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Original research article

A STUDY OF THYROID FUNCTIONS IN PATIENTS WITH CHRONIC KIDNEY DISEASE IN A TERTIARY CARE HOSPITAL

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Abstract

Introduction: Chronic kidney disease is a gradually worsening ailment that impacts more than 10% of the global population, which is equivalent to about 800 million people. Thyroid hormones are necessary for the embryological development and growth of the kidneys. Conversely, the kidney influences the metabolism, degradation, and removal of thyroid hormone. Chronic renal disease patients may experience a range of changes in thyroid hormones due to the connection between thyroid hormones and kidney function.

Methods: CLIA measured thyroid function tests [TT3, TT4, FT4, TSH] in a cross-sectional study of 60 patients with chronic renal disease at different stages. The symptoms of hypothyroidism, anomalies in thyroid hormone levels, and stage of chronic kidney disease (CKD) were evaluated using the Chi-square test and ANOVA tests.

Results: Out of the total of 60 patients included in the study group, 38 patients were diagnosed with stage 5 chronic kidney disease (CKD). Among patients with stage 5 chronic kidney disease (CKD), 13.15% were found to have hypothyroidism, but no cases were observed in patients with stage 3 or stage 4 CKD. Among patients with stage 5 CKD, 23.68% exhibited subclinical hypothyroidism, whereas no cases were observed in stage 3 and 16.67% in stage 4. The prevalence of low TT3 or TT4 with normal TSH abnormalities in stage 3 CKD is 0%, but in stage 4 and 5 CKD, the prevalence is 16.67% and 26.31% respectively.

Conclusion: A progressive decline in total T3 and total T4 levels was observed with increasing stages of CKD. No statistically significant correlation was observed between the levels of TT4 (thyroxine) and the stage of chronic kidney disease (CKD). There was a strong correlation between the occurrence of thyroid dysfunction and the severity of chronic renal disease. The incidence of thyroid hormone anomalies is positively correlated with the severity of renal failure. As the severity of renal failure increases, the levels of thyroid profile, specifically T3, T4, and TSH, drop.

Keywords: Chronic kidney disease, hypothyroidism, thyroid dysfunction, TSH, T3 & T4

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Introduction

Chronic kidney disease (CKD) is a medical condition characterized by the permanent loss of kidney function, resulting in various symptoms related to metabolism, hormone production, waste elimination, and synthesis. As a consequence, there is a buildup of nitrogenous waste compounds, leading to metabolic irregularities and noticeable clinical symptoms. Chronic kidney disease (CKD) is identified by the existence of kidney damage or a reduced glomerular filtration rate (GFR) of 60 ml/min/1.73 m2 or less for a duration of three months or more, regardless of the underlying cause [1]. The condition can arise from various causes and pathological mechanisms that harm the kidneys, including diabetic nephropathy, glomerulonephritis, renal disease associated with hypertension (including vascular and ischemic kidney disease), autosomal dominant polycystic kidney disease, other kidney diseases involving cysts and tubules, Alport disease, chronic kidney disease of unknown origin, and so on [2]. The causes of the condition may differ depending on the geographic location, race, and age of the individual.

Chronic kidney disease (CKD) is a prevalent condition that affects a significant portion of the global population. In 2017, the global burden of disease (GBD) study determined that there were 698 million instances of chronic kidney disease (CKD), with a prevalence rate of 9% among adults worldwide [3]. Chronic kidney disease (CKD) accounted for 7.3 million years lived with disability (YLDs), 28.5 million years of life lost (YLLs), and 35.8 million disability-adjusted life years (DALYs). In 2017, China and India accounted for one-third of the global burden of chronic kidney disease (CKD), with 132.3 and 115.1 million cases, respectively [3].

Chronic kidney disease (CKD) can present with a diverse array of signs and symptoms that impact many organ systems. The symptoms related to the kidneys encompass nocturia, oliguria, edema and hypertension. Endocrine and metabolic imbalances can result in elevated levels of potassium in the blood (hyperkalemia), increased acidity in the body (metabolic acidosis), low levels of calcium in the blood (hypocalcemia), high levels of phosphate in the blood (hyperphosphatemia), overactivity of the parathyroid glands (hyperparathyroidism), and malnutrition due to insufficient protein and energy intake (protein-energy malnutrition). Dermatological symptoms may encompass pruritus, alterations in skin pigmentation, uremic frost, and nephrogenic fibrosing dermopathy. Neurological symptoms can include peripheral neuropathies, changes in the sense of smell and taste, disruptions in sleep patterns, muscle cramps, seizures, and asterixis. Cardiovascular complications include conditions such as left ventricular hypertrophy, uremic cardiomyopathy, chronic heart failure, arrhythmias, and other related issues. Hematological disorders can lead to anemia caused by uremia, dysfunction of granulocytes and lymphocytes, platelet dysfunction, bleeding, and abnormalities in blood clotting. Gastrointestinal manifestations may encompass hiccups, loss of appetite, nausea and vomiting, uremic fetor, and nutritional deficiencies [4, 5].

Thyroid hormones play a crucial role in the physiological functioning of the kidneys and the maintenance of the body's internal balance. The kidneys have vital functions in the metabolism and elimination of thyroid hormones. Research has shown that there is a presence of thyroid dysfunction in patients with chronic kidney disease (CKD), although the findings from different studies are inconsistent [5, 6]. Research has shown

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that chronic kidney disease has an impact on the hypothalamus-pituitary-thyroid axis and the peripheral metabolism of thyroid hormone. The most commonly observed thyroid disorder associated with CKD is subclinical hypothyroidism, which is characterized by low levels of triiodothyronine (T3) in laboratory tests [7]. Additionally, it has been documented that in a state of hyper-ureamic condition, the pituitary receptor's reaction to thyroxine releasing hormone (TRH) is dulled, resulting in a decrease in the production of thyroid stimulating hormone (TSH). As a result, the TSH response to TRH is delayed due to reduced clearance and increased half-life of TSH. Furthermore, it has been observed that uremia can cause an aberrant serum ingredient to displace T3 and thyroxine (T4) from their usual protein binding site [8].

Thyroid hormones have discernible consequences on cellular proliferation and also control essential physiological systems in the body. The prevalence of thyroid abnormalities has been found to rise as chronic kidney disease (CKD) advances [9]. Advancements in laboratory testing now allow for the identification of subtle fluctuations in thyroid hormone levels. However, it is not currently advised to treat modest changes in thyroid hormone levels in patients with chronic kidney disease who are not undergoing dialysis. The slight fluctuations in thyroid hormone levels in patients with CKD may serve as a risk factor for adverse health outcomes, such as the progression of CKD. Similarly, the advancement of CKD has been associated with the occurrence of thyroid dysfunction [8].

This study aims to ascertain the frequency of thyroid dysfunction in patients with chronic kidney disease (CKD) with the purpose of intervening at an early stage based on hormone abnormalities. The goal is to mitigate both the risk of cardiovascular complications and the progressive deterioration of renal function.

Material and Methods

The present study was conducted at NRI Medical College and Hospital, Guntur, Andhra Pradesh, India. After obtaining clearance from institutional ethical committee for the research work, informed consents were taken from the participants.

Inclusion criteria

The inclusion criteria were as follows: individuals aged more than 18 years; patients who fulfilled the criteria for CKD and were on conservative management; symptoms of uremia for 3 months, ultra sound evidence of chronic kidney disease (Bilateral contracted kidneys, poor corticomedullary differentiaon) and Supportive laboratory evidence of CKD like anemia, urine specific gravity, changes in serum electrolytes, etc.

Exclusion criteria

Patients under the age of 18, patients diagnosed with thyroid problem, and patients taking medications that affect thyroid function such as amiodarone, steroids, dopamine, phenytoin, estrogen pills, iodine-containing pharmaceuticals, thyroid hormone replacement, or antithyroid therapies.

Sample size: 50 patients who full fill the inclusion and exclusion criteria.

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Study design

During an 18-month study period, patients were admitted to the Nephrology ward based on specific criteria. After applying these criteria, a total of 50 patients were included in the study. Patients meeting the criteria for chronic kidney disease (CKD) and undergoing conservative treatment and hemodialysis. Once the patients meeting the specified criteria have been chosen, approximately 5ml of blood sample is obtained using a non-heparinized serum bottle and sent for thyroid profile analysis. The thyroid profile in this study includes measurements of serum total triiodothyronine (TT3), serum total thyroxine (TT4), serum thyroid stimulating hormone (TSH), serum free triiodothyronine (FT3), and 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)

$$= \frac{(140\text{-Age}) \times \text{body weight in kg.}}{72 \times \text{Pcr (mg/dl)}}$$

(multiply by 0.85 for women)

Thyroid function was evaluated by quantifying the levels of triiodothyronine (TT3), thyroxine (TT4), and thyroid-stimulating hormone (TSH) in the serum. Serum FT4 was measured for all TSH values greater than 5 mIU/L. Competitive chemiluminescent immunoassay was used to determine the levels of Serum TT3, TT4 and FT4.

The measurement of TSH was conducted using an ultra-sensitive sandwich chemiluminescent immunoassay (CLIA).

The blood urea level was determined using the diacetyl monoxime (DAM) technique. The determination of serum creatinine was performed using the modified kinetic Jaffe method.

Results

Table 1: Baseline information of study sample (n=60)

Variables	
Age: 21-30-6	12(%)
31-40 -6	12(%)
41-50-10	20(%)
51-60-20	40(%)
>60-08	16(%)
Gender	
Male	33(66%)
Female	17(34%)
Comorbidities	
Hypertension	23(46%)
Diabetes mellitus	22(44%)

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Both Hypertension & Diabetes mellitus	13(26%)
Cardiovascular disease	6(12%)
Hypothyroidism	14(28%)
Haemodialysis	34(68%)

Majority of study participants in this study belonged to the age group of 51 to 60 years. The study group had a mean age of 53.55 years with a standard deviation of 6.65 years. There was a greater prevalence of males compared to females in this study. A significant proportion of individuals with chronic kidney disease exhibit hypertension (46%), Diabetes mellitus (44%), combined hypertension and diabetes mellitus (26%), and cardiovascular disease (12%). Approximately 28% of the patients in the study group were diagnosed with Hypothyroidism, while a total of 68% of the patients were undergoing haemodialysis. The information is presented in (Table 1). The study population examined the symptoms of hypothyroidism, such as fatigue, drowsiness, weight gain, sensitivity to cold, constipation, and hoarseness of voice, in individuals with chronic kidney disease (CKD).

Table 2: Prevalence of abnormalities of thyroid function based on thyroid function tests

Impression	**Cases**	
	Numbers	**(%)**
Hyothyroidism	06	12
Subclinical Hypothroidism	09	18
Low TT3 or TT4 with Normal TSH	13	26
Normal	22	44
Total	50	50

Out of the 60 patients included in this sample, 6 patients (12%) were diagnosed with hypothyroidism. Subclinical hypothyroidism was present in 9 patients, accounting for 18% of the total. Thirteen individuals, accounting for 26% of the total, exhibited low levels of TT3 or TT4 despite having normal TSH. In total, 28 patients, representing 56% of the sample, displayed some form of abnormality in thyroid function.

Table 3: Represents the relationship between CKD Stage and Symptoms of Hypothyroidism

CKD Stage	**Symptoms**				**Total Number**
	Yes		**No**		
	N	%	N	%	50
Stage 3	-	-	6	100	6
Stage 4	2	16.67	5	83.33	6
Stage 5	12	31.58	26	68.42	38

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P Value: 0.22

Among the 50 patients, 14 exhibited symptoms that indicated hypothyroidism. Out of these 14 patients, 2 (15.4%) were in stage 4 chronic kidney disease (CKD), while the remaining 12 patients (84.6%) were in stage 5 CKD. While symptoms were noticeable in cases of advanced renal failure, this association did not reach statistical significance.

Table 4: 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	26.33
Normal	6	100	4	66.67	11	36.81
Total	6	100	6	100	38	100

P value: 0.04

Out of the total of 60 patients included in the study group, 38 patients were diagnosed with stage 5 chronic kidney disease (CKD). Among patients with stage 5 chronic kidney disease (CKD), 13.15% were found to have hypothyroidism, but no cases were observed in patients with stage 3 or stage 4 CKD. Among patients with stage 5 CKD, 23.68% exhibited subclinical hypothyroidism, whereas no cases were observed in stage 3 and 16.67% in stage 4. The prevalence of low TT3 or TT4 with normal TSH abnormalities in stage 3 CKD is 0%, but in stage 4 and 5 CKD, the prevalence is 16.67% and 26.31% respectively. The higher the stage of chronic kidney disease (CKD), the greater the prevalence of thyroid dysfunction. The observed link was determined to have statistical significance.

Table 5: Relationship between CKD Stage & hematological parameters and their significance

Parameters	CKD stage						Significance		
	3		4		5				
	Mean	SD	Mean	SD	Mean	SD	F*	P value	
Bl Urea	72.76	30.65	92.5	23.6	160.04	39.03	14.80	<0.01	HS
Sr Creat	2.92	0.30	3.6	0.7	7.06	2.5	13.63	<0.01	HS
T_3	1.01	0.36	1.08	0.67	1.03	1.92	4.70	0.02	S
T_4	6.88	2.46	5.56	1.52	5.12	2.02	0.336	0.77	NS
TSH	2.18	1.26	3.67	1.38	5.75	3.92	9.681	<0.01	HS

Discussion

Based on the World Health Organisation (WHO) worldwide Burden of Disease project, disorders affecting the kidney and urinary tract are a significant worldwide health burden, resulting in roughly 850,000 deaths annually and causing 115,010,107

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disability adjusted life years. Chronic Kidney Disease (CKD) ranks as the twelfth most common cause of death and the seventeenth most common cause of disability. This is a prevalent chronic illness that has a significant impact on both the number of people affected and the number of deaths it causes globally. Chronic kidney disease (CKD) is a significant global public health challenge, due to the large number of affected individuals and the substantial financial burden associated with its treatment. The kidney lacks the ability to create new nephrons. As a result, any renal injury, disease, or natural ageing process leads to a steady decline in glomerular filtration rate (GFR) and nephron count. This ultimately results in a permanent and irreversible loss in the overall renal function [9-12].

The thyroid gland is a significant factor that impacts almost all organ systems in the body, and the functions of the thyroid and kidney are tightly interconnected. The thyroid's condition has an impact on kidney function starting from the earliest stage of development. Thyroid hormones have an impact on overall tissue growth, as well as the functioning of tubules, the regulation of electrolytes, and the reception of brain signals. The thyroid's hyper-and hypo-functioning indirectly impacts mature kidney function by influencing the cardiovascular system and renal blood flow. It also directly affects glomerular filtration, electrolyte pumps, the secretory and absorptive capacity of the tubules, and the structure of the kidney. There is an elevated likelihood of developing kidney disease and cardiovascular complications in individuals with type 2 diabetes mellitus who also have subclinical hypothyroidism (SCH) [13, 14].

The objective of the present investigation was to ascertain the frequency of thyroid dysfunction in patients with chronic kidney disease (CKD).

Out of the 50 patients examined, 10% (5 patients) were diagnosed with hypothyroidism, 20% (10 patients) had subclinical hypothyroidism, and 28% (14 patients) exhibited thyroid hormone abnormalities characterised by decreased levels of TT3 and TT4. A total of 58% of patients with chronic kidney disease (CKD) exhibited thyroid hormone abnormalities.

Out of the 14 patients with thyroid hormone abnormalities, 3 patients (6%) had exclusively reduced TT4 levels, 6 patients (12%) had reduced TT3 levels, and 5 patients (10%) had reduced levels of both TT4 and TT3. All of these patients exhibited normal thyroid function and their levels of thyroid-stimulating hormone (TSH) were within the acceptable range.

Falhi *et al*. conducted a study on 50 CKD patients between the ages of 20 and 50. Their findings revealed a substantial decrease ($p<0.01$) in T3 and T4 levels, as well as an increase in TSH level, when compared to the control group [15]. The study conducted by Khatiwada *et al*. found that there was no significant drop in T3 and T4 levels in CKD patients. However, there was a substantial increase in the TSH level [16].

The average TSH level in our study is within the normal range, excluding cases of hypothyroidism and subclinical hypothyroidism. The average TSH levels also fall within the normal range for the different GFR values. However, the TSH level does not exhibit any linear association with the severity of renal failure. This aligns with the research carried out by Joseph et.al and Hardy *et al*. [17]. These research showed that uremic individuals have an anomaly in the way their pituitary gland releases thyroid-stimulating hormone (TSH). This is evident from the fact that their TSH response to thyrotropin-releasing hormone (TRH) is weakened.

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In our study, a total of 13 individuals had symptoms indicative of hypothyroidism, with 5 of them being biochemically confirmed as hypothyroid, while the remaining 8 patients had thyroid function test results within the subclinical range. Consequently, several symptoms of CKD can coincide with those of hypothyroidism, which can complicate the process of diagnosis.

Our outcome aligns with the conclusions drawn from other prior investigations [18-20]. In a study conducted on hemodialysis patients, it was shown that 26.6% of the patients had both subclinical and clinical hypothyroidism [21]. A study conducted by Lo *et al*. discovered that the occurrence of hypothyroidism rose as the levels of eGFR decreased. Specifically, the prevalence was 5.4% among subjects with an eGFR of 90 or higher, 10.9% among those with an eGFR of 60-89, 20.4% among those with an eGFR of 45-59, 23.0% among those with an eGFR of 30-44, and 23.1% among those with an eGFR below 30 ($p<0.001$ for trend) [22].

Our study found that 13.15% of patients with stage 5 chronic kidney disease (CKD) had hypothyroidism, but no cases of hypothyroidism were seen in patients with stage 3 or stage 4 CKD. Out of the 9 patients in stage 5, all of them had subclinical hypothyroidism, while none of the patients in stage 3 had it and just 1 patient in stage 4 had it. 1 patient has low TT3 levels and 13 patients have low TT4 levels in stage 4 and stage 5, respectively.

TT3, TT4, and FT4 levels exhibited a gradual decline with the progression of CKD stages, whereas FT4 and TSH levels remained within the normal range, except in individuals with evident hypothyroidism. Although the symptoms of hypothyroidism were noticeable in the later stages of renal illness, the statistical analysis did not reveal a meaningful association.

Although there have been significant advancements in renal replacement therapy, cardiovascular disease continues to be the primary cause of illness and death in patients with chronic kidney disease (CKD).

Malik found no substantial disparity in TT3 and TT4 levels between the patients undergoing conservative therapy and those receiving regular hemodialysis [23]. The research conducted by Kayima *et al*. demonstrated that the average levels of TT4, TT3, free T4, and free T3 were significantly lower in patients compared to the control group ($p<0.01$). Additionally, the average TSH level was significantly higher in patients compared to controls ($p<0.01$). However, no significant differences were observed in these parameters between patients undergoing hemodialysis and those receiving conservative management ($P>0.05$) [24].

Individuals diagnosed with chronic kidney disease (CKD) face a significantly higher likelihood of experiencing thyroid dysfunction. The presence of irregularities in thyroid hormone levels could potentially contribute to the development of cardiovascular disease and may also play a role in the progression of kidney disease.

Conclusions

While hyperthyroidism is typically not directly linked to chronic kidney disease (CKD), it is recognized to hasten its progression. It is crucial to thoroughly evaluate all clinical characteristics and thyroid symptoms in individuals with chronic kidney disease (CKD). Thyroid dysfunction and kidney illness have been observed to have clear connections in numerous evidence-based research and actual clinical cases.

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Based on the findings of recent and prior investigations, it is probable that there is a disruption in the functioning of thyroid hormones, which is accompanied by a decrease in renal function.

Nephrologists need to take into account the potential risks associated with thyroid dysfunction and its proper management when treating chronic kidney disease (CKD). Patients who receive suitable therapy for their thyroid disorder experience a reduced likelihood of acquiring or worsening renal impairment. Nevertheless, administering treatment to patients with a slight increase in TSH levels (below 10 IU/mL) leads to a negative nitrogen balance due to heightened muscle breakdown. Prior to renal transplant, clinicians should assess patients for low T3 levels, as these levels have been linked to renal graft loss.

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