

# Evaluation of Thyroid Dysfunction in Patients of Chronic Kidney Diseases.

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## ABSTRACT

**Background:** Chronic Kidney failures are progressive diseases and are divided into stages 1 to 5 based on the severity. Glomerular filtration rate (GFR) falls as the severity of kidney failure increases. Hypothyroidism was found to be present along with chronic renal failure and a presence of Low T3 was associated with increased chance of mortality due to cardiovascular complications. Significant association was known to exist in between thyroid dysfunction and chronic kidney disease progression. **Aims & objectives:** To study the pattern of thyroid dysfunction in chronic kidney disease population (who are not dialyses dependent) admitted at a tertiary care hospital of Tripura & to evaluate the correlation existing in between severity of kidney failure and thyroid dysfunction. **Methods:** 260 chronic kidney disease patients were included in the study. Diagnosis of chronic kidney failure was performed as per criteria laid down by Kidney Disease Outcome Quality Initiative. Blood was drawn for estimation of serum creatinine, GFR and thyroid profile. Data collected were analysed statistically and  $P \leq 0.05$  was considered statistically significant. The statistical software namely SPSS 15.0 were used for statistical data analysis. **Results:** Among 260 individuals 138 were male and 122 female with age ranging from 20 to 82 years with mean age of  $60.08 \pm 11.35$  years. Calculation of GFR showed a mean GFR of  $35.37 \pm 26.20$  & mean serum creatinine level of  $2.74 \pm 1.61$  mg/dl. Of the 260 patients, 68(26.1%), 74(28.5%), 74(28.5%), 31(11.9%) & 13(5%) patients belonged to CKD Stages 5,4,3,2 & 1 respectively. Low T3 is the most common thyroid dysfunction & the earliest abnormality noticed in CKD patients. The prevalence of low T3 syndrome in this study was 41.5% ( $n=108$ ). Increasing trend for Low T3 prevalence with increasing severity of CKD was noticed in this study and was statistically significant ( $P < 0.001$ ). The prevalence seen for LowT3 was CKD1-7.7%; CKD2-16.1%; CKD3-29.7%; CKD4-50% & CKD5-63.2%. Statistically significant correlation was also seen with increasing prevalence of hypothyroidism & fall in GFR as the severity of kidney dysfunction increased ( $P < 0.001$ ). **Conclusion:** The present study was done to study the correlation of thyroid dysfunctions and chronic kidney diseases. It was observed that hypothyroidism both subclinical and overt exist with CKD and the most early and common dysfunction was lowT3 syndrome. The prevalence of thyroid dysfunction increase significantly as kidney failure progress. Low T3 is associated with increased chance of mortality due to cardiovascular complications and serves as a prognostic indicator in CKD individuals.

**Keywords:** Glomerular filtration rate, chronic kidney disease, Low T3 Syndrome, hypothyroidism.

## INTRODUCTION

Glomerular filtration rate (GFR)  $< 60$  ml/min/1.73 m<sup>2</sup> for three and more months is defined as chronic kidney disease (CKD) according to Kidney Disease Outcome Quality Initiative.<sup>[1]</sup> Chronic kidney diseases are global threat to health in general and for developing countries like ours as the treatments are expensive and lifelong.<sup>[2]</sup>

A presumptive estimate of incidence of End State Kidney Disease (ESRD) in India is 100 per million

population.<sup>[3]</sup> Modi et.al. reported an age adjusted incidence of end stage kidney disease as 229/million population.<sup>[4]</sup> Agarwal et.al. used serum creatinine value of  $> 1.8$  mg/dl as cut-off for defining chronic renal failure (CRF) & the prevalence of CRF in the adult population studied was 0.785%.<sup>[5]</sup>

In another recently published (2013) Indian study named Screening & Early Evaluation of Kidney diseases or the SEEK-study the prevalence of chronic kidney disease in India are as follows.<sup>[6]</sup>

Stage of kidney disease	e-GFR ml/min/1.73m <sup>2</sup>	Prevalence in %
1	$\geq 90$	7
2	60-89	4.3
3	30-59	4.3
4	15-29	0.8
5	$< 15$	0.8

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The total prevalence of CKD was 17.2%.

Chronic kidney disease is a progressive disease with progressive decline in renal function along with GFR.<sup>[7]</sup> The patho-physiological manifestations of chronic renal failure are diverse and results into multiple abnormalities of which fluid-electrolyte disturbances, cardio-vascular –pulmonary disturbances & endocrine-metabolic disturbances are life threatening. As GFR fall below 30% severity of clinical manifestations due to uremia supervene with resultant abnormalities in all body systems. When GFR falls below 5% (ESRD) continued survival is impossible without renal replacement therapy.<sup>[8]</sup>

Thyroid hormones are essential for development and growth of kidney along with water and electrolyte homeostasis. The hormones also help in maintenance of renal blood flow.<sup>[9]</sup> Thyroid hormone status affects renal functioning mass, measured as kidney to body mass ratio with hypothyroidism reducing it.<sup>[10]</sup> These effects of thyroid hormones on renal physiology are termed as pre-renal and direct renal effects. The pre renal effects are the influence of the thyroid hormones in maintenance of renal blood flow and direct effects of thyroid hormones on renal physiology are regulation of GFR & tubular secretory and reabsorptive processes, mainly of water reabsorption.<sup>[11]</sup>

Abnormalities in thyroid functions too have metabolic implications & influences basal metabolic rate, carbohydrate, fat and protein metabolism. Thyroid hormone has direct effect on heart & potentiates positive inotropic and chronotropic actions. These hormones are vital for optimal central nervous system functioning, with hypothyroidism associated with poor mentation, lack of memory and poor initiative.<sup>[12]</sup>

Patients with chronic renal disease have multiple endocrinal dysfunctions, amongst them thyroid involvements are frequently encountered of which spectrum of involvement includes sub-clinical hypothyroidism, hypothyroidism and sick euthyroid syndrome.<sup>[11]</sup> CKD affects hypothalomo-pituitary-thyroid axis and peripheral thyroid hormone metabolism.<sup>[13]</sup> Low T3 is the most common thyroid hormone dysfunction found in CKD.<sup>[14]</sup>

The low T3 syndrome is associated with higher levels of highly sensitive C- reactive protein, IL-6, malnutrition, low level of pre-albumin, increased endothelial dysfunction with poorer cardiac function. It causes poor survival with higher chances of cardiovascular mortality.<sup>[15]</sup>

Low T3 levels prior to renal transplant are associated with post-transplant risk of graft loss and is an independent predictor of mortality in haemodialysis patients.<sup>[16]</sup>

Recently much interest has been focused on sick euthyroid syndrome which is associated with increased risk of cardiac mortality due to increased risk of inflammation in CKD patients.<sup>[17]</sup>

Based on these results assessment of T3 is recommended as it acts as a sensitive predictor of mortality in CKD.<sup>[18]</sup>

It has been hypothesized that hypothyroidism is a modifiable risk factor in CKD & is associated with a burden of cardiovascular disease and mortality in CKD individuals but difficult to test as the testing faces a challenge of accurate testing of thyroid profile due to uremia.<sup>[19]</sup>

Hypothyroidism is termed as a link to cardiovascular diseases and death in CKD population.<sup>[20]</sup>

So increasing interest and focus has been laid in assessing thyroid hormone status in CKD population to identify the risk of deaths.<sup>[21]</sup> And there is a lack of other strong markers of cardiovascular mortality in this population.<sup>[22]</sup>

Low T3 thus serves as an important prognostic indicator of mortality in CKD.<sup>[22]</sup>

But there is a dearth of data in Indian scenario about the prevalence of thyroid dysfunction among CKD population who are not dialysis dependent and the present study was conceptualized with the aim of studying the prevalence of thyroid dysfunction and its pattern in CKD population attending a tertiary care hospital of our state and also to study the correlation of thyroid dysfunction with the different stages of CKD.

#### **Aims and Objectives**

1. To evaluate the pattern of thyroid dysfunctions in chronic kidney disease patients admitted at Department of Medicine of Agartala Government Medical College.
2. To study the correlation between thyroid dysfunction with severity of kidney disease based on the stages of CKD.

#### **MATERIALS AND METHODS**

The study was done at Department of Medicine at Agartala Government Medical College, Agartala Tripura.

The study was undertaken after obtaining due permission from Institutional Research Committee and Institutional Ethics Committee

The study was conducted for a period of one and half years

It is a cross sectional study

To calculate the sample size the Kish-Leslie formula (1965)<sup>[23]</sup> was used and a study population of 260 was estimated for conduction of study.

#### **Inclusion criteria**

All individuals diagnosed with CKD above 18 yrs of age, both male and female on conservative management and not haemodialysis dependent.

Cases were diagnosed on basis of history, physical examination, laboratory findings & ultra sonography All study participants were fully explained about the purpose of the study and consent in written was obtained.

**Exclusion criteria**

- 1) Patients with previously diagnosed thyroid illness, visible goitre & on medications influencing thyroid status.
- 2) Other systemic illness like already having cardiac involvement.
- 3) Those who declined consent.
- 4) CKD individuals who are on maintenance haemodialysis.

**Methodology**

Recruitment of Patients was done by fulfilling the criteria for CKD according to KDOQI.<sup>[1]</sup>

Detailed histories, through general examination were done and blood was drawn for biochemical examinations. Blood urea, serum creatinine and GFR were estimated for diagnosis of CKD & the diagnosis was further confirmed by doing ultrasonography of abdomen. Blood was also investigated for evaluation of thyroid profile.

Serum creatinine were estimated by using Jaffe's alkaline picrate method.<sup>[24]</sup>

GFR was estimated by using 4-variable MDRD formula.<sup>[25]</sup>

Thyroid function tests were estimated by ELFA technique by VIDAS analyzer from Biomerieux.

A decreased GFR < 60ml/min/1.73m<sup>2</sup> was taken as a diagnostic criteria of diagnosing CKD.<sup>[26]</sup>

An elevated serum creatinine level > 1.5 mg/dl has been considered as abnormal.<sup>[27]</sup>

The reference values for thyroid function tests are as follows-

- i) T3 : 0.92- 2.33 nmol/l
- ii) T4 : 60.0-120.0 nmol/l
- iii) FT3 : 4.0 - 8.3 pmol/l
- iv) FT4 : 10.6-19.4 pmol/l
- v) TSH: 0.25- 5.0µIU/ml.

The collected data was subjected for statistical analysis. P value was calculated at 95% confidence interval for variables using one way Anova test.<sup>[28]</sup>

Degrees of correlation were evaluated by Pearson's correlation test.<sup>[29]</sup> A P value ≤ 0.05 was considered statistically significant. The statistical software namely SPSS 15.0 were used for statistical data analysis.

**RESULTS**

**Table 1: Percentage & frequency of patients in various stages of CKD**

CKD Stage	GFR ml/min/1.73m <sup>2</sup>	Frequency	Percentage
Stage 1	≥ 90	13	5%
Stage 2	60-89	31	11.9%
Stage 3	30-59	74	28.5%
Stage 4	15-29	74	28.5%
Stage 5	<15	68	26.1%

**Table 2: Frequency of patients in various stages of CKD in relation to thyroid status function.**

Thyroid status	Total Nos. of individuals in each status of thyroid function (n=260)	CKD stage 1	CKD stage 2	CKD stage 3	CKD stage 4	CKD stage 5	P Value
Euthyroid	109	12	25	43	21	8	< 0.001
Low T3	108	1	5	22	37	43	<0.001
Subclinical hypothyroidism	22	0	1	4	8	9	0.019
Overt hypothyroidism	11	0	0	1	4	6	0.010
Low T4	7	0	0	2	3	2	0.336
Subclinical hyperthyroidism	3	0	0	2	1	0	0.698

A total of 260 participants were worked up for the present study

The ages of the study subjects ranged from 20 to 82 years. The mean age was 60.08±11.35 years. In this study there were 138 male (53.1%) & 122 (46.9%) female patients.

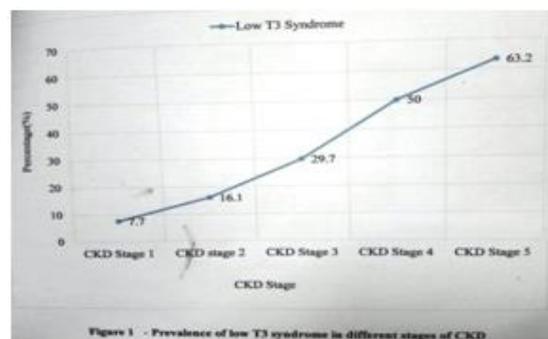
Based on GFR the classification of the study population (n=260) into 5 stages of CKD were done by MDRD formula:

Most of the study subjects are in CKD Stage 3 & 4 followed by stage 5, 2 and lastly 1

Thyroid profile estimation was done in all study subjects and the categories of thyroid status & their prevalence in 5 stages of CKD are:

The most common thyroid dysfunction encountered is Low T3 syndrome (41.5 %) and its prevalence increases with severity of CKD & this finding is statistically significant (P< 0.001). The next

common thyroid dysfunction seen was subclinical hypothyroidism (8.5%) followed by overt hypothyroidism (4.2%)



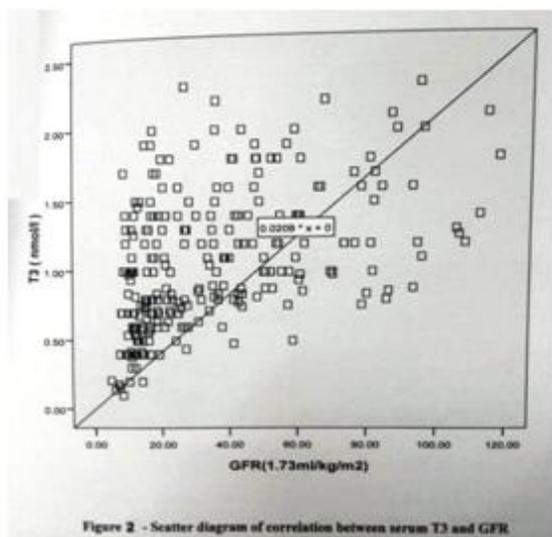
The prevalence of subclinical hypothyroidism and overt hypothyroidism also significantly increased as

the severity of kidney dysfunction increased and these values were also statistically significant ( $P < 0.001$  &  $P = 0.010$  respectively) where as by contrast the prevalence of LowT4 & subclinical hyperthyroidism were not statistically significant. The prevalence of Low T3 syndrome increased from 1.7% in CKD stage1 to 63.2% in CKD stage5. Similarly the prevalence of subclinical hypothyroidism increased from 3.2% in CKD stage 2 to 13.2% in CKD stage 5. Overt hypothyroidism increased from 1.4 % in CKD stage3 to 8.8% in CKD stage5. This increasing trend of prevalence of LowT3 with increasing stages of CKD 1 TO 5 was statistically significant with P value for trend  $P < 0.001$ ; calculated by extended Mantel-Haenszel test.<sup>[30]</sup>

**Table 3: Values of thyroid hormones in different stages of CKD & correlation with GFR.**

Thyroid hormone values	CKD1(GFR $\geq 90$ )	CKD2(GFR 60-89)	CKD3(GFR 30-59)	CKD4(GFR 15-29)	CKD5(GFR <15)
T3	0.88 - 2.31	0.76-2.0	0.48-2.0	0.40-2.2	0.10-1.70
FT3	3.6-7.8	3.1-8.2	2.6-8.2	2.0-7.8	1.0-6.4
T4	76-114	68-116.2	38-116.2	46-120	34-119
FT4	10.9 - 17.4	10.9-18.4	7.7-19.2	6.4-18.8	7.4-19.1
TSH	1.60 -4.0	0.40-8.0	0.16-18.0	0.14-60	0.40-40

The correlation of thyroid hormones & GFR was performed using Pearson correlation test. There was a positive correlation of T3 with decreasing GFR values as the grading of CKD stages increased & this finding was statistically strongly significant ( $P < 0.001$ ).



Alternately as a fall in T3 value is associated with rise in TSH; a negative co-relation was demonstrated in between GFR falling trend and TSH ( $P = 0.005$ ).

## DISCUSSION

The present study was aimed to evaluate the pattern of Thyroid dysfunction in chronic kidney disease patients admitted in medicine ward of Agartala Govt. Medical College and to study the correlation between thyroid dysfunction and decreasing trend of GFR values with increasing severity of kidney failure.

In this study 260 patients of CKD were taken, who fulfils the criteria for CKD according to KDOQI & are on conservative management. Of them 138 are males and 122 are females. Their age varied from 20 to 82 years with mean age of  $60.08 \pm 11.35$  years.

It was seen that gender of the patients bears no statistical significance on prevalence of thyroid dysfunctions in CKD patients.

Of the 260 patients, 68(26.1%), 74(28.5%), 74(28.5%), 31(11.9%) & 13(5%) patients belonged to CKD Stages 5,4,3,2 & 1 respectively. Majority of the patients coming for medical help were in stages 3 to 5 & they make up 83.1% of the study population. This trend shows patients comes late for medical help only when the disease had advanced.

The serum creatinine value varied from 0.6 to 7.0 mg/dl with a mean value of  $2.74 \pm 1.61$ mg/dl. In males the mean value was  $3.08 \pm 1.71$  & in females the value estimated was  $2.36 \pm 1.40$  mg/dl.

GFR was calculated in all cases and it ranged from 5 to 117.68 with a mean value of  $35.37 \pm 26.20$ . In males the mean value for GFR was  $35.50 \pm 27.16$  & females it was  $35.23 \pm 27.16$ .

The distribution and trend of both rising titre of serum creatinine and decreasing GFR values across the different increasing 5 stages of CKD are statistically significant ( $P < 0.001$ ).

Low T3 is the most common thyroid dysfunction & the earliest abnormality noticed in CKD patients. The prevalence of low T3 syndrome in this study was 41.5 % (n=108). These findings were in accordance with other studies done in India and abroad. Spector et.al<sup>[31]</sup> reported a prevalence of 43% and Swaminathan et.al<sup>[32]</sup> reported at 58%.

In concordant with other studies across the globe the increasing trend for Low T3 prevalence with increasing severity of CKD was noticed in this study and was statistically significant. The prevalence seen for Low T3 was CKD1-7.7%; CKD2-16.1%; CKD3-29.7%; CKD4-50% & CKD5-63.2%.

A significant negative correlation with age of the study population with prevalence of Low T3 syndrome was also noticed and this was statistically significant ( $P < 0.001$ ). As the age of the study subjects increase, there was an increasing prevalence of Low T3 across the different stages of CKD.

The prevalence of hypothyroidism in this study was 12.7 % ( n=33) of them 8.5 % ( n= 22) had subclinical hypothyroidism and 4.2 % ( n=11) had overt hypothyroidism. The prevalence of subclinical hypothyroidism and primary clinical hypothyroidism increased progressively with decreased level of kidney functions and hence decreasing trend of fall in GFR value. P= 0.019 & P= 0.010 was achieved for calculation of trend for subclinical and overt hypothyroidism respectively and hence statistically significant.

**Table 4: frequency of patients with free T3 & T4 levels in various stages of CKD**

Thyroid status	CKD -1	CKD -2	CKD -3	CKD -4	CKD -5	Total
Low free T3	1	3	10	20	32	66
Low T4	0	0	2	3	2	7

Of 260 patients 66 had low free T3 levels among them 11 individuals had overt hypothyroidism. 55 of them had low free T3. An increasing trend of having low free T3 in serum was demonstrated with increasing trend of severity of CKD stages and hence decreasing GFR values; excluding the patients who had overt hypothyroidism. This correlation was statistically significant (P<0.001).

The mean level of T3 & free T3 decreased across increasing severity of CKD stages 1 to 5. Statistically significant (P<0.001) correlation was seen with decreasing GFR values and decreased values of T3. Simultaneously TSH values increased as severity of kidney failure increased from stages 1 to 5 (P=0.040)

Statistically significant correlation was achieved with increasing prevalence of hypothyroidism & fall in GFR as the severity of kidney dysfunction increased.

The trend for Low T4 syndrome was not statistically significant and apart from those who had overt hypothyroidism the value of free T4 was within normal range. Its prevalence was 2.7% in this study. In this study CKD individuals are not directly associated with hyperthyroidism. Of the 260 cases only 3 had subclinical hyperthyroidism (1.2%) of which 2 cases are in CKD-3 & the next one case in CKD-4. The prevalence of subclinical hyperthyroidism was not statistically significant (P=0.698).

### CONCLUSION

Chronic kidney diseases are a major threat to mankind, physically, emotionally and financially. Efforts are there to explore the need of predictor markers for mortality in CKD & hypothyroidism was found to be one of them. Low T3 has been found to be associated with increased mortality as it further predisposes CKD individuals to cardiovascular complications. It is found to increase

highly sensitive C- reactive protein level and other biological markers of inflammation.

The present study was designed to explore the correlation existing between CKD severity and thyroid dysfunction. The common thyroid dysfunction found was Low T3 syndrome followed by subclinical hypothyroidism and then overt hypothyroidism. The prevalence of these three conditions consistently increased with severity of CKD individuals as judged by 5 stages of CKD. These findings are statistically significant.

There was significant correlation with decreasing GFR values and low serum T3, free T3 & increased TSH levels.

The present study shows Low T3 & hypothyroidism exist in CKD individuals and their prevalence increases as kidney failure increases from stage 1 to 5 and statistically significant correlation exists in between Low T3 levels and fall in GFR values as kidney failure progressively increases.

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