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Thyroid Functions in CKD: A Single Center Experience

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Abstract

There are several interactions between thyroid and kidney functions in each other organ's disease states. Thyroid hormones affect renal development and physiology. Thyroid hormones have pre-renal and intrinsic renal effects by which they increase the renal blood flow and the glomerular filtration rate (GFR). The present study aims to find out the status of thyroid dysfunction in patients with chronic kidney disease and to correlate between thyroid dysfunction and severity of renal disease in terms of laboratory parameters and zulewski's clinical scoringsystem. Total 100 patients (n=100) were included in the study. The association between thyroid function and Zulewski's clinical scoring system was evaluated in our study, which was not significant statistically. ($\chi 2 = 0.1852$, $p > 0.05$).This indicates lesser utility of Zulewski's clinical scoring system for assessment of thyroid dysfunction. These two disorders, chronic kidney disease and thyroid are managed by specific pharmacological agents, need titration by testing and by clinical signs. A physician must keep the possibility of co-existing chronic kidney disease and thyroid disorders**.**

Key words: Thyroid, CKD, Zulewski, GFR, hormone, renal disease

Introduction

Homeostasis of metabolic functions in all body organs has important role in thewell functioning of human body. This homeostasis is achieved by coordinatedactions of hormones or major regulatory organs. Thyroid hormones have theireffects on cellular growth and differentiation and also regulate important physiological functions in virtually every human tissue[1].And the other

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major organ, the kidney is involved in multiple functions like maintenance of fluid and acid base balance by regulating the concentration of sodium, potassium,hydrogen, phosphate and otherions in the extracellular fluid,metabolic waste excretion,secretion and metabolism of hormones which are involved in red blood cell production and mineral metabolism,haemodynamiccontroletc.

Chronic kidney disease (CKD) includes a spectrum of different Patho-physiological events associated with abnormal renal functions and a progressive decrease in effective glomerular filtration rate (eGFR). Now, it becomes a global public health problem associated with high mortality, decreased quality of life and a very high cost of healthcare[2]. A trend towards an increase incidence andprevalence of CKD has been reported worldwide[3,4] with epidemic proportions in some countries[5]. The adverse outcomes of CKD such as renal failure, cardiovascular complications, dyslipidemia and premature mortality can be prevented or delayedby administering appropriate treatment. Early stages of CKDcan be accessed through authentic laboratory testing and if treatment is effectively administered earlier in the course of illness that would halt down the progression towards end stage renal disease and cardiovascularcomplications.Improvement in the outcomesof people with end stage renal disease would require a well coordinated world-wide approach for prevention of unfavourable outcomes through defining the disease, its prevalence and its possible outcomes worldwide.The identification of disease in earlier stages and associated risk factors andappropriate treatment for populations at increased risk for unfavorable outcome.

Thyroid hormones (T3 and T4) play vital role in cellular growth and differentiation, andregulation of major physiological functions in human tissues including the kidney.They also play a role in balance of water and electrolyte homeostasis.Therefore, thyroid dysfunction, either hypothyroidism or hyperthyroidism is associated with imbalance in the electrolytes and metabolism of water as well as cardiovascular function[6].

The functions of thyroid and kidney are inter-related[7,8,9,10] to each other. The kidney is an major target organ for thyroid hormone actions and for the metabolismand excretion of the thyroid hormones. Renaldysfunction is associatedwith derangement in the thyroid hormone physiology. CKD affects both hypothalamus-pituitary-thyroidal axis and thyroid hormone peripheral conversion and its actions. The effects of renal dysfunction may lead to hypothyroidism, hyperthyroidism and non-thyroidal illness which are associated with cardiovascular complications, dyslipidemia, anemia, hypertension, mineral and bone disorders which will adversely affect the outcome of CKD. The present study aims to find out the status of thyroid dysfunction in patients with chronic kidney disease and to correlate between thyroid dysfunction and severity of renal disease in terms of laboratory parameters and zulewski's clinical scoring system.

Material and methods

This study was an observational, cross-sectional study which included 100 adult patients of chronic kidney disease presenting to the outpatient department or were inpatients of Department of Medicine, Maharaja Yashwantrao Hospital, Indore in the period from December 2016 to May

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2018. The study protocol was approved by the Departmental Scientific Committee and Institutional Ethics Committee before the start of the study. Each participant was subjected to detailed history taking with special emphasis on previous history of thyroid disease, use of thyroid drugs or supplementation. Symptoms of thyroid disorders like palpitations, heat/cold intolerance, and weight gain / weight loss were asked. History also includes the signs and symptoms according to new Zulewski's clinical scoring system.

Inclusion criteria-Age more than 18 years, Patients should already have biochemical and radio-imaging evidence of chronic kidney disease, Patients with stable chronic kidney disease on medical management.

Exclusion criteria-

1. Proteinuria of Nephrotic range
2. Presence of any concurrent uncontrolled medical surgical illness requiring additional active management.
3. Drugs altering thyroid function test like amiodarone, steroids, phenytoin,beta-blocker, iodine-containing drugs.
4. Known thyroid dysfunction in CKD patient.
5. Pregnancy

Methods – The nature of study was explained to all participants and a written informed consent obtained from them. Each participant was subjected to detailed history taking with special emphasis on previous history of thyroid disease, use of thyroid drugs or supplementation. Symptoms of thyroid disorders like palpitations, heat/cold intolerance, and weight gain / weight loss were asked. History also includes the signs and symptoms according to new Zulewski's clinical scoring system.

Zulewski's clinical score:

Zulewski*et al*. set out to establish the classical signs and symptoms of hypothyroidism in compare tomodern laboratory tests. They measured clinical scores,thyroid function, and tissue thyroid status (using anklereflex relaxation time) [ART] and total cholesterol. Based on the signs and symptoms of hypothyroidism, there are total 12 points in this scoring system. Depending upon the points, patients are categorized in various clinicalstates.

Statistical Analysis

All data were collected, organized in a tabulated form and statistically analyzed. The analysis was carried out using SPSS (Statistical Package for Social Science) Version 24 for windows (Software and Services, North California, USA).

1. Quantitative variables such as FT3, FT4, TSH, etc. were expressed as mean, standard deviation and range.

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2. Qualitative variables such as age, sex, thyroid function status, degree of function loss, etc. were expressed as number and percentage.
3. Qualitative variables were compared with each other using Chi-square tests.

Results and Observation

In our study, 100 patients of CKD who were on conservative management fulfilling the criteria for CKD were evaluated, out of which 28 were women (28%) and 72 were men (72%). Most of the patients belonged to the age group of 11 to 30 years (32/100 patients; 32%). Their age ranged from 14 to 70 years with a mean age of (40.0 ± 13.89) years. The duration of disease ranged from 15 days to 18 months, mean (7.2 ± 4.06) months. Only 36 patients (36 %) had disease duration of less than 6 months. 48 patients (48%) patients had duration of disease between 6 month to 1year and 16 patients (16%) had duration more than 1 year.

Of the 100 patients, 83 patients had eGFR less than 15 ml/min (stage 5)accounting to 83%, 13 patients had eGFR ranging from 15-30 ml/min (stage 4) accounting for 13% and 2 patients had eGFR ranging from more than 30-60 ml/minute (stage 3) accounting for 2%, and 2 patients had eGFR ranging from morethan 60-90 ml/minute (stage 2) accounting for 2%. Among the patients studiedmost were in the range of creatinine clearance <15 ml/minute(stage 5) (Table 1).

Table 1: Distribution of subjects according to CKD stage

Stage of CKD	Total Subjects	Male	Female
Stage 2	2	1	1
Stage 3	2	1	1
Stage 4	13	10	3
Stage 5	83	60	23

The blood urea value varied from (78 –200) mg/dl, the mean value being (121.07 ± 22.11) mg/dl.Among the patients studied most of them have blood urea in the range of (81- 120)mg/dl.(59%).

The creatinine values varied from (2.08 – 10.7) mg/dl, the mean value being(5.68 ± 1.51). Among the patients study most of them have serum creatinine in the range of 5 – 8 mg/dl.(76%)(Table 2).

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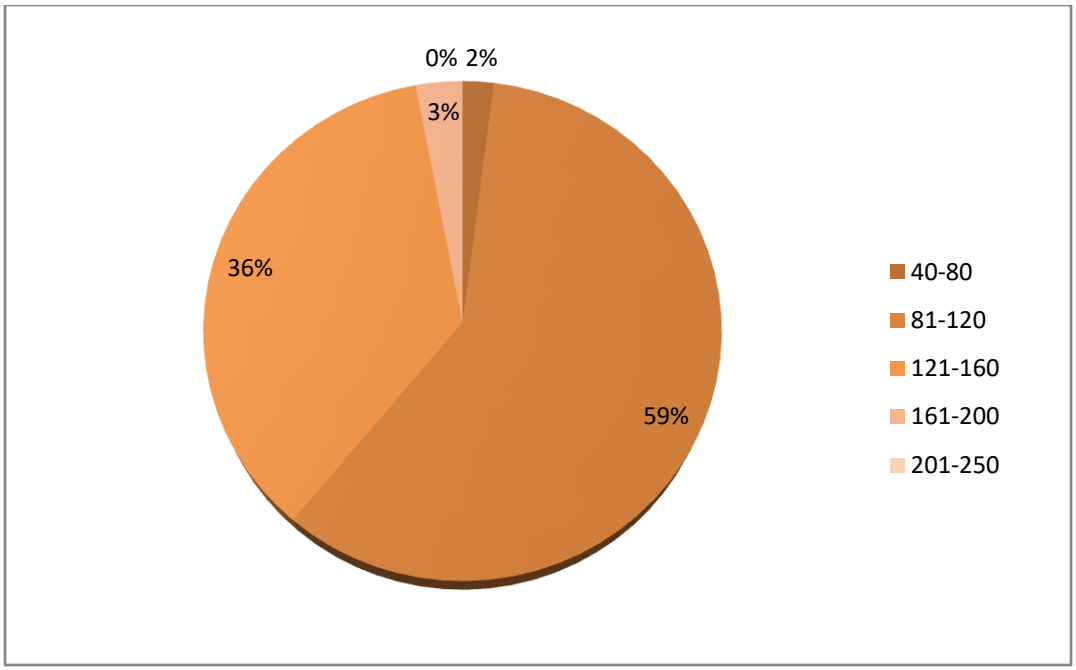


Fig 1: Distribution of Blood urea in CKD patients

Table 2: Distribution of Serum creatinine in CKD patients

Serum creatinine(in mg/dl)	No of patients	Percentage
0-4	21	21%
5-8	76	76%
9-12	03	3%
13-16	0	0%
Total	100	100%

In our study out of 100 patients, 24 patients had low serum FT3 levels(24%). 7 patients among low serum FT3 value, they also had low FT4 and high TSH suggesting primary hypothyroidism (7%). So excluding 7 patients of primary hypothyroidism 17 patients had low FT3 syndrome in our study. There was significantly association between FT3 level in CKD stastistically.
($\chi 2 = 23.83$, $p < 0.05$) (Table 3).

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Table 3: Distribution of subjects according to Thyroid Function Test (n=100)

Thyroid Status	Male	Female	Total	Percentage
Euthyroid	50	20	70	70%
Clinical Hyperthyroidism	0	0	0	0.0%
Subclinical Hyperthyroidism	0	0	0	0.0%
Primary Hypothyroidism(TSH >10 µIU/ml)	3	4	7	7.0%
Subclinical Hypothyroidism	0	0	0	0.0%
Low FT3 (TSH <10 µIU/ml)	13	4	17	17%
Low FT4 (TSH <10 µIU/ml)	2	4	6	6.0%
Total	72	28	100	100.0%

*Normal Reference Range - TSH – 0.35-5.20 µIU/ml; FT3 – 2.3-4.2 pg/ml; FT4 – 0.61 – 1.48 ng/dl

13 patients had low F T4 levels in our study, out of which 7 patients hadlow FT3 and high TSH suggesting primary hypothyroidism. Excludinghypothyroidism 6(6%) patients had low FT4 level in our study. There was significantly association between FT3 levels in CKD stastistically.($\chi 2$ = 50.37, $p < 0.05$).

The TSH values in our study ranged from (0.35-5.20) micro IU/ml, the mean value being (3.55 ± 0.702) . Among 100 patients, 93 patients were in the normal range and 7 patients had high value of more than 5.20 micro IU/ ml. In patients who were in the high range 3 were males and 4 were female.The all four patients with primary hypothyroidism had creatinineclearance of less than 15 ml/min(stage 5 CKD). It indicates the severity of renal failure in hypothyroid patients.In our study of CKD patients with low FT3 syndrome, the mean TSHvalues in several stages of renal failure are found to be in normal range. TSH values did not show any linear correlation with glomerular filtration rate in our study.(Table 4,5)

Table 4: Distribution of low FT3 among various levels of TSH
(Normal TSH – 0.35-5.20 µIU/ml:FT3 – 2.3-4.2 pg/ml)

TSH Levels	Low FT3	Normal FT3
Normal	17	76
High	7	0
Total	24	76

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X^2(chi square value) = 23.83
P <0.05 (significant)

Table 5: Distribution of low FT4 among various levels of TSH
(Normal TSH – 0.35-5.20 µIU/ml: FT4 – 0.61 – 1.48 ng/dl)

TSH Level	Low FT4	Normal FT4
Normal	6	87
High	7	0
Total	13	87

X^2(chi square value) = 50.37
P <0.05 (significant)

Out of 100 patients in our study 85 patients (85%) had the symptoms of hypothyroidism such as tiredness, weakness, cold intolerance, dry coarse skin, constipation, hoarseness of voice, paraesthesia,etc. Patients were assessed by Zulewski's clinical scoring by which 80 patients has score(0-2) suggesting euthyroidism and 10 patients have score (2-5) and 10 patients have score more than 5 suggesting hypothyroidism (Table 6).

Table 6: Analysis of Hypothyroid symptoms in CKD

Variants	Total no. of subjects	No. of patients with symptoms	Percentage
Low FT3	17	17	100%
Low FT4	6	6	100%
Primary Hypothyroidism	7	7	100%
CKD with normal thyroid function Test	70	55	78.5%
Total	100	85	85%

X^2(chi square value) = 0.587
P >0.05 (non significant)

Out of 24 patients who had low FT3 syndrome, 17 patients had symptomssuggestive of hypothyroidism accounting for (70.8%) and 7 patients among the primaryhypothyroidism, all 7 had symptoms of hypothyroidism which accounts for 100% (Table 7)

Table 7: Analysis of Thyroid dysfunction in this study (n=100)

Thyroid dysfunction	No. of patients	Percentage

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Low FT3	17	17%
Low FT4	6	6%
Primary Hypothyroidism	7	7%

Among 100 patients of CKD, 70 patients did not show any thyroidfunction abnormalities but out of them 55 had symptoms ofhypothyroidism which accounts for (78.5%).Features of hypothyroidism such as delayed ankle jerk were also present in 2 patients out of which one is hypothyroid.

Out of 100 patients in our study, 64 patients had anaemia,82 patients were hypertensives and 16 patients had diabetes.Among the patients studied 17% had low FT3 syndrome, 6% had low FT4 syndrome and 7% had primary hypothyroidism.

Creatinine clearance were found to be less than 15 ml/minute (stage 5) in all 17 patients of low FT3 syndrome, constituiting 100%.($\chi2 = 3.67$, $p > 0.05$).Creatinine clearance were found to be less than 15 ml/minute(stage 5) in 6 patients of low FT4 syndrome. ($\chi2 = 1.32$, $p > 0.05$).Age incidence of low FT3 syndrome in CKD patients in our studyshowed that, CKD patients having low FT3 level (12.5%) were less than 30 years of age,(15.5%) were in the age group 30 – 60 years of age and (40%) were more than 60 years of age. It conclude that as the age increases the number of patients with low FT3 syndrome also get increases. ($\chi2 = 2.75$, $p > 0.05$) (Table 8,9)

Sex incidence of low FT3 syndrome in CKD patients in our studyshowed that 18.05% of males and 14.20% females had low FT3 syndrome.($\chi2 = 0.083$, $p > 0.05$).

Among 100 patients included in our study 24 had low FT3 level, amongwhich 7 Patients low FT3 was due to primary hypothyroidism and the rest 17patients had Low FT3 mainly due to progression of CKD which was also significant statistically.($\chi2 = 11.94$, $p < 0.05$).The association between thyroid function and Zulewski's clinical scoring system was evaluated in our study, which was not significant statistically.($\chi2 = 0.1852$, $p > 0.05$) (Fig 2).

Table 8: Association between Thyroid Function andZulewski's clinical score(n=100)
(Normal Reference Range - TSH – 0.35-5.20 µIU/ml; FT3 – 2.3-4.2 pg/ml; FT4 – 0.61 – 1.48 ng/dl)

Variants	**Thyroid function Test**	**Zulewski's clinical score**
Euthyroidism	**70**	**80**
Hypothyroidism	**7**	**10**

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X^2(chi square value) = 0.1852
Critical chi square value = 3.8415
P >0.05 (Non significant) (p value- 0.6669)

Table 9: Correlation of thyroid hormones in this study excluding hypothyroidism
(Normal Reference Range - TSH – 0.35-5.20 µIU/ml; FT3 – 2.3-4.2 pg/ml; FT4 – 0.61 – 1.48 ng/dl)

Thyroid hormones	Normal Range	Study Range	Mean excluding hypothyroidism	SD
Serum FT3	2.3-4.2 pg/ml	2.10- 3.90	3.08	0.56
Serum FT4	0.61 – 1.48 ng/dl	0.48- 1.40	1.08	0.208
Serum TSH	0.35-5.20 µIU/ml	1.06- 14.2	3.55	0.702

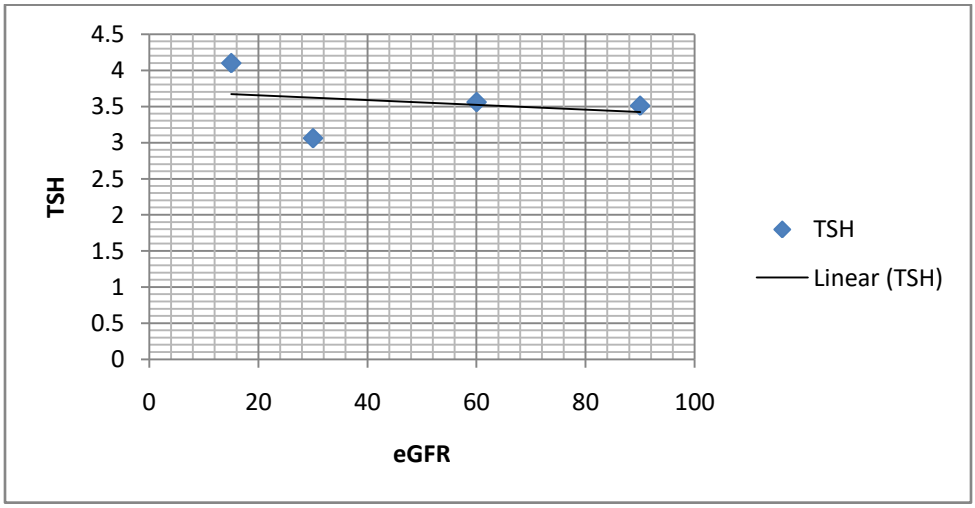


Fig 2: Diagram showing Correlation of thyroid hormones with severity of renal diseasein this study excluding hypothyroidism

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Discussion

The present study was aimed at to assess the status of thyroiddysfunction in CKD patients and to establish the correlation between thyroid dysfunction and severity of renal parenchymal disease. Various studies has been conducted previously about thyroid dysfunction and severity of CKD and they shown different results.In our study, CKD patients (n=100) only on conservative management were studied, this is because thyroid profile undergoes some changes due to dialysis independent of that due to chronic renal failure. Variousstudies have been studied by comparing CKD patients on pharmacologicalManagement and patientsonmaintainance hemodialysis by Ramirez and Kayimaet al.[11]

In our study 100 patients of CKD (n=100) who were on conservative management fulfilling the criteria for CKD were studied, among these 100 patients, 72 weremales and 28 were females, their age varied from 14 - 70 years. Among these 100 patients, patients who were 30 years old and below were 32, between 31 – 60 years were 58 and 60 years of age and above were 10 in number.

In our study the duration of symptoms of CKD varied from (15 days-18 months), Mean (7.2 ± 4.06) months and the creatinine values varied from (2.08 – 10.7)mg/dl, the mean value being (5.68 ± 1.51). The blood urea value varied from (78 –200) mg/dl, the mean value being (121.07 ± 22.11) mg/dl.In our study out of 100 patients, 24 patients had low serum FT3 levels(24%).7 patients among low serum FT3 value, they also had low FT4 level and high TSH suggesting primary hypothyroidism (7%). So excluding 7 patients of primary hypothyroidism, 17 patients(17%) had low FT3 syndrome. There was significantly association between FT3level in CKD stastistically. ($\chi 2 = 23.83$, $p < 0.05$).All patient (17%) who have low FT3 value have eGFR less than 15ml/min suggesting strong correlation of low FT3 with severity of chronic renal failure.Several studies reported in CKD patients showed similar result of low FT3 values,Low FT3 had been reported in studies done by Ramirez et al[12], Hegedus et. a1[13].

Beckett et Al[14]PonAjil Singh et al[15], P Iglesias and JJ Diez[16] and many others.13 patients had low FT4 levels in our study, out of which 7 patients hadlow FT3 andhigh TSH suggesting of primary hypothyroidism. Excludinghypothyroidism6 (6%) patients had low FT4 level in our study. There was significantly association between FT3 level in CKD stastistically.($\chi 2 = 50.37$, $p < 0.05$). All patient (6%) which have low FT4 level have eGFRless than 15ml/min suggesting strong correlation of low FT4 with severity ofchronic renal failure.Similar result is found in study done on CKD patients by Joseph L J[17], Hardy M J in the year 1993 and 1988respectively.

Hypothyroidism was more commonly seen in women as compared to men, although the numbers of women in our study were 28% and major patients were male (72%).This was similar to the observation in other studies that hypo-thyroidismhas a female preponderance[18]. In our study we got similar results, the TSH values in our study ranged from (0.35-5.20) micro IU/ml, the mean value being(3.55 ±0.702) . Among 100 patients, 93 patients were in the normal range and 7 patients had high value of more than 5.20 micro IU/ ml. In patients who were in the high range (primary hypothyroidism) 3 were males and 4 were female.The all seven(7) patients with primary hypothyroidism had creatinineclearance of less than 15 ml/min (stage 5). It indicates the

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severity of renal failure in hypothyroid patients. Hypothyroidism also predisposes to atherosclerosis and dyslipidemia which increases the cardiovascular risk[19,20]. These findings are clinically very important as they justify screening of patient of Chronic kidney disease for thyroid dysfunction and treatment of subclinical hypothyroidism in these patients.The study range of TSH was (0.35-5.20 µIU/ml)and Excluding hypothyroidism, mean TSH value (3.55 ± 0.702) in our study is within normal range. The mean TSH levels were within normal range for the various ranges of eGFR. But TSH level doesn't show any linear correlation with the severity of chronic renal failure.

In our study of CKD patients who have low FT3 values, the mean TSHvalues in various stages of renal failure are found within normal limits. TSH level did not show any linear correlation with glomerular filtration rate in our study. Another study which was conducted by Joseph et al and Hardy et al [21,22] revealed low T3,T4 value with high TSH value suggesting maintenance of pituitary thyroid axis.Among 100 patients of CKD, 70 patients did not show any thyroidfunction abnormalities but out of them 55 had symptoms ofhypothyroidism which accounts for (78.5%).Features of hypothyroidism such as delayed ankle jerk was also present in 2 patients out of which one was hypothyroid. The all patients were evaluated by Zulewski's clinical scoring system. Zulewski et al. set out to re-evaluate the classical signs and symptoms of hypothyroidism in the light of modern day laboratory tests.They measured clinical scores,thyroid functions and tissue thyroid status[using ankle reflex relaxation time]. Of 100 patients in the study 80 patients had Score(0-2) suggesting euthyroid status,10 patients had score (3-5) and 10 patients had score more than (>5) suggesting hypothyroid status of 10 hypothyroid patients based on Zulewski's score 7 patients had laboratory parameter suggesting hypothyroidism.In our study, hypothyroidism is present in 7% of the patients but doesn't correlatewith the severity of the renal failure. The symptoms ofhypothyroidism were distributed equally in both hypothyroid and CKD patients in our study.Thediagnosis of hypothyroidism in chronic renal failure mainly depends on TSH value which should be high (>5.20 µIU/dl) with lowserum FT4 (< 0.61 ng/dl). In this study none of the patients hadbiochemical features or clinical of hyperthyroidism.

The age incidence of low FT3 syndrome inCKD patients in our studyshowed that, CKD patients who have low FT3 syndrome (12.5%) were less than 30 years of age,(15.5%) were in the age group 30 – 60 years and (40%) were more than 60 years of age. It shows that as the age increases the patients having low FT3 level also increases. ($\chi 2 = 2.75$, $p > 0.05$).In our study, sex incidence of CKD patients with low FT3 syndrome showed that 18.05% of males and 14.20% females had low FT3 syndrome.($\chi 2 = 0.083$, $p > 0.05$).The association between thyroid function and Zulewski's clinical scoring system was evaluated in our study, which was not significant statistically.($\chi 2 = 0.1852$, $p > 0.05$). We conclude that there were variation in the results of thyroid function test and assessment done by the Zulewski's clinical score for hypothyroidism.

Our findings justify screening patients of CKD for thyroid dysfunction. Patients of CKD should be routinely asked about symptoms of thyroid disease and testing for thyroid dysfunction should be done when anysymptoms suggestive of dysfunction is present. Also, patients should be asked

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about these symptoms on every follow-up as there is a high prevalence of co-morbid thyroid dysfunction in patients of CKD as is demonstrated in our study. Whenever thyroid dysfunction is found in laboratory studies, they should be treated as it will lead to improvement in quality of life of these patients. Our findings also suggest that more research is needed asthe literature is scarce.

Conclusion

We conclude that all patients of chronic kidney disease should be screened for thyroid diseases as the spectrum of symptoms of both disorders overlaps considerably and management of both diseases is entirely different pharmacologically. So it can be summarized that these two disorders are managed by specific pharmacological agents, need titration by testing and by clinical signs. A physician must keep the possibility of co-existing chronic kidney disease and thyroid disorders. However, further studies are needed to find out the exact significance of this association. The association between thyroid function and Zulewski's clinical scoring system was evaluated in our study, which was not found significant statistically. This indicates lesser utility of Zulewski's clinical scoring system for assessment of thyroid dysfunction.

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