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Correlation Between Albuminuria and Thyroid Function in Patients with Chronic Kidney Disease

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ABSTRACT

Introduction: Decreased renal function is a significant public health issue, increasing the risk of various adverse outcomes. Thus, identifying potentially modifiable factors associated with the onset of chronic kidney disease (CKD) is imperative. 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: We conducted a cross-sectional analysis involving 232 patients with CKD. Patients were categorized on the basis of albuminuria levels, measured by the urinary albumin/creatinine ratio (ACR), following the KDIGO 2012 criteria: ACR1 <30 mg/gr, ACR2 30-300 mg/gr, and ACR3 >300 mg/gr. Thyroid stimulating hormone (TSH), free thyroxine (free T4), and free triiodothyronine (free T3) levels were measured to assess thyroid function.

Results: The ACR among subjects ranged from 1.0 mg/g to 10260.0 mg/g, with a mean urinary ACR of 485.7±1250.9 mg/g. Among the patients, 47.4% (n=110) had an ACR <30 mg/g, 25.4% (n=59) had an ACR 30-300 mg/g was, and 27.1% (n=63) had an ACR >300 mg/g. TSH levels ranged from 0.3 to 14 mU/L, free T3 ranged between 0.6 and 4.8 ng/L, and free T4 ranged from 5.5 to 17.8 ng/L. No significant differences were observed in TSH, free T4, and free T3 values among the ACR1, ACR2, and ACR3 groups ($p>0.05$). 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 suggest that albuminuria may contribute to a reduction in free T3 levels in patients with CKD. However, it is crucial for physicians to recognize that CKD patients with elevated albuminuria levels may exhibit abnormal thyroid function.

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

Introduction

Decreased renal function is a prevalent public health challenge, leading to various adverse consequences. Hence, identifying modifiable factors associated with the onset of chronic kidney disease (CKD) is paramount (1,2). CKD manifests as a persistent loss of renal function or damage, often stemming from conditions such as diabetes mellitus (DM) and hypertension. Despite efforts to manage CKD risk factors, renal function decline persists, suggesting the existence of additional, undiscovered risk factors (3). Proteinuria has emerged as a predictive indicator for cardiovascular events, progression to end-stage kidney disease, and mortality in CKD patients, including DM and glomerulonephritis (4-6). Nevertheless, it is still unknown how thyroid function and proteinuria in CKD are related.

Thyroid hormone exerts numerous effects on almost all tissues, highlighting its pivotal role in physiological functions. Therefore, thyroid dysfunction can precipitate various complications in several terminal organs, including the kidney. CKD manifests diverse effects on thyroid function, with alterations in thyroid function levels often correlating with glomerular filtration rate (GFR) levels (7,8). Although the precise interplay between the thyroid and kidney diseases remains incompletely elucidated, accumulating research and the evidence suggest a bidirectional relationship between these conditions (9,10).

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It is widely recognized that albumin, transthyretin, and thyroxine-binding 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 (11). Furthermore, patients presenting with concurrent nephrotic syndrome and hypothyroidism may require higher doses of thyroid replacement therapy (12).

The relationship between baseline kidney function or the onset of CKD and a comprehensive panel of thyroid indicators, including thyroid-stimulating 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.

Methods

Study Design

This cross-sectional prospective study explored the correlation between albuminuria and thyroid function tests among patients with CKD admitted to the Nephrology and Family Medicine outpatient clinic of a Tertiary Referral Hospital from December 1, 2022, to March 1, 2023. The sample size was determined using the G*Power program based on the effect size derived from the relevant literature. Upon reviewing a reference study (11), the effect size reflecting the correlation between the two variables was calculated as 0.183. Consequently, it was determined that 229 individuals should be enrolled in the study, as per power analysis, ensuring 80% power and a significance level of 0.05, based on a two-way hypothesis for CKD individuals. This study protocol received approval from the Local Ethical Committee of Non-invasive Clinical Research at University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 392, date: 23.12.2022), in accordance with the ethical principles outlined in the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended in October 2013 (www.wma.net).

Patients aged between 18 and 65 years who attended our outpatient clinics from December 1, 2022, to March 1, 2023; and met at least one of the CKD criteria persisting for more than 3 months were recruited for the study. CKD criteria included a decreased GFR (<60 mL/min) and/or markers of kidney damage such as albuminuria [albumin excretion rate ≥30 mg/24 hours; albumin-to-creatinine ratio (ACR) ≥30 mg/gr], abnormalities in urine sediment, structural irregularities identified via imaging, abnormalities detected through histological examination, anomalies related to tubular disorders, and a medical history including kidney transplantation.

Patients were categorized according to the severity of albuminuria, as per the KDIGO 2012 criteria: ACR1 (<30 mg/gr), ACR2 (30-300 mg/gr), and ACR3 (>300 mg/gr). Exclusion criteria comprised individuals below 18 or above 65 years of age, known thyroid disorder necessitating treatment with levothyroxine or thionamide and/or the existence of antibodies targeting thyroid peroxidase, and use of medications known or potential effects thyroid hormone function [such as current or previous use of steroids or furosemide, anticonvulsants (carbamazepine or phenytoin), high-dose amiodarone, heparin or estrogen replacement therapy or anticancer drugs]. According to the inclusion/exclusion criteria, patients were initially informed about the study, and 232 subjects who agreed to participate in the study were enrolled. The height and weight of the patients were measured during outpatient clinic visits, and routine blood tests were conducted.

Laboratory Diagnostics

The following information was recorded: Height, weight, age, gender, body mass index (BMI), and concomitant conditions (dyslipidemia, ischemic heart disease, hypertension, DM, and so forth). Weight (kg)/height (m^2) was the formula used to compute BMI. Routine blood tests, including hemoglobin, hematocrit (HCT), fasting blood glucose, urea, creatinine, GFR, C-reactive protein (CRP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), TSH, free T4, free T3, total cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein, serum albumin, urinary ACR, parathyroid hormone (PTH), (calcium, phosphorus, ferritin, vitamin-D) were collected.

Statistical Analysis

Descriptive statistical techniques were used to summarize the data, which included the mean, standard deviation, median, minimum, maximum, frequency, and percentages. The variable distribution was assessed using the Kolmogorov-Smirnov test. The chi-square test was used to examine qualitative independent data, whereas analysis of variance (ANOVA) and Kruskal-Wallis (Mann-Whitney U test) were used to investigate quantitative independent data. Correlations were investigated using Spearman correlation analysis. SPSS version 28.0 was used for statistical analyses.

Results

Demographic characteristics and laboratory findings of patients with CKD are presented in Table 1. Among the 232 patients included in the study, 129 (55.6%) were female and 103 (44.4%) were male, with a mean age of 51.6±10.3 years. Urinary ACR measurements ranged from 1.0 mg/g to 10260.0 mg/g, with a mean of 485.7±1250.9 mg/g. TSH measurements ranged from 0.3 to 14 mU/L, with a mean level of 2.3±1.7 mU/L. Free T3 measurements ranged from 0.6 ng/L to 4.8 ng/L, with a mean level of 3.0±0.5 ng/L. Free T4 measurements ranged from 5.5 ng/L to 17.8 ng/L, with a mean level of 11.7±1.8 ng/L (Table 1).

The distribution of subjects based on ACR levels was as follows: 47.4% (n=110) had ACR <30 mg/g, 25.4% (n=59) had ACR ranging from 30 to 300 mg/g, and 27.1% (n=63) had ACR >300 mg/g.

The comparison of demographic and laboratory parameters among the ACR1, ACR2, and ACR3 groups is presented in Table 2. Gender distribution, mean age, height, weight, and BMI values did not exhibit any significant

differences among the ACR1, ACR2, and ACR3 groups (p>0.05). Similarly, the mean levels of PTH, calcium, phosphorus, ferritin, and vitamin D did not vary substantially across the groups (p>0.05). However, mean values for hemoglobin and HCT were significantly higher in the ACR1 and ACR2 groups compared to those of the ACR3 group (p<0.05). No significant difference in mean hemoglobin and HCT values was observed between the ACR1 and ACR2 groups (p>0.05) (Table 2).

Table 3 illustrates the correlations among GFR, serum albumin, urinary ACR, and various demographic and laboratory parameters. A significant negative correlation was identified between mean GFR and mean age, urea, creatinine, CRP, PTH, and phosphorus levels (p<0.05). Conversely, a significant positive correlation was detected between mean GFR and mean AST, ALT, HDL, free T3, hemoglobin, HCT (p<0.05). No significant correlation was observed between mean GFR and other demographic and laboratory parameters (p>0.05).

The mean serum albumin level exhibited a significant positive correlation with mean height, AST, ALT, calcium, vitamin D, hemoglobin, and HCT levels (p<0.05). Conversely, a significant negative correlation was found between mean serum albumin and mean urea, CRP, PTH, and phosphorus levels (p<0.05). There was no significant correlation with other demographic and laboratory findings (p>0.05).

Furthermore, a significant positive correlation was identified between median urine ACR and mean fasting blood glucose, urea, creatinine, PTH, and phosphorus levels (p<0.05). Conversely, a significant negative correlation was found between median urine ACR and mean GFR, AST, ALT, HDL, free T3, calcium, vitamin D, hemoglobin, and HCT levels (p<0.05). No significant correlation was detected with the other demographic and laboratory findings (p>0.05) (Table 3).

Table 1. Demographic characteristics and laboratory findings of patients with CKD

Characteristics		**n**	**%**		
Gender	**Female**	**129**	**(55.6)**		
	Male	**103**	**(44.4)**		
		Min.-max.		**Median**	**Mean ± SD**
Age (years)		19.0-65.0		54.0	51.6±10.3
Height (cm)		140.0-195.0		164.0	163.7±10.1
Weight (kg)		37.0-132.0		79.5	81.3±15.8
BMI (kg/m^2)		16.4-55.0		29.4	30.4±5.7
Fasting BG (mg/dL)		11.0-391.0		107.0	123.2±50.9
Urea (mg/dL)		12.5-326.0		35.7	45.2±32.5
Creatinine (mg/dL)		0.4-10.4		1.1	1.4±1.2
GFR (mL/min./1.73 m^2)		7.8-136.8		69.0	69.9±29.1
AST (U/L)		4.0-107.0		18.0	20.0±10.3
ALT (U/L)		4.0-75.0		18.0	20.2±11.6
Total cholesterol (mg/dL)		89.0-1858.0		192.0	205.8±146.4
Triglyceride (mg/dL)		22.0-886.0		152.0	170.5±105.5
HDL (mg/dL)		13.0-134.0		43.0	46.2±14.3
LDL (mg/dL)		26.0-400.0		113.0	119.4±58.9
CRP (mg/dL)		0.3-105.2		3.5	7.0±12.9
TSH (mU/L)		0.3-14.0		1.9	2.3±1.7
Free T4 (ng/L)		5.5-17.8		11.7	11.7±1.8
Free T3 (ng/L)		0.6-4.8		2.9	3.0±0.5
Free albumin (g/L)		16.2-53.7		45.7	44.9±4.7
Urine ACR (mg/g)		1.0-10260.0		39.0	485.7±1250.9
PTH (ng/L)		9.0-507.4		51.2	69.2±65.1
Calcium (mg/dL)		1.0-10.8		9.5	9.4±0.8
Phosphor (mg/dL)		1.9-6.5		3.6	3.6±0.7
Ferritin (µg/L)		3.4-715.7		70.9	108.3±115.8
Vitamin-D (µg/L)		3.0-70.5		15.2	18.2±12.4
Hb (g/dL)		7.6-17.9		13.2	13.0±1.9

CKD: Chronic kidney disease, min.: Minimum, max.: Maximum, SD: Standard deviation, BMI: Body mass index, BG: Blood glucose, GFR: Glomerular filtration rate, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, CRP: C-reactive protein, TSH: Thyroid-stimulating hormone, T4: Thyroxine, T3: Triiodothyronine, ACR: Albumin/creatinine ratio, PTH: Parathyroid hormone, Hb: Hemoglobin

Table 2. Comparison of demographic and laboratory parameters of patients according to ACR1 (n=110), ACR2 (n=59) and ACR3 (n=63) groups

		ACR1 <30 mg/g	ACR2 30-300 mg/g	ACR3 >300 mg/g	p-value
Gender	Female, n (%)	67 (60.9)	29 (49.2)	33 (52.4)	0.285[X²]
	Male, n (%)	43 (39.1)	30 (50.8)	30 (47.6)	
Age (years)	Mean ± SD	52.4±9.7	50.8±11.5	51.1±10.4	0.585[K]
	Median	54.0	53.0	52.0	
Height (cm)	Mean ± SD	163.5±10.0	164.8±10.3	163.0±10.4	0.463[K]
	Median	164.0	166.0	162.0	
Weight (kg)	Mean ± SD	82.4±15.9	80.1±17.0	80.5±14.5	0.326[K]
	Median	80.0	78.0	79.0	
BMI (kg/m²)	Mean ± SD	30.8±5.4	29.6±6.3	30.5±5.6	0.055[K]
	Median	29.8	28.6	29.1	
Fasting BG (mg/dL)	Mean ± SD	113.1±34.4	132.1±58.4	132.5±63.6	0.054[K]
	Median	103.5	112.0	109.0	
Urea (mg/dL)	Mean ± SD	36.1±14.3	40.7±20.5	65.5±50.9	0.156[K]
	Median	33.0	37.0	49.7	
Creatinine (mg/dL)	Mean ± SD	1.1±0.9	1.3±1.4	1.8±1.4	0.436[K]
	Median	1.0	1.1	1.2	
GFR (mL/d/m²)	Mean ± SD	73.5±23.1	72.1±28.4	61.4±36.9	0.711[K]
	Median	70.2	68.4	58.8	
AST (U/L)	Mean ± SD	20.7±9.4	20.3±12.8	18.5±9.3	0.458[K]
	Median	18.0	19.0	17.0	
ALT (U/L)	Mean ± SD	20.6±10.5	20.9±12.6	19.1±12.7	0.730[K]
	Median	18.0	18.0	15.0	
Total cholesterol (mg/dL)	Mean ± SD	219.0±204.9	184.3±42.1	203.0±60.1	0.302[K]
	Median	191.0	189.0	200.0	
Triglyceride (mg/dL)	Mean ± SD	165.3±111.2	163.5±66.6	186.0±123.3	0.408[K]
	Median	141.0	151.0	162.0	
HDL (mg/dL)	Mean ± SD	47.6±13.4	44.2±12.5	45.5±17.2	0.053[K]
	Median	46.0	41.0	42.0	
LDL (mg/dL)	Mean ± SD	117.4±56.2	108.2±36.5	133.4±76.1	0.556[K]
	Median	111.5	111.0	119.0	
CRP (mg/dL)	Mean ± SD	5.5±8.7	8.9±12.8	8.1±18.0	0.264[K]
	Median	3.3	4.0	3.9	
TSH (mU/L)	Mean ± SD	2.1±1.2	2.3±1.6	2.7±2.5	0.928[K]
	Median	2.0	1.8	1.9	
Free T4 (ng/L)	Mean ± SD	11.8±1.8	12.0±1.9	11.3±1.6	0.109[A]
	Median	11.6	12.1	11.5	
Free T3 (ng/L)	Mean ± SD	3.1±0.5	2.9±0.6	2.8±0.5	0.082[K]
	Median	3.0	2.9	2.8	
Serum albumin (g/L)	Mean ± SD	46.0±3.8	46.5±3.1	41.7±5.9	0.522[K]
	Median	46.5	46.4	42.5	
Urine ACR (mg/g)	Mean ± SD	9.6±6.8	97.5±56.3	1680.7±1957.1	**0.001**[K]
	Median	7.5[2,3]	85.0[3]	870.0	
PTH (ng/L)	Mean ± SD	52.1±24.9	64.3±66.5	103.8±93.9	0.523[K]
	Median	47.6	48.6	66.7	
Calcium (mg/dL)	Mean ± SD	9.6±0.5	9.6±0.5	9.1±1.2	0.630[K]
	Median	9.6	9.6	9.2	
Phosphorus (mg/dL)	Mean ± SD	3.4±0.6	3.5±0.6	3.9±0.9	0.637[K]
	Median	3.4	3.5	3.9	
Ferritin (µg/L)	Mean ± SD	98.2±100.6	119.1±137.1	116.0±119.4	0.427[K]
	Median	70.4	78.1	65.6	
Vitamin D (µg/L)	Mean ± SD	20.9±13.6	19.3±12.2	12.6±7.9	0.642[K]
	Median	18.4	16.3	9.9	
Hb (g/dL)	Mean ± SD	13.4±1.7	13.2±1.9	12.3±2.2	**0.001**[A]
	Median	13.6[3]	13.4[3]	11.8	
Hct (%)	Mean ± SD	40.6±4.7	40.0±5.6	37.7±6.3	**0.002**[A]
	Median	41.1[3]	40.3[3]	36.6	

[K]Kruskal-Wallis (Mann-Whitney U test)/[X²] Chi-squared test/[A]ANOVA, [2]Difference with ACR2 group p<0.05, [3]Difference from ACR3 group p<0.05. ACR: Albumin/creatinine ratio, BMI: Body mass index, BG: Blood glucose, GFR: Glomerular filtration rate, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, CRP: C-reactive protein, TSH: Thyroid-stimulating hormone, T4: Thyroxine, T3: Triiodothyronine, PTH: Parathyroid hormone, Hb: Hemoglobin, Hct: Hematocrit

Table 3. Correlation between the glomerular filtration rate, serum albumin, and urinary albumin/creatinine ratio; and the demographics and other laboratory parameters

	GFR		Serum albumin		Urine ACR	
	r	p	r	p	r	p
Age (years)	-0.335	**0.001**	0.056	0.396	-0.028	0.667
Height (cm)	0.058	0.377	0.187	**0.004**	-0.038	0.560
Weight (kg)	0.011	0.866	0.081	0.222	-0.061	0.358
BMI (kg/m^2)	-0.037	0.573	-0.031	0.635	-0.039	0.554
Fasting BG (mg/dL)	-0.062	0.345	-0.057	0.390	0.170	**0.009**
Urea (mg/dL)	-0.794	**0.001**	-0.169	**0.010**	0.285	**0.001**
Creatinine (mg/dL)	-0.929	**0.001**	-0.057	0.390	0.185	**0.005**
GFR (mL/d/m^2)					-0.186	**0.005**
AST (U/L)	0.180	**0.006**	0.164	**0.012**	-0.187	**0.004**
ALT (U/L)	0.310	**0.001**	0.254	**0.001**	-0.182	**0.005**
Total cholesterol (mg/dL)	0.046	0.486	-0.048	0.468	0.041	0.535
Triglyceride (mg/dL)	-0.112	0.088	0.014	0.835	0.113	0.085
HDL (mg/dL)	0.186	**0.004**	0.022	0.742	-0.149	**0.023**
LDL (mg/dL)	0.022	0.740	-0.035	0.592	0.044	0.504
CRP (mg/dL)	-0.199	**0.002**	-0.247	**0.001**	0.126	0.055
TSH (mU/L)	-0.033	0.612	-0.021	0.750	0.098	0.136
Free T4 (ng/L)	0.008	0.907	0.074	0.260	-0.035	0.595
Free T3 (ng/L)	0.395	**0.001**	0.119	0.072	-0.264	**0.001**
PTH (ng/L)	-0.428	**0.001**	-0.245	**0.001**	0.265	**0.001**
Calcium (mg/dL)	0.106	0.109	0.545	**0.001**	-0.280	**0.001**
Phosphorus (mg/dL)	-0.204	**0.002**	-0.248	**0.001**	0.239	**0.001**
Ferritin (µg/L)	-0.128	0.052	0.110	0.095	0.021	0.749
Vitamin D (µg/L)	0.153	0.099	0.287	**0.002**	-0.293	**0.001**
Hb (g/dL)	0.396	**0.001**	0.419	**0.001**	-0.253	**0.001**
Hct (%)	0.396	**0.001**	0.407	**0.001**	-0.239	**0.001**

GFR: Glomerular filtration rate, ACR: Albumin/creatinine ratio, BMI: Body mass index, BG: Blood glucose, AST: Aspartate Aminotransferase, ALT: alanine aminotransferase, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, CRP: C-reactive protein, TSH: Thyroid-stimulating hormone, T4: Thyroxine, T3: Triiodothyronine, PTH: Parathyroid hormone, Hb: Hemoglobin, Hct: Hematocrit

Discussion

This study elucidated the relationship between albuminuria and thyroid function tests among patients with CKD. We found that the mean GFR exhibited significant negative correlations with several demographic and laboratory parameters, including age, urea, creatinine, CRP, PTH, and phosphorus levels. Conversely, a positive correlation was demonstrated between the mean GFR and AST, ALT, HDL, free T3, hemoglobin, and HCT. These findings highlight the intricate relationship between renal function and thyroid function, suggesting potential bidirectional influences.

Furthermore, significant correlations were observed between serum albumin levels and various demographic and laboratory parameters, including height, AST, ALT, calcium, vitamin D, hemoglobin, and HCT. Moreover, mean serum albumin was significantly negatively correlated with urea, CRP, PTH, and phosphorus levels. In addition, our study revealed significant correlations between urinary ACR and several metabolic parameters, including fasting blood glucose, urea, creatinine, PTH, and phosphorus levels. Conversely, a negative correlation was identified between urinary ACR and GFR, AST, ALT, HDL, free T3, calcium, vitamin D, hemoglobin, and HCT. These findings suggest a potential role of albuminuria in modulating thyroid function and vice versa, highlighting an intricate interplay among albuminuria, renal function, and metabolic parameters in patients with CKD.

Several studies have explored the connection between proteinuria and thyroid function in patients with normal renal function (14-18). A study involving 20 young patients (aged 12-50 years) with nephrotic syndrome and high proteinuria levels (mean: 5.2±1.2 g/day) revealed elevated TSH levels (5.9-2.9 mIU/m^2) alongside decreased levels of T4 and T3. In a retrospective analysis by Yang et al. (19), which included 211 patients with an average albuminuria of 2.1±2.0 g/day, a negative association was observed between free T4 levels and albumin excretion, whereas TSH levels remained unchanged. However, this study did not provide information on TBG and free T3 concentrations, nor did it include thyroid antibody status. It is worth noting that the mean levels of proteinuria in the aforementioned studies were higher than those measured in our study. Nevertheless, our study revealed a negative correlation solely between free T3 levels and ACR.

A study conducted by a Chinese group (20) investigated 581 individuals with albuminuria, categorizing patients into three subdivisions of albuminuria similar to our study. They observed a positive correlation between higher serum T4 and fT4 levels in the subgroup with albuminuria >300 mg. However, in the group with albuminuria >300 mg, only a mean of 996±843 mg/g creatinine was measured. TSH, T3, and free T3 levels did not exhibit significant variations among the albuminuria subsets. The study did not provide data on the number of patients in the true nephrotic range (>3 g/day) or TPO-Ab status. The authors attributed the differences between their findings and those of other studies partially to racial distinctions (20). Similarly, in line with previously reported studies, we observed that TSH and free T3 and T4 levels did not differ significantly among the albuminuria groups. However, contrary to previous findings, we discovered a negative correlation between the levels of free T3 and albuminuria. This discrepancy may stem from the fact that our study was single-centered and included patients with CKD in the early stages, without representation from diverse racial groups.

Thyroid hormones within normal levels can directly influence kidney function by impacting both glomerular and tubular functions, as well as indirectly through prerenal effects on cardiovascular hemodynamics and renal blood flow (21). Elevated levels of TSH within the normal range have been associated with reduced estimated glomerular filtration rate (eGFR) (22-24). However, the association between the related levels of T3 and T4 and kidney function remains controversial (13,23,25). The diagnosis of kidney disorders may also be linked to thyroid dysfunction, either due to the leakage of TSH, free T4, and relevant binding proteins into the urine or due to non-thyroidal illness (21,26,27).

A recent study demonstrated a directional association between hypothyroidism and increased TSH, but not free T4, and decreased eGFR using cystatin C and increased CKD (28). Our study further substantiates the significant association between GFR and thyroid function markers. Specifically, we observed a negative correlation between the mean GFR and several demographic and laboratory parameters, including age, urea, creatinine, CRP, PTH, and phosphorus levels. Conversely, a positive correlation was found between the mean GFR and AST, ALT, HDL, hemoglobin, and HCT. The correlations between GFR decline and increased PTH and phosphorus levels and decreased hemoglobin and HCT levels are significant as secondary signs of CKD. Notably, among thyroid function markers, only free T3 levels were positively correlated with GFR. These findings highlight the intricate relationship between renal function and thyroid function, suggesting potential bidirectional influences.

In a prospective study, Reinhardt et al. (11) examined the association between thyroid and kidney function in individuals without thyroid antibodies across all stages of CKD. They observed a negative association between serum albumin levels, and age and CRP, while a positive association was found with T3, T4, fT3. However, no significant correlation was observed between serum albumin and TSH and fT4 (11). Consistent with these findings, our study indicated that TSH and free T4 levels were unaffected by albumin excretion, whereas free T3 showed a significant negative correlation with urinary albumin excretion. Furthermore, we observed significant correlations between serum albumin levels and various demographic and laboratory parameters, including height, AST, ALT, calcium, vitamin D, hemoglobin, and HCT. These findings suggest a potential role for albuminuria in modulating thyroid function and vice versa.

In a study involving 1624 adult patients at stage 3-5 CKD and 200 normal control subjects, it was found that 98.6% of CKD patients had insufficient levels of 25-hydroxyvitamin D [25(OH)D], compared with only 48% of normal subjects (29). Similarly, in our study, serum levels of vitamin D showed a significant negative correlation with ACR. Another report, comprising 9,162 participants from the Dong-gu study's baseline survey conducted in Korea between 2007 and 2010, revealed that higher ACR levels were associated with elevated PTH and lower 25(OH)D levels (30). Consistent with this finding, we found a positive correlation between urine ACR and PTH and phosphorus levels, whereas urine ACR exhibited a significant negative correlation with GFR, calcium, and vitamin D levels. However, our study did not detect any correlation between urine ACR and PTH, GFR, creatinine, calcium, phosphorus, or vitamin D levels.

In a study conducted from 1996 to 1998, which recruited 5801 participants with available hemoglobin measurements from the ARIC study, anemia prevalence was stratified according to ACR. The study revealed an anemia prevalence of 8.1% in attendees with ACR <10 mg/g, 10.7% in those with ACR 10 to 29 mg/g, and 13.3% in those with ACR ≥30 mg/g (31). Furthermore, a retrospective analysis conducted using data from the Clinical Laboratory of the University Hospital of Verona between May 2007 and May 2009 examined ACR and hemoglobin levels in the entire cohort. Within the comprehensive outpatient cohort, an accelerating decline in hemoglobin and an increased prevalence of anemia were observed in patients with microalbuminuria (24%) and macroalbuminuria (32%) compared with those with normoalbuminuria (15%) (32).

In a cross-sectional study by Inker et al. (33), an association between albuminuria stages and laboratory abnormalities (PTH, GFR, creatinine, calcium, phosphorus) was generally lacking or minimal in both CKD cohorts and those representing the general population or at high risk. In addition, they reported little or no association between stages of albuminuria and hemoglobin levels in both CKD cohorts and cohorts representing the general population or individuals at elevated risk. However, increased albuminuria was linked to slightly reduced hemoglobin levels in CKD cohorts (34). Similarly, in our study, a negative correlation was observed between albuminuria and hemoglobin levels. Additionally, significantly lower albuminuria was detected in the ACR3 group than in the ACR1 and ACR2 groups. Furthermore, we found a significant negative correlation between urinary ACR and hemoglobin and HCT levels, which aligns with findings in the existing literature.

Study Limitations

The limitations of our study are the small sample size from a single center, absence of measurement of anti-thyroid peroxidase antibody, and absence of results of total T3 and T4 of patients.

Conclusion

In summary, our study offers valuable insights into the interplay between albuminuria, thyroid function, and renal function in patients

with CKD. This suggests that albuminuria may contribute to a decline in free T3 concentrations in patients with CKD. Additionally, clinicians should remain vigilant regarding the potential for abnormal thyroid function tests in patients with CKD with high albuminuria. Further research encompassing a broader range of parameters and a larger cohort of patients is warranted to fully elucidate the underlying mechanisms and clinical implications of these associations. Such investigations have the potential to inform the development of targeted therapeutic strategies for managing CKD and associated thyroid dysfunction, ultimately improving patient outcomes.

Ethics Committee Approval: This study protocol received approval from the Local Ethical Committee of Non-invasive Clinical Research at University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 392, date: 23.12.2022).

Informed Consent: Retrospective study.

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