

COMPARATIVE STUDY OF THYROID ABNORMALITIES WITH SEVERITY OF CHRONIC RENAL FAILUREMohammed Shamsuddin¹, Makandar Asmabi²**HOW TO CITE THIS ARTICLE:**

Mohammed Shamsuddin, Makandar Asmabi. "Comparative Study of Thyroid Abnormalities with Severity of Chronic Renal Failure". Journal of Evolution of Medical and Dental Sciences 2015; Vol. 4, Issue 80, October 05; Page: 14039-14047, DOI: 10.14260/jemds/2015/1997

ABSTRACT: BACKGROUND: Patients with CRF often have signs & symptoms suggestive of thyroid dysfunctions. Prevalence of hypothyroidism in patients with terminal renal failure is 5%, in comparison with that in hospitalized patients with normal renal function. CKD is associated with higher prevalence of hypothyroidism, both overt and subclinical, but not with hyperthyroidism. In fact, the prevalence of primary hypothyroidism is mainly in the subclinical form, which increases as GFR decreases. **OBJECTIVES:** To estimate thyroid hormone levels i.e. T₃, T₄ & TSH in CRF. To estimate Serum urea & creatinine for selection and categorizing the study subjects in to different grades of CRF. To study the thyroid hormone levels and thyroid abnormalities as the severity of CRF increases. **MATERIALS AND METHODS:** In this study 30 male patients of aged between 40-70yrs. with serum creatinine >5.5mg/dl & urea >55mg/dl and dipstick test positive for protein with symptoms of chronic renal failure are taken as cases. Age and sex matched normal healthy individuals are taken as controls. Serum Urea Estimated by DAM Method, serum creatinine is estimated by Jaffe's method and Serum levels of T₃, T₄ & TSH were analysed by using CLIA method. **Results:** T₃, T₄ decreases and TSH increases significantly in cases compare to the controls as the severity of CRF increases. In our study 10% of patients of CRF are hypothyroid and all these hypothyroid patients belongs to serum creatinine above 6 mg/dl category. **CONCLUSION:** Mean of T₃, T₄ decreases TSH increases significantly in cases compare to controls as the severity of CRF increases. The risk of hypothyroidism in chronic renal failure is very high if serum creatinine level are above 6 mg/dl.

KEYWORDS: Chronic renal failure, Hypothyroidism, Hyperthyroidism, Thyroid Stimulating Hormone (TSH).

INTRODUCTION: Chronic renal failure (CRF) is an irreversible deterioration of renal function, which results from diminished effective functioning renal tissue. Ensuing impairment of excretory, metabolic and endocrine functions of the kidney leads to development of clinical syndrome of uremia. CRF is accompanied by anemia, malnutrition impaired metabolism of lipids, carbohydrates and proteins & defective utilization of energy. With advancing renal disease, clear disturbances in electrolytes and endocrine functions takes place.

Thyroid hormones in the blood are almost entirely bound to plasma proteins. They are bound to a globulin named thyroid binding globulin (TBG), thyroxine binding prealbumin and albumin. Affinity of thyroxine is maximum for thyroid binding globulin and hence TBG is the major determinant of binding. Affinity for T₃ and T₄ are slightly different because T₃ is not bound significantly by thyroxine binding prealbumin and binds to TBG less firmly than T₄. The levels of free T₃ are 8 to 10 times more than T₄. As only the free hormone is available to tissues, metabolic state correlates closely with the concentration of free thyroxine.

ORIGINAL ARTICLE

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.^{1,2}

Serum hormonal concentration may be altered by changes in the binding capacity of serum proteins. In CRF there is massive proteinuria mainly albuminuria. Globulin levels are not much altered. Hypothyroidism in CRF is mainly due to decreased level of albumin & thyroid binding pre-albumin.³

In CRF Circulating thyroid binding inhibitors are increased, which inhibits the binding of thyroid hormones to carrier proteins, it may be additional cause for hypothyroidism.⁴

In CRF hypothyroidism is observed but still many patients are euthyroid with normal T₃, T₄ and TSH, the chances of developing hypothyroidism is increases as severity of the disease increases.

MATERIALS AND METHODS:

Source of Data: The present study was undertaken in Al-Ameen medical college and hospital both in patients & outpatients and patients attending to dialysis unit.

Inclusion Criteria: The study subjects are divided in to 2 groups as cases & controls.

Cases: 30 Male patients aged between 40-70 years of having history of chronic kidney disease with serum creatinine >5.5mg/dl and urea >55mg/dl and dipstick test positive for protein with symptoms of chronic renal failure.

Controls: 30 Healthy men aged between 40 -70 years.

Exclusion Criteria: Patients with diabetic nephropathy, patients on treatment with estrogen, corticosteroids, Sulphonylurea, Phenobarbitones & β -blocker, Female & children's are excluded from the study.

Data Collection: All the subjects i.e. both cases & controls were subjected to medical examination as per a fixed proforma.

Biochemical Tests: -Morning sample blood was drawn after 12 hrs. Fasting. The samples of blood were allowed to stand to clot. Serum was separated by centrifugation, and analyzed by the following methods.

Serum Urea Estimation by Diacetyl Monoxide Method (DAM, Method)

Principal: Urea reacts with diacetyl monoxide in presence of thiosemicarbizide, under acid conditions to form a coloured compound which is estimated calorimetrically at 520nm.

Estimation of Serum Creatinine by Jaffe's method.

Principle: Creatinine in alkaline medium reacts with picric acid to form a red tautomer of creatinine picrate, the intensity of which is measured by colorimeter at 520nm.

Estimation of T₃, T₄ & TSH by Chemiluminescence immunoassay (CLIA)

Estimation of T₃ & T₄: The principle & procedure for estimation of T₃ & T₄ are similar

ORIGINAL ARTICLE

Principle: (Competition principle). The T₃, T₄ assay employs a competitive test principle with polyclonal antibodies specially directed against T₃, T₄. Endogenous T₃, T₄ released by the action of 8 anilino-1-naphthalene sulphonic Acid (ANS), competes with the added biotinylated T₃, T₄ derivate for the binding sites on the antibodies labeled with the ruthenium complex.

Estimation of TSH:

Principle: (Sandwich principle) The TSH assay employs monoclonal antibody specifically directed against human TSH. The antibodies labeled with ruthenium complex consist of chimeric construct from human & mouse specific components. As a result, interfering effects due to HAMA (Human anti-mouse antibodies) are largely eliminated.

RESULTS:

Study Design: A case control study with 30 controls and 30 cases is undertaken to study the thyroid hormone levels and thyroid disorders with severity of chronic renal failure.

Study variables	Cases	Controls	P value
Blood urea (mg/dl)	96.23±12.24	28.47±8.40	<0.001**
S. creatinine (mg/dl)	5.83±0.69	1.09±0.17	<0.001**
T ₃	81.67±15.07	111.96±10.17	<0.001**
T ₄	5.80±0.50	8.36±0.46	<0.001**
TSH	4.81±0.38	3.02±0.79	<0.001**

Table 1: Comparison of study parameters in cases and controls (mean ±SD)

Comparison of study parameters in cases and controls is shown in table 1. Mean of blood urea among cases is 96.23±12.24 and in controls is 28.47±8.40 p value is <0.001 which is statistically significant.

Mean of Sr. creatinine in cases is 5.83±0.69 and in controls is 1.09±0.17 (mg/dl). P value is <0.001 which is statistically significant. Mean of T₃ among all 30 cases is 81.67±15.07 and in 30 controls is 111.96±10.17 (ng/dl). It means T₃ is decreases in cases compares to controls. P value is <0.001 which is statistically significant. Mean of T₄ also decreases in cases compare to controls. P value is <0.001 which is statistically significant. Mean of TSH in cases increases compare to controls. P value is <0.001 which is statistically significant.

Pair	Correlation	P value
Sr. creatinine vs T ₃	-0.791	<0.001**
Sr. creatinine vs T ₄	-0.631	<0.001**
Sr. creatinine vs TSH	0.479	<0.001**

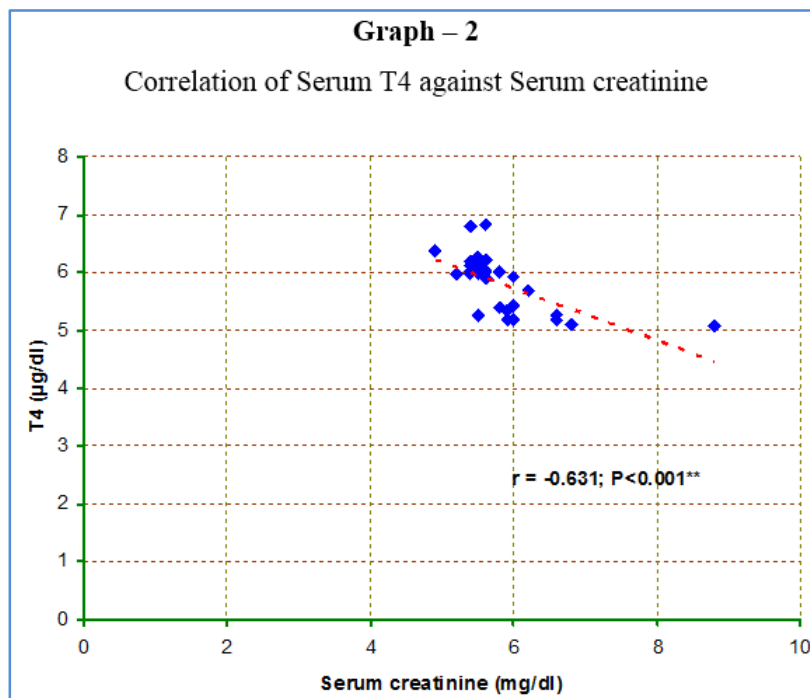
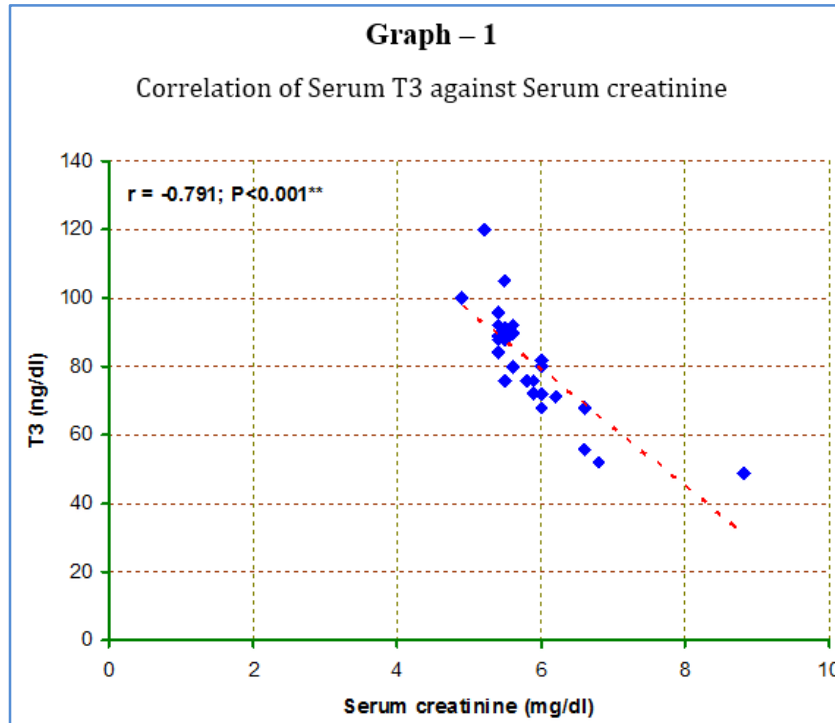
Table 2: Pearson correlation of Serum creatinine and thyroid hormones

Pearson correlation of Serum creatinine and thyroid hormones are shown in table 2 and graphically represented in graph 1, graph 2 and graph 3.

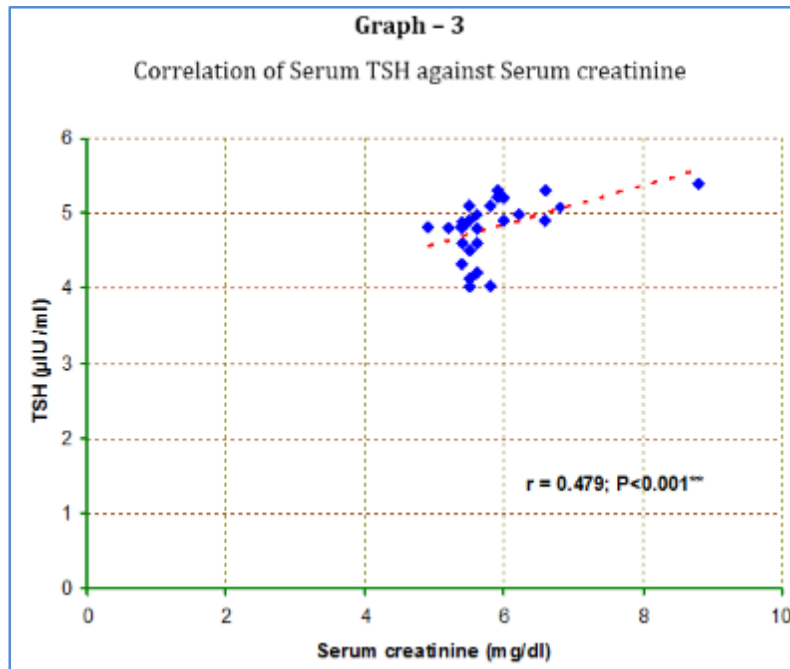
The levels of T₃, T₄ decreases and TSH increases as severity renal failure increases (i.e. Sr. creatinine levels increases, which is a marker for severity of renal failure). Even though the graph

ORIGINAL ARTICLE

thyroid hormones (T₃, T₄&TSH) levels against Sr. creatinine is not linear. P value is <0.001 which is statistically significant.

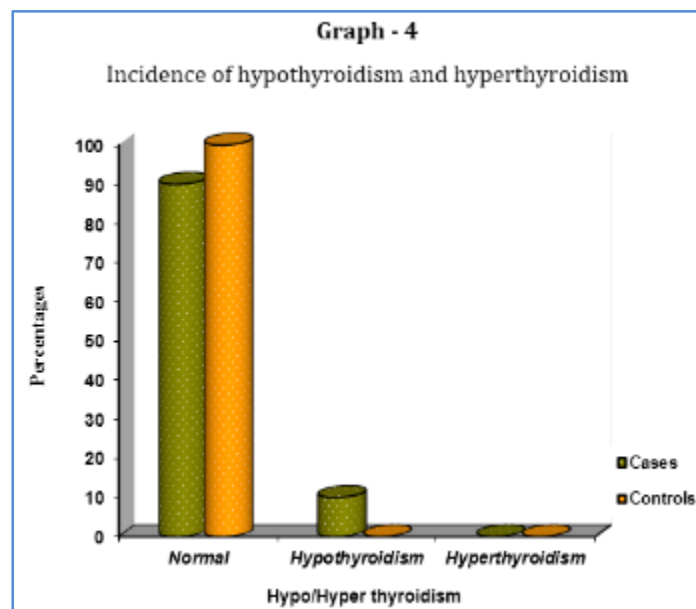


ORIGINAL ARTICLE



Hypo/Hyper Thyroidism	Cases	Controls
Normal	27(90.0%)	30(100.0%)
Hypothyroidism	3(10.0%)	0
Hyperthyroidism	0	0
Total	30(100.0%)	30(100.0%)

Table 3: Incidence of hypothyroidism and hyperthyroidism



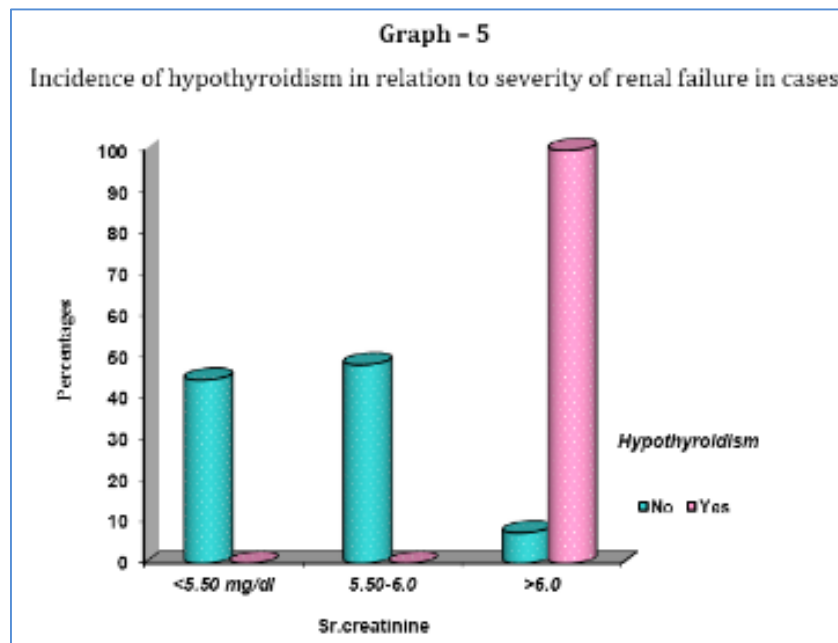
ORIGINAL ARTICLE

Incidence of hypothyroidism and hyperthyroidism are shown in table 3 and graphically represented in graph 4.

The incidence of hypothyroidism is 10% in renal failure cases when compared to controls. P value is 0.237 which is positive correlation between CRF and hypothyroidism. There is no hyperthyroidism found in both cases and controls.

Serum creatinine	Hypothyroidism	
	No	Yes
<5.50 mg/dl	12(44.4%)	0
5.50-6.0	13(48.1%)	0
>6.0	2(7.4%)	3(100.0%)
Total	27(100.0%)	3(100.0%)

Table 4: Incidence of hypothyroidism in relation to severity of renal failure in cases



Incidence of hypothyroidism in relation to severity of renal failure in cases are shown in table 4 and graphically represented in graph 5. Incidence of hypothyroidism is significantly associated with Sr. creatinine >6.0mg/dl with p=0.002. Which is statistically significant.

DISCUSSIONS: A study of thyroid dysfunctions in chronic renal failure is done with 30 cases and 30 controls. Cases and control subjects are selected according to inclusion and exclusion criteria which are mentioned earlier. The cases and controls include different age groups. Among cases 6 patients are in age group 44-49 yrs., 9 patients are in age group 50-54 yrs., 8 patients are in age group 55-59 yrs. and 7 patients are ≥60 yrs. Control subjects are selected almost equal age distribution for comparison of study parameters. Only male subjects are selected as cases and controls for the study.

ORIGINAL ARTICLE

Mean of blood urea levels in cases are 96.23 ± 12.24 mg/dl and in controls are 28.47 ± 8.40 mg/dl. The mean of serum creatinine in cases are 5.83 ± 0.69 mg/dl and in controls are 1.07 ± 0.17 mg/dl. The mean of blood urea and serum creatinine is high when compared to the controls. All patients in cases are positive for frank proteinuria by urine dip stick test.

The mean of T_3 in all 30 cases is decreased when compared to controls. In this study the findings are comparable with the previous study.^{5,6,7,8,9,10} showing decreased levels of T_3 in uremic and hemodialysis patients. This reduction in T_3 concentration has been linked to the decrease in the peripheral synthesis of T_3 from T_4 .^{11,12,13} The mean of T_4 in all 30 cases is decreased when compared to the controls. The findings are comparable with previous study.^{14,15,16,17} 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 CRF. Serum albumin and thyroid binding pre-albumin decreases¹⁷. Decrease in T_4 is also attributed to the presence of circulating inhibitors, which impairs binding of T_4 to thyroxine binding globulin.¹⁸

Mean TSH in cases is 4.81 ± 0.38 μ IU/ml which is high compare to controls of having 3.02 ± 0.79 μ IU/ml. Patients with low T_3 , T_4 and free T_4 showed high TSH suggesting maintenance of pituitary thyroid axis.^{1,19} Studies conducted by G. Avasthi-et. al,²⁰ Joseph et. al,²¹ shows increased TSH in those patients who had low T_3 , T_4 & FT₄ suggesting maintenance of pituitary thyroid axis. Which is similar to this study.

In our study the levels of T_3 , T_4 decreases and TSH increases as severity renal failure increases (i.e. Sr. creatinine levels increases) Even though the graph plotted thyroid hormone (T_3 , T_4 & TSH) levels against Sr. creatinine is not linear. The present study findings are comparable with Mehta H. J et. al.²⁰ Mean TT₃ & TT₄ & FT₃ levels reduced as the severity of renal damage increased. When the individual values plotted against their respective Sr. creatinine levels, no linear correlation was observed between those parameters.

The thyroid function studies on patients with CRF before & after hemodialysis resulted in only slight increase in TT₃ concentration without significant change in other thyroid function.¹² Study conducted by Mehta H. J et. al,²⁰ thyroid function in uremic patients with conservative management & with regular dialysis they found that there is no change in thyroid profile except decrease in TSH in hemodialysates compare to normals. Restoration of renal function with renal transplant resulted in normalisation of all parameters of thyroid function with exception of blunted or absent TSH response to TRH. The latter may be a direct consequence of glucocorticoid administration.^{12,19,22,23}

In this study 3 patients (i.e. 10% of cases) among 30 cases have T_3 , T_4 levels below normal range and TSH above the normal range. These 3 patients are hypothyroid, compared to none among control groups and all these 3 patients (i.e. 100%) belongs to serum creatinine >6mg/dl category. In this study 5 cases among 30 cases have serum creatinine of >6mg/dl. Among them 3 patients are hypothyroid (i.e. 60%) and 2 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.²⁴ CKD is associated with higher prevalence of hypothyroidism, both overt and subclinical, but not with hyperthyroidism.^{25,26,27} In fact, the prevalence of primary hypothyroidism is mainly in the subclinical form, which increases as GFR decreases.²⁸

CONCLUSION: In our study Mean of T_3 , T_4 decreases TSH increases significantly in cases compare to controls. The levels of T_3 , T_4 decreases and TSH increases as severity renal failure increases. The risk

ORIGINAL ARTICLE

of hypothyroidism in chronic renal failure is very high if serum creatinine level are above 6mg/dl. In our study 10% of patients of CRF i.e. cases are hypothyroid compare to 0% in controls and all these hypothyroid patients belongs to serum creatinine above 6mg/dl category.

REFERENCES:

1. Yashpal et al. Thyroid function in uremia. *Ind J Nephrol (New Series)* 1991: 1; 2 vol. 1, no. 2. April June, 1991.
2. Spector DA, Davis PJ, Helderman JH et al. Thyroid function and metabolic state in chronic renal failure. *Ann Int Med* 1976: 85; 724-30.
3. K Neuhaus, G Baumann, A Walter and H Tholen Serum thyroxine and thyroid binding proteins chronic renal failure. *J of Clinical endocrinology and metabolism*, 1975: 41; 395-398.
4. Nephrology division. Dept of Internal Medicine, University Iowa, Iowa city, IA, USA. Thyroid function in patients with chronic renal failure. *Amj kidney dis*, Oct, 2001: 38, 4 (supp 1): 580-4 links.
5. Pasqualini T, Zantelifer D et al. Evidence of hypothalamic pituitary thyroid abnormalities in children with end stage kidney disease. 1991: 118; 873.
6. Ramirez G, O Neill WM, Jubiz w, Bloomer HA. Thyroid dysfunction in uremia; Evidence with thyroid and hypophyseal abnormalities. *Ann Int Med* 1976: 84; 672.
7. Spector DA, Davis PJ, Helderman JH et al: Thyroid dysfunction and metabolic state in chronic renal failure. *Ann Int. Med* 1976: 85; 724.
8. Desanto NG, Fine RN, Carela C et al: Thyroid function in uremic children. *Kidney Int* 1985: 28; 5166.
9. Forest J, Dubey J, Talbot J: Thyroid hormone in patients with chronic renal failure undergoing maintenance hemodialysis. *Amj Clin Pathol* 1982: 77; 580.
10. Wheatly T, Clark PM, Clark DJ. et al. Abnormalities in thyrotrophin(TSH) evening raise and pulsatile release in hemodialysis, *Clin Endocrinol* 1989: 31; 39.
11. Lim VS. Thyroid functions in patients with chronic renal failure. *American Journal of kidney disease* 2001: 38; 580-84.
12. Lim VS, Fang VS, Katz AI. Thyroid function in chronic renal disease. *Journal of clinical investigation* 1977: 60; 522-34.
13. Lo JC, Chertow GM, Go AS and Hsu CY. Increased prevalence of subclinical and clinical hypothyroidism in persons with chronic kidney disease. *Kidney international* 2005: 67; 1047-52.
14. Silverberg DS, RA Ulan, DM Faweett, 1973. Effects of chronic hemodialysis on thyroid function in chronic renal fsailure. *Can Med Asso J* 109; 282-86.
15. Jasso AI, PC Murray, J Parkin, MR Robertson 1974, Abnormalities of in vitro thyroid function tests in renal failure. *QJ Med* 43; 245-61.
16. Spector DA, PJ Davis, JH Helderman, RD Utiger 1976. Thyroid function and metabolic state in chronic renal failure. *Ann Med* 85; 724-30.
17. K Neuhaus, G Baumann, A Walter and H Tholen Serum thyroxine and thyroid binding proteins chronic renal failure. *J of Clinical endocrinology and metabolism*, 1975: 41; 395-398.
18. Nephrology division. Dept of Internal Medicine, University Iowa, Iowa city, IA, USA. Thyroid function in patients with chronic renal failure. *Amj kidney dis*, Oct, 2001: 38, 4 (supp 1): 580-4 links.

ORIGINAL ARTICLE

19. Kohli HJ, Mahajan SK Karla OP. Malhotra KC. Thyroid status in chronic renal failure. Indian J Nephrology.1993: vol 3(2); 32-36.
20. G Avasthi, S Malhotra, APS Narang, S Sengupta. Study of thyroid function on patients of chronic renal failure. Indian J Nephro, 2001: 11; 165-169.
21. Joseph L.J, Desai K.B, Mehta H.J, Mehta M.N et al. Measurement of thyrotrophin levels using sensitive immunoradiometric assays in patients with chronic renal failure. Thyroidology 1993: 5; 35-39.
22. Mehta HJ et al. Total free thyroid hormone levels in chronic renal failure. Journal postgraduate Medicine. 1991: vol 37; issue 2, 79-83.
23. Tietz, Fundamentals of Clinical Chemistry 5th edtn 708, 843-845.
24. Quion-Verde H, Kaptein EM, Choolijan CJ, Radriquez HJ, Massary SG, Prevalence of thyroid disease in chronic renal failure(CRF) and dialysis patients. Los Angeles: 9th Int Congr of Nephrol Abstract 1984: 120.
25. Kaptein EM, Quion-Verde H, Chooljian CJ. Tang WW. The thyroid in end stage renal disease. Medicine 1988: 67; 187-97.
26. Kaptein EM, Thyroid hormone metabolism and thyroid disease in chronic renal failure. Endocrine reviews 1996: 17; 45-63.
27. Kutty S, Atli T, Kosiogullari O, Duman N, Gullu S, Thyroid disorders in haemodialysis patients in iodine deficient community.2005: 29; 329-32.
28. Lo JC, Chertow GM, Go AS and Hsu CY. Increased prevalence of subclinical and clinical hypothyroidism in persons with chronic kidney disease. Kidney international 2005: 67; 1047-52.

AUTHORS:

1. Mohammed Shamsuddin
2. Makandar Asmabi

PARTICULARS OF CONTRIBUTORS:

1. Associate Professor, Department of Bio-Chemistry, Chamarajanagar Institute of Medical Sciences, Chamarajnagar, Karnataka.
2. Assistant Professor, Department of Bio-Chemistry, Al- Ameen Medical College, Vijapur, Karnataka.

FINANCIAL OR OTHER

COMPETING INTERESTS: None

NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Mohammed Shamsuddin,
Associate Professor,
Department of Bio-Chemistry,
Chamarajanagar Institute of Medical Sciences,
District Hospital Campus,
B. Rachaiah Double Road,
Chamrajnagara-571313.
Karnataka.
E-mail: drshamsuddin@yahoo.com

Date of Submission: 08/09/2015.
Date of Peer Review: 09/09/2015.
Date of Acceptance: 28/09/2015.
Date of Publishing: 05/10/2015.