

## Original Research Article

# Prevalence and patterns of thyroid dysfunction in chronic kidney disease patients in a tertiary hospital in southern Nigeria

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## ABSTRACT

**Background:** Several studies have identified that a decline in renal function as occurs in chronic kidney disease (CKD) is associated with thyroid dysfunction among other endocrine disorders. The prevalence and pattern of thyroid dysfunction in CKD patients in our environment is however not known. This study aimed to determine the prevalence and pattern of thyroid dysfunction in dialysis naïve CKD patients in a tertiary hospital in Southern Nigeria.

**Methods:** This was a cross sectional study involving 100 participants with established CKD and 100 age and sex matched healthy controls. Relevant data were collected using an interviewer based questionnaire. Samples collected from the participants were assayed for fT3, fT4, TSH and serum creatinine. Analyses was done using version 25 of the SPSS software at a 95% confidence interval and a p value of <0.05 was considered statistically significant.

**Results:** There were 93 males and 107 females with mean ages of 46.3±15.9 and 45.7±14.9 years for the CKD and control participants respectively (p=0.7587). The prevalence of thyroid dysfunction was 45% in the CKD group and 4% in the control group. Sick euthyroid syndrome was the commonest form of thyroid dysfunction (23%), followed by subclinical hypothyroidism (14%). Thyroid dysfunction increased with increasing severity of CKD but this was not statistically significant.

**Conclusions:** Thyroid dysfunction is highly prevalent in dialysis naïve CKD patients. Further studies need to be carried out to determine risk factors and evaluate the impact of treatment in these patients following which a guideline for screening and management can be developed.

**Keywords:** Chronic kidney disease, Dialysis naïve, Thyroid dysfunction, University of Port Harcourt

## INTRODUCTION

Chronic kidney disease (CKD) is a clinical syndrome characterized by progressive and irreversible decline in renal function resulting in excretory, metabolic and synthetic dysfunction.<sup>1,2</sup> The definition and classification of CKD has changed over the years in an attempt to get a common language of communication between health care providers, patients and their family members, and other stake holders with the aim of achieving a public health approach to care. It has been defined by the National

Kidney Foundation- Kidney Disease Outcome Quality Initiative (NKF-K/DOQI) as the presence of structural or functional abnormality of the kidney for greater than 3 months with implications for health.<sup>3</sup>

CKD is a disease of global concern. This is because; it is associated with significant morbidity and mortality and poses a huge socioeconomic burden to the affected individual, family and nation. It is a common unwanted endpoint shared by the major non communicable diseases

(NCD) of global significance such as hypertension and diabetes mellitus.<sup>4</sup>

CKD has shown a steady and progressive rise in prevalence and is now the 6<sup>th</sup> fastest rising cause of death globally, accounting for about 1.2 million deaths yearly.<sup>5,6</sup> According to the 2015 Global Burden of Disease study, CKD moved from the 27<sup>th</sup> to the 12<sup>th</sup> position in the ranking of global leading causes of death over a period of 25 years (1990-2015) with an increase in mortality rate of 32% in 10 years.<sup>5,6</sup>

A pertinent challenge of CKD is its inevitable tendency to progress. As CKD progresses a lot of complications begin to develop including metabolic, haematologic, endocrine as well as cardiovascular complications.<sup>1</sup> These contribute to its high morbidity and mortality which is mainly cardiovascular related. Several attempts made to halt this progression have proved abortive, and a lot of patients do not survive up to ESRD.<sup>7,8</sup>

Endocrine perturbations are a common complication of CKD especially in the advanced stages.<sup>9</sup> This is attributable to the significant role the kidneys play in hormone homeostasis.<sup>9,10</sup>

Apart from impairment of hormone synthesis, biodegradation and excretion, impairment of hormone transport and binding to target cell (frequently as a result of receptor resistance) has been observed in patients with CKD.<sup>9,10</sup> Inflammation, malnutrition and metabolic acidosis are also pathophysiologic mechanisms by which these endocrine abnormalities occur.<sup>9,10</sup> Disorders of erythropoietin synthesis and hyperparathyroidism are among the most pronounced in clinical practice because of the significant anaemia and mineral bone disease associated with these disorders.<sup>10</sup> However, disorders of thyroid hormone, cortisol, growth hormone, insulin, sex hormones, aldosterone, and catecholamines also occur frequently in CKD.<sup>9</sup> These endocrine abnormalities which can either be in form of hormonal deficiencies or excess have implications for morbidity and mortality and are no longer innocent bystanders in CKD as previously assumed.<sup>11</sup>

The thyroid gland and the kidneys are two vital organs with a close and complex two-way relationship. On one hand, the thyroid gland produces thyroid hormones which play significant roles in the growth and development of the kidney as well as maintenance of fluid and electrolyte homeostasis.<sup>12,13</sup> On the other hand, the kidneys metabolize and excrete thyroid hormones and is a target organ for thyroid hormone action.<sup>12,13</sup> With this functional relationship, it is understandable that diseases of the thyroid gland will likely have effect on kidney function and vice versa. In addition to this functional relationship, thyroid and kidney disease can have same aetiologic origin and medications used to treat one disorder can affect the other buttressing the relationship between these organs.

Several studies have identified that a decline in renal function as occurs in CKD is associated with thyroid dysfunction among other endocrine disorders.<sup>10,14</sup> Hypothyroidism, hyperthyroidism and sick euthyroid syndrome have been reported in CKD patients.<sup>15,16</sup> Structural abnormalities such as goiter and thyroid cancers have also been found to be more prevalent in these patients compared to the general population.<sup>17,18</sup> The mechanisms of these thyroid abnormalities in CKD are complex and multifactorial but believed to be basically due to effect of CKD on the hypothalamo-pituitary-thyroidal axis and thyroid hormone peripheral metabolism.<sup>18</sup> These disorders on their own contribute to poor quality of life with associated increased risk of morbidity and mortality. In the presence of chronic renal failure, they have been found to increase the risk of cardiovascular disease and death while worsening the decline in renal function.<sup>19,20</sup>

## METHODS

This was a descriptive cross-sectional study carried out in the nephrology outpatient clinic of the University of Port Harcourt Teaching Hospital, a tertiary health facility in Southern Nigeria from December 2019 to September 2020. The study population consisted of 100 consecutive participants with CKD aged 18 years and above with an established diagnosis of CKD attending the nephrology clinic of the University of Port Harcourt Teaching Hospital and 100 healthy controls who were matched for age and sex and who met the inclusion criteria.

Before commencement of the study, ethical approval was obtained from the Ethical Committee of the University of Port Harcourt Teaching Hospital. Written informed consent was also obtained from all the study participants before their recruitment into the study.

The following participants were excluded from the study. Participants on dialysis or who have had renal transplant, participants living with or found to have diabetes mellitus, participants who are HIV positive, participants who are pregnant, participants with established thyroid disease, participants on medications known to affect thyroid function such as amiodarone, glucocorticoids, phenytoin, salicylate, nonsteroidal anti inflammatory drugs (NSAIDs), mitotane, participants with co morbid conditions like malignancies and liver disease, participants who are acutely ill, and participants who decline consent were excluded.

Data collection was done over a period of 9 months in 2 stages. First, data was collected from the study participants by a structured interviewer administered questionnaire followed by Blood pressure and anthropometric measurement. Venous blood samples were then collected for free T3, Free T4, TSH, and serum creatinine after an overnight fast. Sample for TSH, Free T3 and Free T4 was collected with a plain bottle and analyzed using enzyme linked immunosorbent assay

technique while sample for serum creatinine was collected using a lithium heparin bottle and analysed using the alkaline picrate method (modified kinetic Jaffe reaction) using a spectrumbiol 23A spectrophotometer. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD EPI) formula.

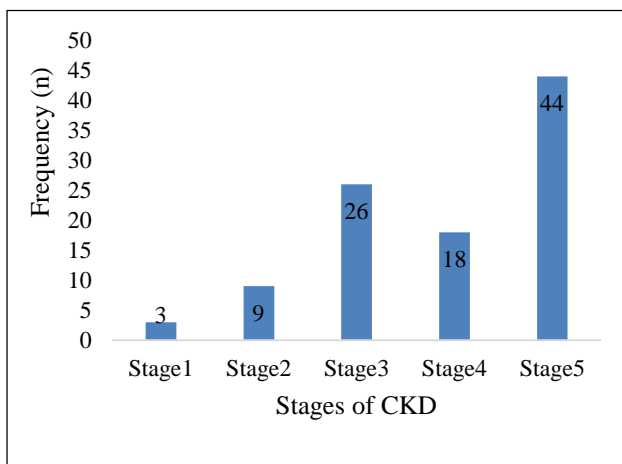
**RESULTS**

**Socio demographic characteristics of study participants**

The ages of the participants in the CKD group ranged between 18 and 83 years with a mean age of 46.3 ± 15.9 years, while the control group had participants in the age range of 18 to 85 years with a mean age of 45.7 ± 14.9 years (p=0.7587). There were a total of 93 male and 107 female study participants. The CKD group consisted of 47 male and 53 female participants while the control group consisted of 46 males and 54 females. There was no statistically significant difference in the sex distribution between both groups (p value=0.887).

**Table 1: Socio-demographic characteristics of study participants.**

	Control (n= 100)%	CKD group (n = 100)%	Chi-square (p-value)
<b>Age groups</b>			
18 - 29 years	14 (14.0)	18 (18.0)	6.49 (0.2610)
30 - 39 years	26 (26.0)	15 (15.0)	
40 - 49 years	26 (26.0)	25 (25.0)	
50 - 59 years	11 (11.0)	19 (19.0)	
60 - 69 years	17 (17.0)	14 (14.0)	
≥ 70 years	6 (6.0)	9 (9.0)	
Mean age±SD	45.67±14.86	46.34±15.93	t- test (0.7587)
<b>Gender</b>			
Male	46 (46.0)	47 (47.0)	0.02 (0.1418)
Female	54 (54.0)	53 (53.0)	



**Figure 1: Distribution of CKD participants according to CKD stage.**

**Prevalence of thyroid dysfunction in study participants**

Of the 100 participants with CKD, 45% had laboratory evidence of thyroid dysfunction while 55% did not. Only 4 of the 100 age and sex matched controls had laboratory evidence of thyroid dysfunction. This gave a prevalence of thyroid dysfunction of 45% in the CKD group and 4% in the control group (Table 2).

**Table 2: Distribution of thyroid dysfunction in CKD and control groups.**

Thyroid dysfunction	Control	CKD group	Chi-square (p- value)
Yes	4 (4.0)	45 (45.0)	45.4 (0.0001)*
No	96 (96.0)	55 (55.0)	
<b>Total</b>	100 (100.0)	100 (100.0)	

\*statistically significant (p<0.05)

**Pattern of thyroid dysfunction in participants with CKD**

The pattern of thyroid dysfunction in participants with CKD is as depicted in Table 3. The commonest form of thyroid dysfunction was sick euthyroid syndrome (23%) followed by subclinical hypothyroidism (14%). Seven percent of the participants with CKD had hyperthyroidism while 1% had an isolated FT3 elevation. More than half of the participants with sick euthyroid syndrome had isolated low FT3 (13), 6 had low FT4, 3 had both low FT3 and FT4 while 1 had high FT4.

**Table 3: Pattern of thyroid dysfunction in participants with CKD.**

Thyroid dysfunction	Frequency	Percentage
<b>Sick euthyroid syndrome</b>	23	23.0
<b>Isolated FT3 elevation</b>	1	1.0
<b>Overt hyperthyroidism</b>	3	3.0
<b>Subclinical hyperthyroidism</b>	4	4.0
<b>Subclinical hypothyroidism</b>	14	14.0
<b>Normal (euthyroid)</b>	55	55.0
<b>Total</b>	100	100.0

**Table 4: Relationship between thyroid dysfunction and severity of CKD in study subjects.**

CKD stage	No of patients	% of patients with thyroid dysfunction in stage	Chi square (P- value)
1	3	0 (0)	6.03 (0.1962)
2	9	2 (22.2)	
3	26	11 (42.3)	
4	18	8 (44.4)	
5	44	24 (54.5)	
<b>Total</b>	100	45	

### Relationship between thyroid dysfunction and severity of CKD

There was a progressive increase in the prevalence of thyroid dysfunction from 0% in stage 1 to 54.5% in stage 5 though this was not statistically significant ( $p=0.1962$ ). Further analysis by Pearson correlation showed a significant negative correlation between eGFR and TSH ( $r=-0.272$   $p=0.006$ ) and non-significant positive correlation between eGFR and FT3 ( $r=0.146$ ,  $p=0.147$ ) and FT4 ( $r=0.049$ ,  $p=0.629$ ) as in Tables 4 and 5.

**Table 5: Pearson correlation of eGFR with TSH, FT3 and FT4 in CKD subjects.**

	Correlation coefficient	Sig. (2-tailed)	N
<b>TSH (0.5-5) <math>\mu</math>iu/ml</b>	-0.272	0.006	100
<b>FT3 (1.4-4.2) pg/ml</b>	0.146	0.147	100
<b>FT4 (0.8-2) ng/ml</b>	0.049	0.629	100

### DISCUSSION

In this study, there was no statistically significant difference between the CKD group and controls in terms of age and sex distribution. This indicates that the two groups were appropriately matched for age and sex for the study.

Majority of the participants in this study were in the middle age group. This is similar to observations in previous studies. Ndu et al reported a mean age of  $45.1 \pm 11.9$  years in a hospital based study of 150 CKD patients in Port Harcourt, South-South Nigeria while Odum et al reported a mean age of  $47.4 \pm 14.9$  years among 164 CKD patients also in Port Harcourt Nigeria.<sup>27,28</sup> Studies from other parts of the country as well as other African countries have also reported similar findings.<sup>29-31</sup> These findings contrast with findings in the USA and other developed countries where CKD is reported to be more prevalent in the elderly especially above 65 years of age.<sup>32</sup> The reason for the difference is related to the differences in the predominant aetiologic factors in CKD in these regions. In Nigeria and other developing countries, infestations and infections (including HIV) contribute significantly to CKD. Hypertension and diabetes which are also leading causes of CKD in these regions are often undiagnosed or recognized late and are often poorly controlled.<sup>30</sup> In addition to these, hypertension and diabetes tend to run a more aggressive course in blacks compared to caucasians so the manifestations of these diseases occur earlier in blacks.<sup>30</sup> Lastly, life expectancy in developing countries is generally reduced compared to the developed countries and therefore majority of the adults in the general population are in the young and middle age group.

There were more females than males in this study, but the sex difference was not statistically significant. Most studies have showed a male preponderance in CKD and

this is inconsistent with the findings in this study.<sup>13,22,16</sup> However female preponderance in CKD (especially the predialysis stage) has also been reported in literature.<sup>33</sup> It can be attributable to a slower rate of progression of CKD in females, longer life expectancy of females as well as better health seeking behaviour especially as females are increasingly becoming bread winners of the families.<sup>33</sup> In addition, the increasing prevalence of pregnancy induced hypertension and autoimmune diseases which are more prevalent in females may be responsible for the higher prevalence of CKD in females.

This study shows that most of the CKD participants were in advanced stages (mainly stage 3 and 5). There were very few cases in stage 4 compared to stage 3 and 5. This reflects the fact that patients with CKD are often detected late due to late presentation.<sup>29</sup> It may also mean that renal function rapidly deteriorates from stage 3 to end stage with fewer cases in stage 4. The finding of only few cases in the early stages may be due to the fact that these early stages are usually asymptomatic or may have only mild symptoms that may delay presentation.

The prevalence of thyroid dysfunction in participants with CKD in this study was 45% as compared to 4% of healthy controls. This finding shows that patients with CKD are approximately 10 times more likely to have thyroid dysfunction compared to the general population. This was similar to findings in similar studies in Kenya (42%) and Southern Nigeria (50%).<sup>16,22</sup> However, a study by Keunmoe et al reported a prevalence of 57.4% among 374 CKD subjects in Cameroun, while Punekar et al reported a prevalence of 70% among 75 CKD patients in a hospital based study in India, which is much higher than what was observed in this study.<sup>31,13</sup> The wide variation in prevalences may be because of differences in sample sizes used in the various studies, clinical characteristics of the study subjects including differences in the severity/stage of CKD and the type of thyroid assay done.

Just as has been reported by several other researchers, several patterns of thyroid functional abnormalities were evident in this study which shows that multifactorial mechanisms are involved in the pathogenesis of thyroid dysfunction in CKD. The main patterns were sick euthyroid syndrome, subclinical hypothyroidism, subclinical hyperthyroidism and overt hyperthyroidism.

The commonest abnormality was the sick euthyroid syndrome (23%) with low T3 representing the commonest form followed by low T4 syndrome. Aarathy et al also reported sick euthyroid syndrome as a more frequent form of thyroid dysfunction with a prevalence of 48% in a prospective study in India.<sup>34</sup> Pan and colleagues in a recent study of 905 non dialysis CKD subjects in China reported sick euthyroid syndrome as the commonest pattern of thyroid abnormality especially in stage 5 disease.<sup>37</sup> This buttresses the fact that sick

euthyroid syndrome, especially low T3 correlates with severity of illness.

Subclinical hypothyroidism is an equally prevalent form of thyroid dysfunction as reported in CKD subjects in several studies. It has equally been reported as the most prevalent form of thyroid dysfunction in CKD patients in some studies.<sup>36</sup> The prevalence of subclinical hypothyroidism of 14% in this study was higher than that in the general population (4-10%).<sup>26</sup> It was also slightly higher than what was observed in a study in Benin that gave a prevalence of 10%.<sup>22</sup> It has been linked to progression of CKD and mortality in CKD patients especially those on chronic maintenance dialysis by virtue of its role in atherosclerosis, dyslipidaemia, inflammation and coagulability.<sup>36</sup> It shares the same risk factors as overt hypothyroidism and is more prevalent in elderly females especially in the presence of thyroid autoantibodies.<sup>38</sup>

Subclinical hypothyroidism carries the risk of progression to overt hypothyroidism, however this has not been extensively studied in CKD patients. It is estimated that 2-5% of patients with subclinical hypothyroidism progress to overt hypothyroidism each year.<sup>35</sup> This rate of progression is faster in those with thyroid autoantibodies as well as those with higher baseline TSH levels.<sup>35</sup> Kim et al in a study in Seoul Korea, reported that half of the CKD patients with subclinical hypothyroidism spontaneously reverted back to a euthyroid state.<sup>35</sup> However, patients with sustained subclinical hypothyroidism showed progression in renal decline which was more marked in stage 3 CKD than stage 4 and patients with mild proteinuria compared to more severe proteinuria. In that study, higher baseline TSH level was associated with higher risk of unresolved subclinical hypothyroidism, progression to hypothyroidism and rapid renal decline. Treatment of subclinical hypothyroidism with levothyroxine has been associated with preservation of renal function as well as prevention of progression to ESRD in CKD patients.<sup>15</sup> There are however no guidelines currently as regards treatment in CKD patients.<sup>35</sup>

Hyperthyroidism is a rarely reported finding in patients with CKD. In the present study, hyperthyroidism was found in 7% of the CKD participants (subclinical 4% and overt 3%) compared to none of the controls. Several studies have indicated that the prevalence of hyperthyroidism in CKD is comparable to that of the general population.<sup>9</sup> However it will be difficult to say if this is true or not in this study because the overall prevalence of hyperthyroidism in Port Harcourt is not known currently. However when compared to the control group in this study, the prevalence will be considered as significantly high.

The prevalence of hyperthyroidism in this study is much higher than what was reported in a recent study among dialysis naive CKD patients in Cameroun (1.6%) and

lower than the finding by Kaggia in Kenya (12.4%).<sup>16,31</sup> The mechanisms of hyperthyroidism in CKD are not well understood. However, retention of inorganic iodine due to renal impairment may cause hyperthyroidism by the Jod-Basedow effect.<sup>12</sup> There has also been reports of graves disease developing in ESRD.<sup>39</sup> This suggests that autoimmunity likely plays a role in the pathogenesis of hyperthyroidism in CKD. Also the observation that majority of the subjects with hyperthyroidism in the present study were females (77%) supports the possible role of autoimmunity and may explain the high rate of hyperthyroidism. This may also explain the higher prevalence in the study in Kenya which included subjects with diabetes which has an association with autoimmunity.

The relationship between thyroid dysfunction and severity of chronic kidney disease is not clear as findings from previous studies show inconsistent results. Few studies have reported that there was no relationship between thyroid dysfunction and severity of CKD.<sup>22</sup> Although the difference is not statistically significant ( $p=0.1962$ ) this study shows that the occurrence of thyroid dysfunction increased with increasing severity of CKD. The progressive increase in the percentage of subjects with thyroid dysfunction from stage 1 to 5 CKD in this study shows that thyroid dysfunction is more likely to occur with more severe kidney disease. This corresponds to what has been reported by most similar studies. Punekar et al in a study of 75 conservatively treated CKD patients reported a progressive increase in frequency of overt hypothyroidism from 6.66% in stage 3 to 47.06% in stage 5 CKD.<sup>13</sup> Rhee also reported that for every 10 mL/min/1.73 m<sup>2</sup> decrease in eGFR, there was an 18% higher risk of hypothyroidism and that a 10 mL/min/1.73 m<sup>2</sup> decrease in eGFR was associated with a 0.11 mIU/L higher serum TSH.<sup>24</sup> Maimoona, Swaminathan and Xin et al in their respective studies found that the frequency of low T3 syndrome increased with declining eGFR.<sup>14,23,25</sup> Similarly, Allawi in a study of 50 CKD patients found that levels of T3 and T4 reduced with increasing severity of CKD but TSH remained normal.<sup>21</sup> These findings can be explained by a lot of factors such as more severe malnutrition, inflammation, acidosis, and protein loss that are more likely to affect thyroid function in more severe illness.

The negative correlation between TSH and eGFR observed in the present study is consistent with the findings in previous studies. Zhang et al found a significant negative correlation between TSH and eGFR among diabetics with CKD on conservative management.<sup>40</sup> Punekar et al in a study of 75 CKD patients also found a significant negative correlation between eGFR and TSH ( $p<0.002$ ) and between eGFR and T3 level ( $p<0.001$ ) but not with T4 level.<sup>13</sup> Increased TSH levels is a diagnostic marker for subclinical hypothyroidism and TSH levels are negatively correlated with eGFR in patients with subclinical hypothyroidism.<sup>35</sup> Elevation of TSH in response to low thyroid hormone

levels is expected to normalize the thyroid hormone levels. If this does not occur, especially in cases of very severe illness, TSH elevation is sustained and overt hypothyroidism can occur. Sustained TSH elevation has been associated with rapid progression of CKD.<sup>35</sup>

This study has some limitations. This study did not assess for thyroid autoantibodies as well as morphological changes in the thyroid gland in CKD participants using ultrasound scan. Also, some of the medications used in managing patients with CKD such as frusemide can affect the thyroid function test result. Attempts were however made to reduce the effect on the results by asking participants to avoid taking frusemide before sample collection. Also, fluid retention in the study participants may affect the anthropometric measurements. Fluid retention was however adjusted for when weights were being measured.

## CONCLUSION

Thyroid dysfunction is highly prevalent (45%) in dialysis naive CKD patients at the University of Port Harcourt Teaching Hospital Port Harcourt, Rivers State. The most frequent pattern of thyroid dysfunction is sick euthyroid syndrome (23%) followed by subclinical hypothyroidism (14%). The prevalence of thyroid dysfunction increases with increasing severity of CKD.

## Recommendations

More research needs to be done in this area to especially studies to assess the impact of treatment of thyroid dysfunction in CKD patients in our setting. A guideline should be developed on screening and management of these patients in our clinical setting.

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