A dissertation on

A STUDY OF PREVALENCE AND CLINICAL SIGNIFICANCE OF LOW T3 IN NON-DIALYSIS PATIENTS WITH CHRONIC KIDNEY DISEASE

Submitted in partial fulfilment for the award of the Degree of

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BRANCH I

INSTITUTE OF INTERNAL MEDICINE

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CERTIFICATE

This is to certify that the dissertation entitled "**A STUDY ON PREVALENCE AND CLINICAL SIGNIFICANCE OF LOW T3 IN NON-DIALYSIS PATIENTS WITH CHRONIC KIDNEY DISEASE"** is a bonafide original work done by **DR.K.GOUTHAM** , in partial fulfilment of the requirements for **M.D. GENERAL MEDICINE BRANCH I** examination of The Tamil Nadu Dr.M.G.R Medical University to be held in April 2019 under my guidance and supervision in 2017 and 2018..

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DECLARATION BY THE CANDIDATE

I hereby solemnly declare that the dissertation entitled **"A STUDY OF PREVALENCE AND CLINICAL SIGNIFICANCE OF LOW T3 IN NON-DIALYSIS PATIENTS WITH CHRONIC KIDNEY DISEASE"** is done by me at the Institute of Internal Medicine, Madras Medical College, Rajiv Gandhi Government General Hospital, Chennai between August 2017 and January 2018 under guidance and supervision of **Prof.Dr.S.TITO, M.D.,.** This dissertation is submitted to the Tamil Nadu Dr.MGR Medical University, Chennai towards the partial fulfilment of requirement of the award of M.D. Degree in General Medicine (Branch I).

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CONTENTS

LIST OF ABBREVIATION

CKD	-	CHRONIC KIDNEY DISEASE
EGFR	-	ESTIMATED GLOMERULAR FILTERATION RATE
RAS	-	RENIN ANGIOTENSIN SYSTEM
ECF	-	EXTRA CELLULAR FLUID
LVH	-	LEFT VENTRICULAR HYPERTROPHY
ECG	-	ELECTROCAR DIOGRAM
RRT	-	RENAL REPLACEMENT THERAPY
MIT	-	MONO - IODOTHYRONINE
DIT	-	DI-IODOTHYTRONINE
T3	-	TRI-IODOTHYRONINE
T4	-	THYROXINE
rT3	-	REVERSE T3
TSH	-	THYROID STIMULATING HORMONE
TRH	-	THYROTROPIN RELEASING HORMONE
HIV	-	HUMAN IMMUNODEFICIENCY VIRUS
TPO	-	THYROID PEROXIDASE
KDIGO	-	KIDNEY DISEASES IMPROVING GLOBAL OUTCOMES
RPD	-	RENAL PARENCHYMAL DISEASE
USG	-	ULTRASONOGRAPHY
CKD-EPI	-	CHRONIC KIDNEY DISEASE EPIDEMIOLOGY COLLABORATION.

INTRODUCTION

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INTRODUCTION

The 2015 Global Burden of Disease Study has reported an stupendous increase in life expectancy globally between the years 1980 and 2015. This enormous improvement in global statistics is due to the decline in mortality from various communicable, non-communicable and nutritional diseases[13]. Chronic kidney is one among the most common non-communicable disease in the world with a significant mortality and morbidity.

Chronic kidney disease is a spectrum disease of various pathophysiological processes associated with an abnormality in renal function and a progressive decline in the glomerular filtration rate[13].

Chronic kidney disease is loosely defined as an abnormal kidney structure or function that lasts for more than three months with associated health implications[6]in the form of synthetic, hormonal, metabolic, excretory, endocrine abnormalities eventually leading on to accumulation of waste products leading on to several homeostatic derangements.

Patients with end stage renal disease (ESRD) have a poor quality of life and die at an early age. However due to improvement in health sector and improved methods of screening the disease early, there is a decrease in mortality rate of dialysis patients and there is also a decline in rate of progression to ESRD due to novel therapies and correction of risk factors[7].

Several factors contribute to high prevalence of CKD in India. Hypovitaminosis A and other nutritional deficiencies during pregnancy can lead to smaller kidney volume of the offspring and a lower eGFR .

Consanguineous marriage and genetic inbreeding can increase risk of congenital anomalies of the kidney and urinary tract. Poverty, poor environmental sanitation, pollution, water contamination, overcrowding, and known and unknown nephrotoxins (including heavy metals and plant toxins in indigenous medical practices) may lead to glomerular and interstitial renal diseases. Added to these, hypertension and diabetes mellitus are the major burdens leading to ESRD. By the end of 2030, India is expected to have the world's largest population of diabetic patients.

Over 50% of patients with advanced CKD are first seen when the eGFR is <15 ml/min per 1.73 m^2

This highlights the need for widespread screening programs for those people who are at risk of CKD. The etiology of CKD varies throughout India. Parts of the states of Andhra Pradesh, Telangana ,Odisha, and Goa have high levels of CKD of unknown etiology designated as CKD presenting as a chronic interstitial nephropathy with insidious onset and slow progression.

Irrespective of the cause, chronic kidney disease is the final pathway of permanent loss of the functional unit of the kidneys, the nephrons, which results in disturbance in the normal homeostasis of the body there by affecting every system. Thyroid gland is no exception to this rule.

Thyroid hormones are an important determinant of somatic and brain development in children and adults[33]. Thyroid hormones affect function of every other organ of the body and they should be constantly available for normal functioning of the body.

The kidneys play a vital role in the metabolism, degradation and excretion of the thyroid hormones[32]. So, impairment of renal function will lead to abnormalities of thyroid physiology.

Iodine is excreted mainly by kidneys and an impaired kidney function leads to increased levels of serum iodine which impairs thyroid hormone synthesis – popularly called as the Wolff chaikoff effect[32].

All the levels of hypothalamic –pituitary-thyroid axis can be involved resulting in disturbances in hormone synthesis, metabolism, distribution and excretion.

Thyroid gland on the other side has a significant role in the development and function of kidneys. It plays a pivotal role in moderation of renal blood flow thereby controlling GFR.

There is a considerable overlap in symptoms related to CKD and hypothyroidism. Hence it is vital to differentiate them and to establish a link between two different conditions.

There have been a paucity of studies conducted to establish a physiological link between thyroid abnormalities in impaired renal function and the outcome upon correcting them.So to establish a concrete association between derangements of thyroid function and chronic kidney disease, a clinical and biochemical study was done in the Institute of Internal Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai.

AIMS AND OBJECTIVES

AIM:

To study the prevalence and clinical significance of low T3 in CKD patients who are not on dialysis

OBJECTIVES:

1. To study the different non-thyroid illness patterns occurring in non - dialysis CKD patients.
2. To find the clinical significance of low T3 in CKD.
3. To establish a correlation between low T3 and severity of CKD.

REVIEW OF LITERATURE

THE KIDNEYS

Kidneys are retroperitoneal bean shape organs.The kidney is one of the most highly differentiated organ in the body[2].The kidney develops from intermediate mesoderm under the timed or sequential control of various genes[1].

The kidney lies between the 12th thoracic vertebra & 3rd lumbar vertebra Each kidney weighs about 125 to 175grams in males & about 115 to 155 in females.

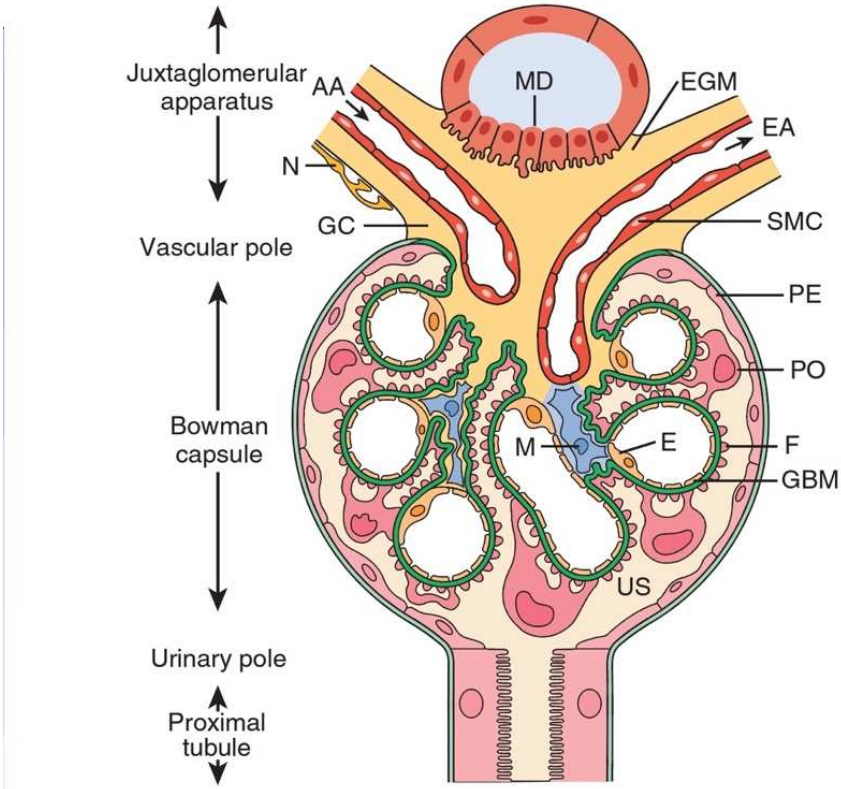
Each kidney is about 12cm in length, 5to7.5cm in breadth, 2.5 to 3cm in thick.

The nephron is the most specific component of the kidney. The nephron consist of glomerulus connected to a complicated twisted tubule that drains into a collecting duct. The number of nephrons is established prenatally & no new nephrons can be formed & a lost nephron cannot be replaced[2].

There are 3 types of nephron based on location of renal corpuscles – superficial, mid-cortical, juxta medullary nephrons[3]. The glomerulus is connected to the collecting duct via the proximal tubule under the distal tubule connected by a loop of Henle. The glomerulus & the bowman capsule are involved in filtration.The glomerulus consist of a cluster of capillaries with an afferent arteriole & efferent arteriole[5].

The fluid that is filtered from the glomerulus capillaries flows into bowman's capsule & then into proximal tubule – loop of Henle – distal tubule

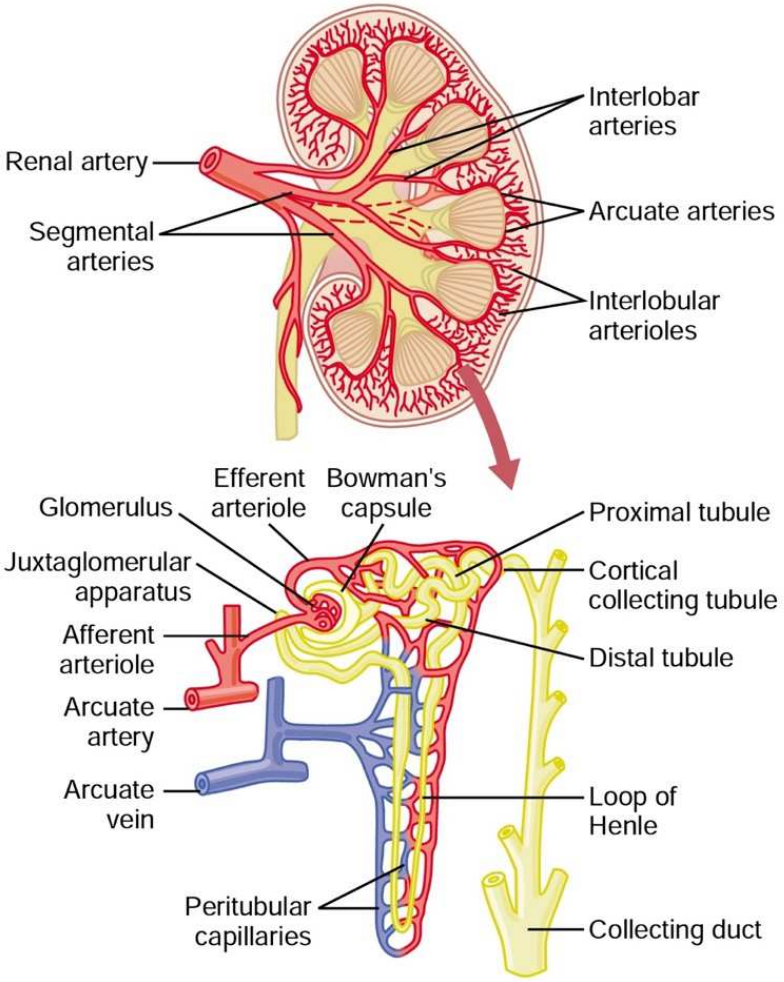
– collecting duct. At the end of thick ascending limb is a short segment called macula densa which plays an important role in nephron function[10]



The functions of kidney[10,7,9]:

- Excretion of metabolic waste & foreign chemicals.
- Regulation of arterial pressure.
- Regulation of water & electrolyte balance.
- Secretion metabolism & excretion of hormones.
- Regulation of body fluid osmolality & electrolyte concentration.

- Gluconeogenesis.
- Regulation erythrocyte production.



The kidneys receive about 22% of cardiac output the renal artery enters through hilum into the kidney & them branches to form interlobar artery - arcuate artery – interlobular artery – afferent arteriole – glomerular capillaries – efferent arteriole – peritubular capillaries[3,4,8,10].

The renal circulation is unique because it consist of two capillary beds, the glomerular & peritubular capillaries which are arranged in series &

separated by efferent arteriole that regulate hydrostatic pressure in both sets of capillaries[4,7,10].

The high hydrostatic pressure in the glomerular capillaries leads to fluid filtration & lower hydrostatic pressure leads to fluid reabsorption.

The peritubular capillaries drain into interlobular vein – arcuate vein - interlobar vein – renal vein[2,5,8].

Each kidney contains about 1 million nephrons. After the age of 40, the number functioning nephron decrease by 10% every 10yrs. So, by 80years there is only 40% of functioning nephrons .

Determinant of the GFR[1,7,9,10,11]:

The GFR is determined by

1. The sum of hydrostatic & colloid osmotic forces across glomerular membrane.
2. The glomerular capillary filtration co-efficient,K_f

$$GFR = K_f \text{ X Net Filtration pressure}$$

Forces favouring filtration:

1. Glomerular hydrostatic pressure.
2. Bowman's capsule colloid osmatic pressure.

Forces Opposing filtration:

1. Bowman's capsule hydrostatic pressure.
2. Glomerular capillary colloid osmatic pressure.

Cockcroft and Gault formula for GFR:

EGFR in ml/min = (140-age) X Lean body weight in (kg) / 72 X plasma creatinine (mg/dl) X 0.85 for women.

Chronic kidney disease:

CKD is defined as abnormality of kidney function or structure, present for greater than 3 month with implication for health[6].

Criteria for CKD[6]:

Criteria for CKD (either of the following present for >3 months)

Markers of kidney damage (one or more)	Albuminuria (AER ≥30 mg/24 hours; ACR ≥30 mg/g [≥3 mg/mmol]) Urine sediment abnormalities Electrolyte and other abnormalities due to tubular disorders Abnormalities detected by histology Structural abnormalities detected by imaging History of kidney transplantation
Decreased GFR	GFR <60 ml/min/1.73 m^2 (GFR categories G3a–G5)

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.

Staging for CKD[6]:

CKD is classified based on cause, GFR category & Albuminuria category.

GFR category in CKD:

GFR categories in CKD

GFR category	GFR (ml/min/1.73 m^2)	Terms
G1	≥90	Normal or high
G2	60–89	Mildly decreased*
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.
*Relative to young adult level
In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

Albuminuria Category in CKD:

Albuminuria categories in CKD

Category	AER (mg/24 hours)	ACR (approximate equivalent) (mg/mmol)	ACR (approximate equivalent) (mg/g)	Terms
A1	<30	<3	<30	Normal to mildly increased
A2	30-300	3-30	30-300	Moderately increased*
A3	>300	>30	>300	Severely increased**

Abbreviations: AER, albumin excretion rate; ACR, albumin-to-creatinine ratio; CKD, chronic kidney disease.
*Relative to young adult level.
**Including nephrotic syndrome (albumin excretion usually >2200 mg/24 hours [ACR >2220 mg/g; >220 mg/mmol]).

MDRD & CKD/EPI Formula:

1. Equation from the Modification of Diet in Renal Disease study

Estimated GFR (mL/min per 1.73 m^2) = $1.86 \times (S_{Cr})^{-1.154} \times (age)^{-0.203}$

Multiply by 0.742 for women

Multiply by 1.21 for African ancestry

2. CKD-EPI equation

$GFR = 141 \times \min(S_{Cr}/\kappa, 1)^{\alpha} \times \max(S_{Cr}/\kappa, 1)^{-1.209} \times 0.993^{Age}$

Multiply by 1.018 for women

Multiply by 1.159 for African ancestry

where S_{Cr} is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of S_{Cr}/κ or 1, and max indicates the maximum of S_{Cr}/κ or 1.

Abbreviation: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

Causes of CKD[6,9,12,13]:

1. Diabetic kidney disease.
2. Chronic glomerulonephritis.
3. Hypertension associate CKD (Vascular causes & primary glomerular disease with hypertension).
4. Autosomal dominant polycystic kidney disease.
5. Other cystic & tubulointerstitial nephropathy.

CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health and CKD is classified based on cause, GFR category, and albuminuria category (CGA).

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/ 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

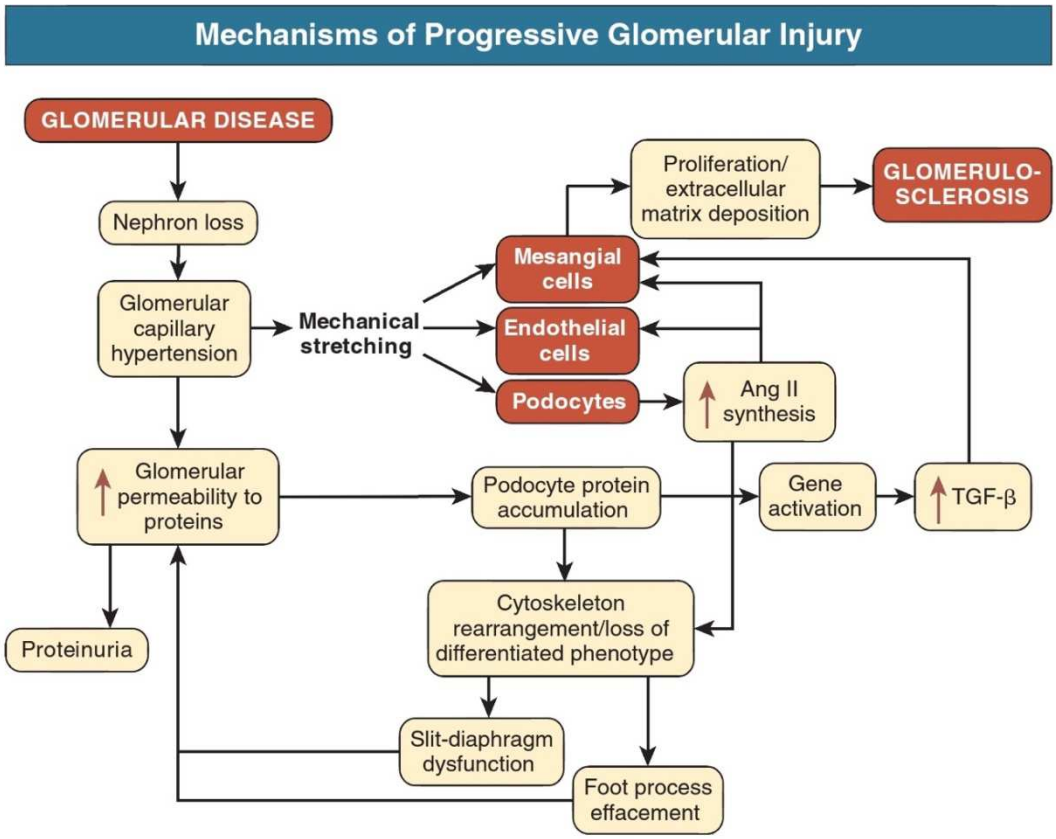
Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

The pathophysiology of CKD:

The pathophysiology of CKD consist of

1. Initiative mechanism specific to the underlying cause: example genetic, immune complex deposition, toxins[15,19,21] .
2. Progressive mechanism consisting of hypertrophy & hyperfiltration of the remaining normal nephrons [14,12,16].

The response to lose of nephrons is mediated by cytokines, vasoactive hormones, growth factor finally these adaption of the kidney to loss of viable renal mass becomes maladaptive & leads to distortion of glomeruli disruption of filtration barrier, abnormal podocyte function leading to sclerosis & dropout of remaining nephrons[16,17,18].



Clinical features.

Fluid & electrolyte abnormality[12,19,21,22]:

With normal kidney function the tubular reabsorption of filtered water & sodium is adjusted so that urinary excretion of sodium matches the intake. In CKD, this balances disrupted leading on to sodium retention & ECF expansion which contribute to hypertension. Hypertension by itself can cause nephron injury. So patience with ECF expansion should be advised salt restriction. Resistance to loop diuretics in CKD leads to use of much more higher doses than in normal patients.

Diureticresistance can be overcome by combining loop diuretic with metolazone, continuous infusion,bolus doses & ultra-filtration . Diuretics resistance with volume overload not responding to conventional therapy is an indication to start dialysis.

Urinary potassium excretion is mediated by aldosterone dependantsecretion in distal nephron.Potassium is also lost in gastrointestinal tract disturbance. In CKD, potassium imbalance can occur by homolyses, haemorrhage, metabolic acidosis, excessive K^+ , protein catabolism & drug induced example RAS inhibitors. Hypokalaemia can be seen in early CKD with markedly decreased dietary potassium, excessive GI loss, excessive diuretic therapy .

Acid base balance[12]:

Hyperkalaemia & hyperchloremic metabolic acidosis is seen in early stage of CKD, diabetic nephropathy obstructive uropathy. As the stage progresses this non – anion gap metabolic acidosis is complicated by anion gap

metabolic acidosis. Mild metabolic acidosiscan be corrected by oral bicarbonate therapy which is recommended when serum bicarbonate falls below 20-23 mmol/ltr.

Mineral metabolism[12,26,27]:

The bone manifestation of CKD can be divided into:

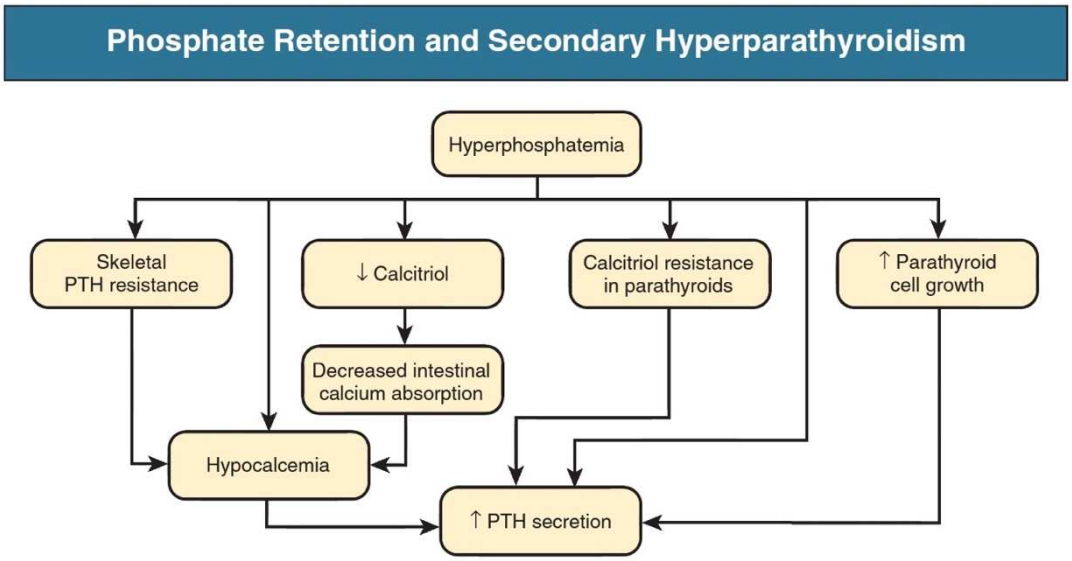
1. High bone turnover with high PTH level.
2. Low bone turnover with low or normal PTH level.

The pathophysiology of high turnover bone disease is due to

- Decrease in renal function leading to decreased phosphate excretion.
- High Phosphate stimulates FGF23 production by osteocyte & growth of parathyroid gland mass.
- Reduced ionised calcium due to suppression of calcitriol production by FGF23 which also stimulate PTH production.

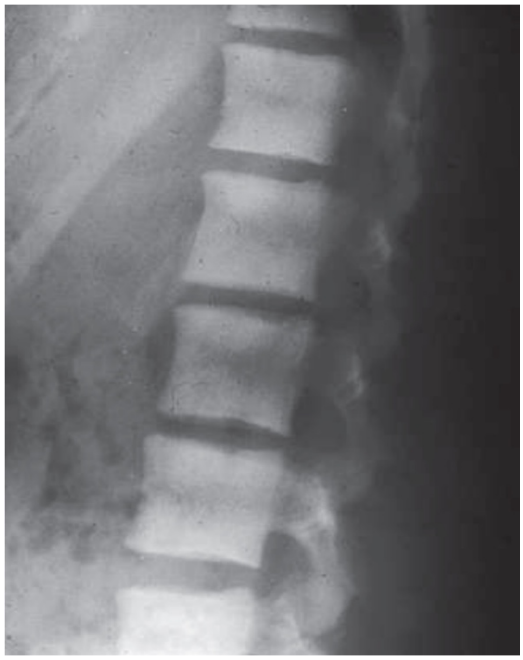
These changes occur when GFR is reduced below 60ml/min FGF23 is a phosphatonin, that maintain serum phosphorus in normal level by

- Increase phosphate excretion by kidney.
- Stimulate PTH and decrease calcitriol formation.



High level of FGF23 is an independent risk factor for left ventricular hypertrophy & mortality in CKD osteitis fibrosa cystica is hallmark of high bone turnover disease. Clinically, patients present with severe bone pain, brown tumor, compression syndrome & erythropoietin resistance.

Rugger jersey spine in renal osteodystrophy [22]



Low turnover bone disease can be grouped into [12]:

1. Adynamic bone disease : it is more common in diabetic & elderly. It occurs due excessive suppression of PTH synthesis & chronic inflammation. It results from use of vitamin D supplements & excessive calcium supplements or high calcium dialysis solution. Patient usual present with bone pain and fractures & then associated risk of increase cardiac & vascular calcification.
2. Osteomalacia.

Hematological alteration:

1.Anemia:[22,23,24,25]

Normocytic normochromic anemia seen in CKD3 and almost in all patients with CKD4

Causes of anemia in CKD include :

- iron deficiency.
- reduced survival of RBC.
- reduced erythropoietin.
- anemia of chronic disease.
- folate and vitamin B12 deficiency.
- bleeding diathesis.
- severe hyperthyroidism with bone marrow fibrosis.

The target Hb concentration is 10 to 11.5g/dl

2.Alteration of normal hemostasis:[12]

Prolongation of bleeding time, decreased platelet factor III, abnormality of platelet adhesion and aggregation and impairment in

prothrombin consumption are seen in CKD. These abnormalities can be temporarily and partly reversed by desmopressin, cryoprecipitate, iv conjugated estrogens, blood transfusions and dialysis.

3.Alteration in cardiovascular system[12,22]:

1.Ischemic heart disease:

It is leading cause of death in CKD. CKD is an independent risk factor for coronary heart disease. Peripheral heart disease and cerebrovascular disease. The CKD related factors which contribute to vascular disease are anemia, hyperphosphatemia, hyperparathyroidism, sleep apnoea, increased FGF-23, and chronic inflammation. Myocardial stunning can occur in patients on haemodialysis. Cardiac troponins are elevated in patients with CKD.

2. Cardiac failure:

Myocardial ischemia ,LVH,cardiomyopathy, salt and water retention all contribute to heart failure. Low pressure pulmonaryedema can occur in CKD. Pulmonary edema can occur without ECF overload due to increased permeability of alveolar capillary membrane. This responds to dialysis.

3. Uremic pericarditis:

It presents with chest discomfort,shortness of breath. Pericardial friction rub can be heard on auscultation. ECG shows PR prolongation and diffuse ST elevation. Pericardial effusion due to CKD can be hemorrhagic and can result

in tamponade requiring pericardiocentesis. It is an absolute indication for renal replacement therapy.

Neurological alterations:[28,29]

These neurological abnormalities involving central nervous system, peripheral nervous system and autonomic nervous system usually starts with stage 3 CKD .Some of them are listed below

- Uremic encephalopathy.
- Peripheral neuropathy.
- Autonomic neuropathy.
- Cranial neuropathies- Most common involves the VIIIth nerve.
- Sleep disturbances – obstructive and central sleep apnoea.
- Restless leg syndrome (ekbom syndrome).
- Posterior reversible encephalopathy syndrome (PRES).
- Neuromuscular alterations leading to hiccups ,cramps,twitching.
- Cognitive impairment.
- Dialysis disequilibrium syndrome.
- Renal replacement therapy is associated with increased risk of subdural hematoma and intracranial bleeding.
- Dialysis encephalopathy or dialysis dementia.

Nutrional and gastrointestinal alteration:

- Uremic fetor.
- Glossitis from iron ,vitamin B12 folate deficiency.
- Gastroesophageal reflex disease.

- Esophagitis.
- Acid peptic disease.
- Delayed gastric emptying and gastroparesis.
- Diverticulosis (ADPKD).
- Gastrointestinal hemorrhage.
- Uremic gastritis.
- Idiopathic dialysis associated ascites.
- Protein energy malnutrition.
- Obesity paradox – a higher body mass is associated with a better survival.

Dermatological abnormalities[31]:

- Uremic pruritis.
- Bullous dermatoses.
- Calcific uremic arteriolopathy.
- Nephrogenic systemic fibrosis.
- Hyperpigmentation due to deposition of urochrome.

Endocrine and CKD[12]:

- Glucose metabolism is impaired in chronic kidney disease. Plasma levels are moderately increased in uremic patients. Because of the decreased renal elimination of insulin and reduced gluconeogenesis, CKD patients are prone for hypoglycaemia and therefore need proper monitoring. Many oral hypoglycemic drugs likesulfonylureas,gliptins,

metformin need dose reduction or may be contraindicated with severe renal impairment.

- Females with chronic kidney disease may have low oestrogen, have menstrual abnormalities,miscarriages and infertility.
- Males with chronic kidney disease have low plasma testosterone,sexual dysfunction and oligospermia.
- Adolescents with CKD may have delayed sexual maturation.

THE THYROID GLAND

The thyroid gland is one of the larger endocrine glands with two main functions [32,33].

1. Secretion of thyroid hormone.
2. Secretion of calcitonin.

The thyroid hormone plays a vital role in metabolism of tissues that is required for normal functions of the body. It regulates lipid and carbohydrate metabolism and influence body mass and mentation.

The calcitonin regulates circulating levels of calcium.

Anatomic considerations:

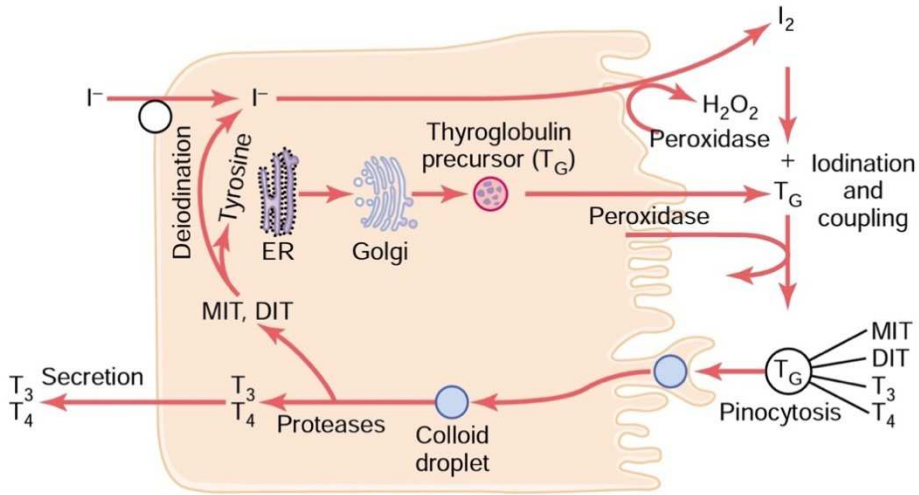
It is a butterfly shaped gland that develops from evagination of floor of pharynx and thyroglossal duct which marks the path of the thyroid from tongue to the neck.

The two lobes are connected by isthmus. Thyroid gland has one of the highest rates of blood flow per gram of tissue[32].

The Thyroid hormone:

The production of thyroid hormone takes place in acini which is surrounded by a single layer of epithelial cells and filled with colloid. In active state , the follicles are small , cells are cuboidal and reabsorption lacunae are seen.Thyroxine (T4) is the primary hormone secreted by thyroid. Triiodothyronine (T3) is secreted in much small amounts. T3 is formed from peripheral conversion of T4 and it is the biologically active hormone[32].

Thyroglobulin is a glycoprotein synthesised in the thyroid cells and secreted into the colloid. The iodine undergoes a process called organification between the thyrocyte and colloid. The oxidised iodine is incorporated into tyrosine residues of the thyroglobulin in the colloid this process is mediated by an enzyme called thyroid peroxidase. Thus the produced thyroid hormone stays as a part of thyroglobulin until need arises. When the need arises, the colloid is internalised by thyrocyte and lysosomal degradation takes place releasing free T4 and T3 into the cytoplasm and then into circulation[33,37].



This is a multistep process. Thyroid peroxidase forms reactive iodine species that attacks thyroglobulin to form monoiodotyrosine(MIT). Monoiodotyrosine is iodinatedagain to form diiodotyrosine(DIT). Two molecules of diiodotyrosine condense to form tetraiodothyronine T4. This condensation reaction is called “coupling reaction “of thyroid hormones. Thyroid peroxidase is involved in this reaction and is the rate limiting step.

T3 is formed by condensation of MIT with DIT. Traces of RT3 is formed by coupling of DIT with MIT. The human thyroid secretes about80micg of T4, 4micg of T3& 2micg of rT3.

The free thyroid hormone is the one that is physiologically activeand that feedback to inhibit TSH secretion. The function of protein binding is maintain the thyroid hormone poolthat can be easily mobilised when needed.

The thyroid hormone binds to albumin,transthyretin,thyroid binding globulin among which albumin has the largest capacity to bind T4. Normally,99.98% of T4 is bound and the free T4 is only 2ng/dl.

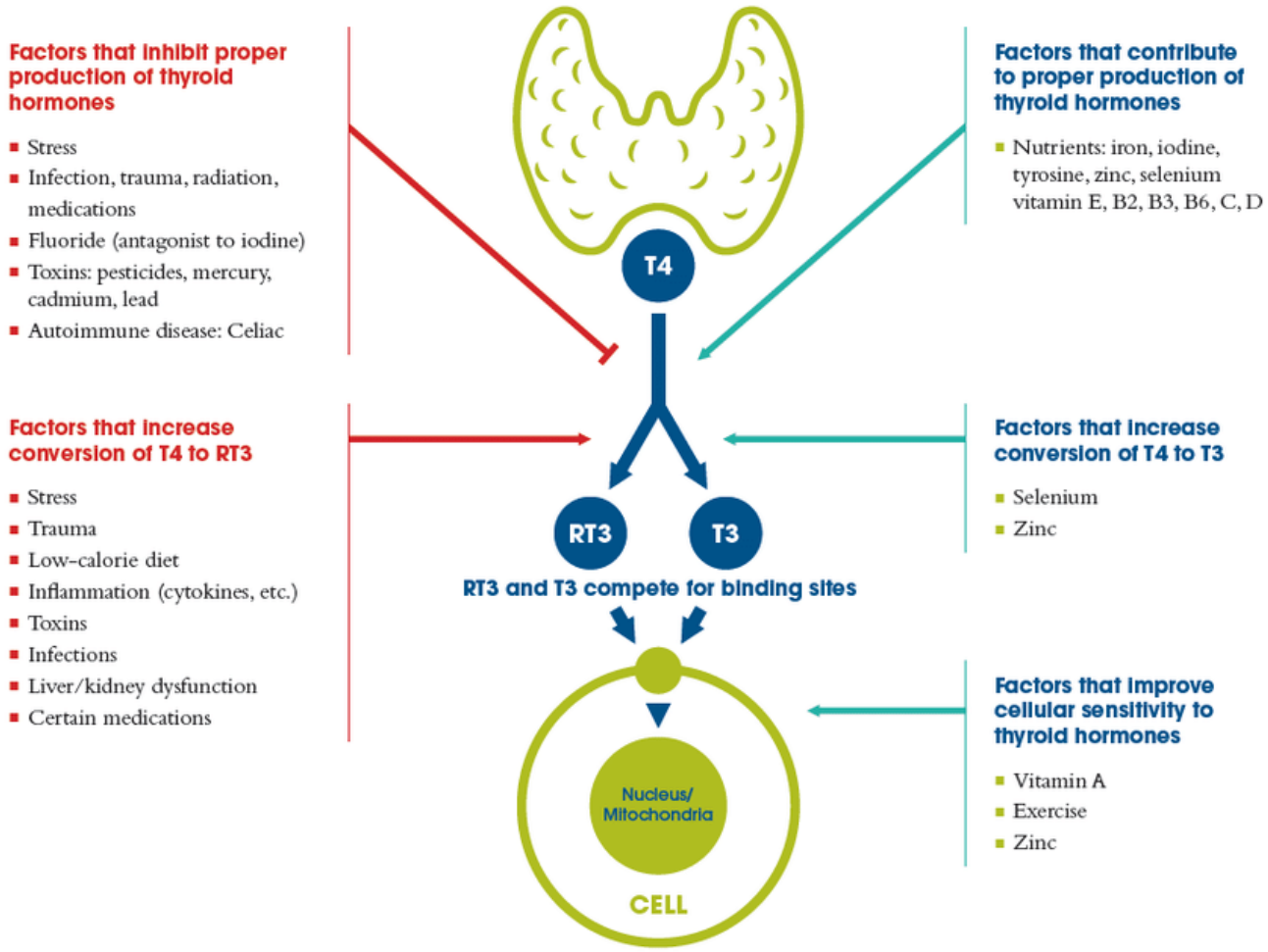
Regulation of thyroid secretion:

The anterior pituitary secretion of TSH is controlled by thyrotropin releasing hormone (TRH) secreted by the hypothalamus. TRH is transported to anterior pituitary through hypophyseal portal blood. TRH

binds to the TRH receptors in the TSH secreting cells to increase the secretion of TSH.

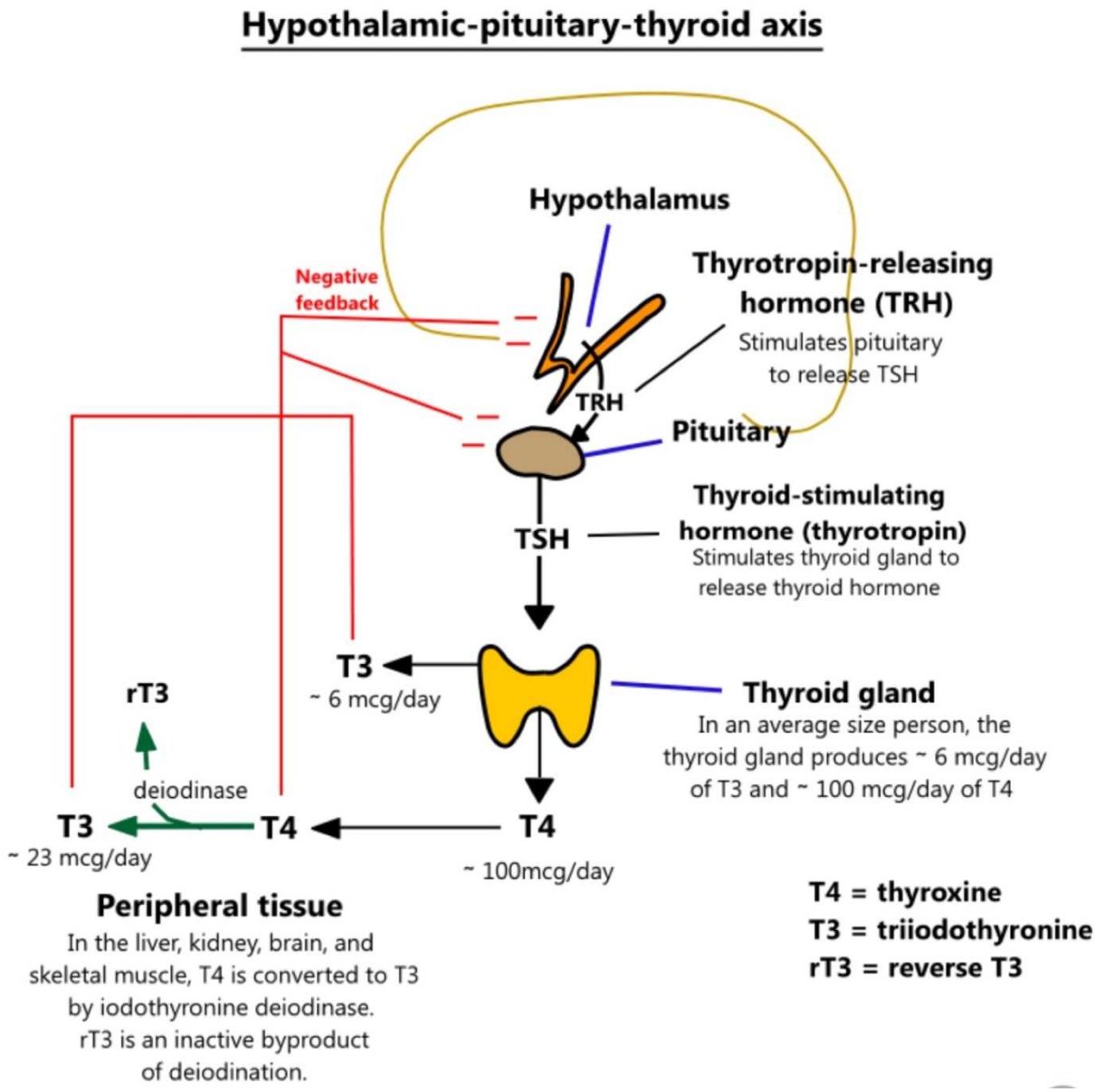
The increase in thyroid hormone in blood decreases the secretion of TSH by the anterior pituitary. Increased thyroid hormone inhibits anterior pituitary secretion of TSH mainly by a direct effect[32,33,40].

FACTORS AFFECTING THYROID HORMONE



Function of Thyroid hormone[32,35]:

- **Nervous system**: It promotes normal brain development.
- **Heart**: Increases the number and affinity of beta adrenergic receptors.
- **Endocrine** :Enhances responses to circulating catecholamines.
- **Muscle**: Increases protein breakdown.
- **Bone**: Promotes normal growth and skeletal development.
- **Gut:** involved in carbohydrate metabolism.
- **Adipose tissue**: Promotes lipolysis.
- **Lipoprotein**: Increases LDL receptors.
- **Bone marrow**: Stimulates the formation of red cells.
- **Others**:
- Stimulates oxygen consumption and increases basal metabolic rate (BMR)
- Promotes the development of reproductive system.
- Required for fetal lung maturation.



Hypothyroidism[32,33,35]:

Hypothyroidism refers to common pathological condition of thyroid hormone deficiency.as there is a large variation in clinical presentation, the definition of hypothyroidism is largely biochemical. Hypothyroidism is more common in patients with autoimmune disorders like type 1

diabetes,autoimmune gastropathy,coeliac disease, and can occur as a part of multiple autoimmune endocrinopathies.Hypothyroidism can be classified into

1. Primary hypothyroidism(thyroid hormone deficiency)
2. Secondary hypothyroidism(TSH deficiency)
3. Tertiary hypothyroidism(TRH deficiency)
4. Peripheral hypothyroidism(extra thyroidal)

Primary hypothyroidism:

Primary hypothyroidism is defined as TSH above normal reference range and free thyroxine below reference range [32].

In iodine sufficient areas , the most common cause of primary hypothyroidism is Hashimoto's thyroiditis.

Iodine is very essential for thyroid homeostasis. Iodine deficiency can result in goitre,thyroid nodules,and hypothyroidism. Cretinism is the most severe form of iodine deficiency manifesting as restricted mental and physical development inutero and in childhood.

Drugs like amiodarone can cause alteration in thyroid hormone production through iodine overload,an effect popularly called as Wolff-Chaikoff effect[33].Iatrogenic causes like radioiodine treatment is one of the causes.

Other causes include transient thyroiditis (de Queverian syndrome),thyroid gland infiltration,and genetic causes[45,46,47,48].

Central hypothyroidism:

Central hypothyroidism is rare and involves often pituitary than hypothalamus but frequently involves both.Biochemically it is defined as low or low normal TSH with low free thyroxine.Most common cause of central hypothyroidism is pituitary adenomas.Other cause include pituitary dysfunction (Sheehan's syndrome),hypothalamic dysfunction(post trauma),drugs,resistance to TSH and TRH,leptin stimulation.

Peripheral hypothyroidism:

Consumptive hypothyroidism is due to aberrant expression of deiodinase 3 enzyme or genetic disease with reduced sensitivity to thyroid hormone(mutation of MCT8)[48].

Sub-clinical hypothyroidism:

It is defined as elevation of thyrotropin level with normal free T4. Confirmation requires ruling out transient elevation of thyrotropin by repeated measurements of thyrotropin and free T4 after a period of 2 to 3 months. the incidence of subclinical hypothyroidism varies largely with factors like age,sex and iodine status. In up to half of the patients with subclinical hypothyroidism with thyrotropin levels below 7 mIU/L ,thyrotropin normalises by two years. When the thyrotropin

levels are above 10 mIU/L ,it is associated with increased risk of hypothyroid symptoms and cardiovascular risk. Therapy is generally recommended in patients lessthan 70 years who have thyrotropin levels of at least 10mIU/L. Therapy should be individualised for patients who are older than 70 years and

with thyrotropin levels less than 10mIU/L based on symptoms,cardiovascular risk and presence of anti-TPO antibodies [40,42,44].

Causes of transient rise of thyrotropin with normal t4

- Recovery from non-thyroid illness
- Recovery from thyroiditis
- Drugs like amiodarone,lithium etc.,
- Lack of adherence to levothyroxine treatment.

Clinical Features

SYMPTOMS	SIGNS
• Lethargy and weakness	Dry coarse skin, cold peripheries
• Feeling of cold	Puffiness of face, myxoedema
• Loss of hair	Alopecia,madarosis
• Poor concentration	Brady cardia
• Poor memory	Pseudo-myotonic reflex
• Constipation	Carpel tunnel syndrome
• Weight gain and poor appetite	Pericardial and pleural effusion
• Menorrhagia	
• Hoarseness of voice	

Thyroid function in non-thyroid diseases[38,42]:

The thyroid function assessment in patients with various non-thyroid illness is tedious especially among critical patients. Most

patients have low T3 and T4 and sometimes low TSH. These patients may actually go into a state of acquired central hypothyroidism.Many patients with chronic disease develop a condition called euthyroid hypothyroxemia with decreased T3 and T4 and normal TSH[52]. This condition was termed as sick euthyroid syndrome.Most of the ill patients who are hospitalised have a low serum level of T3. T3 is produced by the peripheral conversion of T4 by 5'monodeiodinase enzyme. The 5'monodeiodination decreases. with low calorie intake and with any illness[49,51].

Causes of decreased 5'monodeiodination [49,51,52]:

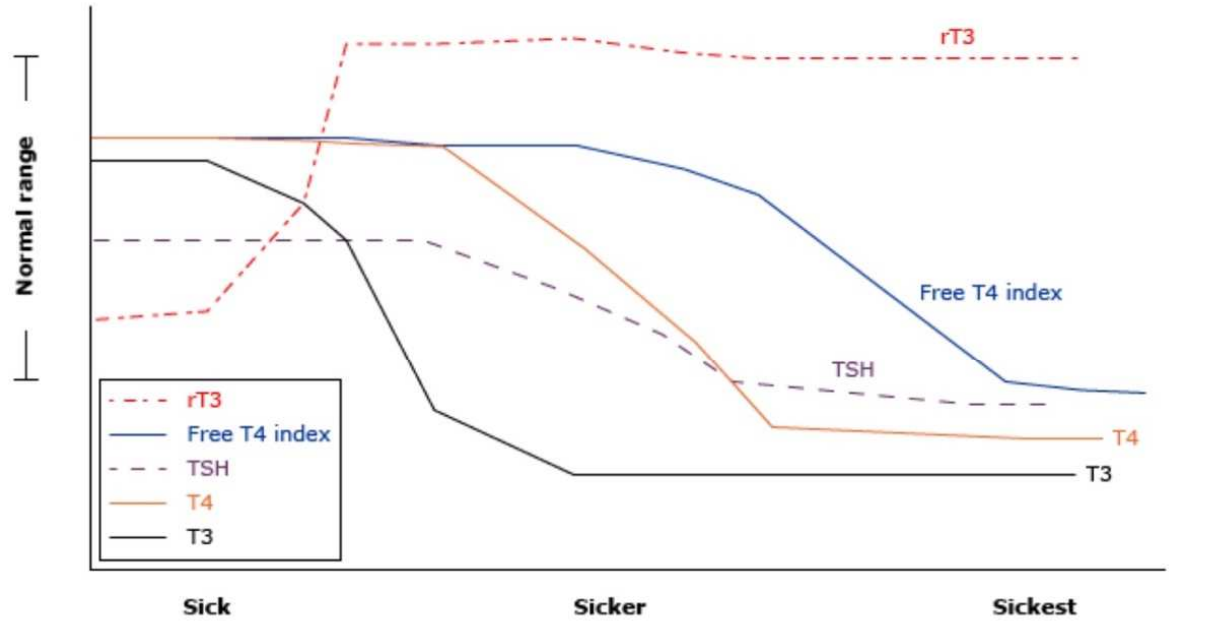
- Drugs like amiodarone, propranolol which inhibit the enzyme.
- High circulating levels of free fatty acids.
- Inflammatory cytokines like interferon alpha, tumor necrosis factor,interleukin-6 etc.,

Steroid therapy and high endogenous serum cortisol**.**

Reverse T3 :

rT3 is a product obtained by 5- monodeiodination of T4. It is increased in nonthyroid illness especially when there is hypoxia or ischemia. Clearance of rT3 to diiodothyronine is decreased in nonthyroid illness due to inhibition of 5'monodeiodination .Therefore the levels of rT3 are high in these patients except in chronic kidney disease and HIV [49,54,55]

Thyroid function tests in nonthyroidal illness



Schematic representation of the changes in thyroid function tests in patients with nonthyroidal illness of increasing severity.

rT3: reverse triiodothyronine; T4: thyroxine; TSH: thyroid-stimulating hormone; T3: triiodothyronine.

Thyroid function test should not be routinely performed critically ill patients unless

there is a strong suspicion suggestive of a thyroid dysfunction, because many other factors in acutely or chronically ill euthyroid patients can influence thyroid function tests.[63,67]

Many critically ill patientshave low serum total thyroxine (T4) and triiodothyronine (T3), and serum thyroid-stimulating hormone (TSH) are typically low, but sometimes may be low-normal or normal.[64]

When thyroid abnormality is suspected in seriously ill patients, measurement of serum TSH alone is not sufficient for the evaluation of thyroid dysfunction.Initial measurement of TSH and free T4 is needed. Some clinicians also measure a total T3 and total T4 at the time of the initial testing.[65,67]

In seriously ill patients without a strong clinical possibility of thyroid disease and minor TSH alteration,thyroid tests (TSH, free T4), is to be repeated after one to two weeks. [64]

In critically ill patients with a possibility of hyperthyroidism (TSH usually <0.01 ,and normal or high-normal serum T4 and/or T3), we suggest antithyroid drug therapy . the patient should be reassessed after recovery from the illness.[66,67]

Seriously ill patients with suspected hypothyroidism having serum TSH ≥20 mU/L with low free T4 low should be considered for treatment with thyroid hormoneand the same should be reassessed after recovery. [67]

In critically ill patients with low free T4 and total T3 who do not appear to have an underlying primary thyroid disorder, treating with thyroid hormone is not recommended as of now.

	PRIMARY HYPOTHYROIDISM	CENTRAL HYPOTHYROIDISM	SICK EUTHYROID STATE
T3	LOW OR LOW NORMAL	LOW OR LOW NORMAL	LOW
T4	LOW	LOW	NORMAL OR LOW OR HIGH
TSH	HIGH	LOW OR NORMAL	HIGH OR NORMAL OR LOW
rT3	LOW OR NORMAL	LOW	HIGH

PATTERNS OF NONTHYROID ILLNESS:

- Changes involve mainly the total hormone levels; changes in free fractions are

  only modest.
- T3 decreased and T4 is also decreased to a lesser extent → decreased basal metabolic rate, decreased protein and fat metabolism.
- Whether these changes are adaptive or maladaptive remains controversial.
- Different patterns are described:

  Low T3 Syndrome (70%)
- Commonest pattern and present to some degree in other patterns
- T3 falls rapidly and progressively within 1/2 24hh of onset of causative illness
- rT3 is increased

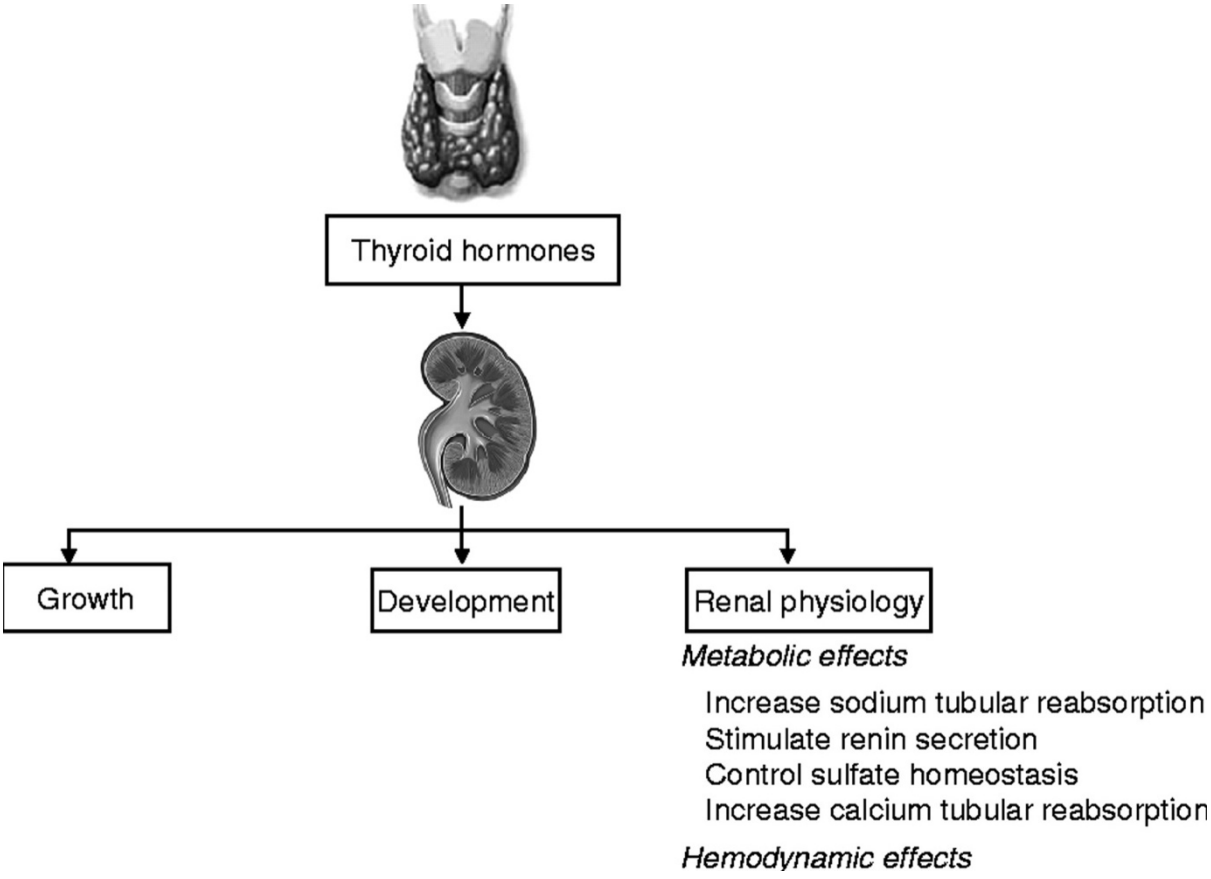
  Low T3, T4 Syndrome (30%)
- Observed in severely ill patients admitted to ICU
- T4 falls over a period of 1 to 2 days

  High T4 Syndrome (1%)
- Acute psychiatric illness
- Hepatitis (increased binding protein production)
- iodine exposure

THYROID AND KIDNEYS

1.EFFECTS OF THYROID DYSFUNCTION ON KIDNEYS:

Derangements associated with hypothyroidism include elevation in serum creatinine ,reduction of GFR and renal plasma flow,decreased free water clearance and hyponatremia[41,42.] Hypothyroid associated kidney dysfunction is due direct effects of thyroid hormone on cardiovascular system and metabolism and indirectly through paracrine and endocrine mediators[40,36,38].



THYROID AND RENAL DEVELOPMENT

Thyroid hormone affects kidney size, weight, and structure components both during development and growth in adults. Thyroid hormone plays a vital role in development of cortical and outer medullary tubular segments, particularly involving the proximal tubule, distal convoluted tubule, and medullary thick ascending limb.

Children with congenital hypothyroidism, so called cretins, have decreased renal mass and a increased incidence of renal abnormalities, like dysplastic kidneys, renal agenesis, ectopic kidney, hydronephrosis, posterior urethral valves, and hypospadias.

Whether renin–angiotensin–aldosterone system component serves directly or indirectly as a thyroid hormone–modifiable growth factor is still not clear.

Thyroid hormone is also important in the development of tubular function.

THYROID AND TUBULAR FUNCTION:

Thyroid hormone directly plays a role in the expression as well as activity of number of ion channels and transporters in the renal tubule. This may be due to direct binding of thyroid hormone to the promoter region of a transporter gene.

Hyperthyroidism can present with polyuria, due to downregulation of aquaporin 1 and 2 along with increased blood pressure, cardiac output, and renal blood flow. This may increase distal delivery of sodium, although there is upregulation of the Na^{+}-K^{+}-$2Cl^{-}$ cotransporter, leading onto increased urine flow rate.

Hyponatremia is a common complication of clinical hypothyroidism. Studies in hypothyroid animals show a decreased capacity to achieve maximal urinary dilution due to non-osmotic vasopressin release, and also, impairment in urinary concentrating ability of the kidneys, increased urine sodium excretion and increased fractional excretion of sodium.

HEMODYNAMIC CHANGES IN THYROID DYSFUNCTION:

Thyroid disease exerts Important effects on the cardiovascular system. Thyroid hormone affects cardiac myocytes by regulating genes that is important for myocardial contraction and electrochemical signalling.

Thyroid hormone also affects smooth muscle tone and reactivity of blood vessels. Nitric oxide synthase activity is increased in the kidney, heart, aorta in hyperthyroid state.

Hyperthyroidism increases cardiac output up to three-fold by increased heart rate, increased inotropy, and decreased systemic vascular resistance.Renal blood flow also increases.

In animal models, hypothyroidism reduces single nephron glomerular filtration rate, renal blood flow, and glomerular transcapillary hydrostatic pressure.

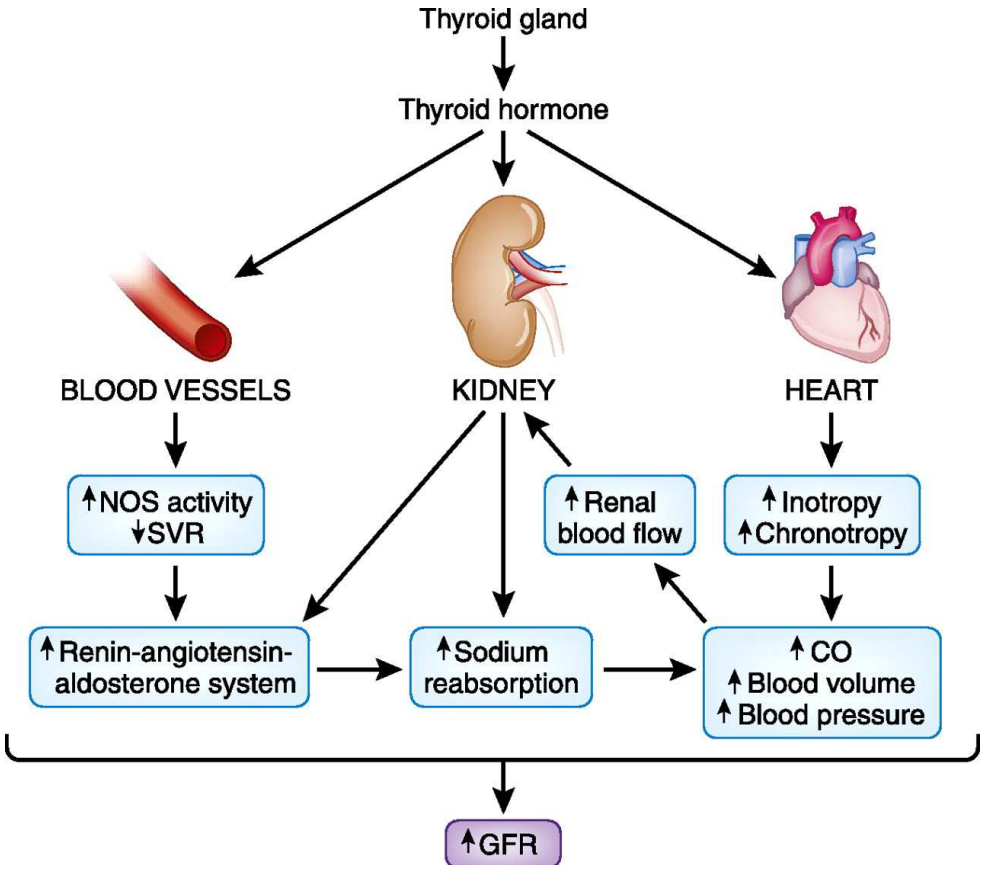
EFFECT OF THYROID DYSFUNCTION ON GFR:

The impact of thyroid disease on kidney function is highlighted by the fact that subclinical and clinical hypothyroidism is common in patients with estimated GFR < 60 ml/min per 1.73 m^2.

This arises a question of whether hypothyroidism is a cause of low GFR .

Elevation of levels of serum creatinine occurs within two weeks of significant overt hypothyroidism. These levels typically normalizes with thyroxine replacement, but slow and incomplete recovery in longstanding severe hypothyroidism.

A fall in serum creatinine with thyroid hormone replacement was associated with anincrease in GFR.



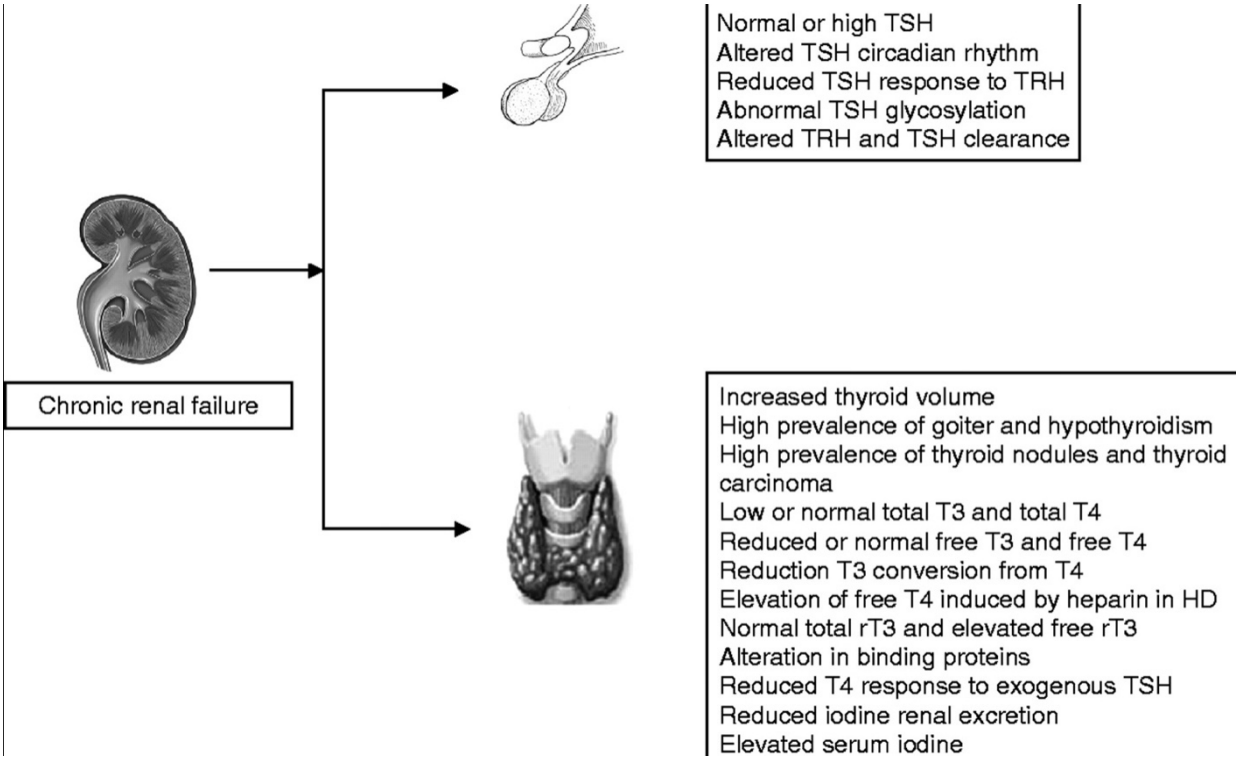
GLOMERULAR DISEASE IN THYROID DYSFUNCTION:

Reversible proteinuria and Glomerulonephritis are associated with hypothyroidism and hyperthyroidism, most commonly in autoimmune thyroiditis. Renal biopsy commonly shows membranous nephropathy, minimal change, membranoproliferative GN, and IgA nephropathy. Immune-mediated processes affecting both the organs may one of the reason supported by presence of thyroid peroxidase and thyroglobulin deposits in the kidney. Anti-neutrophil cytoplasmic antibody-positive crescentic glomerulonephritis is seen after therapy with propylthiouraciland membranous nephropathy after $\mathbf{I}^{131}$treatment.[45]

2.EFFECTS OF KIDNEY DYSFUNCTION ON THYROID:

Thyroid dysfunction can be associated with different types of kidney diseases[34].these include acute kidney injury,chronic kidney disease,glomerulonephritis,nephrotic syndrome and tubular diseases[36].The kidneys play an important role in the metabolism of thyroid hormone.so alteration of renal function can lead to the thyroid dysfunction. Renal dysfunction can involve all the levels of hypothalamic-pituitary-thyroid axisand also the synthesis , distribution and degradation of the thyroid hormone[43,44].

The kidneys are involved in the iodine excretion by glomerular filtration. So, in chronic kidney disease ,decreased iodide excretion results in increased plasma iodide and an initial increase in thyroid iodine uptake. This in-turn results in diminished production of thyroid hormones[50,58].

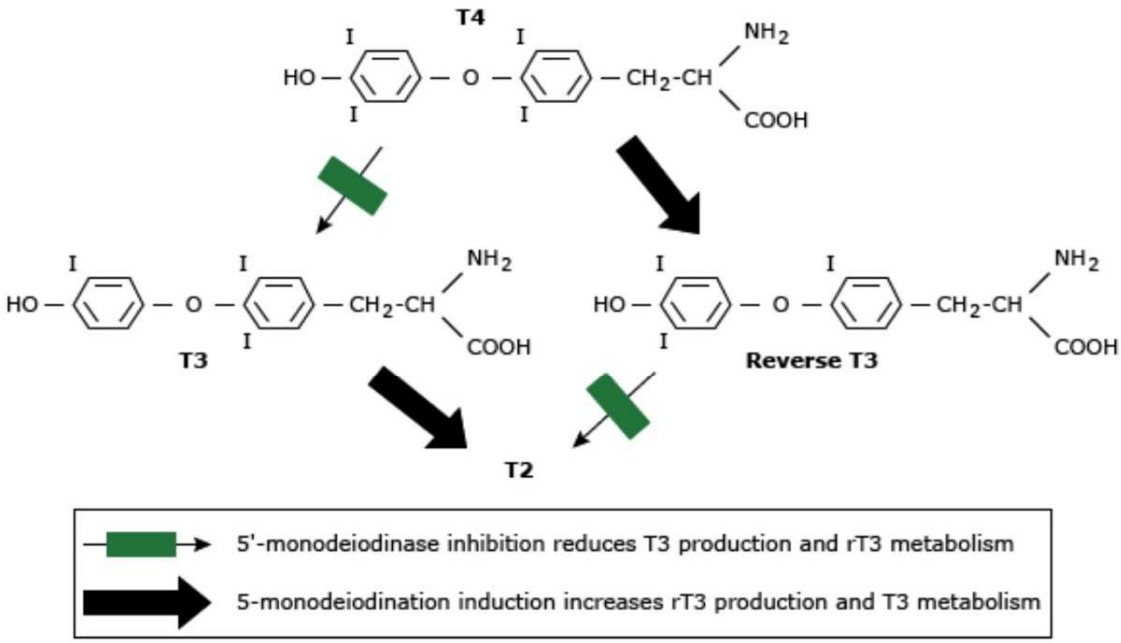


LOW T3:

Low T3 in end stage renal disease is due to reduced peripheral conversion of T4 to T3. But this is not associated with increased conversion of T4 to rt3 because in CKD patients, rT3 is in normal range which differentiates it from other chronic illness [58 ,59].

Low levels of total T3 may be due to metabolic acidosis and decreased protein binding of the thyroid hormones. In CKD, the retained uremic toxins like creatinine, urea, phenols and indoles are all strong inhibitors of hormone binding [54] . This tells why some CKD patients also exhibit low T4 levels. Studies conducted have shown that low T3 in CKD have been associate with reduced overall survival and chronic malnutrition - inflammation syndrome [56] .

T4 metabolism in nonthyroidal illness



The inhibition of 5'-monodeiodinase in nonthyroidal illness leads to decreased conversion of T4 to T3 and reduced metabolism of rT3. The induction of 5-monodeiodinase (D3) leads to increased conversion of T4 to rT3 and the metabolism of T3.

T4: thyroxine; T3: triiodothyronine; T2: diiodothyronine; rT3: reverse triiodothyronine.

Hypothalamic pituitary dysfunction [40,43] .

Usually CKD patients have normal TSH levels. These patients have a decreased response of TSH to exogenously administered TRH.

This may be because of decreased clearance of TSH and TRH by kidneys.However, this also shows a blunted response at the hypothalamic-pituitary level which may be due to the effect of uremic toxins.

Significance of Thyroid test in CKD:

There is a significant overlap between the symptoms of CKD and hypothyroidism like puffiness of face,dry skin,lethargy, cold intolerance etc., End stage renal failure patients also have an increased frequency of goitre[36,38]. Despite this, most of the CKD patients are considered euthyroid because of normal TSH and normal free T3[40] . Absence of delayed tendon reflex time in CKD patients is a confirmatory finding to rule out overt hypothyroidism in these patients[43]. Exogenous T3 supresses TSH and TSH production increases appropriately after thyroid ablation. This is vital because when a CKD patient develops hypothyroidism, the TSH increases [53].

Earlier low T3 syndrome was thought to be an adaptive mechanism in CKD. There is a correlation between the low T3 and inflammatory markers, nutrition and cardiac function. The lower the T3 values the greater the inflammation, poorer the nutritional status and worser the cardiac function.Recent studies have shown an increased all cause mortality and cardiovascular death in uremia. So, low T3 has a survival disadvantage[57].

Effects of dialysis on thyroid function:

Hemodialysis:

Hypothyroidism is common in these patients. The diagnosis of hypothyroidism in hemodialysis patients should not be made on the basis of reduced T_4 and T_3 levels alone . It requires the substantial TSH elevation.TSH>5 mIU/l but <20 mIU/l can occur in 20% of uraemic patients and are more indicative of non-thyroidal illness than hypothyroidism. HD leads to a reduction in serum total and free T_3 concentrations. This reduction may be associated with metabolic acidosis, frequency of dialysis, and few markers of endothelial injury and inflammation . Low T3 may be a protective adaptation for protein conservation. So,inappropriate thyroxine supplementation can lead to excessive protein nitrogen wasting in these patients. HD influences the cellular transport of thyroid hormones. This could act as a compensatory mechanism to maintain euthyroid status

Peritoneal dialysis:

Primary hypothyroidism, especially subclinical hypothyroidism is the most common thyroid dysfunction in these subset of patients. Other common abnormality in thyroid function tests is low T_3 syndrome. The high protein loss caused by this type of dialysis may be related to the increased incidence of thyroid dysfunction.. Nevertheless, thyroglobulin levels remain within normal limits in these subgroup of patients.

Drugs that can cause thyroid dysfunction and/or renal disease:

Drug	Indication	Thyroid dysfunction	Renal disease
Antithyroid drugs	Hyperthyroidism	Hypothyroidism	Glomerulonephritis
Lithium	Bipolar disorder	Hypothyroidism	Nephrogenic diabetes insipidus
Amiodarone	Arrhythmias	Hypo/hyperthyroidism	Acute kidney injury
Rifampicin	Tuberculosis	Hyperthyroidism	Tubulointerstitial nephritis

Drugs used in kidney disease that can affect thyroid function:

Drug	Indication	Thyroid pathology
Alemtuzumab	Renal transplant	Autoimmune thyroiditis
Lenalidomide	Metastatic renal carcinoma	Hyperthyroidism
Sunitinib	Metastatic renal carcinoma	Hypo/hyperthyroidism

MATERIALS AND METHODS

STUDY CENTRE AND SOURCE OF DATA:

Chronic kidney disease patients who were on conservative therapy admitted in institute ofinternal medicine ,madras medical college and RajivGandhi government general hospital.

STUDY DESIGNobservational, cross sectional study.

DURATION OF STUDY:6 months (August 2017 to January 2018).

SAMPLE SIZE:50 patients**.**

This study was conducted on 50 patients who were diagnosed as a case of chronic kidney disease and who were not on any renal replacement therapy who got admitted in the Institute of Internal Medicine , Madras Medical College and Rajiv Gandhi Government General Hospital, between August 2017 and January 2018. The patients were selected by simple random sampling method.

Informed consent was obtained from all patients included in the study. Statistical indices like correlation,standard deviation and mean are used.

INCLUSION CRITERIA:

1.Age greater than 18 years.

2.Patients with chronic kidney disease of different stages who are not on dialysis.

Criteria to say a case as chronic kidney disease:

- Uremic symptoms for more than three months.
- Elevated blood urea , creatinine and reduced eGFR.
- Ultrasonographic evidence of renal parenchymal disease or loss of corticomedullary differentiation.
- Supportive evidence like hypocalcemia,anemia,hyperphosphatemia etc.

EXCLUSION CRITERIA:

- CKD patients who are on renal replacement therapy.
- Pregnant patients.
- Patients who are known case of primary hypothyroidism.
- Post-Surgical patients.
- Patients taking drugs that alter thyroid function.
- Age less than 18 years.

METHADOLOGY:

Patients with CKD and were on conservative treatment ,who were randomly selected were subjected to thorough history taking and detailed clinical

examination. After careful selection , those fulling the criteria were subjected to biochemical tests. About 6 ml of blood was drawn in a sterile vacutainer with clot activator .the following tests were done .

- Blood urea
- Serum creatinine
- Serum sodium and potassium
- Serum calcium and phosphorous
- Complete hemogram
- Urine routine analysis
- Ultrasound abdomen

An early morning sample was also taken for thyroid function test which included

- Total Serum T3
- Total Serum T4
- Serum TSH.

  It was done by enzyme linked immunosorbent assay. the reference values are

Thyroid function test	**Reference range**
Total serum t3	0.6 – 2.1 ng/ml
Total serum t4	5 – 13 micgram/dL
TSH	0.4 – 7 micIU/ml

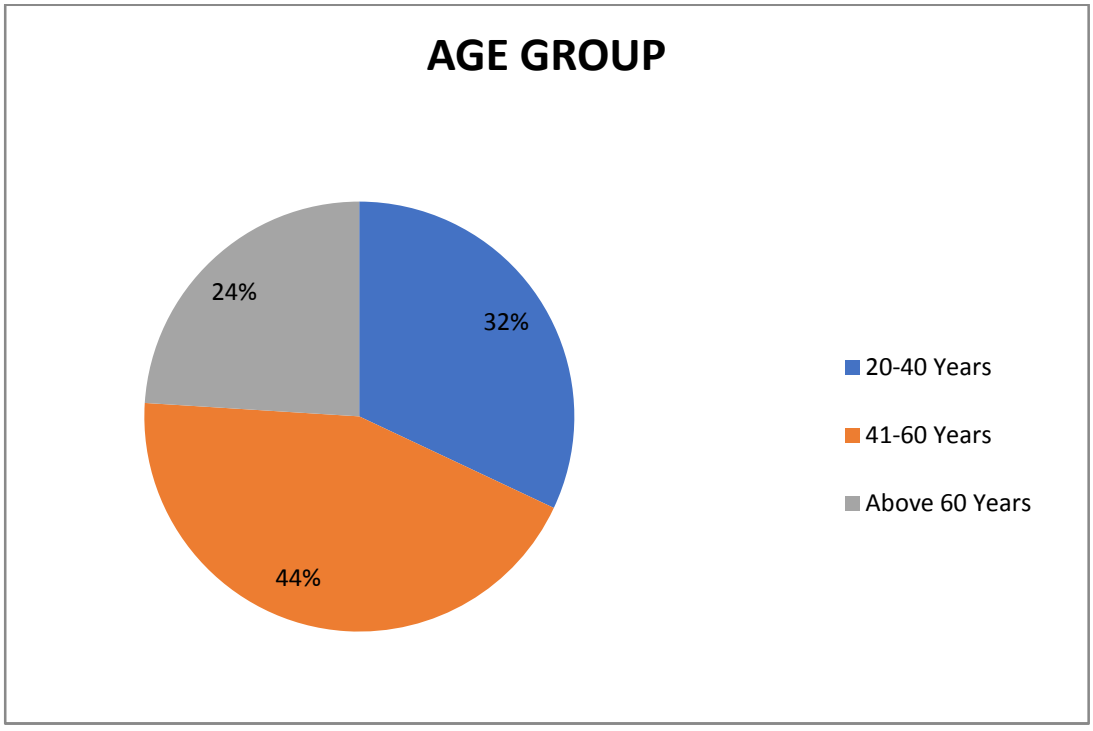
RESULTS & ANALYSIS

AGE WISE DISTRIBUTIONOF CASES

Table 1

Age group	Frequency	Percent
20-40 years	16	32.0
41-60 years	22	44.0
Above 60 years	12	24.0
Total	50	100.0

Chart 1

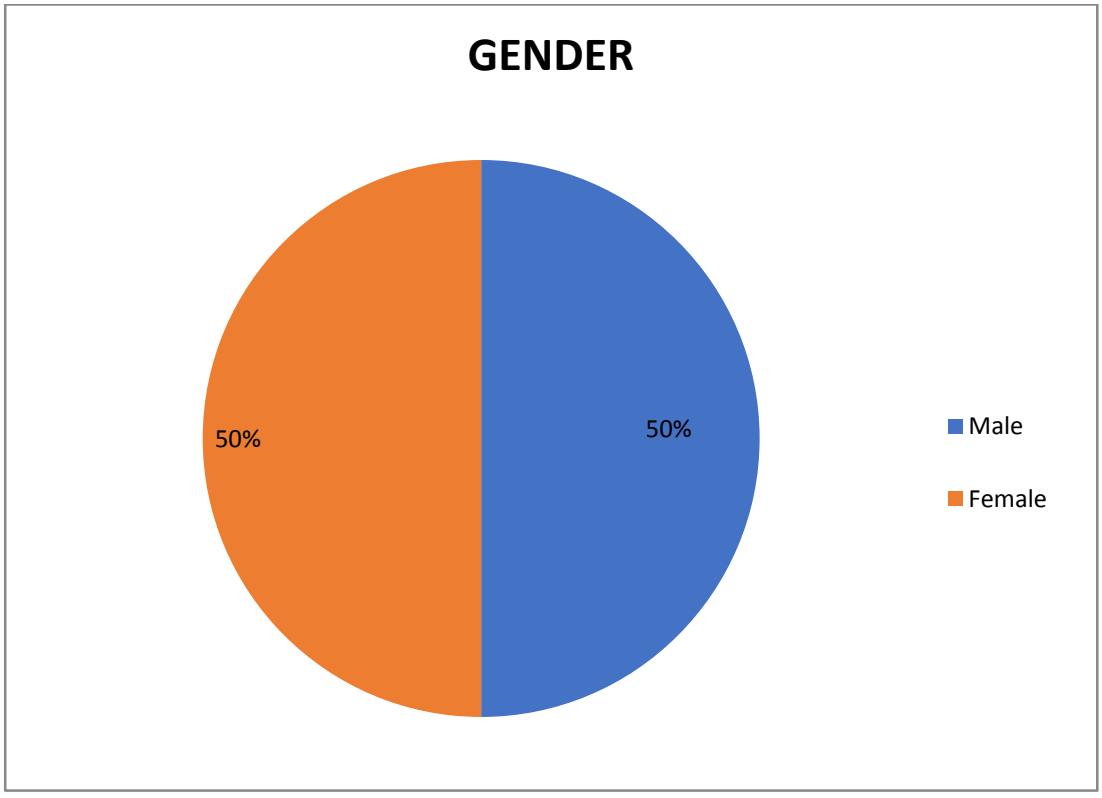


SEX DISTRIBUTION IN CKD PATIENTS

Table 2

Sex	Frequency	Percent
Male	25	50.0
Female	25	50.0
Total	50	100.0

Chart 2

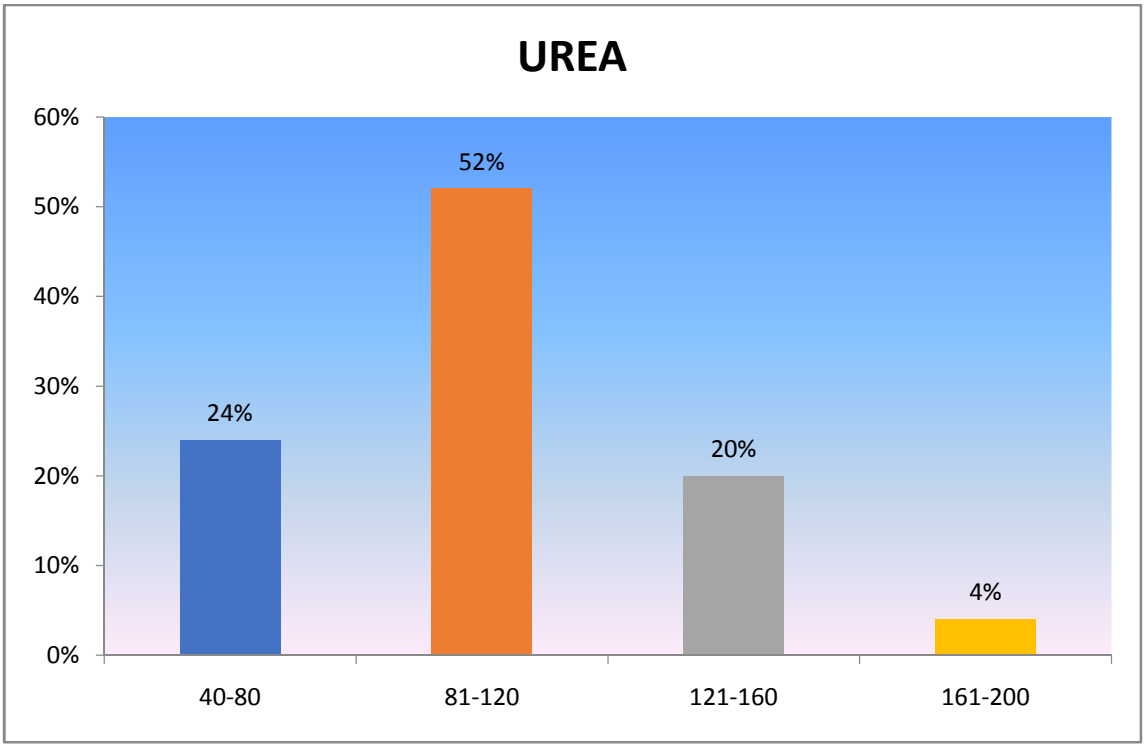


DISTRIBUTION OF BLOOD UREA IN STUDY SAMPLE

Table 3

Urea group	Frequency	Percent
40-80	12	24.0
81-120	26	52.0
121-160	10	20.0
161-200	2	4.0
Total	50	100.0

Chart 3

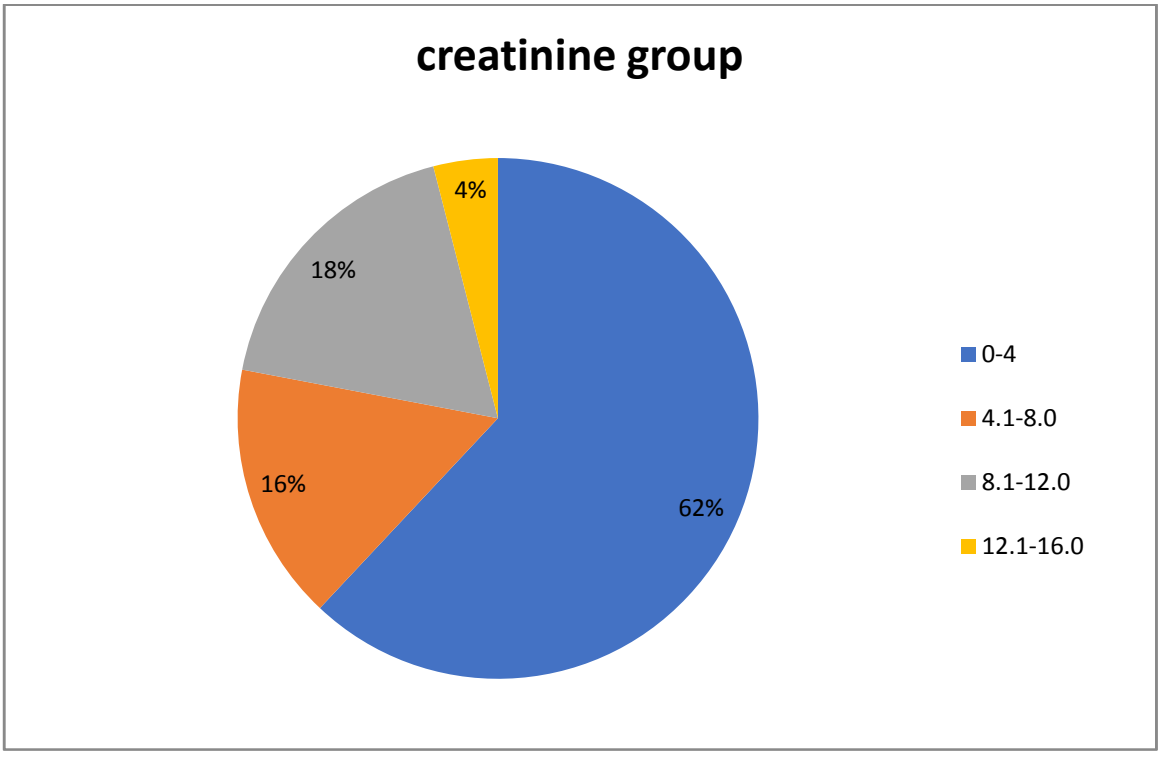


DISTRIBUTION OF SERUM CREATININE IN THE STUDY SAMPLE

Table 4

Creatinine group	Frequency	Percent
0-4	31	62.0
4.1-8.0	8	16.0
8.1-12.0	9	18.0
12.1-16.0	2	4.0
Total	50	100.0

Chart 4

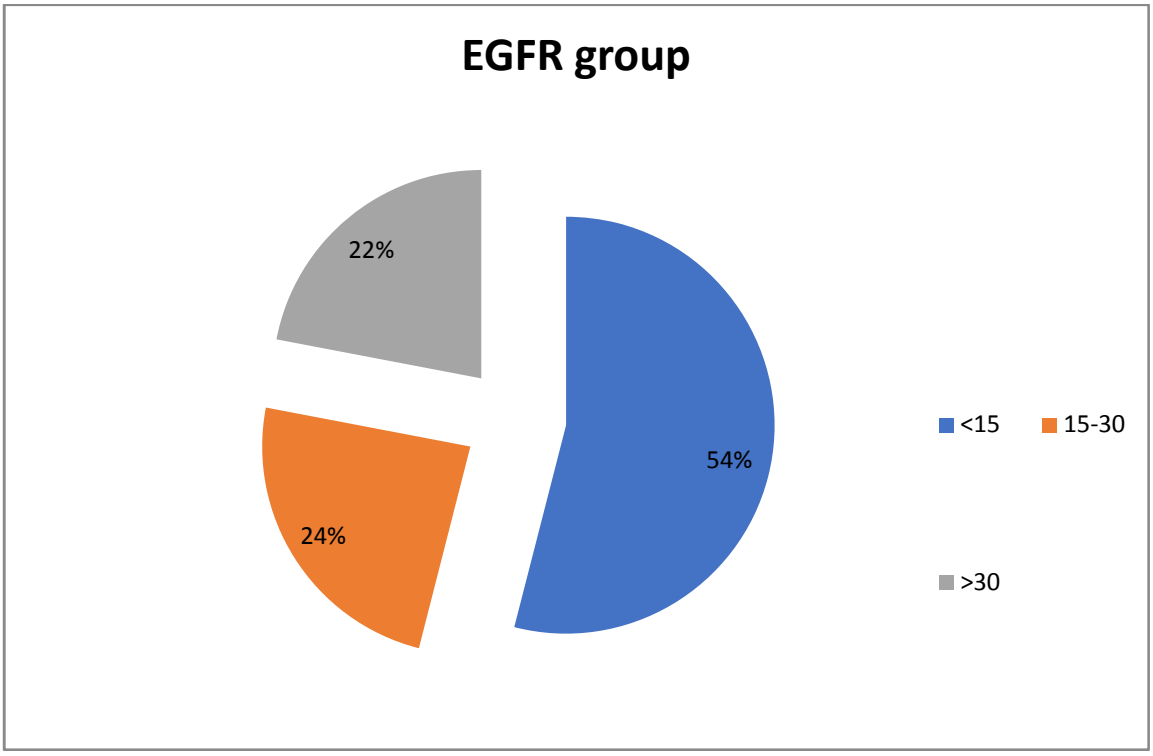


DISTRIBUTION OF EGFR IN CKD PATIENTS

Table 5

Egfrgroup	Frequency	Percent
<15	27	54.0
15-30	12	24.0
>30	11	22.0
otal	50	100.0

Chart 5

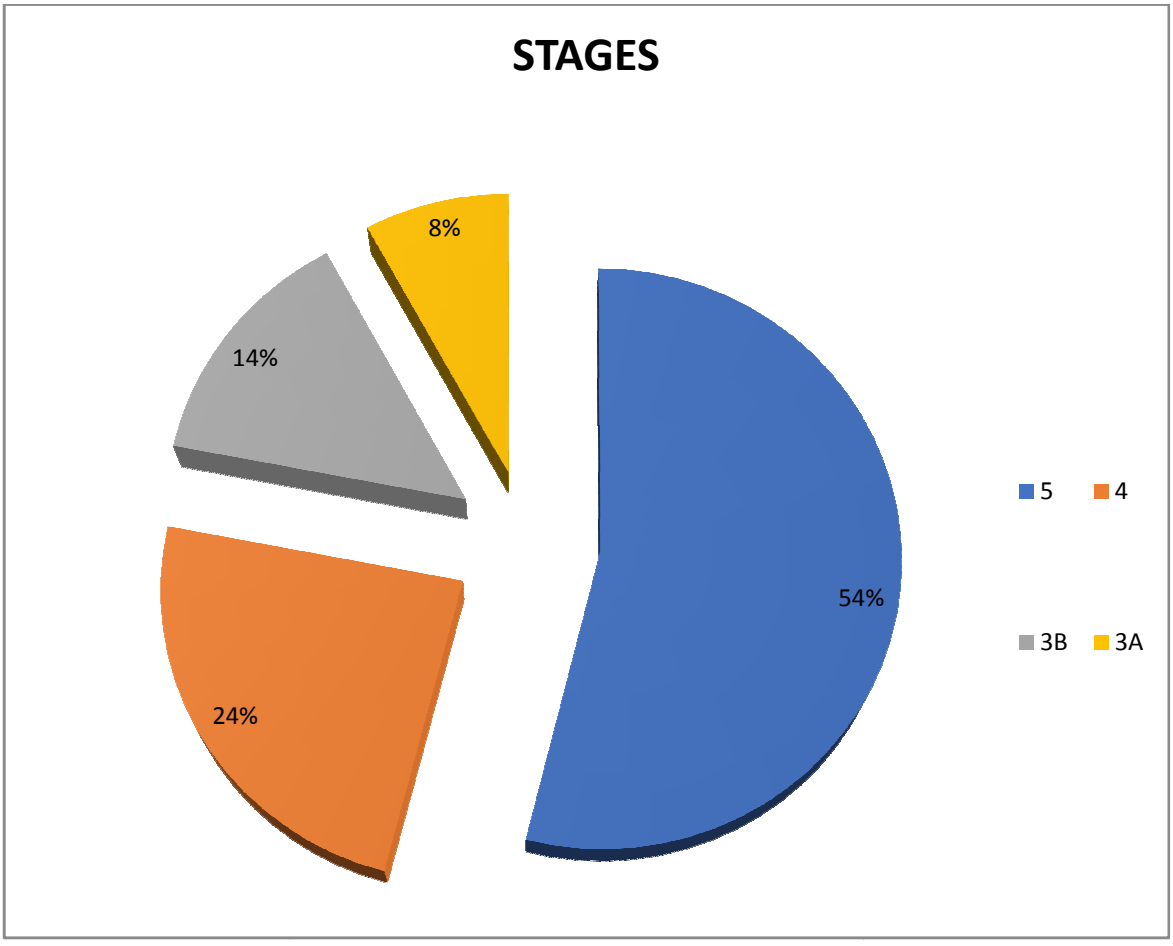


DISTRIBUTION OF CKD STAGES IN CASES

Table 6

Stage	Frequency	Percent
4.00	12	24.0
5.00	27	54.0
3A	4	8.0
3B	7	14.0
Total	50	100.0

Chart 6

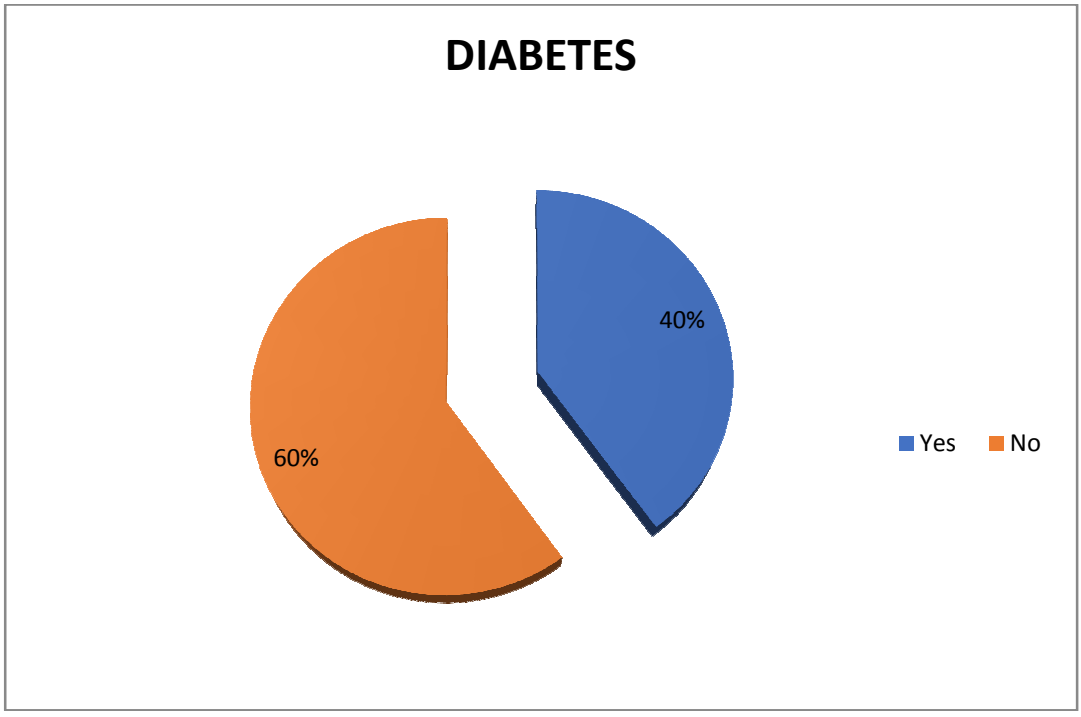


DISTRIBUTION OF DIABETES IN CKD PATIENTS

Table 7

Diabetes	Frequency	Percent
Yes	20	40.0
No	30	60.0
Total	50	100.0

Chart 7

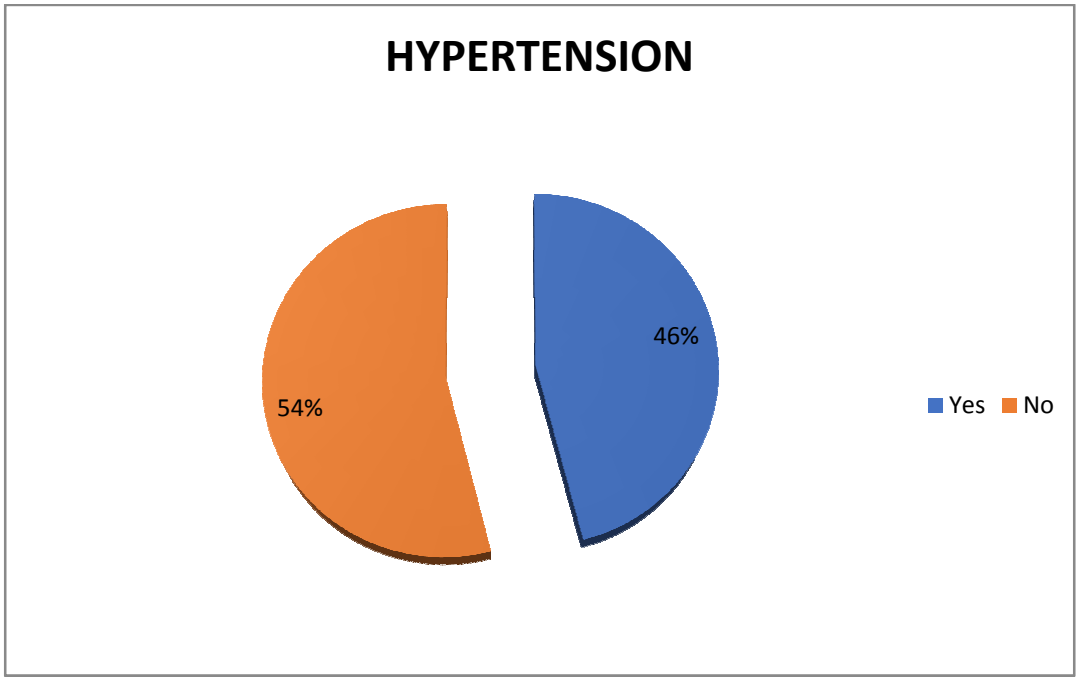


DISTRIBUTION OF HYPERTENSION IN CASES

TABLE 8

Hypertension	Frequency	Percent
Yes	23	46.0
No	27	54.0
Total	50	100.0

CHART 8

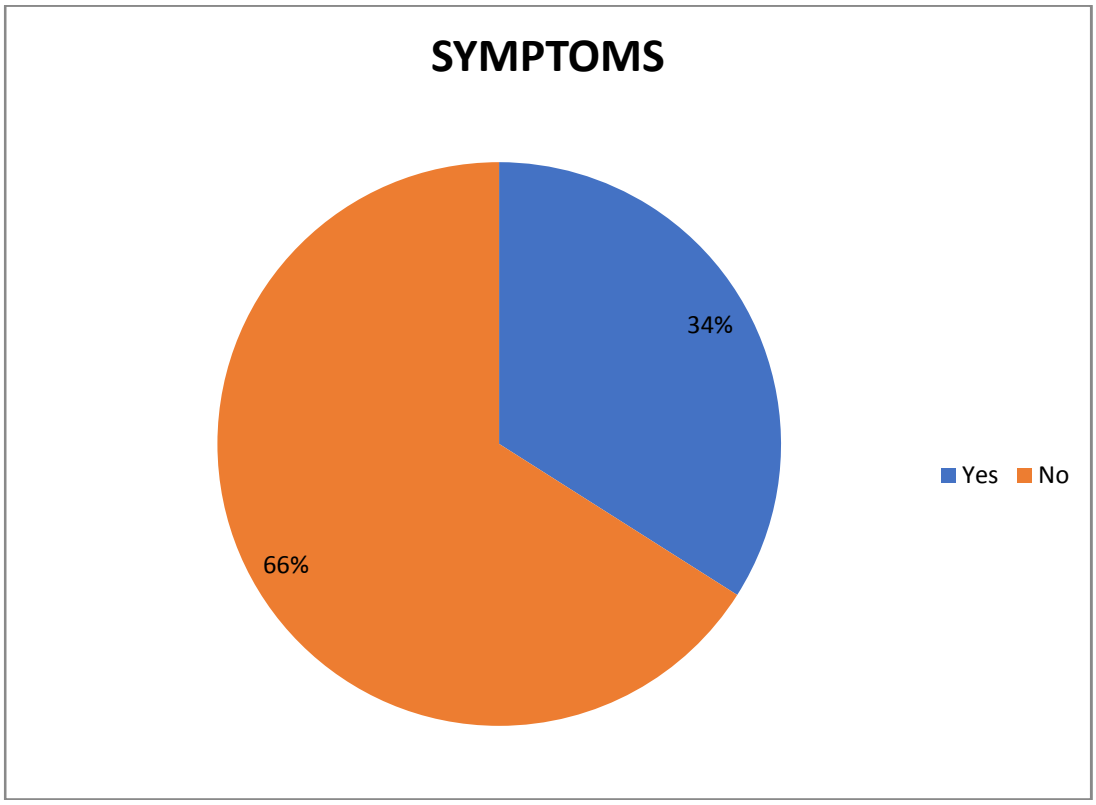


DISTRIBUTION OF HYPOTHYROIDISM SYMPTOMS AMONG STUDYSAMPLE

Table 9

Symptoms	Frequency	Percent
Yes	17	34.0
No	33	66.0
Total	50	100.0

Chart 9

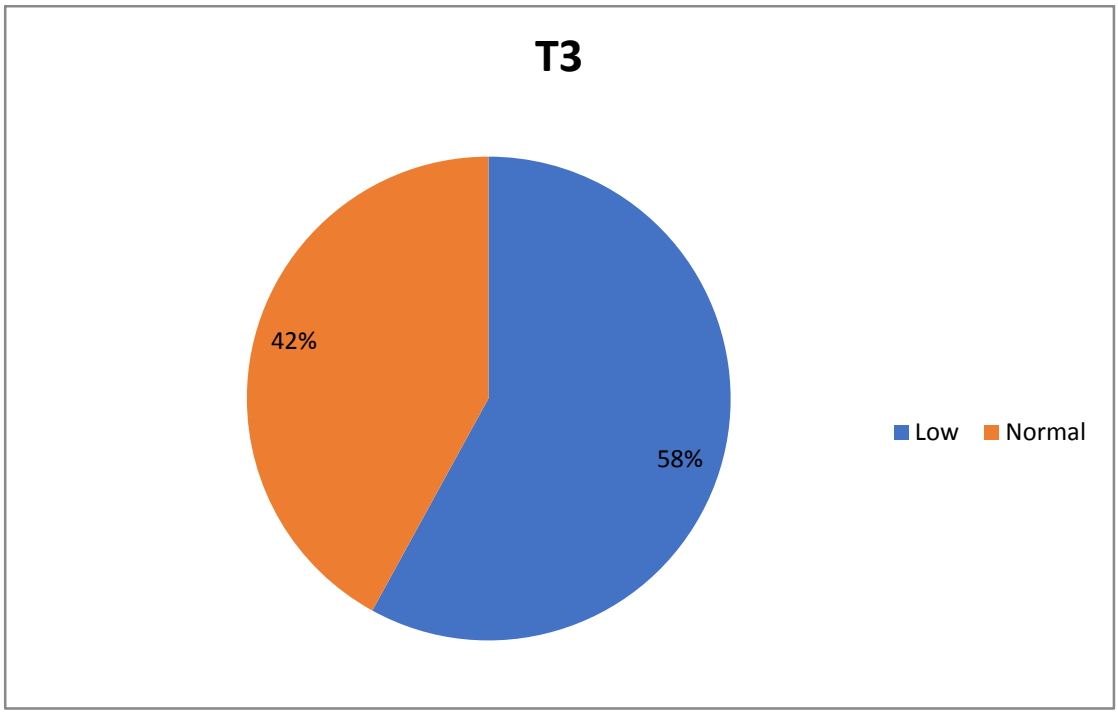


DISTRIBUTION OF SERUM T3 IN STUDY SAMPLE

Table 10

T3_GROUP	Frequency	Percent
Low	29	58.0
Normal	21	42.0
Total	50	100.0

Chart 10



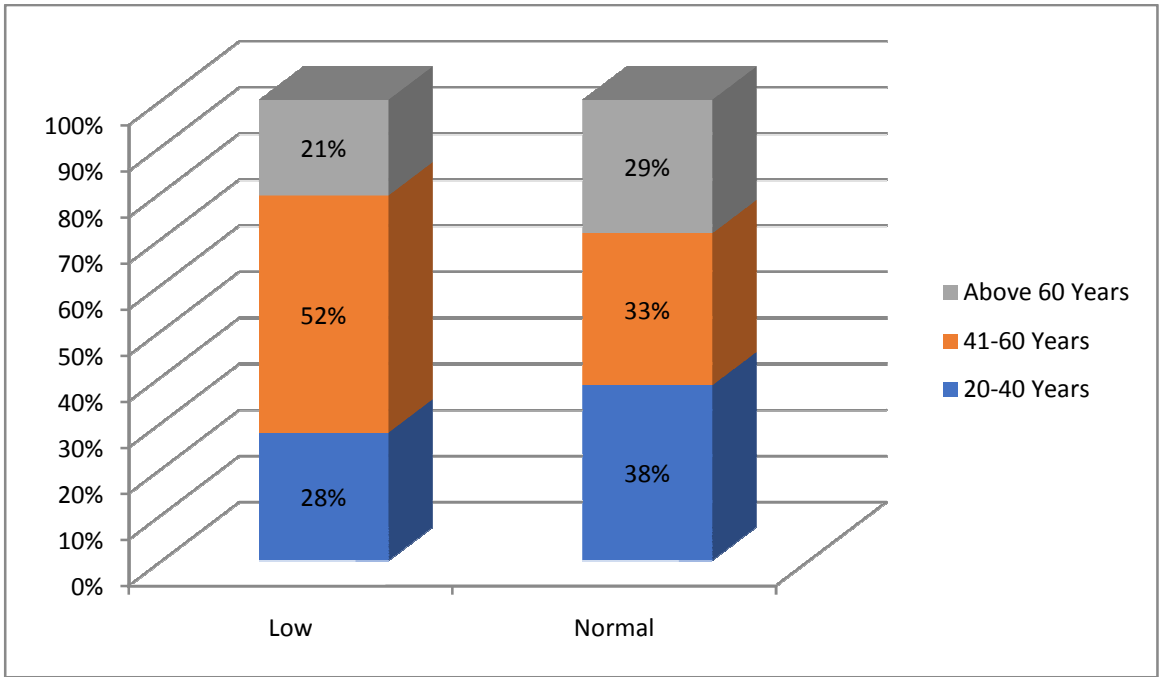
DISTRIBUTION OF AGE AND SERUM T3 AMONG THE CASES

TABLE 11

			T3_GROUP		Total
			Low	Normal	
age_group	20-40 Years	Count	8	8	16
		% within T3_GROUP	27.6%	38.1%	32.0%
	41-60 Years	Count	15	7	22
		% within T3_GROUP	51.7%	33.3%	44.0%
	Above 60 Years	Count	6	6	12
		% within T3_GROUP	20.7%	28.6%	24.0%
Total		Count	29	21	50
		% within T3_GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=1.672. P=0.433

TABLE 11



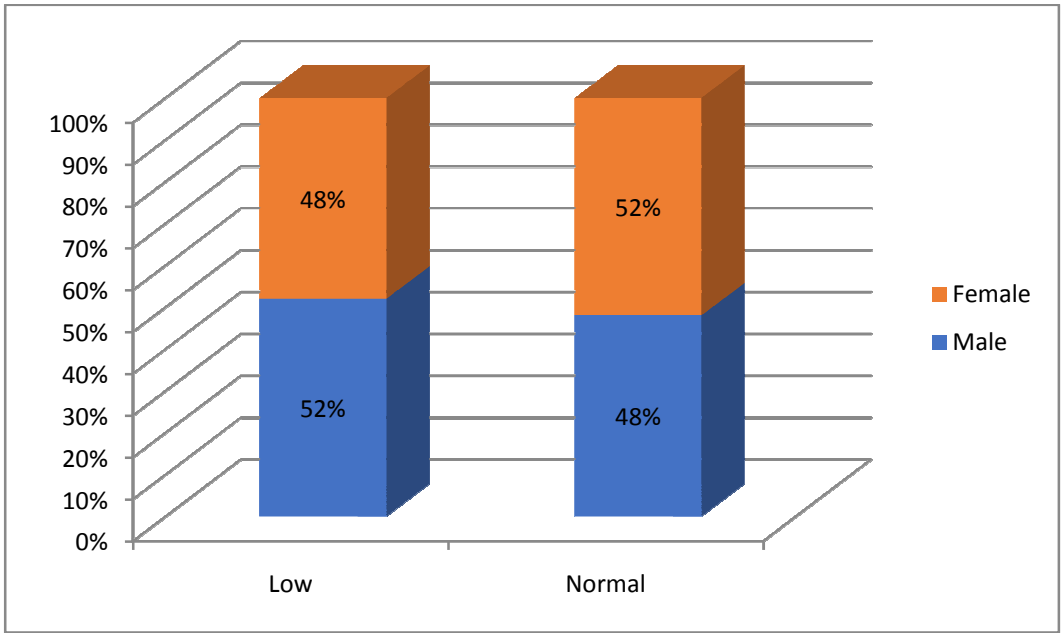
DISTRIBUTION OF SEX AND SERUM T3 AMONG CASES

Table 12

			T3_GROUP		Total
			Low	Normal	
sex	Male	Count	15	10	25
		% within T3_GROUP	51.7%	47.6%	50.0%
	Female	Count	14	11	25
		% within T3_GROUP	48.3%	52.4%	50.0%
	Total	Count	29	21	50
		% within T3_GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=0.082 P=0.774

Chart 12

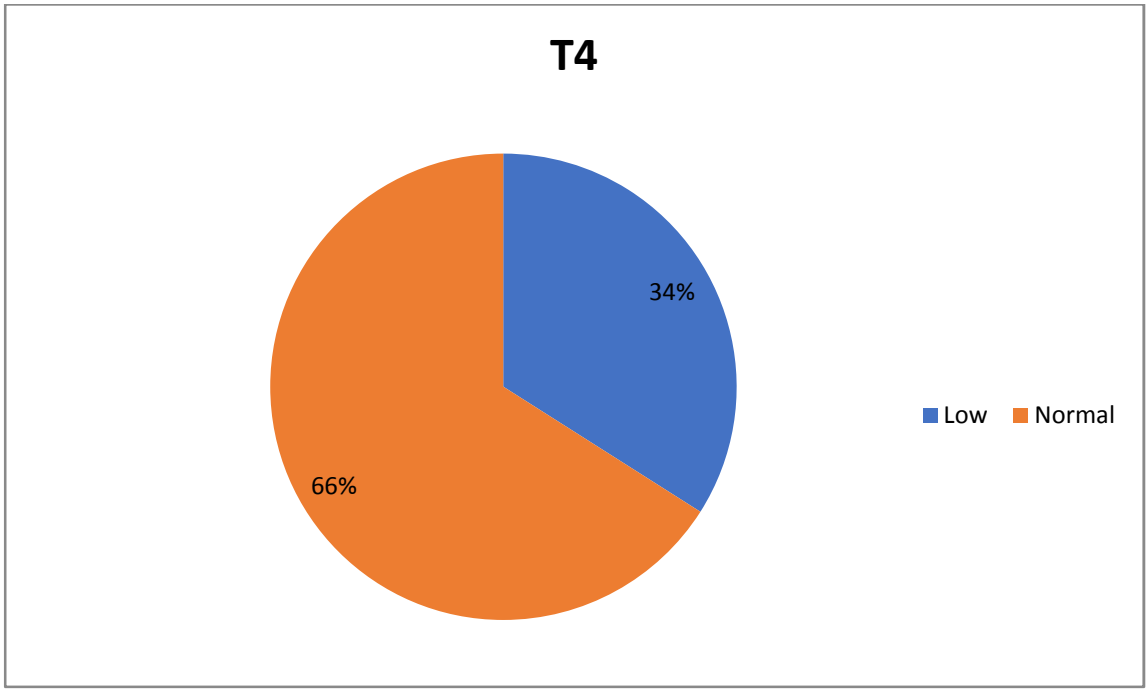


DISTRIBUTION OF SERUM T4 IN THE STUDY SAMPLE

Table 13

T4_GROUP	Frequency	Percent
Low	17	34.0
Normal	33	66.0
Total	50	100.0

Chart 13



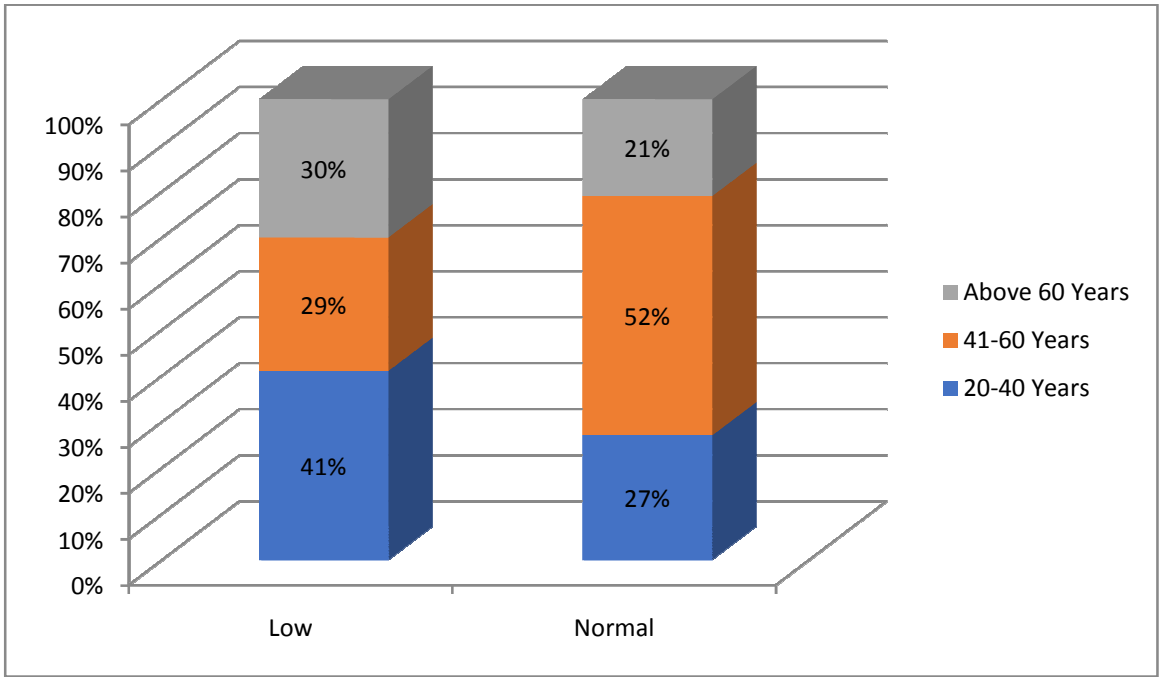
DISTRIBUTION OF AGE AND SERUM T4 AMONG CASES

Table 14

			t4_group		Total
			Low	Normal	
age_group	20-40 Years	Count	7	9	16
		% within t4_group	41.2%	27.3%	32.0%
	41-60 Years	Count	5	17	22
		% within t4_group	29.4%	51.5%	44.0%
	Above 60 Years	Count	5	7	12
		% within t4_group	29.4%	21.2%	24.0%
Total		Count	17	33	50
		% within t4_group	100.0%	100.0%	100.0%

Pearson Chi-Square=2.238 P=0.327

Chart 14

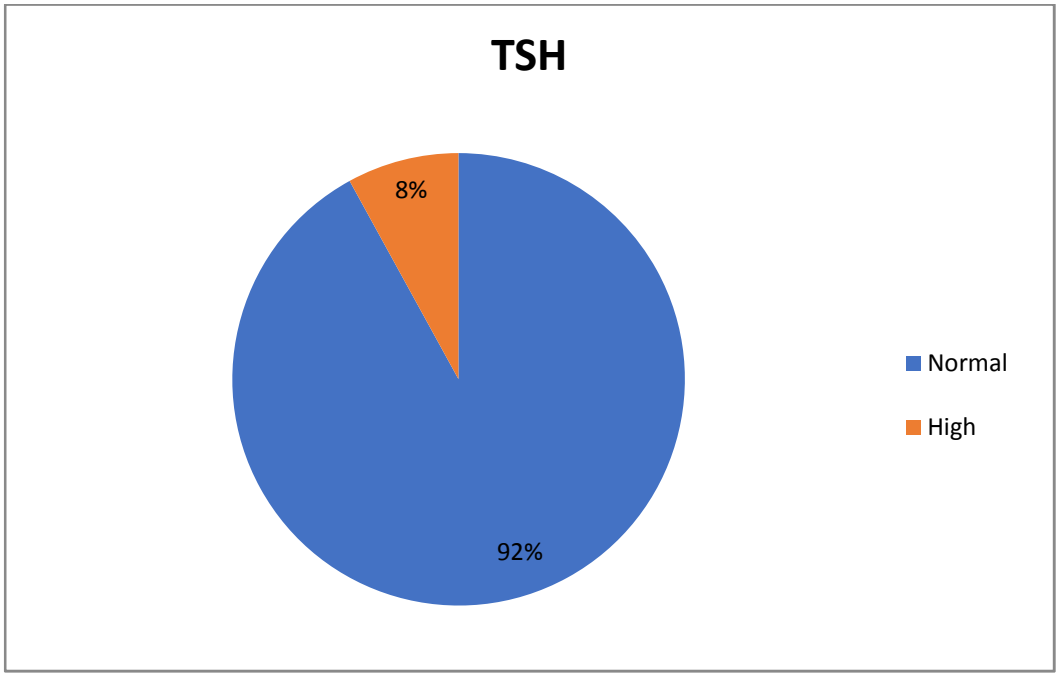


DISTRIBUTION OF TSH IN STUDY POPULATION

Table 15

TSH_GROUP	Frequency	Percent
Normal	46	92.0
High	4	8.0
Total	50	100.0

Chart 15



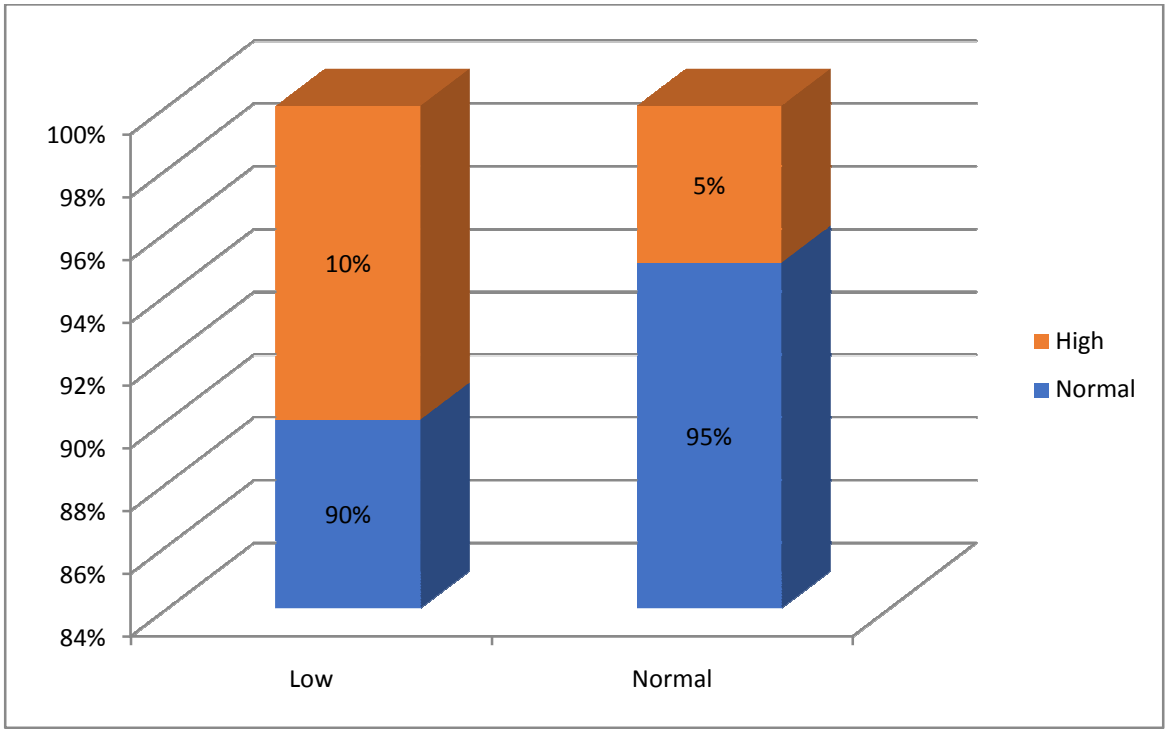
DISTRIBUTION OF LOW T3 WITH DIFFERENT LEVELS OF TSH

Table 16

			T3_GROUP		Total
			Low	Normal	
tsh_group	Normal	Count	26	20	46
		% within T3_GROUP	89.7%	95.2%	92.0%
	High	Count	3	1	4
		% within T3_GROUP	10.3%	4.8%	8.0%
Total		Count	29	21	50
		% within T3_GROUP	100.0%	100.0%	100.0%

- Pearson Chi-Square=0.516 P=0.473

Chart 16



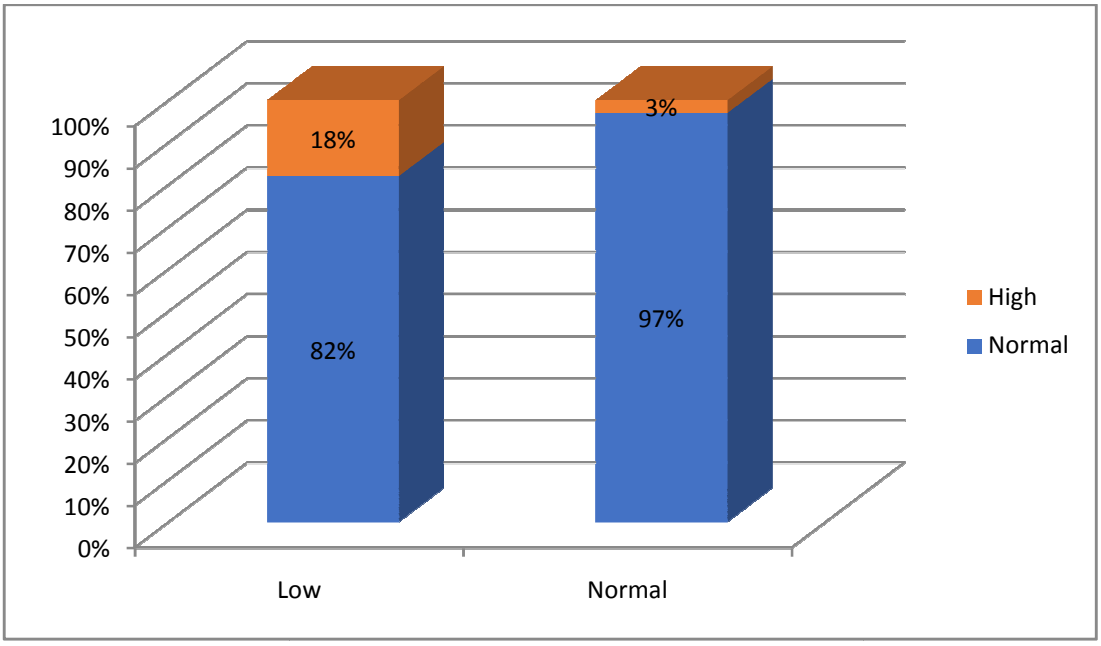
DISTRIBUTION OF LOW T4 WITH DIFFERENT LEVELS OF TSH

Table 17

			t4_group		Total
			Low	Normal	
tsh_group	Normal	Count	14	32	46
		% within t4_group	82.4%	97.0%	92.0%
	High	Count	3	1	4
		% within t4_group	17.6%	3.0%	8.0%
	Total	Count	17	33	50
		% within t4_group	100.0%	100.0%	100.0%

- Pearson Chi-Square=3.257 P=0.071

Chart 17



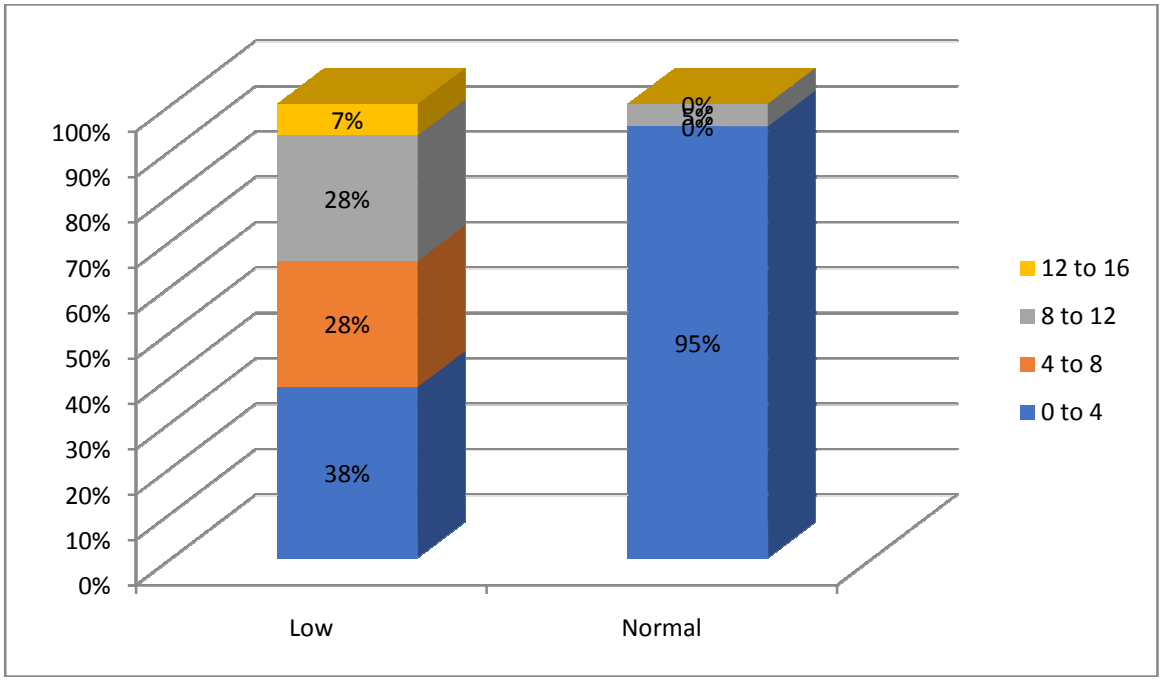
DISTRIBUTION OF SERUM CREATININE AND SERUM T3

Table 18

			T3_GROUP		Total
			Low	Normal	
creatinine_group	0-4	Count	11	20	31
		% within T3_GROUP	37.9%	95.2%	62.0%
	4.1-8.0	Count	8	0	8
		% within T3_GROUP	27.6%	0.0%	16.0%
	8.1-12.0	Count	8	1	9
		% within T3_GROUP	27.6%	4.8%	18.0%
	12.1-16.0	Count	2	0	2
		% within T3_GROUP	6.9%	0.0%	4.0%
Total		Count	29	21	50
		% within T3_GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=17.218** P=0.001

Chart 18



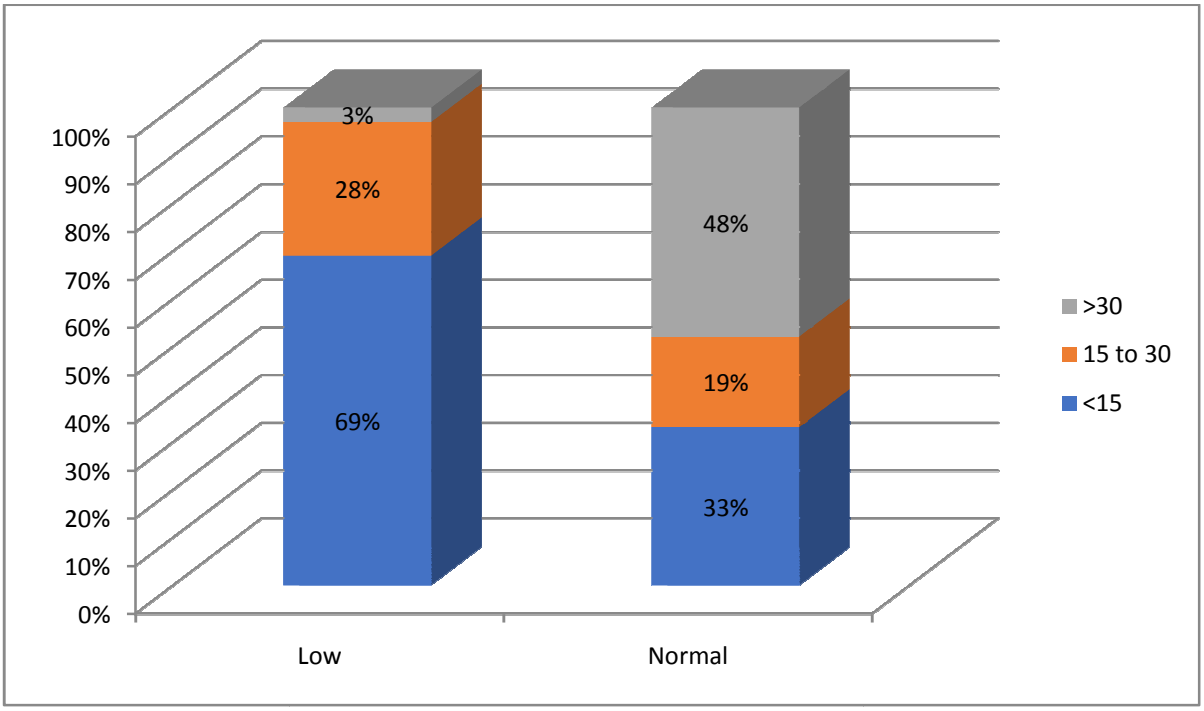
DISTRIBUTION OF SERUM T3 IN VARIOUS EGFR GROUPS

Table 19

			T3_GROUP		Total
			Low	Normal	
egfr_group	<15	Count	20	7	27
		% within T3_GROUP	69.0%	33.3%	54.0%
	15-30	Count	8	4	12
		% within T3_GROUP	27.6%	19.0%	24.0%
	>30	Count	1	10	11
		% within T3_GROUP	3.4%	47.6%	22.0%
Total		Count	29	21	50
		% within T3_GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=14.0.36** P=0.001

Chart 19



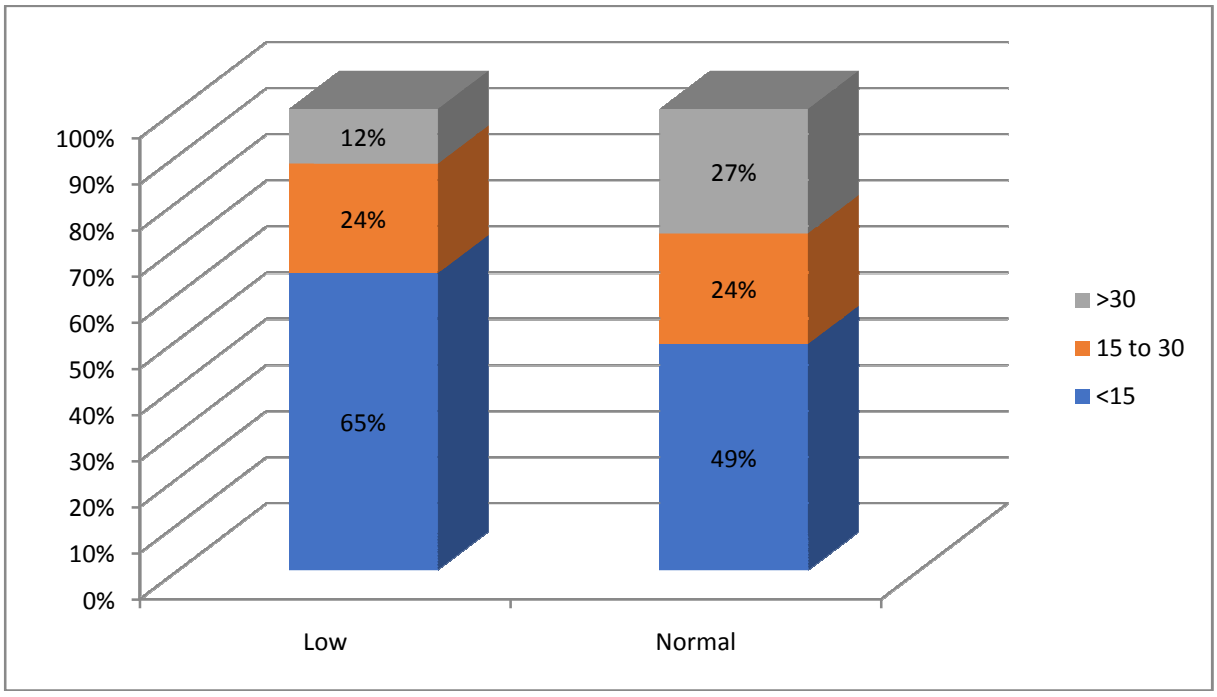
DISTRIBUTION OF T4 IN VARIOUS EGFR GROUPS

Table 20

			t4_group		Total
			Low	Normal	
egfr_group	<15	Count	11	16	27
		% within t4_group	64.7%	48.5%	54.0%
	15-30	Count	4	8	12
		% within t4_group	23.5%	24.2%	24.0%
	>30	Count	2	9	11
		% within t4_group	11.8%	27.3%	22.0%
Total		Count	17	33	50
		% within t4_group	100.0%	100.0%	100.0%

- Pearson Chi-Square=1.776 P=0.412

Chart 20



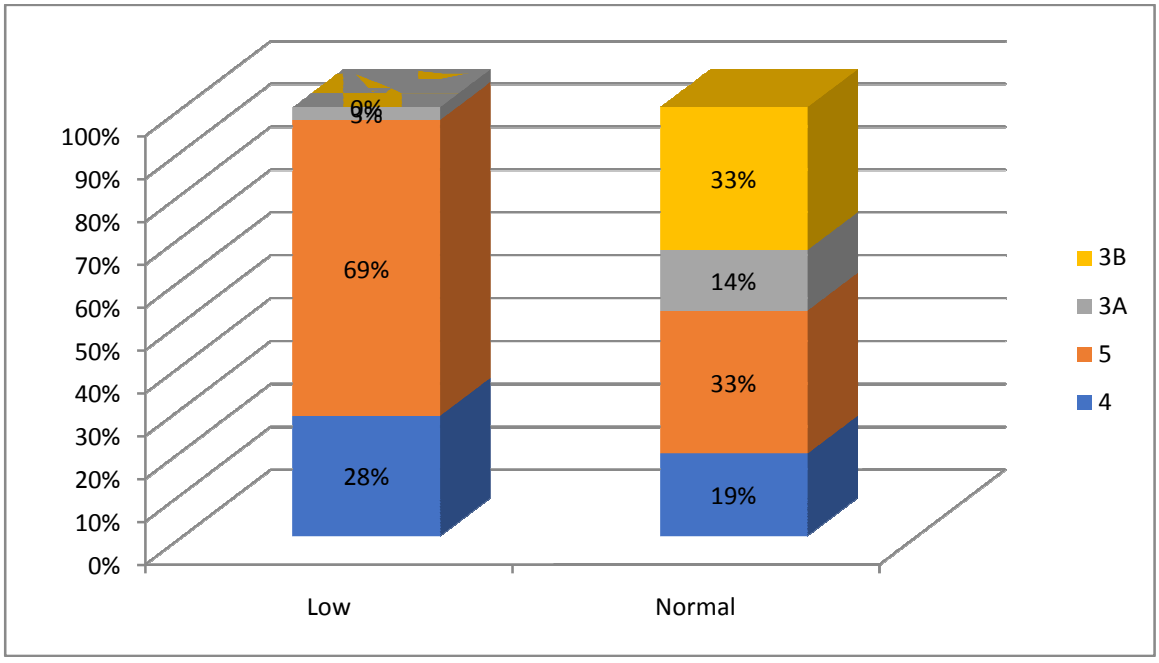
DISTRIBUTION OF LOW T3 IN VARIOUS STAGES OF CKD

Table 21

			T3_GROUP		Total
			Low	Normal	
stage	4.00	Count	8	4	12
		% within T3_GROUP	27.6%	19.0%	24.0%
	5.00	Count	20	7	27
		% within T3_GROUP	69.0%	33.3%	54.0%
	3A	Count	1	3	4
		% within T3_GROUP	3.4%	14.3%	8.0%
	3B	Count	0	7	7
		% within T3_GROUP	0.0%	33.3%	14.0%
Total		Count	29	21	50
		% within T3_GROUP	100.0%	100.0%	100.0%

- Pearson Chi-Square=14.689** P=0.002

Chart 21



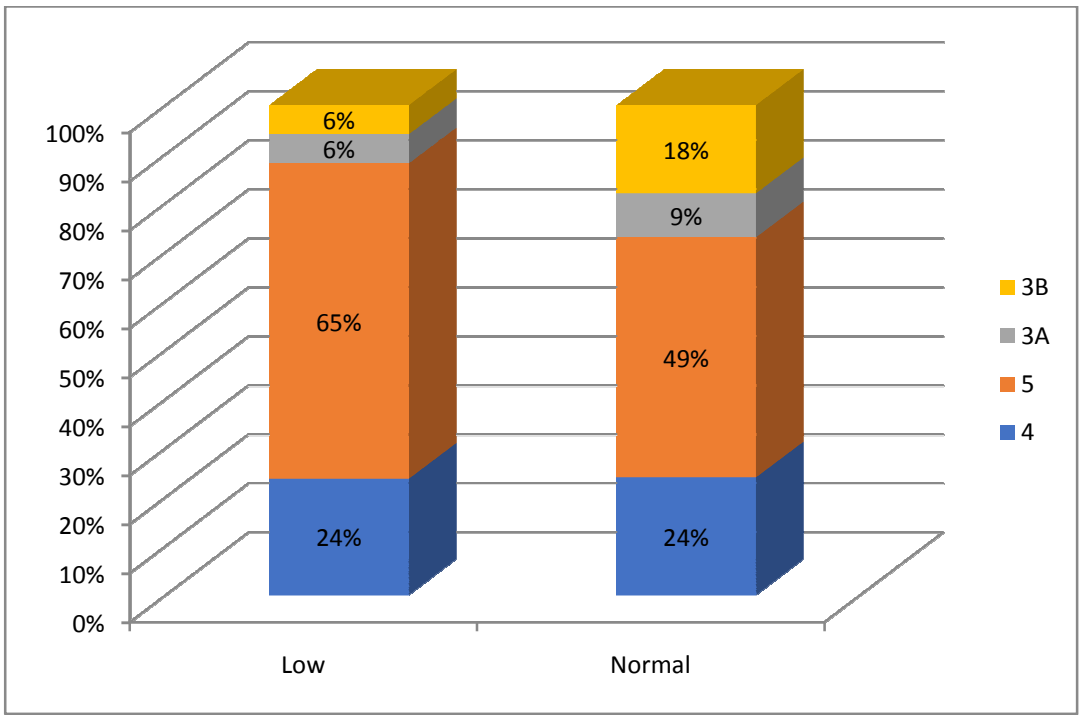
DISTRIBUTION OF LOW T4 IN VARIOUS STAGES OF CKD

Table 22

			t4_group		Total
			Low	Normal	
stage	4.00	Count	4	8	12
		% within t4_group	23.5%	24.2%	24.0%
	5.00	Count	11	16	27
		% within t4_group	64.7%	48.5%	54.0%
	3A	Count	1	3	4
		% within t4_group	5.9%	9.1%	8.0%
	3B	Count	1	6	7
		% within t4_group	5.9%	18.2%	14.0%
Total		Count	17	33	50
		% within t4_group	100.0%	100.0%	100.0%

- Pearson Chi-Square=1.906 P=0.592

Chart 22



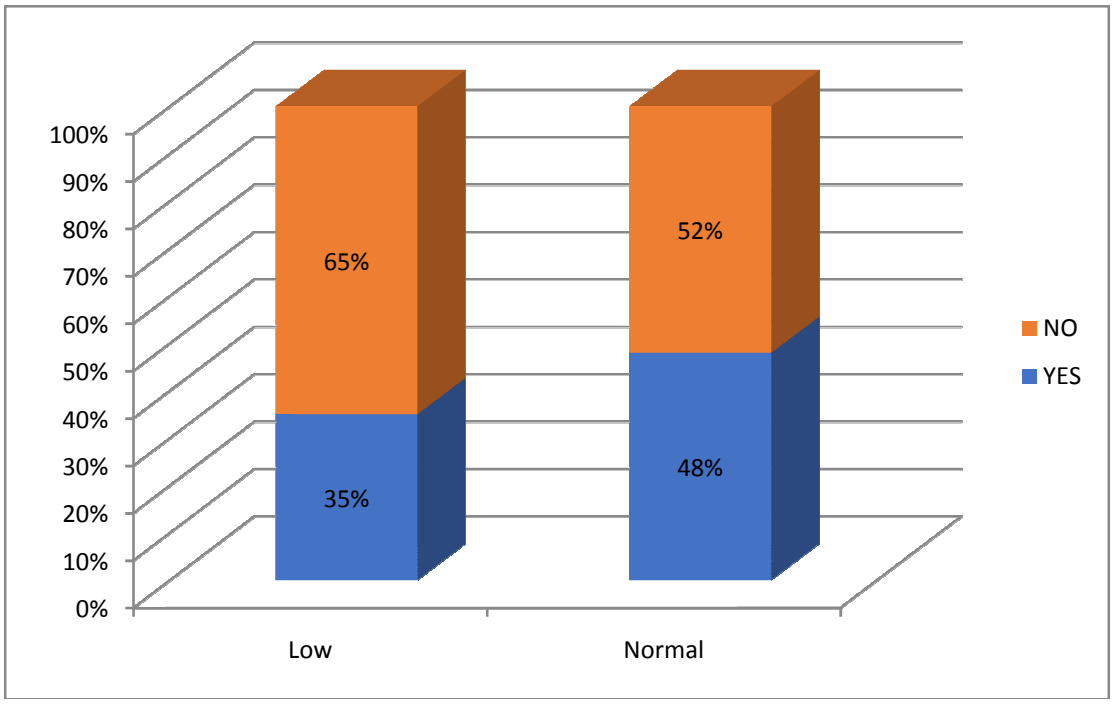
DISTRIBUTION OF DIABETICS IN STUDY CASES

Table 23

			T3_GROUP		Total
			Low	Normal	
Diabetes	Yes	Count	10	10	20
		% within T3_GROUP	34.5%	47.6%	40.0%
	No	Count	19	11	30
		% within T3_GROUP	65.5%	52.4%	60.0%
Total		Count	29	21	50
		% within T3_GROUP	100.0%	100.0%	100.0%

- Pearson Chi-Square=0.876 P=0.349

Chart 23



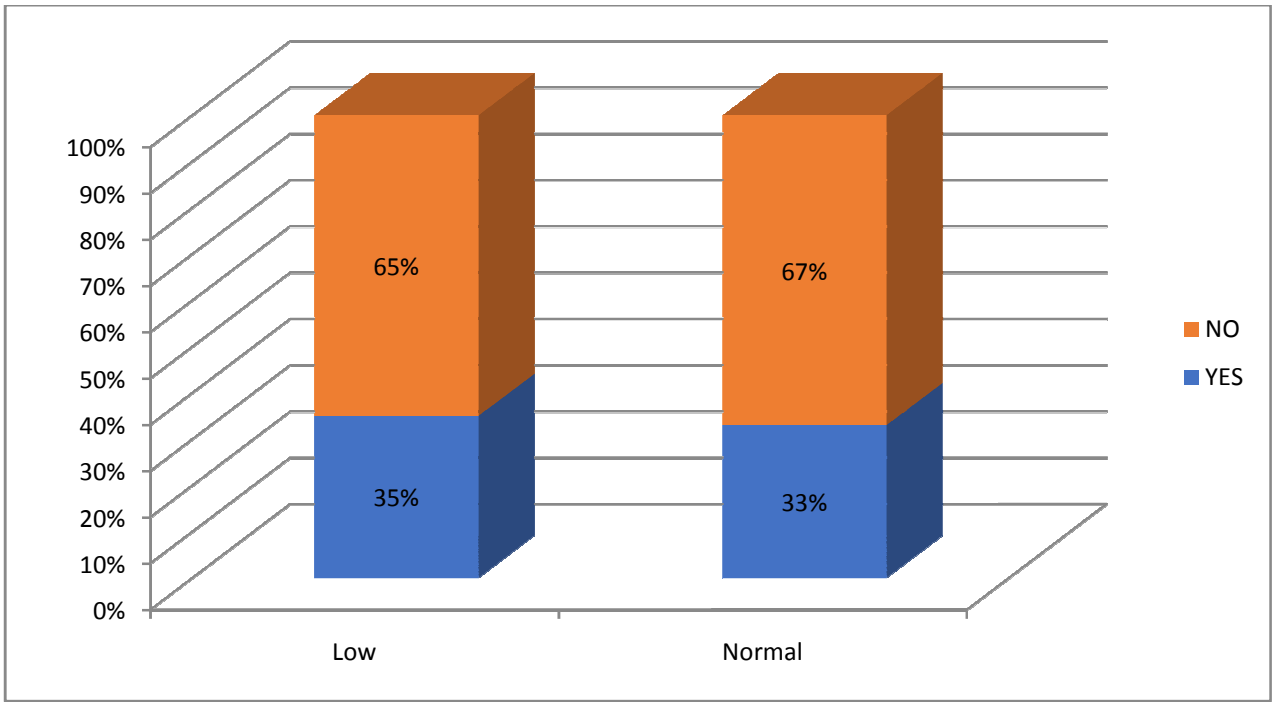
DISTRIBUTION OF HYPOTHYROID SYMPTOMS IN LOW T3 GROUP

Table 24

			T3_GROUP		Total
			Low	Normal	
Symptoms	Yes	Count	10	7	17
		% within T3_GROUP	34.5%	33.3%	34.0%
	No	Count	19	14	33
		% within T3_GROUP	65.5%	66.7%	66.0%
Total		Count	29	21	50
		% within T3_GROUP	100.0%	100.0%	100.0%

- Pearson Chi-Square=0.007 P=0.933

Chart 24



DISTRIBUTION OF T3 AND T4 IN CASES

Table 25

			t4_group		Total
			Low	Normal	
T3_GROUP	Low	Count	13	16	29
		% within t4_group	76.5%	48.5%	58.0%
	Normal	Count	4	17	21
		% within t4_group	23.5%	51.5%	42.0%
Total		Count	17	33	50
		% within t4_group	100.0%	100.0%	100.0%

DISTRIBUTION OF T3 ,T4 AND TSH

Table 26

			T3_GROUP		t4_group		Total
			Low	Normal	Low	Normal	
tsh_group	Normal	Count	26	20	14	32	46
		%	89.7%	95.2%	82.4%	97.0%	92.0%
	High	Count	3	1	3	1	4
		%	10.3%	4.8%	17.6%	3.0%	8.0%
Total		Count	29	21	17	33	50
		%	100.0%	100.0%	100.0%	100.0%	100.0%

MEAN T3 VALUE IN VARIOUS STAGES OF CKD

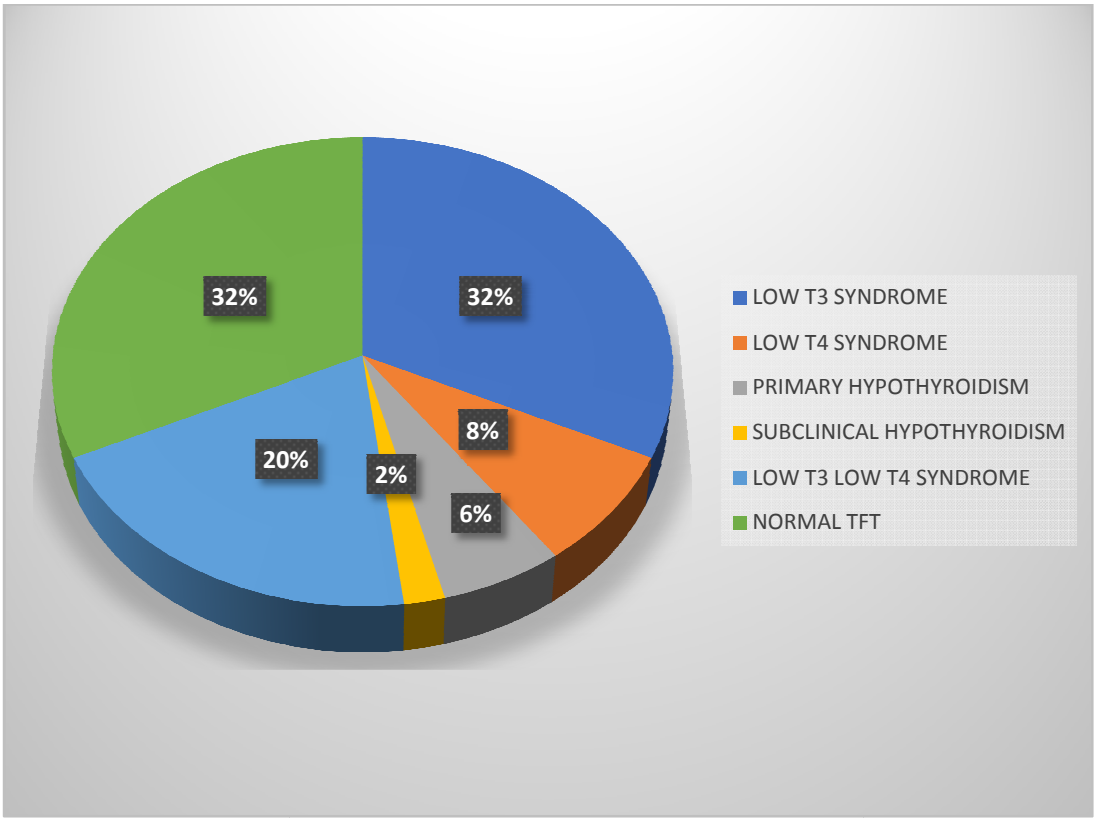
Table 27

t3_ngdl								
	N	**Mean**	**Std. Deviation**	**Std. Error**	**95% Confidence Interval for Mean**		**Minimum**	**Maximum**
					Lower Bound	**Upper Bound**		
4.00	12	.6583	.40555	.11707	.4007	.9160	.20	1.40
5.00	27	.6074	.51210	.09855	.4048	.8100	.20	1.90
3A	4	.7000	.37417	.18708	.1046	1.2954	.20	1.10
3B	7	1.0143	.37161	.14046	.6706	1.3580	.60	1.70
Total	50	.6840	.46963	.06642	.5505	.8175	.20	1.90

This shows that the mean value of T3 in stage 5 and stage 4 CKD is lower than the mean value of T3 in stage 3 depicting a linear correlation between low T3 and severity of CKD.

DISTRIBUTION OF THYROID DYSFUNCTIONS IN VARIOUS STAGES OF CKD

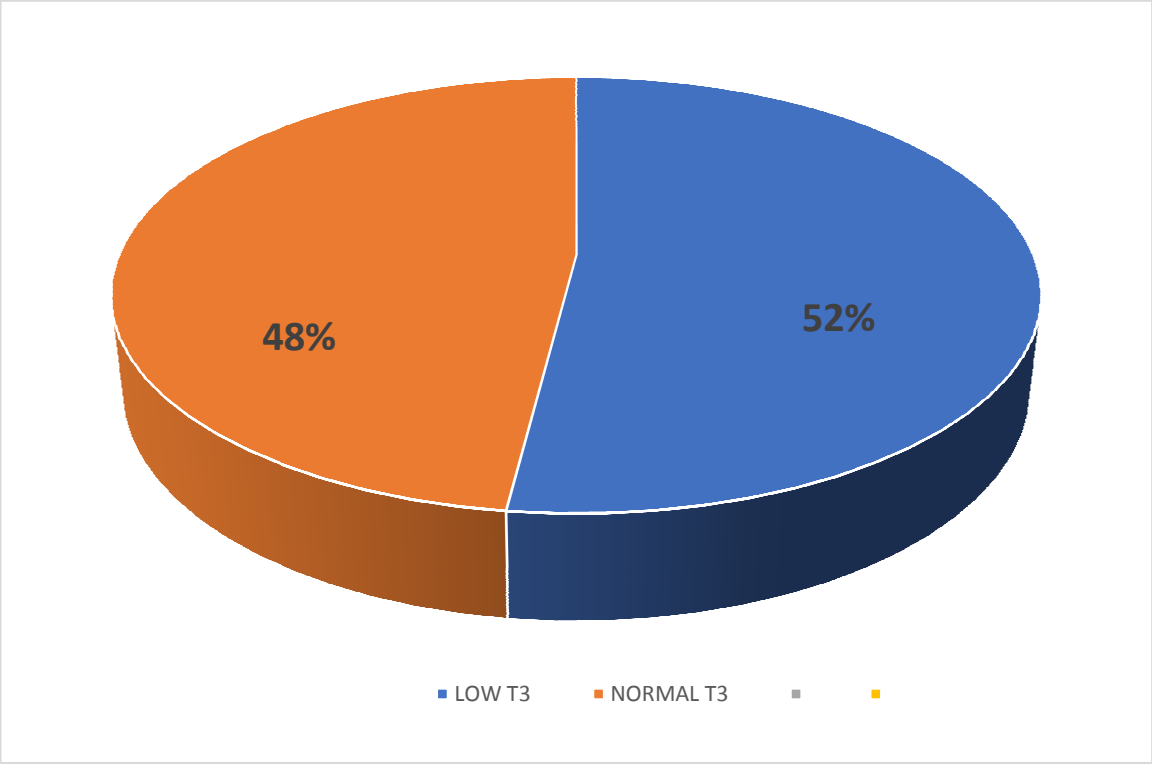
Chart 25



In this study,50 patients of non-dialysis CKD were studied. Among them the thyroid dysfunction was very common accounting to about 68%. Among the various thyroid function alterations, the low T3 syndrome was the most common accounting for 32%. About 20% of the cases had both low T3 and low T4 values. Primary hypothyroidism accounted for 6 %. Low T4 syndrome and subclinical hypothyroidism accounted for 8 % and 2% respectively.

PREVALENCE OF LOW T3 IN NON DIALYSIS CKD PATIENTS

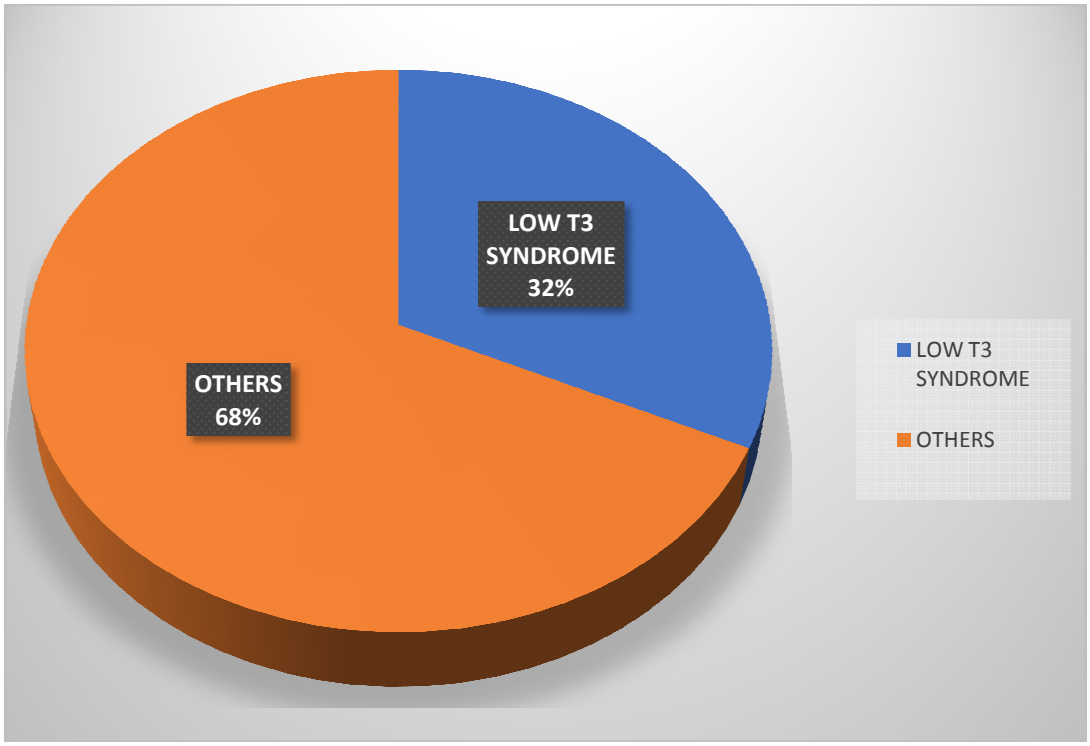
Chart 26



In this study which consisted of 50 patients in different stages of CKD, lowT3 was present in 29 patients accounting to 58%. But, 3 patients had low T3, low T4 and high TSH which lead to the diagnosis of primary hypothyroidism in this patients and hence excluded from low T3 syndrome group. Hence 26 patients(52%) had low T3 values. Among this only 16 (32%) patients had low T3 syndrome.

PREVALENCE OF LOW T3 SYNDROME IN CKD PATIENTS

Chart 27



Among 50 patients included in this study, 26 (52%) patients had low T3 values. In this low T3 group, 9 patients had low T4 values too. So the patients with decreased serum T3 , normal serum T4 and normal serum TSH i.e., low T3 syndrome were 16 patients accounting to 32% of the study sample.

DISCUSSION

Of 50 patients ,27 patients in this study had eGFR calculated by CKD-EPI formula, below 15ml/minute. There were 12 patients who had eGFR between 15 and 29ml/dl. seven patients had an eGFR between 45 and 59ml/dl consistent with stage 3A. Four patients came under stage 3B with eGFR between 30 and 44 mg/dl.

So , in this study most of the patients i.e., 54% belonged to stage 5 CKD.

Ultrasound done in the subjects revealed renal parenchymal disease grade 3 in 78% , renal parenchymal disease grade 2 in 2%. corticomedullary differentiation was lost in 10 patients amounting a total of 20%.

In this study 40 patients had features of anemia supported by completed hemogram.

Serum calcium was also measured in these patients which revealed hypocalcemia in 12 patients accounting to 24% and normal calcium levels in 26 patients accounting for 52% and high calcium levels in 14 patients accounting for 28 %.

Serum phosphorous was high in 16 patients amounting to 32 % and normal in 34 patients accounting to 68%.

In this study which consisted of 50 patients in different stages of CKD, lowT3 was present in 29 patients accounting to 58%. But, 3 patients had low

T3, low T4 and high TSH which lead to the diagnosis of primary hypothyroidism in this patients and hence excluded from low T3 syndrome group. Hence 26 patients(52%) had low T3 values. Among this only 16 (32%) patients had low T3 syndrome

Out of the 50 patients, low T4 was present in 17 patients, but three patients had both low T3 and high TSH suggestive of primary hypothyroidism and excluded from low T4 group. So, 14 patients(28%) had low T4 values. Among which only 4 patients had low t4 syndrome.Both low T3 and low T4 syndrome was present in 10 patients (20%).

In this study, 46 patients had normal TSH values. 4 patients had high TSH values.

CONDITION	**PERCENTAGE**	**NO. OF PATIENTS**
Low t3 syndrome	32%	16
Low t4 syndrome	8%	4
Primary hypothyroidism	6%	3
Subclinical hypothyroidism	2%	1
Low t3 low t4 syndrome	20%	10
Normal tft	32%	16
Total	**100%**	**50**

Among those four patients one had normal T3 and T4 suggesting subclinical hypothyroidism. 3 patients (6%) had primary hypothyroidism.

Among the three patients with primary hypothyroidism, two patients had creatinine clearance below 15ml/dl and one patient belonged to stage 3A.There was one patient with subclinical hypothyroidism who belonged to stage 5 CKD.

Excluding primary hypothyroid patients, the mean TSH in this study was within normal limits across various stages of CKD.so, it did not show any relation to the severity of the disease.

Among 50 patients in this study,16 patients had no abnormality of thyroid status.

17 patients included in this study had symptoms of hypothyroidism such as lethargy,constipation,dry skin,cold intolerance etc,.out of this all three from the primary hypothyroidism group had such symptoms. Delayed ankle jerk was present in one patient and goitre was seen in two patients whohad primary hypothyroidism.

33 patients (66%) did not complain of symptoms suggestive of hypothyroidism.One patient with subclinical hypothyroidism did not have symptoms suggestive of hypothyroidism.

In low T3 group, 10 patients had symptoms of hypothyroidism and 19 did not have so.

According to previous studies conducted by Kaptein et al,[39] the prevalence of hypothyroidism in CKD was 2.5 times higher than general population.In this

study it was found to be only 6%. The diagnosis of hypothyroidism can be made only when the TSH values are high and T3 , T4 are low.

In low T3 group , among 29 patients , 15 patients belonged to the age 41 to 60 years, 6 patients above 60 years , and 8 patients aged between 20 and 40 years. the number of patients above 60 years in this study is 11, so approximately half of them had low T3.

Among 29 patients who had low T3, 20 of them had eGFR less than 15ml/dl
8 patients had eGFR between 15 and 30ml/dl. So, this shows that the prevalence of low T3 is more in end stage renal disease.

Like the same way, out of 17 patients with low T4 , 11 patients had eGFR that is consistent with stage 5 CKD.

The mean T3 value in this study was reduced in stage 5 and stage 4 CKD whereas the mean values of T3 in stage 3 CKD was higher. We could not correlate between the mean values T3 in stage 4 and stage 5 probably because of the smaller sample size.So it shows a direct linear correlation between T3 level and eGFR. [43]

This was supported by studies done in the past by, Hasegawa [43] et al, Ramirez [43a]et al, P Iglesias [41]et al, Plikat K,Langgartner et al [60] which showed a linear correlation of serum T3 and severity of kidney disease.

A study conducted by Quin Ver Deet[39,48]et al., concluded a high prevalence of hypothyroidism in CKD.

Another study by Kaptein[34,36] et al found a prevalence of hypothyroidism to be 2.5 times high in CKD and dialysis. In this study the prevalence primary hypothyroidism was 6%.

Several studies by Karunanidhi et al, Ramirez [43]et al, Dudani[62]et al found an abnormality in hypophyseal mechanism of TSH release in CKD. This is consistent in this study also.

CONCLUSION

⇒ Alteration of thyroid functional status is common among CKD patients.

⇒ It is very important to screen all patients with CKD for thyroid disorders , as about 68% have some form of thyroid disorder according to this study

⇒ The alteration in the thyroid function in CKD is probably an adaptive mechanism to help conserving protein.

⇒ This study was made on 50 patients who were diagnosed to have CKD and who were not on renal replacement therapy. Among these patients,29 patients (58%) had low T3 values and 32% had low T3 syndrome.

⇒ As observed in this study, the number of patients with low T3 and T4 increased with the severity of CKD.

⇒ The risk of primary hypothyroidism is increased in CKD. In this study 6% had TFT suggestive of primary hypothyroidism.

⇒ Low T3 syndrome was seen in 32% and low T4 syndrome was seen in 8% of patients in this study.

⇒ Low T3 syndrome is was common in older patients with CKD in this study.

⇒ Lower the eGFR, lower is the T3 values. So this shows a significance that as the disease severity increases, the T3 values fall progressively depicting a direct relation between eGFR and T3.

SUMMARY

This study was conducted on 50 patients who are known case of chronic kidney disease who are not on dialysis, admitted in institute of internal medicine , madras medical college and government general hospital.

- Age of the patients ranged from 20 to 72 years.
- There was an equal distribution of male and female patients.
- The eGFR ranged from
- The lowest and the highest value of creatinine in this study was
- 27 patients belonged to ESRD ,12 patients were in stage 4 CKD, 11 patients had eGFR consistent with stage 3 CKD.
- The range of T3 in this study was 0.2 to 1.9 ng/dL, the mean value of T3 in stage 5 CKD and stage 4 CKD was 0.65 and 0.60 ng/dL respectively. The mean of T3 in stage 3 was 1.3 ng/dL.
- In this study , 16 patients had low T3 syndrome, 4 patients had low T4 syndrome, 3 patients had primary hypothyroidism,low T3 and low T4 syndrome was found in 20 patients, 1 patient had subclinical hypothyroidism, 16 patients had normal thyroid status.
- Out of 50 patients, 17 had symptoms of hypothyroidism, depicting high prevalence of asymptomatic disease in this population.
- Low T3 syndrome was commonly observed in older patients.
- As the severity of the CKD increases, the T3 values fall to more severe levels showing a linear correlation between them..The values of TSH did not show any correlation with the severity of the disease.

LIMITATIONS OF THE STUDY

⇒ The study sample size is small due to financial and time constraints. This study was conducted only in Rajiv Gandhi government hospital on those CKD patients who are on conservative management.

⇒ The samples were randomly selected irrespective of the etiology, which could influence the thyroid function.

⇒ As the study was done on patients who got admitted to the hospital due to some illness , the prevalence of thyroid dysfunction in CKD in community level is not known.

⇒ The study was limited only to patients on conservative treatment and the prevalence of thyroid dysfunction in CKD patients on renal replacement therapy is not known.

⇒ Lack of experience of the investigator.

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PROFORMA

NAME: AGE: SEX: OCCUPATION:
ADDRESS:
PAST HISTOY: HYPERTENSION- Y/N

DIABETES- Y/N
RECENT SURGERY/TRAUMA-Y/N DRUGS- Y/N

JAUNDICE-Y/N
OTHER SYSTEMIC ILLNESS-Y/N

MENSTRUAL & OBSTRETIC HISTORY: GENERAL EXAMINATION:

1. NOURISHMENT
2. PALLOR
3. HYPERPIGMENTATION 4. FACIAL PUFFINESS
5. PEDAL EDEMA
6. SKIN TEXTURE

IP NO:

7. THYROID SWELLING PULSE: BP: RR:
TEMPERATURE:
CVS:
RS:
ABDOMEN:
CNS:
INVESTIGATIONS:

1. URINE ROUTINE
2. BLOOD: HB- g/dl

    a. TC, DC-P%,L%,E%
    b. RBC-
    c. BT-
    d. CT-

3. BLOOD SUGAR:
4. BLOOD UREA:
5. SERUM CREATININE:
6. SERUM ELECTROLYTES:

i. SODIUM-

ii. POTASSIUM-:

7.a. SERUM PROTEIN:

b. ALBUMIN-

8. ECG:
9. CHEST XRAY:
10. USG ABDOMEN:
11. THYROID PROFILE:

a. TOTAL T3 -

b. TOTAL T4

c. TSH-

Sl.no	name	age	sex	urea mg/dl	creatinine mg/dl	egfr ml/m	stage	diabetes	hypertensio n	symptoms *	t3 ng/dl	t4 ng/dl	tsh micg/dl	usg abd
1	raja	21	m	112	13.5	4.6	5	no	yes	no	0.3	1.1	4.7	RPD3
2	gopalan	39	m	148	10.5	5.5	5	YES	NO	YES	1.8	8.3	4.8	CMDL
3	jeeva	50	m	88	4.7	13.5	5	YES	YES	YES	0.9	7.5	2.9	RPD3
4	murugan	47	m	118	9.5	5.9	5	NO	YES	NO	0.5	7.3	3.8	RPD3
5	desappan	55	m	58	5.6	5.9	5	NO	YES	YES	0.4	3.5	5.5	RPD3
6	vadivel	25	m	78	3.7	9	5	NO	NO	NO	1.9	7.8	5.4	RPD3
7	thanigaivel	69	m	86	3.2	18.7	4	yes	no	no	0.5	2.5	3.6	RPD3
8	mutharasu	72	m	88	10.6	4.3	5	NO	YES	YES	0.3	3.5	28.7	RPD3
9	vinayagam	39	m	88	3.2	23.1	4	NO	YES	NO	1.4	3.5	5.1	RPD3
10	muthu	49	m	87	4.8	6	5	YES	NO	YES	0.8	7.2	2.9	CMDL
11	alaguraj	19	m	70	3.9	21	4	NO	NO	YES	0.4	8.1	6.7	RPD3
12	david	68	m	78	3.3	7	5	YES	YES	YES	0.4	7.5	6.7	RPD3
13	mohammed	42	m	134	3.9	17.8	4	YES	NO	YES	0.3	7.8	4.8	RPD3
14	krishna	71	m	89	7.8	6.3	5	NO	NO	NO	0.3	8.5	6.8	RPD2
15	ravi	28	m	112	12.2	6	5	NO	NO	NO	0.2	1.3	4.7	RPD3
16	kamal	44	m	96	3.7	18.7	4	NO	YES	NO	0.5	2.5	3.6	RPD3
17	kalaiselvan	45	m	76	1.9	42	3B	YES	NO	NO	0.8	5.7	4.9	CMDL
18	karunakaran	27	m	89	2.8	29.5	4	NO	NO	NO	1	8.1	3.5	RPD3
19	rangasamy	60	m	79	5.8	6	5	YES	YES	NO	0.4	8.9	0.7	CMDL
20	deva	69	m	109	7.2	7	5	NO	NO	NO	0.4	1.8	2.9	RPD3
21	josepn	60	m	68	3.3	21.8	4	YES	NO	NO	0.4	8.1	6.1	RPD3
22	naveed	44	m	165	7.8	9	5	YES	YES	NO	0.5	0.7	4.6	RPD3
23	riyaz	43	m	134	2	40	3B	NO	YES	YES	0.6	6.5	5.9	RPD3
24	siva	39	m	67	3.2	7.5	5	NO	NO	YES	1.9	0.8	4.6	CMDL

25	senthil	60	m	67	1.9	38	3B	YES	YES	NO	1.1	7.8	4.6	CMDL
26	kalaivani	20	f	92	9.7	5.2	5	NO	YES	NO	0.4	0.8	3.9	RPD3
27	saroja	64	f	88	4.5	6	5	YES	NO	NO	1.1	6.7	3.8	RPD3
28	devi	22	f	90	1.9	37	3B	NO	NO	YES	1.7	6.6	5.2	RPD3
29	kamala	65	f	89	4.5	6	5	NO	YES	NO	1	6.9	7.5	RPD3
30	nirmala	65	f	154	1.7	36	3B	YES	YES	NO	1	6.7	5.5	RPD3
31	janani	50	f	67	1.1	58.5	3A	YES	YES	NO	1.1	7.2	4.2	CMDL
32	gayathri	40	f	112	2.2	27.1	4	NO	YES	NO	0.8	7.4	4.7	CMDL
33	muniyammal	58	f	89	6.7	6.2	5	NO	YES	YES	0.2	6.8	5.7	RPD3
34	lalitha	41	f	89	1.4	47	3A	NO	NO	NO	0.7	7.6	5.8	RPD3
35	rahamath	39	f	146	10.2	6	5	NO	NO	NO	0.2	1.6	2.9	RPD3
36	radha	68	f	78	1.2	46	3A	YES	YES	YES	0.2	2.4	28	RPD3
37	vadivukarasi	41	f	145	10.5	6	5	NO	YES	NO	0.4	4.9	3.8	RPD3
38	venda	70	f	167	1.3	45	3A	NO	NO	YES	0.8	8	4.8	RPD3
39	vadivukarasi	35	f	132	2.7	21.8	4	NO	YES	NO	1.4	3.5	5	RPD3
40	vasantha	67	f	145	1.4	39	3B	YES	NO	NO	1.2	4.8	4.9	RPD3
41	devika	45	f	119	9.2	8	5	NO	NO	NO	0.2	7.3	3.7	RPD3
42	poornima	49	f	88	4.6	6	5	YES	NO	NO	0.3	8.3	2.8	CMDL
43	alli	39	f	58	2.1	28.9	4	NO	NO	NO	0.5	6.7	3.9	RPD3
44	babyammal	42	f	102	3.1	17.7	4	NO	NO	NO	0.5	6.4	5.7	RPD3
45	kuruvamma	48	f	120	6.7	7	5	NO	NO	YES	0.5	2.8	25	RPD3
46	mathiyalagi	55	f	112	11.5	12	5	YES	YES	NO	0.5	6.7	3.7	RPD3
47	saraswathi	61	f	132	1.8	31	3B	YES	NO	NO	0.7	6.8	5.9	RPD3
48	ebenezar	55	f	98	3	16.8	4	YES	NO	YES	0.2	6.3	5.1	CMDL
49	jothi	38	f	135	13.6	3	5	NO	NYES	YES	0.3	8.5	5.9	RPD3
50	suganthi	20	f	117	5.6	10.1	5	NO	NO	NO	0.3	7.5	5.8	RPD3

INFORMATION SHEET

We are conducting a study on "A STUDY OF PREVALENCE AND CLINICAL SIGNIFICANCE OF LOW T3 IN NON DIALYSIS PATIENTS KONIC KIDNEY DISEASE" among patients attending Rajiv Gandhi Government General Hospital, Chennai and for that your specimen may be valuable to

significance of thyroid profile especially low t3 patients with different stages of us. The purpose of this study is to determine the prevalence and clinical chronic kidney disease who are not on dialysis.

We are selecting certain cases and if you are found eligible, we may be elicit history and clinical examination and using your blood samples to do certain tests..

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no

personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any

loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Investigator

Signature of participant

Date:Place:

ஆய்வுதகவல்தாள்

ஆய்வுதலைப்பு:

நாள்பட்டசிறுநீரகநோயாளிகளில்ஏற்படும்தைராய்டுசுரப்புக்குறைபாட்டின்

நோய்தாக்கம்பற்றியஆய்வு.

ஆய்வாளர்பெயர்

மரு. K.கௌதம்

ஆய்வுநிலையம். : பொதுமருத்துவப்பிரிவு.

சென்னைமருத்துவக்கல்லூரி, சென்னை-3.

இந்தஆய்வில்தங்களைபங்கேற்கஅழைக்கிறோம்.

இந்ததகவல்அறிக்கையில்

கூறப்பட்டிருக்கும்தகவல்கள்தாங்கள்இந்தஆராய்ச்சியில்பங்கேற்கலாமாவேண்டாமா.

என்பதைமுடிவுசெய்யஉதவியாகஇருக்கும்.

இந்தபடிவத்தில்உள்ளதகவல்கள்பற்றி

உள்ளசந்தேகங்களைநீங்கள்தயங்காமல்கேட்கலாம்.

இதில்ஆய்வின்மூலம்நாள்பட்டசிறுநீரகநோயாளிகளில்ஏற்படும்தைராய்டு

கரப்புக்குறைபாட்டின்நோய்தாக்கம்பற்றியஆய்வுஅறிவதற்குதங்கள்ஒத்துழைப்புத்

தேவை.

நீங்கள்இந்தஆராய்ச்சியில்பங்கேற்கநாங்கள்விரும்புகிறோம்.

முடிவுகளை.

அல்லதுகருத்துகளைவெளியிடும்போதோஅல்லதுஆராய்ச்சியின்போதோ

தங்களது

பெயரையோஅல்லதுஅடையாளங்களையோவெளியிடமாட்டோம்என்ப

தையும்,

தெரிவித்துக்கொள்கிறோம்.

இந்தஆராய்ச்சியில்பங்கேற்பதுதங்களுடையவிருப்பத்தின்பேரில்தான்

இருக்கிறது.

மேலும்நீங்கள்எந்தநேரமும்இந்தஆராய்ச்சியில்இருந்துபின்வாங்கலாம்.

என்பதையும்தெரிவித்துக்கொள்கிறோம்.

இந்தசிறப்புப்பரிசோதனையின்முடிவுகளைஆராய்ச்சியின்போதுஅல்லது

ஆராய்ச்சியின்முடிவில்தங்களுக்குஅறிவிப்போம்என்பதையும்தெரிவித்துக்

கொள்கிறோம்.

பங்கேற்பாளர்கையொப்பம்

இடதுகட்டைவிரல்ரேகை

தேதி

ஆராய்ச்சியாளர்கையொப்பம்

தேதி

PATIENT CONSENT FORM

Study Detail: A STUDY OF PREVALENCE AND CLINICAL SIGNIFICANCE OF LOW T3 IN NON DIALYSIS PATIENTS WITH CHRONIC KIDNEY DISEASE

Study Centre :Rajiv Gandhi Government General Hospital, Chennai.
Patient's Name:
Patient's Age:
Identification Number:

Patient may check (v) these boxes

a) I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and U doubts have been answered to my complete satisfaction. ☐

b) I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal U rights being affected. ☐

c) I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to D this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

d) I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual ☐

e) I hereby consent to participate in this study and I hereby give permission to undergo detailed clinical examination and blood investigations as required. ☐

Signature of Investigator
Dr.K.GOUTHAM

Signature thumb impression
Patient Name and address

ஆய்வுஒப்புதல்படிவம்

ஆய்வுதலைப்பு:
நாள்பட்டசிறுநீரகநோயாளிகளில்ஏற்படும்தைராய்டுசுரப்புக்குறைபாட்டின்
நோய்தாக்கம்பற்றியஆய்வு.

பெயர்:
வயது:
பால்:

தேதி:
நோயாளிஎண்:
ஆராய்ச்சிசேர்க்கைஎண்:

இந்தஆராய்ச்சியின்விவரங்களும்அதன்நோக்கங்களும்முழுமையாகஎனக்கு
தெளிவாகவிளக்கப்பட்டது.
எனக்குவிளக்கப்பட்டவிஷயங்களைநான்புரிந்துகொண்டு
நான்எனதுசம்மதத்தைதெரிவிக்கிறேன்.

இந்தஆராய்ச்சியில்நாள்பட்டசிறுநீரகநோயாளிகளில்ஏற்படும்தைராய்டு
சுரப்புக்குறைபாட்டின்நோய்தாக்கம்பற்றியஆய்வுஆராயப்படுகிறதுஎன்பதை
ஆராய்ச்சியாளர்கூறஅறிந்துகொண்டேன்.

மேற்கண்டபரிசோதனையின்போதுஏற்படக்கூடியபின்விளைவுகளையும்,
முழுவதும்உணர்ந்துஇந்தபரிசோதனைக்குமனமாரசம்மதிக்கிறேன். '

நான்ஆராய்ச்சியாளருடன்ஒத்துழைப்பேன்என்றும், எனக்குஏற்படக்கூடிய
ஆசாதாரணநிகழ்வுகள்பற்றியும்உடனடியாகஆராய்ச்சியாளரிடம்தெரிவிப்பேன்என்று

உறுதிகூறுகிறேன்.
இந்தஆய்விலிருந்துஎப்போதுவேண்டுமானாலும்எக்காரணமும் கூறாமல்என்னைவிடுவித்துக்கொள்ளலாம்என்பதைஅறிவேன்.

என்னிடம்இருந்துபெறப்படும்தகவல்களைஅரசு, வரைமுறைஅதிகாரிகள் ஆகியோர்களுடன்பகிர்ந்துகொள்ளஆராய்ச்சியாளருக்குஅனுமதிஅளிக்கி றேன்..
என்னுடையசிகிச்சைக்கட்டுகளைபார்வையிடஉரிமைஉண்டு.
என்னுடைய
தகவல்களின்அடையாளம்இரகசியமாகவைக்கப்படும்என்பதைஅறிவேன் .'

இந்தஆராய்ச்சியில்பங்கேற்கதன்னிச்சையாகமுழுமனதுடன்சம்மதிக்கிறே ன்.'

பங்கேற்பவரின்கையொப்பம்ரேகை
பங்கேற்பவர்பெயர்
இடம்
தேதி

ஆய்வாளர்கையொப்பம்
ஆய்வாளர்பெயர்
இடம்
தேதி

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To

Dr.K.Goutham
I Year PG in MD General Medicine
Institute of Internal Medicine
Madras Medical College
Chennai 600 003

Dear Dr.K.Gowtham,

The Institutional Ethics Committee has considered your request and approved your study titled **"A STUDY OF PREVALENCE AND CLINICAL SIGNIFICANCE OF LOW T3 IN NON DIALYSIS PATIENTS WITH CHRONIC KIDNEY DISEASE " - NO.11062017(A)**

The following members of Ethics Committee were present in the meeting hold on **20.06.2017** conducted at Madras Medical College, Chennai 3

1. Prof.Dr.C.Rajendran, MD.,	:Chairperson
2. Prof.R.Narayana Babu,MD.,DCH., MMC,Ch-3	: Deputy Chairperson
3. Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	:Member Secretary
4. Prof.S.Mayilvahanan,MD,Director,Inst. of Int.Med,MMC, Ch-3	: Member
5. Prof.A.Pandiya Raj,Director, Inst. of Gen.Surgery,MMC	: Member
6. Prof.Rema Chandramohan,Prof.of Paediatrics,ICH,Chennai	: Member
7. Prof. Susila, Director, Inst. of Pharmacology,MMC,Ch-3	: Member
8.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
9.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist
10.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person

13/12/17 We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
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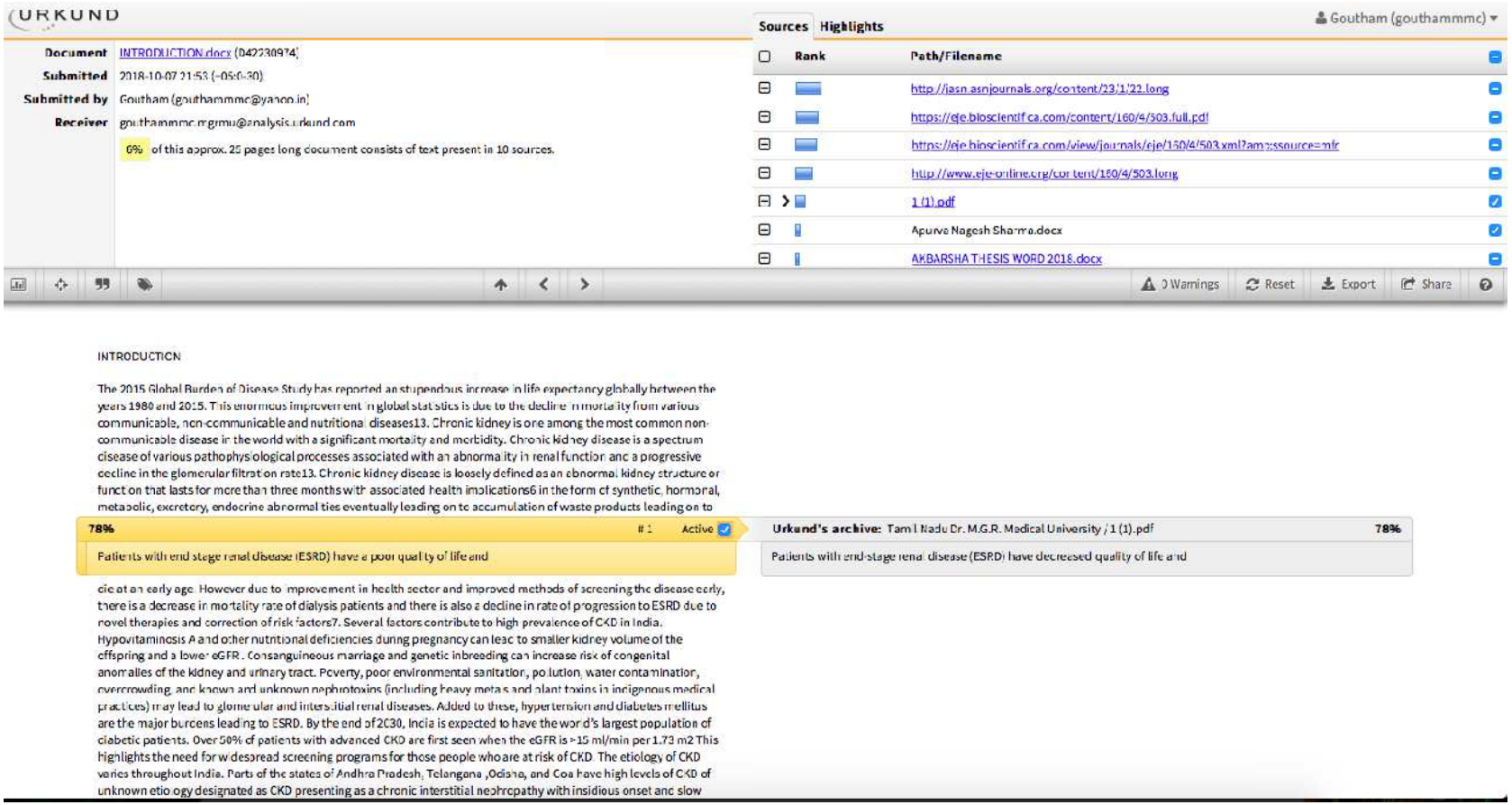
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INTRODUCTION
The 2015 Global Burden of Disease Study has reported an stupendous increase in life expectancy globally between the years 1980 and 2015. This enormous improvement in global statistics is due to the decline in mortality from various communicable, non-communicable and nutritional diseases13. Chronic kidney is one among the most common non-communicable disease in the world with a significant mortality and morbidity. Chronic kidney disease is a spectrum disease of various pathophysiological processes associated with an abnormality in renal function and a progressive decline in the glomerular filtration rate13. Chronic kidney disease is loosely defined as an abnormal kidney structure or function that lasts for more than three months with associated health implications6 in the form of synthetic, hormonal, metabolic, excretory, endocrine abnormalities eventually leading on to accumulation of waste products leading on to
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Patients with end-stage renal disease (ESRD) have decreased quality of life and
die at an early age. However due to improvement in health sector and improved methods of screening the disease early, there is a decrease in mortality rate of dialysis patients and there is also a decline in rate of progression to ESRD due to novel therapies and correction of risk factors7. Several factors contribute to high prevalence of CKD in India. Hypovitaminosis A and other nutritional deficiencies during pregnancy can lead to smaller kidney volume of the offspring and a lower eGFR. Consanguineous marriage and genetic inbreeding can increase risk of congenital anomalies of the kidney and urinary tract. Poverty, poor environmental sanitation, pollution, water contamination, overcrowding, and known and unknown nephrotoxins (including heavy metals and plant toxins in indigenous medical practices) may lead to glomerular and interstitial renal diseases. Added to these, hypertension and diabetes mellitus are the major burdens leading to ESRD. By the end of 2030, India is expected to have the world's largest population of diabetic patients. Over 50% of patients with advanced CKD are first seen when the eGFR is >15 ml/min per 1.73 m2 This highlights the need for widespread screening programs for those people who are at risk of CKD. The etiology of CKD varies throughout India. Parts of the states of Andhra Pradesh, Telangana ,Odisha, and Goa have high levels of CKD of unknown etiology designated as CKD presenting as a chronic interstitial nephropathy with insidious onset and slow

CERTIFICATE – II

This is to certify that this dissertation work titled "**A STUDY ON PREVALENCE AND CLINICAL SIGNIFICANCE OF LOW T3 IN NON-DIALYSIS PATIENTS WITH CHRONIC KIDNEY DISEASE**" of the candidate **DR.K.GOUTHAM** with registration Number 201611007for the award of M.D. in the branch of GENERAL MEDICINE. I personally verified the urkund.com website for plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows 6 percentage of plagiarism in the dissertation.

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