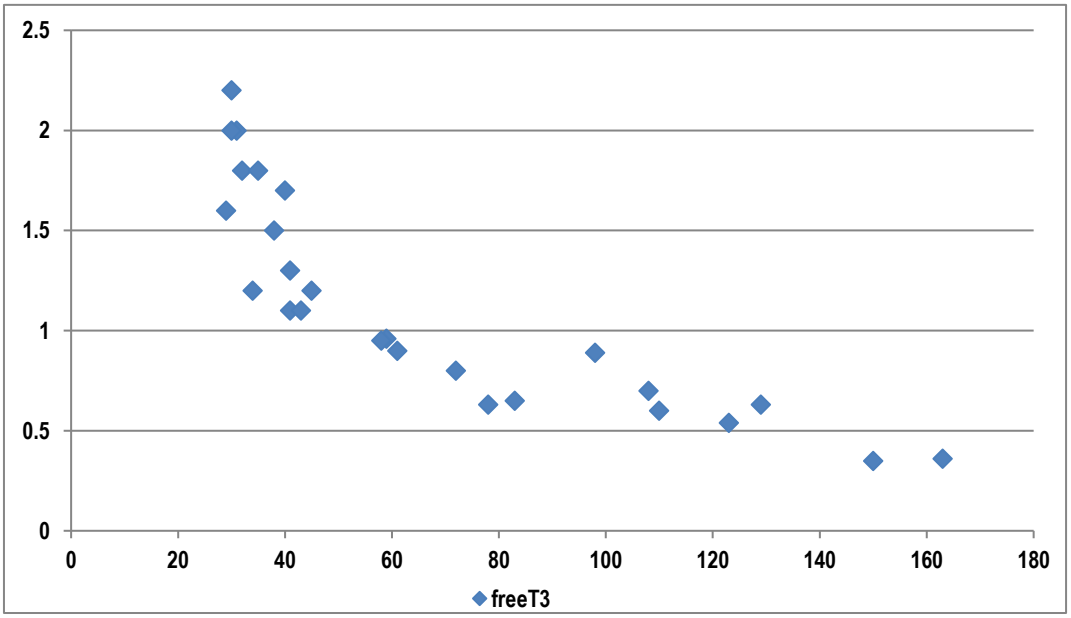
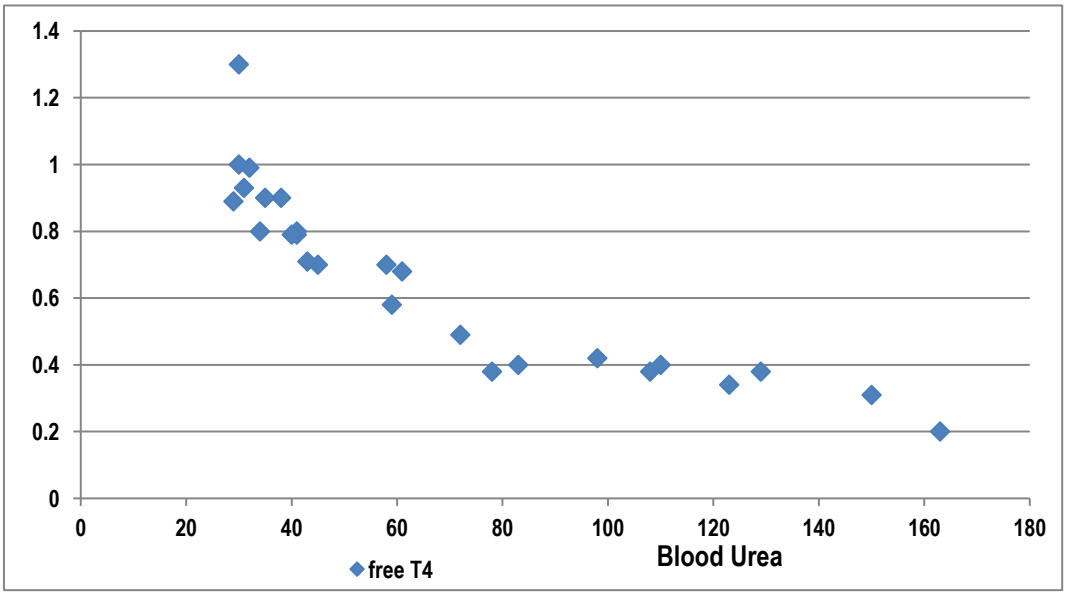


Figure 5: Scatter plot showing correlation between free T4 and blood urea in patients with CKD



DISCUSSION

Patients with chronic kidney disease often have signs and symptoms suggestive of thyroid dysfunction. Hence the diagnosis of thyroid disease is of utmost importance in these patients. A study by Zoccali C et al[12] reported that total and free T3 levels behave as survival markers in patients with chronic kidney disease. The data depicted in our study primarily dealt with clinical symptom sign index and biochemical parameters.

Out of the fifty cases with chronic kidney disease, thirty two patients (64%) had low free T3 and free T4 both. Eleven of these patients had very low free T3 (<1 pg/ml). Low T3 syndrome is the most frequently observed thyroid alteration in patients with chronic renal failure.[13,14]

In uraemia, there is impaired peripheral conversion of T4 into T3. Wiederkehr MR et al[15] documented that chronic metabolic acidosis associated with chronic kidney disease may contribute to this effect. Decreased conversion of T4 into T3 may also be related to malnutrition and humoral factors including cytokines and immune complexes, which are generally associated with chronic kidney disease.[16]

Iodine is primarily excreted by kidneys via glomerular filteration. A study by Ramirez G et al[17] found that serum iodine concentration is high in chronic kidney disease, but it is not correlated with the degree of renal failure. This leads to increased iodine store in thyroid gland, which in turn causes decreased conversion of T4 into T3. This iodine excess has been associated with increased prevalence of goiter and hypothyroidism seen in renal failure.[18]

The decresed T3 levels can also be attributed to the increased excretion of bound and free T4 in urine of chronic renal failure patients.[19] In CKD with glomerulopathy, several mechanisms have been depicted in pathogenesis of hypothyroidism. Proteinuria causes urinary losses of thyroxine binding globulin, albumin and pre-albumin, as well as thyroid hormones bound to them. Hence proteinuria causes decrease in total T4, and sometimes decrease in total T3 as well.[20] These patients may remain euthyroid because their free T3 and free T4 are normal. But in patients with low thyroid reserve, overt hypothyroidism may develop.[21]

In our study, only ten patients (20%) had increased TSH levels(and that too, below 8 μ IU/ml) despite significantly low free T3 and free T4. Both acute kidney injury and chronic kidney disease are accompanied by notable effects on hypothalamus-pituitary-thyroid axis.[22]

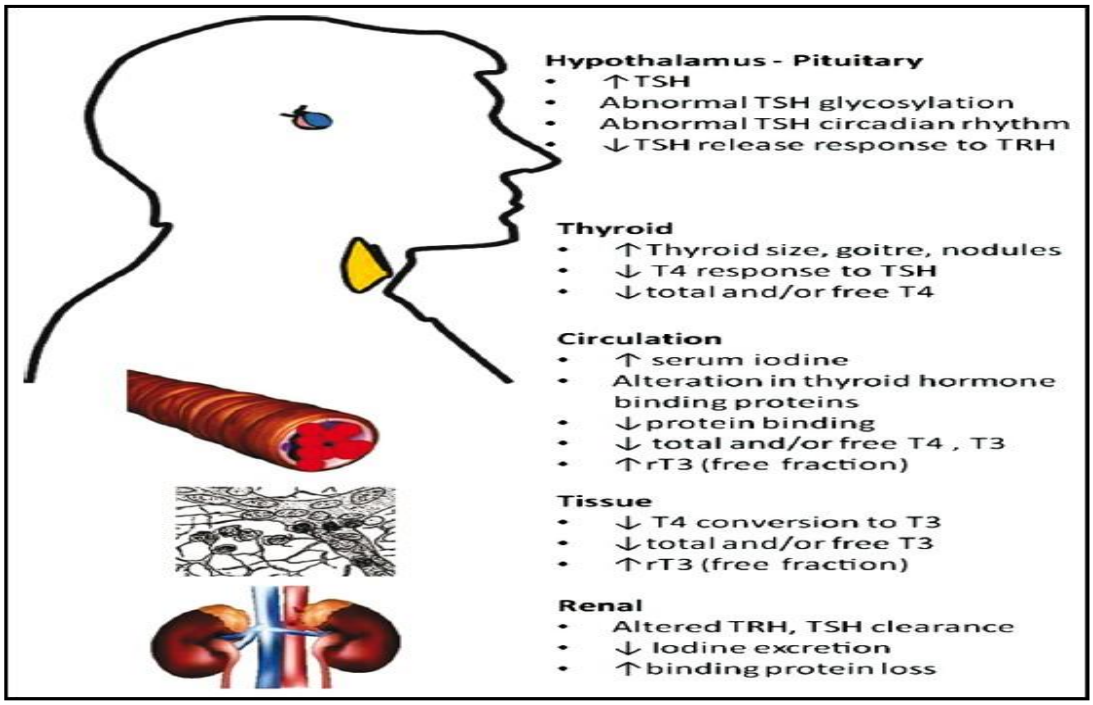


Figure 6: Effects of chronic kidney disease (CKD) on hypothalamus-pituitary- thyroid axis

Iglesias P et al[23] observed that secretion of TSH is impaired in uraemia. In chronic kidney disease, serum TSH concentration is usually normal or elevated, but its response to TRH is generally low.[24,25]

A study by Paqualini T et al[26] supported the evidence of hypothalamus-pituitary-thyroid abnormality in children with end stage renal disease(ESRD). In CKD, cirdanian rhythm of TSH and TSH glycosylation are also affected. The latter may cause decreased bioavailability of TSH.

Another study by Weetman AP et al[27] suggested the association of intrathyroidal and pituitary disturbances in uraemic patients. So thyroid dysfunction acquires special characteristics in those patients with advanced kidney disease.[28]

CONCLUSION

Our study concluded that kidney and thyroid function and dysfunction both are inter-related through several mechanisms. So from a clinical perspective, a physician treating a patient of chronic kidney disease should simultaneously diagnose and treat the associated thyroid disorder. Along with regular monitoring of blood urea and serum creatinine, their laboratory panel should also include freeT3, freeT4 and TSH.

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REFERENCES

1. Knochell JP. Endocrine changes in patients on chronic dialysis. In: "Replacement of function by dialysis". Drukker W, Parsons FM, Maher JF, editors. 2nd edition. Boston: Martinus Nijhoff Publishers; 1983, pp 712-23.
2. Chonchol M, Lippi G, Salvagno G, Zoppini G, Muggeo M and Targher G. Prevalence of subclinical hypothyroidism in patients with chronic kidney disease. Clinical Journal of the American Society of Nephrology. 2008; 3: 1296–1300.
3. Kaptein EM. Thyroid function in renal failure. Contributions to Nephrology 1986; 50: 64–72.
4. Kaptein EM, Feinstein EI and Massry SG. Thyroid hormone metabolism in renal diseases. Contributions to Nephrology.1982; 33:122–35.
5. Gattineni J, Sas D, Dagan A, Dwarakanath V and Baum MG. Effect of thyroid hormone on the postnatal renal expression of NHE8. American Journal of Physiology(Renal Physiology) 2008; 294: F198–F204.
6. Kumar J, Gordillo R, Kaskel FJ, Druschel CM and Woroniecki RP. Increased prevalence of renal and urinary tract anomalies in children with congenital hypothyroidism. Journal of Pediatrics. 2009; 154: 263–266.
7. Vargas F, Moreno JM, Rodriguez-Gomez I, et al. Vascular and renal function in experimental thyroid disorders. European Journal of Endocrinology. 2006; 154: 197–212.
8. Botev R, Mallie JP, Couchoud C, et al. Estimating Glomerular Filtration Rate: Cockcroft–Gault and Modification of Diet in Renal Disease Formulas Compared to Renal Inulin Clearance. Am Soc Nephrol. 2009; 4(5): 899–906.
9. Crook SJ, Murray IPC and Waynes EJ. Staistical methods applied to the clinical diagnosis of thyrotoxicosis. Qr J Med. 1959; 28:211-34
10. Billewicz WZ, Chapman RS, Crooks J, et al. Statistical methods applied to the clinical diagnosis of hypothyroidism. Qr J Med. 1969;38:255-66
11. Clinical Laboratory Technical Procedure Manuals: Approved Guideline; fourth edition 2006, Vol. 22#5(22).
12. Zoccali C, Mallamaci F, Tripepi G, Cutrupi S and Pizzini P. Low triiodothyronine and survival in end-stage renal disease. Kidney International. 2006; 70: 523–528.
13. Lo JC, Chertow GM, Go AS and Hsu CY. Increased prevalence of subclinical and clinical hypothyroidism in persons with chronic kidney disease. Kidney International. 2005; 67: 1047–52.
14. Witzke O, Wiemann J, Patschan D, Wu K, Philipp T and Saller B. Differential T4 degradation pathways in young patients with preterminal and terminal renal failure. Hormone and Metabolic Research. 2007; 39: 355–58.
15. Wiederkehr MR, Kalogiros J and Krapf R. Correction of metabolic acidosis improves thyroid and growth hormone axes in haemodialysis patients. Nephrology, Dialysis, Transplantation. 2004; 19:1190–97
16. Dudani RA, Desai KB, Mehta MN, Mani LS and Charya VN. Thyroid dysfunction in uremia. J Assoc Phys India. 1981; 29: 1038–40.
17. Ramirez G, O Neill W Jr, Jubiz W and Bloomer HA. Thyroid dysfunction in uremia: evidence for thyroid and hypophyseal abnormalities. Annals of Internal Medicine.1976; 84: 672–676.
18. Sato K, Okamura K, Yoshinari M, et al. Reversible primary hypothyroidism and elevated serum iodine level in patients with renal dysfunction. Acta Endocrinologica. 1992; 126: 253–59.
19. Pagliacci MC, Pelicei G and Grigani F. Thyroid function tests in patients undergoing maintenance peritoneal dialysis. Nephron.1987; 46: 225–30.
20. Junglee NA, Scanlon MF and Rees DA. Increasing thyroxine requirements in primary hypothyroidism: don't forget the urinalysis. Journal of Postgraduate Medicine. 2006; 52: 201–203.
21. Feinstein EI, Kaptein EM, Nicoloff JT and Massry SG. Thyroid function in patients with nephrotic syndrome and normal renal function. American Journal of Nephrology. 1982; 2: 70–76.
22. Lim VS, Fang VS, Katz AI and Refetoff S. 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. 1977; 60: 522–34.
23. Iglesias P and Diez JJ. Thyroid dysfunction and kidney disease. Eur J Endo. 2009; 160: 503-15.
24. Singh PA, Bobby Z, Selvaraj N and Vinayagamoorthi R. An evaluation of thyroid hormone status and oxidative stress in undialyzed chronic renal failure patients. Indian Journal of Physiology and Pharmacology. 2006; 50: 279–84.
25. Witzke O, Wiemann J, Patschan D, Wu K, Philipp T and Saller B. Differential T4 degradation pathways in young patients with preterminal and terminal renal failure. Hormone and Metabolic Research. 2007; 39: 355-58.
26. Paqualini T. Zantieifer D, Balzaretti H, et al. Evidence of hypothalamus pituitary thyroid abnormalities in children with end stage renal disease. J Paed. 1991; 118:873-78
27. Weetman AP, Weightman DR and Scanlon MF. Impaired dopaminergic control of thyroid stimulating hormone secretion in chronic renal failure. Clinical Endocrinology. 1981; 15: 451–56.
28. Kaptein EM, Quion-Verde H, Chooljian CJ, et al. The thyroid in end stage renal disease. Medicine. 1988; 67: 187–197.

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