

# A Study of Biochemical Abnormalities of Thyroid Function Test in Chronic Renal Failure Patients

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## ABSTRACT

### BACKGROUND

Chronic renal failure is a progressive decline in renal function with loss of nephrons leading to signs and symptoms of uraemia. CRF affects endocrine systems in multiple ways including abnormal hormone production, metabolism, feedback regulation and altered tissue sensitivity. Thyroid hormones are essential for an adequate growth and development of kidneys; conversely, kidney is not only an organ of metabolism and elimination of thyroid hormones, but also a target of iodothyronine actions. Renal disease leads to significant changes in thyroid function. In CRF, iodide uptake is low due to decreased iodide clearance. Protein loss may alter the binding capacity of hormones and abnormal constituents like urea may blunt the tissue responsiveness to thyroid hormones. The association of different glomerulopathies less frequently tubulointerstitial diseases have been reported with hypo or hyper function of the thyroid.

### METHODS

Patients with chronic kidney disease in Department of Medicine and Nephrology, Down Town Hospital, Guwahati, Assam, were included in the study. Both male and female patients with varying grades of CRF, more than 18 years of age were included in the study. It was cross sectional study.

### RESULTS

Age range in the study varies from 27-87 years. Male patients were 30 accounting for 60% and female patients were 20 accounting for 40%. Creatinine clearance ranges from 3.4 mL/min - 32.3 mL/min. Blood urea values varied from 55-257 mg/dL, the mean being 121.04. Serum creatinine levels varied from 1.8-21.16 mg/dL, the mean value being 7.58 mg/dL. The study range of serum T3 was 0.643 - 2.3 nmol/L, (normal range 1.49 - 2.60 nmol/L), serum T4 was 37.7 - 140 nmol/L (normal range 71.2-142 nmol/L) and serum TSH was <0.015 - >100 micro IU/mL (normal range 0.465-4.68 mIU/mL). In our study 10 patients had low T3 syndrome, 2 patients had low T4 Syndrome, 9 patients had hypothyroidism, 8 patients had subclinical hypothyroidism and 1 patient had hyperthyroidism.

### CONCLUSIONS

In the current study 50 cases with varying grades of chronic renal failure with age >18 years are selected according to inclusion and exclusion criteria as mentioned. The present study is limited in the sense that data comes from a population served in a tertiary healthcare hospital. Therefore, it's not a population-based study. However, the findings of this study will serve to analyse the association between thyroid dysfunction, if any, in chronic renal failure patients.

### KEYWORDS

Thyroid Function Test, Chronic Renal Failure, Thyroid Dysfunction

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**BACKGROUND**

Normal renal function is very important for homeostasis, so much, that situations in which renal functions are impaired can be life threatening. Diseases of the kidneys are among the most important causes of death and disability in many countries throughout the World. The National Kidney Foundation states that kidney diseases rank 3rd amongst life threatening disease, after cancer and heart disease. About 200,000 persons go in to terminal kidney failure every year. Million more suffer from lesser forms of kidney diseases.<sup>1</sup> Chronic kidney disease (CKD) encompasses a spectrum of pathophysiologic processes associated with abnormal kidney function, and a progressive decline in glomerular filtration rate (GFR).<sup>1</sup> The term chronic renal failure (CRF) typically corresponds to stage 3-5 CKD.<sup>1</sup> The term End Stage Renal Disease (ESRD) represents the terminal stage of CKD where there is uremic syndrome.<sup>1</sup> Number of prevalent CKD patients will continue to rise, reflecting the growing elderly population and increasing numbers of patients with diabetes and hypertension.<sup>2</sup> Symptoms and overt signs of kidney disease are often absent until renal failure supervenes.<sup>1</sup>

Chronic renal failure is progressive decline in renal function with loss of nephrons leading to signs and symptoms of uraemia. CRF affects endocrine systems in multiple ways including abnormal hormone production, metabolism, feedback regulation and altered tissue sensitivity. Thyroid hormones are essential for an adequate growth and development of kidneys, conversely kidney is not only organ of metabolism and elimination of thyroid hormones but also a target of iodothyronine actions. Renal disease leads to significant changes in thyroid function. In CRF iodide uptake is low due to decreased iodide clearance, protein loss may alter binding capacity of hormones and abnormal constituents like urea may blunt tissue responsiveness to thyroid hormones. The association of different glomerulopathies less frequently tubulointerstitial diseases have been reported with hypo or hyper function of thyroid organ.<sup>2</sup>

In view of variability of thyroid functions in CRF, we have decided to do a study of thyroid function test in CRF and to establish co-relation if any between thyroid dysfunction and severity of renal disease.

**METHODS**

**Study Site**

This is a cross sectional study conducted in the Departments of General Medicine & Nephrology, Down Town Hospital, Guwahati, Assam, among 50 patients with chronic kidney disease selected through random sampling for a period of one year between January 2017 and December 2017.

**Inclusion Criteria**

- Both male and female patients with varying grades of CRF with age more than 18 years.

**Exclusion Criteria**

- Patients with CRF with age less than 18 years.
  - Patients with diagnosed thyroid disorder before occurrence of renal failure.
  - Patients on thyroid hormone replacement or on anti-thyroid drugs or has undergone any thyroid surgery.

**Justification of Sample Size**

Minimum sample size was calculated using the formula-

$$n = \frac{Z^2 p (1-p)}{d^2}$$

Where n is sample size. Z is standard normal variate corresponding to confidence level. P is expected prevalence. D is precision or margin of error corresponding to effect size.

Minimum Sample size was calculated to be 270.60 with confidence level of 90% and precision of 5%. Expected prevalence was taken to be 50% as determined by reviewing previous studies. Keeping in mind the given duration of the study and concerned patient flow in this setup, the sample size will be 50 subjects, with the aim to complete the study within stipulated time.

After obtaining clearance and approval from the institutional ethics committee and written informed consent, the patients presenting as renal deficit and fulfilling the inclusion/exclusion criteria will be enrolled in the study. Chronic renal failure was diagnosed by recording the clinical profile, biochemical tests (serum creatinine, blood urea, creatinine clearance) and radiological methods (USG abdomen) and staging of chronic kidney disease will be done in all patients by eGFR based on MDRD formula. The clinical diagnosis of CKD was done based on elevation of Serum Creatinine for more than 3 months. Estimated Glomerular Filtration Rate (eGFR) was calculated by the equation from the Modification of Dietin Renal Disease study:

$$eGFR (mL/min/1.73m^2) = 1.86 \times (PCr)^{1.154} \times (age)^{0.203}$$

Multiply by 0.742 for women and multiply by 1.21 for African, Americans. Based on eGFR, patients are categorized in various clinical stages of CKD as follows-

Stage	eGFR, mL/min/1.73m <sup>2</sup>
0	>90
1	≥90
2	60-89
3	30-59
4	15-29
5	<15

Patients in various stages of the disease were studied for changes in clinical manifestations and thyroid function test. Detailed clinical history was collected from the patient. Details were collected from hospital records also. After obtaining the informed written consent, blood was collected under aseptic precautions for investigations for assessment of renal failure: Serum Creatinine by Jaffe’s method. Blood urea estimation was done by using diacetylmonoxime (DAM) method. Investigations for assessment of thyroid function:

Total T3, Total T4, and TSH. Thyroid function will be evaluated on the basis of clinical examination of thyroid gland and biochemical tests such as fasting serum total T3, serum total T4, TSH concentrations using CLIA (chemiluminescence) method.

**Other Investigations Performed**

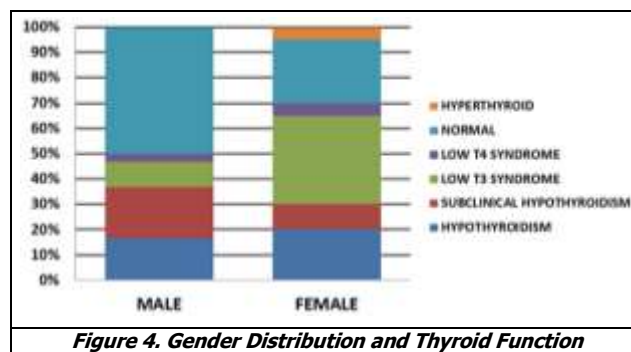
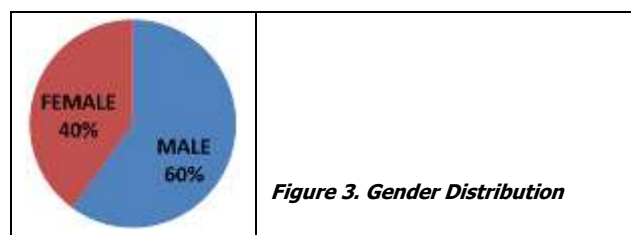
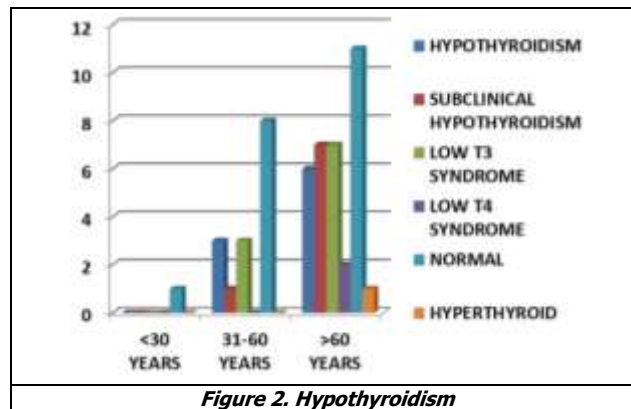
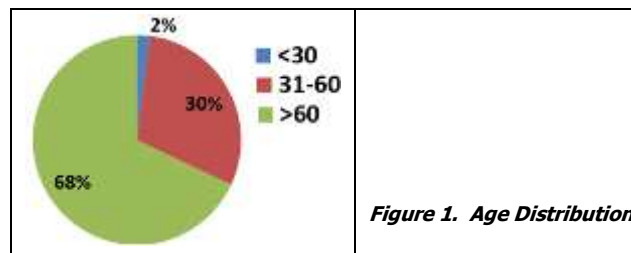
1. Urine for specific gravity and broad cast.
2. Serum calcium and phosphorus.
3. Serum cholesterol for hypothyroidism.
4. 24 hours urine protein and serum protein to rule out nephrotic syndrome and hypoproteinaemia respectively.
5. ECG and chest x ray to look for features for hypothyroidism and renal failure like pleural effusion, pericardial effusion.
6. USG abdomen for evidence of chronic renal failure.
7. Thyroid functions will be correlated to various grades of chronic renal failure and will be evaluated for effect of chronic renal failure on thyroid function.

**Statistical Methods**

Descriptive statistical analysis was carried out in the present study. Results of continuous and categorical measurement are presented on mean and percentage- age, gender, CRF stage, thyroid function test. Data is presented in charts, table formats, bar diagram, pie diagram for ease of understanding and interpretation. Microsoft office word 2007 and Microsoft office excel 2007 was used to generate table, bar diagram and pie diagram.

**RESULTS**

In our study we evaluated 50 patients with various stages of chronic kidney disease. Out of 50 subjects chosen consecutively according to inclusion criteria, the largest proportion belong to age group >60 years 34 (68%) patients followed by 31 to 60 years 15 (30%) patients and 1 (2%) patients below 30 years of age. Mean age group was 64.78 while mean age group for male and female were 66.33 and 62.45 respectively. Out of 50 subjects in different age group more thyroid function derangement was found in age group >60 years of age which is 66.67%, 87.5%, 70%, 100% and 100% patients for hypothyroid, subclinical hypothyroid, low T3 syndrome, low T4 syndrome and hyperthyroid respectively. In age group 31-60 years we found 33.33%, 12.5% and 30% patients of hypothyroid, subclinical hypothyroid and low T3 syndrome respectively, while age group <30 years did not show any thyroid function abnormality. Our study shows that 60% were males and 40% were females. Majority of the subjects in the sample were males. Sex ratio is male: female=1.5:1. In gender distribution of thyroid function, we found that thyroid dysfunction were more common in females compared to males except subclinical hypothyroidism which is more common in males (20%) than in females (10%).



Cases	Hypertension				Total	%
	Yes	%	No.	%		
Diabetes Mellitus						
Yes	34	72	2	4	36	72
No	8	16	6	12	14	28
Total	42	84	8	16	50	100

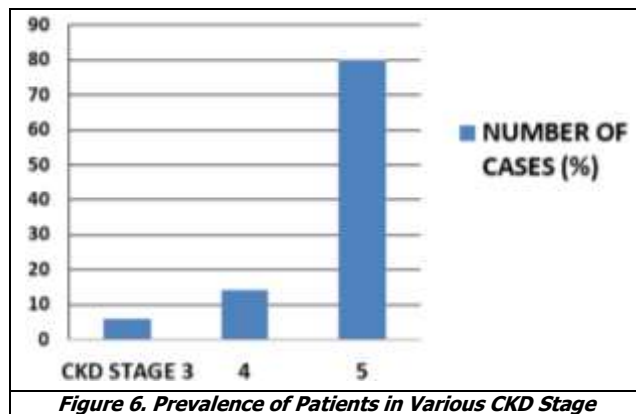
**Table 1. Prevalence of Diabetes Mellitus and Hypertension**

	No.	%
Yes	12	24
No	38	76
Total	50	100

**Table 2. Prevalence of Symptoms of Hypothyroidism**

Thyroid Function	CKD Stage					
	3		4		5	
	No.	%	No.	%	No.	%
Hypothyroid	0	0	1	14.28	8	20
Subclinical Hypothyroid	0	0	1	14.28	7	17.5
Low T3 Syndrome	2	66.67	2	28.57	6	15
Low T4 Syndrome	0	0	0	0	2	5
Normal	1	33.33	3	42.85	16	40
Hyperthyroid	0	0	0	0	1	2.5
Total	3	100	7	100	40	100

**Table 3. Relationship between CKD Stage and Thyroid Function**



Out of 50 patients of CKD 36 (72%) patients were diabetic, 42(84%) were hypertensive while 34(68%) patients were having diabetes as well as hypertension and 6(12%) patients neither had diabetes nor hypertension.

Symptoms of hypothyroidism like tiredness, somnolence, weight gain, cold intolerance, constipation, hoarseness of voice etc. were studied in the study population. Study shows that out of 50 patients of CKD, 12 patients (24%) only were symptomatic and majorities (76%) were asymptomatic. Biochemically 9 patients were hypothyroid and 3 were having subclinical hypothyroid range. ur study shows that out of the 50 patients in the study, 3 patients (6%) belonged to stage 3, 7 patients (14%) to stage 4 and 40 patients (80%) to stage 5. Out of 50 patients in study, 10 patients (20%) had hypothyroidism, 6 patients (12%) had subclinical hypothyroidism, 10 patients (20%) had low T3 syndrome, 2 (4%) low T4 syndrome, while 1 patient (2%) found to be hyperthyroid. Out of 50, 30 patients (60%) had some thyroid dysfunction. Study shows that out of 50 patients in study group, 40 patients(80%) had stage 5 CKD, out of that 8 patients (20%) had hypothyroidism when compared to stage 3 (0%) and stage 4 (14.28%). A 17.5% of patients off stage 5 CKD had subclinical hypothyroidism when compared to stage 3 (0%) and stage 4(14.28%). Low T3 syndrome in stage 3, 4 and 5 CKD were 66.67%, 28.57% and 15% respectively, low T4 syndrome was found to be 5% that too only in stage 5 CRF while 2.5% of patients in stage 5 CKD was found to be hyperthyroid. So, higher the stage of CKD, higher was the prevalence of thyroid dysfunction.

## DISCUSSION

In the current study 50 cases with varying grades of chronic renal failure with age >18 years are selected according to inclusion and exclusion criteria as mentioned. The present study is limited in the sense that data comes from a population served in a tertiary healthcare hospital. Therefore, it's not a population-based study. However, the findings of this study will serve to analyse association between thyroid dysfunction if any in chronic renal failure patients. In our study 50 patients of CRF fulfilling the criteria for CRF were studied, out of these 50 patients, 30 were male

and 20 were female patients with age varying from 27-87 years. Mean age group was 64.78 while mean age group for male and female were 66.33 and 62.45 respectively.

Among the 50 patients studied, 60% of patients were males and 40% patients were females. This study showed male preponderance similar to study done at Coimbatore<sup>3</sup> where male constituted 68% of study population. Other studies done in Ludhiana<sup>4</sup> and Pondicherry<sup>5</sup> revealed male population of 73.33% and 60% respectively. Out of 50 patients of CRF, 36 (72%) patients were diabetic, 42(84%) were hypertensive while 34(68%) patients were having both diabetes as well as hypertension and 6(12%) patients neither had diabetes nor hypertension. Of the 50 patients, 40 patients had GFR of less than 15 mL/minute (stage 5 CRF) accounting to 80%, 7 patients had GFR ranging from 15 - 30 mL/minute (stage 4 CRF) accounting for 14% and 3 patients had GFR ranging from 30-60 mL/minute (stage 3 CRF) accounting for 6%. Among the patients studied most were in the range of creatinine clearance <15 mL/minute.

The blood urea value varied from 55-257 mg/dL, the mean value being 121.04 mg/dL. The creatinine values varied from 1.8-21.16 mg/dL, the mean value being 7.58 mg/dL. In our study, ultrasound abdomen was done in all patients, that showed features of loss of cortico-medullary differentiation in 35 patients accounting for 70% and the remaining 15 patients had bilateral contracted kidneys which accounts for 30%. In this study out of 50 patients, 19 patients had low serum T3 levels (38%). 9 patients among low serum T3 value, they also had low T4 and high TSH suggesting primary hypothyroidism (18%). So, excluding 9 patients of hypothyroidism 10 patients (20%) had low T3 syndrome. 11 patients had low T4 levels in our study, out of which 9 patients had low T3 and high TSH suggesting primary hypothyroidism. Excluding hypothyroidism 2 (4%) patients had low T4.

Most of the studies have reported low T3 values in CRF patients. Low T3 had been reported in Ramirez et al,<sup>6</sup> Hegedus et al,<sup>7</sup> Beckett et al,<sup>8</sup> Ponajil Singh et al,<sup>5</sup> P Iglesias and JJ Diez<sup>2</sup> and many others. Ramirez et al<sup>9</sup> and Spector et al<sup>8</sup> study showed linear correlation between mean serum T3 and T4 and severity of renal failure. We also noticed linear correlation between mean serum T3 and T4 and severity of renal failure in our study. In our study we found that the mean TSH levels (excluding cases of hypothyroidism) were within normal limits for various stages of chronic renal failure. But the TSH levels did not showed any linear correlation ship with severity of renal failure and we noticed that majority of cases showing some thyroid dysfunction were more in stage 5 of renal failure but this can be attributed to small size of study population and relatively less number of patients in stage 3 and 4 of disease. The TSH values in our study ranged from <0.015 - >100 micro IU/mL, the mean value being 5.85. Among 50 patients, 20, 9 and 8 patients were euthyroid, hypothyroid and subclinical hypothyroidism respectively, while 12 patients showed other thyroid disorder in form of low TT3 and low TT4 syndrome. In contrary to many other studies we found 1 case of hyperthyroidism.

Many studies on thyroid hormone levels in CRF have revealed variable results. Overall prevalence of thyroid dysfunction was reported as 48%, 38.6% and 58% by Pakhle K et al,<sup>10</sup> Khatiwada S et al<sup>11</sup> and Manasa A.S. Gowda et al<sup>12</sup> respectively as compared to 60% in our study. 9.5% of patients with CKD had subclinical hypothyroidism. 7% of patients with mild CKD had low thyroid function, compared to 18% of those with moderate CKD.<sup>13</sup> In our study, hypothyroidism is present in 18% of the patients which is relatively higher compared to other studies but this can be attributed to geographical location and high prevalence of hypothyroidism in general population as reported by Neelakshi Mahanta et al.<sup>14</sup> In this study one patient had clinical and biochemical features of hyperthyroidism.

Age incidence of CRF patients with low T3 syndrome in our study was 0% were less than 30 years of age, 30% were in the age group 30-60 years of age and 70% were more than 60 years of age. It tells that as the age increases number of patients with low T3 syndrome also increases. 6 (15%) patients of low T3 syndrome were in stage 5 CRF, 2 (28.57%) patients were in stage 4 CRF and 2 (66.67%) patients were in stage 3 CRF. 2 (5%) patients of low T4 syndrome were in stage 5 CRF and no patients were stage 3 and 4 of CRF. In our study thyroid hormone profile was altered in CRF patients, mainly as the stage of CRF advanced, most of cases were seen in the stage 5 CRF. Most common thyroid dysfunction was low T3 and low T4 with normal TSH levels, which is consistent with Singh S et al<sup>15</sup> study.

Our study has several limitations that are to be considered. First, because this study is cross-sectional, hospital based study not representing the whole population. Second, the definition of kidney function was based on estimated GFR rather than on more precise measurement of kidney function, such as iothalamate clearance. Moreover, thyroid function tests could be requested when there was a clinical suspicion of altered thyroid function, thus tending to inflate the magnitude of the estimate of the relation.

### CONCLUSIONS

In our study, out of 50 patients, the overall prevalence of thyroid dysfunction is 60% in chronic kidney disease. 18% of CKD patients had hypothyroidism. 2% of cases revealed hyperthyroidism. 16% had subclinical hypothyroidism. 24% had some thyroid hormone abnormalities like low T3 syndrome (20%) and low T4 syndrome (4%). As the age increases, thyroid dysfunction also increases. The overall prevalence of thyroid dysfunction was found to be more common in females than in males except for subclinical hypothyroidism which was more in males (20%) compared to females (10%). The change in the serum levels of T3 and T4 in patients with CKD can be considered as being protective, promoting conservation of protein. There is progressive increase in the number of patients with Low T3 and T4 syndrome with the severity of renal failure. There was a significant correlation between the prevalence of

thyroid dysfunction and the stage of chronic kidney disease. Higher the degree of renal insufficiency, higher was the prevalence of thyroid hormone abnormalities and the levels of thyroid profile i.e. T3 and T4 decreases, TSH increases as severity of renal failure increases. Excluding hypothyroidism and subclinical hypothyroidism, the mean TSH level in our study is within normal limits which indicate abnormality in hypophyseal mechanism of TSH release in uremic patients as the as the TSH response to the TRH was blunted.

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