Study of total and free thyroid hormone levels in chronic renal failure

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Abstract

The study is undertaken to estimate the total and free thyroid hormone levels i.e. TT_3, TT_4, FT_3, FT_4 & TSH and thyroid dysfunctions in chronic renal failure. The study also includes the thyroid abnormalities in relation to varying grades of CRF (serum creatinine). A cross sectional study was conducted consisting of 30 male patients of aged between 40-70yrs having serum creatinine > 4.0mg/dl & urea > 50mg/dl with frank proteinuria and symptoms & signs suggestive of CRF are taken in study. Serum levels of TT_3, TT_4, FT_3, FT_4 & TSH are estimated by chemiluminesence immune assay method, and the data obtained by the study subjects were compared with data from normal individuals of same age group using student t test. We got the results that TT_3, TT_4, FT_3, FT_4 decreases TSH increases significantly in study group compare to normal individuals i.e. controls. Out of 30 patients in study group 3 patients (10%) are in hypothyroid range. The hormone levels of TT_3, TT_4 and FT_3, FT_4 decreases and the levels of TSH increases as severity of CRF increases. We finally concluded that Total and free thyroid hormone levels decreases and TSH increases in CRF compare to controls even though are majority them are euthyroid. CRF is associated with increased risk of hypothyroidism and this risk increases as severity of disease increases.

Keywords: Chronic renal failure, Chronic Kidney Disease, End Stage Renal Disease, Hypothyroidism, Thyroid hormones, Thyroid Stimulating Hormone(TSH).

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Introduction

Chronic kidney disease (CKD) encompasses a spectrum of different pathologic processes associated with abnormal kidney functions, a progressive decline in glomerular filtration rate (GFR) and albuminuria. The end stage renal disease (ESRD) represents a stage of CKD where the accumulation of toxins, fluid and the electrolytes normally excreted by the kidneys results in uremic syndrome. This syndrome leads to death unless the toxins are removed by renal replacement therapy, using dialysis or kidney transplantation.

Although the exact burden of CKD in India is still not known, prevalence and incidence of CKD in India which is relevant in planning preventive health policies with limited resources in developing countries such as India have shown the prevalence of CKD ranges from 0.78% to as high as 17.4%, while the incidence is 151 pmp(per million population). Difference in prevalence can be explained on the basis of population bias as well as the use of different methodology in defining CKD. The burden of end-stage CKD needing renal replacement is probably more than the figure of 0.78% but much less than the figure of 17.4%. Considering the cost of renal replacement and the magnitude of the problem it appears that the best way forward for our country would be to adopt the strategy of prevention, as in the model demonstrated by Mani in Chennai[1].

Endocrine function is disturbed in patients of uremia and chronic renal failure secondary to diminished renal degradation of polypeptides, receptor dysfunction, changes in protein binding and abnormal endocrine feedback control. Patients in late chronic renal failure often appear hypothyroid & Thyroid function tests may be abnormal, despite normal free levothyroxine, free tri-iodothyronine levels are low and binding of levothyroxine to thyroxin binding globulin is diminished[28]. Most women's are amenorrheic although occasionally menorrhagia can occur and infertile, at least in the Later stages of chronic renal failure. Impotence & Oligospermia are common in men. FSH & LH levels are high and hyperprolactenemia is present gonadal resistance to hormone & a complicated hypothalamic–pituitary disturbance contributes to these abnormalities.

Patients with CRF often have signs & symptoms suggestive of thyroid dysfunctions. Various Studies of thyroid functions in uremic patients have been carried out which have shown conflicting results. Hyperthyroidism, hypothyroidism & euthyroid state have all been reported by various workers[2,3]. Serum Tri-iodothyronine(T_3) level were consistently found to be low, serum total &free thyroxin(T_4) concentration have been reported as low, normal or high. Serum thyroid stimulating hormone (TSH) levels were found to be normal in most of the patients of CRF even in those whose CRF is complicated by low T_3 concentration[4].

Material and Methods

A cross sectional study was conducted consisting of 30 male patients of aged between 40-70yrs having serum creatinine > 4.0mg/dl & urea > 50mg/dl with frank proteinuria and symptoms & signs suggestive of CRF are taken as study subjects. 30 healthy men of age between 40-70 years are taken as a controls in the study. Source of data: - District hospital attached to chamrajnagar institute of medical sciences, Chamrajnagara and patients admitted in dialysis unit, Al-Ameen hospital attached to Al-Ameen medical college Bijapur. Exclusion criteria: - patients on treatment with β-blocker, phenobarbitones, sulphonylureas, estrogen, corticosteroids and females.

The T_3, T_4 assay employs a competitive immunoluminometric principle: use an anti-T_3/T_4 monoclonal antibody to label AEBI and use a purified T_3/T_4 antigen to label magnetic micro beads. Sample, calibrator or control, AEBI label, and bufferare mixed thoroughly and incubated at 37^0C, then add magnetic micro beads and incubated, the sample and magnetic micro beads competitively binding the AEBI label, forming a immune-complex, after sediment in a magnetic field, decant the supernatant, then cycle washing for one time. Subsequently the starter reagents are added and a flash chemiluminescent reaction is initiated. The Lightsignal is measured by a photomultiplier as RLU within 3 seconds and is proportional to the concentration of T_3/T_4 present in the sample.

The TSH estimation assay employs sandwich immunoluminometric principle: use an anti-TSH monoclonal antibody to label AEBI, and use another monoclonal antibody to label FITC. Sample, calibrator or control are mixed thoroughly with AEBI label, FITC label and magnetic micro beads coated with sheep anti-FITC are incubated at 37^0C, forming a sandwich; after sediment in a magnetic field, decant the supernatant, then cycle washing for one time. Subsequently the starter reagents are added and a flash chemiluminescent reaction is initiated. The Light signal is measured by a photomultiplier as RLU within 3 seconds and is proportional to the concentration of TSH present in the sample.

Statistical Methods[5,6] Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented as Mean ± SD (Min-Max) and results on categorical measurements are presented in Number(%). Significance is assessed at 5 % level of significance. Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups. Student t-test is used to find out the correlation co-efficient. Significant figures are,

P value less than 0.01 – strongly significant.

P value between 0.01-0.05 – moderately significant.

P value more than 0.05 and less than 0.10 – suggestive of significant.

Results

Table 1: Distribution of age in years between two groups

Age in years	Cases		Controls	
	No	%	No	%
44-49	6	20.0	7	23.3
50-54	9	30.0	9	30.0
55-59	8	26.7	10	33.3
60 & above	7	23.3	4	13.3
Total	30	100.0	30	100.0

Distribution of age in cases and controls are shown in table 1. All the study subjects and controls belongs to above 40 category and majority are above 50 years. 30 Cases and 30 controls are selected almost equal proportion of age groups as shown in table no 1 to overcome the age bias.

Table 2: Comparison of study parameters in cases and controls

Study variables	Normal Range	Cases (n=30)	Controls (n=30)
TT_3 (ng/dl)	60 - 200	82.67±15.08	112.96±10.18
TT_4 (µg/dl)	4.5 - 12.0	5.80±0.50	7.98±0.46
FT_3 (pg/ml)	1.0 – 4.0	1.87±0.75	3.40±0.70
FT_4 (ng/dl)	0.9 – 1.6	1.10±0.25	1.26±0.30
TSH (µIU /ml)	0.30 - 5.50	4.81±0.38	2.99±0.79

Comparison of study parameters in cases and controls is shown in table 2. Mean of TT_3 in cases is 82.67±15.08 and in controls is 112.96±10.18 ng/dl, it means TT_3 decreases in cases as compares to controls. P value is <0.001 (statistically significant). Mean of TT_4 in cases is 5.80±0.50 and in controls is 7.98±0.46. Mean of TT4 is also

decreases in cases compare to control group. P value is <0.001 (statistically significant). The mean of TSH in cases is 4.81±0.38 µIU /ml and in controls is 2.99±0.79 µIU /ml. Mean of TSH increases in cases compare to controls. P value is <0.001. (Statistically significant).

Mean $FT_{3\ in}$ cases is 1.87±0.75 and in controls is 3.40±0.70 it means mean of FT3 decreases in cases compare to controls. P value is <0.001 (statistically significant). Mean of FT_4 in cases is 1.10±0.25 and in controls is 1.26±0.30 so mean of FT_4 is also decreases in cases compare to controls. P value is <0.001 (statistically significant).

Table 3: **Thyroid function tests with varying severity of chronic renal failure in cases.**

Study variables	Group I (n=12) (Sr. creatinine <5mg/dl)	Group II (n=13) (Sr. creatinine 5-6mg/dl)	Group III (n=5) (Sr. creatinine >6mg/dl)
TT_3 (ng/dl)	98.37±10.67	91.02±12.12	81.02±15.17
TT_4 (µg/dl)	6.88±1.37	5.91±0.80	4.60±0.96
FT_3 (pg/ml)	2.57±1.20	1.61±0.85	1.28±0.90
FT_4 (ng/dl)	1.12±0.18	1.08±0.61	1.09±0.13
TSH (µIU /ml)	4.81±0.45	4.79±0.38	4.94±0.70

Thyroid function tests with varying severity of chronic renal failure among cases are shown in table 3. We have categorized the study subjects i.e. cases(n=30) in to 3 groups with varying severity chronic renal failure on the bases of sr. creatinine (which is a marker for severity of renal failure). Group I or mild CRF, includes 12 number of patients with serum creatinine less than 5.0mg/dl. Group II or moderate CRF, includes 13 number of patients with serum creatinine between 5.0−6.0mg/dl. Group III or severe CRF, includes 5 number of patients with serum creatinine more than 6.0mg/dl. The mean of TT_3, TT_4 and FT_3, are decreases as the severity of CRF increases P value is <0.001 (statistically significant). The mean of FT_4 is also decreases and TSH increases as the severity of chronic renal failure increases but the values are not statically significant.

Table 4: Incidence of hypo/hyperthyroidism

Hypo/Hyperthyroidism	Cases	Controls
Normal	27 (90%)	30 (100%)
Hypothyroidism	3 (10%)	0
Hyperthyroidism	0	0
Total	30 (100%)	30 (100%)

Incidence of hypo or hyperthyroidism are shown in table no 4. The incidence of hypothyroidism (i.e TT_3, TT_4 and FT_3, TT_4 decreases below the reference range and TSH increases above the reference range) is 10% in CRF patients compare to control subjects. P value is 0.236 which means a positive correlation between CRF and hypothyroidism. We did not found any hyperthyroidism either in cases or in controls.

Table 5: Incidence of hypothyroidism in relation to varying severity of renal failure in cases

Cases	Hypothyroidism	
	No	Yes
Group I (Sr. creatinine<5mg/dl)	12 (44.44%)	0
Group II (Sr. creatinine5-6mg/dl)	12 (44.44%)	0
Group III (Sr. creatinine>6mg/dl)	3 (11.11%)	3 (100.0%)
Total	27 (100.0%)	3 (100.0%)

Incidence of hypothyroidism in relation to varying severity of renal failure in cases are shown in table no-5. Group I or mild CRF, includes 12 number of patients with serum creatinine less than 5.0mg/dl. Group II or moderate CRF, includes 12 number of patients with serum creatinine between 5.0−6.0mg/dl. There is no hypothyroidism in group I and group II patients. Group III or severe CRF, includes 6 number of patients with serum creatinine more than 6.0mg/dl, out of these 6 patients 3 are hypothyroid. Which is statistically significant.

Discussions

The mean of TT_3 in cases is decreased when compared to controls. Our study the findings are comparable with the previous studies[7,8,9] showing decreased levels of T_3 in uremic patients and patients on regular hemodialysis. This reduction in T_3 concentration is due to decrease in the peripheral synthesis of T_3 from T_4[10,11]. The mean of TT_4 in all 30 cases is decreased when compared to the controls. Our study findings are comparable with previous studies[12,13]. The different studies mentioned various reasons to decreased levels of T_4. The decreased levels of T_4 may be secondary to the protein loss, which occur in chronic renal failure. Serum globulin levels not much altered, serum albumin and thyroid binding pre-albumin decreases[13]. Joasso et.al. Found that uremic patients had low serum TT_4 & elevated T_3 resin uptake suggesting a decrease in TBG. However actual measurement of TBG was normal. They postulated that uremic toxins might have displaced T_4 from TBG[12]. Study conducted by Victoria Sy Lim et. Al[10]. patients whose TBG capacity was decreased, their TT_4 was always low, but low TT_4 was not necessarily accompanied by a reduction in TBG capacity, suggesting that factor other than decreased binding might, in part, be responsible for the slightly decreased serum TT_4 concentration. Decrease in T_4 is also attributed to the presence of circulating inhibitors, which impairs binding of T_4 to thyroxin binding globulin[14].

The mean of FT_3 in cases is decreased as compare to the controls, our study findings are comparable with previous study[3,15,16] The reduction in TT_3, and FT_3 is thought to be due to impairment in deiodination of T_4 a principle process by which T_3 is produced at peripheral levels. The mean of ^{FT4} is also decreased in cases as compare to the controls, our study findings are similar to the previous studies[3,16,17]. The most likely cause for low levels both FT_4& FT_3 could be defective release of T_4&T_3 in response to TSH. Mehta HJ et.al[15] shows normal levels of both FT_4 and TSH, even though low T_4, T_3 and FT_3, which indicate functional euthyroid status. FT_4 is the most active biological fraction, consisting of 0.03% of T_4 and its levels in blood are not dependent on carrier proteins, so FT_4 levels in blood shows thyroid status accurately.

Mean TSH in cases is high compare to controls, even though majority of cases TSH still remains within the normal range. The previous study findings are variable. Patients with low T_3, T_4 and free T_4 showed high TSH suggesting maintenance of pituitary thyroid axis[1,18], Studies conducted by G Avasthi-et.al,[3] Joseph et.al,[19] shows increased TSH in those patients who had low T_3, T_4 & FT_4 suggesting maintenance of pituitary thyroid axis. Which is similar to our study. In some studies plasma TSH levels are not increased in spite of low T_3 & T_4 levels. It is not due to dysfunction in hypothalamo-pituitary axis but because truly hypothyroid renal failure patients can mount a high TSH response[3,14].

In our study the levels of TT_3, TT_4, FT_3, and FT_4 decreases and TSH increases as severity renal failure increases (i.e Sr. creatinine levels increases) Even though few of the values are not statistically significant. The present study findings are comparable with G Avasti et.al[3].showing significant difference in the values of T_3, T_4, FT_4, and TSH in cases with varying severity of renal failure (creatinine clearance) but not statistically significant. Study conducted by Mehta H.J et.al[15] shows Mean of TT_3 & TT_4 & FT_3 levels reduced as the severity of renal damage increased, but the individual values plotted against their respective Sr. creatinine levels, no linear correlation ship was observed between those parameters.

In our study 3 patients out of 30 are hypothyroid (i.e. TT_3, TT_4 and FT_3, TT_4 decreases below the reference range and TSH increases above the reference range) the incidence rate is 10% and all these 3 patients belongs to serum creatinine above 6mg/dl category. None among the control group is hypothyroid. In our study 6 patients among 30 in study group belongs to serum creatinine of>6 mg/dl category among them 3 patients are hypothyroid(i.e. 50%) and 3 are euthyroid inspite of high sr. creatinine levels. In this study, findings are comparable with previous studies. Prevalence of hypothyroidism in patients with terminal renal failure is 5%, in comparison with that in hospitalized patients with normal renal function[18].CKD is associated with higher prevalence of hypothyroidism, both overt and subclinical, but not with yperthyroidism[20,21]. In fact, the prevalence of primary hypothyroidism is mainly in the subclinical form, which increases as GFR decreases[11].

Conclusion

Mean of TT_3, TT_4 and FT_3, FT_4 decreases and TSH increases significantly in study group i.e. cases compare to controls. The levels of TT_3, TT_4 and FT_3, FT_4 decreases and TSH increases as severity renal failure (serum creatinine) increases. Prevalence of hypothyroidism in CRF is 10% compare to 0% in controls and there is no hyperthyroidism both in cases & controls. The risk of hypothyroidism in chronic renal failure is increases as severity renal failure (serum creatinine) increases.

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Source of Support: Nil

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