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ORIGINAL ARTICLE

A Study of Hypothyroidism in Chronic Kidney Disease (CKD) Patients

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Abstract

Introduction: Chronic kidney disease (CKD) is a progressive condition affecting over 800 million people worldwide, primarily attributed to diabetes, hypertension, and other risk factors. The progression of CKD leads to significant complications, including cardiovascular disease, anemia, and metabolic bone disorders. Hypothyroidism, a condition marked by deficient thyroid hormone levels, is known to affect patients with CKD through impacts on thyroid metabolism. **Materials and Methods:** A hospital-based cross-sectional study was conducted over three months in a tertiary care center in South India. The study involved 237 CKD patients who provided informed consent and met inclusion criteria. Patients with medication histories that could influence thyroid function or those with acute kidney injury were excluded. Detailed clinical assessments and laboratory analyses of renal and thyroid functions were performed. **Results:** The study population had a mean age of 50.6 years, with 61.2% females. Hypothyroidism was observed in 27.4% of the patients, predominantly subclinical (22.36%) rather than overt hypothyroidism (5.06%). CKD severity correlated significantly with hypothyroidism prevalence, with increased hypothyroidism rates in advanced CKD stages ($p < 0.001$). Correlation analysis revealed a negative association between estimated glomerular filtration rate (eGFR) and TSH ($r = -0.147$, $p = 0.023$), suggesting declining kidney function aligns with thyroid dysfunction. **Conclusion:** This study highlights a notable correlation between CKD progression and the occurrence of hypothyroidism, particularly subclinical hypothyroidism. Findings suggest a need for routine thyroid evaluation in CKD patients to facilitate early detection and management of thyroid-related complications, improving patient outcomes.

Keywords: Chronic kidney disease, hypothyroidism, thyroid dysfunction, CKD stages, subclinical hypothyroidism

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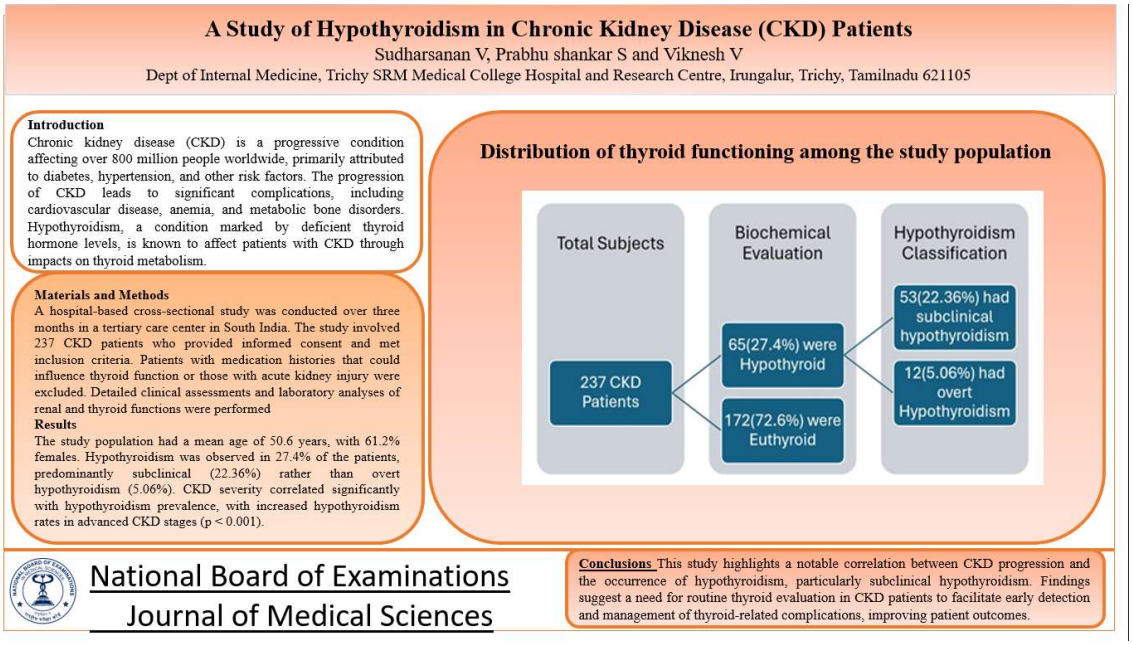
Graphical Abstract



Introduction

Chronic kidney disease (CKD), a progressive condition impacting more than 10% of the global population, exceeds 800 million individuals worldwide [1]. The primary causes of CKD in the majority of adults are typically diabetes and high blood pressure. Additional risk factors comprise heart disease, obesity, familial predisposition to CKD, inherited kidney disorders, prior kidney damage and advancing age [2]. The advancement of CKD is linked to several significant complications, such as a heightened risk of cardiovascular disease, hyperlipidemia, anaemia, and metabolic bone disease [3].

CKD diagnosis in adults involves identifying patients with a Glomerular Filtration Rate (GFR) persistently below 60 ml/min/1.73 m^2 for three months or more [4]. The 2012 KDIGO CKD classification provides guidelines regarding the etiology of chronic kidney disease (CKD) and categorizes it into six groups based on the glomerular filtration rate (G1 to G5, with G3 further divided into 3a and 3b). Additionally, it includes staging based on three levels of albuminuria (A1, A2, and A3). Each CKD stage is further subclassified according to the urinary albumin-creatinine ratio, measured in either milligrams per gram (mg/g) or milligrams per millimole (mg/mmol), using an early morning "spot" urine sample [5].

Hypothyroidism is a widespread pathological condition characterized by deficiency of thyroid hormones. Without proper treatment, it can cause significant adverse health outcomes eventually leading to death. Overt or clinical primary hypothyroidism is identified by thyroid-stimulating hormone (TSH) concentrations surpassing the reference range and free thyroxine concentrations falling below the reference range. Mild or subclinical hypothyroidism, often considered an early indication of thyroid dysfunction, is characterized by TSH concentrations exceeding the reference range while free

thyroxine concentrations remain within normal limits [6].

CKD had been known to influence the pituitary-thyroid axis as well as the peripheral metabolism of thyroid hormones. Low T3 levels are the most common laboratory finding followed by subclinical hypothyroidism in CKD patients [7]. The kidney typically plays a vital role in the metabolism, breakdown, and elimination of thyroid hormones. In CKD, the hypothalamus-pituitary-thyroid axis is impacted, leading to various effects on thyroid function such as decreased circulating hormone levels, modified peripheral hormone metabolism, inadequate binding to carrier proteins, diminished tissue thyroid hormone content and altered iodine storage in the thyroid gland. Consequently, CKD impairs thyroid hormone metabolism [8]. This study endeavours to discern hypothyroidism in individuals with chronic kidney disease (CKD) to enable early intervention and mitigate the risk of complications.

Methodology

A hospital-based cross-sectional study was conducted in a tertiary care center in South India, involving patients of both sexes admitted with chronic kidney disease under the Department of General Medicine. The study was carried out over a period of three months, from November 2023 to January 2024. Based on a literature review, it was determined that approximately 30.4% of individuals with chronic kidney disease (CKD) also had hypothyroidism. Using a relative precision of twenty in the sample size formula with an attrition rate of 95%, the minimum required sample size for the study was calculated as 237 patients. This study received approval from the Institutional Human Ethics Committee (IHEC), and all ethical procedures were strictly followed, ensuring adherence to guidelines for patient safety and confidentiality.

Eligible participants were individuals aged 18 years or older who were willing to undergo an examination after providing informed consent. Patients with a history of medication intake known to affect thyroid function, such as lithium, amiodarone, iodine, methimazole, or propylthiouracil, were excluded. Additionally, individuals with acute kidney injury were excluded to maintain the study's focus on chronic manifestations of kidney disease. These inclusion and exclusion criteria were carefully defined to ensure homogeneity in the study population and to reduce potential confounding factors that could influence the examination of the relationship between hypothyroidism and CKD.

After informed consent was obtained from each participant, a detailed history and clinical examination were performed. Blood and urine samples were collected under aseptic conditions and processed for thyroid profile and renal function tests in the central laboratory of the Trichy SRM Medical College. Following the collection of creatinine values, the respective estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The stages of CKD were defined according to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines. CKD stages were classified as follows: stage 1 with 24-hour proteinuria > 0.15 g and eGFR ≥ 90 mL/min/1.73 m^2, stage 2 with 24-hour proteinuria > 0.15 g and 60 mL/min/1.73 m^2 ≤ eGFR < 90 mL/min/1.73 m^2, stage 3 with 30

mL/min/1.73 m² ≤ eGFR < 60 mL/min/1.73 m², stage 4 with 15 mL/min/1.73 m² ≤ eGFR < 30 mL/min/1.73 m², and stage 5 with eGFR < 15 mL/min/1.73 m².

Thyroid-stimulating hormone (TSH) levels between 0.35 mIU/mL and 4.50 mIU/mL were considered indicative of euthyroid status, while mildly elevated TSH levels (4.6–8.0 mIU/mL) in the presence of normal free T4 were considered subclinical hypothyroidism. The study variables were carefully measured to assess the prevalence of hypothyroidism in relation to CKD severity.

Data was entered into Microsoft Excel 2021 and analyzed using JASP R 4.2.1 software. The prevalence of hypothyroidism among the study population was determined and compared with the severity of CKD. The results were presented as numbers and percentages for categorical variables, and as mean (SD) or median (IQR) for numerical variables. The Chi-square test or Fisher's exact test was used to assess associations between categorical variables. For continuous variables, One-way ANOVA, and Pearson rank correlation were applied to determine the association between CKD and hypothyroidism. A p-value of less than 0.05 was considered statistically significant.

Results

Descriptives

Socio-demographic profile

Around 237 patients were enrolled in the study as per selection criteria and after obtaining detailed history, clinical and biochemical evaluation were done. The mean ± SD of age the study population was 50.6 ± 9.8 years, among which 92 (38.8%) were males and 145 (61.2%) were females respectively. The mean ± SD of height, weight, and BMI of the study population were 162.2 ± 9.6 cm, 69.5 ± 11.2 cm, and 26.5 ± 4 kg/m^2 respectively.

Figure 1 explains the thyroid function evaluation among 237 patients with chronic kidney disease (CKD). After conducting biochemical assessments, 65 patients (27.4%) were found to have hypothyroidism, while the majority, 172 patients (72.6%), were euthyroid. Among those diagnosed with hypothyroidism, 53 patients (22.36%) were classified as having subclinical hypothyroidism, and 12 patients (5.06%) were identified as having overt hypothyroidism. This distribution indicates that subclinical hypothyroidism is more prevalent than overt hypothyroidism in the CKD population studied.

Figure 2 shows the distribution of patients across different stages of chronic kidney disease. The majority of patients are in **Grade-5 (32.07%)** and **Grade-3 (31.65%)**, indicating that a significant proportion of the study population is in the advanced stages of CKD. **Grade-4** accounts for **23.21%** of patients, while **Grade-2**, representing the earlier stages of CKD, includes only **13.08%** of patients. This distribution suggests that the patient population is skewed towards more severe stages of CKD, with a notable majority in Grade-3 to Grade-5 stages, reflecting the progressive nature of the disease.

Table 1 highlights the relationship between chronic kidney disease (CKD) staging and thyroid status, indicating that hypothyroidism becomes more prevalent as CKD severity increases. Among Grade-2 CKD patients, 90.32% were euthyroid and 9.68% were hypothyroid, while in

Grade-3 CKD, 89.33% were euthyroid and 10.67% were hypothyroid. The prevalence of hypothyroidism rises significantly in Grade-4 CKD, where 38.18% of patients were hypothyroid and 61.82% were euthyroid. In the most severe stage, Grade-5 CKD, 44.74% of patients were hypothyroid, with 55.26% remaining euthyroid. The chi-square test revealed a significant association between CKD staging and thyroid status (p-value < 0.001), confirming that hypothyroidism becomes increasingly common as CKD progresses.

Table 2 Depicts the clinical parameters across the different stages of chronic kidney disease (CKD) reveal several key insights. The mean height and weight of patients show minimal variation across CKD stages, with no statistically significant differences (Height: $p = 0.67$, Weight: $p = 0.66$), indicating that these variables do not change significantly as CKD progresses. Similarly, body mass index (BMI) remains relatively consistent across the stages ($p = 0.97$). However, estimated glomerular filtration rate (eGFR), thyroid-stimulating hormone (TSH), proteinuria, serum creatinine, and urea levels show significant differences between the stages (all $p < 0.001$), reflecting the worsening kidney function and thyroid dysfunction as CKD severity increases. For instance, eGFR decreases progressively from Grade-2 to Grade-5 (75.79 mL/min/1.73m² in Grade-2 to 9.01 mL/min/1.73m² in Grade-5), while TSH increases significantly (8.92 mIU/L in Grade-2 to 19.39 mIU/L in Grade-5), highlighting the association between CKD progression and declining renal function alongside increased thyroid dysfunction. Proteinuria, serum creatinine, and urea also exhibit marked increases, indicating the progressive nature of CKD and its impact on kidney function and metabolic waste regulation.

Table 3 shows the correlation analysis demonstrates significant associations between kidney function and thyroid parameters in patients with chronic kidney disease (CKD). A negative correlation between eGFR and TSH ($r = -0.147$, $p = 0.023$) suggests that as kidney function declines, TSH levels increase, indicating worsening thyroid function. eGFR also shows a positive correlation with free T4 (fT4) ($r = 0.203$, $p = 0.002$), meaning better kidney function is associated with higher fT4 levels. A strong negative correlation is observed between eGFR and urea ($r = -0.980$, $p < 0.001$), as well as between eGFR and creatinine ($r = -0.816$, $p < 0.001$), indicating that as kidney function worsens, urea and creatinine levels significantly rise. Furthermore, TSH is negatively correlated with fT4 ($r = -0.578$, $p < 0.001$), showing the expected inverse relationship between thyroid hormones, while it is positively correlated with urea ($r = 0.172$, $p = 0.008$) and creatinine ($r = 0.129$, $p = 0.047$), linking higher TSH levels with markers of declining kidney function. The negative correlations between fT4 and both urea ($r = -0.195$, $p = 0.003$) and creatinine ($r = -0.148$, $p = 0.022$) further highlight the connection between improved thyroid function and reduced kidney dysfunction. Overall, the findings emphasize a clear relationship between worsening CKD and increasing thyroid dysfunction, particularly hypothyroidism.

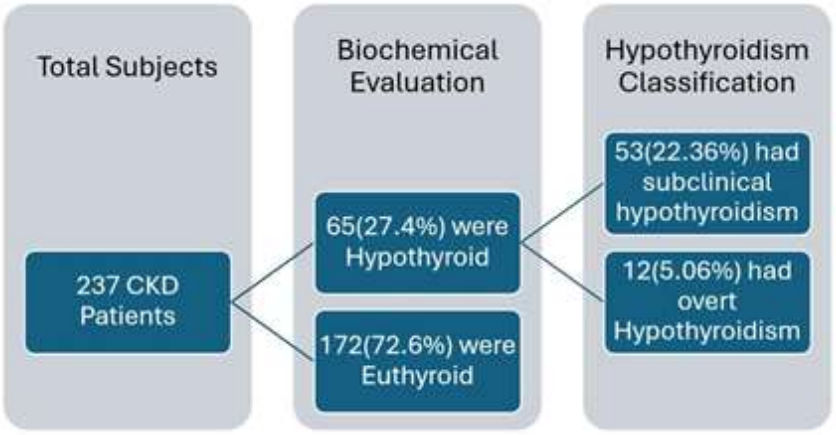


Figure 1. Distribution of thyroid functioning among the study population

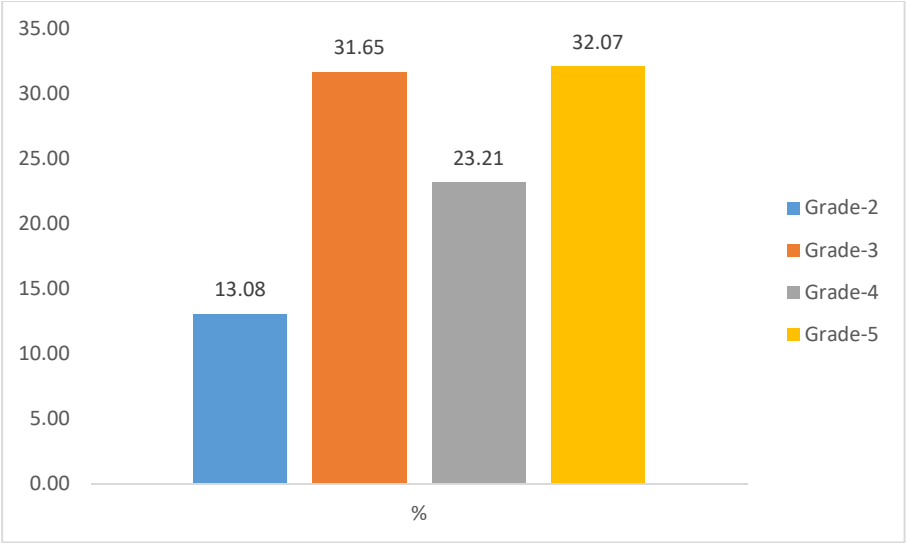


Figure 2. The grade wise distribution of CKD

Table 1. Association between Chronic Kidney disease and Hypothyroidism

Chronic Kidney Disease	Thyroid status				Total	CSV	p-value
	Euthyroid		Hypothyroid				
	N	%	N	%	N (%)		
Grade-2	28	90.32	3	9.68	31(13.08)	**28.95**	**<0.001**
Grade-3	67	89.33	8	10.67	75(31.65)		
Grade-4	34	61.82	21	38.18	55(23.21)		
Grade-5	42	55.26	33	44.74	76(32.07)		

*Chi-square test was performed

Table 2. The biochemical parameters of the patients

Variable	CKD grading	N	Mean	SD	F Value	P Value
Height (in cm)	Grade-2	31	161.28	9.532	0.517	0.67
	Grade-3	75	161.51	10.206		
	Grade-4	55	162.83	9.302		
	Grade-5	76	163.15	9.375		
Weight (in Kg)	Grade-2	31	68.83	9.625	0.5928	0.66
	Grade-3	75	68.59	11.814		
	Grade-4	55	70.51	11.688		
	Grade-5	76	70.53	10.720		
BMI (Kg/m^2)	Grade-2	31	26.66	4.491	0.0626	0.97
	Grade-3	75	26.37	4.538		
	Grade-4	55	26.68	4.576		
	Grade-5	76	26.56	4.060		
eGFR ($mL/min/1.73m^2$)	Grade-2	31	75.79	7.862	1152.06	<0.001
	Grade-3	75	43.61	7.175		
	Grade-4	55	21.57	4.374		
	Grade-5	76	9.01	3.173		
TSH (mIU/L)	Grade-2	31	8.92	1.34	**622.93**	**<0.001**
	Grade-3	75	10.47	1.21		
	Grade-4	55	14.18	1.38		
	Grade-5	76	19.39	1.68		
Free_T4 (ng/dl)	Grade-2	31	1.12	0.483	0.3042	0.82
	Grade-3	75	1.16	0.502		
	Grade-4	55	1.21	0.492		
	Grade-5	76	1.14	0.441		
Proteinuria (mg/dl) Gradually increasing	Grade-2	31	109.23	8.23	1899.30	<0.001
	Grade-3	75	121.19	9.51		
	Grade-4	55	183.27	8.97		
	Grade-5	76	219.65	9.06		
Sr. Creatinine	Grade-2	31	0.786	0.059	44.79	<0.001

(mg/dl)	Grade-3	75	1.114	0.057		
	Grade-4	55	2.212	0.214		
	Grade-5	76	4.396	3.37		
Urea (mg/dl)	Grade-2	31	55.1	2.74	862.05	<0.001
	Grade-3	75	65.7	2.94		
	Grade-4	55	73.6	2.46		
	Grade-5	76	88.02	4.47		

Table 3. Correlation between renal and Thyroid parameters

Variable	**eGFR** r (p-value)	**TSH (mIU/L)** r (p-value)	**fT4** r (p-value)	**Urea** r (p-value)	**Creatinine** r (p-value)
eGFR	1				
TSH (mIU/L)	-0.147* (0.023)	1			
fT4	0.203** (0.002)	-0.578*** (<0.001)	1		
Urea	-0.980*** (<0.001)	0.172** (0.008)	-0.195* 0.003	1	
Creatinine	-0.816*** (<0.001)	0.129* (0.047)	-0.148* (0.022)	0.816*** (<0.001)	1

Pearson co-relation was applied
* p < .05, ** p < .01, *** p < .001

Discussion

In this study, the thyroid profile of 237 chronic kidney disease patients was evaluated, and findings revealed that more than one-fourth (27.4%, n=65) of the study population exhibited hypothyroidism. These findings align with previous research by Lo et al. [14], who reported a similar prevalence of hypothyroidism where they have found the prevalence of hypothyroidism among CKD patients with an eGFR of less than 30 ml/min/1.73m^2.

Hypothyroidism and chronic kidney disease (CKD) may be coupled via a range of multifaceted and insufficiently comprehended mechanisms. The impact of CKD on thyroid hormone metabolism is one such explanation. Low circulating thyroid hormone levels, altered peripheral hormone metabolism, inadequate binding to carrier proteins, reduced tissue thyroid hormone content, and altered iodine storage in the thyroid gland are all consequences of chronic kidney disease (CKD), which additionally impacts the hypothalamus-pituitary-thyroid axis [15].

Further, our study revealed that among those hypothyroid cases, around 17.3% were Subclinical, which was supported by the similar findings reported

by Shreewastav et al. [16], where it has been found that a higher prevalence of subclinical hypothyroidism of about 27.2% among the CKD patients. It is also estimated that through previous studies the occurrence of primary hypothyroidism among the elderly was between 7%-26% [17].

Association between subclinical hypothyroidism and CKD may worsen kidney function by through direct and indirect effects, which were due to reduced cardiac output, raised systemic vascular resistance, intrarenal vasoconstriction, and impairment of glomerular anatomy. Also, studies have demonstrated that thyroid hormone replacement therapy among CKD patients with subclinical hypothyroidism has been led to attenuate the rate of eGFR decline [18].

Also, previous studies have found an increased prevalence of thyroid dysfunction among individuals with end-stage renal disease [19,20], which may be attributed to the underlying chronic inflammation [19]. Other contributing factors through which chronic renal failure may influence the thyroid parameters were low circulating thyroid hormone concentration, altered peripheral hormone metabolism, disturbed binding to carrier proteins, possible reduction in tissue thyroid hormone content, and increased iodine stored in thyroid glands [20].

In our study, we detected that low T4 levels which was in positive correlation with eGFR values, further supporting the evidence of hypothyroidism among CKD patients, and also through various studies, it has been demonstrated that free T4 levels vary from being low to normal among patients with chronic renal diseases [21]. Such heterogeneity might be due to several underlying factors, which include the severity of CKD, the presence of co-morbidities, and variations in levels of thyroid hormone-binding proteins.

Our findings on levels of free thyroxine align with previous research by Srivastava et al. [22], which observed a similar inverse correlation was found between the free T4 levels and renal function markers in a population with CKD, who were not requiring dialysis. The current study strengthens the existing evidence by reestablishing a comparable association in our patient population

Further, prior studies have demonstrated that CKD results in reduced iodide excretion, leading to a rise in serum inorganic iodide level & thyroid iodine content and consequently resulting in thyroid gland swelling, and finally ending up with goiter thyroid nodules and thyroid carcinoma [23].

Conclusion

It has been noted that there is a significant correlation between the severity of hypothyroidism with stages of chronic kidney disease. Additionally, there is a substantial association between CKD patients and prevalence of subclinical hypothyroidism. Our research suggests a comprehensive evaluation of the patient's medical history, encompassing information regarding the beginning and development of thyroid function as well as kidney health. Further the importance of Thyroid function test in all CKD patients for early diagnosis and treatment of hypothyroidism.

Statements and Declarations

Conflicts of interest

The authors declare that they do not have conflict of interest.

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No funding was received for conducting this study.

Human and animal rights

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

Informed consent obtained from all patients

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