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General Medicine

CORRELATION BETWEEN THYROID DYSFUNCTION AND SEVERITY OF RENAL DISEASES IN CHRONIC KIDNEY DISEASE PATIENTS – A PROSPECTIVE STUDY

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ABSTRACT 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. Total number of 100 patients with Chronic Kidney Disease on conservative management were selected in this prospective study. Out of the 100 patients with CKD 55 patients had low T3 syndrome (0.1- 1.8ng/ml,) which accounts for 55% of the patients, 32 patients had low T4 syndrome which accounts for 32%. Low T3 &T4 were 26 patients. of the patients and 7 patients had primary hypothyroidism TSH >20p,IU/ml. Excluding Primary Hypothyroidism, analysis of serum T3,T4 and TSH in the study subjects shows significance $p < 0.005$. Distribution of Thyroid Dysfunction in this study among various creatinine clearance levels showed that as glomerular filtration rate declines, number of patients with low T3 syndrome increased , . In patients with low T3 syndrome, the mean values of TSH in various stages of renal disease are within normal range and, values of mean TSH did not show any linear correlation with glomerular filtration rate. Number of patients with low T4 syndrome did not correlate with severity of renal disease. Thyroid Dysfunction occurred in 55% 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 T3 state of CKD can be viewed as being protective, promoting conservation of protein. The number of patients with low T3 syndrome progressively increase with the renal failure, but there is no linear correlation.

KEYWORDS : Chronic kidney disease, thyroid dysfunction, hypothyroidism,TSH.

1. INTRODUCTION

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 having 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

2.AIMS

To study the correlation between thyroid dysfunction and severity of renal diseases in chronic kidney disease patients

3. METHODS AND MATERIALS

Patients with chronic kidney disease admitted in Government Mohan Kumaramangalam Medical College Hospital, Salem. The present study is conducted on 100 patients of, who are diagnosed to have chronic kidney disease and being admitted in Government Mohan Kumaramangalam Medical College Hospital, Salem 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. ltra 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. Nephrotogenic range of proteinuria
3. Low serum protein especially albumin
4. Other conditions like

a) Acute illness
b) Recent surgery, trauma or burns
c) Diabetes mellitus
d) Liver diseases
e) 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.

- EI 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-ray and 2D echo
- X ray wrist, forearm and spine for evidence of renal osteodystrophy
- USG abdomen for evidence of chronic kidney disease
- FNAC in patients presenting with thyroid swelling After selecting

the patients, fulfilling the above criteria, about 5 ml of blood sample is collected in non heparinised serum bottle and sent for thyroid profile. Components of thyroid profile in this study

- Serum triiodothyronine(T3)
- I Serum thyroxine(T4)
- Serum thyroid stimulating hormone (TSH)

Quantitative determination of T3, T4, 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

4.RESULTS

100 patients with Chronic Kidney Disease (CKD) fulfilling the criteria for CKD who were on conservative management were studied, among these 100 patients 70 were male and 30 were female, Their age varied from 25-75 years, of these 100 patients, patients who were 30 years old and below were 4 patients, of these 3 male 1 female .Age between 30-60 years were 69 of these 46 male 23 female and patients above the age of 60 years were 27, of these 21 male 6 female in number . In our study the duration of CKD varied from 4 months - 5 years, mean duration being 11.16 months + 10.48 and the creatinine clearance varied from 6m1/min — 34m1/min. Of the 100 patients, 28 patients had GFR of <10m1/min accounting to 28%, patients had GFR ranging from 11-20 ml/min accounting for another 52% and the remaining 20 patients had GFR > 20m1/min accounting for 20%.

Blood urea varied from 62 — 180 mg/dl and creatinine levels varied from 3mg - 15.6mg/d1, 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, three patient had pleural effusion in our study, two patients in the study showed evidence of osteodystrophy. Ultrasound abdomen showed evidence of CKD in all patients, with contracted kidney was present in all of the patients and poor corticomedullary differentiation. Among the 100 patients in our study 55 of them had low serum T3 levels (55%), 17 patients among the low serum T3 level also had high TSH value of >20[LIU/m1 with low T4 levels and also symptoms suggestive of hypothyroidism.

Table No 1 : Distribution Of Low T3 & T4 Level Amoung Various Level Of Tsh Level

TSH Level	No. of Patients with Low T3	%	No. of Patients with Low T4	%
<7(73)	35	63.64	16	50.00
7.1-20(17)	10	18.18	6	18.75
>20(10)	10	18.18	10	31.25
Total (100)	**55**	**100**	**32**	**100**

Among these 26 patients had low T3& and T4 value.These patients groped As hypothyroid syndrome .. 32 patients had low T4 levels accounting for 32% of the patients. Symptoms of hypothyroidism such as tiredness, somnolence, weight gain, cold intolerance, hoarseness of voice etc were also studied in the sample In these 42 patients with CKD did not show thyroid dysfunction, among these 2lpatients 28 of them had symptoms of hypothyroidism which accounts to 58.33 Patients with Hypothyroid features clinically like hypothyroid syndrome were 44 ,delayed tenton reflex 6, papilledema 1, goitre 1 and pleural effusion Hypothyroidism did not show any linear correlation with GFR .Increased number of hypothyroid patients of about 8 in number were present in GFR 11- 20m1/min and also 12 patients had hypothyroidism in GFR <10m1/min. 4 of our the patients in our study had diffuse thyroid swelling.

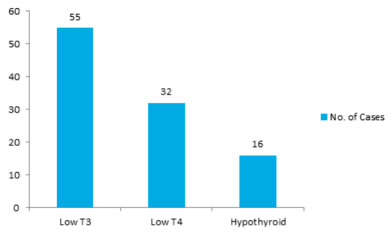

Figure No 1: Patients With Thyroid Disturbances

Age incidence ,patients with age<30 , were 4 cases , patients with age<30 -60 were 69 , patients with age<60 , were 27 , In correlation of T3 level with age ,patients low T3 with the age of <30 were 2 patients , age of <30-60 were 40 patients and age of >60 were 13 patients IT showed that 2% of the CKD patients who had low T3 level were 30 years of age or below and 40% of the patients were between the ages 31-60 years and 13% of the patients were age >60, as the age increased the number of patients with low T3 also increased .

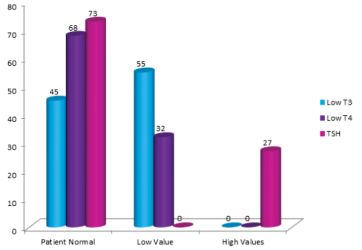

Figure 2 : cases with thyroid dysfunction

Sex incidence ,patients of low T3 syndrome in one study showed that 51.3% of males had low T3 and 38.7% of the females have low T4 syndrome . The T3 levels varied from 0.2 — 1.9 ng/ml . Excluding hypothyroidism T3 levels were studied in relation to GFR, mean value of serum T3 was low (0.534ng/m1) only in patients with GFR <10m1/min . The mean value was low normal in patients with GFR >10m1/min. According to our study, number of patients with low T3 increased with increase in the severity of renal failure , in spite of low T3.

The serum T4 levels varied from 0.5 — 9.514d1.(Mean value of serum T4 among 100 patients was 5.631, excluding hypothyroidism patients the mean value was 5.98pg/ml. this value is within low normal level of T4. Excluding 5 hypothyroid patients who have low T4 values, 11 other patients accounting to 22% had T4 level below normal and low T3 syndrome .

Number of patients with low T4 does not correlate with the severity of renal disease The mean value of T4 excluding hypothyroidism patients was normal at all stages of CKD . None of the patients had T4 values above normal level, Studying level of TSH values varied from 0.6-24.4 RIU/m1 with mean value of 7.28111U/ml, excluding hypothyroidism mean value was 4.85. This shows normal serum level of TSH.

Table No 2 Serum Concentratin Of Thyroid Hormone

Thyroid Hormones	Normal Range	Study Range	Mean	SD	Mean excluding Hypothyroidism	SD
Serum T3	0.6-2.1	0.1-2.0	0.613	0.043	0.698	0.523
Serum T4	5-13	0.4-9.4	5.614	2.248	5.89	2.76
Serum TSH	0.4-7	0.4-27.0	6.526	0.669	5.23	4.62

Among the 100 patients, TSH was normal in 73 patients (73%) and values between 7.1-201A1U/m1 among with low T3 in 10 patients (18.18%). It was elevated >20pIU/ml with low T3 patients 10 (18.18 %) and these more present in male In 100 patients, TSH level between 7.1-201.dU/m1 , with low T4 in 6 patients . It was elevated >20ttIU/m1 with low T4 10 patients .

According to our study, in patients with low T3 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.

- No of patients with low T3 about 55
- No of patients with low T4 about 32
- No of patients with increased TSH value about 27
- No of patients with low T3 & T4 about 26
- No of patients with low T3& high T4 about 17
- No of patients with lowT3& T4 and high T4 value about 13 among these 6 with high TSH value of < 20 and 7 with TSH value of > 20
- No of patients with low T3 &T4 and high TSH value<20 with creatinine clearance value of <10 were 4 and CCL > 11-20 were 2, more than 20 were 0, .
- No of patients with low T3 &T4 and high TSH value >20 with creatinine clearance value of <10 were 3 and CCL > 11-20 were 4 more than 20 were 0
- CCL value <10 with low T3 syndrome were 8 with the percentage

of about 50% , CCL value 11-20 with low T3 syndrome were 8 with the percentage of about 50 CCL value >20 with low T3 syndrome were 0 . The significant value of $P < 0.005$

5.DISCUSSION

Thyroid dysfunction in CKD was extensively studied by Ramirez. 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 and Kayima et al Many studies conducted in CKD patients showed low T3 values. Low T3 had been reported in Ramirez et al, Hegedus et al, Beckett et al Pon Ajil Singh et al, P Iglesias and JJ Diez and many others. Ramirez and Spector et al study showed linear correlation between mean serum T3 and T4 and severity of renal failure.

As with other studies, mean T3 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 T3 level and GFR, which is consistent with Avasthi et al study Mean T4 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 T3 and T4. It is estimated that only 52% (26 patients) of patients have Thyroid Profile abnormality. Remaining 48% of patients have normal thyroid profile. Among 52% of these patients excluding primary hypothyroidism patients 22% have only low T3 level with normal T4 level. Remaining 26% have both low T3 and T4 level. The percentage of patients having low T3 and T4 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. This is consistent with the study conducted by Spector and Ramirez et al 'Dudani et al, Karunanidhi et a. 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 Joseph et al and Hardy et al revealed low T3 T4 level with high TSH level suggesting maintenance of pituitary thyroid axis. In our study, excluding those with hypothyroidism, seventeen patients had mild elevation of TSH with low T3 level There were no clinical features suggestive of hypothyroidism in these patients. Investigations like FT4, FT3 ,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 a 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.

As stated previously, Hemodialysis and continuous ambulatory peritoneal dialysis have shown to affect the thyroid profile independently of CKD. Also drugs like heparin, fi-usemide used during dialysis will affect the thyroid profile. Kayima et al and Giordano et have conducted studies regarding effect of dialysis on CKD patients with thyroid dysfunction. These studies 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 by Quion verde et al reported high prevalence of hypothyroidism in CKD. It was estimated to be about 5% in patients with terminal renal failure. Detailed study by Kaptein et al 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% Kaptein study also estimated the presence of anti thyroid antibody titre in 6.7% of CKD. In our study, hypothyroidism is present in 10% of the patients but doesn't corelate 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 .dU/dl) with low serum T4. In this study none of the patients had clinical or biochemical features of hyperthyroidism.

Goitre

Ramirez et al reported high prevalence of goitre 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 goitre study conducted by Hegedus et al showed thyroid gland volume was significant increased in patients with CKD.

6.CONCLUSION

In patients with CKD Thyroid dysfunction occurs in 52% of the patients, the alteration in the values of T3 and T4 in CKD can be viewed as protective, promoting conservation of protein. Prevalence of hypothyroidism is increased in patients with chronic kidney disease. Number of patients with low T3 and T4 syndrome progressively increase with the severity of chronic kidney disease Excluding patients with hypothyroidism T3 level is low in 46% of the patients, T4 level is low in 20% of the patients.

Serum level of T3 and T4 has no correlation with the severity of chronic kidney disease.

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