

Renal function markers and thyroid hormone status in undialyzed chronic kidney disease

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Abstract: *Objective:* The study was undertaken to quantify thyroid hormones in undialyzed chronic kidney disease patients' verses controls and to study the correlation between renal function markers and thyroid hormones. *Background:* Chronic kidney disease (CKD) is associated with a higher prevalence of primary hypothyroidism (HT), but at the same studies on thyroid hormone status in uremic patients has reported conflicting results. *Methods:* Thyroid hormones and renal function parameters like serum urea, creatinine, creatinine clearance, total protein and albumin were estimated and correlations between thyroid hormones and renal function parameters were studied in 60 undialyzed chronic kidney disease patients' verses 100 healthy controls. *Results:* We found both T3 and T4 were significantly reduced ($p < 0.0001$ for T3 and 0.007 for T4) whereas TSH remains to be unchanged in patient group compared to controls. We also observed that urea and creatinine were negatively correlated whereas creatinine clearance was positively correlated with both T3 and T4 that has high statistical (two-tailed) significance at 0.01 level. But urea alone is negatively correlated with TSH that has statistical (two-tailed) significance at 0.05 level. *Conclusion:* From our data, we speculate that renal insufficiency may lead to thyroid hormone disturbances.

Keywords: chronic kidney disease, renal function markers, thyroid hormones

Introduction

Renal disease leads to significant changes in thyroid function and vice versa. In one hand, thyroid hormones (TH) are necessary for growth and development of the kidney [1], and for the maintenance of water and electrolyte homeostasis [2]. On the other hand, kidney is involved in the metabolism and elimination of TH. Therefore, the decline of kidney function is accompanied by changes in the synthesis, secretion, metabolism, and elimination of TH causing thyroid dysfunction [3].

Chronic kidney disease (CKD) is associated with a higher prevalence of primary hypothyroidism (HT), both overt and subclinical, but not with hyperthyroidism. Prevalence of primary HT, mainly in the subclinical form, increases as GFR decreases [4]. Recently, Chonchol M et al reported increased prevalence of subclinical HT to 17.9% in subjects with GFR < 60 ml/min per 1.73 m² that of 7% in patients with estimated GFR > 90 ml/min per 1.73 m² [5]. Despite of

extensive studies, thyroid status in uremia is still inconclusive due to the complexity of the system studied. Studies on thyroid hormone status in uremic patients have reported conflicting results [6]. Free and total T3 and T4 concentrations are usually normal or low in patients with CKD [7]. The reduction in T3 levels (low T3 syndrome) is the most frequently observed thyroid alteration in these patients [4, 7-8]. Acute kidney injury and CKD are accompanied by notable effects on the hypothalamus-pituitary-thyroid axis. The secretion of pituitary thyrotropin (TSH) is impaired in uremia [9]. Serum TSH concentrations are usually normal or elevated in CKD, but its response to its releasing hormone (TRH) is generally low [7-8]. Furthermore, recent research suggests that TH, especially T3, can be considered as a marker for survival in patients with kidney disease [9]. With this background, we consider biochemical screening of TH quantification to assess thyroid function is of paramount importance in CKD. Although

thyroid status is profoundly influenced by renal function, this has not been studied in detail in human subjects from India, if any [6-7, 10]. The objective of the present study was therefore to determine TH levels in CKD patients and to observe any correlations between renal function markers and TH levels.

Material and Methods

Controls and CKD patients: After obtaining informed consent and clearance from institutional ethical committee, a total of 160 individuals aged 20-60 yr were recruited into the study. Among them were 100 chronic renal failure (CRF) patients selected from the department of Nephrology, Government general hospital, Chennai, TN, India, along with 60 age, and sex matched healthy controls. This study was carried at Biochemistry department, Madras Medical College and Research Institute, Chennai, Tamil Nadu, India. Participants with Diabetes Mellitus, past history of thyroid disorders, history of anti-thyroid drugs, Hepatic dysfunction, and acute/chronic illness were excluded for participation in the study. CKD patients were on conservative line of management, not on dialysis. Healthy controls and CKD patients were grouped according to their age into two groups each. Control group1 and CKD group1 comprises of individuals between 20-40 yr of age whereas, Control group2 and CKD group2 comprises of individuals between 41-60 yr of age.

Blood Sampling and screening: After 12h overnight fasting, 4ml of blood was drawn from all the study participants by venipuncture. Samples were centrifuged at 3000g for 15 min for analysis of TH and renal function markers in serum. Serum obtained was screened for T3, T4 and TSH using Erba ELISA kits. The reference

ranges for this geographic population studied were 0.6-2.1 ng/mL, 5-13 µg/dL, and 0.4-7.0 µIU/mL with the assay sensitivities of 0.2, 0.4, and 0.2 respectively for T3, T4 and TSH. Serum urea, creatinine, total protein, and albumin were quantified by end point Berthelot method, kinetic alkaline picrate method, biuret, and bromo cresol green (BCG) dye binding method, respectively.

Statistical analysis: All the data obtained was presented as Mean±SD. Any differences in parameters between groups were tested for significance by two tailed un-paired t-test. Comparisons were made between total controls Vs total CKD cases, group1 controls Vs group1 CKD cases, group2 controls Vs group2 CKD cases, and group1 CKD cases Vs group2 CKD cases. A ‘p’ value of < 0.05 was considered to be statistically significant. Pearson’s correlation analysis was done to study any correlations between renal and thyroid biochemistries. All the statistical analyses were performed on SPSS for Microsoft windows version 17.0.

Results

The circulating levels of TH, urea, creatinine, total protein, and albumin levels along with creatinine clearance values were depicted in Table 1 along with ‘p’ values. Results of correlation analysis between renal parameters and thyroid status were shown in Table 2. Comparison of means of all the studied parameters between total controls (n=60) and total CKD cases (n=100) were presented graphically in figure1. The Mean±SD values of studied variables were determined to be different to one another in all groups.

Table-1: Mean±SD values of various biochemistries among different groups along with ‘p’ values.

Variable	Total controls	Total CKD cases	Group1 controls	Group1 CKD cases	Group2 controls	Group2 CKD cases	P value
T3	1.6±0.3	1.0±0.4	1.6±0.3	1.0±0.4	1.6±0.3	1.2±0.3	*<0.0001 ^{a,b,c} *0.005 ^d
T4	6.6±1.3	6.0±1.4	6.5±1.1	6.0±1.3	7.3±1.9	6.4±1.2	*0.007 ^a , 0.08 ^b *0.01 ^c , 0.1 ^d

Variable	Total controls	Total CKD cases	Group1 controls	Group1 CKD cases	Group2 controls	Group2 CKD cases	P value
TSH	4.4±1.4	4.7±1.8	4.3±1.4	4.6±1.7	4.3±1.1	4.7±1.8	0.2 ^a , 0.5 ^b , 0.2 ^c , 0.7 ^d
Urea	25.1±4.0	103±39.2	25.2±4.1	108.1±39.4	26.3±5.0	97.0±37.4	*<0.0001 ^{a,b,c} 0.1 ^d
Creatinine	0.8±0.1	5.2±3.1	0.8±0.1	5.3±2.2	0.7±0.1	4.3±1.7	*<0.0001 ^{a,b,c} *0.01 ^d
Creatinine clearance	102.7±20.4	15.4±9.7	110±21.1	15.4±9.6	91.4±13.1	15.2±7.7	*<0.0001 ^{a,b,c} 0.09 ^d
Total protein	6.6±0.5	5.8±0.7	6.6±0.5	5.7±0.2	6.4±0.3	5.7±0.1	*<0.0001 ^{a,b,c} 1.0 ^d
Albumin	4.5±0.3	3.8±2.1	4.4±0.3	3.6±0.3	4.4±0.3	3.6±0.1	*<0.01 ^a *<0.0001 ^{b,c} 1.0 ^d

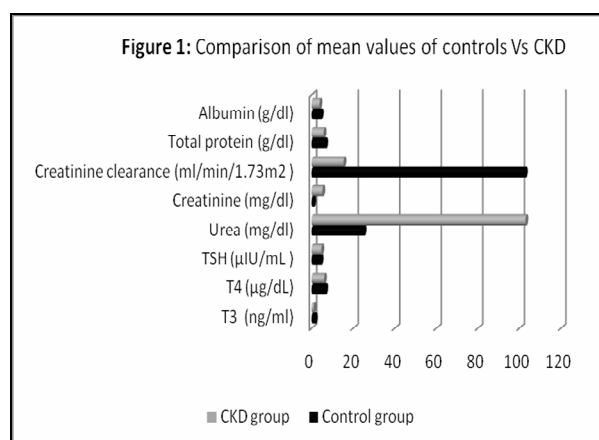
(group1=20-40yrs, group2=41-60yrs, ^atotal controls Vs total CKD, ^bgroup1 controls Vs group1 CKD, ^cgroup2 controls Vs group2 CKD, ^dgroup1 CKD Vs group2 CKD, *p<0.05)

Table-2: significance testing of correlation analysis between renal and thyroid parameters

Variable (n=100)	Correlation	T3	T4	TSH
Urea	Pearson's correlation	-.53	-.40	-.20
	Significance (2-tailed)	.00**	.00**	.04*
Creatinine	Pearson's correlation	-.67	-.50	.005
	Significance (2-tailed)	.00**	.00**	.96
Creatinine clearance	Pearson's correlation	.57	.41	-.07
	Significance (2-tailed)	.00**	.00**	.46

(Significant correlation at *0.05 and **0.01 levels)

None of the study group patients were under dialysis. Creatinine clearance value in CKD group is significantly reduced to 15.4±9.7 ml/min/1.73m² compared to 102.7±20.4 ml/min/1.73m² in control group. Urea and creatinine values were found to be increased significantly in the CKD group considered as a whole (n=100) compared to healthy controls (n=60), (p<0.05), creatinine clearance was found to be significantly decreased (p<0.05). We also observed a significant decrease in total protein and albumin levels in CKD patients Vs controls as a whole (p<0.05). The same is true when 20-40 yr group1 CKD patients (n=50) and 41-60 yr group2 CKD patients (n=50) were respectively compared with group1 (n=30) and group2 (n=30) healthy controls of same age.



Thyroid hormone status: When comparisons were made for TH between total controls and total CKD cases, it was found that both T3 and T4 were significantly reduced (p<0.0001 for T3 and 0.007 for T4) whereas TSH remains to be unchanged in patient group compared to controls. When group1 CKD data was compared with group2 CKD data, all variables were found to be unchanged except T3 found to be significantly increased in group2 CKD patients (p=0.005) with a significant reduction in creatinine concentration (p=0.01), suggesting raise in T3 levels with the fall in creatinine concentration.

Correlation studies: When Pearson correlation analysis was done for renal and thyroid continuous variables in CKD patients considered as a whole, it was observed that urea, and creatinine were negatively correlated whereas creatinine clearance was positively correlated with both T3 and T4 that has high statistical (two-tailed) significance at 0.01 level. But urea alone is negatively correlated with TSH that has statistical (two-tailed) significance at 0.05 level. It is very much evident from our data that thyroid hormone volume disturbances are due to impaired renal function.

Discussion

In the present study there was significant decrease in the levels of T3, T4, total protein and albumin in CRF patients when compared to controls this is in accordance with Singh PA et al [7]. However, the sample size in their study was too small to perform parametric statistical analysis. Lim VS reported despite decreased circulating T3 and T4, TSH is not elevated [11]. Similar findings were seen when 20-40 yr group1 CKD patients and 41-60 yr group2 CKD patients were respectively compared with group1 and group2 healthy controls, except for T4 decrease of which does not reach statistical significance ($p=0.08$) in the former comparison. It is important to note here that in addition to T3, T4 is significantly reduced with the increase in age of CKD patients. Tayal D et al showed a significant negative correlation of creatinine with T3 & T4 levels in overt HT group, whereas a positive correlation was observed with TSH [10].

Recently Iglesias P and Diez JJ thoroughly reviewed thyroid dysfunction in various kidney diseases such as glomerular disease, tubular disease, nephritic syndrome, AKI, and CKD etc. [9]. It was long back reported that about one third to one half of cases of CRF serum T3 are below the normal range [12]. Free and total T3 and T4 concentrations are usually normal or low in patients with CKD [4, 7, 11]. The reduction in T3 levels (low T3 syndrome) is the most frequently observed thyroid alteration in these patients [4, 7-8]. Chronic renal failure affects thyroid function in multiple ways, including low circulating thyroid hormone concentration, altered peripheral hormone metabolism, disturbed binding to carrier proteins, possible reduction in tissue thyroid hormone content, and increased iodine store in

thyroid glands [11]. Our observation of reduction in T3 concentrations has been linked to a decrease in the peripheral synthesis of T3 from T4. Chronic metabolic acidosis associated with the CKD may contribute in this effect [13]. The decreased total T3 levels can also be attributed to the increase in excretion of bound and free T4 in urine of chronic renal failure as reported in other previous study [14]. Moreover, reduction in serum total proteins and albumin observed in this study may partly explain decreased TH levels due cause of decreased binding and transport. Further, Impaired conversion of T4 to T3 may be related to malnutrition and humoral factors including cytokines that are generally associated with CRF [15]. Furthermore, iodine excess has been linked to the development of HT in CKD [16]. Low total T4 values in chronic renal failure patients may be primarily related to impaired T4 binding to serum carrier proteins. It has been reported that many inhibitors of T4 binding to serum carrier proteins are present in CRF patients and thus contributing to the decreased levels of T4 in CRF [17]. In a recent study, Singh PA et al showed 75% of undialyzed CRF patients presented diminished T4 levels [7]. Low levels of both T3 & T4 could also be due to defective release in response to TSH.

CKD is accompanied by notable effects on the hypothalamus-pituitary-thyroid axis. The secretion of pituitary thyrotropin (TSH) is impaired in uremia. It was reported that serum TSH concentrations are usually normal or elevated in CKD, but its response to its releasing hormone (TRH) is generally low [7-8]. From our data it is evident that TSH level in CKD group is similar to that of controls. This can be explained by TH levels in CKD patients reflects euthyroid status, well within the reference range. This suggests that thyroid is able to compensate for hormonal urinary losses keeping the patient euthyroid. Reduced serum TSH levels have not been reported to date in euthyroid CRF patients. CKD is associated with a higher prevalence of primary HT, both overt and subclinical forms. Uremia influences the function and size of the thyroid [18]. Thyroid nodules and thyroid carcinoma are more common in uraemic patients than in the general population [19]. It

is worthwhile to note here that TH, especially T3, can be considered as a marker for survival in patients with kidney disease. Patients with diminished values of T3 before transplantation are at increased risk of graft failure, thus suggesting that T3 quantification might be a potential marker for this risk [20]. Treatment of CKD by dialysis or renal transplantation is also accompanied by specific changes in thyroid physiology. Further, drugs used in treating kidney diseases may have undesirable effects on the thyroid, and vice versa. Understanding of the

clinical importance of thyroid hormone screening in these fields provides scope for future research. To summarize, Chronic renal failure affects thyroid function in multiple ways, including low circulating thyroid hormone concentration, altered peripheral hormone metabolism, disturbed binding to carrier proteins. Our data supports that renal disease leads to significant changes in thyroid hormone levels that unlocks the significance of thyroid hormone quantification in chronic kidney disease patients.

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