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## A prospective study on thyroid functions in chronic kidney disease patients: In tertiary care centre

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### Abstract

**Background and Objectives:** Unusual thyroid function tests are frequent in chronic kidney disease patients. The kidneys play an important role in thyroid hormone metabolism by converting T<sub>4</sub> to T<sub>3</sub> (the active metabolite). Low plasma free T<sub>3</sub> in ESRD is a marker of inflammation and endothelial activation, and it has been linked to an increased risk of death from any cause. The present study has been conducted to look for biochemical abnormalities in thyroid function tests in chronic kidney disease, as well as to correlate the severity of CKD and changes in thyroid indices.

**Methods:** In a cross-sectional study, thyroid function tests [TT<sub>3</sub>, TT<sub>4</sub>, FT<sub>4</sub>, TSH] were estimated by CLIA in 60 patients of chronic kidney disease who were in various stages. Symptoms of hypothyroidism, thyroid hormone abnormalities and CKD stage were analyzed using Chi-square test and ANOVA tests.

**Results:** Among the mean age was 48.8 ± 12.2 years, of which 38 were male and 22 females. The mean value of TT<sub>3</sub> in CKD stage 3, 4, 5 were 1.01±0.39; 1.05± 0.6; 0.95±1.09 µg/mL respectively. (p= 0.02 Significant). The mean value of TT<sub>4</sub> in CKD stage 3, 4, 5 were 6.3± 2.4; 5.5± 1.5; 5.11 ± 1.01 µIU/ml, respectively. (p=0.71 Not significant).

**Conclusions:** Total T<sub>3</sub> and total T<sub>4</sub> levels were found to decrease progressively as the stage of CKD increased. There was no statistically significant relationship between TT<sub>4</sub> and CKD stage. The prevalence of thyroid dysfunction and the stage of chronic kidney disease were found to be significantly related. The severity of renal failure increases the prevalence of thyroid hormone abnormalities; the levels of thyroid profile, i.e. T<sub>3</sub>, T<sub>4</sub>, and TSH, decrease as the severity of renal failure increases. Thyroid hormone abnormalities could represent a risk factor for cardiovascular disease and might also be implicated in kidney disease progression.

**Keywords:** chronic kidney disease, thyroid function test, hypothyroidism, subclinical hypothyroidism

### Introduction

Chronic kidney disease (CKD) is a significant contributor to morbidity and mortality related to non-communicable diseases and should be progressively treated to achieve the UN's Sustainable Development Goal to mitigate premature mortality due to non-communicable diseases by a third by 2030. Since the 1960s, the costs of CKD healthcare have risen, with the availability of renal replacement techniques making it easier for patients with end-stage renal disease (ESKD) to undergo life-saving but expensive treatment in the long term. The number of people receiving renal replacement therapy reportedly exceeds 25 million and is expected to more than double to 54 million by 2030 [1]. CKD is usually a progressive, irreversible condition that is the 8th leading cause of death in the United States. According to the population study, 1 in 10 American adults (more than 30 million people) suffer from some level of CKD. It has been estimated from population survey data that at least 6% of the adult population in the United States has CKD at stages 1 and 2. An unknown subset of this group will progress to more advanced stages of CKD. An additional 4.5% of the U.S. Population is estimated to have stages 3 and 4 CKD. The most frequent cause of CKD is diabetic Nephropathy, most often secondary to Type 2 DM [2].

Indian prevalence of CKD as 13–15.04% with stage 1, 2 and 3 as 6.62%, 5.40% and 3.02% respectively. India being the diabetic capital of the world, diabetic Nephropathy is the commonest cause of CKD. There are about 7.85 million CKD patients in India [3].

Patients with End Stage Renal Disease display a variety of endocrine disturbances. However the evidence of endocrine dysfunction commonly consists only of laboratory abnormalities, many of which are not associated with apparent clinical signs and symptoms of the disease [4]. Among which Thyroid function has been extensively evaluated in patients with CKD.

CKD is a widely recognized cause of no thyroidal illness causing thyroid dysfunction, i.e., alteration in thyroid hormones in the absence of underlying intrinsic thyroid disorder [5].

Chronic kidney disease affects thyroid function in multiple ways, including low circulating thyroid hormone concentration, altered peripheral hormone metabolism, disturbed binding to carrier proteins, possible reduction in tissue thyroid content and increased iodine stores in thyroid glands. TT3, TT4, FT3 are decreased more commonly in patients with CKD. But FT4, TSH levels are expected in these patients and indicate euthyroid status. We speculate that the low thyroid state in uremia serves to defend against protein wasting, and misguided attempts to crowded thyroid hormone stores may worsen protein malnutrition [6]. This research aims to identify the prevalence of thyroid dysfunction in CKD patients to act at an early stage based on hormone imbalances and prevent cardiovascular risk and progressive kidney function decline.

**Aim & Objectives**

- Study of biochemical abnormalities of thyroid function tests in chronic kidney disease.
- To correlate the severity of chronic renal failure and alterations of thyroid indices.

**Source of data**

Minimum 60 male and female patients with CKD for Eighteen months admitted in NRI Medical College and Hospital, Guntur were included under study.

**Study Period**

Study was conducted between March 2019 and August 2020 for a period of 18 months.

**Sample Size**

60 patients both male and female patients with CKD over period of 18 months admitted to NRI Medical College & Hospital, Guntur, AP, India.

**Inclusion Criteria**

- Symptoms of uremia for 3 months or more.
- Ultrasound evidence of chronic kidney disease
- Bilateral contracted kidneys- size less than 8 cm in male and size less than 7 cms in female.
- Poor corticomedullary differentiation.
- Supportive laboratory evidence of CKD like anemia, urine specific gravity, changes in serum electrolytes, etc.,
- Patients with CKD more than 18 years.

**Exclusion Criteria**

- Patients with CKD less than 18 years.
- Patients who have been diagnosed to be having thyroid disorder.

- Patients on drugs altering thyroid profile like amiodarone, steroids, dopamine, phenytoin, estrogen pills, iodine containing drugs.
- Patients on thyroid hormone replacement or on antithyroid drugs.

**Study Design**

Single Centre, cross sectional study. In the study period of 18 months among patients admitted in Nephrology ward after applying inclusion and exclusion criteria 60 patients were included in this study. Patients who fulfilled the criteria for CKD and who are on conservative management and hemodialysis. Informed consent was obtained from all patients.

After selecting the patients, fulfilling the above criteria, about 5ml of blood sample is collected in non heparinized serum bottle and sent for thyroid profile.

Components of thyroid profile in this study are serum total triiodothyronine (TT3), serum total thyroxine (TT4), serum thyroid stimulating hormone (TSH), serum free triiodothyronine (FT3), serum free thyroxine (FT4).

Kidney function was assessed by estimated creatinine clearance which was calculated by using the Cockcroft – Gault Equation.

1. Cockcroft – Gault Equation: Estimated creatinine clearance (ml/mt)

$$= \frac{(140 - \text{Age}) \times \text{body weight in k.g.}}{72 \times \text{Pcr (mg/dl) (multiply by 0.85 for women)}}$$

Thyroid function was assessed by measuring TT3, TT4 and TSH level in serum. Serum FT4 was estimated for all TSH levels >5 mIU/L. Serum TT3, TT4, and FT4 were estimated by competitive chemiluminescent immuno assay. TSH estimation was done by ultra-sensitive sandwich Chemiluminescent Immuno assay (CLIA).

Blood urea estimation was done by using diacetyl monoxime (DAM) method. And Serum creatinine estimation was done by modified kinetic Jaffe method.

Detailed clinical history and clinical examination was undertaken with preference to thyroid and renal diseases. The following investigations were performed.

1. Urine for specific gravity and broad cast.
2. Peripheral smear for anemia and burr cells.
3. Renal parameters like blood urea, Serum creatinine and Creatinine clearance (using Cockcroft- Gault formula).
4. Serum electrolytes with calcium and phosphorus.
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 kidney disease

**Results**

In our study we evaluated 60 patients with various grades of chronic kidney disease

**Table 1:** Sex distribution

Sex	Case	
	Number	Percentage
Male	38	63.67
Female	22	33.34
Total	60	100

Among 60 patients in the sample 38 patients were males, and 22 patients were females.

**Table 2:** Age Distribution

Age group (years)	Cases	
	Number S	Percentage
21-30	8	13.33
31-40	8	13.33
41-50	12	20
51-60	22	36.67
>60	10	16.66
TOTAL	60	100
RANGE	21-70	
MEAN	48.6	
S.D	12.21	

The range was from 21 to 70 years. Most of the patients in the sample were in the age group of 51-60 years. And mean age was 48.6 years.

**Table 3:** Prevalence of diabetes mellitus and hypertension

Cases DM	Hypertension				Total	%
	Yes	%	No	%		
Yes	15	25	11	18.33	26	43.33
No	12	20	22	36.67	34	56.6
Total	27	45	32	53.33	60	100

The out of 60 patients with CKD, 22 patients (44%) had diabetes, and 23 patients (46%) were hypertensive. 13

patients (26%) had both diabetes and hypertension. Eighteen patients (36%) were neither having diabetes nor hypertension.

**Table 4:** Prevalence of symptoms of hypothyroidism

Symptoms	Cases	
	Numbers	Percentage
Yes	18	30
No	42	70
Total	60	100

Symptoms of hypothyroidism like tiredness, somnolence, weight gain, cold intolerance, constipation, hoarseness of voice etc., were studied in CKD in the study population. Of the 60 patients with CKD, 18 patients (30%) only were symptomatic and majorities (70%) were asymptomatic. Biochemically 5 patients were hypothyroid and rest 8 were in subclinical hypothyroid range.

**Table 5:** Prevalence of patients on hemodialysis

Hemodialysis	Cases	
	Number s	Percentage
Yes	36	60
No	24	40
Total	60	100

Out of 60 patients with CKD, 36 patients (60%) underwent multiple hemodialysis and 24 patients were on conservative medical management.

**Table 6:** Prevalence of patients in various CKD stage

CKD stage	Cases	
	Number s	Percentage
3	10	16.66
4	8	13.33
5	40	66.67
Total	60	100

Of the 60patients in this sample, ten patients (16.66%) belonged to stage 3, and 8 patients (13.33%) to stage 4, and

40 patients (66.67%) to stage 5.

**Table 7:** Prevalence of abnormalities of thyroid function based on thyroid function tests.

Impression	Cases	
	Number s	Percentage
Hypothyroidism	6	10
Subclinical hypothyroidism	13	21.67
Low TT3 or TT4 with normal TSH	17	28.33
Normal	24	40
Total	60	100

Out of the 60 patients in this sample, 6 patients (10%) had hypothyroidism 13 patients (21.67%) had subclinical hypothyroidism 17 patients (28.33%) had Low TT3 or TT4

with normal TSH, Totally 35 patients (58.33%) had some abnormalities in thyroid function.

**Table 8:** Relationship between CKD Stage and Symptoms of Hypothyroidism

CKD stage	Symptom s				Total number
	Yes		No		
	Number	%	Number	%	60
Stage 3	-	-	8	100	8
Stage 4	3	33.33	6	66.67	9
Stage 5	14	35.0	26	65.0	40
Chi square value	2.9945				
P value	0.23				

Out of 60 patients 17 had symptoms suggestive of hypothyroidism, of which 3 patient (33.33%) was in stage 4 CKD and rest 14 patients (66.67%) were in stage 5 CKD.

Though symptoms were prominent in advanced renal failure, this correlation was statistically not significant.

**Table 9:** Relationship between CKD Stage & thyroid dysfunction

Thyroid Dysfunction	CKD Stage					
	3		4		5	
	No	%	No	%	No	%
Hypothyroidism	-	-	-	-	5	13.15
Subclinical Hypothyroidism	-	-	1	16.67	9	23.68
Low TT3 or TT4 with Normal TSH	-	-	1	16.66	13	26.31
Normal	6	100	4	66.67	21	36.84
Total	6	100	6	100	48	100
Chi square value						12.785
P value						0.0413

Of the 60 patients in the study group, 48 patients had stage 5 CKD. 13.15% of stage 5 CKD pts had hypothyroidism when compared to stage 3 (0%) and stage 4(0%). A 23.68% of patients of stage 5 CKD had sub clinical hypothyroidism when compared to stage 3(0%) and stage 4 (16.67%).

Low TT3 or TT4 with normal TSH abnormalities in stage 3 is 0% and in 4 & 5 CKD were 16.67% and 26.31% respectively. So higher the stage of CKD, higher was the prevalence of thyroid dysfunction. This correlation was found to be statistically significant.

**Table 10:** Relationship between CKD Stage & hematological parameters and their significance

Parameters	CKD stage						significance		
	3		4		5		F*	P-value	
	Mean	SD	Mean	SD	Mean	SD			
Bl Urea	75.76	29.65	91.5	23.5	163.02	38.03	14.75	<0.01	HS
Sr Creat	2.88	0.29	3.4	0.5	7.05	2.1	13.47	<0.01	HS
T3	1.01	0.34	1.05	0.6	1.07	1.94	4.72	0.02	S
T4	6.33	2.42	5.54	1.55	5.11	2.02	0.335	0.71	NS
TSH	2.16	1.25	3.67	1.35	5.76	3.94	9.683	<0.01	HS

**Discussion**

The kidney is normally involved in the metabolism, degradation, and excretion of numerous thyroid hormones. As a result, it is not surprising that impaired kidney function leads to abnormal thyroid physiology. Changes in hormone production, distribution, and excretion may occur at all levels of the hypothalamic-pituitary-thyroid axis [7, 8]. Many hormonal systems are affected by CKD, yet it remains unclear to what extent these changes are responsible for manifestations of the uremic syndrome. Patients with CKD often have signs & symptoms suggestive of thyroid dysfunction & hence the diagnosis of thyroid disease in these patients has obvious prognostic implications. The data reported deals primarily with the clinical symptoms sign index & biochemical parameters [9]. Several investigators have studied thyroid hormone levels in CKD and obtained variable results. Overall, 9% 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 [10]. Recently, Quion-Verde *et al.* have reported a higher prevalence of upto 5% of frank hypothyroidism in patients with chronic renal failure than hospitalized patients with normal renal function (0.6%) [11]. In an Indian study of 127 patients with CKD studied, 93 patients (73%) showed significant [*p* value (<0.05)] reduction in their TT3, TT4, FT3 levels in serum [12]. Many studies conducted in CKD showed Low TT3 [13], normal TT3 low FT3 [13], normal FT3 in patients on HD. Some studies have reported low TT4 (low T4 syndrome), normal TT4 [14] and low normal or lower FT4 [14] levels. Basal concentrations of circulating TSH have been found at

different levels in different studies. Normal levels of TSH were reported from previous Indian studies [15]. Thus, a multitude of defects at all levels of hypothalamic pituitary-thyroidal-peripheral axis does seem to exist in uremia [8]. In the majority of studies, TT4 concentrations were found to be low or low normal. However, FT4 levels were within normal limits. This is attributed to lowering of thyroxine binding globulin concentration as well as presence of inhibitors of thyroid hormone bindings to the thyroid binding proteins. Levels of TT3 and FT3 suffer further reductions in CKD, which is thought to be due to impairment in denomination of T4, a principal process by which T3 is produced at peripheral levels [12]. In our study, study of thyroid dysfunctions in chronic renal failure is done with 60 cases. Cases were selected according to inclusion and exclusion criteria which are mentioned earlier. The cases and controls included different age groups. The range was from 21 to 70 years. Most of the patients in the sample were in the age group of 51-60 years. Six (10 percent) of the 60 patients in this sample had hypothyroidism. Subclinical hypothyroidism was found in 13 patients (21.67 percent). 17 patients (28.33 percent) had low TT3 or TT4 with normal TSH, and 35 patients (58.33 percent) had some thyroid function abnormalities. Among 14 patients with some thyroid hormone abnormalities 3 patients (6%) had only decreased TT4, 6 patients (12%) had decreased TT3, 5 patients (10%) had decreased TT4 and TT3. All these patients were euthyroid and TSH levels were within normal limits. Excluding hypothyroidism and subclinical hypothyroidism, the mean TSH level in our study is within normal limits. The mean TSH levels are also within normal limits for the

various ranges of GFR. But TSH level does show any linear correlation with the severity of renal failure. This is consistent with the study conducted by Joseph *et al.* and Hardy *et al.* [16]. These studies demonstrated abnormality in hypophyseal mechanism of TSH release in uremic patients as the as the TSH response to the TRH was blunted.

Other studies conducted by Spector and Ramirez *et al.* [17] revealed low T3 T4 level with high TSH level suggesting maintenance of pituitary thyroid axis.

In our study total 13 patients were having symptoms suggestive of hypothyroidism of which 5 were hypothyroid biochemically and rest 8 patients had TFT was in subclinical range. Thus some of the symptoms of CKD tend to be overlap with hypothyroidism and may pose difficulty in diagnosis.

Our study is consistent with the results of Avasthi *et al.* [9] and Zoccali C *et al.* [18] study showing low T3, low T4 and normal or mild elevation of TSH. Yet it is unclear that to what extent these changes are responsible for the manifestations of uremic syndrome. From the various studies it has been suggested that this thyroid profile derangements is a part of body adaptation mechanism.

Relationship between CKD stage and thyroid dysfunction: Higher the stage of CKD, there is an increased prevalence of thyroid dysfunction in CKD patients [19].

In our study, 13.15% of stage 5 CKD patients had hypothyroidism when compared to stage 3 (0%) and stage 4 (0%). 9 patients of stage 5 patients had subclinical hypothyroidism when compared to no patients in stage 3 and 1 patient in stage 4. Low TT3 or TT4 according to stage 4 and stage 5 are found in 1 and 13 patients respectively.

TT3, TT4, FT4 levels progressively decreased as the CKD stage increased but FT4, TSH levels were normal except in patients with overt hypothyroidism. Even though symptoms of hypothyroidism were prominent in advanced stage of renal disease, statistical analysis did not show significant correlation.

Despite the recent considerable improvements in renal replacement therapy, cardiovascular disease still remains the main cause of morbidity and mortality in CKD patients. It is evident from various studies conducted by Cheung, *et al.* (2000) [20], Maurya *et al.* (2021) [21], Castro *et al.* (2021) [22] and etc.

So many traditional and nontraditional risk factors are therefore cardiovascular disease and its related morbidity and mortality. Apart from them hypothyroidism and subclinical hypothyroidism are linked to an increased risk of cardiovascular disease and reduced cardiac function.

Patients with CKD are at greatly increased risk of thyroid dysfunction. "Thyroid hormone abnormalities could represent a risk factor for cardiovascular disease and might also be implicated in kidney disease progression" [10].

## Conclusion

Hyperthyroidism is not typically related with chronic kidney disease (CKD), but it has been shown to exacerbate the disease. When treating patients with chronic kidney disease (CKD), it is critical to take into account all clinical aspects as well as thyroid symptoms. According to the findings of numerous evidence-based research and current clinical cases, there are different links between thyroid dysfunction and renal impairment, as well as the reverse association. Clinicians, including nephrologists, must examine the risks of thyroid disease and the proper treatment for it in the

context of managing chronic kidney disease (CKD). The likelihood of developing or aggravating renal impairment in patients who get proper thyroid disease treatment is lower in these patients. Treatment of individuals with a minor elevation of TSH (less than 10 IU/mL) resulted in a negative nitrogen balance as a result of enhanced muscle catabolism, resulting in a negative nitrogen balance. Patients undergoing kidney transplantation should have low T3 levels checked by their physicians, as low levels are related with graft failure.

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