Current Science International
Volume: 12 | Issue: 03| July – Sept.| 2023

EISSN:2706-7920 ISSN: 2077-4435
DOI: 10.36632/csi/2023.12.3.29
Journal homepage: www.curresweb.com
Pages: 411-423

Serum Free T4/Free T3 Ratio as a Predictor of Subclinical Hypothyroidism in Non-Hemodialysis Dependent Chronic Kidney Disease Patients

Eslam A. Hashish, Gamal F. Elnaggar, Dina I. Abdelhai and Amal Selim

Department of Internal Medicine, Faculty of Medicine, Tanta University, Tanta, Egypt

Received: 15 June 2023 **Accepted:** 30 July 2023 **Published:** 10 August 2023

ABSTRACT

Background: Chronic kidney disease (CKD) is an increasingly prevalent condition, recognized as a public health priority, affecting 10–12% of the population. Subclinical Hypothyroidism is a clinical condition with minimal symptoms or no symptoms of hypothyroidism. Early detection and management decrease the cardiovascular and metabolic complications in CKD patients. **Objective:** The study was conducted to evaluate serum FT4 / FT3 Ratio, as a Predictor of Subclinical Hypothyroidism in Patients with CKD. **Patients and methods**: The study was conducted at Tanta University hospitals, Internal Medicine outpatient clinics, inpatient wards of Nephrology and Endocrinology Units and clinical pathology department. From September 2021 to September 2022.100 subjects were included; 50 normal healthy volunteers as controls and 50 patients suffering from CKD of varying etiology have been considered for the study after fulfilling the inclusion criteria. Data were collected including demographic, clinical, and laboratory data. Statistical analysis was carried out for all collected data using IBM, SPSS version 21. Statistical significance was determined at a P level ≤ 0.05. **Results:** TSH, and free T4 / free T3 ratio were significantly higher in CKD group compared to control group (P value <0.001). Free T3 was significantly lower in CKD group compared to control group (P value <0.001). Free T4 was insignificantly different between both groups. Free T4 / Free T3 ratio can significantly predict incidence of subclinical hypothyroidism with AUC=0.879 and P value <0.001. Free T3 can significantly predict incidence of subclinical hypothyroidism with AUC= 0.071 and P value<0.001.TSH can significantly predict incidence of subclinical hypothyroidism with AUC= 0.643 and P value=0.014. Free T4 was an insignificant predictor of incidence of subclinical hypothyroidism. **Conclusion:** free T4 / free T3 ratio can significantly predict incidence of subclinical hypothyroidism with AUC= 0.879 and P value <0.001. Free T3 can significantly predict incidence of subclinical hypothyroidism with AUC= 0.071 and P value<0.001. Free T4 was an insignificant predictor of incidence of subclinical hypothyroidism.

Keywords: Chronic kidney disease, serum FT4/FT3 Ratio, Type 2 Diabetic Patients, Subclinical Hypothyroidism

1. Introduction

Chronic kidney disease (CKD) is an increasingly prevalent condition, recognized as a public health priority, affecting 10–12% of the population. CKD is defined as abnormalities of kidney structure or function, present for more than 3 months, with implications for health (Liu *et al.,* 2021, Levin *et al.,* 2013). CKD is known as lower Glomerular filtration rate(GFR) of <60 mL/min/1.73m2 for >3 month, with presence or absence of renal damage (Kovesdy and Csaba, 2022). Subclinical Hypothyroidism is a clinical condition with minimal symptoms or no symptoms of hypothyroidism. Subclinical hypothyroidism is defined as increased "thyroid stimulating hormone" (TSH) along with a normal "free thyroxine" (FT4) and "free triiodothyronine" (FT3) level (Jasim *et al.,* 2021). According to the "National Health and Nutrition Examination Survey (NHANES)", the yardstick to identify subclinical hypothyroidism was elevation of TSH between 5 to 10 µIU/mL and with normal Free T4 without any clinical signs and symptoms. Incidence of subclinical hypothyroidism increases with age

Corresponding Author: Eslam Abdelaal Mohamed Hashish, Department of Internal Medicine, Faculty of Medicine, Tanta University, Tanta, Egypt. E-mail: eslamhashish59@gmail.com

and with greater dietary iodine intake (Metwalley and Farghaly, 2021). Prevalence of subclinical hypothyroidism has inverse relation with Glomerular filtration rate (GFR) as subclinical hypothyroidism increases slowly the GFR declines (Metwalley and Farghaly, 2021), few studies showed the connection of subclinical hypothyroidism and CKD which involve inflammation, alteration in iodine metabolism, hormonal issues and immune system attacking thyroid gland. (Wang *el al.,* 2020). Epidemiological data implies that pre-dialysis cases with CKD have a higher risk of hypothyroidism. Furthermore, subclinical Hypothyroidism is prevalent in CKD cases not requiring dialysis (Matsuoka *et al.,* 2022). Many studies reported the interrelationship of thyroid function and metabolic syndromes (Teixeira *et al.,* 2020). Although the link between the free T4/ free T3 and the subclinical hypothyroidism is not clear.

This study aims to investigate the free T4/ free T3 in prediction of subclinical hypothyroidism in CKD patients, which is necessary for clinician in early diagnosis, intervention and managing these patients.

2. Patients and Methods

This cross sectional study was conducted at Tanta University hospitals, Internal Medicine outpatient clinics, inpatient wards of Nephrology and Endocrinology Units and clinical pathology departments, from September 2021 to September 2022.100 subjects were included; 50 normal healthy volunteers as controls and 50 patients suffering from CKD of varying etiology have been considered for the study after fulfilling the inclusion criteria.

Inclusion Criteria

All the patients of CKD >18 years whatever etiology who do not require long-term dialysis (eGFR more than 15 ml/min/1.73m^2 and less than 60 ml/min/1.73m^2) for more than 3 months, (TSH ≥ 5.5 mIU/L) and less than (10 mIU/L).

Exclusion Criteria

Patients <18 years, refusal of the patients, previous history of usage of medication for thyroid diseases, family history of thyroid diseases, pregnant women, Drugs affecting thyroid functions, Patients with End stage renal disease on hemodialysis or eGFR <15 ml/min/1.73m2), Acute illness (major surgery, myocardial infarction, post trauma, infection , acute kidney injury).

The study was approved by the Ethics Committee of Faculty of Medicine, Tanta university, all patients were subjected to the followings:

Full history taking especially age, gender, smoking status, and comorbidities: History of smoking, hypertension, Diabetes Mellitus, dyslipidemia, hepatic disorders, asthma, and drug history.

Complete Clinical examination including the general condition and vital signs as systolic and diastolic blood pressure, heart rate and temperature.

Routine laboratory investigations including: Complete blood count (hemoglobin, white blood cell, and platelets), blood urea, serum creatinine, Estimated GFR (MDRD equation), Lipid profile (cholesterol, triglycerides, HDL, LDL). Calcium (ionized), Phosphorus, Parathyroid Hormone (PTH), serum uric acid ,serum Albumin .serum K, Na, CRP.

Specific laboratory investigations: TSH (normal range 0.5-5.5 mIU/L), Free T3 (normal range 1.5-4.4 ng/dL), Free T4 (normal range 0.8-1.4 ng/dL).

Pelviabdominal Ultrasound to asses kidney grading, size of kidney, gravels prostate, liver, spleen, intraperitoneal free fluid (IPFF).

Statistical analysis

Data were analyzed using the IBM® SPSS statistical software, version 21. Qualitative data were described using numbers and percentages. The Kolmogorov Smirnov test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum),

mean, standard deviation, and median. Chi-squared test was used for comparing the qualitative data and when it was inappropriate it was replaced by the Monte Carlo test. A student t-test was used to compare the two means in different groups. Linear correlation analysis was done by Spearman coefficient correlation and used to test the positive or negative associations between different variables. For the risk estimated, linear regression was used to detect the predictor variables. The level of significance was adopted at $p<0.05$ and statistically highly significant at $P \leq 0.001$.

3. Results

This cross-sectional study was performed on 100 subjects, who were classified into:
Control group: 50 normal healthy volunteers as controls. CKD group: 50 patients suffering from CKD of varying aetiology but not undergoing hemodialysis have been considered for the study after fulfilling the inclusion criteria.

Demographic data (age, gender, weight, height and BMI were insignificantly different between both groups. In CKD group, the duration of CKD min.- max (5-120) months with a mean of 43.42 ± 26.82 months there were 30 (60%) patients who were known the duration of their disease, 1 (2%) patient has known about the disease recently and 19 (38%) patients who didn't know the exact duration of the disease (Table1).

Table 1: Comparison between the two studied groups according to demographic data

	CKD group (N=50)		Control group (N=50)		Test of sig.	P value
	No.	%	No.	%		
Sex						
Male	24	48%	21	42%	X^2 (0.161)	0.687
Female	26	52%	29	58%		
Age (years)						
Min.-Max.	25 - 81		23 - 75		t-test	0.130
Mean ± SD	54.6 ± 13.15		50.4 ± 13.97		(1.526)	
Weight (kg)						
Min.-Max.	50 - 121		60 - 99		t-test	0.112
Mean ± SD	84.7 ± 14.35		80.9 ± 9.1		(1.606)	
Height (m)						
Min.-Max.	1.59 - 1.82		1.55 - 1.79		t-test	0.107
Mean ± SD	1.70 ± 0.05		1.68 ± 0.06		(1.629)	
BMI(kg/m^2)						
Min.-Max.	18.11 - 43.51		23.05 - 37.72		t-test	0.442
Mean ± SD	29.3 ± 5.05		28.6 ± 3.68		(0.770)	
Duration of CKD (month)						
Min.-Max.	5-120		----			----
Mean ± SD	43.42 ± 26.82		----			----

BMI: body mass index, **CKD:** chronic kidney disease, **X^2**: Chi-square test t-test: student t-test
P: Probability value fir comparing the studied groups, ***:** Statistically significant at $p \leq 0.05$

Regarding the risk factors in the studied groups, hypertension, DM, hyperlipidemia, hepatic disease, and cardiac disease were significantly higher in CKD group compared to the control group (P value < 0.05). Risk factors (prostatic disorders, analgesic abuse, history of renal stones, lupus nephritis and other risk factors) were significantly higher in CKD group compared to the control group (P value < 0.05) (Table 2).

Hb was significantly lower in CKD group compared to control group (P value<0.001). (Table 3).

Triglycerides, LDL, and total cholesterol were significantly higher in CKD group compared to control group (P value <0.001). HDL was significantly lower in CKD group compared to control group (P value =0.012) (Table 3).

Serum creatinine, urea, and uric acid were significantly higher in CKD group compared to control group (P value <0.001). Serum albumin and eGFR were significantly lower in CKD group compared to control group (P value <0.001) (Table 3).

Table 2: Comparison between the two studied groups according to the risk factors

		CKD group (N=50)		Control group (N=50)		X^2	P
		No.	%	No.	%		
Smoking		13	26%	11	22%	0.055	0.814
Hypertension		37	74%	0	0%	--	< 0.001*
DM		29	58%	0	0%	--	< 0.001*
Hyperlipidemia		21	42%	0	0%	--	< 0.001*
Hepatic disease		8	16%	0	0%	--	0.005*
Cardiac disease		26	52%	0	0%	--	<0.001*
Asthma		5	10%	0	0%	--	0.056
Others	**History of prostatic disorders**	3	6%	0	0%	2.38	<0.001*
	Analgesic	2	4%	0	0%		
	History of renal stones	8	16%	0	0%		
	Other risk factors	2	4%	0	0%		
	Lupus nephritis	1	2%	1	2%		

DM: diabetes mellitus, **CKD:** chronic kidney disease, X^2: Chi-square test, **P:** Probability value fir comparing the studied groups, ***:** Statistically significant at p≤ 0.05.

Phosphorous, and K^+ were significantly higher in CKD group compared to control group (P value <0.001). Ionized calcium was significantly lower in CKD group compared to control group (P value <0.001). PTH was significantly higher in CKD group compared to control group (P value <0.001).

Fasting and post prandial blood sugar and HBA1C were significantly higher in CKD group compared to control group (P value <0.001). (Table 3).

TSH, and free T4 / free T3 ratio were significantly higher in CKD group compared to control group (P value <0.001). Free T3 was significantly lower in CKD group compared to control group (P value <0.001). Free T4 was insignificantly different between both groups. (Table 4).

Regarding the ABG of the studied groups, pH and HCO_3 was significantly lower in CKD group compared to control group (P value 0.002, and <0.001). (Table 3).

There was a negative significant correlation between free T4 / free T3 ratio and eGFR, HCO_3, pH, HDL, Ionized Ca, Hb and free T3 (P value ≤ 0.05). There was a positive significant correlation between free T4 / free T3 ratio and urea, creatinine, uric acid, total cholesterol, Triglycerides, LDL, fasting blood sugar, HBA1C, TSH, phosphorus, PTH, post prandial sugar, free T4, (P value ≤ 0.05). (Table 5).

Free T4 / Free T3 ratio can significantly predict incidence of subclinical hypothyroidism with AUC=0.879 and P value <0.001

Free T3 can significantly predict incidence of subclinical hypothyroidism with AUC= 0.071 and P value<0.001. (Table 6) (Figure 1).

TSH can significantly predict incidence of subclinical hypothyroidism with AUC= 0.643 and P value=0.014. (Table 6). (Figure 1).

Free T4 was an insignificant predictor of incidence of subclinical hypothyroidism. (Table 6). (Figure 1) .

Table 3: Comparison between the two studied groups according to General laboratory findings:

	CKD Group (N=50)	Control Group (N=50)	T-Test	P
Hb (g/dL)				
Min.-Max.	9-10.9	11.2-13.9	19.14	<0.001*
Mean ± SD	9.93 ±0.56	12.63 ±0.83		
Triglycerides (mg/dL)				
Min.-Max.	161-383	102-162	12.35	<0.001*
Mean ± SD	268.08 ±76.51	130.62 ±18.35		
LDL (mg/dL)				
Min.-Max.	111-204	80-120	14.12	<0.001*
Mean ± SD	160.22 ±29.15	97.96 ±11.07		
HDL (mg/dL)				
Min.-Max.	30-51	36-52	2.55	<0.001*
Mean ± SD	41.26 ±6.13	44.14 ±5.14		
Total cholesterol (mg/dL)				
Min.-Max.	193-280	141-196	14.29	<0.001*
Mean ± SD	228.98 ± 24.51	169.04 ±16.7		
Serum creatinine (mg/dL)				
Min.-Max.	1.7 - 5.5	0.5 - 1.3	16.08	<0.001*
Mean ± SD	3.41 ± 1.11	0.86 ± 0.17		
Urea (mg/dL)				
Min.-Max.	78 – 280	15 – 53	17.96	<0.001*
Mean ± SD	151.6 ± 48.02	28 ± 7.93		
Uric acid (mg/dL)				
Min.-Max.	3.8 - 12.2	3 – 7	8.36	<0.001*
Mean ± SD	6.5 ± 1.82	4.2 ± 0.73		
Serum albumin (g/dL)				
Min.-Max.	3 - 3.6	4 - 4.5	25.84	<0.001*
Mean ± SD	3.31 ± 0.19	4.23 ±0.17		
eGFR(mL/min/1.73 m2)				
Min.-Max.	16.03 - 54.08	65.16 - 171.06	19.44	<0.001*
Mean ± SD	25.95 ± 8.56	111.14 ± 29.77		
Phosphorous (mg/dL)				
Min.-Max.	5.1 ± 1.1	3 ± 0.43	12.06	<0.001*
Mean ± SD	3.5 - 8.4	2 - 4.5		
Ionized calcium (mg/dL)				
Min.-Max.	1.1 ± 0.09	1.3 ± 0.07	12.05	<0.001*
Mean ± SD	0.86 - 1.2	1.2 - 1.4		
K+ (mmol/L)				
Min.-Max.	4.3 ± 0.59	3.9 ± 0.25	3.94	<0.001*
Mean ± SD	3.5 - 6.2	3.5 - 4.7		
PTH (pg/mL)				
Min.-Max.	70 – 450	19 – 64	14.59	<0.001*
Mean ± SD	263 ± 105.88	42.8 ± 13.17		
Fasting blood sugar (mg/dL)				
Min.-Max.	78 – 35	79 – 108	5.34	<0.001*
Mean ± SD	147.1 ± 63.47	99 ± 4.81		
Post prandial blood sugar (mg/dL)				
Min.-Max.	120 – 386	102 – 175	6.65	<0.001*
Mean ± SD	224.2 ± 88.47	139.4 ± 17.02		
HBA1C (%)				
Min.-Max.	4.8 - 9.1	4.1 - 5.5	7.75	<0.001*
Mean ± SD	6.4 ± 1.24	5.03 ± 0.25		
pH				
Min.-Max.	7.34-7.39	7.36-7.41	3.11	<0.001*
Mean ± SD	7.36 ±0.02	7.37 ±0.02		
HCO_3				
Min.-Max.	12-16	18-26	19.20	<0.001*
Mean ± SD	14.22 ±1.33	22.42 ±2.71		

Table 4: Comparison between the two studied groups according to thyroid function tests:

	CKD group (N=50)	Control group (N=50)	T-test	P
FT4 (ng/dL)				
Min.-Max.	0.8 - 2.3	0.99 - 1.5	0.31	0.741
Mean ± SD	1.2 ± 0.25	1.2 ± 0.16		
F T3 (ng/dL)				
Min.-Max.	1.4 - 3.1	1.99 - 6.37	**7.69**	**<0.001***
Mean ± SD	2.4 ± 0.45	3.2 ± 0.59		
TSH (mIU/L)				
Min.-Max.	5.5-9	1.08-4	**24.23**	**<0.001***
Mean ± SD	7.24 ±1.09	2.74 ±0.63		
FT4 / FT3 ratio				
Min.-Max.	0.36 - 1.15	0.21 - 0.5	**6.94**	**<0.001***
Mean ± SD	0.5 ± 0.14	0.4 ± 0.06		

Table 5: Correlation between Free T4 / Free T3 ratio and other variables in CKD group

Variables	Correlation with Free T4/Free T3 Ratio	
	R	P value
HB	-2.95	0.003*
Urea	0.455	<0.001*
Creat	0.558	<0.001*
eGFR	-0.497	<0.001*
Uric Acid	0.312	<0.002*
PH	-0.249	<0.001*
HCO3	-0.603	<0.001*
Total cholesterol	0.588	<0.001*
LDL	0.513	<0.001*
HDl	-0.466	<0.001*
TGS	0.284	<0.004*
Fasting Blood Sugar	0.199	<0.047*
Post prandial Sugar	0.245	<0.014*
HBA1C	0.304	<0.002*
K	0.566	<0.001*
Ionized Calicum	-0.438	<0.001*
Phosphorus	0.377	<0.001*
PTH	0.410	<0.001*
TSH	0.356	<0.001*
Free T4	0.487	<0.001*
Free T3	-0.702	<0.001*

*: Statistically significant at p≤ 0.05

Table 6: Validity for Free T4, Free T3, TSH and Free T4 / Free T3 ratio as a predictor for subclinical hypothyroidism in CKD patients.

	AUC	SE	P value	CI 95%	
				Lower	Upper
Free T4	0.490	0.059	0.860	0.375	0.605
Free T3	0.071	0.025	<0.001*	0.022	0.120
TSH	0.643	0.055	0.014*	0.535	0.751
Free T4 / Free T3 ratio	0.879	0.034	<0.001*	0.812	0.946

AUC: Area under the curve, SE: Standard error, CI: Confidence Interval
*: Statistically significant at p≤ 0.05

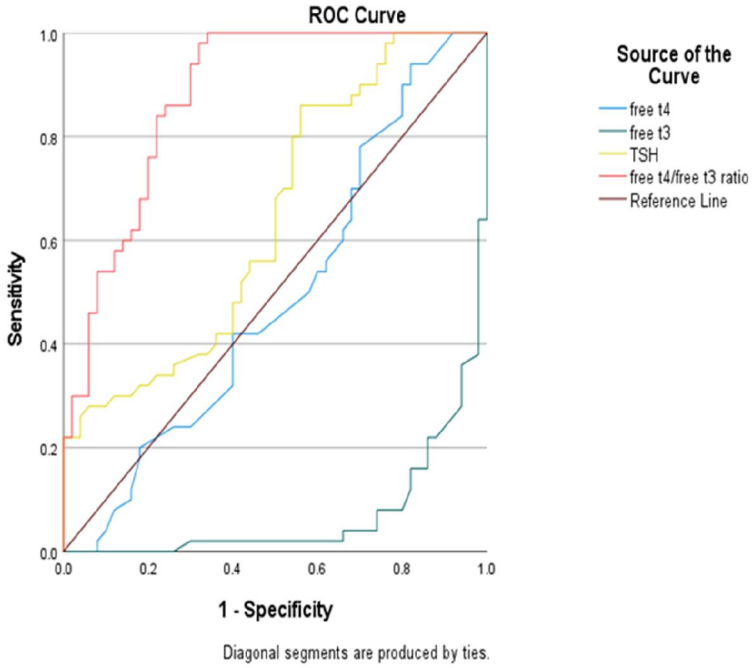

Fig. 1: ROC curve of Free T4/ Free T3 Ratio as a predictor for subclinical hypothyroidism

4. Discussion

Chronic kidney disease (CKD) is a global health problem that has reached epidemic proportions, with an estimated prevalence rate of 8–16% (Kovesdy, 2022). Currently, CKD is gaining increased attention as a potential driver of cardiovascular and cerebrovascular diseases . Similar to the global trend, the burden of CKD has increased by 35.7% in Egypt, ranking CKD as the 5th in leading causes of death from 2009 to 2019 (Farag and El-Sayed, 2022). This has become a major public health concern in Egypt, as untreated CKD can progress to kidney failure and early cardiovascular disease resulting in disability and heavy socioeconomic burden (Li, *et al.,* 2020). The FT4/FT3 Ratio can predicit the earlier incidence of subclinical hypothyroidism in CKD patients than TSH alone because in CKD patients , there is decrease in formation of FT4 which is the active form of the thyroid hormones because of the uremia that causes blunting of pituitary thyroid axis, the malnutrition in those patients , the presence of chronic metabolic acidosis ,the chronic inflammatory status and the circulating cytokines and, impairememt of idodine metabolism, impairement of Thyroid hormones excretions and hormone binding protein so the net result is increase of the level of FT3 at the level of the tissue with decrease of the level of FT4 because lack of its formation before the increase of TSH . There are several known risk factors for CKD, such as diabetes, hypertension, and urinary tract disorders (Erfanpoor *et al.,* 2021). Clinical investigations have revealed substantial variation in the onset and progression of CKD that cannot be fully explained by preexisting risk factors (Ejaz *et al.,* 2020). Thus, efforts are needed to identify more potential risk factors in the development of CKD.

Subclinical Hypothyroidism (ScHt) is a medical condition with least symptoms or not any symptoms of hypothyroidism (Peeters and Brito 2020). ScHt is an increased serum thyroid-stimulating hormone level accompanying a normal free FT4 and FT3 amount (Kimoto *et al.,* 2019.

It is widely recognized that thyroid hormones are of clinical and public health importance for renal physiology and functional development (Li *et al.,* 2020). From epidemiological aspects, a nationally representative cohort of U.S. patients with moderate-to-severe CKD showed an inverse association between estimated glomerular filtration rate (eGFR) and the risk of hypothyroidism (Iqbal *et al.,* 2022). In addition, a retrospective cohort study in Taiwan indicated that higher concentrations of thyroid stimulating hormone (TSH) were associated with greater risk of subsequent CKD (Chuang *et al.,* 2016).

Moreover, another prospective cohort study in middle-aged and elderly Shanghainese revealed that high free thyroxin (FT4), but not TSH and free triiodothyronine (FT3), was associated with

increased risk of incident CKD and rapid eGFR decline (Huang *et al.,* 2016). The reasons for these inconsistencies are multiple, likely due to heterogeneous study populations, different study designs, or unaccounted-for residual confounders.

The association between the FT4/FT3 ratio and the ScHt is not understood. In the present study, as regards the demographic data (age, gender, weight, height, and BMI were insignificantly different between both groups. On the other hand, hypertension, DM, hyperlipidemia, hepatic disease, and cardiac disease were significantly higher in CKD group compared to the control group (P value < 0.05). Risk factors (prostatic disorders, analgesic abuse , history of renal stones and lupus nephritis and other risk factors) were significantly higher in CKD group compared to the control group (P value < 0.05). In the present study, heart rate was significantly lower in CKD group compared to control group (P value = 0.024) and this may be due to hyperkalemia or betablockers or calcium channel blockers in the CKD patients. SBP and DBP were significantly higher in CKD group compared to control group (P value <0.001). Temperature and respiratory rate were insignificantly different between both groups.

The pathophysiology of CKD associated hypertension is multi-factorial with different mechanisms contributing to hypertension. These pathogenic mechanisms include sodium dysregulation, increased sympathetic nervous system and alterations in renin angiotensin aldosterone system activity (Hamrahian and Falkner, 2017).

Diabetes is the leading cause of CKD and may be considered thereby to contribute to a significant proportion of the CVD associated with CKD. Patients with diabetic nephropathy have a disproportionally higher risk for CVD when compared to patients with diabetes who do not have kidney disease (Pálsson and Patel 2014).

Our findings agreed with Ghelichi-Ghojogh *et al.,* (2022) who studied the associations of several behavioral and health-related factors with CKD in Iranian patients. History of diabetes, hypertension and cardiovascular diseases were significantly higher in CKD patients compared to healthy control. Their results documented that the history of smoking was also significantly associate with CKD.

Our results came in line with Li *et al.* (2020) who conducted a retrospective study involved 3563 participants evaluating association of serum thyroid hormones with the risk and severity of chronic kidney disease. They reported that diabetes and hypertension were significantly associated with CKD as risk factors.

In the present study, Hb was significantly lower in CKD group compared to control group (P value<0.001). PLT and WBCs were insignificantly different between both groups. The production of erythrocytes is regulated by the hormone erythropoietin (EPO), which maintains the blood haemoglobin (Hb) levels constant under normal conditions. The kidneys are the primary source of EPO, and its synthesis is controlled by hypoxia-inducible transcription factors. This hypothesis explained the lower level of Hb in CKD when compared with normal populations (Ghelichi-Ghojogh , *et al.,* 2022).

Our findings are in harmony with Panjeta *et al.,* (2017) who performed a cross-sectional, observational study included 356 patients with CKD and control group consisted of 206 age and sex matched healthy subjects with GFR rate ≥90 mL/min/1.73 m^2. They reported The CKD patients had significantly lower levels of haemoglobin (p<0.0005) when compared to control group.

In agreement with our findings, Khatiwada, *et al.,* (2015) conducted a cross-sectional study among 360 chronic kidney disease patients to investigate thyroid function and lipid profile in CKD patients. Diabetes mellites, hypertension and hyperlipidemia were significant risk factors for CKD. In the present study, triglycerides, LDL and total cholesterol were significantly higher in CKD group compared to control group (P value <0.001). HDL was significantly lower in CKD group compared to control group (P value =0.012).

Our results agreed with Peters *et al.,* (2021) who investigated the prevalence of thyroid hormone abnormalities and the relationship between free triiodothyronine (fT3), thyroid stimulating hormone (TSH) and free thyroxine (fT4) serum levels with kidney function and proteinuria in 4108 subsequent patients. All patients were categorized based on their estimated glomerular filtration rate (eGFR) as follows: normal— eGFR ≥ 60 ml/min, mild kidney impairment eGFR more than 30 ml/min and < 60 ml/min, and severe kidney impairment—eGFR < 30 ml/min. They documented that regarding lipid profile; triglycerides (TRGs) and LDL (mg/dl) were significantly lower in normal

group compared to mild kidney impairment while HDL was significantly higher in normal group in comparison with mild kidney disease.

In the present study, serum creatinine, urea, and uric acid were significantly higher in CKD group compared to control group (P value <0.001). Serum albumin and eGFR were significantly lower in CKD group compared to control group (P value <0.001).

Our results were in consistent with Peters *et al.,* (2021) who documented a significant decline in the eGFR (ml/min) in CKD patients than normal individuals.

In the same line with our findings, Li *et al.,* (2020) reported that, uric acid, serum creatinine and albumin-to-creatinine ratio were significantly associated with CKD progression.

Also, Panjeta *et al.,* (2017) reported that serum creatinine was significantly higher in CKD compared to control group.

In addition, Khatiwada *et al.,* (2015) elevation of creatinine and urea levels are significantly associated with CKD progression.

In the present study, phosphorous, and K^+ were significantly higher in CKD group compared to control group (P value <0.001). Ionized calcium was significantly lower in CKD group compared to control group (P value <0.001). PTH was significantly higher in CKD group compared to control group (P value <0.001). Na+ was insignificantly different between both groups. The series of changes that occur in renal dysfunction, including decreases in serum calcium levels due to impairment in vitamin D activation, hypersecretion of parathyroid hormone (PTH, i.e., secondary hyperparathyroidism), bone decalcification, and weak bones (osteomalacia), were collectively regarded as renal osteodystrophy (Tsuchiya and Akihisa 2021).

The kidneys play a vital role in the regulation of electrolyte and acid-base balance. With progressive loss of kidney function, electrolytes disorders occur such as hypervolemia, hyperkalemia, hyperphosphatemia, hypocalcemia and metabolic acidosis (Dhondup and Qian 2017).

Further more, elevated PTH and decreased calcitriol levels are found in 40% of patients with CKD and 80% of patients with end stage renal disease (Natikar *et al.,* 2020) .

Our results were in the same line with Natikar *et al.,* (2020) who conducted a case control study evaluating mineral disturbances in patients with CKD. 50 patients diagnosed with CKD and 50 healthy controls were included in their study. They reported that a statistically significant increase in phosphorus levels in CKD patients compared to controls. Also, PTH was significantly elevated in CKD patients compared to controls. Calcium level was significantly lower in CKD patients than control.

In the current study, fasting and post prandial blood sugar and HbA1C were significantly higher in CKD group compared to control group (P value <0.001).

Our results are supported by Li *et al.,* (2020) who reported that increasing the HbA1C was significantly associated with the CKD progression.

Similar to our findings, Subramanyam *et al.,* (2018) performed a case control study evaluating the role of HBA1c due to type II diabetes mellitus with estimated GFR and serum creatinine parameters. 60 patients with CKD and sixty age and sex matched controls were enrolled for the study. On comparison, the values of fasting blood sugar and HBA1c, levels were significantly higher in CKD patients than in controls (p< 0.001), Diabetes mellitus is an important factor for chronic kidney disease and its progression.

In contrast to our findings, Khatiwada *et al.,* (2015) reported that fasting blood glucose (mg/dl) level did not show significant relation with the CKD progression. Adequate glycemic control with hypoglycemics medications may be an appropriate explanation for this difference from our findings.

In the present study, pelviabdominal ultrasound examination was done for diagnosis and grading CKD paients, Size of kidney, gravels, back pressure, prostate, liver, spleen, intraperitoneal free fluid were significantly different between both groups. Obstructive uropathy is a risk factor for chronic kidney disease and its progression. Our results are supported by Kovesdy *et al.,* (2022) who reported that the obstruction of the urinary tract either unilateral or bilateral affects the kidney fuction and is an important risk factor for chronic kidney disease and its progression.

In the present study, TSH, and free T4 / free T3 ratio were significantly higher in CKD group compared to control group (P value <0.001). Free T3 was significantly lower in CKD group compared to control group (P value <0.001). Free T4 was insignificantly different between both groups.

Our results are confirmed by Peters,*et al.,* (2021) who documented that TSH level was significantly higher in patients with GFR< 60 ml/min while free T3 and free T4 were significantly lower in patients with GFR< 60 ml/min compared to normal GFR ≥60 ml/min individuals.

In the same context, Chagamreddy *et al.,* (2020) carried out a case control study to assess the ratio FT4/FT3 in identifying subclinical hypothyroidism (ScHt) in CKD patients. 53 known CKD samples and 60 normal samples were opted for the study. TSH levels were remarkable enhanced in patients without undergoing dialysis and with CKD in comparison to control groups (P<0.034). FreeT3 level was significantly lower (P<0.001) and FT4/FT3 ratio was significant higher (p< 0.001) in patients of CKD without undergoing dialysis in comparison with controls.

In the same line with our findings, Li *et al.,* (2020) who documented that elevation in TSH level was significantly associated with CKD progression. Also, they reported that FT3 and FT4 decrease were significantly associated with CKD progression.

Also, Khatiwada *et al.,* (2015) who reported that TSH level was significantly associated with CKD progression.

Regarding the ABG of the studied groups, pH and HCO_3 was significantly lower in CKD group compared to control group (P value 0.002, and <0.001), and PCO_2 was insignificantly different between both groups.

Our results are compatible with Peters *et al.,* (2021) who documented that pH and HCO_3 was significantly lower in CKD group compared to normal group.

There was a negative significant correlation between eGFR and Free T4 / Free T3 ratio (r=-0.4970, P value <0.001). Also, according to our results, there was a negative significant correlation between free T4 / free T3 ratio and HCO_3, pH, HDL, Ionized Ca, eGFR, Hb and free T3 (P value ≤ 0.05). There was a positive significant correlation between free T4 / free T3 ratio and urea, creatinine, uric acid, total cholesterol, LDL fasting blood sugar, HBA1C, TSH, TGS, Phosphorus, PTH, post prandial sugar, free T4(P value ≤ 0.05).

DM and thyroid disease are two closely associated disorders. The NHANES III study reported a higher prevalence of thyroid disorders in subjects in the United States with diabetes compared with those without diabetes, especially in patients with positive anti-thyroperoxidase (TPO) antibodies (Abs) (Hollowell *et al.,* 2002).

Hypothyroidism is associated with hyperlipidemia through modifications in lipid synthesis, absorption, circulation, and metabolism. Thyroid hormones increase cholesterol synthesis by increasing the expression of HMG-CoA reductase in the liver (Choi and Choi 2000). Thus, hypothyroidism leads to decreased hepatic cholesterol synthesis. However, two additional concomitant mechanisms outweighed this effect. First, there is an increase in gastro-intestinal cholesterol absorption mediated by the Niemann-Pick C1-like 1 protein, the target of the lipid-lowering molecule ezetimibe, in the gut. Second, there is a decrease in cell-surface LDL-cholesterol receptors, possibly via T3-mediated effects on the sterol regulatory element-binding protein-2 (SREBP-2), leading to reduced plasma LDL-cholesterol clearance and increased apo-B lipoproteins (Mavromati and Jornayvaz, 2021).

Observational studies confirm that among patients with overt hypothyroidism, 30% have increased total cholesterol and LDL levels, and 90% have dyslipidemia. Furthermore, levothyroxine treatment reverses lipid alterations, with the exception of patients with underlying hyperlipidemia (Pearce, 2012).

The effect of subclinical hypothyroidism on lipid levels is less obvious, and the results of clinical studies have been inconsistent. Some observational studies found no difference in lipid levels among subclinical hypothyroid patients and matched controls (Vierhapper *et al.,* 2000 , Hueston and Pearson 2004), whereas others found significantly higher total cholesterol, triglycerides and LDL-C levels in subclinical hypothyroidism (Kanaya *et al.,* 2002, Canaris *et al.,* 2000). Insulin resistance and smoking are believed to be possible confounding factors since they both induce higher cholesterol increase in the presence of hypothyroidism (Mavromati and Jornayvaz, 2021) .

Supporting our findings, Marwah *et al.,* (2015) reported that Hypothyroidism causes significant increase in serum uric acid.

Regarding correlation between renal dysfunction severity and subclinical hypothyrodim, our results are in agreement with Patil *et al.,* (2018) who reported serum creatinine levels were higher and

eGFR was lower significantly in the subclinical hypothyroid group when compared to the control group ($P < 0.001$).

In terms of the relation between thyroid function and anemia, our findings came in line with Wopereis *et al.,* (2018) who revealed that participants with abnormal thyroid status had an increased risk of having anemia compared with euthyroid participants (subclinical hypothyroidism) 1.21 (1.02 to 1.43) and the pooled hazard ratio for the risk of development of anemia was 1.38 (95% CI 0.86 to 2.20) for subclinical hypothyroidism.

Thyroid hormones modulate the renal response to an acid challenge and alter the expression of several key acid-base transporters. Our results were supported by Mohebbi *et al.,* (2007) who reported that mild hypothyroidism is associated with a very mild defect in renal acid handling, which appears to be mainly located in the proximal tubule and is compensated by the distal nephron. Hypothyroidism is associated with incomplete distal renal tubular acidosis, presenting as the inability to respond appropriately to an acid challenge by excreting less acid.

Regarding serum minerals status in subclinical hypothyroid, our findings agreed with Jat *et al.,* (2021) who investigated that serum calcium and phosphorus levels in patients of subclinical hypothyroidism was 8.75 ± 0.40 mg/dL and 3.80 ± 0.62 mg/dL respectively while in control group they were 9.67 ± 0.97 mg/dL and 3.70 ± 0.71 mg/dL, respectively and the difference was significant ($p<0.001$).

In the present study, free T4 / free T3 ratio can significantly predict incidence of subclinical hypothyroidism with AUC= 0.879 and P value <0.001

Our results are confirmed by Chagamreddy *et al.,* (2020) who stated that AUC of ROC curve for the steady variables of serum FT4/FT3 ratio was 0.914 with CI: 0.832 to 0.997.

In the present study, free T3 can significantly predict incidence of subclinical hypothyroidism with AUC= 0.071 and P value<0.001. TSH can significantly predict incidence of subclinical hypothyroidism with AUC= 0.643 and P value=0.014. Free T4 was an insignificant predictor of incidence of subclinical hypothyroidism.

In the same line with our findings, Li *et al.,* (2020) reported that free T3, TSH, free T4 / free T3 ratio were significant predictors for thyroid disorders. However, in contrast to our findings they reported that free T4 was significant predictors for thyroid disorders.

Also, Chagamreddy *et al.,* (2020) who stated free T3, TSH and Free T4 / Free T3 ratio were significant predictors of incidence of subclinical hypothyroidism.

5. Conclusion

From our results, we concluded that free T4 / free T3 ratio can significantly predict incidence of subclinical hypothyroidism with AUC= 0.879 and P value <0.001. Free T3 can significantly predict incidence of subclinical hypothyroidism with AUC= 0.071 and P value<0.001. Free T4 was an insignificant predictor of incidence of subclinical hypothyroidism.

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