

A study of thyroid abnormalities in chronic kidney disease patients at tertiary care hospital
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Abstract:

Background: Chronic kidney disease is a progressive condition that affects >10% of the general population worldwide, amounting to >800 million individuals. Thyroid hormones are required for the kidney's embryological development and growth. On the other hand, thyroid hormone metabolism, degradation, and elimination are all influenced by the kidney. Due to association between thyroid hormones and kidney function there will be a spectrum of abnormalities with respect to thyroid hormones in chronic kidney disease patients.

Objectives: To quantify thyroid function anomalies in people with chronic kidney disease and correlate them with severity of renal failure.

Settings & Design: A community based Cross sectional Study conducted in Kurnool.

Methods & Materials: A total of 200 non-dialysis chronic kidney disease patients attending nephrology department in government general hospital, Kurnool were considered as study population. T3, T4, TSH, Free T3 & Free T4 were measured. Patients with past history of any medication for thyroid disorder or family history of thyroid disorder or history of any surgery or radiological exposure to thyroid gland were excluded from the study.

Statistical analysis: Collected data was entered in Microsoft Excel & SPSS trial version- 22.

Results: Out of 200 CKD patients, 62% patients have thyroid abnormalities while 38% remain euthyroid. Sub Clinical Hypothyroidism is seen in 27.5% whereas Euthyroid Sick Syndrome, hyperthyroidism, hypothyroidism is seen in 28.5%, 1.5%, 4% of study population respectively. There was a positive correlation between T3, FT3 and eGFR; negative correlation between T3, FT3 and Serum creatinine in CKD stage 4 & 5.

Conclusion: High prevalence of SCH in present study population than in normal population, but it is not statistically significant. SCH is an additional risk factor in CKD patients and the present study finds SCH & ESS as very common thyroid dysfunctions in CKD patients not requiring chronic dialysis. In the study revealed a significant association between CKD progression and thyroid dysfunction.

Keywords: Chronic kidney disease, Sub Clinical Hypothyroidism, thyroid dysfunction, TSH, Free T3 & T4.

INTRODUCTION:

Chronic kidney disease (CKD) is the progressive loss of function of the kidney over a long period of time due to which the kidney cannot filter blood and nutrients properly¹. Chronic kidney disease is a progressive condition that affects >10% of the general population worldwide, amounting to >800 million individuals². Global Burden of Disease collaboration identifies chronic kidney disease (CKD) as a major contributor to global morbidity and mortality with estimated 1.4 million deaths globally from CKD in 2019, a 20% increase from 2010, one of the largest rises among the top causes of death^{3,4}. In recent times the association between Thyroid abnormalities and renal diseases is a global debate. Thyroid hormones are required for the kidney's embryological development and growth. On the other hand, thyroid hormone metabolism, degradation, and elimination are all influenced by the kidney^{5,6}. Due to association between thyroid hormones and kidney function there will be a spectrum of abnormalities with respect to thyroid hormones in chronic kidney disease patients. The actual cause of this link is unknown; however, some theories suggest that thyroid derangement is caused by nonthyroidal disease, in which thyroid hormone deficiencies exist without a primary gland dysfunction⁷.

One of the most common thyroid abnormalities encounter in CKD patients is Sub clinical Hypothyroidism (SCH). Subclinical hypothyroidism (SCH) is defined as high Serum TSH concentration with normal serum Free Thyroxine (FT4) and Free Triiodothyronine (FT3) concentrations, associated with few or no signs and symptoms of hypothyroidism⁸. Subclinical hypothyroidism is the most prevalent thyroid disorder affecting 3–15%⁹ of the normal adult population but is more prevalent in patients with CKD. An inverse

relation was observed between estimated GFR and TSH levels, i.e., with progressively lower GFR, TSH was either normal or high and there was a graded increase in the probability of SCH¹⁰.

Another most common thyroid abnormality that is usually seen is Euthyroid Sick Syndrome (ESS). The most common hormone pattern in euthyroid sick syndrome is a decrease in total and unbound T₃ levels (low T₃ syndrome) with normal levels of T₄ and TSH. The magnitude of the fall in T₃ may correlate with the severity of the illness. T₄ conversion to T₃ via peripheral deiodination is impaired. Fluctuation in TSH levels also creates challenges in the interpretation of thyroid function in sick patients. The underlying mechanism may be mediated by cytokines including IL-12 and IL-18¹¹. As kidney plays a significant role in thyroid hormone metabolism by conversion of T₄ to T₃ and excretion of inorganic iodides, thyroid function has been evaluated by many investigators in patients with CKD. Levels of Total T₃ and Free T₃ suffer reduction in CKD, which is thought to be due to impairment in deiodination of T₄, secondarily to decrease activity of deiodinase enzymes¹¹.

Furthermore, low free triiodothyronine (FT₃) syndrome [combined low FT₃ levels with normal thyroid-stimulating hormone (TSH) levels] is seen in some CKD cases¹². The low T₃ syndrome in CKD is protective and promotes conservation of protein. The low T₃ syndrome increases with severity of renal failure¹³. Hypo- and hyper-thyroidism are caused by the Wolff–Chaikoff effect and the Jod–Basedow phenomena, respectively, when elevated iodine reserves result from a decrease in renal iodine excretion and subsequent iodine retention¹⁴.

It has been hypothesized that hypothyroidism may lead to altered kidney function via effects on cardiac output, intra-renal hemodynamics, and renin angiotensin aldosterone system (RAAS), as well as structural changes including decreased kidney-to-body weight ratio, truncated tubular mass, and altered glomerular architecture¹⁵.

In conclusion, chronic kidney disease can lead to thyroid abnormalities and vice versa hypothyroidism can lead to chronic kidney disease and its progression. Present study's objective was to quantify thyroid function anomalies in people with chronic kidney disease and correlate them with severity of renal failure.

METHODOLOGY:

This was a Hospital based Cross sectional Study conducted in Kurnool medical college, Kurnool, Andhra Pradesh for a period of six months (July 2022 to December 2022). Chronic kidney disease patients attending nephrology department in government general hospital, Kurnool were considered as study population. A total of 200 patients were taken as a study population after fulfilling the inclusion criteria. Patients of age above 18 years & those who gave consent were included in the study. Clearance from the Institutional Ethics Committee was obtained prior to the start of the study. After obtaining permission from the Head of the department, Nephrology patients were interviewed and their data regarding CKD was collected with their consent.

INCLUSION CRITERIA:

Chronic kidney disease was diagnosed on the basis of history, physical examination and on National Kidney Foundation (NKF) criteria.

Chronic kidney disease patients of age >18 years.

Kidney disease of 3 or more than 3 months duration.

Patients with Chronic Kidney Disease on conservative management either by admission or outpatient basis.

Patients with Chronic Kidney Disease who are willing to participate in the study and give informed consent.

EXCLUSION CRITERIA:

Family history of thyroid disorder.

History of any trauma, surgery or radiological exposure to thyroid gland.

Past history of usage of any thyroid medication.

Patients on dialysis.

Patients suffering from acute illness.

Patients who have received drugs altering thyroid profile like Amiodarone, Phenytoin, Beta blocker, Steroids, Pregnant women.

STATISTICAL CONSIDERATIONS:

Data was analyzed using Microsoft Excel and Trial version of SPSS 23 statistical packages. The data was then presented in proportions and percentages using tables, bar charts and scatter plot graphs,

etc. Pearson's correlation coefficient (r) was used to assess the correlation of serum free T3, T3 with serum creatinine and eGFR.

The normal reference range in present study institute for TSH was 0.5–5 mIU/L, T4 5 - 12 micro g/dl, FT4

0.7 - 1.8ng/dl, T3 0.92 – 2.76 nmol/L, and FT3 1.7 - 4.2 pg/ml. Clinical hyperthyroidism was defined as decreased TSH with increased FT4, TT4 and/or FT3, TT3; clinical hypothyroidism was defined as increased TSH with decreased FT4 and decreased or normal FT3; subclinical hyperthyroidism was defined as decreased TSH with normal FT4, TT4, FT3, TT3; subclinical hypothyroidism was defined as increased TSH with normal FT4, TT4 and/or FT3, TT3; ESS was defined as normal or decreased TSH with decreased FT3, TT3 and/or lower FT4, TT4.

STUDY TOOLS (INSTRUMENTS):

eGFR is calculated using age, gender and serum creatinine and based on eGFR, chronic kidney disease stages were classified through National Kidney Foundation (NKF) criteria.

CKD stages classified as;

- CKD-1 (G1): Patients with eGFR ≥ 90 ml/min/1.73 m².
- CKD-2 (G2): Patients with eGFR 60-89 ml/min/1.73 m².
- CKD-3a (G3a): Patients with eGFR 45-59 ml/min/1.73 m².
- CKD-3b (G3b): Patients with eGFR 30-44 ml/min/1.73 m².
- CKD-4 (G4): Patients with eGFR 15-29 ml/min/1.73 m².
- CKD-5 (G5): Patients with eGFR <15 ml/min/1.73 m².

ETHICAL CONSIDERATIONS:

Clearance from the Institutional Ethics Committee was obtained prior to the start of the study. IEC ref no 28/2022. Date of approval is on 6th July, 2022.

RESULTS:

The study group comprises of 200 cases of CKD patients, 127 (63.5%) were male and 73 (36.5%) were female. The mean age of the male patient in present study is 53.37 ± 12.63 years, the mean age of female patient in present study is 51.82 ± 14.25 years. The age range of the patients included is 20 years to 80 years.

The proportion of patients among male and female distributed over different age groups is shown in Table 1 and fig 1. out of 200 patients, maximum was in the age group of 51 – 60 years (Table 1 and fig 1)

Patients were classified into different CKD Stages according to NKF criteria and the distribution among different stages is shown in table 2 and figure 2. CKD stage 4 has the maximum portion of the study population with 28.5%.

Table 1: Distribution patients according to their Age

Age	Male	Female
≤ 30	5	8
31 - 40	14	7
41 - 50	31	16
51 - 60	44	22
61 - 70	22	16
71 - 80	11	4

Table-2: Distribution of Patients according to stage of CKD

Stage of CKD	Male	Female	Total	Percentage
CKD 1	8	4	12	6%
CKD 2	13	10	23	11.5%
CKD 3a	20	15	35	17.5%
CKD 3b	23	10	33	16.5%
CKD 4	42	15	57	28.5%
CKD 5	21	19	40	20%

Table 3: Comparison between Thyroid profile vs CKD stage

	CKD stage-1	CKD stage-2	CKD stage-3a	CKD stage-3b	CKD stage-4	CKD stage-5
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Mean Age	42.66	49.78	55.88	53.76	54.37	51.87
Mean S. Creatinine mg/dl	0.86	1.13	1.43	1.98	3.41	5.84
Mean eGFR ml/min	100.58	71.65	51.51	37.24	19.98	10.5
Mean T3 nmol/L	1.6	1.32	1.26	1.14	1.32	1.13
MeanT4 mcg/dl	9.68	7.56	7.66	6.86	7.66	6.98
TSH mIU/L	7.05	3.82	4.57	4.41	5.01	5.32
Free T3 pg/ml	3.62	2.17	2.3	2.06	2.22	1.97
Free T4ng/dl	1.29	1.12	1.07	1.09	1.1	0.96

Pearson correlation coefficient between T3, FT3 and eGFR, Serum creatinine shown from tables 4-7, fig 3-6 states that there was positive correlation between T3, FT3 and eGFR; negative correlation between T3, FT3 and Serum creatinine in CKD stage 4 & 5.

Table 4: Comparison between T3 and eGFR Table 5: Comparison between Free T3 and eGFR

CKD Stage	R Value
1	-0.01999
2	-0.23181
3	-0.03372
3	0.12629
4	0.100366
5	0.434411

CKD Stage	R Value
1	-0.0737
2	-0.42332
3	-0.06981
3	-0.34435
4	0.200413
5	0.329154

Table 6: Comparison between T3 and Serum Creatinine

CKD Stage	R Value
1	0.308947
2	0.259912
3	-0.01172
3	0.498321
4	-0.13949
5	-0.19421

Table 7: Comparison between Free T3 and Serum Creatinine

CKD Stage	R Value
1	-0.14113
2	0.035346
3	-0.10655
3	0.148725
4	-0.01232
5	-0.22842

Sub clinical hypothyroidism is seen in 27.5% of the study population and distribution of cases among different CKD classes is shown in table 8 and figure 9. 15.5% of males have SCH which is greater than in females 12%. Around 31.5% of patients from CKD Stage 4 is highest followed by 30.3%, 30%, 28.5%, 21.7%, 16.6% in CKD 3b, CKD 5, CKD 3a, CKD 2, CKD 1 respectively.

Table 8 Distribution of CKD patients according to Sub clinical Hypothyroidism status

CKD Stages	SCH		ESS	
	Male	Female	Male	Female
CKD 1	1	1	0	0
CKD 2	2	3	3	3
CKD 3a	5	4	4	6
CKD 3b	7	2	3	6
CKD 4	11	7	13	5
CKD 5	5	7	8	6
Total	31	24	31	26
%among total	15.5%	12%	15.5%	13%

Euthyroid Sick Syndrome is seen in a total of 28.5% among study population as shown in table 8. Around 15.5% of Males have ESS compared to 13% of females. CKD Stage 5 have highest proportion

affected with 35% followed by 31.5%, 28.5%, 27.3%, 21.7% in CKD 4, CKD3a, CKD 3b, CKD 2 Stages respectively.

Table 9: Distribution of euthyroid, hyperthyroid and hypothyroid cases

CKD Stages	Euthyroid	Hyper Thyroid	Hypo Thyroid
CKD 1	8	0	1
CKD 2	11	1	0
CKD 3a	12	1	2
CKD 3b	10	0	2
CKD 4	16	1	2
CKD 5	7	0	1
Total	64	3	8

DISCUSSION:

The present study was aimed to quantify thyroid function anomalies in people with chronic kidney disease and correlate them with severity of renal failure. Various studies were conducted about thyroid dysfunction and severity of chronic kidney disease and have shown different results. Since thyroid profile undergoes changes due to dialysis¹⁶. Previous studies have shown rising trend of frequency of hypothyroidism in ESRD requiring maintenance hemodialysis as well as peritoneal dialysis, and an increased prevalence of goiter. Only a few of the previous studies have examined the prevalence of hypothyroidism among patients with CKD not requiring dialysis¹⁷. In present study of 200 CKD patients who are not receiving dialysis treatment, the maximum number of patients were in the category of 51 – 60 years age. The extreme age groups had few patients with chronic kidney disease, there were 2 males at 80 years of age and 2 females and 1 male at 20 years of age. There was a cluster of cases in middle age and with preponderance towards male sex. Based on Pearson correlation analysis eGFR had a positive relationship with T3 and FT3, serum creatinine had a negative relationship with T3 and FT3 in CKD stage 4 & 5.

One of the most common thyroid abnormalities encounter in CKD patients is Sub clinical Hypothyroidism (SCH). Subclinical hypothyroidism (SCH) is defined as high Serum TSH concentration with normal serum Free Thyroxine (FT4) and Free Triiodothyronine (FT3) concentrations, associated with few or no signs and symptoms of hypothyroidism⁸. Subclinical primary hypothyroidism is most commonly caused by chronic autoimmune thyroiditis, which is typically characterized by a mild asymptomatic goiter with diffuse hypo echogenicity on thyroid ultrasound and by the presence of a high titer of serum thyroid autoantibodies¹⁸. Drug-induced hypothyroidism, subacute thyroiditis, radiation thyroiditis, and postpartum thyroiditis are some other less frequent causes of transient or permanent primary hypothyroidism¹⁹. Independent of its specific etiology, several studies have demonstrated that subclinical primary hypothyroidism may affect both diastolic and systolic cardiac function, worsen traditional risk factors for cardiovascular disease, such as blood pressure, plasma lipid profile, and endothelial function²⁰⁻²⁴. Present study showed that, frequency of subclinical hypothyroidism is higher in persons with decreased estimated GFR as compared to normal population, but it was not statistically significant.

Present study showed that, frequency of subclinical hypothyroidism was 27.5% which was more than in studies conducted by Shantha et al, Abhishek Gupta where they found the prevalence of SCH was 24.8%, 25% respectively^{25,26}. prevalence of SCH in present study was equal when compared to a study done by Khatiwada S et al where prevalence is 27.2%²⁶. The prevalence of SCH in present study is more in males (56.3%) as compared to females (43.6%). This is similar to the study of Shantha et al, which showed prevalence of disease was higher in males (73.5%) as compared to females (26.5%) out of 137 ESRD patients²⁵. But this contrasts with study done by Abhishek Gupta which showed prevalence of disease was higher in females (52%) as compared to males (48%)²⁷.

Present study showed that ESS is seen in 28.5% of the study population. Males (54.4%) have greater prevalence than females (45.6%). The proportion of patients with ESS increases with an increase in CKD stage with highest seen in CKD stage 5 (35%) followed by CKD stage 4, 3a, 3b & 2 with 31.5%, 28.5%, 27.3%, 21.7% respectively.

The scattered plot between T3 and eGFR depicts that cluster of patients in between 0.5 - 2 nmol/L

of T3 and 1.5 - 2.5 pg/ml of Free T3. The trendline from those scatter plot indicates that if patients have decreased eGFR then they will most likely have low T3 & Free T3 levels.

Overall, 62% of the study population have thyroid abnormalities when compared to 38% of euthyroid patients. Hypothyroidism and hyperthyroidism are seen in 4% and 1.5% of the study population respectively. Although numerous contributing factors have been hypothesized, the precise underlying mechanisms relating severe CKD and primary thyroid dysfunction are still unknown, despite several potential contributing factors, such as altered iodine metabolism, decreased peripheral sensitivity to hormones, and autoimmune thyroiditis, having been hypothesized. On the other hand, hyponatremia, which is caused by a reduction in renal diluting capacity and leads in water retention, is the most prominent manifestation of alterations in renal function in clinically overt primary hypothyroidism (myxedema)²⁸. Furthermore, renal hemodynamic changes brought on by a lower cardiac output may result from clinically overt hypothyroidism and cause a progressive fall in GFR.

The percentage of population in a CKD stage with TSH >5mIU/L seems to increase linearly with the progression of the CKD, with CKD stage 5 group having highest portion of 37.5%. But it is not statistically significant.

Present study has several potential limitations that may confound the interpretation of present study findings. First, the cross-sectional design limits present studyability to establish causal or temporal relationships between subclinical primary hypothyroidism and kidney disease. Secondly, the study did not adjust for the age gender, race, blood glucose levels, serum cholesterol, hypertension, diabetes mellitus and serum triglycerides levels. Third, the definition of kidney function was based on estimated GFR rather than on more precise measurement of kidney function, such as iothalamate clearance. Fourth, this study was conducted in a single center; which may lead to crowd bias therefore, future studies with a larger sample size and involving multiple centers should be done to confirm the findings of present study.

Even with all the limitations present study has several strengths. Firstly, present study is one of the few studies which correlated thyroid dysfunction among different CKD classes. Second, subclinical hypothyroidism was diagnosed according to widely accepted diagnostic criteria (*i.e.*, high TSH with normal FT4 levels). Finally, present study is one of the few that focuses just on CKD patients not getting any dialysis.

CONCLUSION:

Thyroid disorders and CKD are independently some of the most prominent medical conditions found in patients in INDIA. Due to the high prevalence of both, it is important to consider the physiological association of thyroid dysfunction in relation to kidney disease. The present study finds thyroid dysfunction being SCH to be very common in CKD patients and reveals significant association between CKD progression and thyroid dysfunction. As the literature suggests SCH itself is a great risk factor for CVD in CKD patients, adult patients with CKD should be routinely screened for Sub Clinical Hypothyroidism. Further research is needed regarding treatment options for thyroid dysfunction in CKD patients because Patients who receive appropriate treatment for their thyroid disease have a decreased chance of developing or exacerbating renal dysfunction. However, treating patients with a mild elevation of TSH (less than 20 IU/mL) results in a negative nitrogen balance by increased muscle catabolism. Even for renal graft patient's clinicians should look for T3 levels as low levels are associated with renal graft loss.

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