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Thyroid Dysfunction in Chronic Kidney Disease: A Study from North Kerala

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Abstract

Introduction: Chronic kidney disease (CKD) is a leading cause of morbidity and mortality Worldwide. The understanding of metabolic and hormonal abnormalities in milder forms of renal dysfunction is expanding, but the knowledge of thyroid dysfunction in people with CKD is still limited. The growth, differentiation, and regulation of physiological mechanisms in all tissues, including the kidney, depend on thyroid hormones. They are essential for maintaining the balance of electrolytes and water. Prevalence of hypothyroidism in end stage renal disease (ESRD) has been estimated to be in the range of 0 to 9%. Patients with ESRD also have a higher prevalence of goitre. Although there are several indicators that can predict both overall mortality and the severity of renal impairment, thyroid dysfunction is one of the major ones. In order to improve the outcome, it is wise for the internist and treating physician to be aware of thyroid dysfunction. The importance of knowing the prevalence of thyroid dysfunction in CKD patients also lies in the fact that it adds to the already high cardiovascular mortality risk in this patient group.

Objectives

1. To find the proportion of thyroid dysfunction in patients with chronic kidney disease.
2. To study the correlation between thyroid dysfunction and severity of renal diseases.

Methodology

A single center cross sectional study conducted in Departments of General Medicine and Nephrology in a tertiary care hospital in Calicut, Kerala. In the study period of 12 months, among patients admitted in Medical Ward after applying inclusion and exclusion criteria, 100 patients were included in the study. Patients who fulfilled the criteria for CKD and who are on conservative management and haemodialysis were taken up for the study. Thyroid profile was done in all patients who fulfilled the criteria. The prevalence of thyroid dysfunction in chronic kidney disease was described and analyzed in terms of percentages and averages. One way ANOVA test was used to analyze various parameters like T3, T4, Blood urea and Serum creatinine in relation to various grades of renal failure.

Results

Low T3 levels were seen in 65% and subclinical hypothyroidism was seen in 17% of the study subjects. Low T4 was seen in only 6% of the study subjects. There was no significant association observed between CKD stages and T3, T4, TSH values categorized as low, high and normal.

Conclusion

Low T3 syndrome was the commonest abnormality detected. This may be viewed as protective mechanism to conserve protein in chronic kidney disease patients. Subclinical hypothyroidism was the

second most common abnormality detected and the number of patients with subclinical hypothyroidism progressively increased with the severity of chronic kidney disease. As subclinical hypothyroidism is associated with increased cardiovascular mortality in CKD patients, adult patients with CKD should be routinely screened for subclinical hypothyroidism and further studies are required concentrating on improving clinical and biochemical criteria to diagnose thyroid dysfunction in CKD.
Key words: thyroid dysfunction, chronic kidney disease, subclinical hypothyroidism, mortality

Introduction

With a growing incidence and prevalence, poor prognoses, and exorbitant out of pocket expenditure, chronic kidney disease is a global public health concern. Chronic kidney disease (CKD) is a leading cause of morbidity and mortality worldwide, according to the Global Burden of Disease collaboration (1). The prevalence and death rates of CKD across all age groups increased by 29.3 and 41.5%, respectively, between 1990 and 2017. Between 2001–2003 and 2010–2013, renal failure accounted for 38% more deaths in India than any other cause (2). CKD is a major risk factor for cardiovascular disease (CVD), which is the primary cause of disability-adjusted life years and premature deaths. In developing nations like India, opportunities for secondary and tertiary prevention of CKD are frequently overlooked. Only when kidney function is assessed for other medical conditions or, less frequently, for routine screening, does CKD become apparent in its initial stages. The understanding of metabolic and hormonal abnormalities in milder forms of renal dysfunction is expanding, but the knowledge of thyroid dysfunction in people with CKD is still limited. The growth, differentiation, and regulation of physiological mechanisms in all tissues, including the kidney, depend on thyroid hormones.

Chronic renal disease patients may exhibit signs and symptoms of thyroid dysfunction. Kidney is a target organ for thyroid hormone and for the metabolism and elimination of hormones. Thyroid hormone function abnormalities are linked to declining renal function. Hypothyroidism, hyperthyroidism, and non-thyroidal illnesses can result from these consequences of impaired renal function. Modulations in the metabolism of water, electrolytes, and cardiovascular function occur with either hypothyroidism or hyperthyroidism, resulting in cardiovascular dysfunction in the long run, which will negatively impact the prognosis of CKD. Prevalence of hypothyroidism in end stage renal disease (ESRD) has been estimated to be in the range of 0 to 9%. Patients with ESRD also have a higher prevalence of goiter. Although there are several indicators that can predict both overall mortality and the severity of renal impairment, thyroid dysfunction is one of the major ones. In order to improve the outcome, it is wise for the internist and treating physician to be aware of thyroid dysfunction. The importance of knowing the prevalence of thyroid dysfunction in CKD patients also lies in the fact that it adds to the already high cardiovascular mortality risk in this patients group.

Objectives:

1. To find the proportion of thyroid dysfunction in patients with chronic kidney disease.
2. To study the association between thyroid dysfunction and severity of renal diseases.

Material and Methods:

Study Design: Single center cross sectional study.

Study Setting: The study was conducted in the Departments of General medicine and Nephrology at a tertiary care facility in, Calicut, Kerala, India.

Study Period: The study was conducted over a period of 12 months from September 2021 to August, 2022.

Study Population: Patients who fulfilled the criteria for CKD and who are on conservative management and hemodialysis were taken for the study.

Inclusion Criteria: Adult patients with varying grades of CKD defined using KDOQI criteria

Exclusion Criteria: Patients undergoing peritoneal dialysis, Age < 18yrs, Patients with diagnosed thyroid disorder before occurrence of renal failure, Patients on thyroid hormone replacement or on antithyroid drugs.

Sample Size

In the study period of 12 months, among patients admitted in Medical Ward after applying inclusion and exclusion criteria, 100 patients were included in the study.

Sampling Technique: Consecutive sampling till the sample size was met.

Study Procedure

The following investigations were performed: Urine routine and microscopic examination, CBC, Peripheral smear for anemia, Blood urea, serum creatinine, Serum electrolytes including calcium and phosphorous, Serum lipid profile, RBS, serum protein, Ultrasound abdomen, KUB for CKD, Thyroid function test - T3, T4, TSH. Details of clinical history and clinical examination were undertaken with reference to thyroid and renal diseases.

Study Tool

A structured Performa was used to collect patient information and note the results of laboratory investigations and clinical findings of the patients.

Statistical Analysis

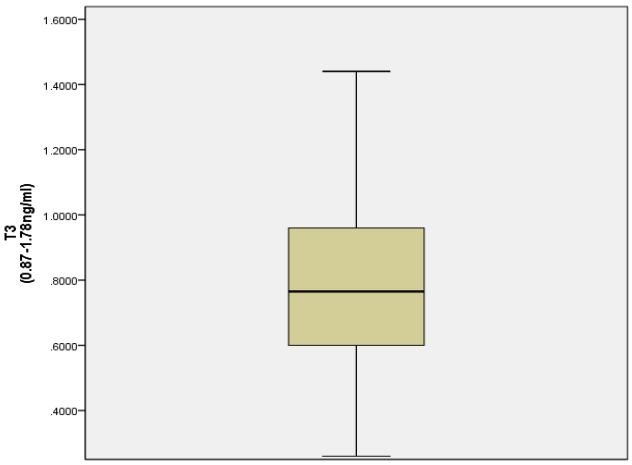
The prevalence of thyroid dysfunction in chronic kidney disease was described in terms of percentages and averages. One way ANOVA test was used to analyse various parameters like T3, T4, Blood urea and Serum creatinine in relation to various grades of renal failure. The value of P <0.05 was considered to be significant.

Ethical Considerations

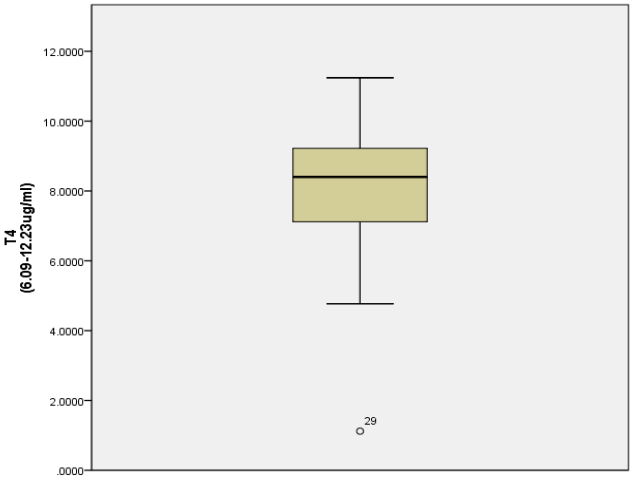
The study was formulated only after obtaining approval from the Institutional Research and Ethical committee. Informed consent was obtained from all patients satisfying the inclusion criteria, in the local language. Data safety norms were followed to preserve confidentiality and privacy of the patient. There has been no conflict of interest as well.

Results

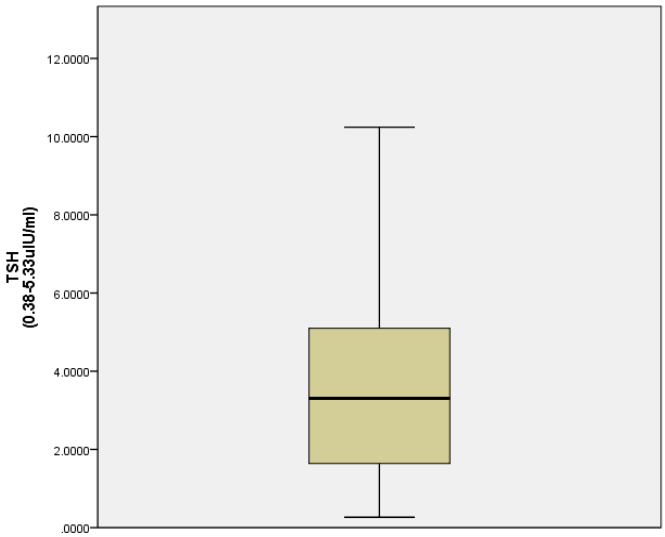
The mean age of study participants was found to be 64.97±10.76 years. More number of study participants belonged to 61-70 years of age group. The least number of patients was in the 31-40 years age group. Of the total 100 patients, 59 (59%) were females. The mean T3, T4 and TSH values of study participants were 0.78 ng/ml, 8.11 ug/ml and 3.38 uIU/ml respectively. The mean eGFR value of study population was found to be 18.65 ± 10.6 ml/ min /1.73m2.



Box plot showing T3 values among the study population



Box plot showing T4 values among the study population



Box plot showing TSH values among the study population

Comparison of T3, T4, Tsh Values With Stages of Ckd

The mean T3 values of the study population were below the normal reference range (0.87-1.78ng/ml) in all the stages of CKD. But, the mean T4 and TSH values of the study participants were found to be falling within the normal reference range (6.09-12.23ug/ml and 0.38-5.33uIU/ml respectively) in all the stages of CKD. On doing ANOVA test, there was no significant difference observed in the mean T3 values of different stages of CKD, p value = 0.736. Similarly, different CKD stages didn't show significant difference in the mean T4 and TSH values also. (p values 0.743 and 0.760 respectively).

		T3		Total	P VALUE
		Low	Normal		
CKD STAGE	Stage 3	8	9	17	0.161
		47.10%	52.90%	100.00%	
	Stage 4	32	10	42	
		76.20%	23.80%	100.00%	
	Stage 5 not on HD	14	8	22	
		63.60%	36.40%	100.00%	
	Stage 5 on HD	11	8	19	
		57.90%	42.10%	100.00%	
Total		65	35	100	
		65.00%	35.00%	100.00%	
		T4		Total	
		Low	Normal		
CKD STAGE	Stage 3	1	16	17	0.305
		5.90%	94.10%	100.00%	
	Stage 4	4	38	42	
		9.50%	90.50%	100.00%	
	Stage 5 not on HD	1	21	22	
		4.50%	95.50%	100.00%	
	Stage 5 on HD	0	19	19	
		0.00%	100.00%	100.00%	
Total		6	94	100	
		6.00%	94.00%	100.00%	
		T4		Total	
		Low	Normal		
CKD STAGE	Stage 3	1	16	17	0.305
		5.90%	94.10%	100.00%	
	Stage 4	4	38	42	
		9.50%	90.50%	100.00%	
	Stage 5 not on HD	1	21	22	
		4.50%	95.50%	100.00%	
	Stage 5 on HD	0	19	19	
		0.00%	100.00%	100.00%	
Total		6	94	100	
		6.00%	94.00%	100.00%	

Discussion:

There was no significant difference observed in the mean T3 values of different stages of CKD, Similarly, different CKD stages didn't show significant difference in the mean T4 and TSH values also. It was observed that 76.2% of stage 4 CKD patients were having a low T3 when compared to 63.6 % in stage 5 CKD patients not on haemodialysis and 57.9% in stage 5 CKD patients on haemodialysis. But, when the different stages of CKD were checked for any association with low values of T3 levels, it has shown no significance. The findings of present study were found to be in agreement with what was found by Sang Heon Song , Ihm Soo Kwak and Dong Won Lee. They had observed that the low T3 syndrome was highly prevalent in CKD and was a remarkable finding in early CKD. (4)

Of the total 42 stage 4 CKD patients, 9.5% were found to have low T4 value and the corresponding proportion in stage 3 was 5.9%. All the stage 5 CKD patients on haemodialysis were having a normal T4 value. No significant association was observed between CKD stages and T4 value categorized as low and normal. Only 1 patient of stage 5 CKD without hemodialysis was having a low TSH level. Of the total 22 Stage 5 patients not on HD, 27.2% were having a high TSH. On doing a chi square test, no significant association was observed between CKD stages and TSH value categorized as low, high and normal. If we consider the high TSH as suggestive of hypothyroidism, this proportion is comparatively higher than that was reported by Michel Chonchol, Giuseppe Lippi and Gianluca Salvagno in the year 2008. They had observed that subclinical primary hypothyroidism is a relatively common condition in approximately 18% CKD patients not requiring chronic dialysis. Apart from this finding, it was also observed by them that the hypothyroidism was independently associated with progressively lower estimated glomerular filtration rate in a large cohort. (5)

The proportions of stage 4 CKD patients and stage 5 CKD patients without hemodialysis who were shown to have a low T3 value are more when compared to the proportions observed by PonAjil Singh, Zachariah Bobby and N Selvaraj in their case control study. But, at the same time the corresponding proportion was with respect to low T4 values was extremely small in present study in comparison to PonAjil Singh et al's. They had found out a low serum T4 concentration 75% of the patients with chronic renal failure. (6)

G Avasthi, S Malhotra, APS Narang had concluded in their study in 2001 that thyroid dysfunction occurs both clinically and biochemically in patients with chronic renal insufficiency.(7) Their finding of low mean serum T3 is in agreement with present study results. But, in comparison with respect to the mean T4 and TSH, the results are not found to be in agreement as present study had observed the mean serum T4 and TSH values to be in the reference range.

According to Joseph L J and Hardy M J, the low T3 and T4 levels and high TSH levels observed in the CKD patients are possibly suggestive of maintaining the pituitary axis.

Mehta HJ, Joseph LJ and Desai KB had compared the levels of serum T3, T4, FT3, FT4 and TSH of CKD patients on conservative management with those in normal subjects. There was reduction in the levels of serum T3, T4 and TSH. But, TSH and FT4 levels did not show significant alterations. (8) This is in contrast to the present study findings except for the T3 value. As per their study, those patients on regular dialysis showed similar values as those on conservative management except for a decrease in TSH levels as compared to the normal subjects.

Kaptein and Quion Verde also had findings suggestive of a comparatively higher prevalence of primary hypothyroidism in patients with chronic renal failure and dialysis. Kaptein's study also estimated the presence of anti - thyroid antibody titre in 6.7% of patients with chronic renal failure. (9)

In agreement to what was found in the present study, German Ramirez, William O Neill and William Jubiz had observed in the year 1976 that in patients with chronic renal failure not on dialysis the mean T3 levels were low. (10) In addition, they had also observed that both T4 and T3 concentrations were decreasing as the renal function worsened. As per Basu G et al, the most common laboratory finding in CKD patients is a low T3 value and the most common thyroid disorder observed among them is subclinical hypothyroidism. (11) This finding of low T3 value in present study goes well in agreement with the current understanding of the mechanism of thyroid function in the chronic kidney patients. There are several possible mechanisms proposed for a low T3 levels in such patients. It may be due to the enzyme iodothyronine deiodinase which may be affected by chronic metabolic acidosis or chronic protein malnutrition that can happen in CKD patients. These may affect the protein binding to T3. Decreased clearance of the inflammatory cytokines such as TNF-alpha and IL-1 which can result in decreased peripheral conversion of T4 to T3 is the other possible mechanism. This is because the expression of the enzyme 1 5′-deiodinase that helped convert T4 to T3 is getting inhibited by the cytokines like TNF – alpha and IL-1.

The low T3 values in CKD patients are shown to have predictive capacity in several aspects such as the mortality in patients on hemodialysis and the risk of graft loss in patients undergoing renal transplantation. The predictive capacity of the thyroid function test and especially that of T3 values were not explored in present study. But, this opens up scope for future research in this area. P Iglesias and J J Diez had showed that in their study in 2009 that thyroid hormone especially T3 can be considered as a marker for survival in patients with kidney disease. They had observed that CKD is associated with higher prevalence of primary hypothyroidism, but not with hyperthyroidism. (12)

Limitation:

The chance of differences in the thyroid status across geographies and ethnicities will be a limiting factor while comparing findings of different studies done at different settings.

Conclusion

Low T3 syndrome was the commonest thyroid abnormality detected. This may be viewed as protective mechanism to conserve protein in chronic kidney disease patients. Subclinical hypothyroidism was the second most common abnormality detected. It occurred in 17% of patients indicating significant alteration of thyroid hormone physiology in chronic kidney disease patients. Frank hypothyroidism was the least commonly detected thyroid abnormality.

Number of patients with subclinical hypothyroidism progressively increased with severity of chronic kidney disease. Due to the positive correlation between SCH and CKD, multidisciplinary management, including Endocrinologists and Nephrologists is advised to keep a regular check on these patients. As subclinical hypothyroidism has been associated with increased cardiovascular risk in CKD patients, adult patients with CKD should be routinely screened for SCH and further studies are required concentrating on improving clinical and biochemical criteria to diagnose thyroid dysfunction in CKD.

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