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Study of thyroid profile in patients with Chronic Kidney Disease: a cross sectional study

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ABSTRACT

Chronic kidney diseases is associated with disorders of structure and functioning of thyroid gland. Metabolism and hormonal levels may vary in patients having chronic renal failure (CRF). The objective of the study is to analyse the biochemical abnormalities of thyroid function tests in CRF and to correlate its severity and alterations of thyroid indices. Blood samples were analysed from patients (N=152) for serum triiodothyronine (TT3), serum thyroxine (TT4), serum free triiodothyronine (FT3) serum free thyroxin (FT4), thyroid stimulating hormone (TSH). Blood urea estimation was done using diacetyl monoxime (DAM) method and serum creatinine estimation by Modified Kinetic Jaffe method. Clinical examination and history was performed considering thyroid and renal diseases. Mean age of patients was 53.93 ± 9.91 years of which 115 (75.66%) were males and 37 (24.34%) were females. The mean value of TT3 in CRF stage 3, 4, 5 were 118.38±16.66, 111.26±23.13, 85.35±28.77 ng/mL respectively (p= < 0.00). The mean value of FT3 in CRF stage 3, 4, 5 were 2.84±0.43, 2.41±0.58, 2.07±0.66 pg/mL respectively (p=<0.01). The mean value of TT4 in CRF stage 3, 4, 5 were 1.22±0.17, 1.05±0.21, 0.96±0.27 respectively (p= < 0.001). The mean value of FT4 in CRF stage 3, 4, 5 were 1.19±0.00, 1.04±0.24, 0.98±0.24 pg/dL respectively (p= <0.001). TT3, TT4 and FT3 were found to decrease progressively as the stage of CRF increased. Thyroid hormone abnormalities could be a risk factor for cardiovascular disease and kidney disease progression.

1. Introduction

Chronic kidney disease (CKD) is defined as a decrease in kidney function manifested as kidney damage or an estimated glomerular filtration rate (eGFR) of less than 60 ml per minute per 1.73 m^2 body surface area for 3 or more months [1]. As kidneys are involved in metabolism and conversion of thyroid hormones, abnormalities in the function of the thyroid gland and its hormones are common in patients with CKD [2], [3].

Various studies of thyroid functions in CKD patients have shown conflicting results in which there are variability in Thyroid Function Tests. Although the relation between the severity of CKD and thyroid

dysfunction is not yet clear, it is reported that CKD is associated with higher prevalence of primary hypothyroidism, both overt and sub-clinical but not with hyperthyroidism [4]. In patients with end stage renal disease (ESRD) the prevalence of hypothyroidism has been estimated to be 0-9% and an increased prevalence of goitre. Studies report that thyroid hormones such as T3 can be considered as a marker for survival in patients with kidney disease [5]. The aim of this study is to analyse the prevalence of thyroid dysfunction in patients with CKD and to establish a correlation if any, between thyroid dysfunction and severity of renal diseases.

2. Materials and Methods

Patients (N=152) with CRF, who were admitted to Raja Rajeswari Medical College and Hospital, Bangalore, between March 2013 and August 2014 were included in this cross sectional study. Institutional Ethics Committee approved the study. Patients of age 18-65 years willing to give consent, patients with symptoms of uraemia for 3 months or more, Elevated blood urea, serum creatinine and decreased creatinine clearance, ultra sound evidence of chronic renal failure, Bilateral contracted kidneys – size < 8 cm in male and size < 7 cm in female, Poor corticomedullary differentiation, Type 2 or 3 renal parenchymal changes and patients with supportive laboratory evidence of CRF like anemia, low specific gravity, changes in serum electrolytes were included in the study. Patients below 18 years, patients undergoing peritoneal dialysis, Nephrogenic range of proteinuria, Low serum protein especially albumin, other conditions like acute illness, recent surgery, trauma or burns, diabetes mellitus, and liver diseases, individuals on drugs altering thyroid profile like amiodarone, steroids, dopamine, phenytoin, beta-blocker, estrogen pills, iodine-containing drugs were excluded from the study.

Blood samples of 5 ml were collected in non-heparinised serum bottles and subjected to thyroid profile analysis. Among the components analysed, serum triiodothyronine (TT3), serum thyroxine (TT4), serum free triiodothyronine (FT3) and serum free thyroxin (FT4) were estimated by competitive chemiluminescent immunoassay whereas serum thyroid stimulating hormone (TSH) was estimated by ultrasensitive sandwich chemiluminescent immune assay (CLIA). Blood urea estimation was done using diacetyl monoxime (DAM) method and serum creatinine estimation by Modified Kinetic Jaffe method). Normal values of these components are given in Supplementary table 1. Kidney function was assessed by estimating creatinine clearance which was calculated by using the Cockcroft – Gault equation.

$$\text{Cockcroft – Gault equation} = \frac{(140 - \text{age}) \times \text{body weight in kg}}{72 \times \text{Pcr (mg/dl)}}$$

(Multiply by 0.85 for Women)

3. Statistical Analysis

Descriptive and inferential statistical analysis was carried out in the present study. Results on continuous measurements are presented on Mean+ SD (Min-Max) and results on categorical measurements are presented in number (%). Significance is assessed at 5% level of significance. Student t test was used to find the significance of study parameters on continuous scale between two groups. Chi-square/ Fisher Exact test was used to find the significance of study parameters on categorical scale between two or more groups.

Statistical softwares such as SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data.

4. Results

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Among 152 subjects, 37(24.34%) were female and 115 (75.66%) were male. The age range of the patients was from 28 years to 67 years with the mean age of 53.93 ± 9.91 years. The mean Urea and creatinine levels were 114 and 6.10 respectively, as shown in the Table 1.

Patients who were categorized in the CRF stage 5 were 97 (63.82%), CRF stage 4 were 34 (22.37%), CRF stage 3 were 16 (10.53%), CRF stage 2 were 3 (1.97%) and CRF stage 1 were 2 (1.32%). USG abdomen was B in 134 (88.16%) and C in 18 (11.84%). (Table1)

The Mean T3 and FT3 was 95.48±29.58 and 2.24 ± 0.66, respectively. Mean T4 and FT4 was 4.92±1.54 and 1.01 ± 0.26, respectively as shown in the Table 1. Mean TSH was found to be 5.78 ± 4.89.

Of 152 patients, 55 (36.18%) had normal result, 22 (14.47%) of them were diagnosed with Subclinical Hypothyroidism, 15 (9.87%) of the individuals had Hypothyroidism and 60 (39.47%) of patients had some other hormonal abnormalities as revealed in the Table 1.

Table 1: Distribution of subjects according to different variables.

Variables	Sub Category	Number of Subjects (%)
Age (years)	Mean ± SD Median (Min, Max)	53.93 ± 9.91 55 (28, 67)
Gender	Female	37 (24.34%)
	Male	115 (75.66%)
Urea	Mean ± SD Median (Min, Max)	117.59 ± 27.87 114 (50, 187)
Creatinine	Mean ± SD Median (Min, Max)	6.25 ± 2.58 6.10 (2.20, 13.40)
CRF Stage	1	2 (1.32%)
	2	3 (1.97%)
	3	16 (10.53%)
	4	34 (22.37%)
	5	97 (63.82%)
USG Abdomen	B	134 (88.16%)
	C	18 (11.84%)
T3	Mean ± SD Median (Min, Max)	95.48 ± 29.58 102 (40, 155)
T4	Mean ± SD Median (Min, Max)	4.92 ± 1.54 5.20 (1.32, 7.98)
TSH	Mean ± SD Median (Min, Max)	5.78 ± 4.89 4.11 (0.77, 22.40)
FT3	Mean ± SD Median (Min, Max)	2.24 ± 0.66 2.20 (1.05, 3.60)

FT4	Mean ± SD Median (Min, Max)	1.01 ± 0.26 0.98 (0.34, 1.98)
Impression	Hypothyroidism	15 (9.87%)
	Normal	55 (36.18%)
	Subclinical Hypothyroidism	22 (14.47%)
	Some other hormonal abnormalities	60 (39.47%)

From Chi square test, we observe that, there is significant difference in the distribution of Gender, USG Abdomen and Result over CRF stage.

From Kruskal Wallis test, we observe that, there is significant difference in the distribution of age, urea, creatinine, T3, T4, TSH, FT3 and FT4 over CRF stage.

From post hoc analysis (Dunn's test), we observe that, distribution of age is significantly different between those with CRF stage 2 and 4 (p= 0.0168) and CRF stage 4 and 5 (p = 0.0132). There is significant difference in the distribution of urea between CRF stage 1 and 5 (p= 0.0261), CRF stage 3 and 5 (p < 0.001) and CRF stage 4 & 5 (p< 0.001). There is significant difference in the distribution of creatinine between CRF stage 1&5 (p = 0.0306), CRF stage 3 and 5 (p < 0.001) and CRF stage 4 & 5 (p< 0.001). There is significant difference in the distribution of T3 between CRF stage 3 and 5 (p < 0.001) and CRF stage 4 and 5 (p< 0.001). There is significant difference in the distribution of T4 between CRF stage 3 and 5 (p < 0.001) and CRF stage 4 and 5 (p = 0.001). There is significant difference in the distribution of TSH between CRF stage 3 and 5 (p< 0.001) and CRF stage 4 and 5 (p= 0.0120). There is significant difference in the distribution of FT3 between CRF stage 3 and 5 (p < 0.001). There is significant difference in the distribution of FT4 between CRF stage 3 and 5 (p< 0.001). (Table 2 and 3)

Table 2: Compariaon of variables over different CRF stages

Variables	**Sub Category**	**CRF stage**					**p-value**
		1	**2**	**3**	**4**	**5**	
Age (years)	Mean ± SD Median (Min, Max)	47 ± 0 47 (47, 47)	38 ± 5.57 39 (32, 43)	56.75 ± 5.43 56 (47, 66)	59.38 ± 5.02 59.5 (51, 67)	52.2 ± 10.81 55 (28, 67)	**0.0013^{K}***
Gender	Female	0	0	9(56.25%)	8(23.53%)	20(20.62%)	**0.027^{MC}***
	Male	2(100%)	3(100%)	7(43.75%)	26(76.47%)	77(79.38%)	
Urea	Mean ± SD Median (Min, Max)	65 ± 0 65 (65, 65)	99 ± 5 99 (94, 104)	83.25 ± 17.59 85 (50, 122)	103.62 ± 24.14 98 (58, 165)	129.81 ± 22.09 129 (85, 187)	**< 0.001^{K}***
Creatinine	Mean ± SD Median (Min, Max)	3.05 ± 0.21 3.05 (2.9, 3.2)	5.43 ± 0.21 5.5 (5.2, 5.6)	3 ± 0.52 3 (2.2, 3.7)	3.97 ± 0.92 3.7 (2.9, 6.9)	7.67 ± 2.06 7.2 (4.4, 13.4)	**< 0.001^{K}***
USG Abdomen	B	0	3(100%)	3(18.75%)	34(100%)	94(96.91%)	**< 0.001^{MC}***
	C	2(100%)	0	13(81.25%)	0	3(3.09%)	

Abbreviation: MC – Chi square test with Monte Carlo simulation, K – Kruskal Wallis test, * indicates statistical significance.

Table 3: Comparison of Thyroid test results with CRF stages

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Variable	Sub Category	CRF stage					p-value
		1	2	3	4	5	
T3	Mean ± SD Median (Min, Max)	105.5 ± 0.71 105.5 (105, 106)	115.33 ± 36.23 107 (84, 155)	118.38 ± 16.66 114 (79, 144)	111.26 ± 23.13 108 (69, 150)	85.35 ± 28.77 85 (40, 155)	< **0.001**^{K}*
T4	Mean ± SD Median (Min, Max)	6.8 ± 0 6.8 (6.8, 6.8)	5.04 ± 0.14 4.96 (4.96, 5.2)	6.62 ± 0.94 6.7 (5, 7.98)	5.57 ± 1.04 5.69 (3.2, 6.9)	4.38 ± 1.49 4.2 (1.32, 7.03)	< **0.001**^{K}*
TSH	Mean ± SD Median (Min, Max)	1.78 ± 0 1.78 (1.78, 1.78)	3.34 ± 0.48 3.06 (3.06, 3.9)	2.4 ± 0.53 2.26 (1.46, 3.4)	3.93 ± 2.07 3.89 (0.77, 9.62)	7.14 ± 5.52 4.81 (1.17, 22.4)	< **0.001**^{K}*
FT3	Mean ± SD Median (Min, Max)	2.54 ± 0.18 2.54 (2.41, 2.66)	2.27 ± 0.21 2.2 (2.1, 2.5)	2.84 ± 0.43 2.85 (2.18, 3.6)	2.41 ± 0.58 2.32 (1.52, 3.21)	2.07 ± 0.66 2.11 (1.05, 3.3)	< **0.001**^{K}*
FT4	Mean ± SD Median (Min, Max)	1.19 ± 0 1.19 (1.19, 1.19)	1.17 ± 0.03 1.19 (1.14, 1.19)	1.22 ± 0.17 1.21 (0.93, 1.6)	1.05 ± 0.21 0.98 (0.74, 1.44)	0.96 ± 0.27 0.94 (0.34, 1.98)	< **0.001**^{K}*
Result	Hypothyroidism	0	0	0	0	15(15.46%)	< **0.001**^{MC}*
	Normal	2(100%)	3(100%)	16(100%)	15(44.12%)	19(19.59%)	
	Subclinical Hypothyroidism	0	0	0	3(8.82%)	19(19.59%)	
	Some other hormonal abnormalities	0	0	0	16(47.06%)	44(45.36%)	

From Kruskal Wallis test, we observe that, there is significant difference in the distribution of T3, T4, TSH, FT3 and FT4 over result.

From post hoc analysis (Dunn's test), we observe that, distribution of T3 is significantly different between all the possible pairs of result except subclinical hypothyroidism & some other hormonal abnormalities. There is significant difference in the distribution of T4, TSH, FT3 and FT4 between all the possible pairs of result. (Table 4).

Table 4: Comparison of overall test results

Variable	Result				p-value
	Normal	Hypothyroidism	Subclinical Hypothyroidism	Some other hormonal abnormalities	
T3	121.02±16.95 120 (79, 155)	56.6 ±11.47 55 (40, 77)	91.45 ± 13.78 86.5 (72, 127)	83.25 ± 26.98 88.5 (42, 140)	< **0.001**^{K}*
T4	6.33 ± 0.75 6.54 (4.7, 7.98)	2.68 ± 0.94 2.9 (1.5, 4.2)	5.13 ± 0.57 5.15 (3.4, 6.2)	4.12 ± 1.18 3.8 (1.32, 6.3)	< **0.001**^{K}*
TSH	3.04 ± 0.92 3.21 (1.19, 5.2)	18.25 ± 2.85 18.91 (13.6, 22.4)	9.56 ± 1.51 9.64 (3.3, 11.2)	3.78 ± 1.28 4.29 (0.77, 5.6)	< **0.001**^{K}*

FT3	2.73 ± 0.44 2.84 (1.8, 3.6)	1.25 ± 0.22 1.12 (1.05, 1.6)	2.29 ± 0.52 2 (1.78, 3.22)	2.02 ± 0.54 2.12 (1.06, 3.3)	< **0.001^{K}***
FT4	1.19 ± 0.16 1.2 (0.87, 1.6)	0.63 ± 0.1 0.66 (0.45, 0.77)	0.82 ± 0.2 0.89 (0.34, 0.98)	1.02 ± 0.22 0.96 (0.74, 1.98)	< **0.001^{K}***

Abbreviation: K – Kruskal Wallis test, * indicates statistical significance

5. Discussion

Kidney dysfunction affects the hypothalamic-pituitary-thyroid axis and hence alters hormone production, distribution, and excretion [6- 8]. Various hormonal systems are affected by CRF, but it is still unclear as to what extent these changes causes uremic syndrome. Patients with CRF often have symptoms of thyroid dysfunction and hence the diagnosis of thyroid disease in these patients has obvious prognostic implications [9].

In this study among the 152 patients the male ratio was more than female ratio. The mean age was 53.93± 9.91 years. Similarly a research by [10] a study about the alteration in thyroid profile in chronic kidney disease showed that the male ratio was more than female ratio (24/16) and the maximum number of patients were in the age group of 50-70 years. The mean urea and creatinine levels of the patients was found as 114 mg/dl and 6.10 mg/dl respectively in our study. Study results by [10] is in concordance with this study results revealing that the levels of urea and creatinine were 120mg/dl and 9.13mg/dl respectively, which implies that the high levels of creatinine and urea are sign of CKD.

A study by [11] showed that 9.5% of patients with CKD had subclinical hypothyroidism and 7% of patients with mild CKD had low thyroid function, compared to 18% of those with moderate CKD. In this study the patients in CRF stage 4 and 5 had subclinical hypothyroidism and hypothyroidism (22% and 15%) which is in line with the study by [11]. Recently, [12] have also reported higher prevalence of upto 5% of frank hypothyroidism in patients with CRF, in comparison with hospitalised patients with normal renal function (0.6%). In an Indian study by [13] out of 127 patients with CRF studied, 93 patients (73%) showed significant ($p<0.05$) reduction in their T3, T4, FT3 levels in serum. Similarly in our study the same results were observed there was a significant changes in the thyroid hormones levels ($p<0.001$).

Many studies conducted in CRF showed low TT3 [14- 17] normal TT3 [16], low FT3 [14], [17], normal FT3 in patients on HD [18]. Even some studies have reported low TT4 (low T4 syndrome), normal TT4 [15], [16] and low normal or lower FT4 levels [15]. Basal concentrations of circulating TSH have been found at different levels in different studies. Normal levels or TSH were reported from previous Indian studies [19], [20]. Thus defects at various levels of hypothalamic pituitary-thyroidal-peripheral axis are observed in uremia [7].

In most of the studies, TT4 concentrations were found to be low or normal. However, FT4 levels were within normal limits. This is attributed to lowering of thyroxine binding globulin concentration as well as presence of inhibitors of thyroid hormone bindings to the thyroid binding proteins. Levels of TT3 and FT3 suffer further reductions in CRF, which is thought to be due to impairment in deiodination of T4 [13].

In our study, study of thyroid dysfunctions in CRF is done with 50 cases. Cases were selected according to

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inclusion and exclusion criteria which are mentioned earlier. The age of the patients ranged from 21 to 69 years. Most of the patients in the sample were in the age group of 51-60 years.

Of the 152 patients studied, 15 patients (9.87) had hypothyroidism, 7 patients (14%) had subclinical hypothyroidism and 21 patients (42%) had some thyroid hormone abnormalities in the form of reduction in TT3, TT4 and FT3 levels. So totally 64% of patients with CKD had some thyroid hormone abnormalities.

Among 21 patients with some thyroid hormone abnormalities, 14 patients (28%) had decreased FT3, 7 patients (14%) had decreased TT4. All these patients were euthyroid and TSH levels were within normal limits.

Excluding hypothyroidism and subclinical hypothyroidism, the mean TSH level in our study is within normal limits. The mean TSH levels are also within normal limits for the various ranges of GFR. But TSH level does show any linear correlation with the severity of renal failure. This is consistent with the study conducted by [21], [22]. These studies demonstrated abnormality in hypophyseal mechanism of TSH release in uremic patients as the TSH response to the TRH was blunted.

Other studies conducted by [16], [23] revealed low T3 T4 level with high TSH level suggesting maintenance of pituitary thyroid axis.

In our study, total 10 patients were having symptoms suggestive of hypothyroidism of which 4 were hypothyroid biochemically and the remaining 6 patients with TFT was in subclinical range. Thus some of the symptoms of CRF tend to overlap with hypothyroidism and may pose difficulty in diagnosis.

Out study is consistent with the results of [9], [16], [24] study showing low T3, low T4 and normal or mild elevation of TSH. Yet it is unclear that to what extent these changes are responsible for the manifestations of uremic syndrome. From the various studies it has been suggested that this thyroid profile derangements is a part of body adaptation mechanism.

5.1 Relationship between CRF stage and thyroid dysfunction

Higher the stage of CKD, there is an increased prevalence of thyroid dysfunction in CRF patients [25]. In our study, 12.5% of stage 5 CKD patients had hypothyroidism when compared to stage 3 (0%) and stage 4 (0%). 6 patients of stage 5 patients had subclinical hypothyroidism when compared to no patients in stage 3 and 1 patient in stage 4. Some hormone abnormalities according to stage 4 was observed in 5 and 16 patients respectively.

TT3, TT4, FT4 levels progressively decreased as the CRF stage increased but FT4, TSH levels were normal except in patients with overt hypothyroidism. Even though symptoms of hypothyroidism were prominent in advanced stage of renal disease, statistical analysis did not show significant correlation.

Although there are improvements in renal replacement therapy, cardiovascular diseases (CVDs) still remains the main cause of morbidity and mortality in CRF patients [6], [26- 29].

Hypothyroidism and subclinical hypothyroidism are linked to an increased risk of CVDs and reduced cardiac function. Patients with CKD are at greatly increased risk of thyroid dysfunction. Thyroid hormone abnormalities could represent a risk factor for CVDs and might also be implicated in kidney disease progression [11].

Further research including more patients is required to obtain more relevant conclusions. One of the limitations of the study is that as the prevalence of hypothyroidism increases with age there are possibilities of influence of age on the results which need to be considered.

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