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Research Article

Prevalence of thyroid hormone abnormalities in stage 5 chronic kidney disease: a tertiary care center study of Nepal

Samir Singh[1]*, Aman Verma[2], Gopi Aryal[3], Santosh Thapa[4]

[1]Department of Clinical Biochemistry, [3]Department of Pathology, [4]Department of Nephrology, KIST Medical College, Lalitpur, Nepal
[2]School of Life and Basic Sciences, Jaipur National, University, Jaipur, Rajasthan, India

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***Correspondence:**
Dr. Samir Singh,
E-mail: samirbiochem.jnu@gmail.com

ABSTRACT

Background: Chronic kidney disease (CKD) implies progressive, long-standing and irreversible impairment in renal function that results in end stage renal disease (ESRD). ESRD is a frequent cause of Non-thyroidal illness (NTI) with low free triidothyronine (fT3), usually elevated reverse T3 (rT3), normal or low thyroid stimulating hormone (TSH), and if prolonged, low free thyroxine (fT4), despite patient remaining clinically euthyroid. Present study aimed to estimate the prevalence of thyroid hormone abnormalities in stage 5 CKD patients and also to compare these changes with healthy controls.
Methods: The present cross-sectional observational study was conducted on thirty eight stage 5 CKD patients and 38 age-sexes matched healthy volunteers as control. The demographic data, medical history, etiology, physical examination and laboratory results were recorded on a special form developed by the researchers.
Results: The mean age of male and female stage 5 CKD patients were 50.81±17.30. 44.73% of the stage 5 CKD patients had low fT3 whereas 28.94% had low fT4 values below the reference range. 5.26% patients had increased TSH values above the normal reference limit. The mean TSH values were not significantly differing among diseased and control groups. Among the risk factors for CKD, diabetic nephropathy (44.73%) was found to be the lead primary cause followed by chronic glomerulonephritis (26.31%) and hypertension (21.05%).
Conclusions: From this study, it was concluded that the prevalence of thyroid hormone abnormalities especially low fT3 and fT4 is very common in stage 5 CKD patients. Diabetic nephropathy was among the lead cause of stage 5 CKD.

Keywords: Chronic kidney disease, Thyroid hormone abnormalities, Nepal

INTRODUCTION

The term chronic kidney disease (CKD) is now replacing terms such as chronic renal failure or insufficiency.[1] CKD implies progressive, long-standing and irreversible impairment in renal function that results in end stage renal disease (ESRD).[2] Thyroid hormone profile includes the test like plasma triiodothyronine (T3), thyroxine (T4) and thyroid stimulating hormone (TSH). T3 and T4 are produced from thyroid gland whereas TSH is produced by anterior pituitary gland. T3 and T4 are present in both bound and free form. The free hormones are really active molecules. The free fractions of the hormones can be measured accurately by Chemiluminiscence Immunoassay (CLIA).[3] Kidney and thyroid function are interconnected through several mechanisms. Thyroid hormones are necessary for the maintenance of electrolyte and water. Similarly, kidney is also involved in the regulation of thyroid hormones metabolism.[4] Failure of metabolic, excretory and synthetic functions are commonly associated with the irreversible loss of renal function that ultimately results in uremia or

azotemia i.e. retention of urea and other non-protein nitrogenous substances in the blood. CKD affects thyroid function in several ways that include low circulating thyroid hormone concentration, alteration in peripheral hormone metabolism, disturbance in binding them to carrier proteins, possible reduction in tissue thyroid hormone content and increased iodine store in thyroid gland resulting in the reduction of serum triidothyronine (T3) and thyroxin (T4).[5]

In 2009, Iglesias P and Diez JJ published a review article entitled thyroid dysfunction and kidney disease in a European Journal of Endocrinology in which they report that serum TSH concentrations are usually normal or elevated in CKD. Free and total T3 and T4 concentrations are usually normal or low in patients with CKD. The reduction in T3 (low T3 syndrome) is most frequently observed thyroid alteration in these patients. This reduction in T3 concentration has been linked to a decrease in the peripheral conversion of T4 to T3.[6]

ESRD is a frequent cause of non-thyroidal illness (NTI) that refers to a syndrome found in seriously ill or starving patients with low fT3, usually elevated reverse T3, normal or low TSH and if prolonged, low fT4 despite patient remaining clinically euthyroid.[7]

The aim of the present study was i) to estimate the prevalence of thyroid hormone abnormalities in stage 5 CKD patients and ii) to compare these changes with healthy controls.

METHODS

The present cross-sectional observational study was conducted in the Department of Biochemistry in collaboration with the Department of Nephrology and dialysis unit of KIST Medical College and Teaching Hospital, Lalitpur, Nepal. This study was conducted for a period of six months from July 2015 to December 2015. Study population consisting thirty eight stage 5 CKD patients (21 men and 17 women) with different causes with age range 21 to 77 years. The demographic data, medical history, etiology, physical examination and laboratory results were recorded on a special form developed by the researchers. Patients had different duration of chronic illness ranging from 6 months to 4 years.

Out of thirty eight, 24 patients were on HD and 14 were on conservative treatment. Thirty eight age-sex matched healthy volunteers with normal GFR were taken as control. Patients with stage 5 CKD were confirmed by serum creatinine level, clinical features of uremia and glomerular filtration rate (GFR) estimation. GFR was measured by using Cockcroft-Gault formula. Written informed consent was taken from the study subject. Patient with known history of thyroid function abnormalities and pregnancy were excluded from the study. Five ml of blood sample were collected from cubital vein in vacutainer plain tubes and were allowed to clot and centrifuged to separate serum. Serum levels of creatinine were measured by creatinine kit supplied by Accurex Biomedical, India. Serum fT3, fT4 and TSH were measured by using Immunoassay system which is a CLIA technique from Siemens Healthcare Diagnostics, USA.

All variables were presented as number and frequency and were arranged in tables. Data were expressed as mean ± standard deviation. The independent sample t test was used to compare stage 5 CKD patient with healthy controls group. Statistical analyses were done by SPSS software (Statistical Package for the Social Sciences, version 21.0, SPSS Inc, Chicago, USA). The level of significance (P) was set to be <0.05.

The normal range of 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.

RESULTS

Among thirty eight stage 5 CKD patients, 21 (55.26%) were males and 17 (44.73%) were females (Table 1). The mean age in stage 5 CKD patients and healthy control group were 50.81±17.30 and 51.44±15.34 respectively, which was not significantly different in two groups (P>0.05).

Table 1: Frequency and percentage of male and female chronic renal failure.

Gender	Frequency (n)	Percentage (%)
Male	21	55.26
Female	17	44.73
Total	38	100.0

Table 2: Factors causing chronic renal failure.

Causes	Frequency (n)	Percentage (%)
Diabetic nephropathy	17	44.73
Chronic glomerulonephritis	10	26.31
Hypertension	8	21.05
Others (Obstructive uropathy, polycystic kidney disease, etc.)	3	7.89

As shown in Table 2, diabetic nephropathy (44.73%) was the leading cause of stage 5 CKD followed by chronic glomerulonephritis (26.31%) and hypertension (21.05%). Other causes (7.89%) of stage 5 CKD were obstructive uropathy, polycystic kidney disease etc.

Seventeen (44.73%) stage 5 CKD patients had low fT3 whereas eleven (28.94%) had low fT4 values that were below the reference range. There were no any reduction in TSH level but two patients (5.26%) had increased TSH values compared to normal limit (Table 3).

Table 3: Distribution of chronic renal failure having normal and deranged fT3, fT4 and TSH.

Thyroid profile	Normal		Decreased		Increased	
	n	%	n	%	n	%
fT3 (pg/ml)	21	55.26	17	44.73	0	0.0
fT4 (ng/dl)	27	71.05	11	28.94	0	0.0
TSH (µIU/ml)	36	94.73	0	0.0	2	5.26

In Table 4, mean and standard deviation of thyroid hormone and serum creatinine were compared between stage 5 CKD and healthy control. The mean value of serum creatinine in stage 5 CKD patients and control group were 7.77±2.87 and 0.88±0.19 which was statistically significant (P<0.001).

Significant differences in the mean level of fT3 and fT4 were seen among stage 5 CKD patients and healthy control group. The mean value of fT3 in stage 5 CKD patients and control group were 2.18±0.56 pg/ml and 2.96±0.49. The P value in both group were <0.001, which was significant.

Table 4: Comparison of age, serum creatinine, fT3, fT4 and TSH in healthy controls with chronic renal failure.

Variables	Healthy control (n=38)	CRF patients (n=38)	P* value
Age	51.44±15.34	50.81±17.30	0.867
Serum creatinine	0.88±0.19	7.77±2.87	<0.001
fT3 (pg/ml)	2.96±0.49	2.18±0.56	<0.001
fT4 (ng/dl)	1.37±0.48	0.99±0.22	<0.001
TSH (µIU/ml)	2.68±1.41	2.71±1.66	0.934

* Independent sample t test

The mean value of fT4 in stage 5 CKD patients and control group were 0.99±0.22 ng/dl and 1.37±0.48 respectively. Here the P value in both group was <0.001, which was statistically significant. Mean value of TSH in stage 5 CKD patients (2.71±1.66) and healthy control (2.68±1.41) did not vary with each other. So, TSH value in these two groups were not differed significantly (P>0.05).

DISCUSSION

Thyroid hormones (TH) are necessary for growth and development of the kidney and for the maintenance of water and electrolyte homeostasis. On the other hand, kidney is involved in the metabolism and elimination of TH and is an important target organ for TH actions.[8,9]

The present study was carried out to estimate the prevalence of thyroid hormone abnormalities in stage 5 CKD patients. In our study, there was significant reduction in the level of fT3 and fT4 in stage 5 CKD patients as compared to the healthy control group.

Serum fT3 concentration was lowered in 17 (44.73%) out of 38 stage 5 CKD patients. The mean serum fT3 concentration 2.18±0.56 pg/ml in ESRD patients was significantly lower than the control subjects (2.96±0.49 pg/ml). Similarly, serum fT4 was also below the normal range in 11 (28.94%) out of 38 stage 5 CKD patients. The mean value of fT4 in stage 5 CKD patients and healthy control group were 0.99±0.22 and 1.37±0.48 respectively. This difference revealed that the mean values of fT4 in stage 5 CKD patients were significantly reduced as compared to control group. These results agree with the results of other studies.[5,10-13]

Low T4 values in ESRD patients may be related to impaired T4 binding to serum carrier proteins. It has been reported that many inhibitors of T4 binding to serum carrier proteins are present in CRF patients and thus

contributing to the decreased level of T4 in CRF.[10] CKD affects thyroid function in several ways that include low circulating thyroid hormone concentration, alteration in peripheral hormone metabolism, disturbance in binding them to carrier proteins, possible reduction in tissue thyroid hormone content and increased iodine store in thyroid gland resulting in the reduction of serum triidothyronine (T3) and thyroxine (T4).[14]

CKD affects the hypothalamus-pituitary-thyroid axis and the peripheral metabolism of thyroid hormone. Low T3 is the most common laboratory finding found in CKD patients. Normal or low levels of T4 may be due to the mono-deiodinase action occurring in the inner benzene ring instead of outer ring of T4, resulting in the formation of reverse T3.

Reverse T3 levels, however, are found to be normal in CKD patients because it moves from the vascular space to extra vascular and intracellular spaces. Low T3 levels in CKD may be due to the iodothyronine deiodinase (helps in T3 synthesis from T4) affected by fasting, chronic metabolic acidosis, and chronic protein malnutrition seen in CKD. Such factors influence the proteins binding toT3.[15] Low T3 levels in CKD may also be due to the decreased peripheral (extra thyroidal) conversion from T4 to T3 due to decreased clearance of the inflammatory cytokines such as TNF-alpha and IL-1.[16] In CKD, physiological compensation for low T3/T4 (with normal TSH levels) causes a reduction in protein catabolism which increases the nitrogen waste overload.

In the present study, serum TSH concentrations were within the normal range in 36 (94.73%) stage 5 CKD patients out of 38. Only two patients had TSH value increased above the normal range. Mean TSH value in stage 5 CKD patients (2.71±1.66) were similar to that of control group (2.68±1.41). This means that the TSH values in stage 5 CKD patients was not significantly altered. This results agreed with the previous studies.[5,6,10,11,17]

Reduced serum TSH levels were not seen in any subjects. Rajagopalan B et al. published an article entitled “Renal function marker and thyroid hormone status in undialyzed CKD” in which he reported that unchanged status of TSH level in CRF compared to normal patients reflects euthyroid status which suggests that thyroid is able to compensate for hormonal urinary losses keeping the patient euthyroid. Reduced serum TSH levels have not been reported to date in euthyroid CRF patients.[11]

Data from our study revealed the fact that the normal thyroid status was found only in half of our stage 5 CKD subject which will fulfilled the criteria for NTI. DeGroot LJ reported in NCBI Bookself about NTI in which he had described that NTI refers to a syndrome found in seriously ill or starving patients with low fT3, usually elevated reverse T3, normal or low TSH and if prolonged, low fT4 despite patient remaining clinically euthyroid.[7]

Recently KC Shiva Raj reviewed the thyroid function tests and its interpretation and reported that the fT4 and fT3 become low or low-normal while TSH remain normal or even low in NTI.[18] In our study, the pattern of NTI was found with low fT3 particularly common in 44.73% as well as low fT4 in 28.94% with TSH normal in 94.73%. This study is similar to the study done by Horacek J et al.[17]

5.26% stage 5 CKD patients had TSH level increased above the normal range with fT3 and fT4 within the normal limit. These findings suggested that the patients had subclinical hypothyroidism. This result is similar to the study by Chonchol M et al. in which 9.5% of CKD patients had subclinical hypothyroidism.[19]

Diabetic nephropathy (44.73%) was the leading cause of stage 5 CKD followed by chronic glomerulonephritis (26.31%) and hypertension (21.05%). Other causes (7.89%) of stage 5 CKD were obstructive uropathy, polycystic kidney disease etc. This is similar to the study done by Foley RN and Marshall SM in which they reported that diabetic nephropathy is the leading cause of ESRD worldwide.[20,21]

In present study, chronic glomerulonephritis was the second leading cause of stage 5 CKD which was differ from the study done by Khakurel S et al in which they reported that chronic glomerulonephritis was the leading cause of ESRD followed by diabetic nephropathy and hypertension.[22]

CONCLUSION

From this study, it was concluded that the prevalence of thyroid hormone abnormalities especially low fT3 and fT4 is very common in stage 5 CKD patients. Diabetic nephropathy was among the lead cause of stage 5 CKD. Therefore, these findings reflect thyroid hormone abnormalities which are common in stage 5 CKD patients and will fulfill the criteria for NTI.

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