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Research Article

The spectrum of Thyroid function Abnormalities and associated Biochemical factors in Patients with Chronic Kidney Disease in Cameroon

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Abstract

Background: Chronic Kidney Disease (CKD) can lead to thyroid function disorders. The extent to which this relationship exists among Cameroonian CKD patients is not known. The aim of this study, was to determine the spectrum of thyroid dysfunction (TD) and their associated factors among CKD patients in Cameroon.

Methods: A cross-sectional study was conducted over a period of 12 months (July 2018 to August 2019) in three referral hospitals (Douala General Hospital, Laquintinie Hospital, Bafoussam Regional Hospital) in Cameroon with patients aged 18years and above diagnosed of CKD stage 1 to 5. Patients with stage 5 dialysis and those on thyroid altering medication were excluded. For each participant, we collected socio-demographic and clinical data. Sera were used to determine thyroid hormone profile, lipid profile, liver test, urea, creatinine, calcium, phosphate and uric acid levels. Albumin creatinine ratio (ACR) was estimated. The diagnosis of CKD was done by a nephrologist and classifies using estimated Glomerular Filtration Rate (eGFR) or urinary albumin creatinine ratio at the time of the study.

Results: A total of 374 participants were enrolled with male forming the majority (233(63.66%)). The mean age was 55.85(±13.72) years with an overall prevalence of TD was 57%. Hypertension, diabetes, and gout were the most common comorbidities. In total, 14 types of TDs were identified and grouped into major and minor types. The major types were subclinical hypothyroidism, primary subclinical hypothyroidism, primary overt hypothyroidism, subclinical hyperthyroidism, and overt hyperthyroidism. Low T_3 syndrome, low FT_3, combine low T_3 and low FT_3 were the most common minor types. TD increases with the stages of CKD. After logistic regression, albumin [OR: 0.961(0.93-0.991); p=0.015], phosphate [OR: 1.028 (1.014 - 1.045); p=0.001] and calcium [OR: 0.963 (0.941-0.983); p <0.001)] were independently associated to TD.

Conclusion: The Spectrum of TD is vast. Low T_3, Low FT_3, hypothyroidism, combine Low T_3 and Low FT_3 are the most common thyroid dysfunction. Altered calcium, Phosphate and albumin, were associated to TD in CKD.

Keywords: Chronic Kidney Disease, Thyroid Dysfunction, Prevalence, Spectrum, Hypothyroidism, Associated Factors

Introduction

Chronic kidney disease affects almost every organ-system in the body, and its common complications include; abnormal levels of metabolic waste such as urea and creatinine, mineral bone disorders like hypocalcemia, and hyperphosphatemia, dyslipidemia and thyroid dysfunction [1].

The kidney plays an important role in the metabolism, degradation, and excretion of thyroid hormones [2-4]. Therefore, long-standing and progressive deterioration of renal structure and function such as in chronic kidney disease (CKD) can alters the synthesis, secretion, metabolism, and degradation of thyroid hormones which then presents with different clinical syndromes of thyroid dysfunction [5-8]. Multiple mechanisms can account for these syndromes: lowering circulating thyroid hormone concentration, alteration of peripheral hormone metabolism, disturbed binding to carrier proteins, possible reduction in tissue thyroid content and increased iodine stores in thyroid glands [9]. Tri-iodothyronine (T_3), the most metabolically active thyroid hormone, for instance, can be reduced in CKD patients even with a normal TSH level. This is termed as 'Low T_3 Syndrome' [9,10]. Thyroid dysfunction may present in one of the following patterns: thyroid enlargement (diffuse or nodular); thyroid hormone deficiency or excess (hypothyroidism or hyperthyroidism); asymptomatic or symptomatic (the subclinical state or overt) [11].

Epidemiological studies have shown that the prevalence of thyroid function abnormalities especially hypothyroidism, is substantially higher in persons with chronic kidney disease compared to the general population [10]. In Nepal, South Korea, thyroid dysfunction was found in 38.6 % of patients, with subclinical hypothyroidism (27.2 %), overt hypothyroidism (8.1 %) and subclinical hyperthyroidism (3.3 %) being the most common types encountered [2,3]. In North India (Chennai), 66 % of CKD patients were reported to have thyroid dysfunction. Low T_3 syndrome accounted for 58% against 8 % for hypothyroidism [13]. In Nairobi, Kenya, 42% of patients were found to have thyroid dysfunction. 14% had non-thyroidal illness, subclinical and primary hypothyroidism accounting for 15% while different forms of hyperthyroidism accounted for 13 % [7]. Many cases of hypothyroidism may remain latent or undiagnosed in advanced CKD due to symptoms overlapping with uremia and co-existing Comorbidities. The kidney is not only an organ for metabolism and elimination of TH, but also a target organ of some of the iodothyronines' actions. Thyroid dysfunction causes remarkable changes in glomerulo tubular functions, electrolyte and water homeostasis. Hypothyroidism is accompanied by a decrease in glomerular filtration, hyponatremia, and an alteration of the ability for water excretion. Excessive levels of TH generate an increase in glomerular filtration rate and renal plasma flow. Renal disease, in turn, leads to significant changes in thyroid function. The association of different types of glomerulopathies with both hyper- and hypofunction of the thyroid has been reported. Less frequently, tubulointerstitial disease has been associated with functional thyroid disorders. Nephrotic syndrome is accompanied by changes in the concentrations of TH due primarily to loss of protein in the urine. Acute kidney injury and chronic kidney disease are accompanied by notable effects on the hypothalamus–pituitary–thyroid axis. The secretion of pituitary thyrotropin (TSH [6]. These patients with thyroid dysfunction may have clinically important reductions in estimated glomerular filtration rate (eGFR), which can be attenuated by using thyroid hormone replacement therapy [14]. When hypothyroidism becomes severe it can cause reduced cardiac function and lead to progressively worsening of kidney function. Thus thyroid dysfunction may worsen the morbidity in CKD patients and increase cardiovascular mortality [15]. Hypothyroidism can also lead to hyperlipidemia and atherosclerosis in coronary and peripheral vessels. Previous studies have indicated that subclinical and clinical hypothyroidism were the risk factors for all-cause mortality and CVD (Cardiovascular Disease) death. Low T_3 syndrome is an independent predictor of cardiovascular mortality in CKD patient [9,10].

Biochemical factors in CKD that affect thyroid function as well as the spectrum of thyroid function abnormalities are not well known, as such we sort to determine the spectrum of thyroid dysfunction and its associated biochemical profile in CKD patients.

Materials and Methods

We carried out a cross-sectional study at the Littoral region (Laquintinie and Douala General Hospitals) and West Region (Bafoussam Regional Hospital) of Cameroon. These health facilities were selected because they provide care to a vast majority of the population in their respective regions and they host a wide range of socio-economic classes. Each of these hospitals is equipped with a nephrology unit that is under the responsibility of at least 1 nephrologist.

Ethical Consideration

The protocol of this study was submitted to and approved by the institutional review board of the Faculty of Health Sciences of the University of Buea (Ref: 2018/753-01B/UB/SG/IRB/FHS). Administrative authorizations were obtained from the Directorate of each institution. Participation was strictly voluntary, after having provided written informed consent.

Inclusion criterion

The target population was made of adult (≥ 18 years) patients diagnosed with CKD by the nephrologists of the study centers.

Exclusion criteria

Patients with known thyroid disorders, those on medications affecting thyroid function (e.g Amiodarone, propranolol), those

on maintenance hemodialysis or with nephrotic range proteinuria were not included in the study.

Study procedure

After a detailed explanation of the study and obtaining written consent or assent, a questionnaire was used to collect socio-demographic features (age and sex) and clinical data from each participant and using their medical records. A blood sample (5 ml) was collected from each the subjects who agreed to participate in the study as well as those who met the inclusion criteria using a vacutainer plain tubes and was left for a short time to allow the blood to clot and then serum samples were obtained by centrifugation at 3000 rotation per minutes for 10 minutes. The serum obtained after centrifugation was used to determine thyroid hormone profile (TSH_3, FT_4, and FT_3) using the immune fluorescent assay (MINI VIDAS, BIOMERIEUX, Marcy Etoile, France), TT_4 and TT_3 were analyzed using ELIZA (Enzyme-Linked Immunosorbent Assay) method (Biorex Diagnostic, Antrim, United Kingdom). The biochemical test for serum creatinine, urea, calcium, phosphorus lipid profile, transaminase and albuminemia, was done using the COBAS C111 (La Roche Diagnostic System, Swiss, Germany) and the spot urine was tested for albuminuria (Roche Diagnostic GMBH, Mannheim, Germany) and creatinuria using COBAS C111and their ratio (ACR) was determined. eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and stages were classify by the Kidney Disease Improving Global Outcomes (KDIGO):

Calculation of sample size

Using the prevalence of 42 % of a study done in Nairobi thor":[{"dropping-particle":"","family":"Kaggia","given":"S N N","non-dropping-particle":"","parse-names":false,"suffix":""}],"id":"ITEM-1","issued":{"date-parts":[["2013"]]},"title":"Thyroid Hormone Profiles in Patients With Chronic Kidney Disease at Kenyatta National Hospital","type":"article-journal"},"uris":["http://www.mendeley.com/documents/?uuid=9daa3261-a1d0-467d-b567-65ef368139a5"]}],"mendeley":{"formattedCitation":"(6[6], the sample size was calculated using the formula below for a cros.....

$$n = (Z_{1-\alpha/2})^2 \times \frac{p(1-p)}{d^2}$$

Where

n = Sample size is 374 patients with CKD;

$Z_{1-\alpha/2}$ Standard normal deviate at 5% level of significance (95% CI) is 1.96;

d = Margin of error at 5%.

Determination of CKD Parameters

Chronic Kidney Disease: eGFR< 60 ml/min per 1.73 m^2 for more than 3 months with or without evidence of kidney damage or albuminuria (≥ 30 mg/g) with or without decreased GFR for ≥ 3 months, as diagnosed by a nephrologist [17-19].

Estimated glomerular filtration rate (eGFR) was computed from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [20].

Chronic kidney disease stages were defined as described by the Kidney Disease Improving Global Outcomes (KDIGO) and classify using estimated eGFR or urinary albumin creatinine ratio at the time of the study as:

- CKD1: eGFR> 90 ml/min and albuminuria,
- CKD 2:60-89 mil/min and albuminuria,
- CKD 3a: 45-59ml/min,
- CKD 3b: 44-30ml/min,
- CKD 4: 29 - 15 ml/min and
- CKD 5:<15ml/min or dialysis [21].

Albuminuria was used to describe albumin creatinine ratio(ACR) between 30 and 299 mg/g and 300 mg/g or over, respectively [22,23].

Nephrotic range Proteinuria was defined as proteinuria of 3+ to 4 or as albuminuria of > 2.2g/g [24].

Definition and classification of categories of thyroid dysfunction

Thyroid dysfunction was considered if patients' thyroid hormones fall outside the reference range. The categories of thyroid dysfunction were classified based on the reference intervals for the hormones and pattern of derangement in the thyroid hormones profile.

The abnormal thyroid function tests result was classified into any of the following:

Subclinical hypothyroidism: TSH elevation between >4.7 mIU/L in patients with normal serum TT_3 or FT_3 and TT_4 or FT_4.

Primary subclinical hypothyroidism: TSH >4.7 mIU/L and suppressed serum TT_3 or FT_3 and TT_4 or FT_4T_4.

Primary overt hypothyroidism: TSH (>20 µIU/dl) with low serum FT_4 and low FT3 [25].

Subclinical hyperthyroidism: suppressed TSH (<0.27) mIU/L and normal TT_3 or FT_3 and TT_4 or FT_4 serum concentration.

Overt hyperthyroidism: suppressed TSH (<0.27) mIU/L and elevated serum TT_3 or FT_3 and TT_4 or FT_4 concentration.

Non-thyroidal illness or low T_3 syndrome: Low TT_3 or FT_3 in the presence of normal TSH, TT_4 and FT_4 levels.

Euthyroid hyperthyroxinaemia: isolated elevation of FT_4 or TT_4 in the presence of TSH, FT_3 and TT_3 within reference limits [26].

Reference ranges for the thyroid hormones were: TSH: 0,27 - 4,7 mIU/L, FT_4: 10,6 - 19,4 pmol/L, FT_3: 2,6 - 5,4pmol/LTT_4: 5,0 - 13,0 ug/mL TT_3: 0.52–1.85 ηg/dL. Creatinine: 0.6–1.2 mg/dL for women and 0.7-1.4mg/dL for men according to the manufacturer.

Statistical analysis

Data were analyzed using SPSS version 20.0. Nominal variables were summarized using counts and percentages while continuous variables such as age, creatinine, and serum albumin levels were summarized using means, standard deviations. Group comparisons for categorical variables were done using the Chi-squared test (or Fisher's exact test where appropriate) while the independent samples t-test (or ANOVA where appropriate) was used for comparing group means for continuous variables. Logistic regression was used to assess the association between predictor variables and thyroid dysfunction. The *p*-values below 5% were considered statistically significant.

Results and Discussions

Results

Biochemical characteristics

In a total of 374 participants enrolled for this study, 233(63.66%) males. The mean age was 55.85(±13.72) years**.** 210 patients had thyroid dysfunction. Serum urea, creatinine, phosphate and TSHwere significantly high in patients with thyroid dysfunction while calcium, albumin, FT_4 and FT_3 where significantly low in these patients (Table I).

Table 1: Biochemical profiles of the study population.

Parameters	Total mean± (standard error)	Thyroid dysfunction(yes)	Thyroid dysfunction(No)	p-value
Liver profile				
ASAT	23.87± (1.17)	23.50± (1.52)	24.36± (1.84)	0.71
ALAT	21.78± (1.40)	20.80± (1.41)	23.09± (2.69)	0.42
GGT	58.63± (4.36)	61.74± (6.12)	54.44± (6.07)	0.4
Kidney profile				
Urea	0.92± (0.03)	1.05± (0.05)	0.74± (0.48)	<0.001
Creatinine	5.27± (0.30)	6.48± (0.47)	3.63± (0.25)	<0.001
ACR	140.52± (17.45)	160.32± (25.63)	113.86± (21.94)	0.18
Calcium	86.23± (0.58)	84.43± (0.84)	88.65± (0.73)	<0.001
Phosphate	44.22± (0.94)	47.35± (1.48)	40.01± (0.82)	<0.001
Uric acid	77.58± (1.54)	79.93± (2.41)	74.43± (1.59)	0.07
Albumin	37.89± (0.36)	37.11± (0.52)	38.96± (0.48)	0.01
Lipid profile				
Total cholesterol	1.78± (0.03)	1.79± (0.04)	1.77± (0.05)	0.75
Triglycerides	1.44± (0.14)	1.58± (0.24)	1.25± (0.07)	0.25
HDL cholesterol	0.55± (0.01)	0.53± (0.01)	0.58± (0.02)	0.06
LDL cholesterol	1.21± (0.23)	1.00± (0.03)	1.50± (0.54)	0.28
Thyroid profile				
TSH	3.15± (0.46)	4.08± (0.81)	1.89± (0.07)	0.02
FT4	14.41± (0.21)	14.02± (0.33)	14.02± (0.17)	0.02
FT3	2.96± (0.06)	2.76± (0.10)	3.23± (0.03)	<0.001
TT4	11.87± (2.36)	11.52± (3.36)	12.34± (3.23)	0.86
TT3	0.88± (0.06)	0.80± (0.08)	0.99± (0.08)	0.11

Prevalence by stages of CKD

The prevalence of thyroid dysfunction was 57, 38% and was found to increase with the severity of CKD, with stage 5 having the highest prevalence of 25.1 % (Figure 1).

The spectrum of thyroid function abnormalities

In all, we identified 14 types of thyroid dysfunction which were grouped into major and minor types. The major types were Subclinical Hypothyroidism (4.6%), primary subclinical hypothyroidism (3.6%), primary overt Hypothyroidism (1.1%), subclinical Hyperthyroidism (1.1%), and overt hyperthyroidism (0.5%) (Figure 2A). While Low T_3 syndrome (14.8%), low FT_3 (9.8%), combine low T_3 and low FT_3 (7.4%) were the most common minor types (Figure 2B).

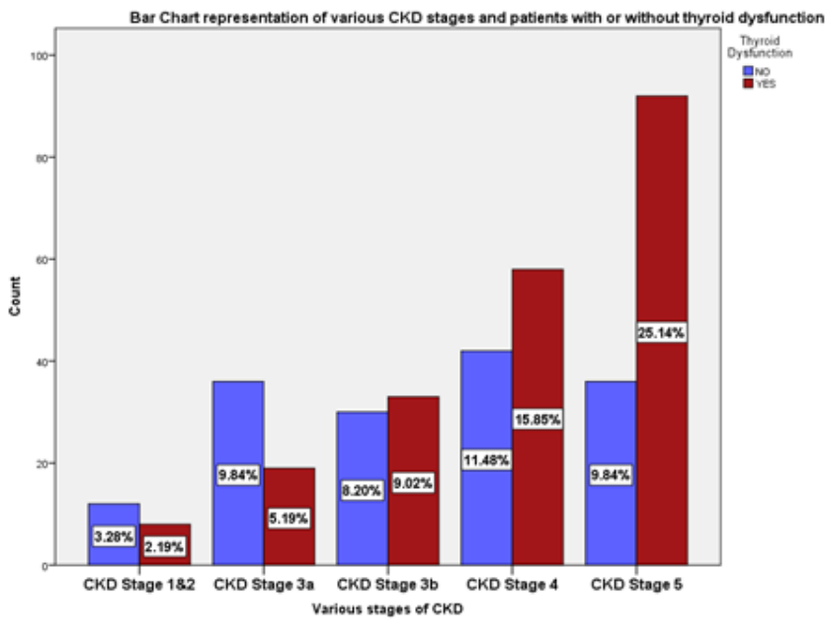

Figure 1: The Prevalence of thyroid dysfunction by stages of CKD.

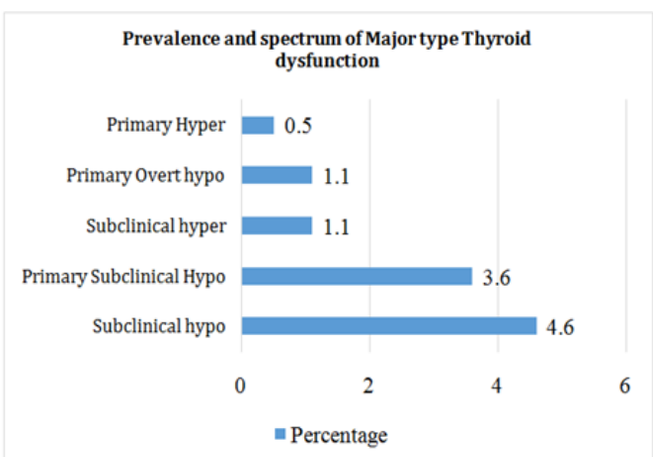

Figure 2A: Prevalence and spectrum of major type thyroid dysfunction.

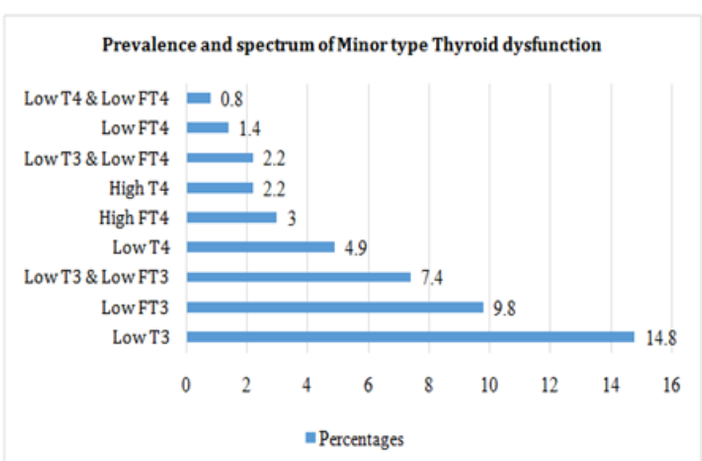

Figure 2B: Prevalence and spectrum of minor type thyroid dysfunction.

Comorbidities associated with thyroid dysfunction

Age above 50years was the only factor significantly related with thyroid dysfunction($p<0.05$) (Table 2).

Table 2: Comorbidities associated with thyroid dysfunction.

Comorbidities and age range		Examined (n)	Thyroid dysfunction (n)	Percentage	p-value
Hypertension	NO	93	56	60.22	0.4
	YES	273	154	56.41	
Diabetes Mellitus	NO	218	124	56.88	0.4
	YES	148	86	58.11	
Hepatitis B	NO	351	202	57.54	0.4
	YES	15	8	53.33	
Hepatitis C	NO	350	201	57.43	0.5
	YES	16	9	56.25	
CVA	NO	358	205	57.26	0.5
	YES	8	5	62.5	
Malignancy	NO	364	208	57.14	0.3
	YES	2	1	50	
Gout	NO	269	153	56.88	0.4
	YES	97	57	58.76	
HIV	NO	345	198	57.39	0.4
	YES	21	12	57.14	
Tuberculosis	NO	365	208	56.98	0.3
	YES	2	1	50	
BMI	<26	153	89	58.17	0.4
	>26	213	119	56.67	
Age	>50	279	166	59.5	0.01*
	<50	87	44	50.57	
UTI Infections	NO	346	197	56.94	0.4
	YES	20	13	65	

CVA: Cerebrovascular Accident, **BMI:** Body Mass Index, **HIV:** Human Immune deficiency Virus, **UTI:** Urinary tract infections

Association between biomarkers of CKD and thyroid dysfunction

Serum urea, creatinine, albumin, ACR, calcium and phosphate were significantly associated with all forms of thyroid dysfunction ($p<0.05$) (Table 3).

Table 3: Association between Thyroid Function Abnormalities with Kidney Biomarkers.

Parameters		Examined	Abnormalthyroidfunction		χ^2	p-value
			n	%		
Urea	Normal	88	38	43.18	9.546	0.002004*
	High	278	172	61.87		
Creatinine	Normal	23	6	26.09	9.8253	0.001721*
	High	343	204	59.48		
eGFR	Normal	3	1	33.33	0.715	0.003977*
	High	363	209	57.58		
ACR	Normal	214	133	62.15	4.7991	0.028475*
	High	152	77	50.66		
Albumin	Low	20	16	80	4.4274	0.035366*
	Normal	346	194	56.07		
Calcium	Low	150	100	66.67	12.7915	0.01669*
	Normal	13	10	76.92		
	High	203	100	49.26		

Phosphate	Low	10	7	70	5.0739	0.019106*
	Normal	175	90	51.43		
	High	181	113	62.43		
Uricacid	Low	2	1	50	3.1382	0.20823
	Normal	199	106	53.27		
	High	165	103	62.42		
ACR: Albumine creatinine Ratioe, GFR: Estimated Glomerular Filtration Rate						

Association of Thyroid Function Abnormalities with Liver Biomarkers

Only ALT was significantly associated with all forms of thyroid dysfunction (p<0.05) (Table 4).

Table 4: Association between Thyroid Function Abnormalities with Liver Biomarkers.

Parameters		Examined	Abnormalthyroidfunction		χ2	p-value
			n	%		
ALT	Normal	298	193	64.77	35.7986	<0.00001*
	High	68	17	25		
AST	Normal	333	191	57.36	0.0006	0.980694
	High	33	19	57.58		
GGT	Low	4	2	50	1.2552	0.533865
	Normal	262	146	55.73		
	High	100	62	62		

Association of Thyroid Function Abnormalities with Lipid Profile

Only HDL was significantly associated with all forms of thyroid dysfunction (p<0.05) (Table 5).

Table 5: Association between Thyroid Function Abnormalities with Lipid Profile.

Parameters		Examined	Abnormalthyroidfunction		χ2	p-value
			n	%		
HDL-C	Low	59	42	71.19	5.4848	0.019182*
	Normal	307	168	54.72		
LDL-C	Normal	336	192	57.14	0.0919	0.761737
	High	30	18	60		
TG	Low	41	25	60.98	0.9909	0.609292
	Normal	231	128	55.41		
	High	94	57	60.64		
TC	Normal	63	40	63.49	1.1636	0.280727
		303	170	56.11		
TC: Total Cholesterol, **HDL-C:** High density lipoprotein, **LDL-C:** Low density lipoprotein, **TG:** Triglyceride						

Associated factors to thyroid dysfunction in chronic kidney disease

After logistic regression analysis only albumin, calcium and phosphate were independently associated to thyroid dysfunction. Albumin [OR: 0.961 (0.93 - 0.991); p=0.015], Phosphate [OR:1.028 (1.014 - 1.045); p=0.001]and calcium[OR: 0.963(0.941 (Table 6).

Table 6: Association between biomarkers of thyroid dysfunction and chronic kidney disease.

Parameters	Standard_ error	OR	95%ci	p-value
Age	0.008	1.006	0.991 - 1.021	0.412
Sex	0.22	1.033	0.67 - 1.589	0.882
Serum Creatinine	0.029	1.125	1.068 - 1.196	<0.001
eGFR	0.006	0.973	0.961 - 0.984	<0.001
Urea	0.204	2.302	1.572 - 3.499	<0.001
Albuminemia	0.016	0.961	0.93 - 0.991	0.015

Albumine-Creatinine Ratio	0	1	1 - 1.001	0.195
UricAcid	0.005	1.008	1 - 1.018	0.086
Calcium	0.011	0.963	0.941 - 0.983	0.001
Phosophate	0.008	1.028	1.014 - 1.045	<0.001
ASAT	0.005	0.998	0.989 - 1.008	0.693
ALAT	0.004	0.997	0.988 - 1.005	0.413
GGT	0.001	1.001	0.998 - 1.004	0.445
Total Cholesterol	0.173	1.033	0.737 - 1.461	0.849
Triglycerides	0.117	1.12	0.973 - 1.44	0.333
HDL Cholesterol	0.493	0.41	0.153 - 1.066	0.071
LDL Cholesterol	0.054	0.962	0.369 - 1.124	0.469

Discussion

In this study, of which our objectives were to determine the prevalence, describe the spectrum and biochemical factors associated with thyroid function abnormalities in patients with CKD, we found a high prevalence of thyroid dysfunction and an impressive array of abnormalities. We, however, proceeded to classify them as either major or minor based on data reported in recent literature; the most frequently identified and cited as well as those of proven direct clinical significance were classed as major and vice.

The prevalence of thyroid function abnormalities was 57.4%. This is similar to that in India, estimated at 58% [25]. It is, however, higher than that in Nepal (38.6 %) and Nairobi (42%) [3,7]. Given that thyroid function deteriorates as CKD worsens, it was most likely to find patients with thyroid dysfunction. The high prevalence of thyroid dysfunction can be explained by several factors;

a. Metabolism of thyroid hormones occurs mostly in the kidney, as a consequence deterioration in kidney function leads to altered thyroid physiology [27]. Our population consist principally of persons with altered kidney function as such a high prevalence of thyroid dysfunction.

b. Age; most participants were elderly with a mean age of 55years and the 61-70years age group being the most frequent. The D1-785T variant of the D1 receptor involved in the conversion of T_4 to T_3 can undergo polymorphism and results in a decreased activity of D1 [28]. Although the D1-785T variant is not associated with serum rT_3 levels in the general population, its association with lower levels of T_3 in an elderly population can supports the hypothesis of lower activity of D1 in carriers of this polymorphism [28]. In young subjects, a decreased T_3 production by D1 may be masked by the production of serum T_3 by skeletal muscle D2. Throughout adult life, skeletal muscle size and strength gradually decline, resulting in a decrease in D2-expressing skeletal muscle. Furthermore, rT_3 levels increase with age, and degradation of the D2 protein is accelerated when it is exposed to its substrates T_4 and rT_3 [28,29]. This results in the increased possibility of developing thyroid dysfunction in advanced age (Table 2). Swaminathan observed the same trend [30].

c. Other factors such as comorbidities or hereditary disorders, severe illness and nutrition may also have increased the prevalence especially in non-thyroidal illness [31].

These factors put together can result in an amalgam of thyroid function abnormalities.

In all, we identified 14 types of thyroid function abnormalities in patients with chronic kidney disease. To make sense of this data, we decided to group them into major and minor disorders. The major types of thyroid dysfunction were subclinical hypothyroidism (4.6%), primary subclinical hypothyroidism (3.6%), primary overt hypothyroidism (1.1%) and Hyperthyroidism (1.1%) (Figure 2A). Only primary subclinical hypothyroidism was statistically significantly associated with the stages of CKD ($p<0.05$).However, in our study, the overall hypothyroidism was 9.3%. Similar study was done by Tewari in India who had 10.9% of hypothyroidism affecting the study population [32] but different from Ayree in Ghana who had 2% of hypothyroidism [33].

Among the minor type of thyroid dysfunction, the majority of patients had Low T_3(14.8 %). Followed by Low FT_3 (9.8 %), combine Low T_3& LowFT_3 (7.4%), Low T_4 (4.9%), High FT_4(3.0%), High T_4(2.2%), LowT_3 & LowT_4 (2.2%), Low FT_4(1.4%), and Low T_4 & Low FT_4 (0.8%) (Figure 2B).

Low T_3 has been reported in recent literature to be the most frequent type of thyroid dysfunction in patients with CKD [31]. Free and total T_3 and T_4 concentrations are usually normal or low in patients with CKD [33]. This reduction in T_3 concentration has been linked to a decrease in the peripheral conversion of T_4 to T_3 [6]. Low T_3 levels have been reported by Gowda in 28% patients with CKD [25]. Zoccali et al. had similar results in 2006 [34]. The high prevalence of LowT_3 can be explained by the fact that there is free inorganic iodide accumulates in CKD. This then results in inhibition of iodine tapping and consequent decrease in T_4 to T_3 production. The drop in the levels of T_3 stimulates the thyroid–pituitary feedback loop, leading to excessive secretion of TSH [35,36]. In some cases the levels of T_3 and T_4 are normalized. Failure of this coping mechanism

will lead to overt hypothyroidism. Furthermore, low T_3 syndrome is closely associated with both malnutrition-inflammation complex syndrome (MICS) and anemia, conditions common in CKD [37]. A Decrease in D1 (de-iodinase) activity caused by the accumulation of uremic toxins, metabolic acidosis, and markers of inflammation such as TNFα, IL-1 results in decreased peripheral conversion of T_4 to T_3 leading to Low T_3 as well as Low FT_3, accumulation of T_4, consequently High T_4 and High FT_4, thus producing the spectrum of minor thyroid dysfunctions seen above [10].

CKD populations had lower albumin and calcium but higher phosphate using linear regression (Table 6) in our study. This is similar to Singh's study in 2010 who found significant association between thyroid dysfunction, calcium and phosphate in CKD patients ($p<0.05$) using Kruskal-Wallis test [37]. Thyroid hormones play an important role in homeostasis of Calcium and Phosphorous levels by their direct action on bone turnover. Thyroid hormones Stimulate bone resorption directly there by increasing the serum calcium and phosphorous levels and suppressing PTH [38]. In CKD, patients usually have symptoms of nausea, vomiting, bad appetite because of accumulation of toxin, and anemia. Therefore, it is common to observe malnutrition in these patients which can result in various mechanisms: spontaneous reduction of dietary protein-caloric intake, all the more pronounced as the renal function is more impaired, alteration of the metabolism of the main nutrients, exaggerated protein catabolism linked to metabolic acidosis, insulin resistance and hyperparathyroidism due to undercurrent infectious or inflammatory pathologies [38]. This can result in a malnutrition-inflammation complex syndrome which is a major cause of non-thyroidal illness, characterized by the minor thyroid function abnormalities seen above. Thus, hypoalbuminemia is an independent predictor of thyroid dysfunction. Pan et al observed similar association [10].

Metabolic toxin such as urea and creatinine inhibit peripheral conversion of T_4 to T_3 as such leading to thyroid function abnormalities. Following linear regression analysis, phosphate, calcium and albumin were identified as factors associated with thyroid dysfunction. Albuminaemia [OR: 0.961 (0.93 - 0.991); p=0.015], phosphatemia [OR: 1.028 (1.014 - 1.045); p=0.001]and calcium[OR: 0.963 (0.941 - 0.983); p <0.001)] (Table 6).

Conclusion

The prevalence of thyroid dysfunction in CKD is very high, with Low T_3 being the most common type. The spectrum of TD is vast. Low T_3, Low FT_3, Hypothyroidism, combine LowT_3 and Low FT_3 are the most common thyroid dysfunction. This study supported the contribution of chronic kidney disease in thyroid dysfunction. Increased phosphataemia, as well as decreased calcaemia and albuminaemia were identified as predictors of TD in CKD patients.

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Authors' Contributions

PK: Participated in the conception and study design, collected, and interpreted data, reviewed literature and drafted the manuscript.

MPH: Conceived and supervised the work, oversaw data collection, participated in data analysis and interpretation, drafted the manuscript. A critical review of the manuscript

NAJ: Over saw data collection, participated in data analysis, drafted the manuscript, Critical review of the manuscript

JCAN: Contributed in the conception and supervised the work, oversaw data collection, participated in data analysis and interpretation, drafted the manuscript. A critical review of the manuscript

TJF: Participated in the study design and reviewed literature and data interpretation

MNN: Study design and supervised the work, oversaw literature search and revised the manuscript.

All authors read and approved the final manuscript.

Conflict of Interest

The authors declare that they have no competing interest.

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