Original Research Article

Study of Thyroid Dysfunction in Chronic Kidney Disease

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ABSTRACT

Background
In order to act at an early stage based on hormone abnormalities and lower the risk of cardiovascular disease and the progressive deterioration of kidney function, we sought to ascertain the incidence of thyroid dysfunction in patients with CKD (Chronic Kidney Disease) through this study.
Methods
This was a hospital-based prospective observational correlation study conducted among 60 patients with CKD in various stages who visited inpatients and outpatients at the Department of HAL Hospital, Bangalore, from 1st April 2014 to 1st October 2015, after obtaining clearance from the institutional ethics committee and written informed consent from the study participants.
Results
In our study, 53% of the patients who were on MHD (Maintenance Hemodialysis) were Euthyroid, which was statistically significant as compared to patients who were not on hemodialysis. 70% of patients who were not on maintenance hemodialysis had low thyroid values, which was statistically significant. Hypothyroidism and subclinical hypothyroidism were seen in patients with chronic kidney disease; however, none of the patients were hyperthyroid. With the exception of hypothyroidism and subclinical hypothyroidism, the majority of patients on maintenance hemodialysis were euthyroid, and the mean TSH level in our study was within normal ranges. A considerable number of patients have low FT3. A tiny proportion of patients experienced goiter. The stage of chronic kidney disease and the frequency of thyroid dysfunction did not significantly correlate.
Conclusion
The mean TSH level in our study, excluding hypothyroidism and subclinical hypothyroidism, is within normal ranges, indicating abnormalities in the hypophyseal mechanism of TSH release in uremic patients, as seen by the attenuated TSH response to TRH. A considerable number of patients

have low FT3. A tiny proportion of patients experienced goiter. The stage of chronic kidney disease and the prevalence of thyroid dysfunction did not significantly correlate.
Keywords: Thyroid Dysfunction, Chronic Kidney Disease.

INTRODUCTION

"The world is facing a global pandemic of chronic kidney disease. As the morbidity and mortality from infectious diseases decline, life expectancy increases and chronic degenerative diseases have become more prevalent. CKD is unique amongst the chronic non-infectious illnesses."[1] Diabetic nephropathy is the most common cause of CKD, usually resulting from type 2 DM.[2] In India, there are roughly 7.85 million people with CKD.[3] Numerous endocrine abnormalities are present in patients with end-stage renal disease. However, laboratory abnormalities-many of which are unrelated to the disease's apparent clinical signs and symptoms-are frequently the only indication of endocrine dysfunction.[4] In the absence of an underlying intrinsic thyroid condition, CKD is a well-known cause of non-thyroidal sickness that results in thyroid dysfunction, or changes in thyroid hormones.[5,6] Thyroid function is impacted by chronic renal illness in a number of ways, such as decreased levels of thyroid hormone in the blood, changes in peripheral hormone metabolism, problems with binding to carrier proteins, potential decreases in thyroid content in tissue, and elevated iodine reserves in thyroid glands. TT3, TT4, and FT3 are more frequently reduced in CKD patients. However, FT4 and TSH readings in these patients are normal, indicating euthyroid health. We hypothesize that uremia's low thyroid condition protects against protein waste, and that ineffective attempts to replenish thyroid hormone levels could make protein deficiency worse.[7] Studies have indicated that patients with CKD had a higher incidence of subclinical hypothyroidism, while patients with terminal renal failure have a higher prevalence of hypothyroidism. Compared to 0.6 to 1.1% of the general population, it has been predicted that up to 9.5% of ESRD patients may experience primary hypothyroidism.[8] Increased severity of hypothyroidism can result in decreased heart function and increasing deterioration of renal function. Therefore, the frequency of subclinical hypothyroidism in CKD patients may be associated with an increased risk of cardiovascular illness as well as kidney disease progression.[8]

AIMS AND OBJECTIVES

- Study of biochemical abnormalities of thyroid function tests in chronic kidney disease.
- To correlate the severity of chronic kidney disease and alterations of thyroid indices.

MATERIALS & METHODS

This was a hospital-based prospective observational correlation study conducted among 60 patients with CKD in various stages who visited inpatient/outpatient at the Department of HAL Hospital, Bangalore, from 1st April 2014 to 1st October 2015, after obtaining clearance from the institutional ethics committee and written informed consent from the study participants.

Inclusion Criteria

- Kidney damage more than or equal to 3 months as defined by structural or functional abnormalities of kidney with or without or decreased GFR manifest with either.
  i. Pathological abnormalities.
  ii. Markers of kidney damage including abnormalities in blood and urine.

- Ultrasound evidence of chronic kidney damage.
  i. Bilaterally contracted kidney.
  ii. Poor corticomedullary differentiation.

Exclusion Criteria

- Patients with pre-existing thyroid disorder.
- Patients on drugs altering thyroid profile like amiodarone, steroids, estrogen pills, phenytoin, lithium etc.

Sample Size

Based on findings from previous literature/reports/records, for an outcome variable to measure the thyroid dysfunction in CKD patients in different stages of disease, with 90% statistical power and 5% levels of significance, the sample size of 60 is adequate for an observational correlation study.

Study Procedure

A total of 60 patients with CKD in various stages were taken for the study, visiting the inpatient/outpatient department of HAL hospital. Patients with chronic kidney disease in different stages were chosen from both outpatients and inpatients depending upon inclusion and exclusion criteria based on National Kidney Foundation recommendations [KDOQI (Kidney Dialysis Outcomes Quality Initiative)], which describe the phases of CKD based on estimated GFR. The measurements of TT3, TT4, FT3, FT4, and TSH levels in serum were used to evaluate thyroid function. A competitive chemiluminescent immunoassay was used to assess serum levels of TT3, TT4, FT3, and FT4. The highly sensitive sandwich CLIA (Chemiluminescent Immunoassay) was used to quantify TSH. We estimated blood urea using the DAM (Diacetyl Monoxime) technique. Additionally, the modified kinetic Jaffe method was used to estimate serum creatinine.

The focus of a thorough clinical examination and history was mostly on thyroid and renal conditions. The ensuing inquiries were carried out.

1. Urine for specific gravity and broad cast.
2. Peripheral smear for anemia and burr cells.
3. Renal parameters like blood urea, serum creatinine, and creatinine clearance (using the Cockcroft-Gault formula).
4. Serum calcium and phosphorus
5. Serum cholesterol for hypothyroidism.
6. 24 hours' urine protein and serum protein to rule out nephrotic syndrome and hypoproteinemia, respectively.
7. USG abdomen and pelvis for evidence of chronic kidney disease.

Statistical Methods

Student t-test, chi-square test, Fisher exact test, effect size and multivariate logistic/regression analysis were used.

RESULTS

Co-Morbid Conditions	Impression				P Value
	Euthyroid (N = 24)	Low Thyroid Values (N = 25)	Subclinical Hypo (N = 7)	Hypothyroid (N = 4)	
DM	16 (66.7%)	18 (72%)	5 (71.4%)	3 (75%)	**0.966**
HTN	15 (62.5%)	13 (52%)	3 (42.9%)	2 (50%)	**0.794**
MHD	16 (66.7%)	11 (44%)	5 (71.4%)	2 (50%)	**0.358**

Goiters	0 (0%)	0 (0%)	0 (0%)	3 (75%)	**<0.001****

Table 1: Co-Morbid Conditions of Patients Studied in Relation to Impression Category

In our study, 67% of patients who were on MHD were euthyroid; however, it was not statistically significant. 5% of patients who had goiter had hypothyroidism, which was statistically significant.

Variables	**CKD**			**Total**	**P-Value**
	3	**4**	**5**		
TT3	100.75±19.48	98.67±28.25	98.71±19.6	99.30±21.99	0.983
TT4	5.21±1.17	4.64±1.03	5.35±1.40	5.09±1.23	0.304
TSH	4.90±3.35	3.95±1.95	4.66±4.14	4.51±3.27	0.835
FT3	2.43±0.70	2.72±0.80	2.74±0.78	2.63±0.76	0.550
FT4	1.69±0.64	1.94±0.68	1.47±0.57	1.69±0.64	0.156
Comparison of Thyroid Variables in Relation to CKD Stage					
ANOVA Test					
Impression	**CKD**			**Total**	
	3	**4**	**5**		
Euthyroid	6 (28.6%)	6 (33.3%)	12 (57.1%)	24 (40%)	
Low Thyroid values	11 (52.4%)	9 (50%)	5 (23.8%)	25 (41.7%)	
Subclinical hypo	2 (9.5%)	3 (16.7%)	2 (9.5%)	7 (11.7%)	
Hypothyroid	2 (9.5%)	0 (0%)	2 (9.5%)	4 (6.7%)	
Total	21 (100%)	18 (100%)	21 (100%)	60 (100%)	
Correlation of Impression in Relation to CKD Stage of Patients Studied					
P=0.277, Not significant, Fisher Exact test					
Table 2					

In our study, no statistically significant changes with thyroid functions were seen in relation to the stage of CKD.

In our study, 57% of patients who were in stage 5 of CKD were euthyroid; however, this was not statistically significant, and 52% of patients in stage 3 of CKD had some form of low thyroid values, which was not statistically significant.

Thyroid Abnormality	**MHD**		**Total**	**P-Value**
	No	**Yes**		
Euthyroid	6 (23.1%)	18 (52.9%)	24 (40.0%)	0.019*
Low Thyroid values	16 (69.6%)	9 (26.5%)	25 (41.7%)	0.006**
Subclinical hypo	2 (7.7%)	5 (14.7%)	7 (11.7%)	0.402
Hypothyroid	2 (7.7%)	2 (5.9%)	4 (6.7%)	0.781
Total	26 (100.0%)	34 (100.0%)	60 (100.0%)	-
Correlation of Thyroid Abnormality in Relation to MHD				
P=0.030*, significant, Fisher exact test				
Table 3				

In our study, 53% of the patients who were on MHD were euthyroid which was statistically significant (p value = 0.019) as compared to patients who were not on hemodialysis. 70% patients who were not on maintenance hemodialysis had low thyroid values, which was statistically significant (p-value = 0.006).

Thyroid Profiles	**MHD**	**Total**	**P-Value**

		No (n = 26)	Yes (n = 34)	(n = 60)	
TT3 (ng/dl)	<75	3 (11.5%)	5 (14.7%)	8 (13.3%)	1.000
	75-200	23 (88.5%)	29 (85.3%)	52 (86.7%)	
	>200	0 (0%)	0 (0%)	0 (0%)	
TT4 (ug/dl)	<4.5	6 (23.1%)	10 (29.4%)	16 (26.7%)	0.582
	4.5-11.5	20 (76.9%)	24 (70.6%)	44 (73.3%)	
	>11.5	0 (0%)	0 (0%)	0 (0%)	
TSH (IU/mIC)	<0.3	0 (0%)	0 (0%)	0 (0%)	0.967
	0.3-5	20 (76.9%)	26 (76.5%)	46 (76.7%)	
	>5	6 (23.1%)	8 (23.5%)	14 (23.3%)	

Table 4: Thyroid Profiles in Relation to MHD

In our study, no single thyroid variable was found statistically significant in comparison to the patients who were on MHD.

Free Thyroid Profiles		MHD		Total (n = 60)	P-Value
		No (n = 26)	Yes (n = 34)		
FT3C (pg/ml)	<2.3	9 (34.6%)	8 (23.5%)	17 (28.3%)	0.345
	2.3-4.2	17 (65.4%)	26 (76.5%)	43 (71.7%)	
	>4.2	0 (0%)	0 (0%)	0 (0%)	
FT4 (ng/dl)	<0.8	0 (0%)	0 (0%)	0 (0%)	0.574
	0.8-2.8	24 (92.3%)	33 (97.1%)	57 (95%)	
	>2.8	2 (7.7%)	1 (2.9%)	3 (5%)	

Table 5: Free Form of Thyroid Profile in Relation to MHD

In our study, no single thyroid variable was found statistically significant in comparison to the patients who were on MHD.

DISCUSSION

Normally, the kidney is involved in the metabolism, breakdown, and excretion of various thyroid hormones. Therefore, it is not surprising that abnormal thyroid physiology results from kidney function impairment. Changes in hormone production, distribution, and excretion may be implicated, as may all levels of the hypothalamic-pituitary-thyroid axis.[9,10,11]

Although CKD affects many different hormonal systems, it is still unknown how much of these alterations cause symptoms of uremic syndrome.

The diagnosis of thyroid disease in patients with CKD carries significant prognostic implications, as these patients frequently exhibit signs and symptoms suggestive of thyroid dysfunction. The clinical symptoms sign index and biochemical markers are the main topics of the data presented.[12]

The results of several researchers' studies on thyroid hormone levels in CKD have been inconsistent.

In our study, subclinical hypothyroidism was present in 12% of CKD patients. In 7% of CKD patients, overt hypothyroidism was present. Low TT3, low TT4, and low FT3 thyroid abnormalities were present in 42% of the individuals. In contrast to hospitalized individuals with normal renal function (0.6%), Quion-Verde et al. have recently observed a greater prevalence of up to 5% of frank hypothyroidism in patients with chronic kidney disease.[13]

The majority of MHD patients were found to be euthyroid in a research by P. Iglesias and J. J. Díez, which included 53% of our patients. TSH's cellular transit is impacted by MHD, which may serve as a compensatory strategy to preserve euthyroid state.[14]

Numerous CKD research revealed low TT3,[15,16] normal TT3 low FT3,[17] and normal FT3 in HD patients. Low TT4 (low T4 syndrome), normal TT4, and low normal or lower FT4 levels have all been observed in several investigations. In several studies, basal concentrations of circulating TSH have been detected at various levels. Previous Indian investigations revealed TSH levels to be normal.[18,19] Thus, it appears that uremia is associated with a wide range of abnormalities at all levels of the hypothalamus pituitary-thyroidal-peripheral axis.

TT4 concentrations were found to be low or low normal in most studies. FT4 levels, however, were within normal bounds. This is explained by both the presence of inhibitors that prevent thyroid hormone from binding to thyroid binding proteins and the reduction in the content of thyroxine binding globulin. With CKD, levels of TT3 and FT3 are further reduced. This is believed to be caused by a disturbance in the primary process of deiodination of T4, which is how peripheral T3 is created.

Additional research by Spector and Ramirez et al. showed that the pituitary-thyroid axis was maintained by low T3 and T4 levels and high TSH levels.

Six individuals in all in our study had symptoms suggestive of hypothyroidism, of which four had hypothyroidism. High TSH levels in hypothyroidism indicate that the pituitary-thyroid axis is still functional. The findings of Avasthi et al. are in line with our investigation.[16]

Research by Zoccali C et al.,[20] and Ramirez et al.,[21] demonstrates low T3, low T4, and a normal or slightly elevated TSH level. However, it's unknown how much of these modifications are to blame for the uremic syndrome's symptoms. Numerous investigations have indicated that the body's adaptation mechanism includes this disruption of the thyroid profile.

In Our Study, 3% Patients had Goiters

Patients with CKD had a higher prevalence of goiter (0–9%). Goitre6 may result from a hypertrophic effect on thyroid gland tissue brought on by a reduction in the elimination of inorganic iodides. A contributing component could potentially include CKD-induced reduced clearance of goitrogenic chemicals such as aryl acid. Studies have indicated that elevated serum iodine levels have the potential to extend the Wolff-Chaikoff effect.

Three patients (5%) out of the sixty subjects in our study had goiter. Two of the patients had stage 5 CKD. One patient had hypothyroidism. Thyroid dysfunction with the stage of chronic kidney disease:

Thyroid dysfunction is more common in CKD patients at higher stages of the disease. Compared to stage 3 (9.5%) and stage 5 (9.5%) CKD patients, 16% of stage 4 CKD patients in our study had hypothyroidism. The CKD stage raised TSH levels were normal, with the exception of individuals with overt hypothyroidism, and the TT3, TT4, and FT4 levels did not significantly progress. Statistical research revealed no significant link between the symptoms of hypothyroidism and advanced stages of renal illness, despite the prominence of these symptoms.

The primary cause of morbidity and death in individuals with CKD is still cardiovascular disease, even with the significant advancements in renal replacement therapy in recent times. Numerous investigations by Lindner et al. (1974),[22] Stenvinkel et al. (1999),[12] Cheung et al. (2000), and others make this clear.[23] Thyroid dysfunction is significantly more common in CKD patients. "Abnormal thyroid hormone levels may be linked to the development of kidney disease and may serve as a risk factor for cardiovascular disease."[24]

CONCLUSION

According to our study, 60% of patients with chronic renal illness have thyroid dysfunction overall. Among patients with CKD, 7% had hypothyroidism, 0% had hyperthyroidism, 12% had subclinical hypothyroidism, 42% had some abnormalities related to thyroid hormones, and 3% had goiter. Comparing patients on MHD to those not on MHD, we found that 53% of MHD patients had euthyroid, which was statistically significant. Additionally, we found that 70% of non-MHD patients had low thyroid levels, which was statistically significant. The stage of chronic renal disease and the prevalence of thyroid dysfunction did not significantly correlate. The mean TSH level in our study, excluding hypothyroidism and subclinical hypothyroidism, is within normal ranges, indicating abnormalities in the hypophyseal mechanism of TSH release in uremic patients, as seen by the attenuated TSH response to TRH.

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