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Assessment of Thyroid Function Status in Patients with Chronic Kidney Disease: A Prospective Study

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Abstract
Background and Objectives:
Chronic Kidney Disease is a worldwide health problem with an increasing incidence and prevalence. Abnormalities in the structure and function of the thyroid gland and in the metabolism and plasma concentration of thyroid hormones are common in patients with Chronic Kidney Disease. In view of variability of thyroid function tests in patients with CKD in previous studies, a prospective study of various thyroid functions is undertaken to establish a correlation if any between thyroid dysfunction and severity of renal diseases.
Method:
Total number of 40 patients with Chronic Kidney Disease on conservative management who were admitted to Basaveshwar Teaching & General Hospital attached to Mahadevappa Rampure Medical College, Gulbarga during the period between November 2016 – May 2018 were selected in this prospective study.
Results*:*
Out of the 40 patients with CKD 19 patients had low T_3 syndrome (0.2-2ng/ml, mean 0.679) which accounts for 47.5% of the patients, 12 patients had low T_4 syndrome (0.4-8.9µg/ml, mean 5.58) which accounts for 30% of the patients and 5 patients had primary hypothyroidism TSH >20µIU/ml. Excluding Primary Hypothyroidism, analysis of serum T_3,T_4 and TSH in the study subjects shows very high significance $\chi^2 = 31.77$, $p < 0.001$. Distribution of Thyroid Dysfunction in this study among various creatinine clearance levels showed that as glomerular filtration rate declines, number of patients with low T_3 syndrome increased $\chi^2 = 0.163$, $p < 0.05$, significant difference. In patients with low T_3 syndrome, the mean values of TSH in various stages of renal disease are within normal range mean 4.85, values of TSH did not show any linear correlation with GFR. Number of patients with low T_4 syndrome did not correlate with severity of renal disease.
Conclusion:
Thyroid Dysfunction occurred in 60% of the patients with chronic kidney disease in our study, it does not indicate a state of hypothyroidism, but a reflection of the state of chronic illness/malnutrition. The low T_3 state of CKD can be viewed as being protective, promoting conservation of protein. The number of patients with low T_3 syndrome progressively increase with the severity of renal failure.
Key Words*: Thyroid dysfunction; chronic kidney disease; low T_3 syndrome*

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I. Introduction

Chronic kidney disease (CKD) encompasses a spectrum of different pathophysiologic processes associated with abnormal kidney function and a progressive decline in glomerular filtration rate (GFR)[1,2,3].

Chronic kidney disease (CKD) is a clinical syndrome due to irreversible renal dysfunction leading to excretory, metabolic and synthetic failure culminating into accumulation of non-protein nitrogenous substances and present with various clinical manifestations.

End stage renal disease is described as a terminal stage of chronic kidney disease that without replacement therapy would result in death. Despite various etiologies, CKD is the final common pathway of irreversible destruction of nephrons ultimately resulting in alteration of 'Milieu interior' that affects every system in the body. One such system in the body is thyroid hormonal system. Kidney is closely related to thyroid in the fact that it is the only other organ that competes with iodide clearance.

Patients with CKD have many signs and symptoms suggestive of thyroid dysfunction like sallow complexion, edema, dry skin, cold intolerance, decreased BMR, asthenia and hyporeflexia. So in cases of CKD, it is difficult to exclude thyroid dysfunction on mere clinical background.

Various studies have been conducted on thyroid function in CKD patients. Since the beginning, the results were inconsistent. Hyperthyroidism, hypothyroidism and euthyroidism all have been reported.

The relation between thyroid dysfunction and severity of CKD is not clear. Several previous studies debit conflicting results both positive and negative.

Prevalence of hypothyroidism in end stage renal disease (ESRD) has been estimated between 0 and 9%. There is also increased prevalence of goitre in patients with ESRD.

In view of variability of thyroid function test in patients with CKD in previous studies, a prospective clinical and biochemical study on thyroid function in CKD patients in the Department of medicine, Basaveshwar teaching and general hospital attached to Mahadevappa Rampure medical college has been undertaken.

OBJECTIVES

1. To study the incidence of thyroid dysfunction in patients with chronic kidney disease.
2. To study the correlation between thyroid dysfunction and severity of renal diseases.

II. Methodology

Source of data

Patients with chronic kidney disease admitted in Basaveshwar Teaching & General Hospital, Gulbarga attached to Mahadevappa Rampure Medical College, Gulbarga.

Methods of collection of data

Study subjects: The present study is conducted on 40 patients of, who are diagnosed to have chronic kidney disease and being admitted in Basaveshwar Teaching & General Hospital, Gulbarga during the period of november 2016 to may 2018. These samples are selected by using simple random sampling method. Statistical parameters mean ,standard deviation(SD) and correlations are used and parametric and non parametric tests are used for the analysis.

Informed consent was obtained from all the patients.

Inclusion criteria: Patients with chronic kidney disease.

Patients who fulfill the criteria for CKD and who are on conservative management.

Criteria for Chronic Kidney Disease

1. Symptoms of uraemia for 3 months or more
2. Elevated blood urea, serum creatinine and decreased creatinine clearance.
3. Ultra sound evidence of chronic kidney disease

a) Bilateral contracted kidneys — size less than 8 cm in male and size less than 7 cm in female
b) Poor corticomedullary differentiation
c) Type 2 or 3 renal parenchymal changes

1. Supportive laboratory evidence of CKD like anemia, low specific gravity, changes in serum electrolytes, etc.,
2. Radiological evidence of renal osteodystrophy

Exclusion criteria

1. Patients on peritoneal dialysis or hemodialysis
2. Nephrogenic range of proteinuria
3. Low serum protein especially albumin
4. Other conditions like

a) Recent surgery, trauma or burns
b) Diabetes mellitus
c) Liver diseases
d) Drugs altering thyroid profile like amiodarone, steroids, dopamine, phenytoin, beta-blocker, estrogen pills, iodine-containing drugs.

Detailed clinical history and clinical examination is undertaken with preference to thyroid and renal diseases. The following investigations were performed.

- Urine routine and microscopic examination
- Peripheral smear for anemia and burr cells
- Renal parameters like blood urea, serum Creatinine and creatinine clearance (using Cockcroft — Gault formula)
- Serum electrolytes including calcium and phosphorous
- Serum cholesterol
- 24 hours urine protein and serum protein
- ECG, chest X and 2Decho
- X ray wrist, forearm and spine for evidence of renal osteodystrophy
- USG abdomen for evidence of chronic kidney disease

After selecting the patients, fulfilling the above criteria, about *5* ml of blood sample is collected in nonheparinised serum bottle and sent for thyroid profile.

Components of thyroid profile in this study

- Serum triiodothyronine(T_3)
- Serum thyroxine(T_4)
- Serum thyroid stimulating hormone (TSH)

Quantitative determination of T_3, T_4, TSH is done by Enzyme Linked Immunosorbent Assay.

The normal values:
Total T3 .....0.6 to 2.1 ng/ml
Total T4 ..... *5* to 13 micro g/dl
TSH ..... 0.4 to 7 micro IU/ml.

III. Results

40 patients with Chronic Kidney Disease (CKD) fulfilling the criteria for CKD who were on conservative management were studied, among these 40 patients 26 were male and 14 were female, their age varied from 18-70 years, of these 40 patients, patients who were 30 years old and below were 5, between 30-60 years were 20 and patients above the age of 60 years were 15 in number (table 1).

In our study the duration of CKD varied from 3 months – 5 years, mean duration being 11.16 months + 10.48 and the creatinine clearance varied from 6ml/min – 34ml/min.

Of the 40 patients, 16 patients had GFR of <10ml/min accounting to 40%, 12 patients had GFR ranging from 11-20 ml/min accounting for another 30% and the remaining 12 patients had GFR > 20ml/min accounting for 30%.

Blood urea varied from 64 – 177 mg/dl and creatinine levels varied from 3mg/dl – 17.2mg/dl, 24 hours urine protein excretion was <1g/day in all the patients in our study.

Serum calcium and phosphorous were normal in all our patients, 80% of the patients had anaemia with peripheral smear revealing normocytic normochromic anaemia in 72% and hypochromic anaemia in 8% of the patients

Burr cells were present in 40% of the cases, one patient had pleural effusion in our study, two patients in the study showed evidence of osteodystrophy and none of the patients had pericardial effusion.

Ultrasound abdomen showed evidence of CKD in all patients, contracted kidney was present in 90% of the patients, remaining patients had poor corticomedullary differentiation.

Among the 40 patients in our study 19 of them had low serum T_3 levels (47.5%), 5 patients among the low serum T_3 level also had high TSH value of >20µIU/ml with low T_4 levels and also symptoms suggestive of hypothyroidism.

Therefore these 5 patients were grouped under "Primary Hypothyroidism" as per the criteria (12.5%). 12 patients had low T_4 levels accounting for 30% of the patients.

Symptoms of hypothyroidism such as tiredness, somnolence, weight gain, cold intolerance, hoarseness of voice etc were also studied in the sample population. 70% (29 patients) had the symptoms as shown in table 8.

14 patients of the 19 who had low T_3 syndrome had symptoms accounting for 73.68% and 5 patients among who were hypothyroid had symptoms accounting for 100%.

12 patients with CKD did not show thyroid dysfunction, among these 12 patients 10 of them had symptoms of hypothyroidism which accounts to 83.33%.

Dry, flaky skin was present in 15 patients of which only 4 patients were hypothyroid, sinus bradycardia was present in 7 patients of which only 2 patients were hypothyroid, delayed ankle jerk was present in 8 patients of which only 2 patients were hypothyroid.
Hypothyroidism did not show any linear correlation with GFR. increased number of hypothyroid patients of about 12 in number were present in GFR 11-20ml/min whereas only 16 patients had hypothyroidism in GFR <10ml/min.

None of the patients in our study had diffuse thyroid swelling.

Age incidence of low T_3 syndrome was done in this study as shown in table 6, it showed that 20% of the CKD patients who had low T_3 level were 30 years of age or below and 40% of the patients were between the ages 31-60 years, as the age increased the number of patients with low T_3 also increased, 66.67% of the patients with low T_3 were above the age of 60 years

Sex incidence of low T_3 syndrome in one study showed that 46.15% of males had low T_3 and 50% of the females have low T_3 syndrome (table 7).

The T_3 levels varied from 0.2 – 2.0 ng/ml (table 2), the mean value being 0.679. Excluding the patients with primary hypothyroidism, the mean value was 0.73, this value was in low normal limit.

Excluding hypothyroidism T_3 levels were studied in relation to GFR, mean value of serum T_3 was low (0.534ng/ml) only in patients with GFR <10ml/min (table 10). The mean value was low normal in patients with GFR >10ml/min.

According to our study, number of patients with low T_3 increased with increase in the severity of renal failure (Table 8) in spite of low T_3. The serum T_4 levels varied from 0.4 – 8.9µg/dl.

Mean value of serum T_4 among 40 patients was 5.58, excluding hypothyroidism patients the mean value was 6.20µg/ml. this value is within low normal level of T_4.

Excluding 5 hypothyroid patients who have low T_4 values, 12 other patients accounting to 30% had T_4 level below normal and low T_3 (Table 4).

Number of patients with low T_4 does not correlate with the severity of renal disease (Table 9). The mean value of T_4 excluding hypothyroidism patients was normal at all stages of CKD (Table 10). None of the patients had T_4 values above normal level.

The TSH values varied from 0.6–27 µIU/ml with mean value of 7.28µIU/ml, excluding hypothyroidism mean value was 3.34. This shows normal serum level of TSH.

Among the 40 patients, TSH was normal in 17 patients (42.5%) and values between 7.1-20µIU/ml in 4 patients (11%). It was elevated >20µIU/ml in 5 patients (100%) of which 3 were female and 2 were male.

According to our study, in patients with low T_3 syndrome, the mean values of TSH in various stages of renal disease are within normal range, values of TSH did not show any linear correlation with GFR.

Descriptive and inferential statistical analysis has been carried out in the present study. The results were analysed by using SPSS version 18 (IBM Corporation, SPSS Inc., Chicago, IL, USA)**.** Results on continuous measurements were presented on Mean±SD (Min-Max). Significance was assessed at 5% level of significance. Inferential statistics like Chi-square test/Fischer exact test was used to check the difference between the groups

Table-1: Age and sex wise distribution of cases

Age	Sex	
	Male No (%)	**Female No (%)**
≤ 30	4(15.38)	1(7.14)
31-60	12(46.16)	8(57.14)
>60	10(38.46)	5(35.72)
Total	26(100)	14(100)
Mean±SD	51.92 ±16.93	53.14± 18.17

$X^2 = 0.733$, P=0.693 NS

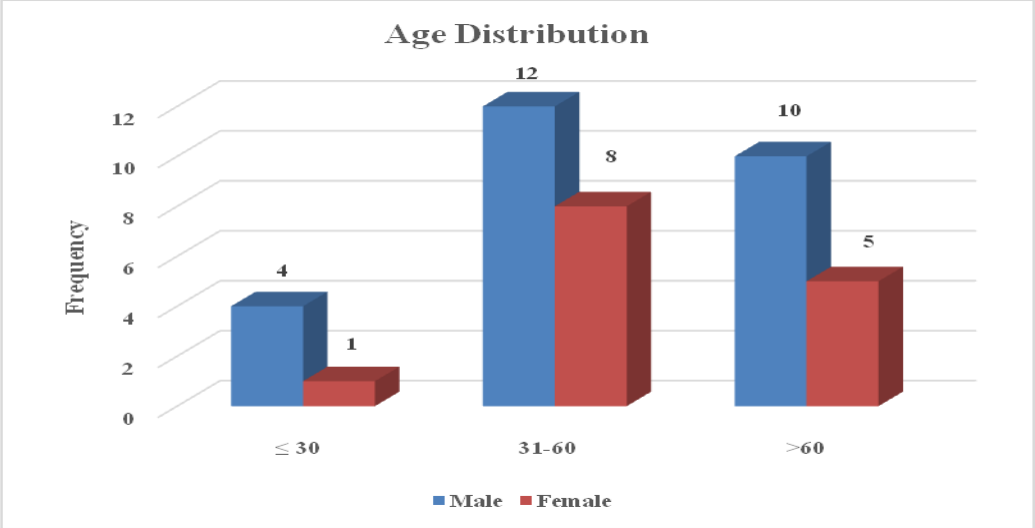

Table-2: Serum concentration of thyroid hormone

Thyroid hormones	Normal range	Study range	Mean±SD	Mean±SD excluding hypothyroidism
Serum T_3(ng/ml)	0.6–2.1	0.2-2.0	0.679±0.42	0.73± 0.39
Serum T_4(µg/dl)	5–13	0.4-8.9	5.58±2.23	6.20±1.65
Serum TSH (µIU/ml)	0.4–7	0.6-27	6.76±7.44	3.34±2.02

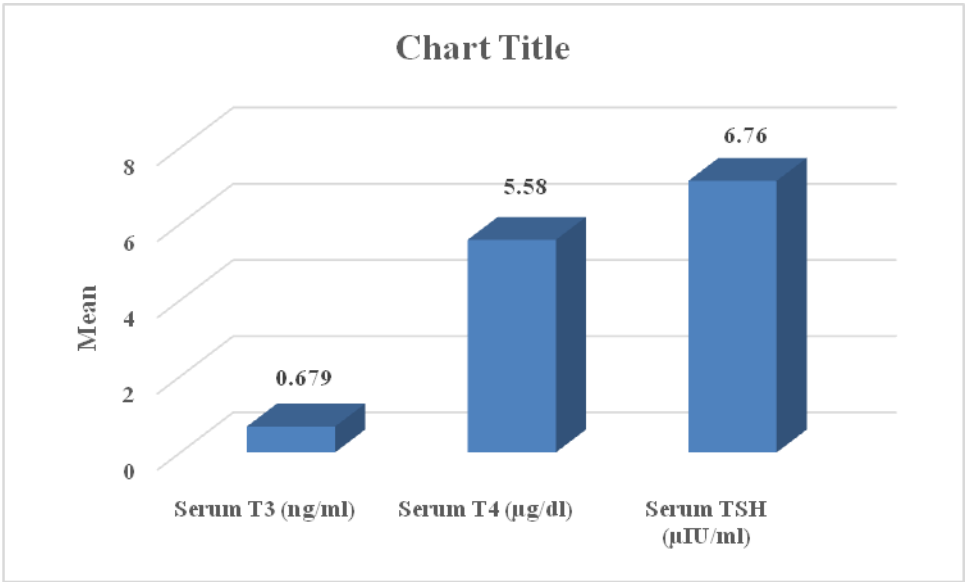

Table-3: Distribution of low T_3 and T_4 among various levels of TSH

TSH level µIU/ml	No. of Patients with Low T_3	No. of Patients with Low T_4
< 7	12(63.16)	5(41.67)
7.1 —20	2(10.53)	2(16.66)
> 20	5(26.31)	5(41.67)
Total	19(100)	12(100)

X^2 = 0.459, P=0.794 NS

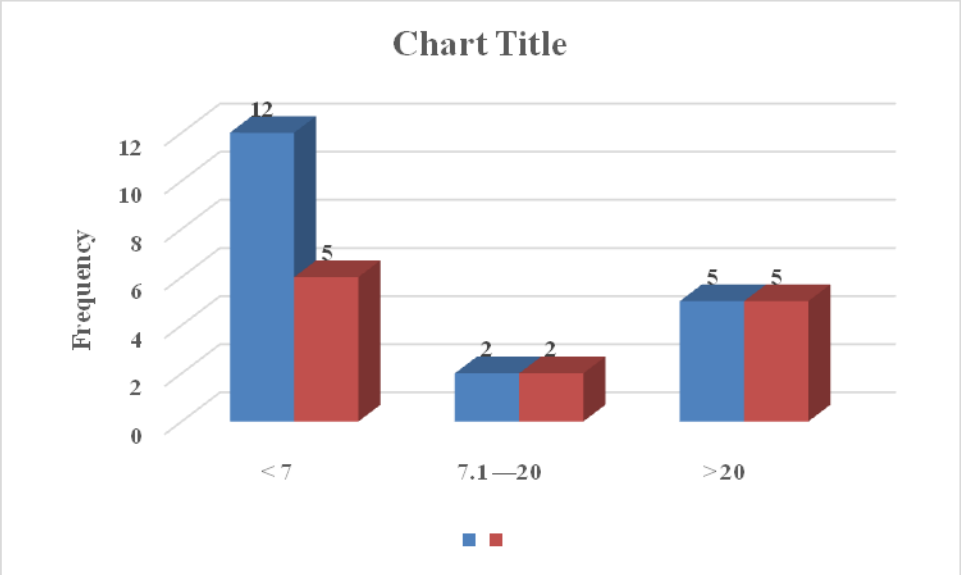

Table-4: Analysis of thyroid dysfunction in this study

Thyroid dysfunction	No. of Patients	Percentage
Low T_3 syndrome	19	47.50
Low T_4 syndrome	12	30
Hypothyroidism	05	12.50

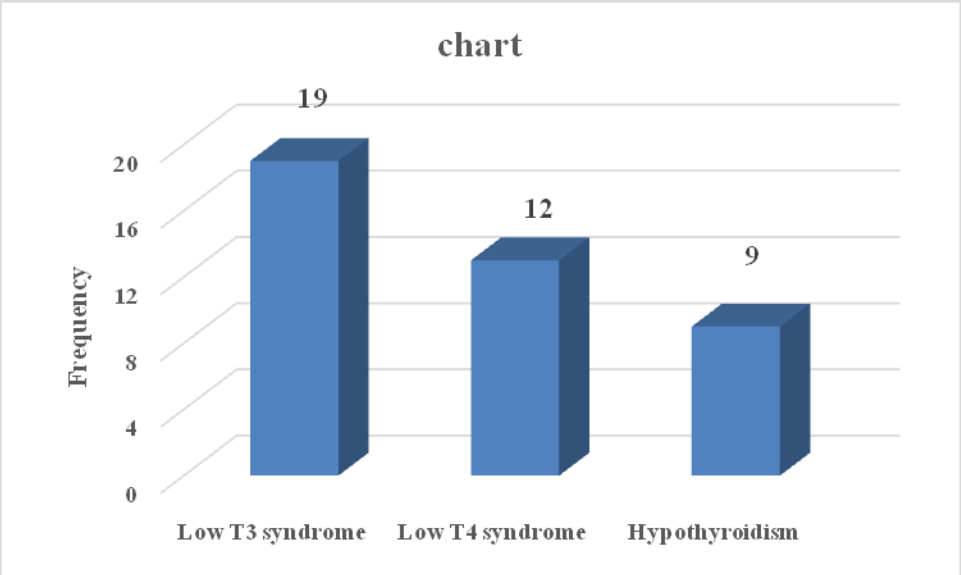

Table-5: Analysis of serum T_3, T_4 and TSH excluding hypothyroidism

Thyroid dysfunction	Normal values No(%)	Low values No(%)	High values No(%)
T3	21(52.5)	19(47.50)	-
T4	28(70)	12(30)	-
TSH	31(77.50)	-	9(22.50)

X^2 =31.77,P=<0.001

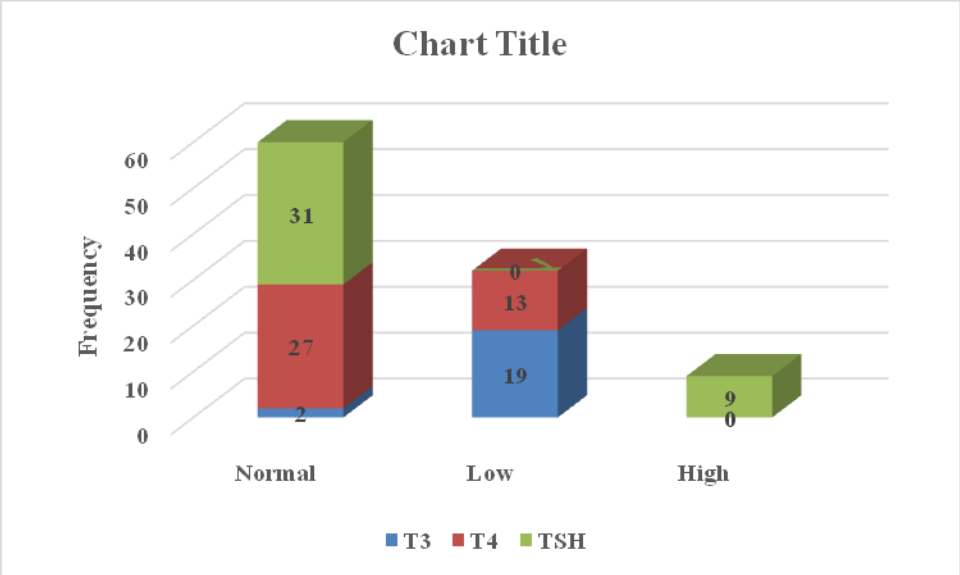

Table-6: Age incidence of Low T_3 syndrome in this study

Age in years	No of patients	Low T_3 syndrome	Percentage
< 30	05	1	20
31-60	20	8	40
>60	15	10	66.67
Total	40	19	47.50

Table-7: Sex incidence of low T_3 syndrome in this study

Sex	No. of patients	Low T_3 Syndrome	Percentage
Male	26	12	46.15
Female	14	7	50
Total	40	19	47.50

Table-8: Analysis of hypothyroid symptoms in CKD

Variants	No. of patients with symptoms	Percentage
Low T_3 Syndrome (n=19)	14	73.68
Hypothyroidism (n=5)	5	100
CKD without thyroid dysfunction (n=12)	10	75
Total (40)	29	70

Table-9: Distribution of low T_3 and T_4 syndrome in this study

Creatinine Clearance (ml/mm)	No. of patients	Low T_3 Syndrome	Low T_4 Syndrome
<10	16	10	7
11–20	12	6	3
>20	12	3	2

$X^2 = 0.162$ P=0.922

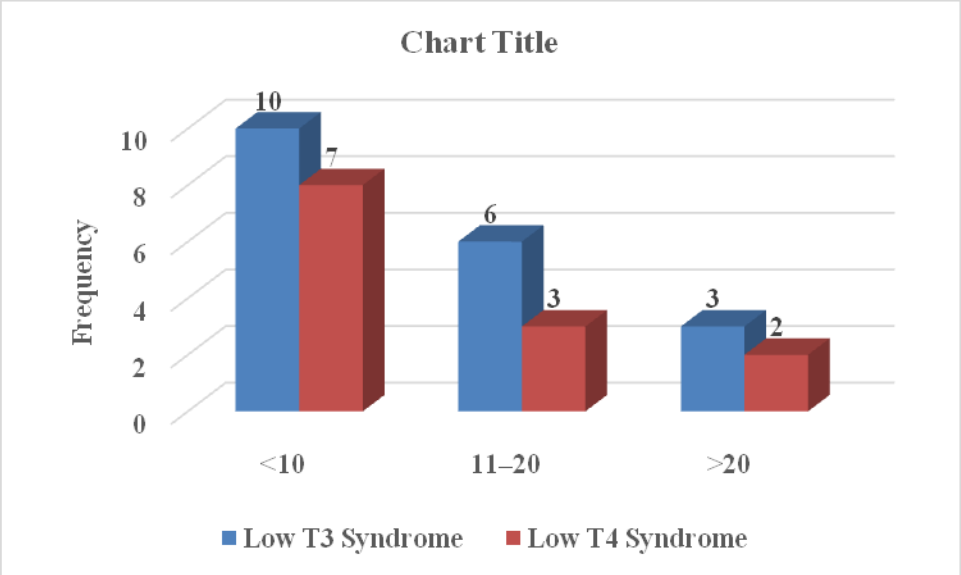

Table-10: Distribution of thyroid dysfunction in this study among various creatinine clearance levels

Creatinine Clearance (ml/mm)	No. of patients	Low T_3 Syndrome	Hypothyroidism
<10	16	10	5
11–20	12	6	3
>20	12	3	1

$X^2 = 0.163$, P=0.94

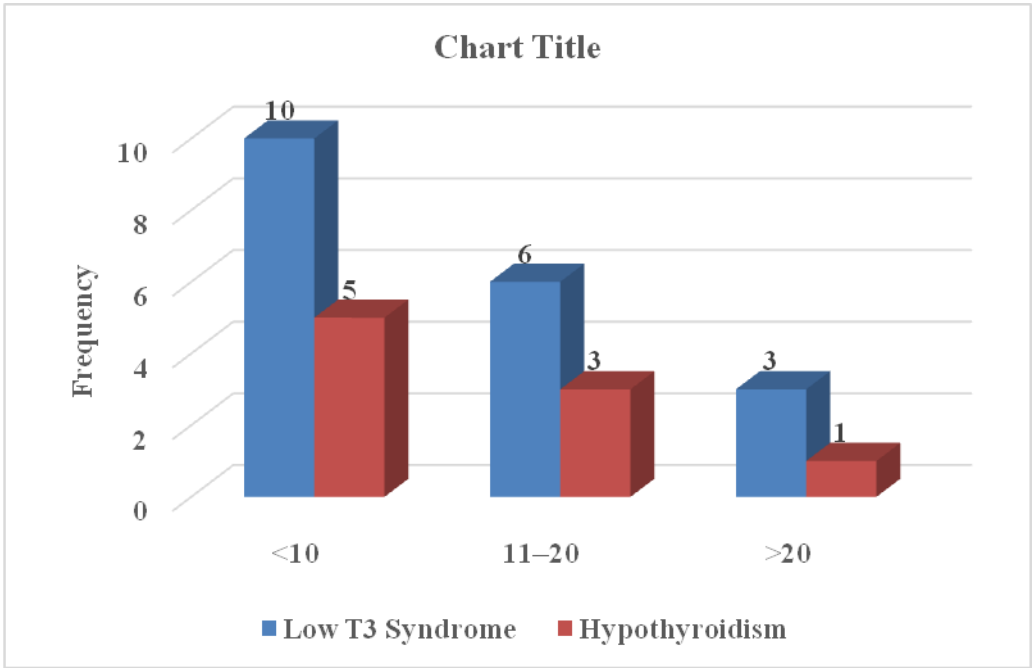

Table-11: Correlation of thyroid hormones with severity of renal failure excluding hypothyroidism

Creatinine Clearance ml/mm	T_3 (ng/dl) Mean±SD	T_4 (µg/dl) Mean±SD	TSH (µIU/ml) Mean±SD
<10	0.53±0.38	4.91±2.21	7.32±7.20
11—20	0.58± 0.30	5.67±2.63	9.40±13.18
>20	0.96±0.45	6.39±1.48	4.60±2.95

IV. Discussion

Thyroid dysfunction in CKD was extensively studied by Ramirez[5]. Apart from his study, various studies conducted in this line have showed different results.

In our study, patients only on conservative management were studied. This is because thyroid profile undergoes changes due to dialysis independent of that due to chronic kidney disease. Dialysis also changes the previous serum status of thyroid hormone in the patients with renal failure. Many studies have been conducted by comparing CKD patients on conservative Management and patients on hemodialysis by Ramirez[5].

Many studies conducted in CKD patients showed low T_3 values. Low T_3 had been reported in Ramirez et al[5], Hegedus et a1, Beckett et al , Pon Ajil Singh et al, P Iglesias and JJ Diez[4] and many others. Ramirez et al[5] study showed linear correlation between mean serum T_3 and T_4 and severity of renal failure.

As with other studies, mean T_3 level in our study was reduced below normal in GFR less than 10 ml/min. In higher GFR, it was present in low normal and there was no linear correlation between T_3 level and GFR, which is consistent with Avasthi et al study[8].

Mean T_4 level in our study is within normal limits in all levels of GFR, but it is in low normal level and also it does not correlate with the severity of renal failure.

In our study, not all the patients with CKD have low T_3 and T_4. It is estimated that only 60% (24 patients) of patients have Thyroid Profile abnormality. Remaining 42% of patients have normal thyroid profile.

Among 58% of these patients excluding primary hypothyroidism patients 28% have only low T_3 level with normal T_4 level. Remaining 20% have both low T_3 and T_4 level. The percentage of patients having low T_3 and T_4 gradually increase with decrease in GFR. The patients who will develop such changes in thyroid profile is not known.

Excluding hypothyroidism, 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 doesn't show any linear correlation with the severity of renal failure. These studies demonstrated abnormality in hypophyseal mechanism of TSH release in uraemic patients as the TSH response to the TRH was blunted.

Other studies conducted by p Iglesias et al[4] revealed low T_3 T_4 level with high TSH level suggesting maintenance of pituitary thyroid axis.

In our study, excluding those with hypothyroidism, seven patients had mild elevation of TSH with low T_3 level. Among these patients, T_4 is within normal limits in 4 of the patients. In the remaining 3 patients T_4 is below normal. There were no clinical features suggestive of hypothyroidism in these patients. Investigations like FT_4, FT_3 ,TRH response and anti thyroid auto antibodies can be done to diagnose hypothyroidism in these patients.

Out study is consistent with the results of Ramirez et a1[5] 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 Uraemic syndrome. From the various studies it has been suggested that this thyroid profile derangements is a part of body adaptation mechanism.

Dialysis

As stated previously, Hemodialysis and continuous ambulatory peritoneal dialysis have shown to affect the thyroid profile independently of CKD. Also drugs like heparin, furosemide used during dialysis will affect the thyroid profile.

P Iglesias et al[4] has conducted studies regarding effect of dialysis on CKD patients with thyroid dysfunction. This study showed no significant improvement in thyroid profile after repeated hemodialysis. But in the patients who have undergone renal transplant surgery, most of the thyroid function parameters returned to normal with TSH below normal.

Hypothyroidism

Previous studies reported high prevalence of hypothyroidism in CKD. It was estimated to be about *5%* in patients with terminal renal failure.

Detailed study by Robert w schrier et al[2] estimated the prevalence of primary hypothyroidism was about 2.5 times much frequent in chronic kidney disease and dialysis. The hypothyroidism in CKD was estimated to range between 0 and 9.5% Robert study also estimated the presence of anti thyroid antibody titer in 6.7% of CKD.

In our study, hypothyroidism is present in 10% of the patients but doesn't correlate with the severity of the renal failure. The symptoms of hypothyroidism were distributed equally in both hypothyroid and CKD patients in our study. Signs of hypothyroidism were more common in CKD without hypothyroidism than with hypothyroidism.

So, diagnosis of hypothyroidism in CKD mainly rest on TSH level which should be very high (>20 µIU/dl) with low serum T_4. In this study none of the patients had clinical or biochemical features of hyperthyroidism.

Goiter

Ramirez et a1[5] reported high prevalence of goiter in patients with CKD especially those on chronic dialysis. Incidence were increased in end stage renal disease. The possible explanation is due to accumulation of iodides in Thyroid gland due to decreased renal clearance in CKD patients. Apart from goiter, study conducted by Hegedus et al showed thyroid gland volume was significantly increased in patients with CKD. In our study, none of the patients had goitre.

V. Conclusion

- In patients with CKD Thyroid dysfunction occurs in 60% of the patients, the alteration in the values of T_3 and T_4 in CKD can be viewed as protective, promoting conservation of protein.
- Incidence of hypothyroidism is increased in patients with chronic kidney disease.
- Number of patients with low T_3 and T_4 syndrome progressively increase with the severity of chronic kidney disease
- Excluding patients with hypothyroidism T_3 level is low in 46% of the patients, T_4 level is low in 20% of the patients.

VI. Summary

40 patients of CKD admitted to Basaveshwar Teaching and General Hospital attached to Mahadevappa Rampure Medical College on conservative management were studied for thyroid dysfunction.

- 26 patients were male and 14 were female.
- Age varied form 18-70 years.
- Duration of CKD varied from 3 months to 5 years mean being 11.16 months + 10.48.
- Creatinine clearance varied from 6ml/min – 34ml/min.
- Urea varied from 64-177mg/dl and creatinine levels varied from 3mg/dl – 17.2mg/dl.
- The study range of serum T_3 was 0.2 – 2.0 ng/ml, mean 0.679 (normal range 0.6 – 2.1), serum T_4 was 0.4 – 8.9µg/dl, mean 5.58 (normal range 5-13) and serum TSH was 0.6 – 27µIU/ml, mean 6.67 (normal range 0.4-7).
- 19 patients had low T_3 syndrome, 12 patients had low T_4 syndrome and 5 patients had hypothyroidism.
- 70%, 29 patients had symptoms of hypothyroidism.
- According to our study number of patients with low T_3 increases with increase in the severity of chronic kidney disease.
- Number of patients with low T_4 syndrome does not correlate with the severity of renal failure and in patients with low T_3 syndrome, the mean values of TSH in various stages of renal disease are within normal range, values of TSH did not show any correlation with GFR.
- The low T_3 state of CKD can be viewed as being protective, promoting conservation of protein.

LIMITATIONS OF THIS STUDY

- Thyroid dysfunction was studied in patients with CKD irrespective of the etiology of CKD therefore individual correlation of the etiology of CKD with thyroid dysfunction could not be studied.
- Thyroid dysfunction was not studied in patients on dialysis, as dialysis itself affects the thyroid profile independently of CKD.

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