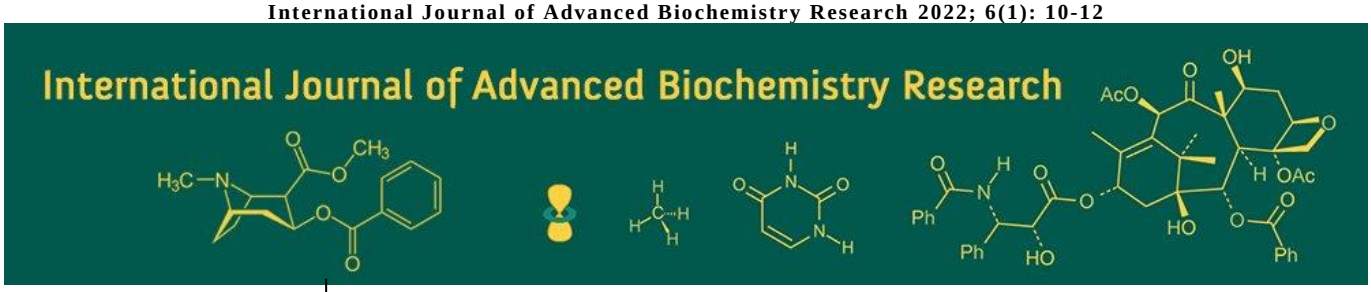

ISSN Print: 2617-4693
ISSN Online: 2617-4707
IJABR 2022; 6(1): 10-12
www.biochemjournal.com
Received: 07-11-2021
Accepted: 10-12-2021

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A study of thyroid dysfunction in patients with chronic kidney disease undergoing maintenance haemodialysis among the patients of tertiary care hospital

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DOI: https://doi.org/ 10.33545/26174693.2022.v6.i1a.7

Abstract
Introduction: Thyroid hormones are necessary for the growth and development of the kidney and for the maintenance of water and electrolyte homeostasis. The kidney normally contributes to the clearance of iodine, primarily by glomerular filtration. Thus iodide excretion is diminished in advanced renal failure, leading sequentially to an elevated plasma inorganic iodide concentration and an initial increment in thyroidal iodide uptake.
Materials and Methods: The present study was conducted in a tertiary care hospital in Belagavi, Karnataka State. 50 cases that were on regular maintenance hemodialysis treatment were selected and 50 controls were taken for study. Age & sex matched controls with normal renal function and no previous history of thyroid dysfunction was included in the study as controls. The quantitative determination of serum T_3, T_4 & TSH was done. The assay principle combines a one step enzyme immunoassay sandwich method with a final fluorescent detection (ELFA). Serum urea and creatinine was estimated by urease/glutamate dehydrogenase method and modified.
Results: There was a significant difference between the control and study group with respect to serum TSH & T_3 levels, serum T_4 levels were found to be not statistically significant. The serum TSH level was increased in 8 patients (16%) among those with CKD; the mean serum TSH concentration was 5.49±11.03 in CKD patients which was significantly increased than in controls (3.27±2.06). Serum T_3 concentration was less than the normal range in 10 of the 50 (20%) CKD patients, the mean serum total T_3 concentration was 1.69±0.67 in CKD patients was significantly lower than that in the control subjects (2.03±1.2). Serum concentration of T_4 was less in cases (81.34±23.87) than in controls (101.41±19.12) but the results were statistically not significant (P=0.083).
Conclusion: The present study finds thyroid dysfunction to be very common in CKD patients and reveals the significant association between CKD progression and thyroid dysfunction and mean of T_3, T_4 decreases and TSH increases significantly in cases as compared to controls. The diagnosis of hypothyroidism can be easily missed in Haemodialysis patients. Timely diagnosis and treatment of hypothyroidism may prevent deterioration of the patient's condition and prolong survival.

Keywords: Thyroid hormones, chronic kidney disease, hemodialysis

Introduction
Thyroid hormones are necessary for growth and development of the kidney and for maintenance of water and electrolyte homeostasis. On the other hand, Kidney plays an important role in the metabolism, degradation and excretion of thyroid hormone. Chronic kidney disease (CKD) encompasses a spectrum of different pathophysiology processes associated with abnormal kidney function, and a progressive decline in glomerular filtration rate (GFR) [1, 2]. CKD is a clinical syndrome due to irreversible kidney dysfunction leading to excretion, metabolic and synthetic failure culminating into an accumulation of non-protein nitrogenous substances and presenting with various clinical manifestations [3]. According the 2010 Global Burden of Disease study, chronic kidney disease was ranked 18th in the list of causes of total number of deaths worldwide.
The kidney normally contributes to the clearance of iodine, primarily by glomerular filtration. Thus iodide excretion is diminished in advanced renal failure, leading sequentially to an elevated plasma inorganic iodide concentration and an initial increment in thyroidal

iodide uptake [4]. Increased total body inorganic iodide can potentially block thyroid hormone production by affecting the pituitary-thyroid axis and peripheral metabolism of thyroid hormones. Such changes explain the higher frequency of hypothyroidism in patients with chronic kidney disease. So, Thyroid dysfunction is a commonly seen endocrine abnormality among CKD patients [5].

Prevalence of Thyroid dysfunction in CKD is found to be ranging from 13% in early CKD to 70% in ESRD according to various studies [6-9]. The relation between thyroid dysfunction and severity of CKD is not clear. Several previous studies depict conflicting results both positive and negative. Thus, there are huge numbers of patients remaining to be diagnosed and/or treated.

Hemodialysis (HD) is the removal of certain elements from the blood by virtue of the difference in the rates of their diffusion through a semi permeable membrane by means of a hemodialysis machine or filter. Hemodialysis is the most common method used to treat advanced and permanent kidney failure. Maintenance hemodialysis is hemodialysis carried out at regular intervals to treat chronic renal failure. A number of studies have shown that serum thyroid hormones levels are frequently abnormal in patients on regular maintenance hemodialysis [10]. The prevalence of primary hypothyroidism mainly in the subclinical form increases with decreasing glomerular filtration rate [11]. The present study was planned to compare the status of thyroid hormones, serum total T_3, T_4 & TSH in CKD patients on regular maintenance hemodialysis irrespective of their stage with that of controls.

Materials and Methods

The present study was conducted in a tertiary care hospital in Belagavi, Karnataka state. 50 cases that were on regular maintenance hemodialysis treatment were selected and 50 controls were taken for study. Age & sex matched controls with normal renal function and no previous history of thyroid dysfunction was included in the study as controls. After taking the consent from cases and controls under strict aseptic precaution venipuncture was done and 3 ml blood was drawn into plane vacutainer and blood was allowed to clot and then centrifuged at 3000 rpm for 3 min to separate the serum, the sample was analyzed within 6 hours. The quantitative determination of serum T_3, T_4 & TSH was done by Enzyme linked Immunofluorescence assay (Minividas, Biomerieux, Germany). The assay principle combines a one step enzyme immunoassay sandwich method with a final fluorescent detection (ELFA). Serum urea and creatinine was estimated by urease/glutamate dehydrogenase method and modified Jaffe's alkaline picrate method respectively in fully automated analyzer Bio-systems.

Results

Comparison of the measured parameters in healthy controls and CKD patients undergoing maintenance hemodialysis.

Table 1. Parameters Values

Parameters	Controls (n=50)	Cases (n=50)	p-value
Triiodothyronine (T_3) nmol/L	2.03±1.2	1.69±0.67	0.000*
Thyroxine (T_4) nmol/L	101.41±19.12	81.34±23.87	0.083 (statistically not significant)
Thyroid stimulating hormone (TSH) mIU/ml	3.27±2.06	5.49±11.03	0.010
Urea mg/dl	18.20±9.7	82.20±38.60	0.000*
Creatinine mg/dl	0.63±0.5	5.47±1.53	0.000*

There was a significant difference between the control and study group with respect to serum TSH & T_3 levels, serum T_4 levels were found to be not statistically significant. The serum TSH level was increased in 8 patients (16%) among those with CKD; the mean serum TSH concentration was 5.49±11.03 in CKD patients which was significantly increased than in controls (3.27±2.06). Serum T_3 concentration was less than normal range in 10 of the 50 (20%) CKD patients, the mean serum total T_3 concentration was 1.69±0.67 in CKD patients was significantly lower than that in the control subjects (2.03±1.2). Serum concentration of T_4 was less in cases (81.34±23.87) than in controls (101.41±19.12) but the results were statistically not significant (P=0.083).

Discussion

A large number of hormonal systems are affected by CRF, yet it remains unclear to what extent these changes are responsible for manifestations of uremic syndrome. Patients with CRF often have signs & symptoms suggestive of thyroid dysfunction & hence the diagnosis of thyroid disease in these patients has obvious prognostic implications. The data reported deals primarily with the clinical symptoms sign index & biochemical parameters. Two patients were clinically & biochemically confirmed to be hypothyroid.

The present study was aimed at to assess the prevalence of thyroid dysfunction in CKD patients and to determine the correlation between thyroid dysfunction and severity of renal disease. Various studies were conducted about thyroid dysfunction and the severity of CKD and shown different results. In our study, CKD 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 thyroid hormone status in patients with renal failure. Various studies have been studied by comparing CKD patients on conservative Management and patients on HD by Ramirez [12] and Kayima *et al.* [13]

Mean TSH levels are high compared to controls, even though in the majority of cases the TSH level still remains within the normal range. Our study shows increased TSH in patients who had low T_3 and T_4 suggesting maintenance of pituitary axis. This is in accordance with the studies conducted by G Avasthi *et al* & Joseph *et al*. [14, 15] In our study, serum TSH concentration was significantly increased in 8 (16%) of CKD patients, similar findings were observed by Gilles R *et al.* [16] Any impairment in kidney function leads to disturbed thyroid physiology; all levels of hypothalamic pituitary thyroid axis are involved, including alterations in hormone production, distribution and excretion [17]. There was more frequent subclinical hypothyroidism in patients on maintenance hemodialysis compared to the control group (16% Vs. 0%). In some studies there was no significant difference in mean TSH

levels in patients on maintenance hemodialysis and healthy controls [18]. In uremia the mean values of both serum T_3 and T_4 were low, this is comparable to various studies done earlier [19]. There are many factors leading to low T_3 and T_4 in patients undergoing Hemodialysis. Due to reduced deiodinase activity, reduced renal excretion and in organic iodide generated by residual deiodinase activity accumulates in CKD, which reduces thyroid hormone synthesis [20].

Many studies demonstrated a low T_4 in CKD patients, primarily because of an impaired protein Binding of T_4. The accumulation of toxic uremic solutes alters the hypothalamic control of the pituitary gland and the TSH response to thyrotropin releasing hormone is subnormal in these patients. In recent studies, it was shown that, the systemic inflammation and metabolic acidosis might alter the thyroid function in CKD patients [21]. The minor increase in TSH levels (5 to 20 mU/l) observed in about 20% of uremic patients are usually not considered to be reflecting hypothyroidism. Thyroid hormone supplementation should not be initiated without substantial elevation in TSH levels and careful consideration [22]. The clinical features of hypothyroidism are often masked with the uremic state; hence it is necessary to conduct periodic screening of thyroid function in all haemodialysis patients. The early diagnosis and treatment of thyroid disease significantly reduce morbidity and mortality.

Conclusion

The present study finds thyroid dysfunction to be very common in CKD patients and reveals the significant association between CKD progression and thyroid dysfunction and mean of T_3, T_4 decreases and TSH increases significantly in cases as compared to controls. The diagnosis of hypothyroidism can be easily missed in Haemodialysis patients. Timely diagnosis and treatment of hypothyroidism may prevent deterioration of the patient's condition and prolong survival. The thyroid disorders on Haemodialysis patients are known to be a strong risk factor for cardiovascular disease and predictor of all cause mortality. The patients with CKD on Haemodialysis should be routinely screened for thyroid disorders.

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