Alteration of thyroid physiology in chronic kidney disease

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Abstract

Introduction: Endocrine abnormalities are very common in CKD and among them thyroid dysfunction is most commonly occurring in CRF patients. Hyperthyroidism, hypothyroidism & euthyroid state have all been reported by various workers but hypothyroidism incidence was found to be more common.

Aim: To assess the prevalence of alteration of thyroid physiology among patients chronic renal failure patients and to correlate between the thyroid hormone levels and the severity of chronic kidney disease.

Materials and Methods: A cross-sectional observational study was conducted at our hospital for a period of one year. A total of 73 patients with chronic renal failure were included in the study. A detailed clinical history and clinical examination was conducted with preference to thyroid and renal diseases. Serum fT3, fT4 and TSH were measured using standard technique.

Results: Majority of the study subjects were in stage V (end stage renal disease) CRF followed by stage IV CRF and only 5 – 8% of the subjects were in stage 1 and stage II CRF. The thyroid profile of our study subjects showed hypothyroidism was present in 43.8% of the CRF patients and in that majority of them had low T3 levels, followed by low T4 levels (36.9%) and an increased TSH levels (19.1%). The correlation between the T3, T4 levels and the various stages of CRF had shown a strong negative correlation, as the stages of CRF increases the number of patients with reduced T3 and T4 levels were found to be increasing and this was found to be statistically significant ($p<.05$), whereas there was no statistically significant positive correlation seen between the stages of CRF and the TSH levels ($p>.05$).

Conclusion: Alteration of thyroid physiology among CRF patients found to be increasingly common and so thyroid screening should be made mandate for all patients with CKD.

Keywords: Chronic kidney disease, Thyroid physiology, Free T3, Free T4 and TSH.

Introduction

Chronic kidney disease(CKD) is an internationally recognized public health problem affecting 5-10% population of the entire globe.[1] According to the 2010 global burden of disease study chronic kidney disease was ranked 18th in the list of causes of total number of deaths worldwide.[2] The National Kidney Foundation (NKF) had defined and classified CKD according to the glomerular filtration rate (GFR).[3,4] Diabetes mellitus, chronic glomerulonephritis, hypertension, and smoking are reported to be the most common triggering factors for CKD.[5] The End-stage renal disease (ESRD) is the most advanced form of CRF for which renal transplant is the treatment of choice.[6,7]

Studies had shown that endocrine abnormalities are very common in CKD. Most of the patients with chronic renal failure often have signs & symptoms suggestive of thyroid dysfunction, which includes dry skin, sallow complexion, low temperature, cold intolerance, decreased basal metabolic rate, lethargy, fatigue, edema & hyporeflexia. Various studies of thyroid functions in uremic patients have been carried out showing conflicting results. Hyperthyroidism, hypothyroidism & euthyroid state have all been reported by various workers.[8-12] Laboratory studies had also shown that serum triiodothyronine (T3) level was consistently low without any regard to treatment of CRF, whereas serum total & free thyroxine (T4) concentrations have been reported as low, normal or high. Serum thyroid stimulating hormone (TSH) levels were found to be normal in most patients of CRF even in those whose CRF is complicated by low T3 concentration. The incidence of goitre has also been variably reported in literature.[13,14] A study had reported reversion of thyroid function to normal after successful renal transplantation.[4] Despite extensive studies, thyroid status in uremia is still inconclusive due to the complexity of the system studied. For example, thyroidal radioiodide uptake is decreased because of reduced renal iodide clearance.[15]

The serum hormonal concentration may be altered by changes in the binding capacity of serum proteins, and abnormal serum constituents in uremia were thought to displace thyroid hormone from its protein-binding sites.[16] Heparin, a standard hemodialysis (HD)' medication, has been shown to increase serum free thyroxine concentration.[17] Peritoneal dialysis is an effective way of removing thyroid hormones from the circulation.[18] Goiter may be induced by the high serum level of inorganic iodide or retention of goitrogenic substances normally excreted by the kidney. Finally, malnutrition may be a contributing factor in altering thyroid function tests.[19]

Studies had shown that goiter is more prevalent among women with CKD. Miki et al. in his study on thyroid carcinoma had quoted that thyroid cancers are more common in CKD and more particular in patients who underwent kidney transplant which might be due to the disturbed cellular immunity and the influence of immunosuppressive drugs.[20] The Wolf-Chaikoff effect had already proven that elevation of serum inorganic iodine with decline in the glomerular filtration rate would block the synthesis of thyroid hormones leading onto diffuse goiter and hypothyroidism among patients undergoing hemodialysis.[21]

Aim

To assess the prevalence of alteration of thyroid physiology among patients chronic renal failure patients and to correlate between the thyroid hormone levels and the severity of chronic kidney disease.

Materials and Methods

The study was conducted at our hospital for a period of one year between Jan 2017 and Dec 2017. It is a cross-sectional observational study. The study was started after getting the approval from the institutional ethical committee. The following inclusion and exclusion criteria was followed for the selection of subjects. Patients with symptoms of uraemia for 3 months or more, patients ultrasound finding showing contracted kidneys with poor cortico-medullary differentiation were included for the study. Patients receiving anti-thyroid or thyroxine drugs, pregnant or lactating mothers, with associated liver disorder and patients who are taking certain drugs which alters the thyroid physiology are excluded from the study.

Based on the above mentioned inclusion and exclusion criteria the total study subjects involved in our study was 73. Informed consent was obtained from all the patients who were involved in the study. A detailed socio-demographic history along with clinical history was obtained from all the patients. Clinical examination pertaining to their renal and thyroid illness was performed on the patients and the findings are noted. The following investigations were performed.

1. Urine for specific gravity and broad cast
2. Peripheral smear for anaemia and burr cells.
3. Renal parameters like blood urea, Serum creatinine and Creatinine clearance (using Cockcroft- Gault formula).
4. ECG and X-ray chest to look for features for hypothyroidism and renal failure like pleural effusion, pericardial effusion to look for features for hypothyroidism and renal failure like pleural effusion, pericardial effusion.
5. USG abdomen for evidence of chronic renal failure.

Serum fT3, fT4 and TSH were measured by using Chemiluminiscence Immunoassay (CLIA) technique. The standard values for fT3, fT4 and TSH were 2.30-4.2 pg/ml, 0.89-1.76 ng/dl and 0.35-5.5 μIU/ ml respectively.

All data were entered and analysed using SPSS version 21. Mean and standard deviation was calculated for all the parametric variables and the statistical inference was derived by applying Man-Whitney U test and spearman's correlation test considered $p < .05$ as statistically significant.

Results

Table 1 shows the age and sex wise distribution of the study subjects. It is seen from the table that majority of the study subjects were in the age group of between 40 and 60 years with a overall mean age of 53.8 years. The minimum age was 28 years and maximum was 73 years. The male: female sex ratio was 1.92: 1 and the distribution of the age group among males and females were almost similar. The duration of CRF among our study subjects varied from 6 months to 5 years and the patients CRF were staged according to their creatinine clearance and eGFR. In our study subjects blood urea varied from 64 to 170 mg/dl and creatinine varied from 3 mg to 17.2 mg/dl, 24 hours urinary protein excretion was less than 1 gm/day in all the patients in this study group. Serum calcium and phosphorous were normal in all the patients. 80% of the patients had anaemia in which their peripheral smear report revealing 90% having normocytic normochromic anaemia and the remaining 10% had hypochromic anaemia. In our study majority of the study subjects were in stage V (end stage renal disease) CRF followed by stage IV CRF and only 5 – 8% of the subjects were in stage 1 and stage II CRF (Table 2). Among the various causes for CRF diabetic nephropathy was found to be the most common cause for CRF in our study subjects followed by chronic glomerular nephritis, hypertension, polycystic kidney disease and obstructive uropathy. The thyroid profile of our study subjects showed hypothyroidism was present in 43.8% of the CRF patients and in that majority of them had low T3 levels, followed by low T4 levels (36.9%) and an increased TSH levels (19.1%). None of our patients had an increased T3 or T4 levels and a decreased TSH levels and so in our subjects there was no evidence of hyperthyroidism among the CRF patients (Table 3). The mean T3 and T4 levels was found to be near normal in stage I and II of CRF and a steady decline in the T3 and T4 levels was observed in patients with stage III to stage V CRF and the difference was found to be statistically significant ($p<.05$). TSH levels was normal in stage I – III of CRF and it was found to be slightly increased in stage IV and V but this increase in TSH levels did not show a statistical significant difference (Table 4). The correlation between the T3, T4 levels and the various stages of CRF had shown a strong negative correlation, as the stages of CRF increases the number of patients with reduced T3 and T4 levels were found to be increasing and this was found to be statistically

significant (p<.05), whereas there was no statistically significant positive correlation seen between the stages of CRF and the TSH levels (p>.05) (Table 5).

Table 1: Age and sex wise distribution of the study subjects

Age group	Gender		Total
	Male	Female	
<30	3 (6.2%)	1 (4%)	4 (5.4%)
30 – 40	6 (12.5%)	3 (12%)	9 (12.3%)
41 – 50	17 (35.4%)	6 (24%)	23 (31.5%)
51 – 60	12 (25%)	8 (32%)	20 (27.3%)
61 – 70	7 (14.5%)	4 (16%)	11 (15%)
>70	3 (6.2%)	3(12%)	6 (8.2%)
Total	48 (100%)	25 (100%)	73 (100%)
Mean ± SD	54.6 ± 7.8	52.5 ± 8.2	

Table 2: Distribution of the study subjects based on the stages of chronic kidney disease

Stage of CKD	Frequency	Percentage
Stage 1	4	5.4%
Stage 2	6	8.2%
Stage 3	12	16.4%
Stage 4	23	31.5%
Stage 5	28	38.3%
Total	73	100%

Table 3: Distribution of the study subjects based on their thyroid hormone levels.

Thyroid profile	Normal	Decreased	Increased
T3	41 (56.1%)	32 (43.8%)	0
T4	46 (63%)	27 (36.9%)	0
TSH	59 (80.8%)	0	14 (19.1%)

Table 4: Thyroid hormone levels among the different stages of CKD patients

CKD stages	T3 (mean ± SD)	T4 (mean ± SD)	TSH (mean ± SD)
Stage 1	3.6 ± 1.1	1.3 ± 0.9	5.3 ± 1.3
Stage 2	3.3 ± 1.4	1.2 ± 0.65	5.4 ± 2.1
Stage 3	2.9 ± 0.89	0.8 ± 0.41	5.3 ± 1.89
Stage 4	1.8 ± 0.74	0.7 ± 0.33	6.6± 1.73
Stage 5	1.1 ± 0.63	0.52 ± 0.09	6.4 ± 1.96
P value	<.001	<.001	0.318

p value derived by applying Man-Whitney U test.

Table 5: Correlation between stages of CKD and hypothyroidism among the study subjects

Stage of CKD	Thyroid status		
	T3 decreased (n=32)	T4 decreased (n=27)	TSH increased (n=13)
Stage 1 (n=4)	0	0	2 (15.3%)
Stage 2 (n=6)	1 (3.1%)	1 (3.7%)	3 (23%)
Stage 3 (n=12)	4 (12.5%)	2 (7.4%)	4 (30.7%)
Stage 4 (n =23)	10 (31.2%)	8 (29.6%)	2 (15.3%)
Stage 5 (n=28)	17 (53.1%)	16 (59.2%)	2 (15.3%)
P value	<.0001	<.0001	0.681

P value derived by applying spearman's correlation test

Discussions

A large number of hormonal systems are affected by CRF, yet it remains unclear to what extent these changes are responsible for manifestations of uraemic syndrome. Patients with CRF often have signs and symptoms suggestive of thyroid dysfunction and hence the diagnosis of thyroid disease in these patients have obvious prognostic implications.[22] Thyroid dysfunction in chronic renal failure was extensively studied by

Ramirez et al and also apart from his study, various studies conducted in this line have showed different results.[13] In this study, patients only on conservative management were studied. This is because thyroid profile undergoes changes due to dialysis independent of that due to chronic renal failure. Dialysis also changes the previous serum status of TH in the patients with renal failure. Many studies have been conducted by comparing chronic renal failure patients on conservative management and hemodialysis by Ramirez et al. and Kayima et al.[13,23] Many studies conducted in chronic renal failure patients showed low T3 values. Low T3 had been reported in Ramirez et al., Hegedüs et al., and Beckett et al. studies, that too in cases of severe renal failure.[13,24,25] Ramirez et al study showed a linear correlation between the mean serum T3 and T4 and severity of renal failure.[13]

It is estimated that 43.8% of patients have thyroid profile abnormality. Remaining 57.2% of patients have normal thyroid profile. Among 43.8% of these patients, excluding primary hypothyroid patients only 6% of the patients had low T3 level with normal T4 level and the remaining 36.9% have both low T3 and T4 levels. The percentage of patients having low T3 and T4 gradually increases, with decrease in GFR.

In our study, the mean values of fT3 were significantly different with decreasing pattern as the stages of CKD increases. These findings are in par with the previous studies which had proven that more than one half of patients with ESRD cases had low T3 values for which the reason quoted was poor conversion T4 to T3 with production of T3 being normal.[26-28] Further in the study done by Singh PA et al., he identified factors such as malnutrition, metabolic acidosis, increased excretion of fT4 in urine and the release of cytokines specifically in patients with CRF stage 5 had also contributed to the poor conversion of T4to T3.[7] In the present study we found a steady decline in thyroid functions as the advancement in the stages of CRF which was substantiated in the study done by Rajagopalan et al.[29]

In the present study we found that all the patients with low fT4 had also decreased fT3 levels mainly in stage 5 CKD patients. The mean value of fT4 was steadily decreasing as the disease (CRF) progression increases. Studies had also shown a similar type of results quoting the reason as poor T4 binding to serum carrier protein like thyroid hormone binding globulin (TBG), albumin or pre-albumin.[30]

In our study the mean value of TSH was found to be almost similar in all stages of CRF except a slight increase in stage V CRF without showing statistically significant difference, which would be due to the glycosylation of TSH the tyrotropin releasing hormone is inhibited and so the thyroid is able to compensate for humoral urinary losses keeping the patient in the euthyroid state.[31,32]

In our study 38.5% of the patients had elevated TSH levels with normal fT3 and fT4 levels and these findings are similar to the previous studies which reported that subclinical hypothyroidism can be independently associated with CKD.[33,34]

Conclusion

Thyroid hormone dysfunction occurs in 43.8% of the chronic renal failure patients. Incidence of hypothyroidism is increased in patients with advanced stages of chronic renal failure. Number of patients with low T3 and T4 syndrome progressively increases with severity of renal failure. Serum level of T3 and T4 has a statistically significant correlation with the severity of renal failure, whereas TSH did not so such correlation. Alteration of thyroid physiology among CRF patients found to be increasingly common and so thyroid screening should be made mandate for all patients with CKD.

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