Research Article ISSN 2639-944X

Journal of Medical - Clinical Research & Reviews

# Correlation Between Biomarkers of Thyroid Function Abnormalities and Stages of Chronic Kidney Disease in Cameroon

**Philomene Keunmoe[1], Marie Patrice Halle[2,3], Jules Clement Nguedia Assob[4*], Abdel Jelil Njouendou[4], John Fonyuy Tengen[3] and Marcelin Ngowe Ngowe[2,5]**

[1]*Department of Medical Laboratory Sciences, Faculty of Health Sciences, University of Buea, South West region Cameroon.*

[2]*Department of Clinical Sciences, Faculty of Medicine and Pharmaceutical Sciences, University of Douala; Littoral Region, Cameroon.*

[3]*Department of Nephrology and Haemo-dialysis, Douala General Hospital, Douala, Cameroon.*

[4]*Medical Research and Applied Biochemistry Laboratory. Department of Biomedical Sciences, Faculty of Health Sciences, University of Buea.*

[5]*Department of Surgery and Specialties, Faculty of Health Sciences; University of Buea, Southwest Region, Cameroon.*

**[*]Correspondence:**
Professor Jules Clement Assob Nguedia, Head of Medical Research and Applied Biochemistry Laboratory, Coordinator for Post-graduate programmes, Faculty of Health Sciences, University of Buea, Southwest Region, Cameroon.

**Received:** 27 October 2019; **Accepted:** 18 November 2019

**Citation:** Philomene Keunmoe, Marie Patrice Halle, Jules Clement Assob Nguedia, et al. Correlation Between Biomarkers of Thyroid Function Abnormalities and Stages of Chronic Kidney Disease in Cameroon. J Med - Clin Res & Rev. 2019; 3(6): 1-8.

## ABSTRACT

***Background:*** *Thyroid dysfunction has been associated with kidney function decline. Biochemical markers of thyroid dysfunction that correlate with stages of chronic kidney disease (CKD) in sub-Saharan Africa are not well known. We therefore decided to determine the correlation between biomarkers of thyroid dysfunction and CKD in Cameroon.*

***Methods:*** *A cross-sectional study was conducted in two health facilities involving patients (≥ 18 years old) diagnosed with CKD. A questionnaire was used to collect socio-demographic and clinical data from the participants and their medical records. Thyroid hormone profile and Serum creatinine levels were analyzed. Urine albumin creatinine ratio (ACR) was estimated. CKD was defined as eGFR<60 ml/min/1.73 $m^2$ or urinary ACR ≥ 30mg/g.*

***Results:*** *Out of the 366 patients, 233 (63.66%) were male and the mean age was 55.85 (± 13.72) years. The mean TT3, FT3 and FT4 were found to decrease as the CKD stages increase. The prevalence of thyroid dysfunction was 57%. There was a significant correlation between thyroid hormone profile (TT4, TT3, FT4, FT3) and stages of CKD (Spearman's rho = -0.173, -0.229, -0.166, -0.45 respectively; p <0.05). These observations were supported by the positive correlation observed between thyroid hormone profile (FT4, FT3, TT3) and the estimated glomerular filtration rate (Pearson's correlation: r = 0.425, 0.188, 0.285, 0.003 respectively; p <0.05). No correlation was found between TSH level and stages of CKD.*

***Conclusion:*** *There exist significant correlations between biomarkers of thyroid dysfunction and stages of Chronic Kidney Diseases in the Cameroonian population.*

## Keywords

Correlation, Chronic Kidney Disease (CKD), Thyroid Dysfunction.

## Background

Thyroid hormones are crucial for renal development and physiology [1,2]. Thyroidal hormones affect the cardiovascular system through their influence on renal blood flow as it modulates

the glomerular function, the tubular secretory and absorptive capacities as well as the electrolyte pumps and the kidney structure [3-5]. Extreme variation in the thyroid function results in changes in different clinical renal parameters such as glomerular filtration rate (GFR), urine specific gravity, urinary protein/ creatinine ratio and markers of tubular function. Reciprocally, kidney disease status can influence circulating thyroid hormones [6] as the kidney is responsible for the metabolism and excretion of thyroid hormones. For instance, due to reduced deiodinase activity, tissue and circulating levels of the active form of the thyroid hormone, T3, are low in kidney disease [7]. Also, as a result of reduced renal excretion, inorganic iodide generated by residual deiodinase activity accumulates in CKD stages 4 and 5, which in turn dampens thyroid hormone synthesis.

Two fundamental mechanisms regulate thyroid hormone turnover. They include firstly the Thyroid - Stimulating Hormone (TSH), thyroxine (T4) and triiodothyronine (T3) feedback loop, which constitutes a sensitive and efficient protection against alterations in thyroid secretion [8]. The second relies on the extra thyroidal production of T3 from T4, which therefore allows rapid adjustments in thyroid hormone availability at tissue level in response to stressful conditions such as non-thyroidal illnesses. This mechanism is of major relevance because about 80% of circulating T3 results from 5'-deiodination of T4 in peripheral tissues by two T4-5'-deiodinases, the type I and type II (D1 and D2). Together with the liver, the kidney is the organ endowed with the most abundant deiodinase activity [8].

This highlights the importance of assessing the role of thyroid function in chronic kidney diseases. Chronic kidney diseases are a consequence of progressive decline in the function and structure with an implication on health [9-11]. Different markers like proteinuria, abnormal urinary sediment or variations on imaging studies and kidney biopsy are used to ascertain kidney damage [12]. A growing body of cross-sectional studies suggests that overt and subclinical hypothyroidism are associated with a decrease in estimated glomerular filtration rate (eGFR) and an increased risk of CKD, whereas hyperthyroidism is associated with a higher eGFR and a lower risk of CKD [13-15].

Interestingly, the reduction of the eGFR was reversible after thyroid hormone substitution therapy [15,16], indicating that thyroid hormone replacement therapy can affect the decline in renal function in CKD patients with subclinical hypothyroidism as reported by Shin et al. [17]. A recent prospective study reported an increased risk of CKD and a decline in eGFR in subjects with lower TSH levels or a hyperthyroid state in the long run, while a protective effect has been seen in hypothyroidism [16]. Another study showed no significant association between thyroid function and renal function change in older adults [18].

In a large Chinese population-based study, the evaluation of the relationships between TSH in euthyroid individuals and eGFR, suggested that serum TSH was negatively associated with the eGFR [19]. The TSH is considered the most important indicator for the evaluation of thyroid function [9], although FT3 and FT4 which are the active biological forms found in plasma, are considered to be sensitive and meaningful indicators for the diagnosis of thyroid disease. However, the determination of free thyroxine is not very reliable and stable; it may be affected by several factors, such as thyroglobulin (TGB), serious illness, or certain drugs that interfere with the binding of hormones.

In addition, there is no direct quantitative determination method for FT3 and FT4 [20]. Therefore, the relevance of TSH combined with FT4 measurements as markers for the evaluation of thyroid function is important for clinicians in the management of patients [20]. In order to provide information necessary in the management of CKD patients, this study was designed to assess the correlation between biomarkers of thyroid function abnormalities (TT4, TT3, FT3, FT4 and TSH) and the various stages of CKD patients in Cameroon. This will help to fill the gap of information that exists in our setting as there are controversial considerations on the role of Thyroid function on the exacerbation of renal dysfunction.

## Materials and Methods

This was a cross sectional study carried out at the Laquintinie and Douala General Hospitals (Littoral region) and the Bafoussam regional hospital (West region) 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 wide range of socio-economic classes. Each of these hospitals is equipped with a nephrology unit that is under the responsibility of a nephrologist.

### Inclusion/Exclusion criteria of participants and study procedure

We included all patients diagnosed by the nephrologist with any of the 5 stages of CKD, aged 18 years and above. All patients on maintenance hemodialysis, pregnant and lactating women as well as patients with nephrotic range proteinuria were excluded from the study.

After detailed explanation of the study and obtaining written consent or assent, a questionnaire was used to collect socio demographic and clinical data from each participant and their medical records. A blood sample (5 ml) was collected from each of the subjects using a vacutainer plain tube. After a short while that allow blood to clot, serum was obtained after centrigation at 3000 rotation per minutes for 10 minutes. The serum obtained was used to determine thyroid hormone profile ($TSH_3$, $FT_4$, and $FT_3$) using the Immunofluorescent Assay (MINI VIDAS, BIOMERIEUX, Marcy Etoile, France), $TT_4$ and $TT_3$ were analysed using the ELISA (Enzyme-Linked Immunosorbent Assay) method (Biorex Diagnostic, Antrim, United Kingdom).

Biochemical tests for serum creatinine was done using the Jaffe method (COBAS C111 La Roche Diagnostic System, Swiss, Germany) and the spot urine was tested for albuminuria (Roche Diagnostic GMBH, Mannhein, Germany) and creatininuria in order to determine the albumin creatinine ratio (ACR).

### Determination of CKD parameters

Chronic Kidney Disease was determined if the eGFR of individuals was less than 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 the nephrologist [9,21,22]. The estimated glomerular filtration rate (eGFR) was computed from serum creatinine measurements using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [23].

Chronic kidney disease stages were determined according to Kidney Disease Improving Global Outcomes (KDIGO).

Staging of CKD:

- 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
- CKD 5 <15ml/min or dialysis [24].

Albuminuria was used to determine the albumine creatinine ratio (ACR) and values categorized between 30 and 299 mg/g and 300 mg/g or over, respectively [25,26]. Nephrotic range proteinuria was defined as proteinuria of 3+ to 4 or as albuminuria of > 2.2g/g [26,27].

### Definition and classification of categories of thyroid dysfunction

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 decretion between (4.7-10 mIU/L) in patients with normal serum $TT_3$ or $FT_3$ and $TT_4$ or $FT_4$.

### Primary subclinical hypothyroidism

TSH>4, 70 mIU/L and suppressed serum TT3 or FT3 and TT4 or FT4. Primary overt hypothyroidism: TSH >20 mIU/L) with low serum $FT_4$ and low $FT_3$ [7].

### 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 T3 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 [28].

### Reference ranges for the thyroid hormones

TSH: 0.27 – 4.7 mIU/L, FT4: 10.6 – 19.4 pmol/L, FT3: 2.6 – 5.4 pmol/L TT4: 5.0 - 13.0 ug/mL TT3: 0.52–1.85 ηg/dL. Creatinine: 0.6–1.2 mg/dL for women and 0.7-1.4mg/dL for men.

### Ethical consideration

The protocol of this study was submitted to the institutional review board of the Faculty of Health Sciences of the University of Buea, and we obtained an ethical approval (Ref: 2018/753-01B/UB/SG/IRB/FHS). Administrative authorizations were obtained from the Management of these hospitals. Participation was strictly voluntary, after having provided a signed written consent or / assent form.

### Statistical analyses

Data were analyzed using SPSS version 20.0. Nominal variables were summarized using counts and percentages while continuous variables were summarized using appropriate measures of central tendency and spread when necessary. Group comparisons for categorical variables were done using the Pearson Chi-squared test while the Kruskal-Wallis one-way analysis test was used to assess the global significant differences between the distributions of biomarkers among the CKD stages. CKD stages were treated in ordinal scale, and data of the patients with lower stages (1 to 2) were merged to provide a considerable sample size for inferential statistics. Spearman's rho correlation test was used to assess the strength of correlation between biomarkers and CKD stages, while the strength of the correlation between these biomarkers and the eGFR was performed using Pearson's correlation. The threshold of significance was set at $p< 0.05$.

## Results

### Characteristics of the study population

**Demographic characteristics:** In this study, we recruited 366 participants of which 233 (63.66%) were male (Table 1). The mean age was 55.85 ± 13.72 years with women being significantly younger than men. The 60-70 years age group was the most represented (36.07%).

**Table 1:** Age and gender distribution of participants.

| Variable | | Gender | | Total (N) |
|---|---|---|---|---|
| | | Male n (%) | Female, n (%) | |
| Age, mean (SD) | | 59.60 (13.59) | 54.82 (14.11) | 55.85 (13.72) |
| Age groups | 18 to 20 | 2 (0.86) | 2 (1.50) | 4 (1.09) |
| | 21-30 | 7 (3.0) | 5 (3.76) | 12 (3.28) |
| | 31-40 | 13 (5.58) | 17 (12.78) | 30 (8.20) |
| | 41-50 | 25 (10.73) | 16 (12.03) | 41 (11.20) |
| | 51-60 | 43 (18.43) | 39 (29.32) | 82 (22.40) |
| | 61-70 | 92 (39.48) | 40 (30.08) | 132 (36.07) |
| | 71-80 | 41 (17.60) | 9 (6.77) | 50 (13.66) |
| | >80 | 10 (4.29) | 5 (3.76) | 15 (4.10) |
| | Total | 233 (63.66) | 133 (36.34) | 366 (100) |

### Clinical characteristics

The distribution of the various co-morbidities assessed is presented in table II. It was observed that hypertension, diabetes and gout were the most common co-morbidities; with HIV, gout and hepatitis C being significantly higher among women ($p<0.05$).

**Table 2:** Distribution of co-morbidities chronic kidney disease participants according to gender.

| Co-morbidities | Study population n (%) | Gender | | p-value* |
|---|---|---|---|---|
| | | Female n (%) | Male n (%) | |
| Hypertension | 273 (74.6) | 100 (75.2) | 173 (74.2) | 0.9 |
| Diabetes mellitus | 148 (40.4) | 51 (38.3) | 97 (41.6) | 0.4 |
| Gout | 97 (26.5) | 19 (14.3) | 78 (33.5) | <0.001 |
| HIV | 21 (5.7) | 16 (12.0) | 5 (2.1) | <0.001 |
| Hepatitis C | 16 (4.4) | 2 (1.5) | 14 (6.0) | 0.04 |
| Hepatitis B | 15 (4.1) | 4 (3.0) | 11 (4.7) | 0.4 |
| CVA | 8 (2.2) | 2 (1.5) | 6 (2.6) | 0.7 |
| Malignancy | 2 (0.5) | 1 (0.8) | 1 (0.4) | 0.3 |
| Tuberculosis | 1 (0.3) | 1 (0.8) | 0 (0.0) | 0.3 |
| **Others | 20 (5.5) | 10 (7.5) | 10 (4.3) | 0.2 |
| Total | 366 | 133 | 233 | 0.29 |

* p-value for Chi-square test.

**Others: Sickle cell anemia, urinary tract infections.

## Distribution of the study population by the stage of CKD

The distribution of the patients according to their CKD stages is illustrated in figure 1. More patients were found with advanced stages of CKD than with lower stages. About 28.4% and 35.2% of the participants respectively were found in stages 4 and 5. Stages 1 and 2 were grouped giving participants (5.2%) for subsequent analysis.

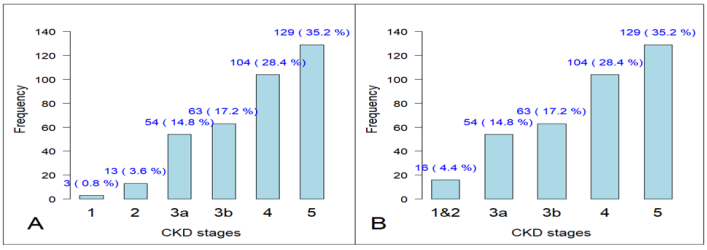


**Figure 1:** Distribution of CKD by all stages (A) and after grouping stages 1 and 2 (B).

## Prevalence of thyroid dysfunction

Out of 366 CKD patients enrolled, 210 displayed thyroid abnormalities, giving an overall prevalence of thyroid dysfunction of 57.38% (Figure 2).

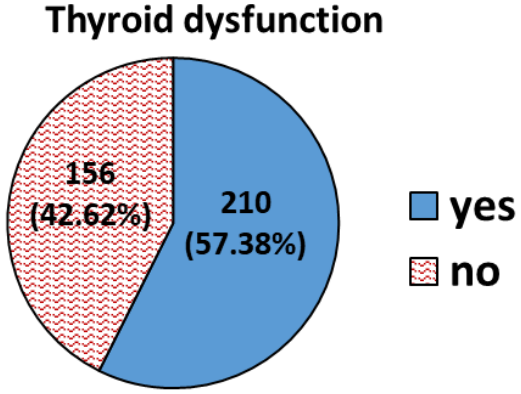


**Figure 2:** Overall prevalence of thyroid dysfunction among CKD participants.

The prevalence of thyroid dysfunction was found to increase significantly with the severity of CKD (p<0.001), with stage 5 having the highest prevalence of 25.41 % (Table 3).

**Table 3:** Distribution of thyroid dysfunction by CKD stages.

| CKD Stages | Thyroid dysfunction N (%) | CKD patients (N) | Prevalence (%) |
|---|---|---|---|
| 1-2 | 7 (36.84) | 19 | 1.91 |
| 3a | 33 (34.54) | 55 | 5.2 |
| 3b | 58 (52.38) | 63 | 9.0 |
| 4 | 93 (58) | 100 | 15.84 |
| 5 | 93 (72.09) | 129 | 25.41 |
| Total | 210 (57.65) | 366 | 57.65 |

Pearson's Chi-squared Test: X2= 20.678, df = 2, p-value < 0.001.

## Spectrum of thyroid function abnormalities and different stages of CKD

The findings below show that thyroid dysfunctions increase from 2.3% in stage 1&2 to 5.2% in stage 3a, and stage 3b recorded 9.0%, with stage 5 having the greatest frequency of dysfunctions 25.1%. Thyroid dysfunction was associated to CKD (p<0.001) with only FT3, high T4 and primary subclinical hypothyroidism which were found to be statistically significant (p<0.05).

## Correlation between biomarkers of thyroid function abnormalities and eGFR level

Positive correlation between thyroid hormone profile (FT3, FT4, TT3,) and the eGFR was observed (r = 0.425, P < 0.001, r= 0.188, P= 0.003; r=0.285, P < 0.0001; Pearson correlation coefficient) respectively, however anon-significant negative correlation was found with TSH (r = -0.0956; p=0.0595) and TT4 (r = 0.0511, P < 0.3320).

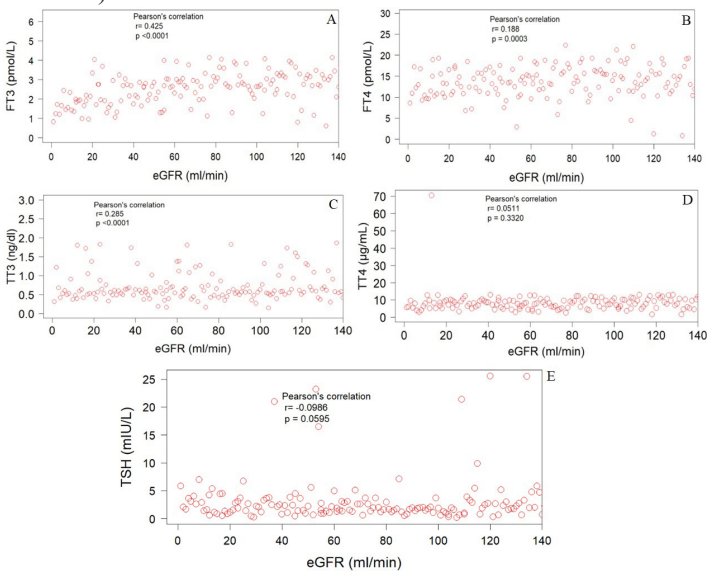


**Figure 3:** Correlation between TSH, TT3, TT4, FT3, FT4 and eGFR.

## Correlation between biomarkers of thyroid function abnormalities and CKD

**Table 4:** Distribution of the types of thyroid dysfunction according to stages of CKD.

| Various thyroid dysfunctions | Stages of Chronic Kidney Disease | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | CKD Stage 1&2 | CKD Stage 3a | CKD Stage 3b | CKD Stage 4 | CKD Stage 5 | Total n (%) | p-value |
| Minor types of thyroid dysfunction | LFT3 | 2 | 0 | 2 | 5 | 27 | 36 (9.8) | <0.001 |
| | LT3 | 1 | 7 | 11 | 19 | 16 | 54 (14.8) | 0.6 |
| | LT3 and LFT3 | 0 | 0 | 5 | 4 | 18 | 27 (7.4) | 0.01 |
| | LT3 and LT4 | 0 | 0 | 0 | 5 | 3 | 8 (2.2) | 0.2 |
| | LT4 and LFT4 | 0 | 0 | 0 | 1 | 2 | 3 (0.8) | 0.8 |
| | LFT4 | 0 | 2 | 0 | 2 | 1 | 5 (1.4) | 0.5 |
| | LT4 | 1 | 2 | 3 | 4 | 8 | 18 (4.9) | 0.6 |
| | HFT4 | 0 | 1 | 4 | 3 | 3 | 11 (3.0) | 0.9 |
| | H T4 | 3 | 2 | 1 | 2 | 0 | 8 (2.2) | <0.001 |
| Major thyroid dysfunction n (%) | PO hypo | 0 | 0 | 0 | 2 | 2 | 4 (1.1) | 0.7 |
| | PSCL Hypo | 0 | 0 | 1 | 5 | 7 | 13 (3.6) | 0.036 |
| | SCL hypo | 1 | 4 | 3 | 5 | 4 | 17 (4.6) | 0.8 |
| | SCL hyper | 0 | 1 | 1 | 1 | 1 | 4 (1.1) | 0.9 |
| | O Hyper | 0 | 0 | 2 | 0 | 0 | 2 (0.5) | 0.08 |
| | Total | 8 (2.3) | 19 (5.2) | 3 (9.0) | 58 (15.8%) | 92 (25.1) | 210 (57.4) | 0.001 |

L: Low, H: High, PO: Primary overt, PSC: Primary subclinical, SCL: Subclinical, Hypo: Hypothyroidism, Hyper: Hyperthyroidism.

**Table 5:** Descriptive parameters of thyroid hormone levels stratified by CKD stages and correlation analysis.

| Parameters | CKD stages | Mean ± SD | Median | Q1-Q3 | Kruskal-Wallis test | | Spearman's rank correlation | |
|---|---|---|---|---|---|---|---|---|
| | | | | | $X^2$ | p-value | Rho | p-value |
| FT3 (pmol/L) | 1-2 | 3.21 ± 0.13 | 3.25 | 2.87-3.61 | 220.8 | 0.1082 | -0.45 | <0.0001 |
| | 3a | 3.48 ± 0.58 | 3.42 | 3.2-3.7 | | | | |
| | 3b | 3.42 ± 0.28 | 3.2 | 2.8-3.6 | | | | |
| | 4 | 2.95 ± 0.67 | 3.04 | 2.66-3.37 | | | | |
| | 5 | 2.50 ± 0.07 | 2.63 | 1.94-3.02 | | | | |
| FT4 (pmol/L) | 1-2 | 16.12 ± 0.54 | 16.27 | 15.28-18.79 | 304.50 | 0.3394 | -0.166 | 0.0015 |
| | 3a | 14.71 ± 0.35 | 14.84 | 12.52-16.39 | | | | |
| | 3b | 15.77 ± 0.69 | 14.51 | 13.24-17.03 | | | | |
| | 4 | 13.82 ± 0.39 | 14.09 | 11.00-16.05 | | | | |
| | 5 | 13.81 ± 0.31 | 13.78 | 13.35-16.34 | | | | |
| TT3 (ηg/dl) | 1-2 | 1.17 ± 0.19 | 1.1 | 0.72-1.45 | 172.55 | 0.0281 | -0.229 | <0.0001 |
| | 3a | 1.09 ± 0.21 | 0.67 | 0.56-1.12 | | | | |
| | 3b | 1.03 ± 0.13 | 0.78 | 0.52-1.35 | | | | |
| | 4 | 0.84 ± 0.16 | 0.6 | 0.49-0.72 | | | | |
| | 5 | 0.70 ± 0.03 | 0.58 | 0.49-0.74 | | | | |
| TT4 (µg/mL) | 1-2 | 10.31 ± 0.69 | 10.68 | 8.5-12.02 | 285.4 | 0.3665 | -0.173 | 0.0009 |
| | 3a | 9.14 ± 0.38 | 9.45 | 7.76-11.17 | | | | |
| | 3b | 8.58 ± 0.42 | 8 | 6.37-10.25 | | | | |
| | 4 | 13.76 ± 50.12 | 9.09 | 6.1-11.13 | | | | |
| | 5 | 13.43 ± 5.51 | 7.95 | 5.82-9.74 | | | | |
| TSH (mIU/L) | 1-2 | 2.29 ± 0.32 | 2.17 | 1.84-2.9 | 2.48.12 | 0.5395 | 0.062 | 0.2364 |
| | 3a | 2.08 ± 0.19 | 1.68 | 1.0-2.51 | | | | |
| | 3b | 2.07 ± 0.18 | 1.72 | 1.15-2.4 | | | | |
| | 4 | 4.45 ± 1.53 | 1.94 | 1.2-2.88 | | | | |
| | 5 | 3.25 ± 0.58 | 1.94 | 1.25-3.12 | | | | |

SD: Standard Deviation; Q1 = Quartiles 1; Q3 = Quartiles3.

The TSH showed a weak non-significant positive correlation (r= 0.062, p >0.05) with stages of CKD. We observed a significant negative correlation between TT3, TT4, FT3 and FT4 (r= -0.229 p<0.001; r= -0.173, p<0.001; r= -0.45, p<0.001; r=-166, p<0.001) with stages of CKD respectively. Additionally, only TT3 was statistically significant with Kruskal-wallis test (P=0.0281).

## Discussions

Thyroid hormones may directly affect the kidney function whereas altered kidney function on the other hand can contribute to thyroid disorders [7]. The two main hormones produced by the thyroid gland are T3 and T4. These hormones can have a significant impact on kidney disease, highlighting the need to assess a correlation between thyroid hormone disorders and CKD.

In this study, most patients had their mean serum levels for FT3, TT3, TT4 and FT4 that were found to decrease progressively and significantly from stage 1Ъ2 through 5 of CKD (Table 4) but with normal serum TSH level. This finding was similar to that Vasudevan in India who also found the same trend [29]. In 2009, Iglesias and Diez published a review article entitled thyroid dysfunction and kidney disease in which they reported that serum TSH concentrations are usually normal or elevated in CKD [30] whereas free and total T3 and T4 concentrations are usually normal or low in patients with CKD [26]. In an Indian study, conducted in Mumbai, out of 127 patients with CKD studied, 73% showed significant (p <0.05) reduction in their TT3, TT4, FT3 levels in serum [31].

The reduction in T3 (low T3 syndrome) is the most frequently observed thyroid alteration in these patients [7,32]. This reduction in T3 concentration has been linked to a decrease in the peripheral conversion of T4 to T3 [7,31,32]. This decrease in T3 levels is caused by the inhibition of iodothyronine deiodinase (T4 conversion to T3), due to fasting, chronic metabolic acidosis, and chronic protein malnutrition seen in CKD patients. The aforementioned factors can lead to decreased T3 level by influencing its protein binding [33]. Low T3 levels may also arise from the decreased clearance of the inflammatory cytokines such as TNF-alpha and IL1 [3] in CKD. Low T4 values in end stage renal disease (ESRD) patients may be related to impaired T4 binding to serum protein's carrier. It has been reported that many inhibitors of T4 binding to serum protein's carrier are present in Chronic Kidney disease patients and thus contributing to the decreased level of T4 in CKD. This trend of decreased thyroid hormones was corroborated by the remarkable increase in the prevalence of thyroid dysfunction as stages of CKD increased in this study (Figure 3).

This relationship was confirmed by a Spearman's rank correlation coefficient where thyroid hormone levels reduce with increase stages of CKD (Figure VI) and pearson correlation where TT3, FT4 and FT3 reduced with decrease in eGFR (Figure 5). The TSH level did not show any linear correlation (r = 0.062; P >0.05) with the progression of CKD in the various stages in this study. This is an indication that serum thyroid hormones levels were associated with severity of CKD although TSH remained normal (p>0.05). This correlation can be explained by the fact that, as a result of reduced de-iodinase activity, tissue and circulating levels of T3, are low in chronic kidney disease.

Also, as a result of reduced renal excretion of inorganic iodides generated by residual de-iodinase activity, tend to accumulate in CKD stages 4 and 5, and in turn dampen thyroid hormone synthesis [34]. Various patterns of alteration of thyroid profile in CKD patients have been reported in literature, Singh et al. also observed a significant decrease in the levels of T3 and T4 [35].

Low T3, Low FT3, low T3&FT3 and subclinical hypothyroidism (Table 5) were found to be the most common type of thyroid dysfunction in our setting. However, the presence of non-thyroidal illness (NTI) also known as low T3 syndrome, primary subclinical hypothyroidism and high T4 (P<0.05%) were significantly related to the stages of CKD. Non-thyroidal illness is characterized by low T3 and fT3 with an increase in rT3 and normal TSH, T4 may be normal or low [33]. Low T3 is commonly seen in advanced stages (stage 4 and 5 CKD) although present throughout CKD stages [33]. The blunting effect of TSH by accumulation of inorganic iodide as well as uremia seen in persons with CKD could result in decreased production of T4 [36]. Similar results were found by other authors ( [34]. Conversely, thyroid hormones have both direct and indirect effects on renal function. The indirect effect is mediated on cardiovascular system and renal blood flow. The direct effects are mediated on glomerular filtration rate, tubular secretory and reabsorptive function and hormonal influences that may result in CKD [34].

We found weak to moderate spearman's and pearson's correlation with the different thyroid profile, eGFR and stages of CKD which were however statistically significant (Figures 5 and 6). This lack of strong correlation as evident by a coefficient closer to 0 than 1, could be explained by the fact that chronic kidney disease is not the only factor that may be affecting thyroid function in our population. Two polymorphisms in D1, involved in the conversion of T4 to T3, (D1-C785T and D1- A1814G) that affect the serum T3/ rT3 ratio in healthy subjects have been identified. It was speculated that the D1-785T variant results in a decreased activity of D1 [37]. Although the D1-785T variant is not associated with serum rT3 levels in the general population, its association with lower levels of T3 in an elderly population supports the hypothesis of a lower activity of D1 in carriers of this polymorphism [37]. In young subjects, a decreased T3 production by D1 may be masked by the production of serum T3 by skeletal muscle D2. Throughout adult life, skeletal muscle size and strength gradually decline, resulting in a decrease in D2-expressing skeletal muscle. Furthermore, rT3 levels increase with age, and degradation of the D2 protein is accelerated when it is exposed to its own substrates T4 and rT3.

Although it has been shown that D1 activity also decreases during aging [38], the relative contribution of D2 to serum T3 production may be less important in the elderly than in young subjects. This would mean that D1 has a relatively greater contribution to serum T3 production at advanced ages [38]. Given that our study

population is composed of elderly persons, we may assume that the high prevalence of thyroid dysfunction, notably low T3 may be due to polymorphism in the D1 gene expressed by our population as well as the degradation of D2 over time. This is however not verifiable as we didn't check for D1-C785T mutation in this study and investigation can be done in future prospect.

## Conclusion

In this study, most patients had their mean serum levels for FT3, TT3, TT4 and FT4 that were found to decrease progressively and significantly from stage 1Ф2 through 5 of CKD patients, although with normal serum TSH level. Low T3, Low FT3, low T3 & FT3 and subclinical hypothyroidism were found to be the most common type of thyroid dysfunction in our setting. The reduction in T3 (low T3 syndrome) is the most frequently observed thyroid alteration in CKD patients in Cameroon. We found a weak to moderate spearman's and pearson's correlation with the different thyroid profile, eGFR and stages of CKD which were however statistically significant. There is a need to initiate a cohort prospective study among CKD patients of all stages in order to determine the incidence of thyroid dysfunction.

## Abbreviations

A: Adenine; C: Cytosine; CKD: Chronic kidney disease; D1: Type 1 Deiodinase; D2: Type 2 Deiodinase ; ESRD: End stage renal disease; $FT_4$: Free Tetra iodothyronine; $FT_3$: Free triiodothyronine; GFR: Glomerular filtration rate; G: Guanine; Hyper: Hyperthyroidism; Hypo: Hypothyroidism; IL1: Interleukin 1; NKF: National Kidney Foundation; PO: Primary Overt; PSC: Primary Subclinical; rT3: Reverse triiodothyronine; SC hypo: Subclinical hypothyroidism; $T_3$: Triiodothyronine; $T_4$: Tetra-iodothyronine; T: Thymine; TRH: Thyroid releasing hormone; TSH: Thyroid stimulating hormone; TNF-alpha: Tumour necrotic factor alpha.

## Declarations

### Ethics approval and consent to participate

The protocol of this study was submitted to the institutional review board of the Faculty of Health Sciences of the University of Buea, and we obtained an ethical approval (Ref: 2018/753-01B/UB/SG/IRB/FHS). Administrative authorizations were obtained from the Management of these hospitals. Participation was strictly voluntary, after having provided a signed written consent or / assent.

### Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

## 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 and ccritically reviewed the manuscript. NTF: Participated in the study design and reviewed of literature and data interpretation. NAJ: Oversaw data collection, participated in data analysis, drafted the manuscript, and critically reviewed the manuscript. JCAN: Conceived and supervised the work, oversaw data collection, participated in data analysis and interpretation, drafted and critically reviewed the manuscript. MNN: Study design and supervised the work, oversaw literature search and revised the manuscript. All authors read and approved the final manuscript.


## Acknowledgement

We heartily thank the management and staff of the Nephrology Units of The Douala General Hospital, the Laquintinie Hospital Douala and the Bafoussam Regional Hospital.


## References


1. Gupta A, Virmani SK, Arora M. Thyroid dysfunction in patients of chronic kidney disease. Int J Adv Med. 2017; 4: 1333-1337.
2. Gupta UN, Jain A, Prakash P, et al. Original Article To Study the Prevalence of Thyroid Disorders in Chronic Renal Disease Patients. 2019; 126-129.
3. Farag SES. Functional and Morphological Thyroid Disorders in Hemodialysis Patients. J Thyroid Disord Ther. 2013; 02: 2-5.
4. Rhee CM, Brent GA, Kovesdy CP, et al. Thyroid functional disease An under-recognized cardiovascular risk factor in kidney disease patients. Nephrol Dial Transplant. 2015; 30: 724-737.
5. Rhee CM. Low-T3 syndrome in peritoneal dialysis: Metabolic adaptation, marker of illness, or mortality mediator. Clinical Journal of the American Society of Nephrology. 2015; 10: 917-919.
6. van Hoek I, Daminet S. Interactions between thyroid and kidney function in pathological conditions of these organ systems A review. Gen Comp Endocrinol. 2009; 160: 205-215.
7. Gowda MAS. Evaluation of Thyroid Function Status in Patients with Chronic Kidney Disease. J Med Sci Clin Res. 2016; 4: 14235-14241.
8. Zoccali C, Mallamaci F. Thyroid function and clinical outcomes in kidney failure. Clin J Am Soc Nephrol. 2012; 7: 12-14.
9. Inker LA, Astor B, Fox C, et al. KDOQI US Commentary on the 2012 KDIGO Clinical Practice Guideline for the Evaluation and Management of CKD. Ajkd. 2014; 63: 713-735.
10. Mohamedali M, Reddy Maddika S, Vyas A, et al. Thyroid disorders and chronic kidney disease. Int J Nephrol. 2014; 2014: 1-6.
11. Miulescu RD, Cristian M, Ma D, et al. Associations between thyroid dysfunction and chronic kidney disease. 2014; 21: 37-42.
12. http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L613094367%0Ahttp://sfx.hul.harvard.edu/sfx_local?sid=EMBASE&issn=0976044X-&id=doi:&atitle=Risk+factors+associated+with+chronic+kidney+disease%3A+An+overview&stitle=Int.+J.+-Pharm.+Sci

13. Basu G, Mohapatra A. Interactions between thyroid disorders and kidney disease. Indian J Endocrinol Metab. 2012; 16: 204.
14. Chonchol M, Lippi G, Salvagno G, et al. Prevalence of subclinical hypothyroidism in patients with chronic kidney disease. Clinical Journal of the American Society of Nephrology. 2008; 3: 1296-1300.
15. Shin DH, Lee MJ, Kim SJ, et al. Preservation of renal function by thyroid hormone replacement therapy in chronic kidney disease patients with subclinical hypothyroidism. J Clin Endocrinol Metab. 2012; 97: 2732-2740.
16. Chaker L, Sedaghat S, Hoorn EJ, et al. The association of thyroid function and the risk of kidney function decline a population-based cohort study. Eur J Endocrinol. 2016; 175: 653-660.
17. Shin DH, Lee MJ, Lee HS, et al. Thyroid Hormone Replacement Therapy Attenuates the Decline of Renal Function in Chronic Kidney Disease Patients with Subclinical Hypothyroidism. Thyroid. 2013; 23: 654-661.
18. Meuwese CL, Gussekloo J, de Craen AJM, et al. Thyroid Status and Renal Function in Older Persons in the General Population. J Clin Endocrinol Metab. 2014; 99: 2689-2696.
19. Wang K, Xie K, Gu L, et al. Association of thyroid function with the estimated glomerular filtration rate in a large Chinese euthyroid population. Kidney Blood Press Res. 2018; 43: 1075-1083.
20. Li H, Yuan X, Liu L, et al. Clinical evaluation of various thyroid hormones on thyroid function. Int J Endocrinol. 2014; 2014: 1-5.
21. Miulescu R, Neamţu M. Associations between thyroid dysfunction and chronic kidney disease. Rom J Diabetes Nutr. 2014; 21: 37-42.
22. Mohamedali M, Maddika SR, Vyas A, et al. Thyroid Disorders and Chronic Kidney Disease. 2014; 2014: 1-7.
23. Levey AS, Coresh J. Chronic kidney disease. Lancet. 2012; 379: 165-180.
24. Levin A, Stevens PE. Summary of KDIGO 2012 CKD Guideline: Behind the scenes, need for guidance, and a framework for moving forward. Kidney Int. 2014; 85: 49-61.
25. Rhee CM, Chen Y, You AS, et al. Thyroid status, quality of life, and mental health in patients on hemodialysis. Clin J Am Soc Nephrol. 2017; 12: 1274-1283.
26. Chen W, Liu Q, Wang H, et al. Prevalence and risk factors of chronic kidney disease A population study in the Tibetan population. Nephrol Dial Transplant. 2011; 26: 1592-1599.
27. Cassia MA, Pozzi FE, Bascape S, et al. Proteinuria and albuminuria at point of care. Nephrol @ Point Care. 2016; 2: E8-E16.
28. Okpara HC. Spectrum of Thyroid Dysfunction among Patients Evaluated by Thyroid Function Tests at a Tertiary Clinical Laboratory in Calabar, Nigeria. 2017; 411-417.
29. Singh S, Verma A, Aryal G, et al. Thyroid hormone profile in patients with chronic kidney disease a single centre study. Hypertension. 2016; 24: 23-30.
30. Iglesias P, Díez JJ. Thyroid dysfunction and kidney disease. Eur J Endocrinol. 2009; 160: 503-515.
31. Srivastava S, Rajput J, Shrivastava M, et al. Correlation of thyroid hormone profile with biochemical markers of renal function in patients with undialyzed chronic kidney disease. Indian Journal of Endocrinology and Metabolism. 2018; 22: 316-320.
32. Iglesias P, Bajo MA, Selgas R, et al. Thyroid dysfunction and kidney disease An update. Rev Endocr Metab Disord. 2017; 18: 131-144.
33. Zhang Y, Chang Y, Ryu S, et al. Thyroid hormone levels and incident chronic kidney disease in euthyroid individuals The Kangbuk Samsung Health Study. International Journal of Epidemiology. 2014; 43: 1624-1632.
34. Lim VS. Thyroid function in patients with chronic renal failure. Am J Kidney Dis. 2001; 38: S80-S84.
35. Singh S, Verma A, Aryal G, et al. Thyroid hormone profile in patients with chronic kidney disease a single centre study. Hypertension. 2016; 24: 23-30.
36. Singh S, Verma A, Aryal G, et al. Prevalence of thyroid hormone abnormalities in stage 5 chronic kidney disease : a tertiary care center study of Nepal. Int J Res Med Sci. 2016; 4: 3929-3933.
37. Peeters RP, Deure WM Van Der, Visser TJ. Genetic variation in thyroid hormone pathway genes polymorphisms in the TSH receptor and the iodothyronine deiodinases. 2006; 655-662.
38. Peeters RP, Van Den Beld AW, Van Toor H, et al. A polymorphism in type I deiodinase is associated with circulating free insulin-like growth factor I levels and body composition in humans. J Clin Endocrinol Metab. 2005; 90: 256-263.