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Evaluation of Thyroid Function in Chronic Kidney Disease Patients with Various Etiopathogenesis

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ABSTRACT

Background & Aim: Patients with chronic kidney disease (CKD) usually have an altered thyroid hormone status, but the significance and correlation is unknown. Objectives: To analyse the relationship between thyroid hormone levels with various stages of CKD and their etiopathogenesis. **Materials and methods:** This was a hospital-based case-controlled study evaluating 50 CKD patients admitted to a tertiary care institution in Eastern India. The staging of CKD was done as per KDOQI definition. The clinical profile and thyroid function tests were analysed in all the CKD cases (conservative and dialyzed patients), in different stages of CKD and under different etiological categories. Those were compared with healthy controls. **Results:** Diabetes mellitus (DM) was the commonest etiology of CKD. Other etiologies were hypertension, SLE, obstructive uropathy and chronic glomerulonephritis. In CKD patients (both groups) it was observed that mean values of the thyroid hormonal indices; total T3, Free T3,Free T4 were lower than controls and total T4 ,TSH values were higher than control group in all stages of CKD Only total T3 value was significantly lower in CKD patients compared to healthy controls (p value; 0.0011). TBG (thyroid binding globulin) was unaffected in both the groups. **Conclusions:** This study highlights the high prevalence of thyroid dysfunction in CKD cases mainly low T3 syndrome.

Keywords: Chronic kidney disease, Thyroid function test, TBG.

INTRODUCTION

Chronic kidney disease (CKD) is defined by functional or structural damage to the kidneys and/or a decrease in GFR to loss than 60 mL/min/1.73 m2 body surface area for > 3 months.[1]

Kidney as an important endocrine organ regulates different body functions by secretion of renin, erythropoietin, active metabolite of Vitamin D3 and prostaglandins. Renal functions and thyroid hormones are related mutually in several ways. Kidneys contribute significantly to effective metabolism, excretion of thyroid hormones from body and certain physiologic action of these hormones on body. Hence worsening of renal function is associated with deranged thyroid hormone levels. Similarly, thyroid hormones exert influence on water and electrolyte balance in our body.[2] Though CKD in some instances causes clearly recognizable endocrinopathies, more commonly the endocrine dysfunction consists of only laboratory abnormalities. Chronic kidney disease alters the thyroid status at biochemical levels, sometimes leading to overt clinical syndromes. The thyroid status in CKD has been studied extensively by many workers. Most of them have demonstrated biochemical evidence of hypothyroidism, few have detected hyperthyroidism; even goiter and exophthalmos have been observed by some.[3,4] Although uremia shares some of the clinical features of myxoedema, overt clinical disturbances of thyroid function is rarely seen.[5]

In previous studies, CKD cases undergoing haemodialysis showed that besides biochemical evidence of hypothyroidism, goiter was seen in a number of cases.[6] Some studies found clinical as well as biochemical evidence of hypothyroidism in their series of uremic patients.[7] Clinical euthyroidism was universally found among the CKD patients in many studies.[5] Various workers have attributed different cause of the trivial clinical abnormalities, frequent biochemical hypothyroidism and the occurrence of goiter in substantial number of uremic patients. Various pathogenetic mechanisms were proposed behind the thyroid dysfunction in CKD patients,[1] there is a blunted TSH response to TRH suggesting pituitary dysfunction, secondly there occurs intrathyroidal defects in hormonogenesis and/or hormonal secretion,[2] Impaired conversion of T4 to T3 in extra thyroidal tissues, resulting in selective and marked reduction in serum total T3 concentration.[8]

With these implications and controversies in opinion this work was undertaken to make an attempt to correlate various abnormalities of thyroid function in CKD patients with different etiopathogeneses and to find out correlation between the severity of renal

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failure and the alteration of the thyroid hormone levels.

MATERIALS AND METHODS

This was a hospital based cross-sectional study conducted in the Post Graduate Department of Medicine, SCB Medical College and hospital, Cuttack, Odisha. Consecutively admitted 50 cases (age > 15) of CKD were taken, diagnosed and staged by following the criteria given by- National kidney foundation: KDOQI guidelines.[1] They were divided into two groups- group-A- those on conservative management (n=35) & group-B- those on hemodialysis (n=15). Group A patients were further classified into various stages based on their glomerular filtration rate (GFR) which was calculated using Cockroft-Gault Equationand KDOQI definition.[1] CKD stage 5 cases were taken in Group B as per the recommendation. Twenty number of age and sex matched healthy persons were taken as control (Group-C). Those patients having past history of thyroid dysfunction i.e. either hypo- or hyperthyroidism, pregnancy, those on thyroid supplement therapy or on antithyroid drugs were excluded from the study.

Informed consent was taken from each patient. All patients were underwent detailed clinical examination followed by routine and biochemical tests including CBC, blood sugar, blood urea, serum creatinine, serum electrolytes, urine routine/microscopic, liver function tests and thyroid function tests. The thyroid hormone assay was done by Chemiluminescence Immunoassay using Maglumi 600 Chemiluminescence Immunoassay Analyser for Thyroid. The normal values of different thyroid hormones are: TSH: 0.34-4 IU/mL, total T4 (TT4): 5.4-11.7 µg/dL, total T3 (TT3): 77-135 ng/dL, free T4 (FT4): 0.7-1.53 ng/dL, free T3 (FT3): 260-480 pg/dL. Thyroid binding globulin (TBG) was done by radio immuno assay (normal value; 15-30µg/dL). Ultrasonography of thyroid gland, abdomen and pelvis was done using GE healthcare LOGIQ V3 ultrasound system. USG of abdomen was done for evaluation of kidney size and cortico-medullary differentiation.

Statistical analysis was done using SPSS version 20.0. Quantitative variables were described as mean +/−standard deviation (SD) unless otherwise indicated. Qualitative variables were described by percentage. For all statistical tests, p value < 0.05 was considered significant.

RESULTS

Out of 50 cases of CKD, 37 cases (74%) were males and 13 cases (26%) were females with M: F ratio of 2.9:1. Amongst them 50% cases were in stage 5, 28% cases in stage 4, 20% in stage 3 and 2% in stage 2 of CKD. All cases had pallor followed by hypertension was found in 84% cases, coarse skin in 54%, pedal edema in 40% and facial puffiness in 20% of cases. None of the patients had thyromegaly [Table1].

Table 1: showing baseline characteristics of CKD patients

Features		No of cases (n=50)	Percentage (%)
Sex	Male	37	74
	Female	13	26
	M:F	2.9	
Stages of CKD	1	0	0
	2	1	2
	3	10	20
	4	14	28
	5	25	50
Clinical features	Pallor	50	100
	Edema	20	40
	Puffy face	10	20
	Coarse skin	27	54
	HTN	42	84
	Thyromegaly	0	0

Diabetes mellitus was found to be the commonest cause of CKD (40%),hypertension, SLE and obstructive uropathy accounted for 10% each. No definite cause of CKD was found in 12 (24%) cases [Table2].

Table 2: Etiologies of CKD

Etiologies	No. of cases	Percentage
Diabetes Mellitus	20	40
Hypertension	5	10
SLE	5	10
Obstructive Uropathy	5	10
Chronic Glomerulonephritis	2	4
Polycystic Kidney Disease	1	2
Unknown Etiology	12	24
Total	50	100

[Table3] shows the comparison between the thyroid function indices between the CKD cases of group A (conservative) and group C (control). CKD cases of group A had TT3, FT4, and FT3 lower than the control group C. TT4 was higher in group A than group C. Among these only TT3 was significantly low in CKD patients of Group A than control (p=0.004). Though TSH of group A CKD patients was higher than group C (control), but it was not statistically significant. We did not find any difference in TBG values between these two groups.

[Table4] shows the comparison between the thyroid function indices between the CKD cases of group B (hemodialysis) and group C (control). The mean values of TT3, FT3 and FT4 were lower in group B than the healthy group C, whereas the mean values of total T4 was higher in group B than group C. Among these, only TT3 was significantly low (p=0.0071). Though TSH of group B patients was higher than group C but it was not statistically significant.The mean TBG values were not significantly different in both the groups.

[Table5] shows the comparison between the thyroid function indices between all the CKD cases i.e. both

group A (conservative) and group B (hemodialysis) vrs group C (control). The mean values of TT3, FT4, and FT3 were lower in CKD group than the control group, whereas the mean values of TT4 was higher in CKD group than group C. Among these, TT3 was significantly low (p=0.0011).Though mean TSH of all CKD patients was higher than group C but it was not statistically significant. The mean TBG values were not significantly different in both the groups.

Table 3: Comparison of thyroid hormone levels between conservatively managed CKD patients and healthy Controls

Groups	Total T4	Total T3	Free T4	Free T3	TSH	TBG
Group A (n=35) Conservative	7.772 ±2.547	1.193 ±0.423	1.146± 0.423	2.898 ±1.074	7.38± 11.66	19±1.029
Group C(n=20)Control	7.325± 1.42	1.54± 0.39	1.256 ±0.268	3.05± 0.39	2.487± 1.5	19± 0.917
P-value	0.474	0.004	0.299	0.5475	0.0684	>0.99

Table 4: Comparison of thyroid hormone levels between dialyzed CKD patients and healthy Controls

Groups	Total T4	Total T3	Free T4	Free T3	TSH	TBG
Group B Hemodialysis (n=15)	7.62 ± 1.475	1.196 ± 0.292	1.245 ± 0.23	3.101 ± 0.425	3.505 ± 1.133	19 ± 1.069
Group C Control (n=20)	7.325± 1.42	1.54± 0.391	1.256 ±0.268	3.05± 0.393	2.487± 1.50	19 ± 0.917
p Value	0.5537	0.0071	0.8993	0.716	0.354	0.889

Table 5: Comparison of thyroid hormone levels between all CKD patients and healthy Controls

Groups	Total T4	Total T3	Free T4	Free T3	TSH	TBG
All CKD Patients (A+B) (n=50)	7.726 ±2.65	1.194 ±0.386	1.176 ±0.376	2.959 ±0.928	6.218 ±9.986	19± 1.03
Control (n=20)	7.325± 1.42	1.54± 0.391	1.256 ±0.268	3.05± 0.393	2.487± 1.50	19 ± 0.917
p Value	0.4655	0.0011	0.3896	0.6742	0.0994	>0.99

Table 6: Thyroid hormone levels between all stages of conservatively managed CKD patients

Thyroid Function Tests	Stage-2 (n=1)	Stage-3 (n=10)	Stage-4 (n=14)	Stage-5 on conservative management (n=10)
Total T4 (mcg/dl)	9.4	9.32 ±1.486	7.0885 ±2.739	7.048 ±2.701
Total T3 (ng/ml)	2.34	1.361 ±0.221*	1.1085 ±0.362*	1.029 ±0.46*
Free T4 (ng/dl)	1.46	1.367 ±0.282	1.037 ± 0.415	1.065 ±0.515
Free T3 (pg/ml)	3.66	3.47 ±0.855	2.515 ± 0.962	2.807 ±1.287
TSH (micro U/ml)	1.25	3.889 ±5.795	11.34 ± 16.37	5.9 ± 6.94
TBG (mcg/dl)	20	19.4 ±1.074	19.07 ± 1.141	18.5 ± 0.707

Table 7: Comparison of thyroid hormone levels between diabetic and non-diabetic CKD patients

	Total T4	Total T3	Free T4	Free T3	TSH	TBG
Diabetic (n=20)	6.939 ±2.188	1.096 ±0.3510	1.127 ±0.3703	2.756 ±0.6209	6.765 ±9.892	18.95 ±1.05
Non Diabetic (n=30)	8.251 ±2.194	1.2593 ±0.3992	1.208 ±0.3828	3.0947 ±1.0749	5.836 ±10.05	19.03 ±1.033
p Value	0.0434	0.144	0.4614	0.2095	0.7487	0.791

The thyroid function tests were correlated with different stages of CKD. It was found that as renal function worsens in terms of stages of CKD from stage 2 to stage 5, the mean values of TT4, TT3, FT4, FT3, and TBG levels were in decreasing trend from stage 2 to stage 5.The mean TSH was found to be higher in CKD stage 4 and 5 [Table6].

Out of all CKD cases, 20 were diabetic. When the thyroid hormone levels of the diabetic CKD cases (n=20) were compared with those with non-diabetic CKD cases(n=30) it was found that the mean values of TT4,TT3, FT4, and FT3 were lower in diabetic group than non-diabetic group and the TSH level was higher in diabetic group. But these differences were not statistically significant except for TT4 [p=0.0434] [Table7]. Thyroid hormone levels in other etiologies, we did not find any significant correlation.

DISCUSSION

Our study revealed DM and hypertension as the most common cause of CKD (50% cases) which is in accordance to various studies from India.[2] Thyroid function abnormalities have been reported in association with CKD patients. We conducted a hospital based cross-sectional study to evaluate thyroid dysfunction in CKD patients, both on conservative therapy and maintenance hemodialysis (HD), knowing the fact that HD changes thyroid hormone profile.

Our study revealed low levels of TT3, FT4, FT3 in both the CKD groups vrs control group, where low TT3 level was statistically significant (Group A vrs Control, p-value: 0.004; Group B vrs Control, p-value: 0.007), but low FT3, FT4 levels were not statistically significant. TT4 & TSH were higher in both the CKD groups vrs control group but were not statistically significant. TBG level was not significantly different in both the groups. Comparison of thyroid hormone levels between all CKD patients vrs control group revealed similar observation but TT3 was significantly lower in CKD patients than controls (p-value:0.001). Ramirez et al. observed significantly reduced T3 in CKD patients compared to controls. They have reported significantly reduced T4 in HD group which is in contrast to our observation. TBG was unaffected

indicating pathophysiology independent of binding proteins.[6] Another study by Singh et al. in undialyzed CKD patients revealed significant decrease in TT3 and T4 levels compared to controls.[9] One study by Haria J et al. reported reduced TT3 and FT3 levels in 74% CKD patients whereas FT4 and TSH were similar to controls.[10]

Mehta et al. reported significant decrease in TT3, FT4, and FT3 levels in patients with progressive renal damage.[11] Another study by Rajagopalan et al. showed significant reduction in T4, T3 with unaffected TSH in patients with CKD compared to controls.[12] Srivastava et al. found significantly lower values of FT3, FT4 in undialyzed CKD patients compared to controls which were having negative correlation with progressive decline in renal function.[13] Pan B et al. evaluated thyroid dysfunction in conservatively managed CKD patients and found low TT3 and FT3 proportionate to the decline in renal function. Low TT3 concentration could be due to reduced peripheral synthesis of T3 from T4.[14]

Our study revealed higher TSH levels in stage 4 and stage 5 CKD patients. Joseph et al reported high TSH in the presence of low thyroid hormones in CKD patients. They have demonstrated rising thyrotrophin values with progressive renal insufficiency indicating a normal thyroid hypophyseal feedback loup.[15] Studies have demonstrated reduced thyroid hormone response to TSH and glycosylation of TSH in patients of CKD affecting thyroid hormone levels.[6,9,16] Srivastava et al. revealed no significant alterations in mean TSH level in CKD patients irrespective of severity of renal failure.[13]

CONCLUSION

Abnormal thyroid hormone profile sine thyroid gland disorder can occur in CKD patients causing difficulty in interpretation. Our study highlights significant lowering of total T3 (low T3 syndrome) in patients of CKD (both dialyzed and non-dialyzed) patients. There is a need of larger studies evaluating clinical significance of thyroid hormone levels in patients of chronic renal insufficancy for better understanding.

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