Journal of Cardiovascular Disease Research
ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 2, 2024

CORRELATION BETWEEN ALBUMINURIA AND THYROID FUNCTION IN PATIENTS WITH CHRONIC KIDNEY DISEASE

Shaivya Morwal[1*], Ashutosh Jain[2], Jaya Jain[3]

1-PhD Scholar, Department of Biochemistry, Index Medical College Hospital & Research Centre, Indore M.P.
2-Assistant Professor, Department of Physiology, Index Medical College Hospital & Research Centre, Indore M.P.
3-*Associate Professor, Department of Biochemistry, Index Medical College Hospital & Research Centre, Indore M.P.*

Abstract

Introduction: Decreased renal function is a significant public health issue, increasing the risk of various adverse outcomes. Albuminuria, the presence of albumin in the urine, is a well-established marker of kidney damage and is associated with an increased risk of cardiovascular disease in CKD patients. Although CKD has been demonstrated to impact thyroid function through various mechanisms; there remains insufficient and contentious data regarding the association between albuminuria and thyroid function in patients diagnosed with CKD. This study aimed to elucidate the association between albuminuria and thyroid function tests in patients with CKD. **Methods:** An observational, case control study was carried out for 2 years with a Sample Size of 180 with two groups1 (n=90): CKD subjects and group 2 (n=90): Non-CKD subjects. Estimation of Kidney functions, Estimation of Endothelial Function, Estimation of Albumin level was assessed by albumin-to- creatinine ratio (ACR) and Estimation of Thyroid function was done. **Results:** The study revealed notable differences in serum creatinine, urea, TSH, and fT3 levels between the two groups, while serum fT4 levels remained unchanged. The biological parameters, including fT3, creatinine, urea, and fT4, exhibit distinct correlations with GFR in different stages of CKD, emphasizing the relationship between kidney function and thyroid hormone levels. A significant positive correlation was found between glomerular filtration rate and free T3 ($r=0.395$, $p<0.05$), whereas a significant negative correlation was noted between ACR and free T3 ($r=-0.264$, $p<0.05$). **Conclusion:** Our findings research provides important information about how thyroid function, renal function, and albuminuria interact in CKD patients. This implies that a decrease in free T3 levels in CKD patients may be facilitated by albuminuria.

Keywords: Chronic kidney disease, albuminuria, thyroid function, free T3

***Corresponding Details:**

Dr. Shaivya Morwal,

PhD Scholar, Department of Biochemistry,

Index Medical College Hospital & Research Centre,

Indore, Madhya Pradesh

INTRODUCTION

Chronic kidney disease (CKD) is a major public health concern that results in progressive and irreversible loss of renal function and a concomitant increase in cardiovascular disease (CVD) related mortality that accounts for more than half of all deaths in patients with CKD**.** Proteinuria is common in patients with chronic kidney disease (CKD), e.g., the glomerulonephritis and renal complications caused by diabetes mellitus, and has become a prognostic variable in CKD patients regarding mortality, cardiovascular events, and progression to end-stage kidney disease **[1, 2].**

The link between thyroid dysfunction and CKD is complex and multifactorial. Thyroid hormones regulate renal blood flow and glomerular filtration rate (GFR), and disturbances in thyroid hormone levels can exacerbate renal injury by influencing renal vasculature and interstitial fibrosis (3). Furthermore, hypothyroidism in CKD patients has been shown to promote sodium retention, leading to increased blood pressure and worsening of kidney function. Studies suggest that thyroid hormone abnormalities, particularly low T3 levels, are associated with poor outcomes in CKD patients, including increased cardiovascular morbidity and mortality [3].

Endothelial dysfunction is a hallmark of cardiovascular disease and has been widely recognized as a key factor in the pathogenesis of CKD. The endothelium, a single layer of cells lining blood vessels, plays a crucial role in regulating vascular tone, blood flow, and maintaining the balance between pro- and anti-inflammatory factors. Endothelial dysfunction occurs when the endothelial cells lose their ability to maintain vascular homeostasis, leading to vasoconstriction, increased permeability, and inflammation. In CKD, endothelial dysfunction is considered a precursor to atherosclerosis, which is highly prevalent in CKD patients and contributes to increased cardiovascular mortality [4].

It is widely recognized that albumin, transthyretin, and thyroxinebinding globulin (TBG) are the key serum proteins that bind to thyroid hormones. Consequently, depletion of levothyroxine, TBG, or both can result in (subclinical) hypothyroidism, particularly in young individuals, especially when proteinuria is in the nephrotic range. Furthermore, patients presenting with concurrent nephrotic syndrome and hypothyroidism may require higher doses of thyroid replacement therapy [5, 6].

The relationship between baseline kidney function or the onset of CKD and a comprehensive panel of thyroid indicators, including thyroidstimulating hormone (TSH), free triiodothyronine (free T3), and free thyroxine (free T4), remains poorly understood (13). These indicators have yet to be fully characterized for their association with clinical categories of albuminuria severity in patients with CKD. Thus, the purpose of this study was to elucidate the association between thyroid function tests and albuminuria in patients with CKD.

MATERIAL & METHODS:

Study Setting: This observational, case control study explored the correlation between albuminuria and thyroid function tests among patients with CKD admitted to the Nephrology unit, Tertiary Referral Hospital..

Selection of Study Sample

Number of groups :– Two
• Group 1 (n=90): CKD subjects.
• Group 2 (n=90): Non-CKD subjects

- **Inclusion criteria:**
- **Selection of Cases:** Cases will be known Non-Diabetic CKD patients of age group 25-60 years. (n=90)
- **Selection of Controls:** Controls will be non-CKD patients (Age and Sex matched) will be selected. (n=90)
- **Exclusion criteria:** Previous known thyroid disorder requiring thionamides or levothyroxine treatment.

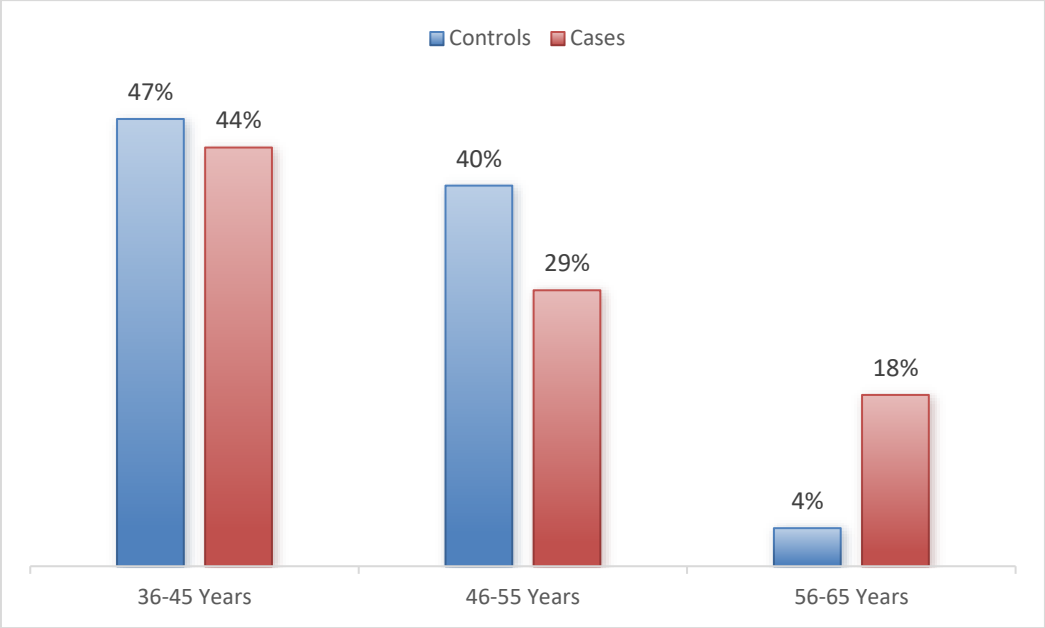
- **Methodology:** All study subjects fulfilled the inclusion criteria will enroll and following parameter details will be entered in pre designed performa ;

  - Parameters studied:
    - **Anthropometric parameters:** Age, Height, Weight, waist hip ratio, BMI.
    - **Basal parameters:** Heart rate, Respiratory rate, Systolic blood pressure, Diastolic blood pressure, Rate pressure product, Mean arterial pressure, Pulse pressure.
- Then for serum samples collection under aseptic condition. After centrifugation, serum samples will store frozen (−80°) and further analyze.
- **Estimation of Kidney functions**: (a) To assess kidney function, we will calculate the estimated glomerular filtration rate (eGFR) by referring to the abbreviated modification of diet in renal disease formula [10].
- **Estimation of Endothelial Function**: Endothelial function will be estimated by Vascular Reactivity Index using Digital Thermal Monitoring. [11]
- **Estimation of Albumin level**: Serum and urinary albumin and creatinine and serum c-reactive protein (CRP) will be determined by standard methods. Albuminuria will be assessed by albumin-to- creatinine ratio (ACR).
- **Estimation of Thyroid function**: • Euthyroidism: it is defined as TSH 4 mIU/L and/or receipt of thyroid hormone replacement and further categorized as hypothyroid status

Statistical Analysis: Descriptive statistics will be applied and proper statistical tests will be applied. Data will be presented as mean ±SD. Multivariable logistic regression adjusting for age, sex, race, and comorbidities was used to estimate odds ratios (OR) for CKD by thyroid status.

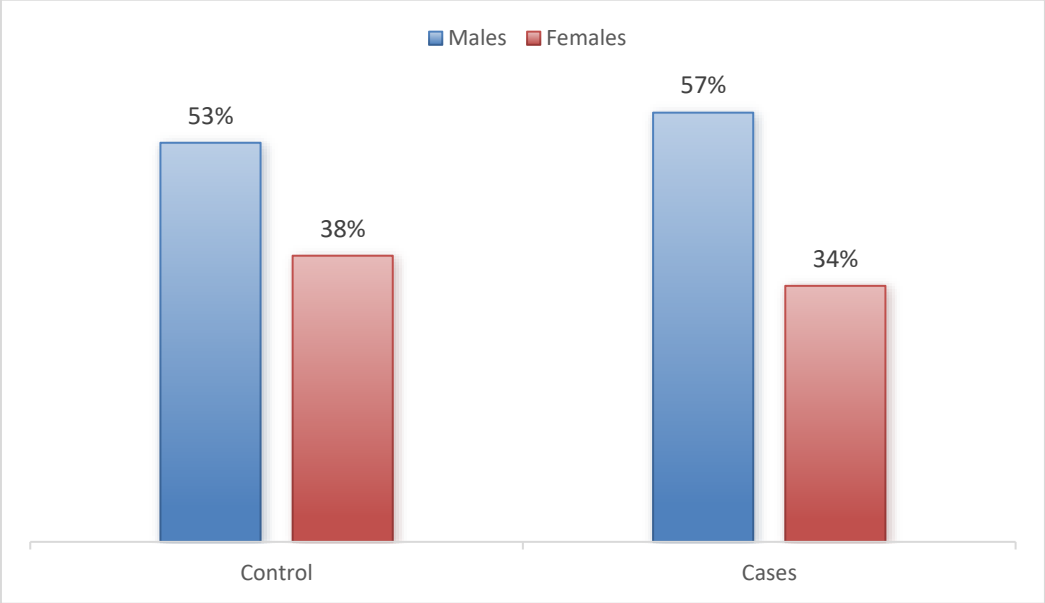
RESULTS:

Fig 1: Age Distribution Among CKD Patients and Healthy Controls



The majority of study participants were in the 36 to 45 years age group. The mean age in the study group was 47.67 ± 6.12 years, while the control group had a mean age of 48.53 ± 5.24 years (Fig. 1).

Fig 2: Male to Female Ratio in CKD Patients and Control



The male to female ratio in the study group was 1.7:1, and in the control group, it was 1.2:1 (Fig. 2). In both the study and control groups, a higher number of males were observed compared to females.

Table 1: Biochemical Parameter Comparison Control Group and Study Group

Parameter	Biological Reference Interval	Control Group (N=100)			Study Group (N=100)			Statistical Significance
		Min.	Max.	Mean ± SD	Min.	Max.	Mean ± SD	
Creatinine (mg/dl)	0.7-1.2	0.72	0.80	0.7±0.20	4.24	5.21	4.91±1.90	t=21.21 **p=0.0001**
Urea (mg/dl)	15-40	18.67	21.34	20.45±5.89	118.23	137.27	128.16±39.76	t= 24.55 **p=0.0001**
TSH (µIU/ml)	0.4-4.2	2.35	2.78	2.55±0.34	7.23	6.98	5.98±4.53	t= 5.89 **p=0.0001**

fT3 (pg/ml)	2.5-5.8	3.26	3.60	3.22±0.31	3.62	3.87	3.30±2.34	t= 2.12 **p=0.01**
fT4 (pg/ml)	10-21	13.42	14.50	14.23±1.98	15.87	15.76	13.88±5.87	t= 1.23 p=0.15

- **Serum Creatinine, Urea, and TSH Levels:** The study found a highly statistically significant increase in serum creatinine, serum urea, and serum TSH levels in the study group compared to the control group ($p<0.001$).
- **fT3 Levels:** A statistically significant decrease in free triiodothyronine (fT3) levels was observed in the study group when compared to the control group ($p<0.05$).
- **fT4 Levels:** No significant difference in serum free thyroxine (fT4) levels was found between the study and control groups.
- The study revealed notable differences in serum creatinine, urea, TSH, and fT3 levels between the two groups, while serum fT4 levels remained unchanged.
- **Serum fT3 Levels**: The study found a significant decrease in serum fT3 levels as glomerular filtration rate (GFR) decreased. Additionally, serum fT3 levels showed a positive correlation with estimated GFR (eGFR) in the study group.
- **Serum Creatinine and Urea**: Serum creatinine and urea levels were negatively correlated with the calculated GFR, indicating higher values as GFR declined.
- **Serum fT4 Levels**: Serum free thyroxine (fT4) levels were also negatively correlated with the calculated GFR, showing lower levels with a decrease in GFR.

The biological parameters, including fT3, creatinine, urea, and fT4, exhibit distinct correlations with GFR in different stages of CKD, emphasizing the relationship between kidney function and thyroid hormone levels.

DISCUSSION

Chronic kidney disease (CKD) represents a significant global health burden, affecting millions of individuals worldwide and often resulting in cardiovascular complications and progressive kidney dysfunction. The interplay between kidney function, cardiovascular health, and endocrine abnormalities, particularly thyroid dysfunction, has become an area of growing interest. Thyroid hormones are integral to the regulation of various physiological processes, including metabolism, growth, and cardiovascular function, and emerging evidence suggests that alterations in thyroid hormone levels play a crucial role in the pathophysiology of CKD. This study aims to explore the relationship between thyroid hormonal changes, endothelial function, and albuminuria in CKD patients. Our findings, while limited by the study's cross-sectional nature, suggest that thyroid dysfunction, particularly hypothyroidism, is significantly associated with endothelial dysfunction and albuminuria in CKD.

In Du X et al. [7] study has demonstrated that TT4 and FT4 were significantly different in three ACR groups that classified as <30mg/g, 30–300mg/g and >300mg/g (both *P*<0.001). Positive correlation between TT4, FT4 and albuminuria was evaluated by correlation analysis (Spearman correlation coefficient were 0.162 and 0.165, respectively, with *P*= 0.001 and <0.001). Albuminuria was an independent variable of T4 (TT4 and FT4) after reduced adjustment and full adjustment. In contrast, TT3, FT3 and TSH were not associated with albuminuria. Moreover, it showed that there was a significant difference in the prevalence of different thyroidism among three ACR groups (*P*= 0.029).

Euthyroid sick syndrome and hypothyroidism were more prevalent than hyperthyroidism in CKD. The prevalence of euthyroid sick syndrome was 38.3% in normal albuminuria patient (defined as ACR< 30mg/g). Thyroid hormone affects nearly every organ system in the body. T4 is produced only by the thyroid gland, whereas T3, the more biologically active form of thyroid hormone, is produced primarily through local deiodination of T4 by the enzyme T4–5′-deiodinase in other tissues, including the kidney. The kidney contains the D1 isoform of this enzyme, which becomes less active in CKD. The kidney plays a role in clearance of iodine, TSH, and thyrotropin-releasing hormone. However, some patients with CKD are euthyroid, with normal TSH and free T4 levels. Patients with CKD may have changes in thyroid function tests consistent with the euthyroid sick syndrome; that is, low T4, T3, and TSH concentrations. End stage renal disease (ESRD) patients have decreased levels of free T3. These changes in CKD patients are due to alterations in the peripheral 5′-monodeiodination of T4, reduced levels of plasma proteins that bind T4, the presence of inhibitors of T4 binding to plasma proteins, metabolic acidosis, and effects of medications. [8].

Patients with nephrotic syndromes have urinary losses of proteins that bind thyroid hormones, including thyroxine binding globulin, transthyretin, and albumin. Urinary T4 excretion was measured in patients with proteinuria. One study showed that, it was detectable in the urine in five cases, who had significantly lower serum free T4 and free T3 concentrations than the five patients without detectable urinary T4 [9]. This can result in reductions in total plasma T4 and less commonly total T3 levels that are roughly proportional to the severity of hypoalbuminemia and degree of proteinuria.

Many such patients remain euthyroid, however, as the result of increased secretion of TSH and thyroid hormone synthesis, albeit clinical hypothyroidism can occur. Heparin and furosemide can inhibit T4 binding to plasma proteins and may transiently elevate free T4 levels.

No previous study focused on the association between thyroid dysfunction and albuminuria. There might be several possible reasons for the higher TT4 and FT4 inmacroalbuminuria. Firstly,

the higher T4 is probably related to glomerular hyperfiltration and hypertension, changes in tubular protein handling, or changes in the structure of glomerular barrier, all of which may increase albuminuria19. The higher T4 (or hyperthyroidism) may result in glomerular hyperfiltration. [10,11]

Secondly, thyroid gland is able to compensate for hormonal urinary losses keeping the patient euthyroid in macroalbuminuria. Although TT4 and FT4 were both higher in macroalbuminuria group than microalbuminuria group and nomal albuminuria group, serum TT4 and FT4 did not exceed reference ranges in most patients in our study. Hypothyroid humans and rats can have an increased transcapillar leaking of the plasma proteins such as albumin, which leads to mild proteinuria and albuminuria. [12]

The albuminuria is considered to be present before the decrease in GFR in hypothyroid patients which proved our study by showing that the microalbuminuria and macroalbuminuria patients had hypothyroidism. Patients with proteinuria have higher TSH levels, consistent with urinary loss of thyroid hormones. [13]

However, our study has following limitations;

- **Sample Size and Population Diversity**: A small or homogenous sample size may limit the generalizability of the findings. The results may not be applicable to all CKD patients, particularly those from different ethnic or demographic backgrounds, or those with other comorbidities such as diabetes or hypertension, which may also influence thyroid function and kidney health.
- **Potential Confounding Factors**: Several factors, such as medications (e.g., diuretics, ACE inhibitors), dietary habits, and other comorbid conditions (e.g., diabetes, hypertension), could confound the relationship between thyroid hormones, endothelial function, and albuminuria. Controlling for these variables may be challenging and may impact the accuracy of the findings.
- **Limited Longitudinal Data**: Without longitudinal data, it is difficult to assess the long-term impact of thyroid hormonal changes on endothelial function and kidney health over time. Long-term studies are needed to understand the dynamics of these relationships in CKD patients.
- **Thyroid Hormone Variability**: Thyroid hormone levels can fluctuate due to a variety of factors, including acute illness, medications, and time of testing. This variability may introduce errors in the assessment of thyroid dysfunction and its impact on endothelial function and albuminuria.
- **Lack of Detailed Pathophysiological Mechanisms**: While the study may highlight associations between thyroid dysfunction, endothelial dysfunction, and albuminuria, it may not fully elucidate the underlying molecular or cellular mechanisms driving these relationships. Further experimental studies are needed to explore these mechanisms in greater detail.

CONCLUSION

This research provides important information about how thyroid function, renal function, and albuminuria interact in CKD patients. This implies that a decrease in free T3 levels in CKD patients may be facilitated by albuminuria. Clinicians should also be on the lookout for abnormal thyroid function tests in patients with chronic kidney disease (CKD) who have elevated albuminuria. To completely understand the underlying mechanisms and therapeutic implications of these relationships, more study with a bigger patient cohort and a wider range of parameters is necessary. These studies could help guide the creation of focused treatment plans for the treatment of CKD and related thyroid disorders, which would eventually benefit patients.

REFERENCES

1. E. Ritz; Nephropathy in patients with type 2 diabetes mellitus; N. Engl. J. Med. (1999) 341, 1127–1133

2. A. S. Levey, P.E. de Jong, J. Coresh et al.; The definition, classification and prognosis of chronic kidney disease: a KDIGO Controversies Conference report; Kidney Int. (2011) 80, 17–28

3. Garofalo, C., et al. (2013). "Thyroid hormones and chronic kidney disease: pathophysiology and clinical implications." *European Journal of Endocrinology*, 169(3), 1-10.

4. Arosio, E., et al. (2008). "Endothelial dysfunction and inflammation in chronic kidney disease: A review of the literature." *Nephrology Dialysis Transplantation*, 23(6), 1660-1665.

5. Reinhardt W, Mülling N, Behrendt S, Benson S, Dolff S, Führer D, et al. Association between albuminuria and thyroid function in patients with chronic kidney disease. Endocrine 2021; 73: 367-73.

6. Benvenga S, Vita R, Di Bari F, Fallahi P, Antonelli A. Do Not Forget Nephrotic Syndrome as a Cause of Increased Requirement of Levothyroxine Replacement Therapy. Eur Thyroid J 2015; 4: 138-42.

7. Du, X. *et al.* Albuminuria is an independent risk factor of T4 elevation in chronic kidney disease. *Sci. Rep.* **7**, 41302; doi: 10.1038/srep41302 (2017).

8. Sawant SU, Chandran S, Almeida AF, Rajan MG. Correlation between Oxidative Stress and Thyroid Function in Patients with Nephrotic Syndrome. Int J Nephrol 2011; 2011: 256420.

9. Fonseca, V. *et al.* Can urinary thyroid hormone loss cause hypothyroidism? *Lancet*. **338,** 475–476 (1991).

10. van Hoek, I. & Daminet, S. Interactions between thyroid and kidney function in pathological conditions of these organ systems: a review. *Gen Comp Endocrinol*. **160,** 205–215 (2009).

11. Ford, H. C. *et al.* Renal function and electrolyte levels in hyperthyroidism: urinary protein excretion and the plasma concentrations of urea, creatinine, uric acid, hydrogen ion and electrolytes. *Clin Endocrinol*. **30,** 293–391 (1989)

12. Feinstein, E. I. *et al.* Thyroid function in patients with nephrotic syndrome and normal renal function. *Am J Nephrol*. **2,** 70–76

13. Gilles, R. *et al.* Thyroid function in patients with proteinuria. *Neth J Med*. **66,** 483–485 (2008).