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Thyroid Function Test in Patients with Chronic Kidney Disease

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Background: Kidneys have a significant role in the metabolism, degradation and excretion of thyroid hormones. Both thyroid hormones and kidney functions have a multifaceted mutual interdependence.
Objectives: To find out the possible association between the severity of chronic kidney disease and thyroid dysfunction; To estimate the correlation between thyroid dysfunction and various stages of chronic kidney disease.
Materials and Methods: A prospective Cross-sectional study was done on 50 patients with Chronic kidney disease who were not on dialysis and fulfilled all the inclusion criteria at Saveetha medical college over a period of 6 months. Free T3, Free T4 and TSH levels were estimated for those patients.
Results: Results of this study showed that majority of subjects included in our study were in the age group of 50-60 years with Male predominance. Out of 50 patients included in our study, 8 patients(16%) were found to hypothyroidism; 5 patients (10%) were having subclinical hypothyroidism; 20 patients (40%) were having low T3 syndrome and 17 patients (34%) were having normal functioning thyroid gland. Staging of CKD was done in relation to the glomerular filtration rate .Most of the patients(n=20) were in Stage 5 of Chronic kidney disease out of which 18 patients were having thyroid disorders.

Conclusion: There is a positive correlation between the severity of CKD and thyroid dysfunction. Hence a routine thyroid function status should be evaluated in each and every patient of CKD to reduce the morbidity and mortality rate of CKD patients as well as reduce the social burden and health expenditure.

Keywords: Chronic kidney disease (CKD); hypothyroidism; subclinical hypothyroidism; low T3 syndrome.

1. INTRODUCTION

Chronic kidney disease is a wide spectrum of pathophysiologic processes associated with progressive decline in glomerular filtration rate (GFR) and abnormal kidney function [1]. As defined by US National Kidney Foundation's Kidney Dialysis Outcome Quality Initiative guidelines, the estimated eGFR for CKD is <60 ml/min/1.73 m2 for >3 months [2]. Stage 5 CKD is the End Stage Renal disease (ESRD) with a GFR of < 15ml /min/1.73m2 which needs dialysis or renal replacement [3].

Both thyroid hormones and kidney functions have a multifaceted mutual interdependence [4] (List 1). Thyroid hormones play an important role in regulating the basal metabolic rate, development, protein synthesis and it also influences the function of some other hormones [5]. In the kidney, thyroid hormones play a significant role in its growth and development and for the maintenance of water and electrolytes. On the other hand, Kidney has a significant role in the metabolism, degradation and excretion of thyroid hormones [6].

In patients of CKD , all levels of the hypothalamic-pituitary-thyroid axis may be involved as a result of which abnormalities in thyroid function tests are frequently encountered in uraemia [7] (List 1). Clearance of Iodine is contributed by the Kidney, primarily by glomerular filtration. In advanced cases of renal failure, as the kidney is unable to perform its normal function efficiently, there is a rise in the plasma inorganic iodide concentration due to its impaired excretion leading to increment in thyroidal iodide uptake [8].This increase in total body inorganic iodide can potentially block thyroid hormone production which is known as the Wolff Chaikoff effect [9,10]. This rise in the plasma inorganic iodide concentration affect the pituitary thyroid axis and peripheral metabolism of thyroid hormones [4] (List 1). There can be a decreased peripheral conversion of T4 to T3 due to decreased clearance of inflammatory cytokines such as TNF-alpha and IL-1. This is the reason behind the increased frequency of hypothyroidism among patients with chronic kidney disease [11].

The levels of thyroid stimulating hormones in chronic kidney disease patients may be normal or increased but there is a reduced response to thyrotropin releasing hormone [3] (List 1). Circadian rhythm and activity are altered, suggesting abnormality in the level of hypophysis [12]. According to various studies, prevalence of thyroid dysfunction is found to be ranging from 13% in early CKD to 70% End stage renal disease [13,14,15,16].

This study was conducted to find out the possible association between the severity of chronic kidney disease and thyroid dysfunction and also to estimate the correlation between thyroid dysfunction and various stages of chronic kidney disease.

2. METHODS AND MATERIALS

A prospective Cross-sectional study was conducted at Saveetha medical college and hospital over a period of 6 months on patients attending outpatient departments and also those admitted in the medicine ward.

A total of 50 patients were included in this study who fulfilled the inclusion criteria. An informed consent was taken from all the patients before they were included in the study.

2.1 Inclusion Criteria

- Chronic kidney disease patients aged above 18 years.
- Kidney disease of 3 months or more than 3 months duration.

All the 50 cases included in the study were classified into stages of chronic kidney disease according to the glomerular filtration rate (List 2).

2.2 Exclusion Criteria

- If the patient is on dialysis
- Family history of thyroid disorder

- Past history of any anti thyroid drugs or any other medications for thyroid disease
- History of any recent surgery, trauma or burns
- Children
- ANC patients

Morning blood samples were collected after 12 hours of fasting. The blood samples were analyzed for free triiodothyronine (FT3), free Thyroxine (FT4), and thyroid stimulating hormone (TSH) by electrochemiluminescence.

3. RESULTS

Result shows that out of 50 patients included in our study 60% (n=30) were Male and 40% (n=20) of them were Female. Age of the patients ranged from 20-60 years. Majority of the patients were in the age group of 50-60 years (36%,n=18) followed by 40-49 years (30%,n=15) .22%(n=11) of them were in the age group of 30-39 years and 12%(n=6) of them were in the age group of 20-29 years (Table 1).

List 1. Effects of chronic kidney disease on thyroid profile

Hypothalamus - Pituitary	1. Increased TSH 2. Decreased TSH response to TRH 3. Abnormal TSH circadian rhythm 4. Abnormal glycosylation of TSH
Thyroid	1. Goitre, nodules or increased size of the thyroid gland 2. Decreased T4 response to TSH 3. Decreased total or free T4
Circulation	1. Decreased protein binding 2. Decreased total or circulating free T3, T4 3. Increased iodine levels in the serum 4. Alteration in thyroid hormone binding proteins 5. Increased rT3
Tissue	1. Increased rT3 2. Decreased total or free T3 3. Decreased conversion of T4 to T3
Renal	1. Altered clearance of TRH, TSH 2. Decreased Iodine excretion 3. Increased protein binding loss

List 2. Staging of chronic kidney disease was done on the basis of GFR

Stage of kidney disease	GFR
Stage 1	>90 ml/min
Stage 2	60- 89 ml/min
Stage 3	30-59 ml/min
Stage 4	15-29 ml/min
Stage 5	<15ml/min

Table 1. Distribution of CKD patients according to age and gender

Age (years)	Male	Female	Total%
20-29	5(10%)	1(2%)	12%(6 patients)
30-39	7(14%)	4(8%)	22%(11 patients)
40-49	8(16%)	7(14%)	30%(15 patients)
50-60	10(20%)	8(16%)	36%(18 patients)
Total	30(60%)	20 (40%)	100% (50 patients)

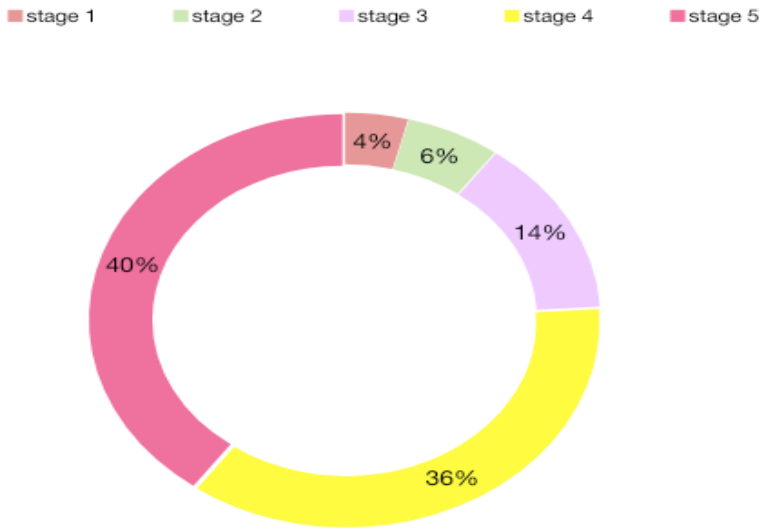

Fig. 1. Distribution of patients according to the staging of chronic kidney disease

Result shows that 4%(n=2) of the patients were in stage 1 of CKD, 6%(n=3) of them were in stage 2 of CKD, 14% of them were in stage 3 of CKD ,36%(n=18) of them were in stage 4 of CKD and 40% (n=20) of them are in stage 5 of CKD (Fig. 1).

Result shows that according to the glomerular filtration rate the patients were classified into various stages of chronic kidney disease. Stage 1 of CKD includes patients who has a GFR of>90 ml/min and out of 50 patients included in our study 2 patients(4%) were in Stage 1 of CKD. 3 patients(6%) with GFR of 60-89 ml/min were classified under Stage 2 and 7 patients(14%) with GFR of 30-59 ml/min under stage 4 and 20 patients with GFR of <15 ml/min were classified under stage 5 of CKD (Table 1).

Result shows that out of 50 patients included in our study, 8 patients(16%) were having hypothyroidism that is low T3; low T4; high TSH. 5 patients (10%) were having subclinical hypothyroidism that is normal T3; high TSH and 20 patients (40%) were having low T3 syndrome and 17 patients (34%) were having normal functioning thyroid gland (Fig. 2).

Table 2. Staging of CKD in relation to the glomerular filtration rate

Stage of kidney disease	GFR	No of patients	Percentage
Stage 1	>90 ml/min	2	4%
Stage 2	60- 89 ml/min	3	6%
Stage 3	30-59 ml/min	7	14%
Stage 4	15-29 ml/min	18	36%
Stage 5	<15ml/min	20	40%

Table 3. Summary of correlation of thyroid disorders with the GFR and stage of chronic kidney disease

Stage of CKD	Hypothyroidism	Subclinical hypothyroidism	Low T3	Percentage of patients
Stage 1	0	0	0	0
Stage 2	0	0	1	2%
Stage 3	2	1	2	10%
Stage 4	2	2	5	18%
Stage 5	4	2	12	36%
Total number of patients	8	5	20	66%

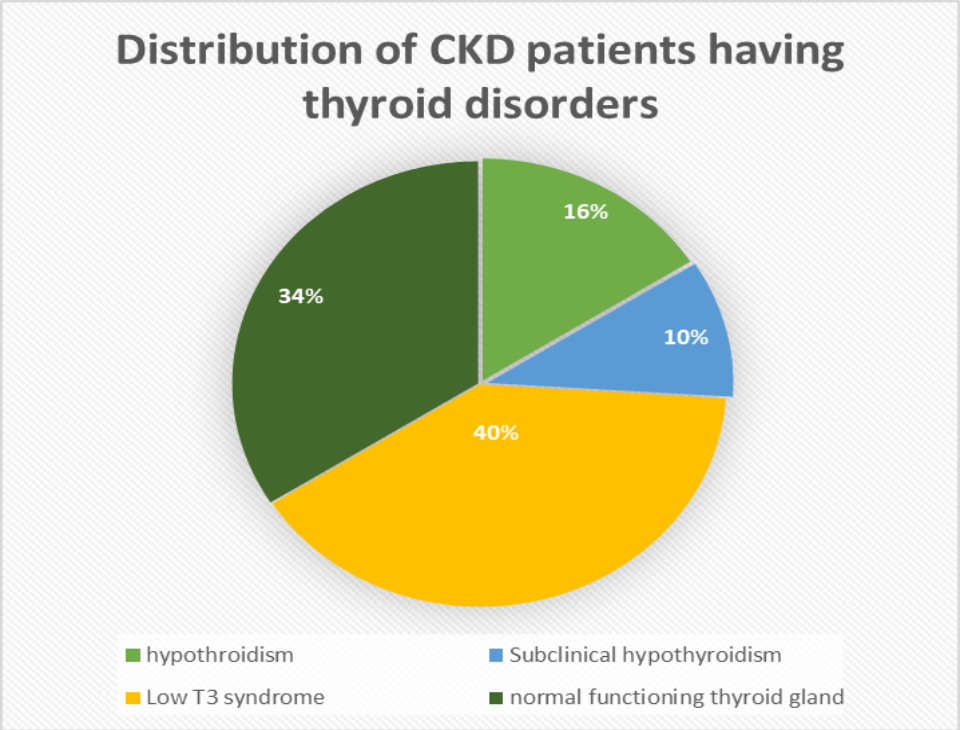

Fig. 2. Distribution of CKD patients having thyroid disorders

Result shows that thyroid disorders in patients with chronic kidney disease were more common in patients with stage 3,4 and 5 of CKD with stage 5 of CKD being the predominant one. One patient in stage 2 was having low T3 levels. A total of 10% of patients with stage 3 CKD were having thyroid disorders out of which 1 patient was diagnosed to have subclinical hypothyroidism, 2 patients with hypothyroidism and 2 patients with low T3. In patients with Stage 4 of CKD, 2 patients were having overt hypothyroidism; 2 patients were having subclinical hypothyroidism and 5 patients were having low T3 and a total of 18% (n=9) are having thyroid disorders. In patients with stage 5 of CKD, 4 patients are having hypothyroidism,2 patients were having subclinical hypothyroidism and 12 patients were having low T3 syndrome and a total of 18 patients (36%) of patients are having thyroid disorders.Thus a total of 66%(n=33) of patients in our study are having thyroid disorder(Table 3).

4. DISCUSSION

One of the major worldwide public health problems is CKD. According to WHO, 2004, they are the 12th cause of death and 17th cause of disability in the world [17]. In patients with CKD, several alterations in thyroid function has been reported. It affects the peripheral conversion of T4 to T3, decrease binding of thyroid hormones by transport proteins and peripheral hormone metabolism. Some patients with CKD often have signs and symptoms suggestive of thyroid dysfunction and few patients have subclinical hypothyroidism [18]. The aim of this study is to access the prevalence of thyroid dysfunction in CKD and to determine correlation between thyroid dysfunction and the severity of CKD. There was a significant reduction of serum T3 level, T4 level and elevation of TSH levels in CKD patients [19,20,21,22].

In our study 50 patients were included who fulfilled all the inclusion criteria. Patients on dialysis were excluded because dialysis changes the previous serum status of thyroid hormones in the patients with renal failure out of which 60% (n=30) of them were Male and 40% (n=20) of them were Females (Table 1). In a study conducted by Dr.J. Punekar et al. [6] the male:female ratio was 1.08:1 in case group. In a study by Upendra Nath Gupta et al. [23] out of 100 patients of CKD, 60 were Male and 40 of them were Female and in a study by Md Mosharruf Hossain et al. [17] 63% patients were Male and 37% were Female giving rise to a Male:Female ratio of nearly 1.7:1.In contrast to our study Abhishek Gupta et al. [4] showed that

prevalence of SCH was more in Females (52%) compared to Males (48%). In our study, majority of patients included in the study with Chronic Kidney Disease were in the age group of 50-60 years (Table 1). Similar to our study, Md Mosharruf Hossain et al. [17] showed that prevalence of thyroid dysfunction in patients with Chronic Kidney Disease were more in the age group of 50-60 years. In contrast to our study, Abhishek Gupta et al. [4] showed that patients of Chronic Kidney Disease with thyroid dysfunction were more in the age group of 40-50 years.

Our study shows that 4%(n=2) of the patients were in stage 1 of CKD, 6%(n=3) of them were in stage 2 of CKD, 14% of them were in stage 3 of CKD, 36%(n=18) of them were in stage 4 of CKD and 40% (n=20) of them are in stage 5 of CKD (Fig. 1). In a study done by Md Mosharruf Hossain et al. [17] shows that 2%(n=2) of the patients were in stage 1 of CKD, 6%(n=6) of them were in stage 2 of CKD, 13%(n=13) of them were in stage 3 of CKD ,31%(n=31) of them were in stage 4 of CKD and 48% (n=48) of them are in stage 5 of CKD which is almost in line with our study. In our study according to the glomerular filtration rate the patients were classified into various stages of chronic kidney disease. Stage 1 of CKD includes patients who has a GFR of>90 ml/min and out of 50 patients included in our study 2 patients (4%) were in Stage 1 of CKD. 3 patients (6%) with GFR of 60-89 ml/min were classified under Stage 2 and 7 patients (14%) with GFR of 30-59 ml/min under stage 4 and 20 patients with GFR of <15 ml/min were classified under stage 5 of CKD (Table 2).

In a study by Chandra et al. [24] subclinical hypothyroidism were reported in ~40% of patients and clinically apparent hypothyroidism have been reported to occur in 16% of patients. Our study differs from these previous observations by demonstrating a prevalence of hypothyroidism in 16%(n=8) of patients;10%(n=5) of patients were having subclinical hypothyroidism; 40%(n=20) of patients were having low T3 syndrome and 34%(n=17) of patients were having normal functioning thyroid gland (Fig. 2). Our study is in line with the observation made by Chonchol et al. [25], Upendra Nath Gupta [23]. Similar to our study, a study done by Md Mosharruf Hossain et al. [17] showed that 11%(n=11) were suffering from primary hypothyroidism,5% (n=5) were subclinical hypothyroidism and 45%(n=45) were of low T3 syndrome .In contrast to this Dr. J. Punekar et al. [6] showed that out of 75 patients included in their study, 21.33% (n=16) of them were having Low T3 and normal TSH, hypothyroidism (Low T3, Low T4, high TSH) in 42.66% (n=32)patients , subclinical hypothyroidism in 13.33%(n=10) patients, High T4 in 2.66% (n=2) patients and hyperthyroidism in 2.66%(n=2) patients and Khatiwada S et al. [26] showed that the prevalence of subclinical hypothyroidism was 27.2%. Hypothyroidism increases cardiovascular risk in patients with CKD (List 3).

In our study thyroid disorders in patients with Chronic Kidney Disease were more common in patients with stage 3,4 and 5 of CKD with stage 5 of CKD being the predominant one. One patient in stage 2 was having low T3 syndrome. A total of 10% of patients with stage 3 CKD were having thyroid disorders out of which 1 patient was diagnosed to have subclinical hypothyroidism, 2 patients with hypothyroidism and 2 patients with low T3. In patients with Stage 4 of CKD, 2 patients were having overt hypothyroidism; 2 patients were having subclinical hypothyroidism and 5 patients were having low T3 and a total of 18% (n=9) are having thyroid disorders. In patients with stage 5 of CKD, 4 patients are having hypothyroidism,2 patients were having subclinical hypothyroidism and 12 patients were having low T3 levels and a total of 18 patients (36%) of patients are having thyroid disorders. Thus a total of 66%(n=33) of patients in our study are having thyroid disorders (Table 3). Thus the chances of developing thyroid dysfunction increases with the severity of CKD.In a study done by Upendra Nath Gupta et al. [23] there were 33 CKD patients with subclinical hypothyroidism out of which 3 were Stage 2 CKD, 6 Stage 3 CKD patients, 9 Stage 4 CKD patients and 15 Stage 5 CKD patients and there were 20 CKD patients with overt hypothyroidism of which 3 patients had Stage 2 CKD, 3 Stage 3 CKD patients, 8 patients had Stage 4 CKD and 8 patients had Stage 5 CKD. In a study by Md Mosharruf Hossain et al. [17] among 11(11%) of total hypothyroid patients, 3(27.3%) were in stage 3, another 3 (27.3%) were in stage 4 and the rest 5(45.4%) were of stage 5. Among 5(5%) of subclinical hypothyroidism 1(20%) of stage 3, another 1(20%) were of stage 4 and rest 3 (60%) were stage 5 but no patient of subclinical hypothyroidism was found in stage 1 and 2. Among 54 (54%) of Low T3 syndrome 3(5.5%) were of stage 2, 4(7.4%) were of stage 3, 11 (20.4%) were of stage 4 and rest 27 (66.7%) were of stage 5 .A relatively similar results were obtained in a study by Dr.J.Punekar et al. [6]. A

List 3. Cardiovascular risk in patients of ckd with hypothyroidism [27]

Sequelae of hypothyroidism related to cardiovascular system	Pathogenesis
1. Decreased cardiac output 2. Decreased systolic and diastolic function	1. Because of decreased erythropoietin and erythropoiesis there will be decreased blood volume 2. Cardiac ion channels will be altered 3. Decreased peripheral oxygen consumption and requirements 4. Alterations in the genes responsible for transcription of myocyte contractility and relaxation.
Endothelial function 1. Arterial stiffness 2. Diastolic hypertension 3. Increased systemic vascular resistance 4. Impaired vasoreactivity	1. Decreased synthesis and activity of vasodilator 2. Decreased metabolic activity of tissues and thermogenesis
Metabolic status Increase in total cholesterol, LDL and triglycerides	1. Decreased catabolism of cholesterol into bile by cholesterol 7-alpha-hydroxylase enzyme 2. Decreased hepatic LDL receptor density and activity
Vascular disease 1. Atherosclerosis 2. Vascular calcification	1. Dyslipidemia 2. Hypertension 3. Hyperhomocysteinemia 4. Decreased vascular calcification inhibitors
Cardiac conduction Ventricular arrhythmia	Changes in cardiac ion channel expression.

total of 46% (n=23) of patients in our study are having thyroid disorders. In a study by Upendra Nath Gupta et al. [23] 53% of patients with CKD had thyroid dysfunction. This shows the higher prevalence of thyroid dysfunction in patients with CKD. Although several hypotheses for factors contributing to the thyroid dysfunction in patients with CKD like altered iodine metabolism, autoimmune thyroiditis and decreased peripheral sensitivity to hormones have been proposed, the exact mechanism linking advanced CKD and primary thyroid dysfunction remains unclear [25].

To summarise, our study showed higher prevalence of thyroid dysfunction in patients with advanced CKD which is of great clinical significance suggesting the importance of regular screening and treatment of thyroid dysfunction in patients with CKD which may further help to prevent CVD risk (List 3).

5. CONCLUSION

This study was conducted among the patients with all stages of CKD to show that thyroid dysfunction is an additional risk factor in CKD patients who fulfilled all the inclusion criteria. Our study finds thyroid dysfunction being low T3 syndrome followed by hypothyroidism followed by subclinical hypothyroidism to be very common in CKD patients. There is a positive correlation between the severity of CKD and thyroid dysfunction. Hence a routine thyroid function status should be evaluated in each and every patient of CKD to reduce the morbidity and mortality rate of CKD patients as well as reduce the social burden and health expenditure. Further studies for improving the clinical and biochemical criteria to diagnose thyroid dysfunction in CKD patients are needed.

CONSENT

It is not applicable.

ETHICAL APPROVAL

As per international standard or university standard ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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