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Status of thyroid hormones and its relation with eGFR in non-hemodialyzed advanced chronic kidney disease – A hospital-based cross-sectional study

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ABSTRACT

Background: Patients with chronic kidney disease (CKD) and significantly low estimated glomerular filtration rate (eGFR) or end-stage kidney disease have been linked to thyroid dysfunction. Renal function is also negatively impacted by thyroid disease. **Aims and Objectives:** This study was conducted to find out magnitude of thyroid disorder in advanced CKD and to correlate eGFR with thyroid function status. **Materials and Methods:** A hospital-based study was conducted among CKD patients to assess the thyroid disorders and its associated factors. A thorough clinical history was taken on chief complaints, any additional precipitating factors or co-morbidities (such as diabetes and hypertension), the use of any medications other than those for CKD in the past, any significant surgical procedures, and any episodes of hemodialysis. A morning blood sample was collected for thyroid function (T3, Free T3, T4, Free T4, and thyroid-stimulating hormone [TSH]) and kidney function test. According to KDIGO's criteria 2017, CKD was identified. **Results:** The current study included 60 individuals, with a majority of men (56.7%) and a mean (SD) age of 48.8 (8.4) completed years. 28.3% had low T3 syndrome. Hypothyroidism was seen by 15% and 28.3% had subclinical hypothyroidism. There was no identified hyperthyroidism patient. eGFR had positive correlation with free T3 ($r = 0.46$, $P = 0.0002$). It had a low positive ($r = 0.03$, $P = 0.7$) and weakly positive ($r = 0.14$, $P = 0.2$) correlation with total T3 and total T4. Free T4 and TSH both had negative correlations with eGFR ($r = -0.17$, $P = 0.1$ and $r = -0.09$, $P = 0.4$, respectively). **Conclusion:** Patients with CKD had non-specific thyroid impairment, or decreased total T3 alone but no hyperthyroidism at presentation. The progression of CKD stage made it worse. There was significant positive correlation between free T3 and eGFR.

Key words: Thyroid profile; Chronic renal impairment; Single center study

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INTRODUCTION

Kidney plays not only as major organ of excretion but also plays crucial effect for some hormone metabolism, degradation, activation; takes part in acid-base disturbance, calcium homeostasis, etc.[1] The kidney typically contributes to iodide clearance, primarily by glomerular filtration, but in chronic kidney disease (CKD), this function is impaired, causing an initial increase in thyroidal iodide pool as well as the subsequent accumulation of plasma inorganic iodine. This thyroidal iodide pool diminishes uptake of radiolabeled iodide by the thyroid in uremic patients.[2] According to Wolff-Chaikoff effect, thyroid hormone production could be potentially blocked by increase in total body inorganic iodide. This may explain the slightly higher frequency of goiter and hypothyroidism in patients with CKD. The plasma

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concentration of thyroid stimulating hormone (TSH) is usually normal in CKD. Although often suppressed and delayed, the TSH response to exogenous thyrotropin releasing hormone (TRH) takes a long time to restore to baseline levels. Since TSH and TRH are routinely removed by the kidney, decreased renal clearance may be a contributor in a longer recovery.[3]

CKD patients often have thyroid functioning disorders and few studies reported it to be a physiologic adaptation in kidney disease patients.[1,4] Compared to patients with normal function, those with severe renal disease had disproportionately higher rates of primary hypothyroidism.[5] Furthermore, CKD patients typically exhibit multiple thyroid functional test abnormalities due to changes in the production, metabolism, and control of thyroid hormones.[6]

Gap in existing research

Although there are several studies of correlation of thyroid hormone profile and failing kidneys with conflicting outcome, no study was showing thyroid hormone relation with estimated glomerular filtration rate (eGFR) specifically in non-hemodialyzed advanced CKD (ACKD) patients separately.

Aims and objectives

1. To find out the magnitude of thyroid disorder in patients of non-hemodialyzed ACKD.
2. To determine the association of eGFR with thyroid function status.

MATERIALS AND METHODS

A hospital-based cross-sectional study was done among in-patient and outpatient (OPD) Department of General Medicine and OPD of Department of Nephrology at R.G. Kar Medical College and Hospital, Kolkata. The study was conducted from June 2020 to May 2021. The study population was included patients admitted in the General Medicine Department and attending those two OPDs, manifesting with symptoms and signs of ACKD. The patients aged more than 18 years and <80 years and non-hemodialyzed patients of ACKD were included in the study. The exclusion criteria were known case of hypothyroid or any thyroid disorder on therapy, acute systemic illness, acute kidney injury, and pregnant women. A written informed consent was taken from each patient before inclusion in the study. The study was being approved by Ethics committee of R. G. Kar Medical College, (Approval no. RKC/125).

Sample size

Srivastava et al. found significant association between the creatinine clearance values and FT4 ($r=0.699$ $P<0.01$) using Pearson's coefficient among unanalyzed CKD patients.[7]

The Statistical formula used for sample size calculation: $n=((1.96+0.84)/C(r))\ ^2+3=58.5$

Where $C(r)=½ \log (1+r)/(1-r)$; here r is the coefficient=0.699. A minimum of 60 was studied based on case selection criteria of patients.

Data collection

A pretested, semi-structured pro forma was used for data collection. A detailed clinical history of presenting chief complaints, details about urine output, other precipitating factors, and co-morbidity (e.g. Diabetes, Hypertension), drug history of any other (than CKD) medicine use, major surgical event, and episodes of hemodialysis were taken. All patients were carefully examined for fever, anemia, dehydration, pedal edema, features of volume overload, and altered mental status. CKD was diagnosed as per definition by KDIGO 2017.[8] eGFR value was calculated using application-based formula of CKD-EPI and classified accordingly.[9] Those qualifying eligible criteria were evaluated for thyroid profile (FT3, FT4,T3, T4, and TSH). Thyroid hormones were measured by chemiluminescence immunoassay method using Centaur XP, Siemens machine. The other relevant investigations such as complete hemogram, blood urea and serum creatinine, serum electrolytes, and urine for albumin-creatinine ratio (ACR) were also done.

Operational definition

CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health. CKD is classified based on cause (C), GFR category (G1-G5), and albuminuria category (A1-A3), abbreviated as CGA.[8] Normal reference interval of parameters of thyroid profile according to our laboratory was following: FT3 2.27–4.3 pg/mL, FT4 0.8–2 ng/dL, Total T4 5–12 μg/dL, Total T3 1.15–3 nanomole/L, and TSH 0.55–4.78 μIU/mL.

Statistical analysis

The data were entered into Microsoft (MS) Excel and analyzed by GraphPad Prism version 5 and SPSS (version 27.0; SPSS Inc., Chicago, IL, USA). Mean and standard deviation were used to characterize the continuous variables (SD). Categorical variables were given the frequencies. Independent samples were tested using Student t-tests for a mean difference. The categorical variables were compared using the appropriate Chi-square test or Fischer's exact test. $P<0.05$ was used to determine statistical significance.

RESULTS

There were 60 participants in the present study. The mean (SD) age of the participants was 48.8 (8.4) completed years. The minimum and maximum age was 31 and 59 years, respectively. Males (56.7%, n=34) were dominant in the study population.

The mean age of males (50.6 years) was higher than females (46.6 years). There were 65% (n=39) of the study population with known case of diabetes mellitus and males (77%) were predominantly diabetic. Four-fifth (n=48, 80%) were in Stage 5 kidney disease whereas the remaining in Stage 4 (Table 1).

The mean value of hemoglobin (8.7 g/dL, SD=1.2) was under moderate anemic category. Other blood and urine parameters were deranged in relation to the ACKD. The mean eGFR value (11.3 mL/min/1.73 m^2, SD=3.8) was very low, showing the poor function of the kidneys. The present study showed that the mean urine ACR (SD), mean (SD), and albumin of patients were 864.2 (57.5) and 3.1 (0.5).

The earliest thyroid dysfunction seen among CKD patients is low T3 level (particularly total T3 than Free T3) known as low T3 syndrome. It was present among 93% of the study participants. TSH was in high range for 43% of the CKD patients. There were nine participants with high TSH and low free T4, suggestive of hypothyroidism. There was no hyperthyroidism. It was found that 28.3% had subclinical hypothyroidism and another 28.3% had low total T3 alone (Table 2).

Normal reference range: FT3 2.27–4.3 pg/mL, FT4 0.8–2 ng/dL, Total T4 5–12 μg/dL, Total T3 1.15–3 nanomole/L, TSH 0.55–4.78 μIU/mL.

There was statistically significant mean difference seen for serum total T3, total T4, FT3 between the stage IV and V CKD patients (Table 3).

eGFR had positive moderate correlation with free T3 and significant statistically. (r=0.46, P=0.0002). Free T3 increases as eGFR increase, that is, with decline in eGFR, free T3 decreases proportionately. It had weak positive correlation with total T3 (r=0.03, P=0.7), and total T4 (r=0.14, P=0.2) but insignificant. eGFR had insignificant negative correlation with free T4 (r=−0.17, P=0.1), and TSH (r=−0.09, P=0.4) (Figure 1).

Table 1: Study population characteristics (n=60)

Variable	Frequency	Percentage
Age category		
31–40	13	21.7
41–50	13	21.7
51–60	34	56.7
Gender		
Male	34	56.7
Female	26	43.3
Known case of diabetes mellitus		
Yes	39	65.0
No	21	35.0
CKD stage by KDIGO		
Stage IV	12	20.0
Stage V	48	80.0

DISCUSSION

The present study was done among adults with ACKD who were non-hemodialyzed attending tertiary care hospital. In these patients, we observed the relationship of thyroid hormones with eGFR. The kidney contributes to iodine clearance primarily through glomerular filtration. High serum iodine concentrations have been reported in CKD patients, and high exposure to iodine may facilitate the development of hypothyroidism.[2,10] The interactions between kidney and thyroid functions have been known for many years, and thyroid dysfunction causes significant changes in kidney function.[11]

Largely, in this study, TSH, total T4, free T3, and free T4 were almost in the normal range irrespective of the CKD stage. Except for total T3, which was low overall, slightly even more low in stage 5 CKD. Low levels of T3 may reflect diminished conversion from T4 which may be due to metabolic acidosis or reduced protein binding. The increased level of Urea, Creatinine, Indols, and Phenols strongly inhibit protein binding of thyroid hormones which is also responsible for low level of T4 in CKD. Some studies showed that resin and activated charcoal, present in solid-phase matrices used in measuring T4 level also causes inhibition of it. Few other studies showed that in ACKD, there is a decrease level of FT3 and FT4, which are unbound form of thyroid hormones that mainly bound to thyroid binding globulin and to lesser extent to pre-albumin and albumin.[6,11-14] Overall, there was no typical hyperthyroidism disorder observed in our study, in contrast few case of hypothyroidism were seen. Nevertheless, isolated low T3 were seen, that is, low T3 syndrome. Patients with hypothyroidism, both overt and subclinical, are characterized by a decrease in the GFR and renal plasma flow, resulting in increased serum creatinine. Although, it has been reported that these changes can be reversed with levothyroxine administration.[15] There have been few studies to show the extent of the improvements and long-term changes of renal function after thyroid hormone replacement therapy (THRT) in CKD patients.[16,17] On the other hand, CKD is associated with a high prevalence of primary hypothyroidism. Lo et al.

Table 2: Thyroid biomarkers of the study participants (n=60)

Category	TSH n (%)	Total T3 n (%)	Total T4 n (%)	Free T3 n (%)	Free T4 n (%)
Normal range	33 (55.0)	4 (6.7)	34 (56.7)	60 (100.0)	47 (78.3)
Less than normal	1 (1.7)	56 (93.3)	26 (43.3)	-	12 (20.0)
More than normal	26 (43.3)	-	-	-	1 (1.7)

TSH: Thyroid-stimulating hormone

Table 3: Association between thyroid markers and stage of CKD (n=60)

Thyroid markers	Stage IV (n=12)	Stage V (n=48)	Overall (n=60)	P-value
Serum TSH in μIU/mL				
Mean (SD)	3.2 (2.6)	3.1 (2.0)	3.1 (2.1)	0.8
Median (Min-max)	1.5 (1.0–7.6)	1.9 (0.1–7.5)	1.9 (0.1–7.6)	
Serum total T3 in nanomole/L				
Mean (SD)	1.0 (0.3)	0.7 (0.2)	0.7 (0.2)	0.0009
Median (Min-max)	1.0 (0.5–1.5)	0.7 (0.5–1.1)	0.5 (0.5–1.5)	
Serum total T4 in nanomole/L				
Mean (SD)	112.6 (0.9)	74.6 (26.4)	82.2 (28.1)	<0.0001
Median (Min-max)	112.0 (112.0–114.0)	70.0 (20.0–110.0)	90.0 (20.0–114.0)	
Serum FT3 in picogram/ml				
Mean (SD)	3.9 (0.4)	2.8 (0.3)	3.0 (0.5)	<0.0001
Median (Min-max)	3.8 (3.0–4.3)	2.8 (2.4–3.2)	2.9 (2.4–4.3)	
Serum FT4 in nanogram/dl				
Mean (SD)	0.7 (0.3)	0.9 (0.3)	0.8 (0.3)	0.06
Median (Min-max)	0.8 (0.1–1.0)	0.9 (0.1–2.0)	0.9 (0.1–1.9)	

CKD: Chronic kidney disease, TSH: Thyroid stimulating hormone

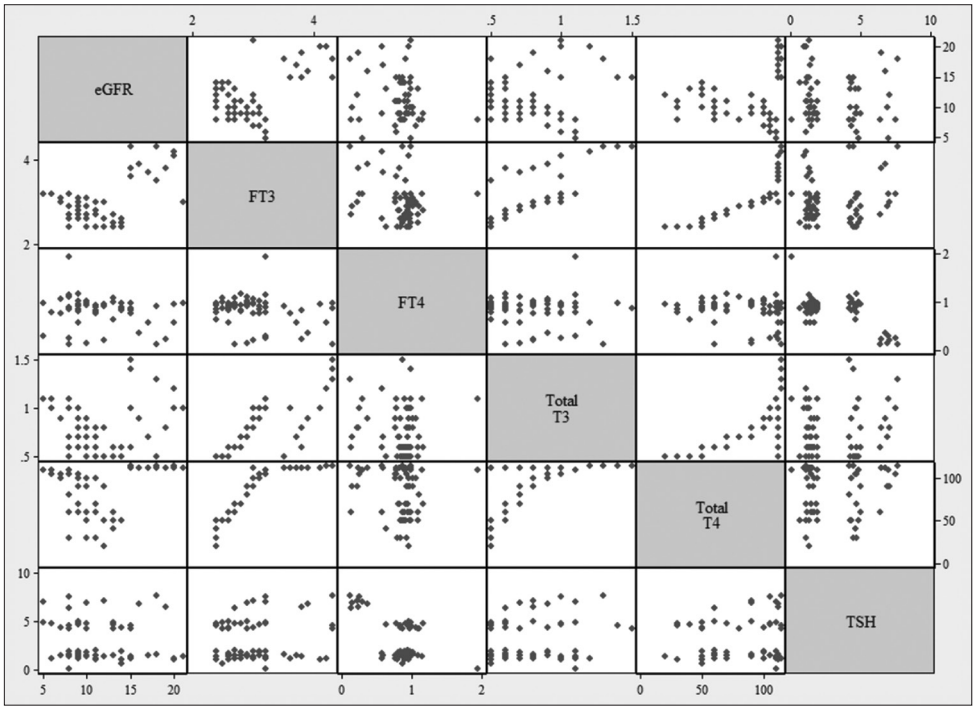

Figure 1: Correlation of estimated glomerular filtration rate with the thyroid hormone biomarkers

reported that the prevalence of hypothyroidism increased with progressively lower levels of kidney function in a nationally representative cohort of US adults.[5] The kidney contributes to iodine clearance primarily through glomerular filtration. High serum iodine concentrations have been reported in CKD patients, and high exposure to iodine may facilitate the development of hypothyroidism.[2,10]

This is in line with the present study findings. The earliest thyroid dysfunction seen among CKD patients is low T3 level (particularly total T3 than Free T3).[18,19] This is known as low T3 syndrome. This was observed in our study. Low T3 syndrome occurs in CKD due to chronic metabolic acidosis, fasting, protein malnutrition, reduced peripheral conversion of T4 to T3, and iodothyronine deiodination. The inflammatory cytokines such as tumor necrosis factor alpha interleukin-1 In CKD patient inhibits the expression of enzyme type 1 5' deiodinase, which is necessary for peripheral conversion of T4 to T3.[20]

Pan et al., in 2019, found that FT3 or T3 became more prevalent with increasing eGFR with the lowest level in CKD5 (P<0.01). No significant differences were found between groups in FT4, T4, or TSH (P>0.05). The frequency of euthyroid sick syndrome in CKD groups was high, especially in CKD stage 5. eGFR had positive correlation with T3 and FT3 and statistically significant.

Whereas in the present study, FT3 had positive correlation with eGFR but not with T3.[20]

Lo et al., in 2005, conducted a study among 14,623 adult's participants and measure their serum creatinine and thyroid function test results. The mean age was 48.7 years similar to the present study. In contrast to our finding, the former study reported higher proportion of women (52.6%). The prevalence of hypothyroidism increased with the lower levels of GFR (in units of mL/min/1.73 m^2), occurring in 5.4% of subjects with GFR ≥90, 10.9% with GFR 60–89, 20.4% with GFR 45–59, 23.0% with GFR 30–44, and 23.1% with GFR <30 (P<0.001 for trend). Overall, 56% of hypothyroidism cases were considered subclinical. Compared with GFR ≥90 mL/min/1.73 m^2, reduced GFR was associated with an increased risk of hypothyroidism, after adjusting for age, gender, and race/ethnicity: Adjusted odds ratio 1.07 (95% confidence interval: 0.86–1.32) for GFR 60–89, 1.57 (1.11–2.22) for GFR 45–59, 1.81 (1.04–3.16) for GFR 30–44, and 1.97 (0.69–5.61) for GFR <30 mL/min/1.73 m^2 (P=0.008 for trend).[5]

Carter et al. studied effects of administration of Triiodothyronine in patients with CKD. The study showed that there was no change in serum T3 level over a span of 12 weeks. The mean serum T4 and TSH levels were affected significantly. However, there was no subjective improvement seen in this group of patients.[21]

Based on above observations, it has been suggested that low serum T3 level in patients with CKD is metabolically protective and it is interpreted as physiological adaptation to a reduced basal metabolic rate (BMR) and to conserve energy in an adverse environment. Because of that, this condition has been renamed as "Thyroid hormone adaptation syndrome."[22]

In fact, the prevalence of primary hypothyroidism, mainly in the subclinical form, increases as GFR decreases to 40. A recent study has shown a prevalence of subclinical hypothyroidism of 7% in patients with estimated GFR 90 mL/min per 1.73 m^2 that increased to 17.9% in subjects with GFR <60 mL/min per 1.73 m^2. The prevalence of hypothyroidism is higher in women and is associated with an increased frequency of high titers of anti- thyroid antibodies.[23]

The prevalence of hypothyroidism was reported in more numbers than other thyroid dysfunctions. The risk of cardiovascular diseases was high and reported common among renal dysfunction patients with overt hypothyroidism. Hence, appropriate and timely intervention with THRT would both reduce the risk of cardiovascular diseases and result in delay in the progress of renal dysfunction. Thus, help in delay in the need for renal replacement.[24,25]

The CKD mediated thyroid function abnormalities can be recovered after renal transplantation. A thyroid profile with abnormalities is caused by CKD can be reversed by kidney transplantation. After transplantation, the low T3 and T4 levels rise, albeit slightly, over the first 3–4 months. Patients with kidney transplants typically show a fall in T4 levels below the pre-transplant level in the first few months after transplantation, before it progressively climbs back to normal. The low T3 levels observed in the initial months of kidney transplantation can therefore be treated without adding thyroid hormone supplements.[26,27]

Thyroid function abnormalities enhance the risk of adverse renal events and all-cause mortality in patients with mild to moderate CKD.[28]

Limitations of the study

It was small sample study from one hospital. The study was done during COVID pandemic with lockdown rules. Hence, it could not be a true representation of the whole CKD patients attending hospital.

CONCLUSION

Most common thyroid dysfunction was seen among CKD patients were low total T3 alone, which was present 93% of study participants. It was worsened with the increase in CKD stage. There was significant positive correlation between free T3 and eGFR. Renal transplantation may help in reversion of the thyroid disorder but over few months without any replacement therapy.

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RB- Concept design, data analysis, manuscript editing, manuscript revision, submission of article; **SP**- Implementation of study protocol, data collection, data analysis; **KM**- Prepared first draft of manuscript, literature survey, statistical analysis; **PSK**- Manuscript revision and coordination.

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