

**THYROID HORMONE PROFILES IN PATIENTS
WITH CHRONIC KIDNEY DISEASE AT KENYATTA
NATIONAL HOSPITAL**

**A dissertation submitted to the University of Nairobi in part fulfilment of the requirements for the
degree of Master of Medicine in Human Pathology.**

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DECLARATION

I, Sarah Kaggia, declare that this dissertation for Master of Medicine in Human Pathology is my original work and has not, to the best of my knowledge, been presented by any other individual at any other institution of higher learning.

This proposal represents an original study; and has not been presented to any other institution for review and approval.

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DEDICATION

This work is dedicated to all who believe in me.

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LIST OF ABBREVIATIONS

CKD	Chronic Kidney Disease
CVD	Cardiovascular Disease
CRP	C - Reactive Protein
DM	Diabetes Mellitus
eGFR	estimated Glomerular Filtration Rate
ELISA	Enzyme Linked Immunosorbent Assay
ERC	Ethical Research Committee
ESRD	End Stage Renal Disease
fT3	free Triiodothyronine
GFR	Glomerular filtration rate
IL	Interleukin
IQC	Internal Quality Control
IQR	Interquartile range
KDOQI	Kidney Disease Outcome Quality Initiative
KNH	Kenyatta National Hospital
MDRD	Modification of Diet in Renal Disease
NKF	National Kidney Foundation
NTI	Non-thyroidal Illness
PI	Principle Investigator
PTRH	Pituitary Resistance to Thyroid Hormones
rT3	Reverse Triiodothyronine

SES	Sick Euthyroid Syndrome
SOP	Standard Operating Procedures
T3	Triiodothyronine
T4	Thyroxine
TBG	Thyroxine binding globulin
TH	Thyroid hormone
TNF- α	Tumour Necrosis Factor Alpha
TRH	Thyrotropin Releasing Hormone
TSH	Thyroid Stimulating Hormone
TTR	Transthyretin
UoN	University of Nairobi
VCAM-1	Vascular Adhesion Molecule

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ABSTRACT

Background: Chronic Kidney Disease (CKD) is a disease spectrum characterized by progressive loss of renal function over a period of time. It has reached epidemic proportion in many countries with an incidence of approximately 11% among the adult population in the United States of America. There is no local data on CKD prevalence, however regionally a study done in Nigeria reports a prevalence of 12.4%. Early identification and management of CKD has been shown to reduce the adverse outcomes which include kidney failure and cardiovascular disease. Thyroid dysfunction including hypothyroidism, hyperthyroidism and non-thyroidal illness has been reported in CKD patients. Non thyroidal illness or low T3 syndrome has been shown to worsen CKD by increasing cardiovascular morbidity and mortality and has been reported as an independent predictor of the cardiovascular mortality in these CKD patients. There is need to determine the thyroid hormone profiles in these CKD patients and thus prevent the adverse outcomes.

Objective: The study determined the thyroid hormone profiles in patients with chronic kidney disease at Kenyatta National Hospital.

Study design: Descriptive cross-sectional study

Study area: The study was conducted at the Renal Clinic at Kenyatta National Hospital, a tertiary and referral hospital in Nairobi, Kenya.

Study population: Patients with chronic kidney disease who attended the renal clinic.

Methods: A total of 137 study participants with CKD were recruited. Demographic and medical data were obtained from the participants using a questionnaire designed for this study. Estimation of glomerular filtration rate was done using the 4 variable Modification of Diet in Renal Disease (MDRD) formula with subsequent staging of chronic kidney disease. Thyroid Stimulating Hormone (TSH), Total Thyroxine (T4), Total Triiodothyronine (T3), Free triiodothyronine (f T3), and Free Thyroxine (fT4) were estimated using enzyme immunoassay on these patients with CKD.

Data management: The data obtained included demographics, CKD stage and hormone levels. These were entered and analyzed using Epidata program version 3.1.

Results: A total of 137 participants were recruited into the study. Eighty three (60.6%) of these were males and 54 (39.4%) were females. Majority of the participants 56 (40.9%) were in stage 4 of CKD and only 2 (1.5%) were in stage 2. Forty one (29.9%) and 38 (27.7%) were in CKD stage 3 and stage 5 respectively. There were no participants in CKD stage 0 and 1 recruited. Diabetes mellitus and hypertension were the main primary disease processes leading to CKD. Majority of the participants (58%) were euthyroid, while 42% had abnormal thyroid results; of these, 13.9% had non-thyroidal illness and 15.3% and 12.4% had hypothyroidism and hyperthyroidism respectively. The difference in mean duration of CKD amongst the thyroid hormone categories was not statistically significant ($p=0.345$). The proportion of patients with non-thyroidal illness increased with increasing severity of CKD. This was statistically significant ($P = 0.0004$).

Conclusion: In this study, abnormalities in the thyroid profile were found in 42% of the participants. The most common thyroid derangement was isolated low T3 values. Non-thyroidal illness was shown to increase with increased severity of CKD. As the CKD patients in KNH have deranged thyroid profiles, regular thyroid hormone assays should be incorporated in their follow up. Prevalence of hyperthyroidism is higher in this study than reported in other literature.

Recommendations: There is need to assay thyroid hormone profiles in patients with CKD stage 3 and above. Studies on thyroid hormone profile on lower CKD stages should also be done. There is need for further studies to evaluate the relationship between hyperthyroidism and CKD in Kenya.

INTRODUCTION

Maintenance of a balance or homeostasis of metabolic functions in all body organs is critical in the human body. This balance is achieved by actions of hormones or key regulatory organs. Thyroid hormones have effects on cellular growth and differentiation and also modulate important physiological functions in virtually every human tissue (1). On the other hand, the kidney is involved in metabolic waste excretion, maintenance of fluid and acid base balance by regulating the concentration of hydrogen, sodium, potassium, phosphate and other ions in the extracellular fluid, secretion and metabolism of hormones which are involved in haemodynamic control, red blood cell production and mineral metabolism.

Chronic kidney disease (CKD) encompasses a spectrum of different pathophysiologic processes associated with abnormal kidney function and a progressive decline in glomerular filtration rate (GFR). It is a global public health problem associated with premature mortality, decreased quality of life and a high cost of healthcare (2). A trend towards an increase in its incidence and prevalence has been reported worldwide (3, 4), with epidemic proportions in some countries (5). The adverse outcomes of CKD such as kidney failure, cardiovascular disease and premature death can be prevented or delayed. Early stages of CKD can be detected through laboratory testing and if treatment is effectively administered would slow down progression towards kidney failure and cardiovascular disease. Improving outcomes for people with CKD would require a co-ordinated world-wide approach to prevention of adverse outcomes through defining the disease and its outcomes, estimating disease prevalence, identifying earlier stages of disease and antecedent risk factors, and detection and treatment for populations at increased risk for outcomes.

Thyroid hormones are important in cellular growth and differentiation, and modulation of physiological functions in all human tissues including the kidney. They also play a role in maintenance of water and electrolyte homeostasis. Therefore, thyroid dysfunction, either hypothyroidism or hyperthyroidism is accompanied by alterations in the metabolism of water and electrolytes, as well as cardiovascular function(6). On the other hand, the kidney is an important target organ for thyroid hormone actions and for the metabolism and elimination of the thyroid hormones. Derangement in kidney function is associated with abnormalities in the thyroid hormone physiology. CKD affects both hypothalamus-pituitary-thyroidal axis and

thyroid hormone peripheral metabolism. The effects of impaired kidney function may lead to hypothyroidism, hyperthyroidism and non-thyroidal illness which are associated with deranged cardiovascular function which will adversely affect the prognosis of CKD.

LITERATURE REVIEW

1. Chronic Kidney disease

Chronic kidney disease (CKD) entails the presence of kidney damage or decreased level of function for 3 months or more. While no local prevalence data exist, the risk factors such as post-streptococcal glomerulonephritis, hypertension, diabetes mellitus and lately HIV-associated nephropathy (HIVAN) are on the rise. Recent studies show that early diagnosis allows for institution of therapy to either arrest or reverse progression of the global challenge that CKD has become. In 2000, the National Kidney Foundation (NKF) Kidney Disease Outcome Quality Initiative (KDOQI) Advisory Board approved development of clinical practise guidelines to define CKD and to classify stages in the progression of CKD. CKD was thus defined as the presence of kidney damage or decreased level of kidney function for three months or more, irrespective of diagnosis. The stages of CKD are defined according to the estimated GFR (KDOQI).

Table 1: CLASSIFICATION OF CHRONIC KIDNEY DISEASE (7)

Stage	Description	GFR mL/min/1.73m ²	Prevalence (%)
0	At increased Risk	≥90 ^a	-
1	Kidney damage with normal or increased GFR	≥90 ^b	3.3
2	Kidney damage with mild reduction of GFR	60-89	3
3	Kidney damage with moderate reduction in GFR	30-59	4.3
4	Severe reduction in GFR	15-29	0.2
5	Kidney failure	<15 or dialysis	0.1

^a Patients with CKD risk factors which include hypertension, diabetes mellitus, autoimmune diseases, presence of proteinuria, abnormal urinary sediment, or structural abnormalities of the urinary tract.

^b Patients with demonstrated kidney damage (e.g. persistent proteinuria, abnormal blood and urine chemistry or abnormal imaging studies).

Glomerular diseases such as post-streptococcal glomerulonephritis contribute to a large proportion of early CKD. Chronic pyelonephritis and tuberculosis are notable infectious risk

factors of which HIV-associated nephropathy is routinely encountered. Congenital anomalies e.g. polycystic kidney disease and obstructive processes such as calculi are also culpable causative factors. Collagen disease e.g. SLE and vascular diseases such as renal nephrosclerosis may also lead to CKD. Nephrotoxic agents e.g. aminoglycoside therapy are occasionally implicated. Chronic kidney disease may be a progression from acute renal failure.

The level of glomerular filtration rate (GFR) is widely accepted as the best overall measure of kidney function in health and disease. Providers and patients are familiar with the concept that “the kidney is like a filter.” GFR is the best measure of the kidneys’ ability to filter blood. The ‘gold standard’ of measuring GFR is by the renal clearance of exogenous markers Inulin, radio-labelled EDTA ($^{51}\text{Cr-EDTA}$) and technecium-labelled diethylene-triamine-pentacetate ($^{99\text{m}}\text{Tc-DTPA}$) and iohexol. These tests are however time-consuming, labour-intensive, invasive, costly and require specialized equipment restricting their use in routine individual cases monitoring or in large epidemiological studies. While an ideal endogenous marker should meet 3 criteria of complete filtration at the glomerulus, absent tubular secretion and no tubular reabsorption, serum creatinine is widely accepted as an endogenous marker for assessing renal function. Currently, a spot serum creatinine level is favoured with creatinine-based equations for estimating GFR being employed. They include; the Cockcroft-Gault (CG), the 4-variable Modifications of Diet in Renal Disease (4v-MDRD) and the Mayo Clinic Quadratic formulae (8). These equations are used interchangeably to suit various study populations.

Most chronic kidney diseases tend to progress and worsen over time. The risk of adverse outcomes in CKD can be further stratified by the severity of disease and rate of progression. Therefore, for most patients, the risk of adverse outcomes tends to increase over time. The outcomes of CKD include loss of kidney function leading to kidney failure and development of cardiovascular disease.

The evaluation and management of CKD as recommended by the work group includes: treatment of co-morbid conditions, prevention or slowing the loss of kidney function, prevention and treatment of cardiovascular disease, prevention and treatment of complications of decreased kidney function, preparation for kidney failure, and replacement of kidney function by dialysis and kidney transplantation.

2. Thyroid hormone synthesis, transport, metabolism and action

The thyroid gland produces two related hormones, thyroxine (T4) and Triiodothyronine (T3). Acting through nuclear receptors, these hormones play a critical role in cell differentiation during development and help maintain thermogenic and metabolic homeostasis in the adult. Thyroid stimulating hormone (TSH), secreted by the anterior pituitary plays a pivotal role in control of the thyroid axis (9). Thyroid hormones are derived from thyroglobulin, a large iodinated glycoprotein, which is iodinated on tyrosine residues. T4 is secreted from the thyroid gland in about twenty-fold excess over T3. Both hormones are bound to plasma proteins, including thyroxine-binding globulin (TBG); transthyretin (TTR, formerly known as thyroxine-binding prealbumin, or TBPA); and albumin. The plasma-binding proteins increase the pool of circulating hormone, delay clearance, and may modulate hormone delivery to selected tissue sites. When the effects of various binding proteins are combined, approximately 99.98% of T4 and 99.7% of T3 are protein bound. T4 is converted to T3 by the deiodinase enzymes (9). T4 to T3 conversion is impaired by fasting, systemic illness and a variety of medications including propyl thiouracil, propranolol, amiodarone, glucocorticoids. Type III deiodinase inactivates T4 and T3 and is the most important source of reverse T3 (rT3) (10).

3. Thyroid hormone and renal physiology

Thyroid hormones (TH) are necessary for growth and development of the kidney and for the maintenance of water and electrolyte homeostasis (11, 12). On the other hand, the kidney is involved in the metabolism and elimination of TH and is an important target organ for TH actions(11) (13). From a clinical practice viewpoint, both hypothyroidism and hyperthyroidism are accompanied by remarkable alterations in the metabolism of water and electrolytes, as well as in cardiovascular function. Moreover, the decline in kidney function is accompanied by changes in the synthesis, secretion, metabolism and elimination of TH. The major pathway of thyroid hormone metabolism is by deiodination and only 25% is conjugated(3), deaminated or decarboxylated. Although the liver is the major site of metabolism, the kidney also participates to a lesser extent by deamination and decarboxylation. Renal conversion of T4 to T3 and reverse T3 (rT3) also occurs (14). The kidney also is the most important route of inorganic iodine excretion and in renal failure the

plasma levels of inorganic iodine are elevated(14). Thyroid dysfunction acquires special characteristics in those patients with advanced kidney disease (15). On the other hand, the different treatments used in the management of patients with kidney and thyroid diseases may be accompanied by changes or adverse events that affect thyroid and kidney function respectively.

The decrease in the activity of TH is accompanied by an inability to excrete an oral water overload, this effect is due to reduction in the GFR (16). TH also have a role in tubular transport of sodium, via their actions on the sodium-potassium ATP pump (Na/K ATPase) and on the potassium permeability in the membrane of proximal tubules (17, 18). TH stimulate rennin release by the juxtaglomerular cells through a mechanism independent of the ouabain-sensitive sodium pump and protein synthesis and influence kidney angiotensinase activity (19). T3 is also involved in sulfate homeostasis through the regulation of kidney sodium-sulfate cotransport (20).

4. Effects of thyroid dysfunction on CKD

Both hypothyroidism and hyperthyroidism affect kidney function in different ways. Hypothyroidism is associated with decreased GFR and renal plasma flow resulting in increased serum creatinine, decreased sodium reabsorption, hyponatremia and decreased renal ability to dilute urine (21, 22). The reduction in GFR and renal plasma flow in primary hypothyroidism normalize after administration of levothyroxine (22). Similarly, normalization of circulating TH concentrations with replacement therapy in hypothyroid patients with CKD can significantly improve (23). Hyperthyroidism on the other hand, is associated with increased renal plasma flow, GFR and tubular reabsorption leading to decreased serum creatinine levels. These changes also normalize after treatment of the thyroid dysfunction(24). Hemodynamic changes associated with hyperthyroidism also play a role in the alteration of renal function. These changes are due to the increased circulating demands as a result of hypermetabolism and the need to dissipate excess heat associated with hyperthyroidism (11, 24).

5. Effects of chronic kidney disease on thyroid hormone function

Chronic kidney disease is characterized by multiple abnormalities in the thyroid hormone physiology. These include the state of chronic illness, malnutrition and negative nitrogen balance, the presence of circulating inhibitors of hormone metabolism and a multitude of hormone alterations (25). CKD affects both hypothalamus-pituitary-thyroidal axis and TH peripheral metabolism. Uraemia influences the function and size of the thyroid (15, 26). Uraemic patients have an increased thyroid volume compared with subjects with normal renal function and a higher prevalence of goitre, mainly in women (15, 26, 27). Also, thyroid nodules and thyroid carcinoma are more common in uraemic patients than in the general population (28).

5.1 Thyroxine

Total T4 levels are frequently reduced or normal in CKD, and this seems to be related to impaired hormone binding to serum carrier proteins (15). The concentrations of major carrier proteins are usually normal, and it has been suggested that serum accumulations of many Uraemic toxins that inhibit T4 binding to carrier proteins could explain low total T4 levels (29). The reduction in serum protein binding of T4 is expected to affect total but not free, hormone levels. However, the available tests tend to result in misleadingly low estimates of free T4 (30). Because free T4 measurement often employs equilibrium dialysis, dialyzable circulating inhibitors of T4 binding to carrier proteins are removed. This increases T4 binding to carrier proteins in vitro, resulting in reduced free T4 levels (31). Although free and total T4 concentrations may be normal or reduced, sometimes free T4 may be high due to the effect of heparin used in anticoagulation during haemodialysis, which inhibits T4 binding to its binding proteins (32).

5.2 Triiodothyronine (T3)

Total and free T3 serum levels are also low in CKD. The reduction in T3 levels (low T3 syndrome) is the most frequently observed thyroid alteration in these patients (15, 33, 34). This reduction in T3 concentrations has been linked to a decrease in the peripheral synthesis of T3 from T4. Chronic metabolic acidosis associated with the CKD may contribute in this effect (35). Similar to T4, reduced total T3 levels could be explained by impaired binding to serum carrier protein due to accumulation of Uraemic toxins (36). Low serum free t3 levels in

uraemia have been interpreted as an appropriate response aimed at reducing energy expenditure and minimizing protein catabolism (37). Conversely, it has been suggested that it might also be an indicator of maladaptation contributing to worsening of the disease (38, 39). Several clinical studies have shown that reduced T3 levels are strongly correlated to systemic inflammatory markers and are an independent predictor of mortality in patients undergoing dialysis (40, 41).

5.3 Thyroid stimulating hormone (TSH)

Serum TSH concentrations are usually normal or elevated in CKD, but its response to its releasing hormone (TRH) is generally low (30, 42). These findings suggest the presence of intrathyroidal and pituitary disturbances associated with uraemia (43). Also, both TSH circadian rhythm and TSH glycosylation are altered in CKD. The latter may compromise TSH bioactivity. Both normal nuclear T3 levels and thyroid hormone receptor action in pituitary cells could explain normal serum TSH concentration. In Uraemic rats, nuclear T3 content was shown to be normal in the pituitary despite reduced T3 serum concentration (44). In fact, the abnormal pattern of TSH glycosylation, altered diurnal rhythm and pulsatile secretion, and blunted TSH response to exogenous thyrotropin-releasing hormone observed in Uraemic organisms point to a disordered function at the hypothalamic-pituitary level (45). Interestingly, in Uraemic patients with primary hypothyroidism, TSH levels increase appropriately (33).

6. Hypothyroidism in Chronic kidney disease

CKD is associated with a higher prevalence of primary hypothyroidism, both overt and subclinical, but not with hyperthyroidism (15, 30, 34, 46). In a study done locally on patients with chronic renal failure on conservative management and haemodialysis, hypothyroidism was found to be the pattern of thyroid derangement(47). In fact, the prevalence of primary hypothyroidism, mainly in the subclinical form increases as the GFR decreases (34). In patients with stage 1 and stage 3 disease, the prevalence of subclinical hypothyroidism has been found to be 7% and 17.9% respectively (48). Michel Chonchol et al also reported subclinical primary hypothyroidism to be relatively common at a prevalence of approximately 18% among patients with CKD not requiring dialysis. The increased frequency of high titres of anti-thyroid antibodies is associated with a higher prevalence of hypothyroidism in women (30). A greater prevalence of non-auto-immune primary

hypothyroidism has been reported in patients with advanced diabetic nephropathy under conservative treatment in comparison with non-diabetic patients with nephropathy. It is possible that these patients had impaired renal handling of iodine resulting in an elevation of serum iodine levels (49). The kidney contributes to the iodine clearance through glomerular filtration. In CKD, serum iodine concentrations are high but are not correlated with the degree of kidney failure (50). The increased prevalence of goitre and hypothyroidism reported in CKD, have been linked to this iodine excess (30, 51). A high exposure to iodine facilitates the development of hypothyroidism in CKD patients (51).

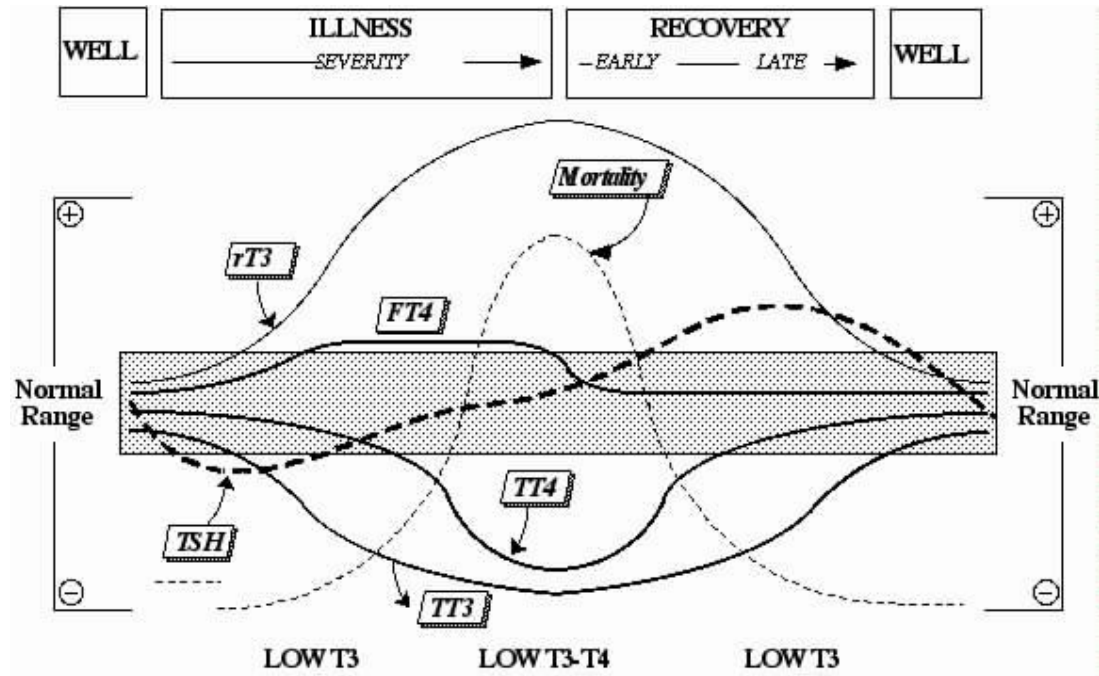
7. Hyperthyroidism in chronic kidney disease

In areas with inadequate iodine intake, the prevalence of hyperthyroidism in CKD was found to be similar to that in the general population at approximately 1% (50). Hyperthyroidism has also been reported in different forms of glomerular disease (52). Unfortunately, not many studies on hyperthyroidism in CKD have been done.

8. Non-thyroidal illness in CKD

Non-thyroidal illness is the biochemical alteration in thyroid hormones in the absence of an underlying intrinsic thyroid disorder; it is also known as sick euthyroid syndrome (SES). The most common hormone pattern in SES is a decrease in total and free T₃, an increase in reverse T₃ with normal levels of TSH and T₄. The magnitude of the fall in T₃ correlates with the severity of the illness.

Figure 1: The changes in thyroid function test in relation both to the severity and stages of illness.



The National Academy of Clinical Biochemistry – Laboratory medicine practice guidelines 2002 (53).

Non-thyroidal illness is thought to arise from maladjusted central inhibition of hypothalamic releasing hormones, including TRH (54). The proposed mechanisms include cytokines particularly IL-1, IL-6, Tumour Necrosis Factor alpha (TNF- α) which inhibit the expression of 5' deiodinase, the enzyme responsible for T4 to T3 conversion in peripheral tissues. (55). The cytokines also affect the hypothalamus, the pituitary and other tissues inhibiting production of TSH, TRH, thyroglobulin, T3 and thyroid binding globulins (54). The reduction in T3 levels is the most frequent observed thyroid alteration in CKD patients and has been linked to a decrease in the peripheral synthesis of T3 from T4 and also metabolic acidosis associated with CKD (33, 34). CKD is however characterized by the absence of a rise in reverse T3, which is a typical feature in other patients with non-thyroidal illness. Despite the fact that rT3 clearance in CKD patients is diminished, there is a redistribution of rT3 from the vascular space to the extravascular space and an increase in rT3 cellular uptake (56, 57).

9. The effect of chronic kidney disease and the thyroid function on morbidity and mortality

The reduction in thyroid hormone levels and especially T3 has been interpreted as an adaptive response aimed at sparing calories and protein, this may not have a detrimental effect in the short term but may cause high risk situation in the long term (58). In patients with CKD, a relationship between plasma levels of T3 and various inflammatory markers, nutrition, and endothelial activation has been reported(55). The inflammatory markers include elevated levels of high sensitivity C-reactive protein, interleukin (IL) 6 and vascular adhesion molecule-1 (VCAM-1). The lower the concentration of T3, the greater is the degree of inflammation with poor nutritional status and cardiac function. Thus, low T3 is associated with reduced survival rate. The relationship between survival and T4 is less defined.

Carrero J. J. et al (55) found that low T3 levels are independent predictors of cardiovascular mortality in CKD patients and also confirmed the association between low thyroid hormones, inflammation and increased mortality in the CKD population(41, 55). T3 and fT3 behave as survival markers in patients with CKD both on haemodialysis and peritoneal dialysis (41). Some authors have thus recommended measuring T3 levels to assess the relationship between thyroid dysfunction and risk of mortality in this population. However, the use of thyroid hormone therapy in non-thyroidal illnesses is still controversial (59). Studies have shown that Cardiovascular disease (CVD) occurs at higher rate in patients with elevated serum creatinine levels (60), it has been suggested that earlier identification and treatment of CVD in patients with CKD may reduce severity of disease, thereby improving the outcomes of those who reach ESRD treatment. According to the United States Renal Data System 2002 Annual Data Report, the high rates of CVD are associated with cardiovascular death, which contributes to 20% to 23% annual prevalent mortality of the dialysis population (61).

10. Effects of thyroid dysfunction on cardiovascular system

The clinical presentation seen in patients with overt hyperthyroidism and hypothyroidism is due to the increased or reduced action of thyroid hormone on the heart and the cardiovascular system respectively. Hyperthyroidism induces a hyperdynamic cardiovascular state and is associated with atrial arrhythmias, increased left ventricular mass and increased cardiovascular mortality (62). The cardiovascular effects of thyroid hormone deficiency are opposite to those

caused by thyroid hormone excess. There is an increase in peripheral resistance and an increase in arterial stiffness, and impaired left ventricular diastolic function (63). Hypothyroidism also leads to elevated low density lipoprotein levels and thus increased risk of atherosclerotic coronary arterial disease and myocardial infarction (62)

RATIONALE

Chronic kidney disease is a major public health problem and its prevalence has reached epidemic proportions in some countries. It is an important cause of morbidity and mortality. Impaired kidney function can affect thyroid hormone metabolism and hypothyroidism, non-thyroidal illness as well as hyperthyroidism have been reported in CKD patients. Thyroid dysfunction may worsen the morbidity in CKD patients and increase cardiovascular mortality. Low T3 has been found to be an independent predictor of cardiovascular mortality in CKD patients (55).

A local study done 20 years ago in CKD patients on haemodialysis and conservative management showed biochemical features of hypothyroidism. This study sought to describe the nature and magnitude of thyroid hormone derangements in CKD patients, given the global increase in CKD prevalence. The information can provide evidence on the value of including thyroid hormone estimations in CKD patients.

RESEARCH QUESTION

Are there thyroid hormone profile derangements in patients with chronic kidney disease at Kenyatta National Hospital?

STUDY OBJECTIVES

Broad objective

To describe thyroid hormone profiles in patients with CKD at KNH.

Specific objectives

1. To estimate plasma creatinine in CKD patients at KNH.
2. To estimate eGFR using 4-variable MDRD formula.
3. To determine the levels of TSH, T3, fT3, T4, fT4 in CKD patients.
4. To describe the types of thyroidal dysfunctions in CKD patients.

Secondary objective

1. Determine the correlation between T3 and different stages of CKD.

METHODOLOGY

Study Design

This was a descriptive Cross-sectional Study

Study Site

The study took place at Kenyatta National Hospital's renal clinic. The renal clinic is conducted every Friday from 8 a.m. with an average attendance of 40 patients of all age groups.

Study Population

Patients aged 18 years and above with renal disease for a period of three months or more attending the renal clinic at KNH were recruited into the study.

Inclusion Criteria

1. Patients with CKD
2. Patients aged 18years and above
3. Informed consent

Exclusion Criteria

1. Patients on dialysis
2. Pregnancy
3. Patients with a visible goiter
4. Decline consent

Case definition: patients aged ≥ 18 years with chronic kidney disease. CKD was defined as $eGFR \geq 90$ mL/min/1.73m² with abnormal urine and blood chemistry, persistent proteinuria or abnormal imaging studies of the kidney OR $eGFR \leq 90$ mL/min/1.73m². The eGFR was done using the 4v-MDRD formula which is one of the recommended methods and has fewer parameters as depicted below (64) (www.renal.org/eGFR).

Estimation of GFR using the 4-variable MDRD formula.

$$eGFR = 186.3 \times (sCreatinine)^{-1.154} \times age^{0.203}$$

(Creatinine in $\mu\text{mol/l}$, Age in years, Females x 0.742, blacks x 1.21)

Table 2: Staging of CKD (KDQOI)

Stage	eGFR mL/min/1.73m ²
1	≥ 90
2	60-89
3	30-59
4	15-29
5	<15 or dialysis

Sample size

To calculate the sample size, the Kish and Leslie formula of 1965 for cross sectional studies was used.

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

n = Sample size is **137** where:-

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

P Prevalence of Hypothyroidism 9.5 % (P=0.095), Chonchol et al (48).

d Margin of error at 5%

Sample size (n) = 137 CKD patients

Recruitment

Recruitment of study participants was done at the renal clinic by the principal investigator and a trained research assistant. A pilot study had been done prior to the commencement of the main study. The research assistant, a clinical officer by training, was involved in the pilot study and was supervised during recruitment of the first 10 participants in the main study to ensure he understood all the aspects of obtaining consent and data collection.

Sampling technique

All consecutive patients who met the inclusion criteria were assessed for eligibility and recruited until the desired sample size was achieved.

Screening

Files for patients scheduled for review were perused in the morning of the clinic day to assess eligibility for recruitment into the study. Determination of serum creatinine level was done

and eGFR estimated using the 4v-MDRD formulae with subsequent CKD staging. Screening of the patients then followed using a screening questionnaire (Appendix 1).

Administration of consent form

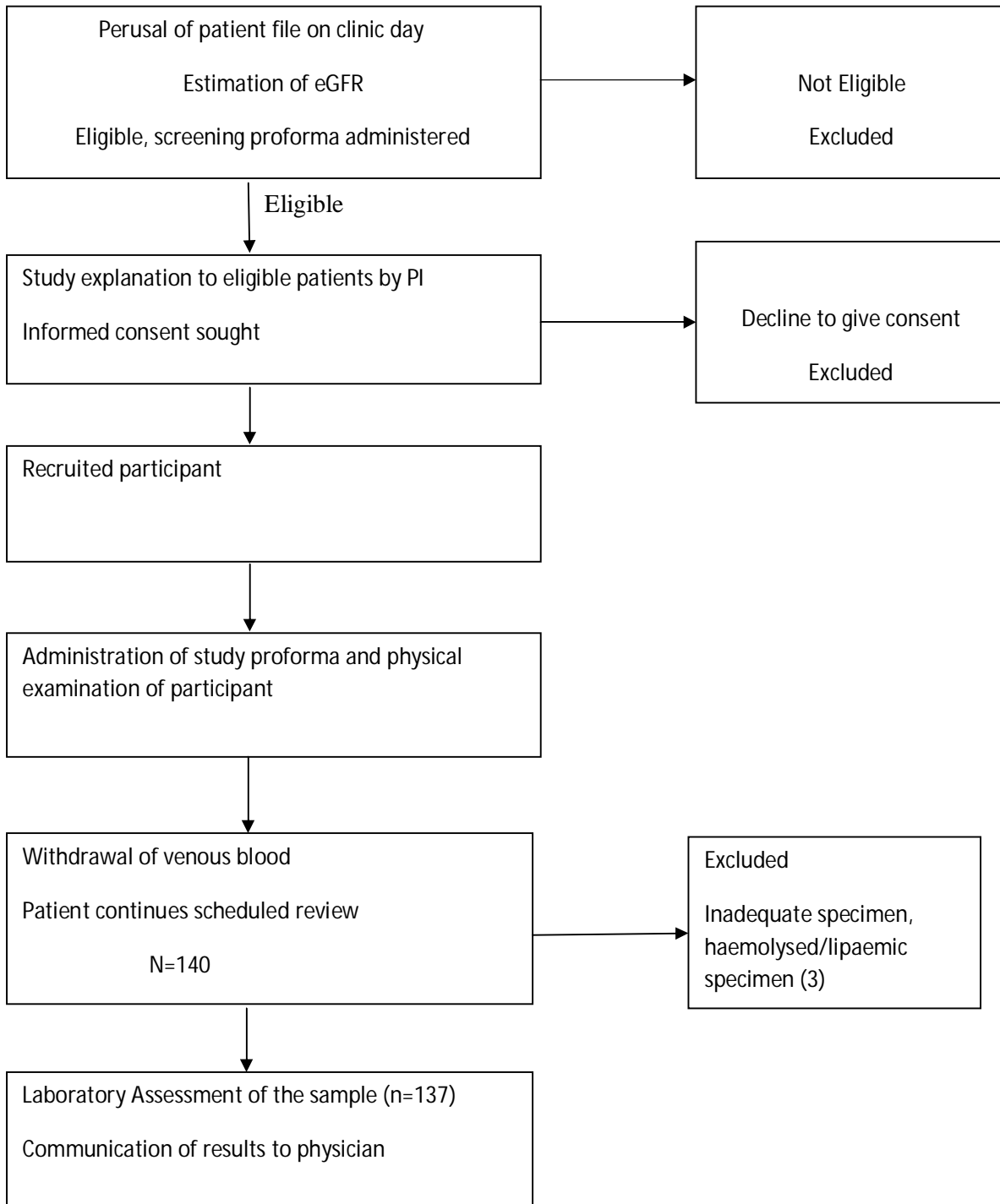
The PI then explained the purpose of the study; the benefits and risks involved (Appendix 3) and then sought informed consent (Appendix 4).

Clinical examination and specimen collection

A study questionnaire (Appendix 2) was administered according to the inclusion criteria above. History, physical examination and specimen collection was then carried out by the PI and research assistant. The files were marked with a sticker so as to avoid duplication in the recruitment process.

Figure 2: Flow chart

Fig 2: Flow chart for recruitment of study participants



Laboratory

Specimen collection

Five millilitres of blood was aseptically drawn from the participant's vein into a well labelled plain bottle during their visits at the renal clinic on Fridays. Samples were put in a cooler box and transported to the Immunology Laboratory, University of Nairobi by the PI.

Separation and Storage

Blood in the labelled plain vacutainer was left to clot and serum pipetted into well labelled cryovials for refrigeration at -20°C in the laboratory. The cryovials were labelled with study numbers for identification and analyzed in batches.

Specimen Analysis

Reagents were obtained from PISHTAZTEB DIAGNOSTICS from Korbach/Germany

Creatinine

The alkaline picrate method (modified kinetic Jaffe reaction) using an *Olympus 400/640* autoanalyzer was used.

Serum TSH

TSH ELISA test based on the principle of a sandwich enzyme-linked immunosorbent assay was used

T4, fT4, T3, fT3

Competitive enzyme immunoassay using semi-automated ELISA (Enzyme linked Immunosorbent Assay) micro-well reader was used as per appendix V (PISHTAZTEB DIAGNOSTICS from Korbach/Germany).

Quality Assurance

Measures were taken to ensure that the laboratory results were reliable. Pre-analytical quality measures included exclusion of lipaemic or haemolysed samples, samples were only thawed once at room temperature and use of stable reagents was employed. Analytical measures; analysis were done according to manufacturer's specifications, commercial control materials (IQC) were included in each batch and results were only accepted if the IQC was within acceptable limit. Post analytical measures including data interpretation were done based on

the reference ranges given by the manufacturer and three people counter-checked the results to ensure that there was no transcription error.

The analysis was done by the PI and qualified laboratory personnel using Standard Operating Procedures (SOPs) derived from the manufacturer insert.

Table 3: Classification of thyroid dysfunction

	TSH	T4	fT4	T3	fT3
Euthyroid	N	N	N	N	N
Primary hyperthyroidism	L	H	H	H	H
Secondary hyperthyroidism	H	H	H	H	H
Primary hypothyroidism	H	L	L	L	L
Secondary hypothyroidism	L	L	L	L	L
Non-thyroidal illness	N	N	N/L	L	L
Subclinical hyperthyroidism	L	N	N	N	N
Subclinical hypothyroidism	H	N	N	N	N

N - Normal, H - high, L – Low

Data management and analysis

Data was collected using a structured questionnaire. The data was entered into Epidata version 3.1 (Freeware from www.epidata.dk) and Epidata Analysis was used for data analysis. The data was cleaned for errors and inconsistent (conflicting) results, missing entries and duplicate entries to ensure high quality data. The following variables were collected as categorical data; sex, diagnosis, CKD stage and thyroid status. Categorical data was presented using percentages and frequencies. Continuous variables included age, creatinine levels, duration of CKD and thyroid hormone profile. Normally distributed variables were presented using mean and standard deviation while variables that did not have normal distribution were presented using median and interquartile range (IQR). In univariate analysis, the chi-square test was used to assess association between categorical variables while the student *t* test and Fischer's exact tests were used to assess association between continuous variables. The level of significance was set at 0.05.

Ethical considerations

The study commenced upon approval by the Kenyatta National Hospital/ University of Nairobi (UoN) Ethics and Research Committee (KNH/UoN, ERC).

Pre-consent counselling involved

- i. Information and explanation on the research nature and overall goal
- ii. Detailed explanation of the procedures involved, outlining their safety or lack of.
- iii. Assurance that participation was voluntary and one could withdraw at any point without losing other benefits from KNH.
- iv. Confidentiality and custody of patient information, specimen and results
- v. Assurance on free access to their results and their medical interpretations. Appropriate referrals for medical intervention.
- vi. The benefits and unforeseen harm of participating in the study was explained in unambiguous language as contained in the Study explanations (Appendix).

The results were communicated back to the physician to improve patient management.

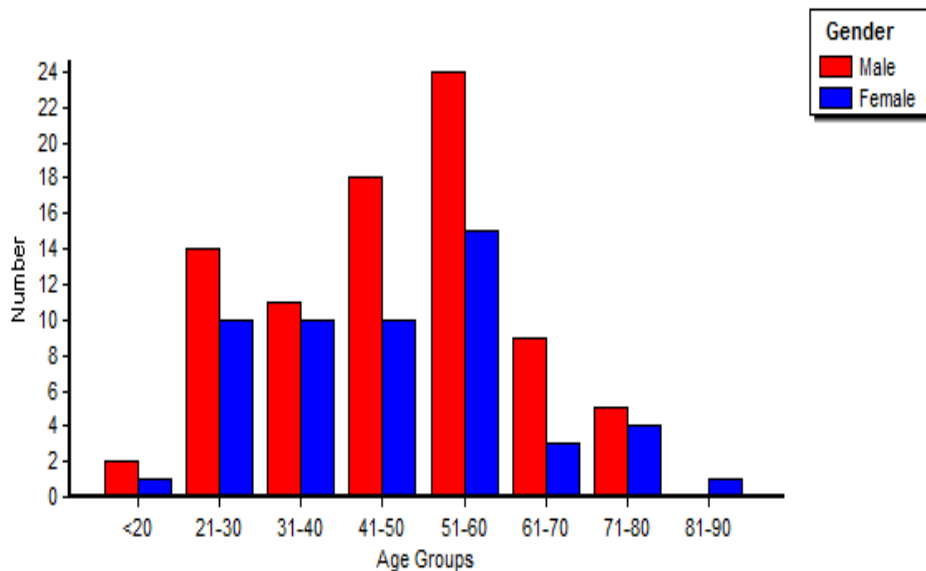
RESULTS

The study was conducted between May and September 2011. A total of 140 participants were recruited into the study. Three of them were excluded from analysis due to lipaemic and haemolysed samples. The remaining 137 met the inclusion criteria and were analyzed.

Demographic characteristics of the participants

A total of 137 participants were recruited into the study. Of these, 83 (60.6%) were males and 54 (39.4%) were females. The ages of the participants were not normally distributed and ranged from 18 to 86 years. The median age was 50 years (IQR 34.5, 59), as depicted in the histogram in figure 3.

Figure 3: Histogram of age and gender distribution of the study participants (n=137)



Summary of the results

The laboratory results for creatinine and thyroid function tests were compared between the two sexes. The differences in these test results between males and females were not statistically significant as shown in table 4.

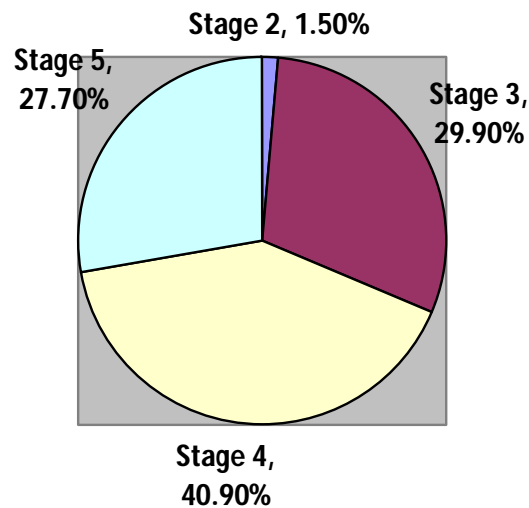
Table 4: the median age, creatinine levels and thyroid profiles in CKD patients (n=137)

	Male	Female	P value
Age (yr) - Median (Range)	50 (18-79)	48.5 (18-86)	0.937
Creatinine (mol/l) – Mean (SD)	373.88 (267.11)	342.65 (283.97)	0.515
TSH (μ IU/ml)– Mean (SD)	2.21 (2.05)	2.74 (3.69)	0.2 80
FT3 (pg/ml) – Mean (SD)	3.38 (1.8)	3.61 (1.6)	0.436
T3 (ng/ml)– Mean (SD)	0.978 (0.45)	0.998 (0.44)	0.798
FT4 (ng/dl)– Mean (SD)	1.42 (0.71)	1.51 (0.57)	0.417
T4 (μ g/dl)– Mean (SD)	7.65 (3.42)	7.43 (3.26)	0.713

Classification of participants into CKD stages using the 4-variable MDRD formula

Majority of the participants 40.9% (n=56) were classified as CKD stage 4. Only 2 participants (1.5%) were classified as stage 2, and none was in CKD stage 1. The rest of the study participants were in CKD stage 3 (29.9%) and stage 5 (27.7%), figure 4.

Figure 4: Pie chart of the CKD stages (n=137)



The disease process leading to chronic kidney disease

The primary disease processes leading to CKD were mostly a combination. For the monodiagnosis, 38 (27.7%) had hypertension, 2.9% (4) had diabetes and 1.5% had glomerulonephritis.

In co-morbidities, hypertension and diabetes accounted for 37.2% (n=51), while hypertension, glomerulonephritis, autoimmune renal disease and polycystic kidney disease were the other co-morbidities accounting for 24.8% (34). The category of others was at 7.3% and included HIV infection, obstructive uropathy, pyelonephritis and cardiomyopathies. This is shown on Table 5.

Table 5: The disease process leading to CKD

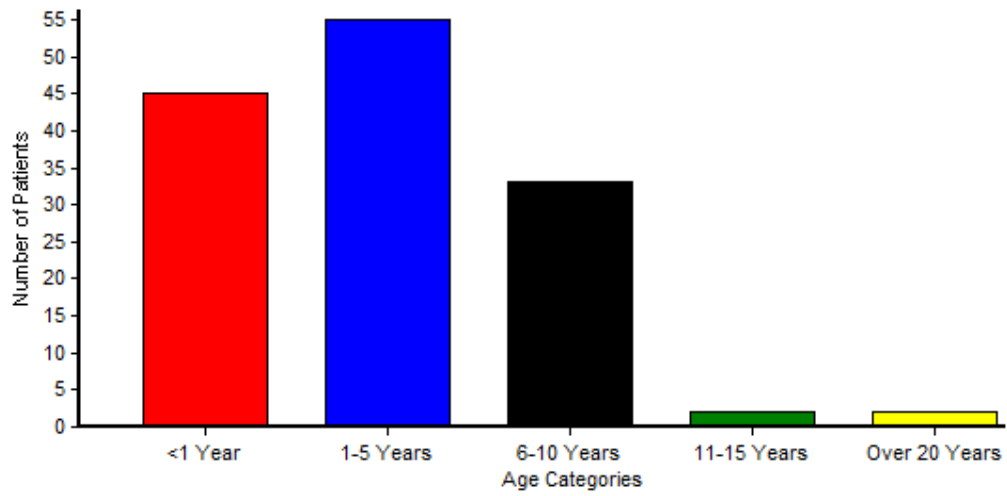
Diagnosis	Number	Percentage
Hypertension	38	27.7
Hypertension and DM	51	37.3
Hypertension and Other Diseases	34	24.8
Other Diseases	10	7.3
Diabetes	4	2.9
Total	137	100

Other diseases with hypertension included glomerulonephritis, autoimmune diseases, and polycystic kidney disease. The category of other diseases included HIV infection, obstructive uropathy, pyelonephritis and cardiomyopathies.

Duration of chronic kidney disease

The participants had been diagnosed with CKD for varying duration of time, ranging from 3 months to 28 years with a median of 30 months. This is evidenced by the fact that the category of 1-5 years had the highest number of patients. Majority of the participants had the disease for 5 years or less; this is shown in figure 5 below.

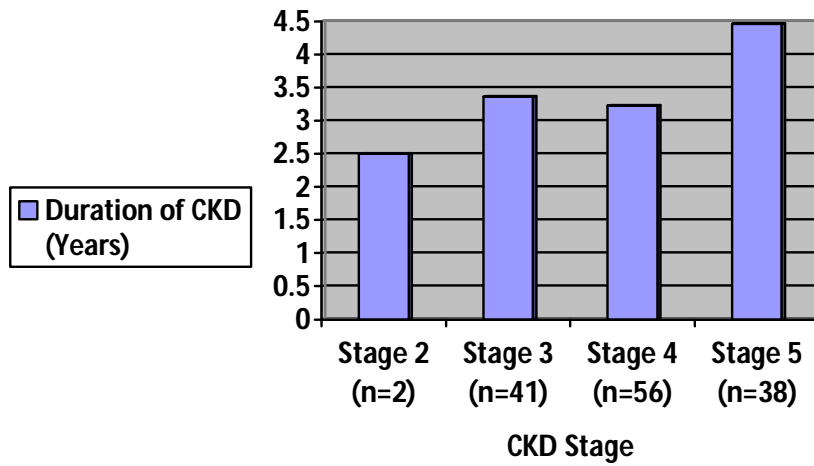
Figure 5: Duration of CKD



Duration of CKD according to CKD stages

The participants in CKD stage 5 had the longest duration of illness with a mean of 53 months followed by participants in CKD stage 3 who had a mean duration of 40.37 months. This trend however was not statistically significant ($p=0.505$). The mean duration of CKD according to each stage is shown in figure 6.

Figure 6: The mean duration of CKD according to each stage (n=137)



Thyroid hormone results of the study participants

Most of the study participants had normal thyroid hormone levels, the percentage normal ranging from 65% for total T4, to 85.4% for total T3. Of the participants who had abnormal thyroid hormone levels apart from TSH where most (15.3%) were elevated compared with only 4.4% having low values, all the other thyroid hormones were mainly low (T3, FT3, T4, FT4). This is depicted in table 6 below.

Table 6: The thyroid hormone results (n=137)

	Low	Normal	High
TSH (uIU/ml)	6 (4.4%)	110 (80.3%)	21 (15.3%)
T3 (ng/ml)	19 (13.9%)	117 (85.4%)	1 (0.7%)
FT3 (pg/ml)	40 (29.2%)	95 (69.3%)	2 (1.5%)
T4 (ug/dl)	33 (24.1%)	89 (65.0%)	15 (10.9%)
FT4 (ng/dl)	31 (22.6%)	91 (66.4%)	15 (10.9%)

The thyroid hormone mean, standard deviation and range of all the participants

The mean values of the thyroid hormones were within the normal laboratory (and manufacturer's) reference ranges in all the CKD stages. However, the TSH and FT3 results showed markedly deranged values as shown in table 7.

Table 7: Thyroid hormone profiles of all the participants

TEST	REFERENCE RANGE	MEAN (SD)	RANGE OF PATIENT RESULTS
TSH (uIU/ml)	0.32 - 5.2	2.42 (2.81)	0.2 – 23.94
T3 (ng/ml)	0.6 – 2.1	0.99 (0.44)	0.3 – 2.2
FT3 (pg/ml)	1.9 – 4.3	3.47 (1.72)	0.4 – 10.0
T4 (ug/dl)	4.7 – 12.5	7.56 (7.56)	2.3 – 13.5
FT4 (ng/dl)	0.7 – 1.8	1.46 (0.66)	0.3 – 3.9

The thyroid hormone profile of the participants according to the CKD stages

All the study subjects in CKD stage 2 had normal hormone profiles. In CKD stage 3, T3 was the thyroid hormone that had the least number of participants with deranged results while the FT3, T4 and FT4 had the highest number as shown in table 8. The details of the study subjects with deranged results are shown in table 6.

Table 8: Thyroid hormone results in CKD Stage 3 (n=41)

TEST	REFERENCE RANGE	MEAN (SD)	RANGE OF PATIENT RESULTS	NUMBER OF PATIENTS WITH DERANGED RESULTS
TSH (uIU/ml)	0.32-5.2	2.12 (1.80)	0.25 – 6.8	7
T3 (ng/ml)	0.6-2.1	1.11 (0.45)	0.5 – 2.1	3
FT3 (pg/ml)	1.9-4.3	3.79 (1.30)	1.1 – 7.4	9
T4 (ug/dl)	4.7-12.5	8.34 (3.26)	2.5 – 13.5	9
FT4 (ng/dl)	0.7-1.8	1.5 (0.58)	0.5 – 3.0	9

The mean values in CKD stage 4

The results of the T3 and T4 were mildly deranged while those of TSH, FT3 and FT4 showed large variations from the reference ranges as depicted in table 9. The details of the study subjects with deranged results are shown in table 6.

Table 9: Thyroid hormone tests in CKD Stage 4 (n=56)

TEST	REFERENCE RANGE	MEAN (SD)	RANGE	NUMBER OF PATIENTS WITH DERANGED RESULTS
TSH (uIU/ml)	0.32-5.2	2.64 (2.35)	0.2-8.5	12
T3 (ng/ml)	0.6-2.1	1.01 (0.40)	0.4 – 1.9	6
FT3 (pg/ml)	1.9-4.3	3.61 (1.53)	1.0 – 8.1	19
T4 (ug/dl)	4.7-12.5	7.76 (3.5)	2.3- 12.8	18
FT4 (ng/dl)	0.7-1.8	1.53 (0.64)	0.5 – 3.9	19

The mean values in CKD stage 5

There were some participants with very high TSH levels in stage 5 of CKD. The FT3 had the largest number of participants with deranged results across all test results as shown in table 10. The details of the study subjects with deranged results are shown in table 6.

Table 10: Thyroid hormone tests in CKD Stage 5 (n=38)

TEST	REFERENCE RANGE	MEAN (SD)	RANGE	NUMBER OF PATIENTS WITH DERANGED RESULTS
TSH (uIU/ml)	0.32-5.2	2.47 (4.13)	0.25 – 23.4	8
T3 (ng/ml)	0.6-2.1	0.816 (0.46)	0.3 – 2.2	11
FT3 (pg/ml)	1.9-4.3	2.90 (2.26)	0.4 – 10.0	20
T4 (ug/dl)	4.7-12.5	6.35 (3.02)	2.3 – 11.3	15
FT4 (ng/dl)	0.7-1.8	1.29 (0.75)	0.3 – 3.1	18

Summary of the results of the thyroid hormones in each CKD stage

The study participants in CKD stage 2 had thyroid hormone profiles within the expected reference ranges. The levels of T3 decreased with an increase in the CKD stage. This difference was statistically significant ($p=0.024$). The mean values of T4 also showed a decreasing trend with increase in the CKD stages. This difference was statistically significant ($p=0.049$).

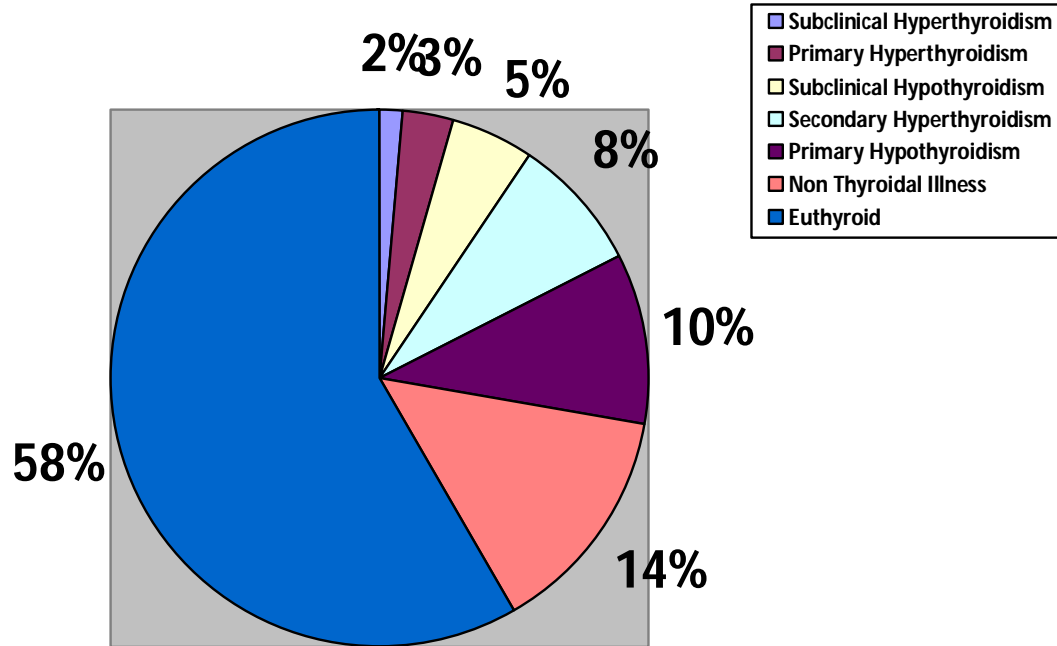
Table 11: Summary of the results of the thyroid hormones in each CKD stage

CKD Stage	TSH Mean(SD)	T3 Mean(SD)	FT3 Mean(SD)	T4 Mean(SD)	FT4 Mean(SD)
3	2.12 (1.80)	1.11 (0.45)	3.79 (1.30)	8.34 (3.26)	1.5 (0.58)
4	2.64 (2.35)	1.01 (0.40)	3.61 (1.53)	7.76 (3.5)	1.53 (0.64)
5	2.47 (4.13)	0.816 (0.46)	2.90 (2.26)	6.35 (3.02)	1.29 (0.75)
P value	0.789	0.024	0.107	0.049	0.326

Categorization of the thyroid hormone profiles

The thyroid hormone levels (TSH, T3, T4, fT3 and fT4) were used to categorize the participants into euthyroid, hyperthyroid, hypothyroid and non-thyroidal illness. Majority of the participants 80 (58%) were euthyroid, 19 (14%) had non-thyroidal illness, subclinical and primary hypothyroidism accounted for 21 (15%) while different forms of hyperthyroidism accounted for 17 (13%). Figure 7 shows the different categories of thyroid status.

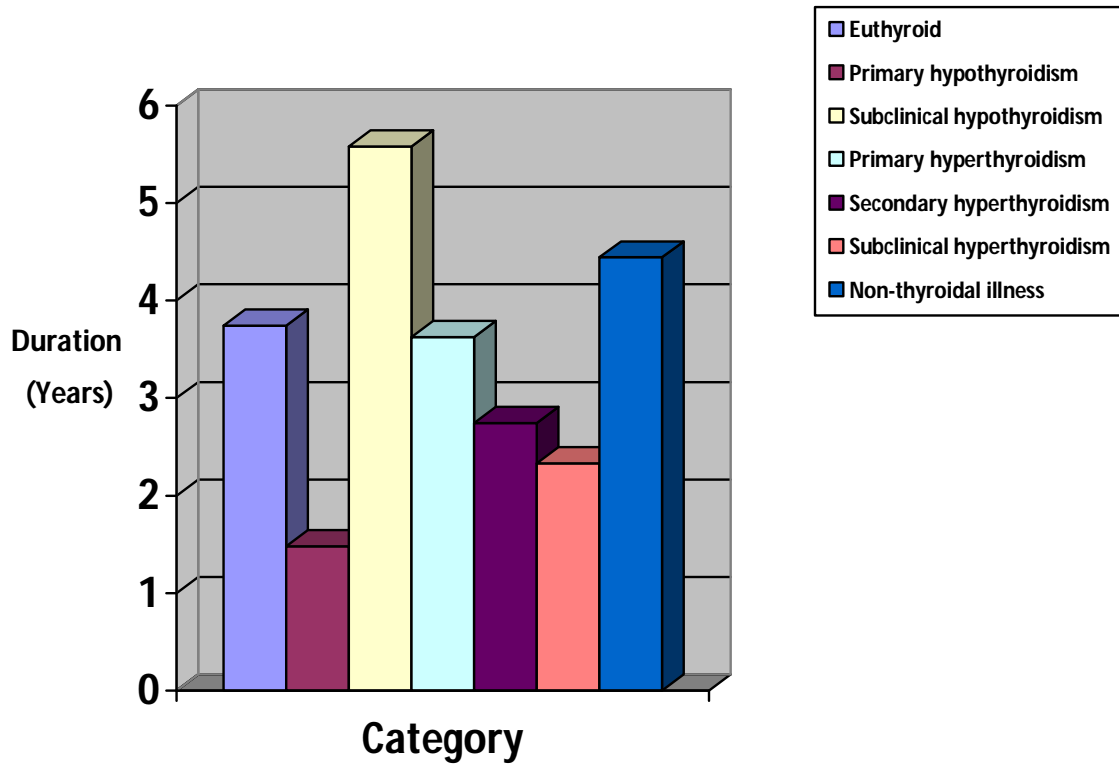
Figure 7: The categories of thyroid profiles



Duration of CKD and the thyroid hormone category

The participants with subclinical hypothyroidism had the longest duration of CKD at a mean of 67 months (5.6 years) while those with primary hypothyroidism had the shortest duration of 17.79 months (1.5 years) as shown in figure 6. However, the difference in mean duration of CKD amongst the thyroid status was not statistically significant ($p=0.345$) as shown in figure 8.

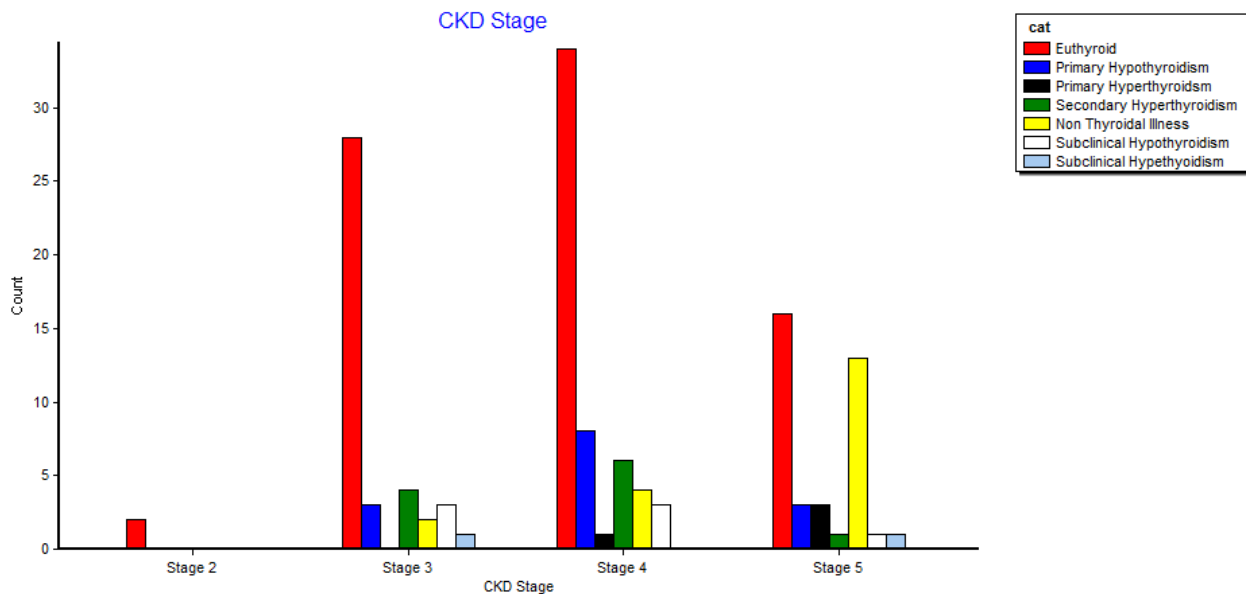
Figure 8: Duration of CKD and the thyroid category



CKD stages and the thyroid status

Majority of the participants in all the CKD stages were euthyroid, non-thyroidal illness was increasing with each CKD stage with the highest number of participants being in CKD stage 5. CKD stage 4 had the highest number of participants with primary hyperthyroidism; this is depicted in figure 9.

Figure 9: CKD stages and the thyroid status



The proportion of non-thyroidal illness (NTI) in the different CKD stages

The proportion of patients with non-thyroidal illness increased with increasing severity of CKD as shown in table 12. This was statistically significant (P= 0.0004)

Table 12: Proportion of non-thyroidal illness in the different CKD stages

CKD STAGE	NTI	TOTAL
2	0(0%)	2
3	2(4.9%)	41
4	4(7.1%)	56
5	13(34.2%)	38

DISCUSSION

A total of 137 participants were recruited in this study, majority of who were males. The higher proportion of males in this study could reflect the local current change in health seeking behaviour of the male gender. This may also be explained by the fact that men are the breadwinners in most families and hence are more economically empowered to seek health care. In a similar study done 20 years ago on chronic renal failure patients, on conservative management and regular haemodialysis at KNH, females constituted 62% of participants, again reflecting on the changed attitudes in the males (47). Majority of the participants in this study were between the ages of 38 to 68 years with a median of 50 years. Majority of these patients had a diagnosis of hypertension, diabetes or both as the primary condition leading to CKD. These can be attributed to the increasing prevalence of DM and hypertension in this age group (65).

There are no reports on local prevalence of CKD. Regionally, a study done in Nigeria by Afobai et al (66), gave a prevalence of 12.4% in patients aged between 20 years and 74 years who had CKD with demonstrable association with modifiable risk factors including hypertension, diabetes and abnormal waist-hip ratio. This is similar to a study done in the US, which found that the prevalence of albuminuria and decrease in GFR increased from 1988-1994 to 1999-2004 and this was attributed to an increase in diabetes, hypertension and high body mass index. It is estimated that the prevalence of CKD among adults in the United States has risen to 13% (3). The changing lifestyles in our population leading to increase in diabetic and hypertensive cases could also play a role in the rising CKD cases. In this study, hypertension and diabetes mellitus were the major causes leading to CKD while HIV-

associated nephropathy accounted for a minority. HIV infection was also found in a younger age group compared to hypertension and DM.

Classification of CKD into different stages in this study was done as per National Kidney Foundation guidelines (2), with estimated GFR using the 4-variable MDRD formula.

Majority of the participants were in CKD stage 4 (40.9%), none of the participants sampled were in CKD stage 0 or 1. This could be attributed to delay in seeking medical treatment hence patients were seen when the disease had progressed to the more severe stages. The clinicians use creatinine levels and only estimate GFR when the creatinine levels are elevated. It is recommended that estimation of GFR should be done in all cases after creatinine levels have been determined. It has been estimated from population survey data that at least 6% of the adult population in the United States has CKD at stages 1 and 2. An unknown subset of this group progresses to more advanced stages of CKD. An additional 4.5% is estimated to have stages 3 and 4 CKD (65).

Thyroid hormone metabolism is disturbed at multiple levels in patients with CKD including iodine accumulation in the thyroid gland; protein binding and peripheral tissue metabolism, actual tissue concentration and availability (30).

In this study all the participants were on conservative management and the thyroid hormone profiles demonstrated abnormal measurements of TSH, T3, T4, FT3 and FT4 in 42%. All the participants on the basis of history and physical examination were regarded as euthyroid.

However the abnormal hormone levels seen suggest the presence of thyroid disease in these patients. Majority of the participants (58%) were euthyroid, 14% had non-thyroidal illness, subclinical and primary hypothyroidism accounted for 15% while different forms of hyperthyroidism accounted for 13%.

Non-thyroidal illness is defined as biochemical alteration in thyroid hormones in the absence of underlying intrinsic thyroid disease. It is characterized by low T3 and fT3 with an increase in rT3 and normal TSH, T4 may be normal or low. In this study, the levels of T3 and fT3 were found to be low and these were noted to decrease as the renal insufficiency progresses. This is primarily related to diminished peripheral tissue conversion of T4 to T3. These low T3 and fT3 levels have been reported in other studies (67). Zocalli et al found fT3 but not fT4 to be reduced in ESRD patients suggesting that low fT3 is unlikely to be an in vitro artefact because substances inhibiting binding of fT3 are expected to affect fT4 to a greater extent than fT3 (41). Therefore, reduced fT3 seems to reflect a true selective T3 deficiency due to a defect in T4 to T3 conversion. The lack of increase in TSH as a result of low T3 and fT3 concentration in patients with non-thyroidal illness may be due to stress inhibition of pituitary secretion of TSH (10). Patients with chronic renal failure have been reported to exhibit a blunted and delayed TSH response to thyroid releasing hormone (TRH), in addition chronic metabolic acidosis in ESRD may contribute to low fT3 levels (10). Inflammation has been shown to play an important role in the causation of deranged thyroid function associated with non-thyroidal illness. Inflammatory cytokines including IL-6 have been implicated in the genesis of low T3 syndrome. IL6 decreases the mRNA of the liver type 5' deiodinase as well as thyroid type 5' deiodinase a mechanism that has also been implicated in low T3 induced by bacterial endotoxins (68). Carrero et al found low T3 levels to be independent predictors of cardiovascular mortality in CKD patients and low T3 as a more sensitive predictor of mortality in CKD than fT3 (55).

The number of participants in this study with low T3 levels increased with severity of CKD, this have been reported in other studies. Sang et al reported that low T3 syndrome is highly

prevalent in CKD. They also found an increasing trend for the population of low T3 according to the increase of CKD stage (69) .

The definition of subclinical hypothyroidism is purely a biochemical one, defined as elevated serum TSH levels but normal FT4 levels. Studies have shown subclinical hypothyroidism to be common, especially among older adults; laboratory tests show low thyroid function in 4 to 10 percent of the general population (48). Increased rates of thyroid abnormalities have been reported in patients with ESRD and newer studies show an increased rate of subclinical hypothyroidism in CKD patients not requiring chronic dialysis (48). This study reported primary and subclinical hypothyroidism at 10.2% and 5.1% of the participants respectively, majority of who were in CKD stage 4. This is similar to a local study done about 20 years ago on patients on conservative management and dialysis (47). Michel Chonchol et al also found that the prevalence of hypothyroidism was common at 18% of all patients with CKD not requiring dialysis. In those with stage 1 and stage 3 of CKD, the prevalence of subclinical hypothyroidism was found to be 7% and 17.9% respectively (48). High titre of anti-thyroid antibodies is associated with a higher prevalence of hypothyroidism in women (31) however this study did not analyze thyroid antibodies. The concentration of serum iodine in patients with CKD is higher due to lower iodine clearance caused by the reduced glomerular filtration. Elevated levels of serum inorganic iodine in patients with CKD may potentially block thyroid hormone synthesis and explain higher prevalence of diffuse goitre and hypothyroidism in these patients (70).

Several studies have shown subclinical hypothyroidism to be associated with cardiovascular risk and cardiac impairment, any derangement in the serum TSH level may accelerate the development of atherosclerosis (45). Bradley et al found that in clinically overt primary

hypothyroidism, the significant manifestation of renal function change is hyponatremia that results from impairment in the renal diluting capacity resulting in water retention (23).

Decreased cardiac output resulting from overt hypothyroidism may also contribute to renal hemodynamic alterations leading to progressive decline in GFR. Thus as hypothyroidism becomes more severe it may cause reduced heart function which in turn leads to progressively worsening kidney function.

Secondary, primary and subclinical hyperthyroidism was reported in 8%, 2.9% and 1.5% of the participants respectively in the present study. The finding of hyperthyroidism is uncommon and presents with similar signs and symptoms as uraemia. Niemczyk et al found multinodular goitre and Grave's disease in patients with ESRD and hyperthyroidism(71).

Ramirez et al found that the prevalence of hyperthyroidism in CKD was similar to that in the general population in areas with inadequate iodine intake (50). Hyperthyroidism could be attributable to abnormal feedback loop due to impairment of hypothalamic pituitary thyroid axis associated with pituitary resistance to thyroid hormones (PTRH) (72). PTRH results from alterations in physiological mechanisms that regulate HPT axis. The imbalance between hypothalamus pituitary and peripheral response to systemic thyroid hormones leads to thyrotoxicosis. However not many studies have been done on hyperthyroidism in CKD.

Pharmacologic agents administered to patients who have CKD may confound the interpretation of thyroid function tests. Glucocorticoids affect the hypothalamic-pituitary-thyroid axis at multiple levels including suppression of TSH secretion, down-regulation of T4 to T3 conversion by 5' deiodinase and decrease of TBG concentration and hormone binding capacity (32). Furosemide at therapeutic doses has little or no effect on thyroid parameters; however at high doses it causes a transient elevation in free T4 and a decrease in T4 due to the displacement of T4 from TBG. This change depends on serum albumin concentrations

which also bind furosemide (32). In this study, some patients were on steroids and antihypertensives including furosemide which were considered a limitation to the study.

Considering the fact that clinical features of thyroid dysfunction are often masked with uraemic state it may be necessary to conduct periodic screening of thyroid function in CKD patients. In CKD stage 5 patients awaiting kidney replacement therapy, early diagnosis and treatment of thyroid disease significantly reduces morbidity and mortality. It has been shown that low T3 and fT3 before renal transplant is associated with decreased graft survival thus early diagnosis and may be treatment should be considered to improve the outcome (73).

CONCLUSION, RECOMMENDATIONS AND LIMITATIONS

Conclusions

1. Most of the participants in this study were euthyroid.
2. There were abnormalities in the thyroid hormone profiles in 42% of the participants.
3. The most common thyroid hormone derangement was low T3 values (non-thyroidal illness).
4. Non-thyroidal illness increased with the severity of chronic kidney disease.
5. The prevalence of hyperthyroidism in this study (12.4%) is higher than has been reported.

Recommendation

1. There is need to do thyroid hormone profiles in CKD patients who are in stage 3 and above (normal algorithm may be employed).
2. There is need for studies to determine the thyroid profiles in lower CKD stages (stage 0-2).
3. Hyperthyroidism in chronic kidney disease in Kenya should be studied further in both iodine deficient and sufficient regions.
4. Adoption of the policy on estimation of GFR on renal disease patients.

Study limitations

1. Other disease processes e.g. liver disease, vasculitis and medications that reduce the peripheral conversion of T4 to T3 may interfere with interpretation of the thyroid hormone profiles. However efforts were made to exclude the patients with these diseases from the medical history in the participant's files.

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APPENDICES
Appendix 1 Screening Questionnaire

Study on thyroid hormone profile in patients with Chronic Kidney Disease at KNH.

	YES	NO
Age \geq 18years		
Gender (M/F)		

<u>Diagnosis:</u>	YES	NO
a) Duration of illness >3/12		
b) On dialysis		
 <u>Eligibility</u>		
1. Are you willing to participate in this study?		

If answers to ALL questions are YES, except dialysis, Recruit and issue Study No. If NO, do NOT Recruit.

FOR OFFICAL USE:

RECRUITED (encircle)

YES

NO

STUDY NUMBER:

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Once recruited, proceed to Study Questionnaire (Appendix II).

Appendix 2 Study Questionnaire

Thyroid hormone profiles in patients with Chronic Kidney Disease at KNH.

Date

--	--	--	--	--	--

dd / mm / yy

A. Demographic data

Name.....

--	--

 Age (Years):

Gender: 1. Male 2. Female

Study No.

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Hospital No

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B. Medical History

i) Diagnosis:

1. Diabetes Mellitus YES NO
2. Hypertension YES NO
3. Glomerulonephritis YES NO
4. Polycystic Kidney Disease YES NO
5. Autoimmune renal disease YES NO
6. Others (Specify)

LABORATORY RESULTS

	Reference Range	Value
TSH (μ IU/ml)	0.4 – 7.0	
T4 (nmol/L)	60 - 130	
FT4 (pmol/L)	9- 20	
T3 (nmol/L)	0.9 – 2.5	
FT3 (pmol/L)	4 - 8	

Classification of results (Tick one)

Euthyroid	
Primary Hypothyroidism	
Secondary Hypothyroidism	
Primary hyperthyroidism	
Secondary hyperthyroidism	
Non-thyroidal illness	
Sub-clinical thyroid disease	

Appendix 3 Consent Explanation

THYROID HORMONE PROFILE IN PATIENTS WITH CHRONIC KIDNEY DISEASE AT KNH

Introduction and objectives of the study:

I am Dr. Kaggia S, a master's student in Human Pathology at the University of Nairobi and conducting a study on kidney disease and its effects on thyroid function. The kidneys are a pair of organs that carry out 3 key functions: removal of body waste, maintain volume and composition of body fluid and hormone production. Thyroid gland produces thyroid hormones that are essential for normal growth and development and have many effects on metabolic processes. Kidney disease and any serious illness can cause alteration in the thyroid hormones and this has been used to predict prognosis. The study aims to:

- i. To determine the thyroid hormone profiles in patients with CKD.
- ii. This study will also provide a basis for future research on low T3 syndrome as an independent predictor of mortality in CKD patients at KNH.

Benefits and risks of the study to you:

Your participation will help improve the care of patients with chronic kidney disease and screening of at risk population. There will be no payment for participating.

By participating in it, you will benefit by:

1. Having examination and laboratory tests done on you at no additional cost.
2. A report of your thyroid function status being sent to your physician.

Risk: 10 ml of blood will be drawn from the antecubital vein. The prick will be painful and a haematoma may form around the prick area.

If you Consent to participate, you will:

- Sign a Consent form (Appendix 4)
- Answer a number of questions contained in the screening and study questionnaire (Appendices I and II)

- Undergo physical exam.

Confidentiality:

Participation is voluntary and you can withdraw at any time. Any information given to us will remain confidential and your privacy will be respected. You may ask me questions regarding the study now or any time during the study. If you have any question relating to the study, kindly Contact:

1. Dr Kaggia 0722-283944 (PI)
2. My supervisors: Prof Kigonde 0733-730796, Dr Amayo 0733-617678 Prof Kayima 0733-730650
3. The Secretary to the Ethical Research Committee. KNH Tel No. 272260 Ext. 44102

Appendix 4 Consent Form for Participants

Thyroid hormone profiles in patients with Chronic Kidney Disease.

I.....
.....after reading and being explained to on the study purpose by Dr.
Kaggia S. N., do hereby give informed consent to participate in the study on **THYROID
HORMONE PROFILES IN PATIENTS WITH CHRONIC KIDNEY DISEASE.**

I am aware that I can withdraw from the study without any benefits or quality of management of my medical condition being interfered with.

Signed:.....

Thumbprint: Date:

.....

Signature of the PI (Dr Kaggia).....

Witness:

Date:.....