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ORIGINAL RESEARCH ARTICLE

A Crossectional Study on Association between Thyroid Dysfunction and Albuminuria in Patients with Chronic Kidney Disease

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ABSTRACT

BACKGROUND

Proteinuria is common in patients with chronic kidney disease, however the relationship between proteinuria in Chronic Kidney Disease (CKD) and thyroid function remains unclear. Hence the objective of this study was to explore the association between thyroid dysfunction and albuminuria in CKD patients.

MATERIALS AND METHODS

A hospital based study was conducted among 185 CKD patients between January 2023 and January 2024. The stage of CKD was determined based on the eGFR values. Albuminuria was classified as mild, moderate and severe based on the albumin creatinine ratio (ACR). To evaluate the thyroid functions, TSH, Free T3, Free T4 were measured.

RESULTS

Among the study population, 40% had Type 2 Diabetes Mellitus, 22.70% had nephrosclerosis, 18.9% had Glomerulonephritis and 61.62% were on antihypertensive medication. Albuminuria was categorized as mild in 86(46.49%) cases, moderate in 62(33.51%), and severe in 37(20%). There was a negative association between albumin-to-creatinine ratio (ACR) and estimated glomerular filtration rate. 40 (21.62%) patients had hypothyroidism. There was a positive correlation between FT4 and ACR but no relationship between FT3 or TSH with ACR. Hypothyroidism and Euthyroid sick syndrome was more common in all groups of ACR than hyperthyroidism.

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CONCLUSION
There was a positive correlation between FT4 and ACR but no relationship between FT3 or TSH with ACR.

KEYWORDS
Chronic Kidney Disease, Albuminuria, Thyroid Dysfunction.

INTRODUCTION

CKD is a condition marked by an ongoing and irreversible decrease in kidney function, leading to impaired excretion, metabolic processes, and synthetic dysfunction.[1,2] Over time, the definition and categorization of CKD have evolved to foster effective communication among healthcare providers, patients, families, and other stakeholders, aiming for a public health-oriented approach to treatment. The National Kidney Foundation-Kidney Disease Outcome Quality Initiative (NKF-K/DOQI) has characterized CKD as the persistence of structural or functional abnormalities in kidneys for more than three months, impacting health.[3]

The prevalence of CKD has steadily increased over time, now ranking as the sixth fastest-growing cause of death worldwide, resulting in approximately 1.2 million deaths annually. According to the 2015 Global Burden of Disease study, CKD has climbed from the 27th to the 12th position among the leading global causes of death over a span of 25 years (1990-2015), with a 32% rise in mortality rate within a decade.[4,5]

Endocrine imbalances frequently occur in advanced stages of CKD due to the crucial role played by kidneys in maintaining hormone homeostasis.[6,7] Multiple studies have indicated that the decrease in kidney function seen in CKD is linked to thyroid dysfunction, alongside other endocrine disorders.[7,8] CKD patients may experience hypothyroidism, hyperthyroidism, and sick euthyroid syndrome, and also issues like goiter and thyroid cancers in higher proportions as compared to the general population.[9-12] The mechanisms behind these thyroid abnormalities in CKD are complex and involve the impact of CKD on the hypothalamo-pituitary-thyroidal axis and peripheral thyroid hormone metabolism.[12]

Proteinuria is prevalent in individuals with chronic kidney disease (CKD), such as those with glomerulonephritis or renal complications due to diabetes mellitus, and has emerged as a prognostic factor for mortality, cardiovascular events, and advancement to end-stage kidney disease.[13,14] Nevertheless, the association between proteinuria in CKD and thyroid function remains uncertain.

The present study was conducted to assess if there was an association between albuminuria and thyroid functions in patients with Chronic Kidney Disease.

MATERIALS AND METHODS

This retrospective study conducted at Ambedkar Medical College in Bangalore between January 2023 and January 2024, examined the records of 185 patients with chronic kidney disease, available in the hospital's Medical Records Department. Sample size was calculated based on the prevalence of CKD as 14%[15] with the formula $Z^2p(1-p)/d^2$, where the allowable error was kept at 6%. The minimum sample size was calculated to be 185. Adult patients more than 18 years of age with their records containing details regarding their urinary albumin to creatinine ratio, serum creatinine, and thyroid function tests were included for the study. It was assured that only thyroid antibody negative patients were included for the study. eGFR was calculated by referring to the abbreviated modification of diet in renal disease.[16] CKD stages were defined by eGFR:

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Stage 1= eGFR ≥90ml/min; Stage 2= eGFR ≥60 ml/min but ≤ 90 ml/min; Stage 3= eGFR ≥ 30 ml/min but ≤ 60 ml/min; Stage 4: ≥ 15 ml/min but ≤ 30 ml/min; Stage 5: < 15 ml/min. Serum and urinary albumin and creatinine and serum c-reactive protein (CRP) were determined by standard methods. Albuminuria was assessed by albumin-to-creatinine ratio (ACR) and classified as mild, moderate, or severe when ACR < 30 mg/g (ACR1), 30–300 mg/g (ACR2), and >300 mg/g (ACR3). TFT panel investigations were performed using the Erba Lisa Scan ELISA method analyser (Transasia BioMedicals Ltd.).

Statistical Analysis

The data was entered in Microsoft Office Excel 2007 and IBM SPSS version 21 was used for analysis. Chi square test was used to find the statistical significance between two categorical variables. Correlations were calculated using Pearson correlation. P value less than 0.05 was considered to be statistically significant.

RESULTS

Characteristics	ACR 1	ACR 2	ACR 3
Age	62.32 ± 8.23	62.47 ± 8.77	61.32 ± 9.19
Gender (Male/Female)	43 / 43	39 / 23	18 / 19
FT3 (pmol/L)	3.54 ± 0.34	3.57 ± 0.76	3.57 ± 0.41
FT4 (pmol/L)	9.54 ± 2.08	10.1 ± 1.25	13.7 ± 1.48
TSH (mIU/L)	4.83 ± 0.69	5.31 ± 0.48	4.56 ± 0.99
ACR (mg/g)	9.81 ± 2.49	110.00 ±25.32	963.01 ± 162.85
S Creat (mg/dl)	1.04 ± 0.98	1.22 ± 0.15	1.88 ± 0.12
eGFR (ml/min)	91.86 ±13.51	87.15 ± 14.94	62.64 ± 12.02
Table 1: Characteristics of the study population in various ACR groups			
ACR 1: Less than 30mg/g; ACR 2: 30 – 300 mg/g; ACR 3: More than 300 mg/g			

ACR Group	Normal	Hypothyroidism	Hyperthyroidism	Sick Thyroid Status
ACR 1 (86)	31 (36.04%)	21 (24.41%)	1 (1.16%)	33 (38.37%)
ACR 2 (62)	21 (33.87%)	11 (17.74%)	3 (4.84%)	27 (43.55%)
ACR 3 (37)	15 (40.54%)	8 (21.62%)	1 (2.70%)	13 (35.14%)
TOTAL	67 (36.21%)	40 (21.62%)	5 (2.70%)	73 (39.45%)
Table 2: Proportion of different thyroid issues in each ACR group				

CKD Stage	Normal	Hypothyroidism	Hyperthyroidism	Sick Thyroid Status
1N (91)	32 (35.16%)	18 (19.78%)	3 (3.29%)	38 (41.75%)
2N (38)	14 (36.84%)	8 (21.05%)	1 (2.63%)	15 (39.47%)
3N (35)	15 (42.85%)	9 (25.71%)	0 (0%)	11 (31.42%)
4N (15)	4 (26.67%)	4 (26.66%)	1 (6.66%)	6 (40%)
5N (6)	2 (33.33%)	1 (16.66%)	0 (0%)	3 (50%)
Table 3: Proportion of different thyroid issues in each CKD stage				

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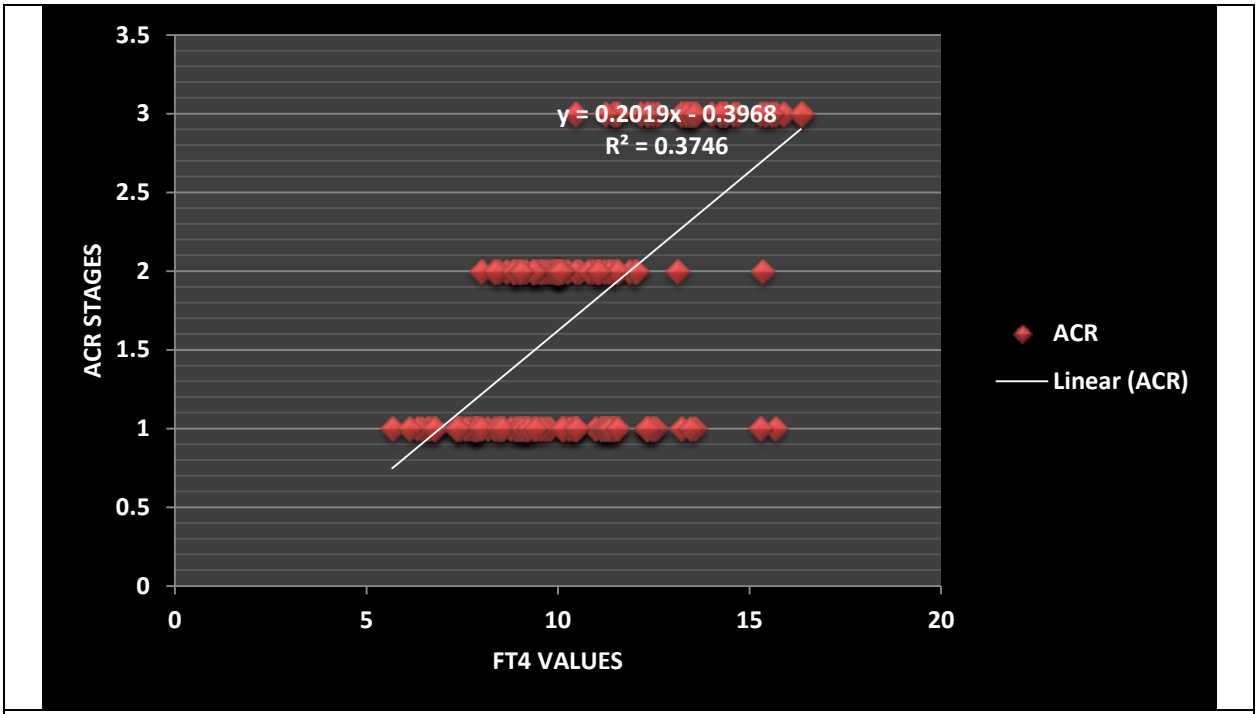

Figure 1: Correlation between FT4 levels and stages of ACR

The study involved 185 patients with underlying chronic kidney disease. Among the study population, 40% had Type 2 Diabetes Mellitus, 1.62% had Type 1 Diabetes Mellitus, 22.70% had nephrosclerosis, 18.9% had Glomerulonephritis, 4.86% had polycystic kidney disease, 7.02% had interstitial nephritis, and 4.86% were unknown. 77(41.62%) of the study population were taking oral antiglycemic medication and/or insulin, 114 (61.62%) were on antihypertensive medication, and 30 (16.22%) were on statins due to elevated lipids. No patients were on a restricted diet. Blood samples were collected in the morning after an overnight fast.

Regarding the severity of chronic kidney disease, 91(49.19%) patients were in Stage 1, 38(20.54%) in Stage 2, 35(18.92%) in Stage 3, 15(8.11%) in Stage 4, and 6(3.24%) in Stage 5. Albuminuria was categorized as mild in 86(46.49%) cases, moderate in 62(33.51%), and severe in 37(20%). There was a negative association between albumin-to-creatinine ratio (ACR) and estimated glomerular filtration rate (eGFR) ($r = -0.6393$; $p<0.0001$). Additionally, 40 patients had hypothyroidism, accounting for 21.62% of the study population.

CKD patients exhibited a higher prevalence of euthyroid sick syndrome and hypothyroidism accounting for 113 (61.08%) patients (Table 2). Further there was a positive correlation between FT4 and ACR indicating that a low FT4 levels would be seen in patients with decreased albumin and vice versa (R value =0.6120 and p value <0.0001*) (Figure 1). There was no relationship between FT3 or TSH with ACR. Hypothyroidism and Euthyroid sick syndrome was more common in all groups of ACR than hyperthyroidism (Table 2). The prevalence of euthyroid sick syndrome showed a rising pattern as the ACR decreased. There was no significant association of ACR with different clinical types of thyroid dysfunction (Table 2). There was a significant difference in the proportion of different thyroid dysfunctions among patients of different CKD stages ($P = 0.004$).

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DISCUSSION

In the present study, it was demonstrated that there was a positive correlation between FT4 levels and albumin creatinine ratio. This means that FT4 levels were more in patients with severe kidney disease. In contrast, there was no association between albuminuria and FT3 or TSH. Euthyroid sick syndrome and hypothyroidism were more prevalent than hyperthyroidism in patients with CKD. The prevalence of euthyroid sick syndrome was 38.37% among patients with normal albuminuria (ACR 1).

Thyroid hormone plays a vital role in regulating various bodily functions, impacting almost every organ system. While T4 is exclusively produced by the thyroid gland, T3, the more active form, is mostly generated through the conversion of T4 by an enzyme called T4–5′-deiodinase in other tissues including the kidney. In conditions like chronic kidney disease (CKD), the kidney's ability to produce T3 may decrease due to the reduced activity of this enzyme.[16] Thus some patients might have an increased T4 level but a normal or decreased T3 levels. Drugs like heparin and furosemide can inhibit T4 binding to plasma proteins and may also result in transient elevation of free T4 levels.[16]

Patients with CKD often exhibit abnormalities in thyroid function tests, resembling a condition known as euthyroid sick syndrome. This syndrome is characterized by low levels of T4, T3, and thyroid-stimulating hormone (TSH). End-stage renal disease (ESRD) patients typically have decreased free T3 levels. These changes are attributed to various factors such as alterations in the peripheral 5′ -monodeiodination of T4, reduced levels of plasma proteins that bind T4 in the blood, metabolic acidosis, and effects of certain medications.[16]

In nephrotic syndromes, the loss of proteins in urine, including those that bind thyroid hormones, can lead to urinary excretion of thyroid hormones. This can result in decreased levels of total plasma T4 and, less commonly, T3, which may vary depending on the severity of protein loss[17]. However, many patients with nephrotic syndromes remain euthyroid due to compensatory mechanisms by the thyroid gland.[18]

Limited research has focused on the relationship between thyroid dysfunction and albuminuria. The present study showed that FT4 was higher in macroalbuminuria. There might be several possible reasons for this. It can possibly be due to factors such as glomerular hyperfiltration and hypertension, changes in tubular protein handling, or changes in the structure of glomerular barrier, all of which may increase albuminuria[19]. The higher T4 may result in glomerular hyperfiltration.[20] Sometime, it might be because thyroid gland is able to compensate for hormonal urinary losses keeping the patient euthyroid in macroalbuminuria.[21]

Subclinical hypothyroidism and euthyroid sick syndrome are prevalent conditions in individuals with chronic kidney disease (CKD).[22-24] A study indicated a high occurrence of low T3 syndrome in CKD, particularly noteworthy in its early stages.[25] Another study found a considerable prevalence of euthyroid sick syndrome, reaching 60% in elderly hospitalized patients.[26] In the current study, the prevalence of euthyroid sick syndrome was determined to be 39.45%.

Among the alterations observed in thyroid hormone profiles in CKD, low T3 levels are the most common.[26] While previously regarded as a benign adaptation to chronic illness, low T3 levels are now recognized for their association with endothelial dysfunction, a precursor to atherosclerosis. Moreover, in stage 3 and 4 CKD patients, low T3 levels correlate with cardiovascular disease and increased mortality risk.[27-28]

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Limitations

Urinary total protein levels were not included in the study, thus preventing an investigation into the connection between proteinuria and thyroid dysfunction. Because the study is cross-sectional, it cannot determine causation. Furthermore, the small sample size presents another potential limitation.

CONCLUSION

The results of the present study showed that there was a positive correlation between Serum FT4 levels and albuminuria. But albuminuria was not associated with FT3 levels or TSH levels. Further studies with large sample size is required to elucidate the causal association between albuminuria and FT4 levels.

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