Scholars Journal of Applied Medical Sciences (SJAMS) **ISSN 2320-6691 (Online)**
Sch. J. App. Med. Sci., 2016; 4(2A):358-365 **ISSN 2347-954X (Print)**

(An International Publisher for Academic and Scientific Resources)
www.saspublisher.com

Original Research Article

Study of thyroid function in patients of chronic kidney disease

Dr Shivendra Verma[1], Dr Richa Giri[2], Dr Vaibhav Srivastava[3], Dr Rajendra Verma[4]
[1]Assistant Professor of Medicine GSVM Medical College, Kanpur, UP, India
[2]Professor& Head of Medicine, GSVM Medical College, Kanpur, UP, India
[3]Lecturer of Medicine, GSVM Medical College, Kanpur, UP, India
[4]Assistant Professor of Medicine, GSVM Medical College, Kanpur, UP, India

***Corresponding author**
Dr. Shivendra Verma
Email: dr.shivendra@gmail.com

Abstract: Forty two patients with chronic renal insufficiency underwent clinical evaluation & studies of thyroid function. The results were compared with age & sex-matched controls. Two patients had clinical hypothyroidism with low serum T3, T4, FT4 & high serum TSH. The remaining patients did not have goitre & they were clinically euthyroid. A linear decline in TT3 levels was seen when linear correlation was tested between GFR and TT3 levels. There was no significant decline in TT3 and FT3 levels in mild CKD. Thus, TT3 and FT3 levels tend to fall at GFR levels below 60ml/min. When controls were compared with mild CKD cases, no significant decline in TT4 levels was found but when compared with moderate and severe CKD cases there was a tendency of fall of TT4 as CKD progressed. However, a linear correlation between TT4 levels and GFR was not found. A significant reduced level of TT4 as compared to TT3 and FT3 was found in severe CKD thus, TT4 can be used as a specific indicator of severe CKD. Contrary to FT3, levels of FT4 remained normal through all the stages of CKD. TSH levels remained normal throughout the course of CKD. There was an increased incidence of signs and symptoms simulating hypothyroid state in pts of severe CKD but this does not signify that they had primary hypothyroidism. However, Incidence of hypothyroidism in CKD patients is increased. Only TSH and FT4 levels can be relied upon to diagnose and treat primary hypothyroidism. There was no incidence of goiter, hyperthyroidism or thyroid nodules in CKD pts. To conclude thyroid dysfunction occurs both clinically & biochemically in patients with chronic renal insufficiency.
Keywords: clinical hypothyroidism, chronic renal, TSH and FT4 levels, CKD pts.

INTRODUCTION

Patients with chronic renal failure often have signs & symptoms suggestive of thyroid dysfunction [19]. These findings include dry skin, sallow complexion, low temperature, cold intolerance, decreased basal metabolic rate, lethargy, fatigue, edema & hyporeflexia. Various studies of thyroid functions in uremic patients have been carried out which have shown conflicting results. Despite extensive studies, thyroid status in uraemia is still inconclusive due to the complexity of the system studied. Hyperthyroidism, Hypothyroidism & euthyroid state have all been reported by various workers.

All levels of the hypothalamic pituitary thyroid axis may be involved, including alterations in hormone production, distribution and excretion [3,5,15,16]. As a result, abnormalities in thyroid function tests are frequently encountered in chronic kidney disease. For example, thyroidal radio iodide uptake is decreased because of reduced renal iodide clearance. The serum hormonal concentration may be altered by changes in the binding capacity of serum proteins, and abnormal serum constituents in uraemia were thought to displace thyroid hormone from its protein-binding sites [8]. In various studies it was found that, patients with CKD have multiple alterations of thyroid hormone metabolism in the absence of concurrent thyroid disease. These may include elevated basal TSH values, which may transiently increase to greater than 10 mu/liter, blunted TSH response to TRH, diminished or absent TSH diurnal rhythm, altered TSH glycosylation, and impaired TSH and TRH clearance rates. In addition, serum total and free T_3 and T_4 values may be reduced, free rT_3 levels are elevated while total values are normal, serum binding protein concentrations may be altered, and disease-specific inhibitors reduce serum T_4, binding. Changes in T_4 and T_3 transfer, distribution, and metabolism resemble those of other nonthyroidal illnesses, while changes in rT_3 metabolism are disease specific. In view of the variability of thyroid function tests in patients with CKD in previous studies, it was

decided to undertake a clinical & biochemical study of various thyroid functions & to establish a correlation, if any between thyroid dysfunction & severity of renal disease.

STUDY METHODS

The present study was conducted on 42 patients of chronic kidney disease, admitted in emergency department and indoor department of K.P.S., P.G. institute of medicine G.S.V.M. Medical College Kanpur. 40 healthy age and sex matched controls not having any evidence of CKD were also studied for valid comparison.

Inclusion criteria

Patients fulfilling criteria for chronic kidney disease as per The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF K/DOQI GUIDELINES) were included in the study [14].

Exclusion criteria

- Patients of nephrotic syndrome.
- Patients taking estrogens, corticosteroids and beta blockers.
- Patients of diabetes mellitus [21]
- Not willing for study.
- Patients with concomitant thyroid disease diagnosed by raised TSH and decreased FT4 levels [19]
- Patients taking iodine containing drugs

Methods

Evaluation for thyroid dysfunction based on a clinical scoring system [4]

		clinical score	
Symptoms	**On the basis of**	**Present**	**absent**
Diminished sweating	Sweating in the warm room or a hot sunny day	1	0
Hoarseness	Speaking or singing voice	1	0
Paresthesia	Subjective sensation	1	0
Dry Skin	Dryness of skin noticed spontaneously, requiring treatment	1	0
Constipation	Bowel habit, use of a laxative	1	0
Impairment Of Hearing	Progressive impairment of hearing	1	0
Weight Gain	Recorded wt. increase, tight of clothes	1	0
Physical signs	**On the basis of**		0
Slow Movements	Observe pt removing his clothes	1	0
Delayed Ankle Reflex	Observe the relaxation of the reflex	1	0
Coarse Skin	Examine hands, forearms, elbow, for roughness and thickening of skin	1	0
Periorbital Puffiness	This should obscure the curve of the malar bone	1	0
Cold Skin	Compare the temp. of hands with that of examiner	1	0
Sum of all symptoms & signs		12	0

Hypothyroid=> 5 points, euthyroid = < 3 points, intermediate=3-5

Other signs of thyroid dysfunction:

- Palpitations
- Arrhythmias
- Loss of wt.
- Increased appetite
- Tremors
- Eye signs: proptosis, difficulty in accommodation, decreased blinking etc.
- Goiter

INVESTIGATIONS

- CBC
- Liver function tests
- SGPT
- Serum bilirubin
- Renal function tests
- Serum creatinine
- BUN
- Urine R/M
- Spot urine estimation for proteinuria
- 24 hr urine protein

GFR as a measure of renal function and stage of CKD was calculated by using the abbreviated modification of diet in renal disease (MDRD) study equation with the help of GFR calculator available at www.mdrd.com given by:

GFR=186.3× (serum creatinine in mg/dl) $^{-1.154}$×age in yrs$^{-0.203}$
Multiply by 0.742 for women.

- Blood sugar fasting & postprandial
- Serum electrolytes
- USG whole abdomen
- USG thyroid
- Renal biopsy
- SERUM THYROID PROFILE which includes:
- Total & free T4 levels using competitive chemi luminescent immune assay.
- Total & free T3 levels using competitive chemi luminescent immune assay.
- TSH using ultra sensitive sandwich chemi luminescent immune assay

OBSERVATION

Table 1. Distribution of cases and controls in the present study

Cases/controls	Number
GFR <15 (severe CKD)	22
GFR 15–59 (moderate CKD)	16
GFR >60 (mild CKD)	04
Controls	40

In this study a total of 82 cases were taken, 42 of them were cases of chronic kidney disease which were divided in 3 subgroups on the basis of GFR. 40 age and sex matched subjects were taken as controls.

Table 2. Distribution of Cases as Per Etiology

Etiology	Number of cases	%
Hypertensive glomerulosclerosis	20	47.6
Chronic glomerulonephritis	13	31.0
Chronic pyelonephritis	2	4.8
Obstructive uropathy	5	11.9
Polycystic kidney disease	1	2.4

In the present study on 42 patients , 20 patients had hypertensive glomerulosclerosis as the cause of CKD and these constitute highest number of cases (47.6%), chronic glomerulonephritis constitute second largest no. of cases (31%). 4.8% and 11.9% of cases were of Chronic pyelonephritis and Obstructive uropathy, respectively. Only one case was of polycystic kidney disease.

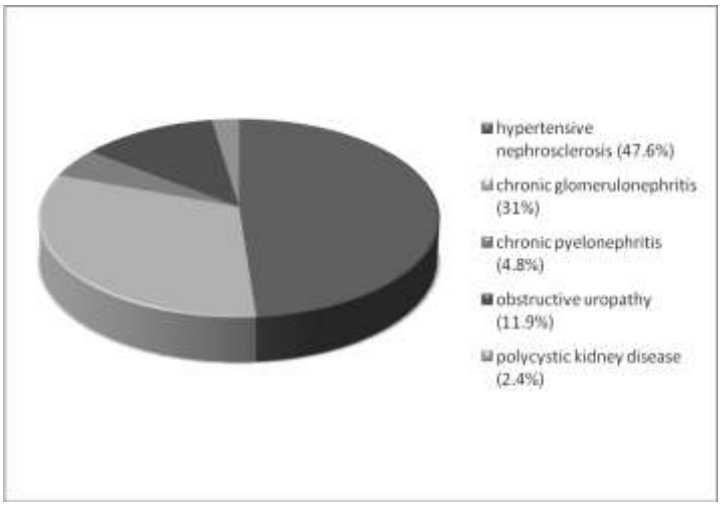

Fig-1. graph representimg distribution of cases as per etiology

Table 3. Comparison of total T3 levels in subgroups of cases and controls.

Subjects under study	number	Mean TT3 ± SD (ng/dl)	t score b/w controls and cases	P value b/w controls and cases
Controls	40	136.85 ± 22.53834	NA	NA
mild CKD	04	130.75 ± 16.0494	0.696	> .05
Moderate CKD	16	103.625 ± 24.31975	5.3	< .001
Severe CKD	19	72.1578947 ± 20.07835528	10.99	< .0001
Total (CKD)	39	91.07692 ± 29.25243	7.78	< .0001

On comparing TT3 levels between cases and controls and analyzing the data statistically, it was found that the study is significant when controls are compared with moderate and severe CKD patients. P value = > .05 between controls and mild CKD pts while it was < .001 and < .0001, respectively, when moderate and severe CKD patients were compared. On comparing controls with total cases, p value = < 0.0001 which is highly significant

Table 4. Comparison of total T4 levels in subgroups of cases and controls

Subjects under study	number	Mean TT4 ± SD (µg/dl)	t score b/w controls and cases	P value b/w controls and cases
Controls	40	6.705 ± 1.815935	NA	NA
mild CKD	04	6.05 ± 0.506623	1.72	> .05
Moderate CKD	16	5.693125 ± 1.429316	2.21	< .05
Severe CKD	19	4.432105 ± 1.416755	5.22	< .0001
Total (CKD)	39	5.115385 ± 1.497795	1.956	> .05

On comparing TT4 levels between cases and controls and analyzing the data statistically, it was found that the study was significant when controls were compared with moderate and severe CKD patients. P value = > **.05** between controls and mild CKD pts while it was **< .05** and **< .0001,** respectively, when moderate and severe CKD patients were compared. On comparing controls with total cases, p values -> **0.05** which is not significant.

Table 5. Comparison of TSH levels in subgroups of cases and controls

.Subjects under study	number	Mean TSH ± SD (µIU/ml)	t score b/w controls and cases	P value b/w controls and cases
Controls	40	2.7605 ± 1.018219		NA
mild CKD	04	4± 1.498888	1.61	> .05
Moderate CKD	16	3.2775 ± 2.422226	0.82	> .05
Severe CKD	19	2.894211 ± 1.360291	0.38	> .05
Total (CKD)	39	3.164872 ± 1.866882	1.19	> .05

On comparing TSH levels between cases and controls and analyzing the data statistically, it was found that the study was no significant when controls were compared with mild, moderate and severe CKD patients. P value = **> .05** between controls and all CKD pts.

Table 6. Comparison of FT3 levels in subgroups of cases and controls.

Subjects under study	number	Mean FT3 ± SD (pg/ml)	t score b/w controls and cases	P value b/w controls and cases
Controls	40	2.69525 ± 0.705949	NA	NA
mild CKD	04	3.005 ± 0.59411	0.98	> .05
Moderate CKD	16	1.790588 ± 0.438954	5.864	< .0001
Severe CKD	19	1.585789 ± 0.207239	9.146	< .0001
Total (CKD)	39	1.846667 ± 0.51295	8.63	< .0001

On comparing FT3 levels between cases and controls and analyzing the data statistically, it was found that the study is significant when controls are compared with moderate and severe CKD patients. P value = **> .05** between controls and mild CKD pts while it was **< 0.0001**, when moderate and severe CKD patients were compared. On comparing controls with total cases, p value = **< 0.0001** which is highly significant.

Table 7. Comparison of FT4 levels in subgroups of cases and controls.

Subjects under study	number	Mean FT4 ± SD (ng/dl)	t score b/w controls and cases	P value b/w controls and cases
Controls	40	1.27525 ± 0.256575	NA	NA
mild CKD	04	1.375 ± 0.328786	0.587	> .05
Moderate CKD	16	1.175 ± 0.149041	1.45	> .05
Severe CKD	19	1.17 ± 0.232666	1.57	> .05
Total (CKD)	39	1.185897 ± 0.224085	1.622	> .05

On comparing FT4 levels between cases and controls and analyzing the data statistically, it was found that the study was not significant when controls were compared with mild, moderate and severe CKD patients. P value = **> .05** between controls and all CKD pts.

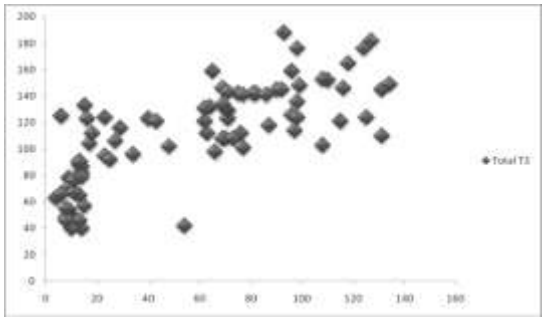

Fig- 2: Correlation of GFR and total T3 levels

X axis = GFR (ml/min/1.73m$^{2)}$

Y axis = total T3 levels (ng/dl)

r = 0.756115863

For correlation between GFR levels and total T3 levels scatter diagram was used which showed greater decline in TT3 levels as GFR falls below 20. On analyzing the data statistically, **correlation coefficient** (r) = 0.756115863 which shows a significant positive correlation

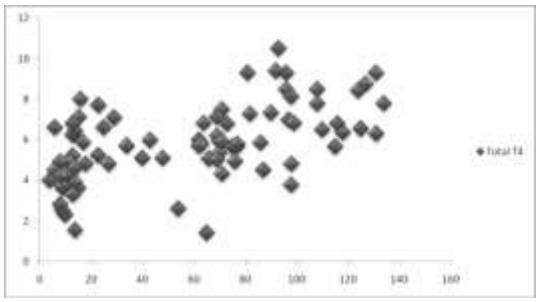

Fig-3. Correlation of GFR and total T4 levels

X axis = GFR (ml/min/1.73m$^{2)}$
Y axis = total T4 levels (µg/dl)
r = 0.559919

For correlation between GFR levels and total T4 levels scatter diagram was used which showed greater decline in TT4 levels as GFR falls below 20. On analyzing the data statistically **correlation coefficient (r)** = 0.559919 which does not show a significant correlation

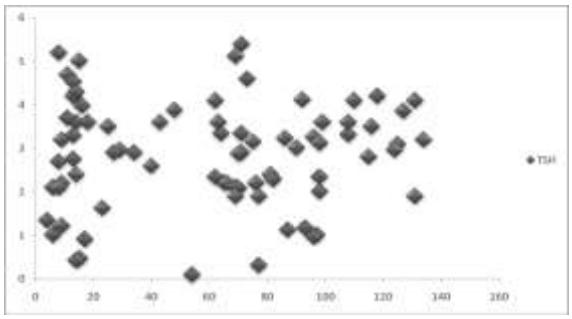

Fig-4: Correlation of GFR and TSH levels

X axis= GFR (ml/min/1.73m$^{2)}$
Y axis= TSH (µIU/ml)
R= 0.045032

For correlation between GFR levels and total TSH levels scatter diagram was used which showed no decline in TSH levels as GFR falls. On analyzing the data statistically **correlation coefficient (r)** = **0.045032** which does not show any correlation.

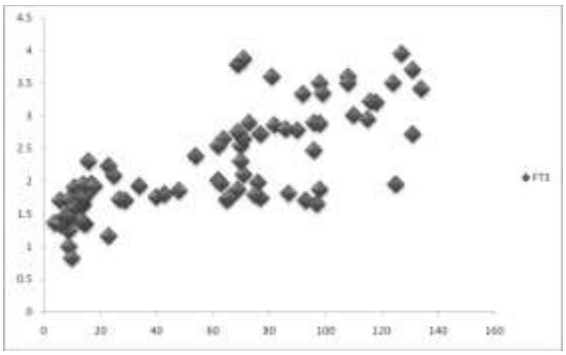

Fig-5:Correlation of GFR and free T3 levels

X axis = GFR (ml/min/1.73m$^{2)}$
Y axis = FT3 (pg/ml)
r = 0.760881

For correlation between GFR levels and free T3 levels scatter diagram was used which showed greater decline in FT3 levels as GFR falls below 20. On analyzing the data statistically **correlation coefficient (r)** = **0.760881** which shows a significant positive correlation.

Table 8. Clinical features suggestive of thyroid dysfunction in pts of CKD

Clinical score for hypothyroidism	Number (%)			
	GFR < 15	**GFR 15 - 59**	**GFR > 60**	**Total**
> 5	6(100)	0(0)	0(0)	06
3 to 5	8(61.5)	5(38.5)	0(0)	13
< 3	8(34.8)	11(47.83)	4(17.39)	23
total	22	16	4	42

Clinical scoring of the pts was done on the basis of scoring criteria[4]. Hypothyroid=> 5 points, euthyroid = < 3 points, intermediate=3-5.

As is clear from the table 8, most of the clinical features suggestive of hypothyroidism were present in pts with GFR < 15. On applying chi square test to test the significance of this observation, **chi square value = 4.8655** and the **p value = > 0.05**. Thus, the apparent signs of hypothyroidism in stage 5 CKD had no significance.

Table 9: Incidence of true hypothyroidism

subjects	Number of hypothyroid pts	%
Controls	0	0
Mild CKD	0	0
Moderate CKD	0	0
Severe CKD	3	14.3

Hypothyroidism was diagnosed based on clinical features and decreased FT4 and raised TSH levels[19] . The incidence of true hypothyroidism is thus high in stage V CKD. But as the total number of cases was very few, a larger study is needed to prove the point.

CONCLUSION

From the study it was concluded that thyroid dysfunction occurs commonly in patients of CKD although it is uncommon in earlier stages but becomes progressively more common as disease advances. There is also an increased prevalence of signs and symptoms mimicking hypothyroidism in advanced CKD along with increased true prevalence of the disease. Most common cause of CKD among cases was hypertensive glomerulosclerosis followed by chronic glomerulonephritis and obstructive uropathy. A linear decline in TT3 levels was seen when linear correlation was tested between GFR and TT3 levels. Correlation coefficient of 0.756115863 was seen. When linear correlation between GFR and FT3 was tested a significant correlation ($r = 0.760881$) was found. There was no significant decline in TT3 and FT3 levels in mild CKD pts with GFR > 60ml/min/1.73m^2.

Thus, TT3 and FT3 levels tend to fall at GFR levels below 60 supporting earlier studies[7,9]. When controls were compared with mild CKD cases, no significant decline in TT4 levels was found but when compared with moderate and severe CKD cases the difference of TT4 had p values < 0.05 & < 0.0001 respectively. This might be due to inhibitors of T4 binding [8]. A linear correlation between TT4 levels not found across all stages of CKD. A reduced level of TT4 as compared to TT3 and FT3 is a more specific indicator of severe CKD as the levels of TT4 fall very significantly in stage 5 CKD. Contrary to FT3, levels of FT4 remained normal through all the stages of CKD, p value was > 0.05 when controls were compared with mild, moderate and severe CKD pts. When TSH levels were compared between controls and cases, no significant alteration in TSH levels was found in any stage of CKD. TSH levels remain normal throughout the course of CKD. This is in accordance with earlier study [3]. There was an increased incidence of signs and symptoms simulating hypothyroid state in pts of severe CKD but this does not signify that they always have primary hypothyroidism. Incidence of hypothyroidism in CKD pts was 14.3% compared to 0% in controls and all hypothyroid pts were in severe CKD group and had markedly elevated TSH and diminished

FT4 levels. Thus, as suggested in earlier work only TSH and FT4 levels can be relied upon to diagnose and treat primary hypothyroidism as rest other tests are also altered in euthyroid CKD pts [7]. There was no incidence of goiter, hyperthyroidism or thyroid nodules in CKD pts. There was no correlation seen between the stages of CKD and age, gender and body weight of the subjects. There was no effect of etiology of CKD on the thyroid function tests in pts of CKD.

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