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Original Article

Thyroid Function Abnormalities in Patients with Chronic Kidney Disease - A Prospective Study

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Abstract

Introduction: The kidney normally plays an important role in the metabolism, degradation, and excretion of several thyroid hormones (THs). It is not surprising therefore that impairment in kidney function leads to disturbed thyroid physiology. All levels of the hypothalamic-pituitary-thyroid axis may be involved, including alterations in hormone production, distribution, and excretion.

Aim: The aim of this study is to study the correlation between TH dysfunction and severity of renal diseases and to differentiate primary thyroid diseases from thyroid dysfunction due to chronic renal failure.

Materials and Methods: Patients with chronic renal failure who are on conservative management were included in the study. Thyroid profile would be done in all patients who fulfill the inclusion criteria.

Results: Excluding patients with hypothyroidism, T_3 level is low in 46% of the patients, and T_4 level is low in 20% of the patients. Excluding 5 hypothyroidism patients who have low T_4 values, 9 (21.33%) other patients had T_4 level below normal and low T_3 syndrome. Number of patients with low T_4 does not correlate with severity of renal disease.

Conclusion: Chronic kidney disease leads to significant changes in the TH levels, which need to be interpreted carefully in these patients.

Key words: Chronic kidney disease, Low T_3 syndrome, Thyroid dysfunction

INTRODUCTION

The function of the thyroid gland is one of the most important in the human body as it regulates majority of the body's physiological actions. The thyroid produces hormones (T_3 and T_4) that have many actions including metabolism, development, protein synthesis, and the regulation of many other important hormones. Any dysfunction in the thyroid can affect the production of thyroid hormones (THs) (T_3 and T_4) which can be linked to various pathologies throughout the body. The interactions between kidney and thyroid functions are known for years.[1-3] THs are necessary for growth and development of the kidney and for the maintenance of water and electrolyte homeostasis. On the other hand, the kidney is involved in the metabolism and elimination of TH. From a clinical practice viewpoint, it should be mentioned that both hypothyroidism and hyperthyroidism are accompanied by remarkable alterations in the metabolism of water and electrolyte, as well as in cardiovascular function.[4,5] All these effects generate changes in water and electrolyte kidney management. Moreover, the decline of kidney function is accompanied by changes in the synthesis, secretion, metabolism, and elimination of TH. Thyroid dysfunction acquires special characteristics in those patients with advanced kidney disease.[6] On the other hand, the different treatments used in the management of patients with kidney and thyroid diseases may be accompanied by changes or adverse events that affect thyroid and kidney function, respectively.

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Aim

The aim of this study is to study the correlation between TH dysfunction and severity of renal diseases and to

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differentiate primary thyroid diseases from thyroid dysfunction due to chronic renal failure.

MATERIALS AND METHODS

This prospective observational study was conducted in the Department of General Medicine, Aarupadai Veedu Medical College Hospital, Puducherry. Patients with chronic renal failure who are on conservative management were included in the study. Inclusion criteria: Symptoms of uremia for 3 months or more, elevated blood urea, serum creatinine, ultrasound evidence of medical renal disease, bilateral contracted kidneys - size <8 cm in male and size <7 cm in female, poor corticomedullary differentiation, Type 2 or 3 renal parenchymal changes, and supportive laboratory evidence of chronic renal failure such as anemia, urine specific gravity, and changes in serum electrolytes. Exclusion criteria: Patients who underwent peritoneal dialysis or hemodialysis, nephrotic range of proteinuria, low serum protein, especially albumin, history of long time hypothyroidism, other conditions such as acute illness, recent surgery, trauma or burns, and diabetes mellitus. Patients with liver diseases, patients taking drugs altering thyroid profile like amiodarone, steroids, dopamine, phenytoin, estrogen pills, and iodine containing drugs were excluded. Thyroid profile would be done in all patients who fulfill the inclusion criteria. Informed consent was obtained from all patients. Detailed clinical history and clinical examination were undertaken with preference to thyroid and renal diseases. The following investigations were performed urine for specific gravity and broadcast, peripheral smear for anemia and burr cells, renal parameters such as blood urea, serum creatinine, and creatinine clearance (using Cockcroft-Gault formula), serum calcium and phosphorus, 24 h urine protein, and serum protein to rule out nephrotic syndrome and hypoproteinemia, respectively.

RESULTS

50 patients with chronic renal failure who were on conservative management were studied. Among 50 patients, 10 patients were female and 40 patients were male. The age varied from 12 to 70 years. Among 50 patients, 10 patients were 30 years and below, 33 patients were in the age group of 30-60 years, and 7 patients above 60 years. The duration of chronic renal failure in this study varied from 3 months to 5 years. The creatinine clearance varied from 6 to 34 ml/min. 20 patients had glomerular filtration rate (GFR) 10 ml/min accounting for 40%, 20 patients had GFR 11-20 ml/min accounting for another 40%, and remaining 10 patients had GFR more than 20 ml/min (accounting for 20%) (Table 1). Blood urea varied from 64 to 170 mg/dl and serum creatinine varied from 3 to 17.2 mg/dl. 24 h urinary protein excretion was <1 g/day in all the patients in this study group. Serum calcium and phosphorous were normal in all the patients. 80% of the patients had anemia with peripheral smear revealing normocytic normochromic anemia in 72% and hypochromic anemia in 8% of the patients. T_3 level in this study varied from 0.2 to 2 ng/ml. The mean value of T_3 is 0.67 ng/ml (Table 2). Age comparison of low T_3 syndrome in Table 3 shows about 30% of chronic renal failure patients below 30 years of age have low T_3 syndrome. The percentage increases to 51.51% in the age group 31-60 years. This is probably due to increased chronic renal failure patients in this age group. In age above 60 years, 42.85% have low T_3 syndrome. Sex incidence in this study, 50% of males have low T_3 syndrome, and only 30% of the females have low T_4 syndrome (Table 4).

Ultrasound study of the abdomen showed evidence of

Table 1: Distribution of level of GFR in CRF patients

GFR	Patients (%)
<10 ml/min	20 (40)
11-20 ml/min	20 (40)
>20 ml	10 (20)

GFR: Glomerular filtration rate, CRF: Chronic renal failure

Table 2: Serum concentration of TH in CRF patients studied

THs	Normal range	Study range	Mean±SD
Serum T_3 ng/ml	0.6-2.1	0.2-2	0.673±0.414
Serum T_4 µg/dl	5-13	0.5-9.5	5.622±2.27
Serum TSH µIU/ml	0.4-7	0.6-27	6.53±6.98

TSH: Thyroid-stimulating hormone, TH: Thyroid hormones, SD: Standrad deviation

Table 3: Distribution of low T_3 and T_4 among various levels of TSH in the study group of CRF patients

TSH level µIU/ml	Patients with low T_3 (%)	Patients with low T_4 (%)
≤7	16 (57.14)	8 (53.33)
7.1-20	7 (25)	2 (13.33)
>20	5 (17.85)	5 (33.33)

TSH: Thyroid-stimulating hormone, CRF: Chronic renal failure

Table 4: Analysis of thyroid dysfunction in this study

Thyroid dysfunction	Patients (%)
Low T_3 syndrome	23 (46)
Low T_4 syndrome	10 (20)
Hypothyroidism	5 (10)

chronic renal failure in all patients. Contracted kidney was present in 90% of the patients. Remaining patients had poor corticomedullary differentiation. Among these 28 patients, 5 patients had low serum T_3 and T_4 and high thyroid-stimulating hormone (TSH) values more than 20 μIU/ml. They also had symptoms of hypothyroidism. These patients as per the criteria were grouped under "primary hypothyroidism." Only 6 patients had slightly elevated TSH ranging between 9 and 14 μIU/ml. In this group, only 3 patients had low T_3 level, among which only one patient had few clinical features of hypothyroidism. Hence, these 6 patients did not satisfy the criteria for hypothyroidism fully. Hence, all 23 patients were grouped under "low T_3 syndrome" or "sick euthyroid syndrome" (Table 5).

Dry, flaky skin was present in 15 patients, of whom only 4 patients were hypothyroid. Sinus bradycardia was present in 7 patients.

Hypothyroidism did not show any linear correlation with GFR. Increased number of hypothyroid patients of about 2 in number was present in GFR 11-20 ml/min, whereas only 3 patients had hypothyroidism in GFR <10 ml/min.

Excluding 5 hypothyroidism patients who have low T_4 values, 9 (21.33%) other patients had T4 level below normal and low T_3 syndrome. Number of patients with low T4 does not correlate with severity of renal disease (Table 6). The mean value of T4 excluding hypothyroidism patients was normal at all the stages of renal failure (Table 7). None of the patients had T4 value above normal level.

Excluding the patients with primary hypothyroidism, the mean value is 0.71 ng/ml. This value was in low normal limit. Excluding hypothyroidism, T_3 levels were studied in relation to GFR. It was found that mean value of serum T_3 is low (0.538 ng/ml) only in patients with GFR <10 ml/min (Table 8). The mean value is low normal in patients with GFR more than 10 ml/min. According to the study, number of patients with low T_3 independently increases with increase in severity of the renal failure irrespective of low T_3 levels.

Serum T_4 level in the study varies from 0.5 to 9.5 μg/dl. Mean value of serum T_4 among 50 patients 5.62 μg/dl, excluding hypothyroid patients, the mean value is 5.99 μg/dl. This value is within low normal level of T_4.

Values of TSH vary from 0.6 to 27 μIU/ml with mean value in 6.53 μIU/ml. Excluding hypothyroidism, mean value is 4.75 μIU/ml. This shows normal serum level of TSH. Among the 50 patients, TSH was normal in 38 patients (76%) and values between 7.1 and 20 μIU/ml in 7 patients (14%). It was elevated more than 20 μIU/ml in 5 patients (10%). According to our study, in patients with low T_3 syndrome, the mean values of TSH in various stages of renal failure are within normal range. However, the values of TSH did not show any linear correlation with GFR.

DISCUSSION

Thyroid dysfunction in chronic renal failure was extensively studied by Ramirez *et al.*[7] Apart from his study, various studies conducted in this line have showed different results. 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.*[7] and Kayima *et al.*[8] Many studies conducted in chronic renal failure patients showed low T_3 values. Low T_3 had been reported in Ramirez *et al.*,[7] Hegedüs *et al.*,[9] and Beckett *et al.*[10] studies, that too in cases of severe renal failure. Ramirez *et al.*[7] study showed a linear correlation between the mean serum T_3 and T_4 and severity of renal failure. As with other studies, mean T_3 level in our study

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

Thyroid dysfunction	Patients with normal values (%)	Patient with low values (%)	Patients with high values (%)
T_3	22 (44)	23 (26)	Nil
T_4	35 (70)	10 (20)	Nil
TSH	38 (76)	Nil	7 (14)

TSH: Thyroid-stimulating hormone

Table 6: Distribution of low T_3 and T_4 syndrome with relation to the creatinine clearance

Creatinine clearance ml/min	Low T_3 syndrome	Low T_4 syndrome
≤10	13 (65)	6 (30)
11-20	7 (35)	3 (15)
>20	3 (30)	1 (10)

Table 7: Distribution of thyroid dysfunction in this study among various creatinine clearance levels

Creatinine clearance ml/min	Patients (%)	Low T_3 syndrome (%)	Hypothyroidism (%)
≤10	20 (40)	13 (65)	3 (15)
11-20	20 (40)	7 (35)	2 (10)
>20	10 (20)	3 (30)	Nil

Table 8: Correlations of THs with severity of renal failure excluding hypothyroidism

Creatinine clearance ml/min	Mean T_3 µg/dl	Standard deviation	Mean T_4 µg/dl	Standard deviation	Mean TSH µIU/ml	Standard deviation
≤ 10 (*n*=17)	0.538	0.40	5.02	2.10	5.22	4.25
11-20 (*n*=18)	0.82	0.43	6.69	2.17	3.77	3.78
>20	0.8	0.31	6.32	2.04	5.72	5.00

TH: Thyroid hormones

was reduced below normal in GFR <10 ml/min. In higher GFR, it was present in low normal T_3 level and there was no linear correlation between T_3 level and GRF which is consistent with Avasthi *et al.* study.[11] Mean T_4 level in this 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 this study, not all the patients with chronic renal failure have low T_3 and T_4. It is estimated that only 58% (29 patients) of patients have thyroid profile abnormality. Remaining 42% of patients have normal thyroid profile. Among 58% of these patients, excluding primary hypothyroid 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 increases, with decrease in GFR. The patient who will develop such change 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. However, TSH level does not show any linear correlation with the severity of renal failure. This is consistent with the study conducted by Spector *et al.*[12] and Ramirez *et al.*[7] These studies demonstrated abnormality in hypophyseal mechanism of TSH release in uremic patients as the TSH response to the thyrotropin-releasing hormone (TRH) was blunted. Other studies conducted by Joseph *et al.*[13] and Hardy *et al.*[14] revealed low T_3, T_4 level with high TSH level suggesting maintenance of pituitary-thyroid axis. In this study, excluding those with hypothyroidism, 7 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 such as FT_4, FT_3, TRH response, and antithyroid autoantibodies can be done to diagnose hypothyroidism in these patients. Out study is consistent with the results of Ramirez *et al.*[7] study showing low T_3, low T_4, and normal or mild elevation of TSH. Yet, it is unclear that to what extent these changes are responsible for the manifestations of uremic syndrome. From the various studies, it has been suggested that this thyroid profile derangements are a part of body adaptation mechanism. As stated previously, hemodialysis and continuous ambulatory peritoneal dialysis have shown to affect the thyroid profile independently of chronic renal failure. Furthermore, drugs like heparin, furosemide used during dialysis will affect the thyroid profile. Kayima *et al.*[8] and Gomez-Pan A *et al.*[15] have conducted studies regarding the effect of dialysis on chronic renal failure patients with thyroid dysfunction. These studies showed no significant improvement in thyroid profile after repeated hemodialysis. However, in the patients who have undergone renal transplant surgery, most of the thyroid function parameters returned to normal with TSH below normal. Previous studies by Quion-Verde[16] reported a high prevalence of hypothyroidism in chronic renal failure. It was estimated to be about 5% in patients with terminal renal failure. Detail study by Kaptein *et al.*[5,17] estimated the prevalence of primary hypothyroidism was about 2.5 times much frequent in chronic renal failure and dialysis. The hypothyroidism in chronic renal failure was estimated to range between 0 and 9.5%. Kaptein *et al.*[5] study also estimated the presence of antithyroid antibody titer in 6.7% of chronic renal failure. In our study, the hypothyroidism is present in 10% of the patients but does not correlate with the severity of the renal failure. The symptoms of hypothyroidism were distributed equally in both hypothyroid and chronic renal failure patients in our study. Signs of hypothyroidism were more common in chronic renal failure without hypothyroidism than with hypothyroidism. Hence, diagnosis of hypothyroidism in chronic renal failure mainly rest on TSH level which should be very high (>20 MIU/dl) with low serum T_4. In this study, no patient had clinical or biochemical features of hyperthyroidism.

CONCLUSION

TH dysfunction occurs in 58% of the chronic renal failure patients. Incidence of hypothyroidism is increased in patients with chronic renal failure. Both clinical and biochemical parameters are essential to diagnose hypothyroidism in patients with chronic renal failure. Excluding patients with hypothyroidism, T_3 level is low in 46% of the patients and T_4 level is low in 20% of the patients. Number of patients with low T_3 and T_4 syndrome progressively increases with severity of renal failure. Serum level of T_3 and T_4 has no correlation with the severity of renal failure. Alteration in the values of T_3 and T_4 occurs as a part of body's adaptation mechanism to conserve energy.

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