e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2024; 16(5); 809-813

Original Research Article

Study of Thyroid Profile and Serum Iron Levels among the Patients with Chronic Kidney Disease in Manipur: North East India: A Cross Sectional Study

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Received: 25-02-2024 / Revised: 23-03-2024 / Accepted: 26-04-2024
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Conflict of interest: Nil

Abstract:

Aims and Objectives: To obtain the correlative association and prevalence of thyroid abnormalities with total iron status of the body among Chronic Kidney Disease patients.

Materials and Methods: Our study is of cross sectional type conducted in Regional Institute of Medical Science, Imphal, during the period from January 2015 to December 2015. This study consists of total 75 patients with positive diagnostic criteria of CKD and patients with hematological profile, iron status, clinical and renal parameters. We have taken adequate number of controls for comparison of the results with the general population.

Results: This study projected that among 75 patients with CKD, 49 patients had low T3 syndrome that comprises of 65% of the patients. 14 patients were with low T4 syndrome that consists of 18% of the patients and 12 patients suffered from primary hypothyroidism with TSH > 20μIU/ml. around 43% of the patients did not possess target serum ferritin of 100 ng/ml and 49.2% of them did not have TSAT of >20%.

Conclusions: Our study shows an increased prevalence of thyroid malfunctions especially hypothyroidism, associated with increased incidence of anemia and iron deficiency projecting symbiotic relationship among body iron status and thyroid function. Thyroid dysfunction, therefore, with patients of CKD, does not indicate hypothyroidism itself, but is considered as a reflection of the state of malnutrition or chronic illness.

Keywords: Iron deficiency Anemia, ferritin, Hypothyroidism, Chronic Kidney Disease.

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Introduction

Chronic Kidney Disease (CKD) comprises of a bunch of several pathophysiologic consequences leading to impaired kidney function, and a gradual deterioration in glomerular filtration rate (GFR). The overall incidence of CKD is 800 per million populations, and that of End Stage Renal Disease (ESRD) is 150-200 per million populations. CKD is considered to be a worldwide epidemic with a number of comorbidities and a disease with increased morbidity and mortality. [1]

Anemia is considered to be an initial complication of chronic kidney disease (CKD) that caused increased morbidity and mortality. [2] Though the main defect is reduced erythropoietin synthesis in the kidney, reduced erythropoietin has recently associated with down regulation of hypoxia-inducible factor (HIF), which is a transcription factor that controls gene expression of erythropoietin. Several other factors may also play contributory roles. For instance, hyperparathyroidism, shortened RBC survival, mild chronic inflammation, aluminum toxicity and iron, folate, vitamin b12 deficiency because of nutritional insufficiency or hemolysis induced blood loss. Several fragmentation of RBC by damaged renovascular endothelium in some conditions like malignant hypertension and glomerulopathy lead to anemia. Prompt diagnosis and treatment of anemia in CKD may reduce cardiovascular morbidity and mortality. [3] Initial treatment of anemia among CKD patients may improve their survival and postpone the onset of ESRD eventually.

Among all living tissues including kidney, thyroid hormones are essential for differentiation and growth and their modulation of physiological functions. Water and electrolyte hemostasis are also modulated by them. [4] It is kidney which is responsible for excretion and degradation of thyroid hormones and iodine clearance, so

dysfunction of kidney will always interfere with thyroid hormone levels. CKD influences the hypothalamus pituitary axis. CKD impairs the thyroid function in various ways, especially by altered peripheral hormone metabolism, low circulating thyroid hormone levels, reduced tissue thyroid hormone content, insufficient attachment with carrier proteins and fluctuated iodine reserve in the thyroid gland. So the overall metabolism of thyroid hormone is impaired in CKD. [5]

Aims & Objectives:-

The main objective of this study was to obtain the inter-relationship between thyroid function status in chronic kidney disease and serum iron indices. It also shows the effect of CKD on thyroid hormonal status and stratifies the severity of renal anomalies by EGFR and therefore correlates the stages of CKD with FT3, FT4, TSH and serum iron level.

Material and Methods

Our study has been conducted in Regional Institute of Medical Sciences, Imphal, Manipur during the period from January 2015 to December 2015. 75 patients in total were concluded in this study who fulfilled the diagnostic criteria of CKD and patients who underwent renal and clinical parameters, iron status and hematological profile. GFR of these patients were calculated by using Cockroft and Gault formula. Renal ultrasound scanning was also conducted among all patients to obtain the features suggestive of CKD.

Inclusion criteria:

1. Stage 2 to 4 CKD as explained by Cockroft and Gault equation: - {Creatine clearance (ml/min) = (140-Age) X (weight in Kg) X1.23/ serum creatinine in micromole/L} multiply by a factor of 0.85 for females.
2. Age > 18 years.
3. Patients without any renal replacement therapy.

Exclusion criteria:

1. Known Hemophilia.
2. Hookworm infestation.
3. Dyspepsia.
4. Coagulopathies.
5. Acute renal failure.
6. Glucose 6 phosphate Dehydrogenase (G6PD) deficiency.
7. Lactation.
8. Pregnancy.
9. A history of any renal replacement therapy.
10. Blood transfusion in the preceding 3 months.

After choosing the patients with aforementioned criteria, 5 ml of venous blood sample is collected in non- heparinized serum bottle for determination of renal parameters, serum electrolytes and thyroid profile.

Serum ferritin: The serum ferritin level was estimated by ELISA method. Iron level was determined with Ferrozine method without any deproteination. Total iron binding capacity (TIBC) was estimated by using Spectrophotometric Assay.

Transferrin saturation calculated by the formula (TSAT):-

TSAT= (serum iron/total iron binding capacity) X100

Ethical clearance has been obtained by Research Ethics Board, Imphal.

Statistical Analysis: Master chart were used for collection of the information of all the selected case. EPI 2010 epidemiological information package were used for all kind of data analysis; developed by Centre of Disease Control, Atlanta. Frequencies, percentages, range, means, chi-square, standard deviations and p-values were calculated by this software. Kruskal Wallis chi-square test was performed to determine the significance of difference between quantitative variables and qualitative variables were performed by Yate's chi-square test. A p-value less than 0.05 is considered to be significant in this test.

Results

In this study, we have studied 75 patient of CKD on conservative management who were fulfilling the criteria for CKD, of their range from 20-68 years, among these 59 and 16 were males and females respectively.

Among the 75 patients, 11 of the patients (15%) were 30 years old or below, 52 (69%) were between 31-60 years and 12 (16%) were above 60 regarding distribution of creatinine clearance in CKD patients (Figure 1).

Among the 75 patients again, 59% or 44 patients had GFR OF <15 ml/min, 25 patients (33%) consist of GFR for 15-30 ml/min and 8% of the patients had GFR of >30 ml/min. Most of the patients studied were in the range of creatinine clearance of <15 ml/min. (Table 1 and Figure 2).

Regarding the serum iron indices between cases and controls, Iron and Ferritin values were different which were significant ($p<0.05$). On the other hand, TIBC, TSA values were not statistically different (Table 2).

Table 3 shows the mean T3, TSH and free T4 levels in various stages of CKD. Here with reduced creatinine clearance, the mean T3 is reduced significantly. The free T4 is also reduced significantly in CKD stage 5.

In our 75 subjects in this study, 20 (26%) patients are associated with hypothyroidism, 16% or 12 patients are with subclinical hypothyroidism, 19

patients or 25% are associated with low T3 syndrome , 6 (8%) are with low T4 syndrome, and only 3% or 2 patients are associated with hyperthyroid. Out of the 75 subjects, 59 patients (78%) are with some dysfunctions of thyroid gland.

Relationship between creatinine clearance with total T3, free T4 and TSH were 0.320 ($p<0.05$), 0.381 ($p<0.01$) and -0.133 ($p<0.05$) respectively.

Table 4 depicts positive correlation between creatinine clearance and total T3 which is statistically significant.

The free T4 and creatinine clearance also shows positive correlation which is statistically significant. On the other hand TSH with creatinine clearance shows negative correlation which is not statistically significant.

Table 1: Distribution of creatinine clearance among CKD patients

Creatinine clearance (ml/min)	No of patients	Percentage
<15	44	59
15-30	25	33
>30	6	8

Table 2: Serum Iron indices regarding Study group and Control group.

Serum Iron Indices	Study group	Study group	Control group	Control group	'p'
	Mean	SD	Mean	SD	
Iron (µg/l)	66.9	30.8	83.2	26.1	0.0196 Significant
TIBC (µg/ml)	283.2	73.2	299.1	44.7	0.821 Not significant
TSAT %	29.56	17.3	29.2	11.2	0.341 Not significant
Ferritin (µg/l)	282.4	342.2	110.5	63.5	0.0485 Significant

Table 3:- Frequency and mean of total T3, free T4 and TSH in several stages of CKD.

Stages of CKD	Frequency	Mean total T3	Mean free T4	Mean TSH
1-3	5	103.4±30.7	1.25±0.1	1.8±1.9
4	16	91±36.6	1.1±0.2	1.2±0.8
5	29	68.8±24	0.9±0.3	4.5±13.7

Table 4: Relation and significance of creatinine clearance

Relation with Cr Clearance	r	Significance
Total T3	0.319	P<0.05
Free T4	0.385	P<0.01
TSH	-0.137	P>0.05

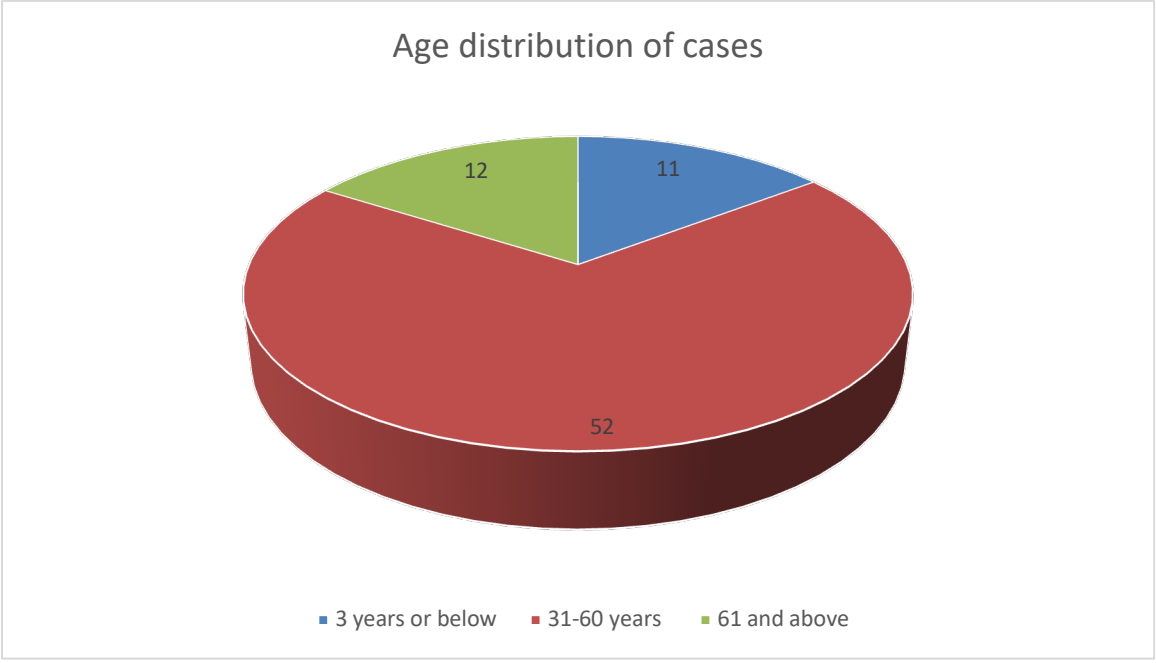

Figure 1: Age distribution regarding cases

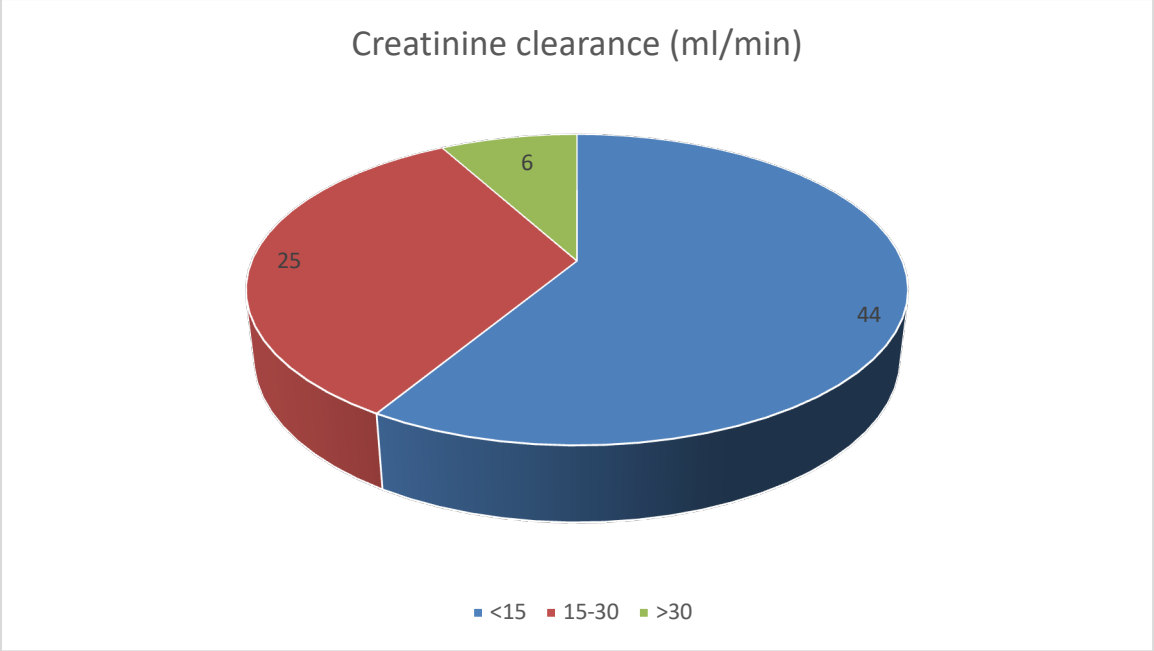

Figure 2: Measurement of creatinine clearance in ml/min

Discussion

Patients associated with CRF after have various signs and symptoms of thyroid dysfunction and the diagnosis of this thyroid disorder among the patients have several prognostic implications. In case of uremic patients the mean values of both serum T3 and T4 were low which was significant. This study is similar to the study conducted by Ramiraz et al [6] and Lin VS et al [7]. In this study, 19 patients (25%) had low T3 syndrome among 75 patients. The prevalence was associated with low T3 which in stage 1-3 was 20%, for stage 4 was 38%, and for stage 5 was 70%.

This observation was similar with the study conducted by Sang Heon Sang et al [8], where the incidence of low T3 is increased as per the increase in the stage of CKD. In this study, there is a positive correlation between creatinine clearance and total T3 which is statistically significant ($p < 0.05$). This projects serum T3 levels were accompanied by the severity of CKD even with the normal level of TSH. Overall incidence of thyroid dysfunction is about 48%, 38.6% and 58% by Pakhle K et al [9], Khatiwada S et al [10] and Manasa A.S Gowda et al [11] respectively where it was 78% in this study.

TSH or thyroid stimulating hormone is excreted by the kidneys and increased half-life of TSH is usual in CKD; though even at lower glomerular filtration rates, majority of patients are associated with normal TSH level. [12] the increased half-life of TSH used to blunt the response of TSH towards TRH or thyroid releasing hormone. Decreasing of the glomerular filtration rate often causes reduced iodine clearance, leads to colloidal degeneration and enlargement of the thyroid gland. The colloidal degeneration of thyroid gland is usually insidious, with very much minor clinical fluctuations which is clinically irrelevant to most of the patients.

On the other hand, dialysis has been accompanied by an increased risk of thyroid cancer and malignant thyroid nodules. [13] On the other aspect, the uremic milieu can blunt the bioavailability of thyroid hormone to peripheral tissues, causing a state of thyroid resistance. T4 and T3 level abnormalities are the most prevalent signs in CKD and low T3 level is the most common abnormality present in advanced CKD stages. [14] Though no test is perfect indicator of the availability of iron stores, the serum ferritin and TSAT are the best indicators as of body's iron status that we presently possess.

As we have the prevalence of iron deficiency for detecting CKD patients, and the sensitivity and specificity of serum ferritin and TSAT for detecting iron deficiency, the prevalence of iron deficiency is very high when serum ferritin is <100 ng/ml and TSAT is <20%. [15] So the serum ferritin and TSAT should be kept at a level of >100 ng/ml and >20% respectively. In this study, 43% of the subjects did not possess target serum ferritin of 100 ng/ml and 49.2% of the subjects did not possess TSAT target of >20%.

In this study mean serum ferritin was about 282.4 ng/ml and 10 cases consisted of serum ferritin level > 500 ng/ml. On the other hand, the low serum ferritin level (200 ng/ml in hemodialysis patients or 100 ng/ml in non-dialyzed patients associated with CKD) is considered to be a major indicator of iron deficiency, but a normal or slight high serum

ferritin level does not rule out iron deficiency or adequacy or too much consumption of dietary Fe. [16]

We all know that occult inflammation is commonly prevalent in CKD and may increase in case of progressive disease. On the other hand, inflammation itself has a high impact on iron indices. Anemia in CKD is a complex process that projects a communication between erythropoietic process of bone marrow with inflammation and iron availability. [17] Serum ferritin value was obtained among the patients and healthy controls which exists a significant difference between them (p value=0.048). Various efforts should be conducted to identify the causes of anemia in CKD patients and treat the coexistent iron deficiency anemia among them.

Conclusion

So as the form of summary, our study projects that thyroid dysfunction is very much prevalent among CKD patients and shows the significant correlation between CKD progressions with thyroid dysfunction. This study also reveals decreased ferritin and serum iron levels in CKD. This study also shows that CKD patients with fluctuated serum iron indices and Thyroid profile parameters consist of strong effect upon morbidity and quality of life. So early diagnosis with treatment for thyroid abnormalities and anemia among CKD patients may decrease the opportunities of developing complications in future.

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