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A study of thyroid function abnormalities in patients with chronic kidney disease

Kishore Moolrajani [1] , Manan Patel [2] ,Dharam Prakash Bansal,[3] Puneet Rijhwani,[4] Mukesh Sarna[5],Aditi Goyal,[6] Saahil Sharma,[7] Krunal Patel,[8] Harshit Sharma[9]

1.Professor and unit head, Department of Medicine, Mahatma Gandhi College and Hospital, Jaipur, India
2.Resident Doctor, Department of Medicine, Mahatma Gandhi College and Hospital, Jaipur, India

3.Professor and unit head, Department of Medicine, Mahatma Gandhi College and Hospital, Jaipur, India
4.Professor and head of department, Department of Medicine Mahatma Gandhi College and Hospital, Jaipur, India
5.Professor and unit head, Department of Medicine, Mahatma Gandhi College and Hospital, Jaipur, India
6. Senior Resident , Department of Medicine, Mahatma Gandhi College and Hospital, Jaipur, India
7. Resident Doctor, Department of Medicine, Santosh Medical College and Hospital, Ghaziabad, UP, India
8. Resident Doctor, Department of Medicine, Mahatma Gandhi College and Hospital, Jaipur, India
9.Resident Doctor, Department of Medicine, Mahatma Gandhi College and Hospital, Jaipur, India

Corresponding author- Aayushi Patel, Resident Doctor, Department of Anesthesia, Mahatma Gandhi College and Hospital, Jaipur, India

Abstract

Aims and objectives: A study was conducted at Department of General Medicine, Mahatma Gandhi Medical College and Hospital, Jaipur, India, to see prevalence of thyroid disorder in CKD patients.

Material and methods: An Observational Cross-Sectional Study was conducted at Department of General Medicine, Mahatma Gandhi Medical College and Hospital form August 2022 to October 2023. Patients who were on conservative management fulfilling the criteria for chronic kidney disease admitted in Department of Medicine, Mahatma Gandhi Hospital, Jaipur

Results: Euthyroid was present in 63% patients, Primary hypothyroidism was present in 11% patients and Subclinical hypothyroidism was present in 26% patients. CKD stage IV showed higher mean T3 value (0.94) as compared to CKD stage V (0.608). CKD stage V showed higher mean TSH value (6.69) as compared to CKD stage IV (4.21). CKD stage IV showed higher mean GFR value (18.17) as compared to CKD stage V (8.16). Mean eGFR value of euthyroid (9.76) was significantly higher than subclinical hypothyroidism (7.11) and primary hypothyroidism (6.25) among eGFR level. Primary hypothyroidism was present 87.5% in CKD stage V patients and Subclinical hypothyroidism was present 84.2%% in CKD stage V patients.

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Conclusion: The mean TSH value was greater in CKD stage V (6.69) than in CKD stage IV (4.21). The mean GFR value for CKD stage IV was greater than that of CKD stage V (8.16), at 18.17. Therefore, it is crucial to check for thyroid disorders in all patients with chronic renal disease, since they may negatively impact the prognosis of the illness as a whole.

Key word: chronic kidney disease, eGFR, TSH, hypothyroidism

1. INTRODUCTION

Patients with chronic kidney disease (CKD) frequently have changes in their thyroid hormone levels, and as the condition worsens, thyroid dysfunction becomes more common.[1] Thyroid hormones have an impact on almost all bodily organ systems and are linked to several factors that worsen renal disease.

Reduced renal plasma flow, poor glomerular filtration rate, decreased sodium reabsorption, and the inability to dilute urine are all linked to hypothyroidism.[2] Replacement therapy can stop the decline in renal function in hypothyroid patients because thyroid hormones have several protective effects on renal function.[3]

In individuals with overt hypothyroidism, the glomerular filtration rate (GFR) is decreased.[4] Patients with low estimated GFR (eGFR) have been found to have a higher prevalence of both overt and subclinical hypothyroidism in large observational studies.[5]

"Low T3 syndrome" is the most prevalent and early thyroid function anomaly in people with chronic kidney disease (CKD). There are multiple causes of this condition. In contrast, free T4 levels in CKD range from low to normal. This is mostly due to T4's decreased protein binding in CKD. The thyroid profile is comparable to that of a number of nonthyroidal illnesses (NTIs), including heart failure, cancer, severe infections, and a number of hospitalised patients without renal disease. This led to the idea of a "sick euthyroid state," or "NTI," being considered in CKD. On the other hand, overall rT3 levels in CKD do not rise, in contrast to other NTI states.[6] Another difference from other NTIs is that the thyroid stimulating hormone (TSH) levels are elevated in CKD.

As a result, CKD patients have normal or low T4 and low or normal T3 levels, which lead to increased TSH and a rise in thyroid gland volume.[7] The lower T3 levels and related problems without a rise in rT3, the decreased free T4 levels combined with an increased TSH, and the TSH's hyporesponsiveness to thyrotropin-releasing hormone cast doubt on the "euthyroid" state and suggest that thyroid supplementation may be beneficial in patients with chronic kidney disease. Specifically, nothing is known about how thyroid hormone replacement affects glomerular filtration rate alterations in patients with chronic kidney disease (CKD) who have subclinical hypothyroidism (SCH). The prevalence of hypothyroidism among CKD patients who do not require dialysis has only been studied once in the past.

While a greater emphasis has been placed upon other endocrine disorders in CKD, e.g., secondary hyperparathyroidism and diabetes, large observational studies show that hypothyroidism is highly prevalent in kidney disease patients. For example, among 14,623 participants in the Third National Health and Nutritional Examination Survey (NHANES III), there was an incrementally higher prevalence of hypothyroidism (defined as TSH > 4.5 mIU/L or receipt of exogenous thyroid hormone) with increasing severity of kidney dysfunction: 5%, 11%, 20%, 23%, and 23.1% with estimated glomerular filtration rates (eGFR) of ³ 90, 60 - 89, 45 - 59, 30 - 44, and < 30 ml/min/1.73 m2 respectively.[8] Even after accounting for differences in age, sex, and race/ethnicity, participants with eGFR < 30 ml/min/1.73 m2 had a 2-fold higher risk of hypothyroidism compared to those with eGFR > 90 ml/min/1.73 m2. In a more recent

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study of 4,61,607 US veterans with stages 3 to 5 CKD who underwent serum TSH testing from 2004 – 2006 (84% of the cohort), 23% had hypothyroidism (defined as TSH > 5.0 mIU/L or receipt of exogenous thyroid hormone replacement).[9]

An endocrine system problem known as hypothyroidism occurs when the thyroid gland does not create enough thyroid hormone. Many symptoms, including poor tolerance to cold, fatigue, constipation, depression, and weight gain, might result from it. TSH is greater than usual in subclinical hypothyroidism while T3 and T4 levels are normal. In Overt Hypothyroidism: TSH is elevated above normal, T4 is down, and T3 is either normal or lowered.

A recent study by Shin (2013)[10] et al demonstrated that thyroid hormone treatment not only preserved renal function but was also an independent predictor of renal outcome. Therefore, it was essential to evaluate the reduction in eGFR in the same patient before and after L-thyroxin replacement in order to determine the precise effect of thyroid hormone medication on the loss in renal function. The study's findings demonstrated that replacing thyroid hormone greatly enhanced kidney function

It is challenging to determine a cause-and-effect relationship, but over time, numerous cases from all over the world have been documented in which severe hypothyroidism has been linked to renal dysfunction and thyroid hormone replacement has improved renal function. These reports lend credence to the possibility that hypothyroidism can cause renal failure.

It's important to assess thyroid function in CKD patients because it helps to halt progression of CKD by timely addressing thyroid illness. A study was conducted at Pravara Rural Hospital in Londa, India, to see prevalence of thyroid disorder in CKD patients. Previous studies on thyroid functions in CKD patients, both worldwide and in India, have shown the correlation of CKD patients with hypothyroidism. However, these studies are limited in India.

2. MATERIAL AND METHODS

Type of Study: An Observational Cross-Sectional Study

Period of Study: From August 2022 to October 2023.

Place of Study: Department of General Medicine, Mahatma Gandhi Medical College and Hospital

Sample Size: Patients who were on conservative management fulfilling the criteria for chronic kidney disease admitted in Department of Medicine, Mahatma Gandhi Hospital, Jaipur

SAMPLE SIZE: Total 73 patients of chronic kidney disease were included in study.

Size n = [DEFF*Np(1-p)]/[(d2 / Z2 1- α/2*(N-1)+p*(1-p)]

Inclusion Criteria:

- Patients with chronic kidney disease.
- Patients who fulfill the criteria for CKD and who were on conservative management.
- Criteria for Chronic Kidney Disease
- Presence of uraemic symptoms for 3 months or more
- Raised blood urea, serum creatinine and reduced creatinine clearance.
- Ultra sonogram evidence of chronic kidney disease
- Bilateral contracted kidneys — size less than 9 cm.
- Poor cortico-medullary differentiation.
- Supportive laboratory evidence of CKD like anaemia, changes in serum electrolytes, etc.,

Exclusion Criteria:

1. Patients on peritoneal dialysis or hemodialysis
2. Nephrotic range of proteinuria

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3. Hypoalbuminemia
4. Other conditions like
- Acute illness
- Diabetes mellitus
- Recent surgery
- Trauma
- Burns
- Liver diseases
- Drugs altering thyroid profile like amiodarone, phenytoin, beta-blocker, dopamine, steroids, estrogen pills and iodine-containing drugs.

Statistical analysis

The data was coded and entered into Microsoft Excel spreadsheet. Analysis was done using IBM SPSS (SPSS Inc., IBM Corporation, NY, USA) Statistics Version 25 for Windows software program. Descriptive statistics included computation of percentages, means and standard deviations. The data were checked for normality before statistical analysis using Kolmogorov Simonov test. The unpaired t test (for quantitative data to compare two independent observations) and ANOVA test (for quantitative data to compare two and more than two observations) were applied. The chi square test was used for qualitative data comparison of all clinical indicators. Level of significance was set at $P \leq 0.05$.

3. OBSERVATIONAL AND RESULTS

In our study patients more than 50-60 years of age group (27.4%) were higher than patients of 40-50 years age group (24.7%) and patients of 20-30 years age group (20.5%). Age of the participants varied from 20 to 68 years with mean age being 44.04±13.2 years.

65.8% of patients were males and 34.2% patients were females. Symptom of duration was 9.68 days. The TSH value varied from 0.6-38 μIU/ml, the mean value being 9.81±4.75 microIU/ml. The T3 values varied from 0.2-2 ng/ml, the mean value being 0.66±0.51 ng/ml. The T4 value varied from 0.9-8.5 microg/dl, the mean value being 5.64±2.27 microg/dl. The GFR value varied from 0.29-24.9 ml/min/1.73m2, the mean value being 8.41±4.76 ml/min/1.73m2. 83.6% cases have stage V which was higher and 16.4% cases have stage IV.

Table 1: Thyroid profile wise distribution of the study

	Frequency	Percent
Euthyroid	46	63.0
Primary hypothyroidism	8	11.0
Subclinical hypothyroidism	19	26.0
Total	73	100.0

Euthyroid was present in 63% patients, Primary hypothyroidism was present in 11% patients and Subclinical hypothyroidism was present in 26% patients.

Table 2: Comparison of Stage of CKD and thyroid levels wise comparison of the study

		N	Mean	Std. Deviation	P value
T3 ng/ml	IV	12	.942	.5791	0.03 (S)
	V	61	.608	.4831	
T4 mg/dl	IV	12	5.283	2.1447	0.55

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	V	61	5.715	2.3043	
TSH mIU/ml	IV	12	4.217	1.3776	0.01 (S)
	V	61	6.695	7.2579	
GFR ml/min/1.73m2	IV	12	18.17	3.380	0.001 (S)
	V	61	8.16	2.882	

CKD stage IV showed higher mean T3 value (0.94) as compared to CKD stage V (0.608).
CKD stage V showed higher mean TSH value (6.69) as compared to CKD stage IV (4.21).
CKD stage IV showed higher mean GFR value (18.17) as compared to CKD stage V (8.16).

Table 3: Comparison of Thyroid profile with thyroid levels

	eGFR	
	Mean	Std. Dev
Euthyroid	9.76	3.85
Primary hypothyroidism	6.25	1.46
Subclinical hypothyroidism	7.11	1.74
P value	0.001 (S)	

Mean eGFR value of euthyroid (9.76) was significantly higher than subclinical hypothyroidism (7.11) and primary hypothyroidism (6.25) among eGFR level.

Table 4: Association between thyroid profile and stage of CKD

			STAGE OF CKD		Total
			IV	V	
Thyroid profile	Euthyroid	N	8	38	46
		%	17.4%	82.6%	100.0%
	Primary hypothyroidism	N	1	7	8
		%	12.5%	87.5%	100.0%
	Subclinical hypothyroidism	N	3	16	19
		%	15.8%	84.2%	100.0%
Total		N	12	61	73
		%	16.4%	83.6%	100.0%

P value=0.001 (S)

Primary hypothyroidism was present 87.5% in CKD stage V patients and Subclinical hypothyroidism was present 84.2%% in CKD stage V patients

4. DISCUSSION

A total of 73 cases of chronic kidney disease (CKD) were included in the study with patients or their legally accepted representatives consenting for the study and all cases of chronic kidney disease belonging to age group of more than 18yrs of both the gender were included.
Patients with CKD often have signs and symptoms suggestive of thyroid dysfunction and hence the diagnosis of thyroid dysfunction in these patients has obvious prognostic implications. Thyroid dysfunctions mainly, subclinical and overt hypothyroidism are highly prevalent in CKD patients.[11]

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In our study patients more than 50-60 years of age group (27.4%) were higher than patients of 40-50 years age group (24.7%) and patients of 20-30 years age group (20.5%). Age of the participants varied from 20 to 68 years with mean age being 44.04±13.2 years. Similarly, in a study by Kenmoe P (2020)[53] et al the mean age of CKD patients was 55.85± 13.72 years. Similar to our study, in a study by Aljabri KS (2019)[47] et al the mean age of CKD patients was 55.9±12.4 years. Also, in a study conducted by Chaudhari ST et al, the maximum number of patients belonged to the age group of 61-70 years with mean age being 57.8 years.[12] Contrary to our study, in a study conducted by Maheshwari N et al, the maximum number of patients were in the age group of 51-60 years.[13] In a study by Sharma M et al, the maximum number of patients were found to be in the age group of 41-50 years.[14] Contrary to our study, the number of patients with middle age group were higher in the study conducted by Gupta UN (2018)[44] et al.

In our study, 65.8% of patients were males and 34.2% patients were females. Similar to our study, in a study by Gupta UN (2018)[44] et al, 60% were males and 40% were females. Similar to our study, in a study by Keunmoe P (2020)[53] et al 63.66% were males which formed the majority followed by 36.34% females. In a study conducted by Chaudhari ST et al, out of 50 patients there were 32(64%) males and 18(36%) females. Similarly, in a study conducted by Alam SM et al. Out of 35 patients there were 22 males (63%1) and 13 females(37%). Our findings were similar to a study conducted by Awasthi G et al, out of 21 cases there were 13 males (65%) and 7 females(35%).[15] Contrary to our study, in a study by Aljabri KS (2019)[47] et al, females (77.1%) formed the majority over males (22.9%).

In the study, prevalence of primary hypothyroidism is 11% and prevalence of subclinical hypothyroidism is 26% and total prevalence of hypothyroidism is 37%. Prevalence of hypothyroidism in patients with terminal renal failure is 5%, in comparison with that in hospitalized patients with normal renal function.[16] CKD is associated with higher prevalence of hypothyroidism, both overt and subclinical, but not with hyperthyroidism.[17] In fact, the prevalence of primary hypothyroidism is mainly in the subclinical form, which increases as GFR decreases.[8] Gupta UN (2018)[45] et al found 53% prevalence of hypothyroidism. Chandra A (2016) found 56.42% prevalence of hypothyroidism. Kannan A (2017)[42] et al showed only 10% prevalence of hypothyroidism. Cotoi L (2020)[18] et al found prevalence of hypothyroidism of 24.4%. Previous study by Quion-Verde (1984)[19] reported a high prevalence of hypothyroidism in chronic renal failure. It was estimated to be about 5% in patients with terminal renal failure. Detail study by Kaptein et al[20,21] estimated the prevalence of primary hypothyroidism was about 2.5 times much frequent in chronic renal failure and dialysis. The hypothyroidism in chronic renal failure was estimated to range between 0 and 9.5%.

In the present study, 83.6% cases have stage V which was higher and 16.4% cases have stage IV. Similar to our study, Gupta UN (2018)[44] et al noticed that most of the patients have Stage V (52%) CKD. Contrary to our study, in a study by Khatiwada S et al, maximum number of patients were in stage 4 CKD (43.4%) followed by stage 3 (40%) and 16.6% patients in stage 5 Chronic kidney disease.[61]

In their study, Lo JC (2005)[8] et al reported a prevalence of hypothyroidism of 23.1% in CKD patients. Our study differs from these previous observations by demonstrating a higher prevalence of hypothyroidism (37%). Previous studies also confirmed that subclinical hypothyroidism was not a rare disorder in CKD patients.[22,23] The data of 14,623 adult participants from the third National Health and Nutrition Examination Survey, a nationally representative sample of the United States population, revealed that the prevalence of hypothyroidism increased with lower levels of eGFR, occurring in 10.9% of patients with stage 2 CKD, 21.0% with stage 3 CKD, and 23.1% with stage 4 or 5 CKD.[8] Limited data also suggest

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that, among patients with "mild" subclinical hypothyroidism and CKD, thyroid hormone replacement may ameliorate kidney disease progression.[24,10]

In our study, CKD stage V showed higher mean TSH value (6.69) as compared to CKD stage IV (4.21). Similar to our study, Bajaj S (2016)[38] et al described the increasing prevalence of hypothyroidism with increasing severity of chronic kidney disease. The TSH level is often elevated in chronic kidney disease in response to thyrotropin from pituitary as a result of uremic effect.[71] TSH also loses its circadian rhythm along with compromised bioactivity due to poor glycosylation. Chronic metabolic acidosis has also been labelled as one of the contributing factors in the rise of hypothyroidism cases in CKD population.[25] The Wolff-Chaikoff effect has been cited as a causative phenomenon behind the rise of this disorder in diabetic kidney disease patients.[29] Ansari I et al[26] was reported that as the CKD stages advance, TSH levels increase, a change that was statistically significant (p=0.04). Higher TSH levels were most frequently found among subjects with CKD stage 5, followed by stage 4. The TSH level is often elevated in CKD in response to thyrotropin from pituitary as a result of uremic effect.[27] TSH also loses its circadian rhythm along with compromised bioactivity due to poor glycosylation. Chronic metabolic acidosis has also been labeled as one of the contributing factors in the rise of hypothyroidism cases in CKD population.[28]

The proposed mechanism of deranged thyroid in CKD may be due to the depressed hypothalamic-pituitary axis, thus reducing the expression of TSH receptors. Other hypotheses may be reduced clearance of inflammatory cytokines such as TNF-alpha and IL-1, which leads to a decrease in the level of 1 5'-deiodinase, which again leads to decreased peripheral conversion of T4 to T3, which again causes low T3 levels causing hypothyroidism.[29,30]

An increased prevalence of subclinical and overt primary hypothyroidism in persons with reduced eGFR independent of age and gender was seen in this study. This is in line with the observation made by Chonchol (2008)[2] et al. In our study, Mean eGFR value of euthyroid (9.76) was significantly higher than subclinical hypothyroidism (7.11) and primary hypothyroidism (6.25) among eGFR level. Primary and subclinical hypothyroidism patients have low eGFR level in our study on comparison with Chang Y (2018)[31] et al involving 74,356 Taiwanese elderly adults in cross section study found that subclinical and clinical hypothyroidism was independently associated with reduced eGFR but less significant association was found with proteinuria.

Primary hypothyroidism was present 87.5% in CKD stage V patients and Subclinical hypothyroidism was present 84.2%% in CKD stage V patients. In Obasuyi JO and Emokpae MA study,[32] non-thyroidal illness prevalence was also high across the stages of the disease progression, though there was none recorded in stage 2 which probably may be due to few patients investigated. The stage to stage stratification of thyroid dysfunction, CKD stage 3 had 54.5% incidence of non-thyroidal illness; stage 4 recorded 51.1% while stage 5 had 37.2% compared to hypothyroidism and hyperthyroidism. This is not consistent with that of Pan et al,[33] who reported that the most common thyroid dysfunction in CKD is non-thyroidal illness which increased with increasing stage of CKD disease rising to 69.1% in CKD stage 5.

Various studies have demonstrated the relation between chronic kidney disease and thyroid disorders, CKD affecting the metabolism of thyroid hormones and thus influencing thyroid morphology.[34]

Literature studies have showed that haemodialysis can cause thyroid abnormalities in both function and also morphology in patients with end stage renal disease.[35,36] Low T3 syndrome or "sick euthyroid syndrome" is a consequence of chronic non-thyroidal illness caused by uraemia and protein malnutrition.[37]

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Although numerous hypotheses exist for contributing factors, such as altered iodine metabolism, decreased peripheral sensitivity to hormones, and autoimmune thyroiditis, the exact underlying mechanisms linking advanced CKD and primary thyroid dysfunction remain unclear.[2]

5. CONCLUSIONS

The mean TSH value was greater in CKD stage V (6.69) than in CKD stage IV (4.21). The mean GFR value for CKD stage IV was greater than that of CKD stage V (8.16), at 18.17. Therefore, it is crucial to check for thyroid disorders in all patients with chronic renal disease, since they may negatively impact the prognosis of the illness as a whole.

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