"STUDY OF THYROID FUNCTION IN PATIENTS OF CHRONIC KIDNEY DISEASE"

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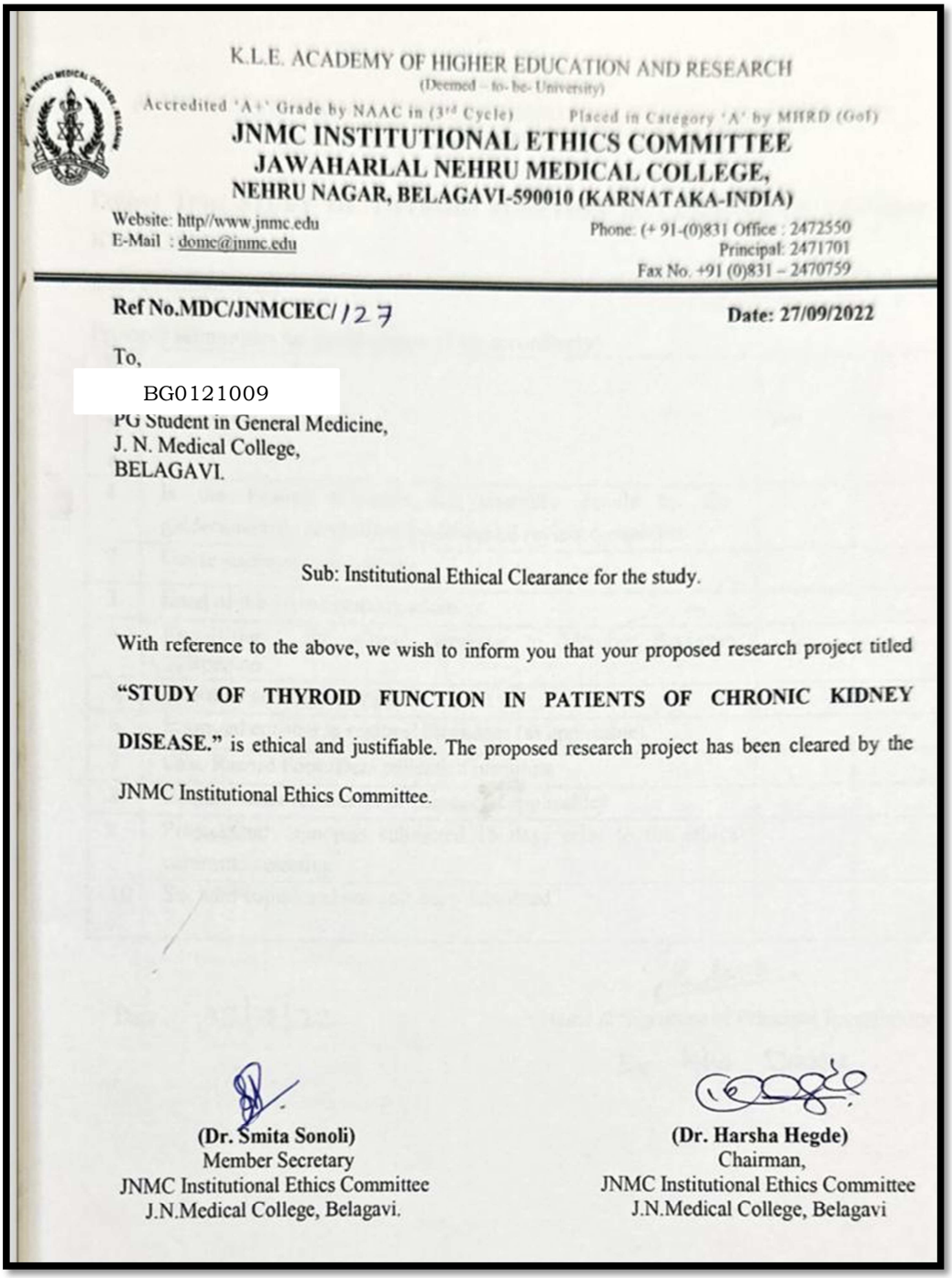

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ABSTRACT

BACKGROUND: Thyroid hormone abnormalities are frequently observed in patients with chronic renal disease. Chronic kidney disease changes the production, metabolism, and excretion of thyroid hormones. It has been noted that the production of thyroid hormone is decreased as a result of the accumulation of iodine in the blood caused by the progressive reduction of GFR in CKD. This results in abnormally low amounts of total and free T3 in serum, but normal levels of reverse T3 and free T4 in the serum. Nevertheless, there is little change in TSH levels in CKD.

OBJECTIVE:

- To study thyroid function of chronic kidney disease patients
- To study the correlation between thyroid dysfunction and severity of chronic kidney disease in patients

METHODOLOGY: A cross-sectional study was conducted involving 87 patients with chronic kidney disease not on dialysis. Data was collected from patients fulfilling inclusion criteria, focusing on patient demographics and laboratory parameters. Statistical analyses were performed to identify significant patterns and correlations

RESULTS

- The present study included 87 patients, of which 30 (34.48%) were female and 57 (65.52%) were male, with the majority being aged 41-60 years.

- The average TSH value was found to be 2.54 mIU/ml. While the mean free thyroxine (T4) level was 1.22 ng/ml and the mean free triiodothyronine (T3) level was 1.98 pg/ml.

- Thyroid abnormalities were significant, with 59.77% having low free triiodothyronine levels, 20.69% with low free thyroxine levels, and 9.20% diagnosed with hypothyroidism. Subclinical hypothyroidism was observed in 12.64% of patients. Overall, the prevalence of thyroid dysfunction increased with the progression of CKD.

CONCLUSION: The present study reveals significant associations between thyroid abnormalities and chronic kidney disease (CKD) stages among the patient population. Thyroid dysfunction is prevalent, with 59.77% of patients having low free triiodothyronine levels, 20.69% with low free thyroxine levels, and 9.20% diagnosed with hypothyroidism. Subclinical hypothyroidism is noted in 12.64% of patients. These findings suggest that thyroid dysfunction is common in patients with CKD, particularly in the more advanced stages of the disease. Mainly thyroid dysfunction is seen in the form of low free triiodothyronine and subclinical hypothyroidism. Thus, highlighting the need for vigilant thyroid function monitoring in advanced CKD.

LIST OF ABBREVIATIONS

CKD	Chronic Kidney Disease
GFR	Glomerular Filtration Rate
CVD	Cardiovascular Disease
ESRD	End Stage Renal Disease
FT3	free triiodothyronine
FT4	free thyroxine
TSH	Thyroid Stimulating Hormone
TRH	Thyrotropin Releasing Hormone
RBF	Renal Blood Flow
RAAS	Renin-angiotensin-aldosterone system
HD	Hemodialysis
TBG	Thyroid-binding globulin
EPO	Erythropoietin
RCC	Renal Cell Carcinoma
PD	Peritoneal Dialysis

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INTRODUCTION

Chronic kidney disease (CKD) is a term that encompasses a group of different pathophysiological processes related to abnormal kidney function and a steady decrease in Glomerular Filtration rate (GFR). Renal metabolic, excretory, endocrine, and synthetic activities are lost in chronic kidney disease (CKD) due to the accumulation of various protein nitrogenous substances. The major killers of CKD patients are various cardiovascular diseases. Patients in the early stages of chronic kidney disease (CKD) are mostly cared for by physicians. Screening for and managing CKD-related complications at an early stage allows physicians to considerably delay the onset of end-stage-renal-disease (ESRD).

Thyroid hormone abnormalities are frequently observed in patients with chronic renal disease. Chronic kidney disease (CKD) changes the production, metabolism, and excretion of thyroid hormones. As part of its normal functioning, glomerular filtration eliminates iodine from the bloodstream, which is necessary for the production of thyroid hormone.

As a result of the "Wolff Chaikoff effect," the production of thyroid hormone is decreased as a result of the accumulation of iodine in the blood caused by the progressive reduction of GFR in CKD. This results in abnormally low amounts of total and free T3 in serum, but normal levels of reverse T3 and free T4 in the serum. Nevertheless, there is little change in TSH levels in CKD. Cystic fibrosis patients may also exhibit signs of hypothyroidism.

Evidence suggests that the development of chronic kidney disease (CKD) is associated with a number of complications, including thyroid dysfunction, dyslipidemia, and cardiovascular disease (CVD). It is common for the kidney to have

an impact on thyroid hormone metabolism, breakdown, and excretion. The hypothalamus-pituitary-thyroid axis is affected by chronic kidney disease. Many aspects of thyroid function are affected by chronic kidney disease (CKD), including but not limited to: altered iodine storage in the thyroid gland, reduced tissue thyroid hormone content, altered peripheral hormone metabolism, altered thyroid hormone levels in the blood, and changed levels of thyroid hormone in the blood. Consequently, CKD impairs thyroid hormone metabolism [5]. Hyperthyroidism is not common in patients with CKD, whereas overt and subclinical hypothyroidism are more common. An increase in the subclinical form of primary hypothyroidism is associated with a decrease in glomerular filtration rate (GFR) [6].

Chronic kidney disease (CKD) and hypothyroidism share several clinical features. Among the many symptoms that these disorders manifest with, additional low levels of total and plasma-FT3, are dry skin, puffiness, constipation, lethargy, and fatigability. Goitre is also associated with end-stage renal disease at much higher rates [12,13]. Most uremic patients are still considered to be euthyroid since their tendon relaxation time, free thyroxine (FT4), TSH plasma concentrations and basal metabolic rate, are normal, even though recent studies have cast doubt on that assertion [14–16]. Consequently, individuals suffering from chronic renal illness sometimes receive the incorrect diagnosis of thyroid dysfunction. The occurrence of thyroid irregularities in chronic kidney disease (CKD) has been estimated in a few studies [17,18] to be between thirteen percent in early CKD and seventy percent in end-stage renal disease (ESRD). The diagnosis and treatments for many individuals remain uncertain due to contradictory results from previous research. Thyroid dysfunctions can go misdiagnosed in CKD patients, leading to a range of comorbidities, because there is presently a dearth of global data on the prevalence and screening of this condition.

Hence, this study set out to determine the frequency of thyroid dysfunction in people with chronic kidney disease (CKD) and the link between various thyroid dysfunctions and renal function indicators.

AIMS AND OBJECTIVES

Aim-

- To study thyroid function of chronic kidney disease patients
- To study the correlation between thyroid dysfunction and severity of chronic kidney disease in patients

REVIEW OF LITERATURE

The thyroid gland regulates a wide variety of physiological functions, making it an essential organ. Among its many important roles, the thyroid produces the hormones T4 and T3, which play a role in metabolism, development, protein synthesis, the regulation of a great number of other necessary hormones. When the thyroid is not working properly, T3 and T4 that are linked to health problems. A major issue that has gotten very little attention is the relationship between thyroid hormone levels and the progression of chronic kidney disease (CKD). Illnesses affecting the kidneys can coexist with thyroid hormone at certain levels. This research aims to provide light on the relevance of the connections between renal illness and thyroid function. Because it links two previously unconnected events, this data is vital.

Thyroid Disease Epidemiology

Thyroid disease affects about 1 in 13 or 20 million Americans, or 7.35% of the population [1]. There are three types of thyroid disorders: subclinical, hyperthyroid, and hypothyroid. NHANES III, the biggest population survey, indicates that 1.3% of Americans have hyperthyroidism and 4.6% of Americans have hypothyroidism (0.3% clinical and 4.3% preclinical)[2]. High rates of morbidity are caused by both hyperthyroidism and hypothyroidism in the US.

Chronic Kidney Disease

Chronic kidney disease (CKD), often an incurable and progressive condition, is the eighth most common cause of death in the United States [3]. Population studies have shown that around 30 million adults, or one in ten, suffer from chronic kidney

disease (CKD) to varying degrees [3]. Chronic kidney disease (CKD) risk factors include diabetes, hyperlipidemia, hypertension, and thyroid problems.

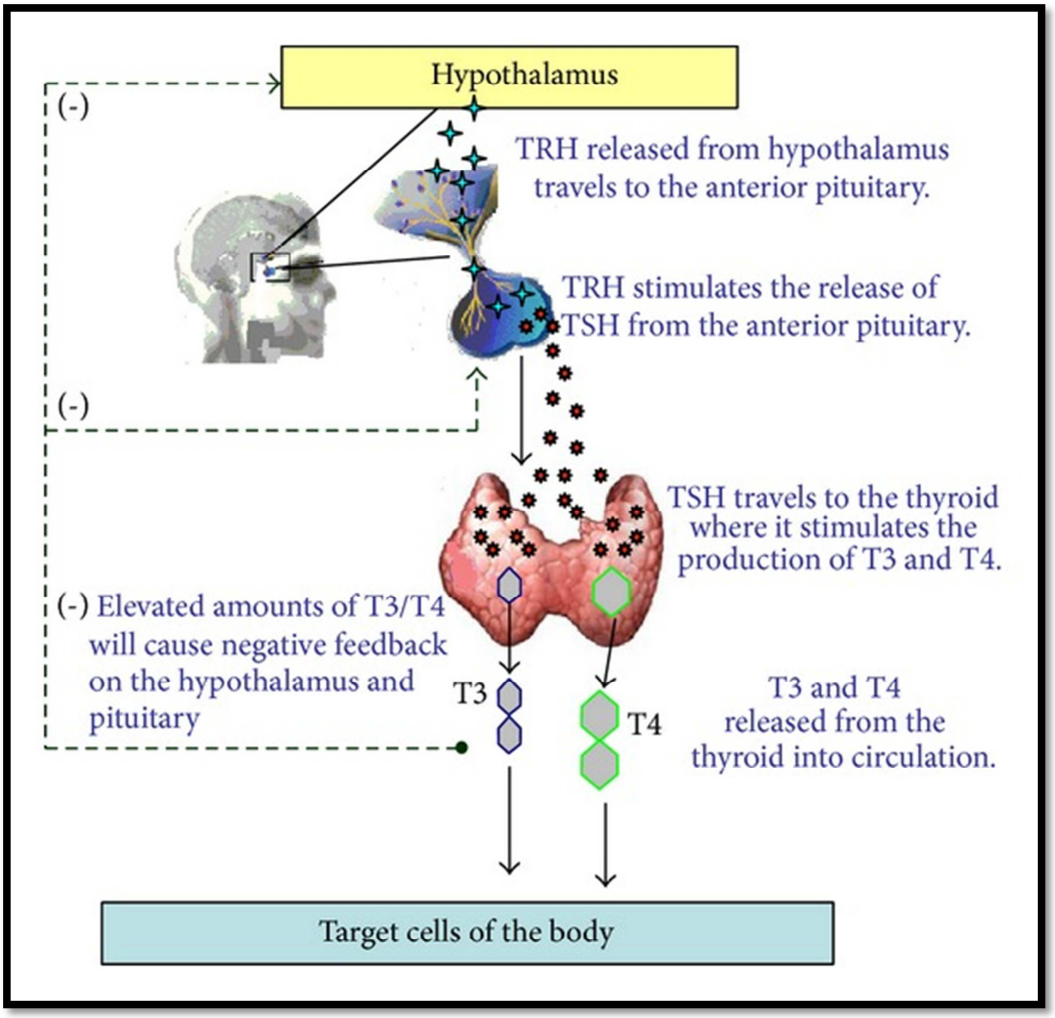

Figure 1 Thyroid-Physiology

Both T3 and T4 are essential for adult metabolic homeostasis and for cell differentiation in development (Figure 1) [4].

Thyrotropin Releasing Hormone (TRH)

The tripeptide amide TRH, which goes by the names L-pyroglutamyl-L-histidyl-L-prolineamide (L-PHP) [5], is very small. The generation of TRH is influenced by circulatory thyroid hormones and the brain's control of these hormones.

TRH leaves the hypothalamus and makes its way to anterior pituitary, where it binds to TRH-receptors and produces TSH through the C-phosphoinositide pathway [3].

TSH -Thyroid Stimulating Hormone

The cystine-knot growth factor superfamily includes TSH, a glycoprotein subunit that weighs 28–30 kDa [6]. The basophilic-cells of anterior pituitary gland are responsible for its synthesis. Once TSH leaves anterior pituitary, it goes to thyroid gland, where it binds to TSH-receptors on thyroid cells. This physiological process initiates second messenger route, which leads to the release of T3/T4 and the transcription of the thyroid gene.

Thyrotropin Molecular Structure

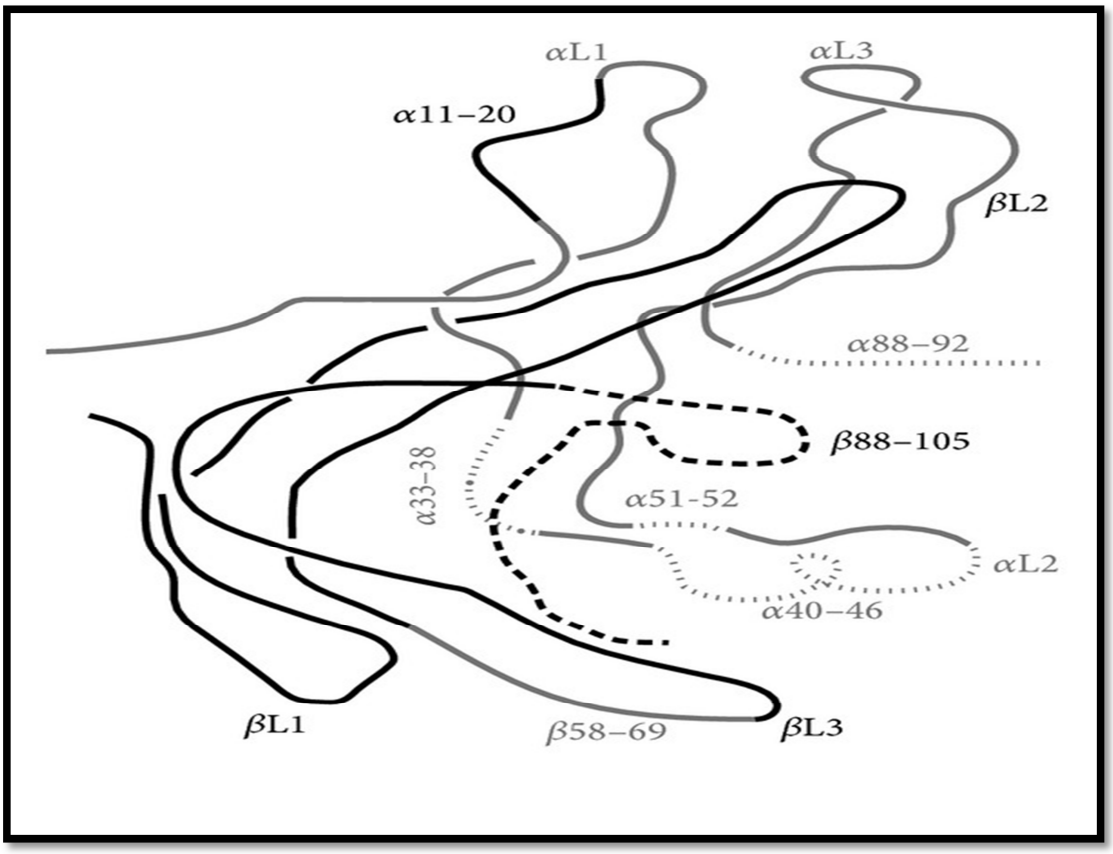

Figure 2 Thyrotropin Structure

The α and β subunits, comprising the thyrotropin hormone, are located on chromosomes 1 and 6, respectively, in humans. The alpha-subunit gene is twice as big as the β subunit gene due to its four exons and three introns, in contrast to the β-subunit gene's three exons and two introns [6]. The alpha-subunit is the site of effect for the second messenger route. The β subunit's physiological activity mostly dictates the receptor specificity of thyrotropin.

THYROID HORMONES EFFECTS ON RENAL DEVELOPMENT

Thyroid hormones affect cell division and protein synthesis. Thyroid hormones have been shown to accelerate the development of the kidneys in studies conducted on newborn rats [2]. The working renal mass is influenced by thyroid hormone status; the kidney to body mass ratio is a measure of this relationship; hyperthyroidism increases this ratio, while hypothyroidism decreases it [3]. Severe hyperthyroidism, however, causes protein deterioration and ultimately renal shrinkage. Furthermore, congenital renal abnormalities are very common in children with congenital hypothyroidism [4]. The renal function of newborns is also influenced by thyroid hormones. The proximal convoluted tubules cells' mitochondrial energy metabolism enzymes are impacted by the perinatal thyroid hormone status [5]. The PCT has shown a rise in the activity of the Na/K ATPase[8] , Na-P co-transporter and Na-H exchanger. Thyroid hormones are therefore crucial for early renal function and renal development.

THYROID HORMONES EFFECTS ON RENAL PHYSIOLOGY

Both direct renal and prerenal effects are caused by thyroid hormones, which impact renal function.

1. Prior to reaching the kidneys, thyroid hormones have an impact on the heart and blood circulation.
2. Hormonal affects on renal tubular physiology, the effects on GFR, and tubular secretory as well as re-absorptive processes are the direct kidney effects of thyroid hormones.

Through their effects on GFR, thyroid hormones influence renal clearance of the water load [9]. It is commonly recognised that Na/K ATPase is essential for the PCT's solute transport. Thyroid hormones mainly affect tubular potassium permeability and Na/K ATPase activity at the PCT, which in turn affects Na reabsorption.[11] Calcium's tubular reabsorption is impacted similarly, while magnesium's is not.[12] Similar to how thyroid hormones control adrenergic receptors, they also govern dopaminergic activation of cells in the kidney tubules. [13] Research has shown that they influence the renin-angiotensin-aldosterone axis by influencing adrenergic modulation, releasing renin, and activating angiotensinase action.[16]

THYROID DYSFUNCTION EFFECTS ON THE KIDNEY

Kidney form, electrolyte balance, tubular function, glomerular filtration rate, and renal blood flow are all affected by thyroid illness. Figure 3 summarises the different ways that hypothyroidism and hyperthyroidism affect renal function. Figure 4 lists the effects on tests of renal function.

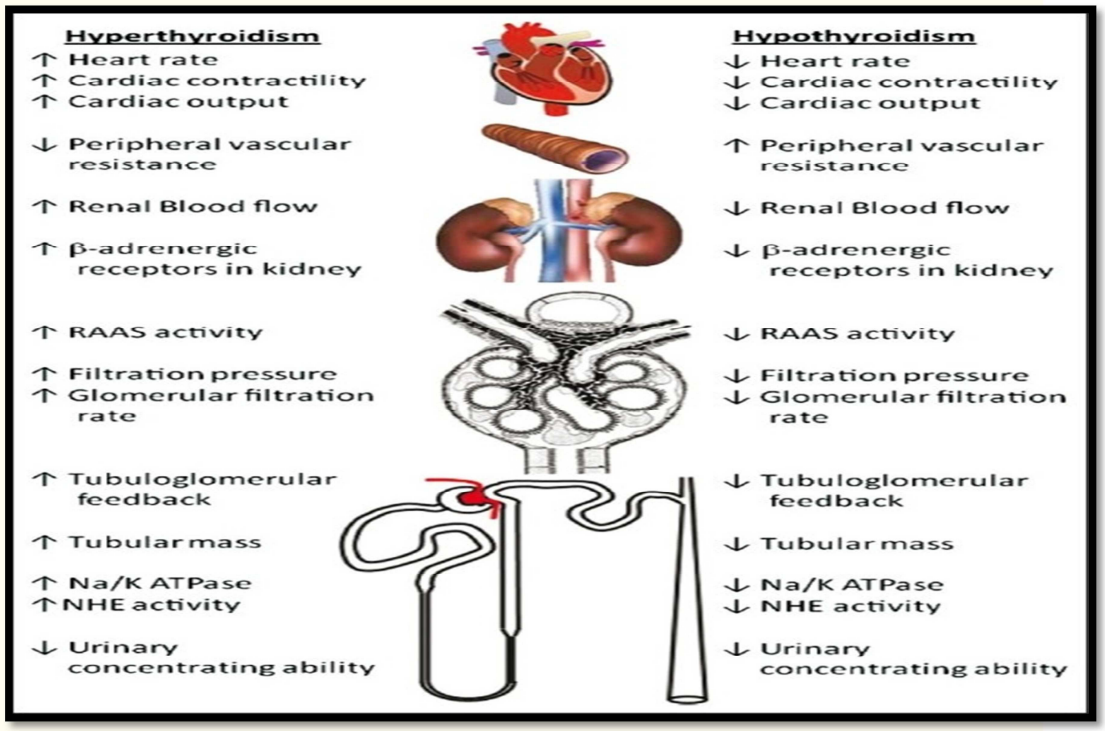

Figure 3. The impact on renal physiology and function of hyperthyroidism and hypothyroidism, as seen in

Tests	Hypothyroidism	Hyperthyroidism
Serum creatinine	Increased	Decreased
Serum cystatin C	Decreased	Increased
Urinary NGAL	Unchanged	Unchanged
24-hour urine protein	Increased	Increased
Water load excretion	Decreased	Increased
Electrolyte imbalance	Hyponatremia	None

Figure 4: Results of clinical testing for renal function in hypothyroidism and hyperthyroidism

EFFECTS OF HYPERTHYROIDISM AND RENAL FUNCTION

Hyperthyroidism is characterised by an increased GFR and RBF.[17] There are several ways in which thyroid hormones affect RBF and GFR. Thyroid hormones are one of the pre-renal agents that improve cardiac output through a decrease in systemic vascular resistance and favourable chronotropic and inotropic effects [18, 19].[20] This increases RBF in an indirect manner. A direct effect of thyroid hormones and an indirect effect of endothelial shear stress associated with high arterial pressure both lead to an increase in endothelial production of nitric oxide (NO) in the renal cortex as well as medulla. This stimulates nitric-oxide synthase.[22] An inverse relationship between renal vasoconstrictor endothelin and this is observed.[23] As a result, there is a net increase in RBF due to an increase in intrarenal vasodilatation and a decrease in vasoconstriction.

In patients with hyperthyroidism, the GFR rises by roughly 18–25%.[17] An higher RBF is not the only factor contributing to this improvement in GFR. The stimulation of the renin angiotensin aldosterone system (RAAS) is another component that leads to an increase in GFR. Thyroid hormones function as multiple stimuli for the RAAS. A rise in RAAS stimulation is caused by hyperthyroidism, which is brought about by an increase in β-adrenergic activity and a concentration of β adrenergic receptors in renal cortex.[24] The renin gene is upregulated by T3. Thyroid hormones increase levels of angiotensin II, renin in plasma, and angiotensin converting enzyme in serum. Both the density of angiotensin receptors and the amount of angiotensinogen produced by the liver are increased.[25] This leads to a net rise in RAAS activity. Afferent arteriolar vasodilatation and efferent arteriolar vasoconstriction lead to an increase in filtration pressure. In addition to the effect of an increase in RBF, this amplifies the magnitude of the GFR increase. One possible

explanation for the hypoperfusion and avid reabsorption of salt and chloride in the PCT is the narrowing of the efferent arteriolar blood vessels. Na-Pi co-transporter, apical Na-H exchanger (NHE), and basolateral NA/K ATPase activity all go up as well. [5, 7].[6] By activating these transporters, the proximal reabsorption of sodium is enhanced. All three of these parameters—tubular mass, tubular reabsorptive capacity and renal mass—increase simultaneously in hyperthyroidism. A rise in the concentration of sodium at the basolateral membrane nourishes the sodium-calcium exchanger. [26]. The basolateral chloride channel and avid Cl reabsorption cause an increase in calcium reabsorption, particularly at loop of Henle, in an indirect way (27). T his causes a decrease in Cl delivery to the distal nephron. When the macula densa picks this up, RAAS activity goes up. The macula densa becomes more sensitive due to hyperthyroidism, which leads to greater RAAS activity.[28] Once the hyperthyroidism is treated, these effects are undone and GFR goes back to normal[17] .Hyperthyroidism is characterised by an increase in glomerular filtration rate (GFR) and a decrease in total muscle mass, both of which lead to a markedly decreased blood creatinine level in patients. [29] The cysteine protease inhibitor cystatin C is released constitutively by every nucleated cell; it is a novel indicator of kidney function and potential future risk of cardio vascular disease. Increased cell metabolism and cystatin C production lead to elevated blood cystatin C levels in hyperthyroidism, even when glomerular filtration rate (GFR) remains same. Serum cystatin C levels and glomerular filtration rate (GFR) are not well correlated with hyperthyroidism. Hyperthyroidism medication causes a rise in blood creatinine and a fall in cystatin C levels. [30]

When hyperthyroidism is treated, the disease goes away, and the 24-hour surge in urine protein is likely caused by glomerular hyperfiltration [3] . An elevation

in urine N-acetyl-β-D-glucosaminidase (NAG) is observed in hyperthyroidism due to damages to the tubules caused by hyperfiltration, hypertrophy, and hyperplasia, together with the rupture of the glomerular basement membrane. [31] The reduced capacity for urine concentration is likely due to an increased RBF along with osmotic diuresis instead of vasopressin insensitivity. [32] When a person has hyperthyroidism, their potassium transferrable levels drop, but their sodium and total body water levels stay the same. However, sodium and potassium levels in the blood tend to remain normal. Hypokalemia, also known as thyrotoxic hypokalemic periodic paralysis of channelopathies, can be caused by genetic abnormalities in either the potassium inward rectifier 2.6 or the L-type calcium channel α1-subunit. On rare occasions, this condition can be associated with hyperthyroidism. [33]

HYPOTHYROIDISM EFFECTS AND RENAL FUNCTION

In contrast to hypothyroidism, hyperthyroidism typically has the reverse effect on the kidneys. Here are some factors that contribute to the reduction of RBF in hypothyroidism: reduced cardiac output , amplified peripheral vascular resistance, intra-renal vasoconstriction, decreased renal response towards vasodilators, and reduced expression of renal vasodilators like vascular endothelial growth factor and insulin-like growth factor-1 [38] . Pathologic changes in the glomerular architecture, such as hypothyroidism-associated glomerular basement-membrane thickening and the mesangial matrix enlargement, can also lead to decreased RBF.

Reversible reductions of around 40% in GFR occur in more than 55% of adult hypothyroidism patients due to a number of factors [40] . The reduction in sensitivity to β-adrenergic stimulation, renin release, angiotensin II, and RAAS activity leads to the loss of GFR [3].[25] The Due to renal parenchymal growth retardation, hypothyroidism puts a structural constraint on the glomerular surface area for filtration. [39] The

absorption of water, salt, and chloride through the proximal tubules is decreased. Furthermore, there is a decrease in the expression of the renal basolateral chloride channel [41] . As a result, decreased chloride reabsorption raises the distal chloride supply and causes the tubuloglomerular feedback mediated by the macula densa, which lowers RAAS activity. As a result, the GFR decreases.

Reductions in the proximal tubules' tubular transport capacity and Na/K ATPase activity occur later in nearly every segment of the nephron. [42] Furthermore, hypothyroidism is associated with a decrease in NHE activity. [43] As a result, the net absorption of salt and bicarbonate is decreased. Defective urine acidification is caused by an increase in salt and bicarbonate loss. Medullary hypertonicity cannot be maintained due to decreased tubular reabsorptive capacity. Urinary concentration is mostly caused by medullary hypertonicity. The hypothyroidism-related decrease of medullary hypertonicity is the root cause of the kidney's incontinence. [44] In contrast, hypothyroidism increases the collecting ducts' sensitivity to vasopressin (or antidiuretic hormone, or ADH), which increases the absorption of free water; this increase is reversible. Nevertheless, in cases of hypothyroidism, the increased fluid retention falls short of effectively lowering ADH to its maximum potential. [45] ADH activity is sustained and free water retention is increased as a result of the pituitary response's resistance to increased fluid retention. Low cardiac output from hypothyroidism activates the carotid baroreceptors, which in turn raises the release of non-osmotic ADH. [46] Some patients have higher urine sodium levels than one might anticipate from their lower cardiac output. It's possible that the ADH secretion in these people is deemed improper. Reduced glomerular filtration rate (GFR), reduced salt reabsorption, significantly increased ADH production, and impaired free water clearance mediated by renal ADH supersensitivity are all contributors to

hyponatremia in hypothyroidism. [40] Patients with hypothyroidism with an increased serum creatinine level are twice as likely to experience hyponatremia as those with a normal serum creatinine level.

Treatment for hypothyroidism causes the renal mass to almost double, and the ratio of kidney to body weight decreases, which is reversible. A reversible increase in blood creatinine, myopathy, and rhabdomyolysis can all be symptoms of hypothyroidism, which is caused by a reduction in glomerular filtration rate (GFR).

Because there is less formation of cystatin C in hypothyroidism, there is less cellular metabolism, which lowers serum cystatin C levels. [30] With the therapy of hypothyroidism, both of these alterations are reversible. Increased glomerular capillary permeability to proteins is another effect of hypothyroidism. [47] The ensuing proteinuria frequently occurs before the hypothyroidism-related decline in GFR. [48]

CHRONIC KIDNEY DISEASE AND THYROID DYSFUNCTION

Hyperthyroidism can induce or exacerbate chronic kidney disease (CKD) in many ways. One consequence of hyperthyroidism is hyperfiltration, which in turn causes intra-glomerular hypertension, also known as increased filtration pressure. A second risk factor for hyperthyroidism is proteinuria, which is known to directly harm the kidneys. Thirdly, hyperthyroidism-induced down-regulation of superoxide dismutase as well as increase in mitochondrial energy utilisation lead to an increase in free radical production and ensuing renal injury. [49] Hypertension, a complication of oxidative stress in hyperthyroidism, speeds up the progression of chronic kidney disease.the third Increased RAAS activity may hasten the progression of renal fibrosis. Those who suffer from chronic kidney disease (CKD) are more likely to develop anaemia, and hyperthyroidism is associated with EPO resistance. [50] Due to

all the things said before, hypothyroidism only helps CKD develop in one way: by mildly to moderately lowering GFR. Those suffering from chronic kidney disease (CKD) may see an improvement in their GFR after receiving therapy for hypothyroidism.

The non-autoimmune syndrome known as primary hypothyroidism is common in people with chronic kidney disease [51]. More specifically, the prevalence of subclinical hypothyroidism rises steadily in tandem with decreasing GFR. The most common and initial impairment of thyroid function in individuals with chronic renal disease is low T3 levels, namely total T3 rather than free T3. Patients with chronic kidney disease can develop "low T3 syndrome" for a variety of causes. Fasting, metabolic acidosis over time, and protein deprivation over time all have an effect on iodothyronine deiodination and the binding of T3 proteins. T3 protein binding and peripheral conversion to T4 are both reduced under these circumstances. Furthermore, inflammatory cytokines such as interleukin (IL)-1 and tumour necrosis factor (TNF)-α block type 1 5'-deiodinase, an enzyme that peripherally converts T4 to T3.[54] The In addition, elevated blood iodine levels caused by poor renal iodine processing lead to a protracted Wolff-Chaikoff effect. [55] A consensus on clinical relevance of low T3 syndrome has not yet been reached. Studies have shown that low T3 levels in CKD patients are associated with various health problems. These include inflammation (hsCRP, IL-6, etc.), malnutrition (lower prealbumin and IGF-1), raised endothelial dysfunction, poor cardiovascular function, poor survival as well as higher mortality from cardiovascular and all causes. [54,56] Not all of the studies were powerful enough to detect associations, and some of those that were wrongly eliminated potential confounders. [57] There is some evidence that suggests a correlation between reduced free T3 levels and an increased mortality risk, independent of total T3 levels. Free T3

levels might not be related with long-term mortality in persons with chronic renal disease and dialysis, according to recent studies. Subsequent studies confirmed that decreased T4 levels were present in many CKD patients [59]. The opposite is true with CKD, when free T4 levels are often low to normal. The main reason for this is because T4's protein binding is reduced in CKD. Many non-thyroidal diseases (NTIs) share a thyroid profile, such as cancer, heart failure, serious infections, and some hospitalised patients who do not have renal disease. As a result, chronic kidney disease (CKD) was formerly referred to as a "sick euthyroid state," a term that has now been replaced with "non-thyroidal illness." Contrary to other NTI states, CKD does not cause an increase in total rT3 levels. [60] Because of this, there is an increase in rT3 translocation into both intracellular and extravascular areas. Low renal clearance may cause slightly elevated free rT3 levels in some individuals. Differentiating CKD from other NTIs is the fact that it is linked to elevated levels of thyroid stimulating hormone (TSH). Nevertheless, thyrotropin releasing hormone induces TSH synthesis in CKD subjects, which may indicate pituitary disturbances in uremia. In addition, chronic kidney disease (CKD) hinders the effectiveness of TSH by interfering with its circadian rhythm and glycosylation. [61] Consequently, individuals with chronic kidney disease (CKD) experience increased TSH and an elevation in thyroid gland volume due to low T3 and normal to reduced T4 levels. [62–64] The reduction in nitrogenous waste, protein catabolism, and protein nitrogen turnover is presumably a physiological adaptation to chronic kidney disease. A number of factors cast doubt on the "euthyroid" condition, including elevated TSH levels with decreasing free T4, hyporesponsiveness of TSH to TRH, lower T3 levels and an associated issues without a rise in rT3, and the possibility of thyroid supplementation helping persistent hypothyroidism. Thirty years of study into CKD have not resolved the question of whether thyroid hormone replacement is necessary.

Because attempts to restore T3 have often resulted in increased muscle catabolism and negative nitrogen balance, it is wise to avoid doing so in CKD patients with low T3. Hypothyroidism is obviously dangerous for the patient's health, but when exactly thyroid malfunction gets severe enough to necessitate thyroxine replacement treatment for CKD is unknown. When TSH levels are mild, whether or not T3/T4 levels are low, it is usually not required to use thyroid hormone supplements. It is imperative to consider the potential side-effects of hyperthyroid state, the benefits of hypothyroid state in CKD, and the absence of evidence for the benefits of thyroid-hormone-replacement before making a therapeutic decision. Treatment endocrinologists and nephrologists should thoroughly evaluate each patient's clinical characteristics, possible hypothyroid symptoms, risks, and benefits of thyroid hormone treatment (or lack thereof) before making a therapeutic choice.

Thyroid enlargement, increased blood inorganic iodide levels, and reduced iodide excretion are all symptoms of CKD. Compared to general population, those with chronic kidney disease are more likely to have thyroid nodules, thyroid cancer, and goitre; women, in particular, have a greater risk of goitre.[65]

The Autoimmune thyroid disease is not more common in patients with chronic renal disease. Surprisingly, antibodies against thyroid microsomal and thyroglobulin are not commonly seen in individuals with chronic kidney disease. Lupus nephritis and type 1 diabetes mellitus are two autoimmune diseases associated with chronic kidney disease (CKD), although autoimmune thyroid ailment can occur alongside them. When elevated TSH is detected alongside another autoimmune disease, it’s essential to check for antithyroid antibodies. The managing method remains unchanged when CKD and autoimmune thyroid disease are present together.

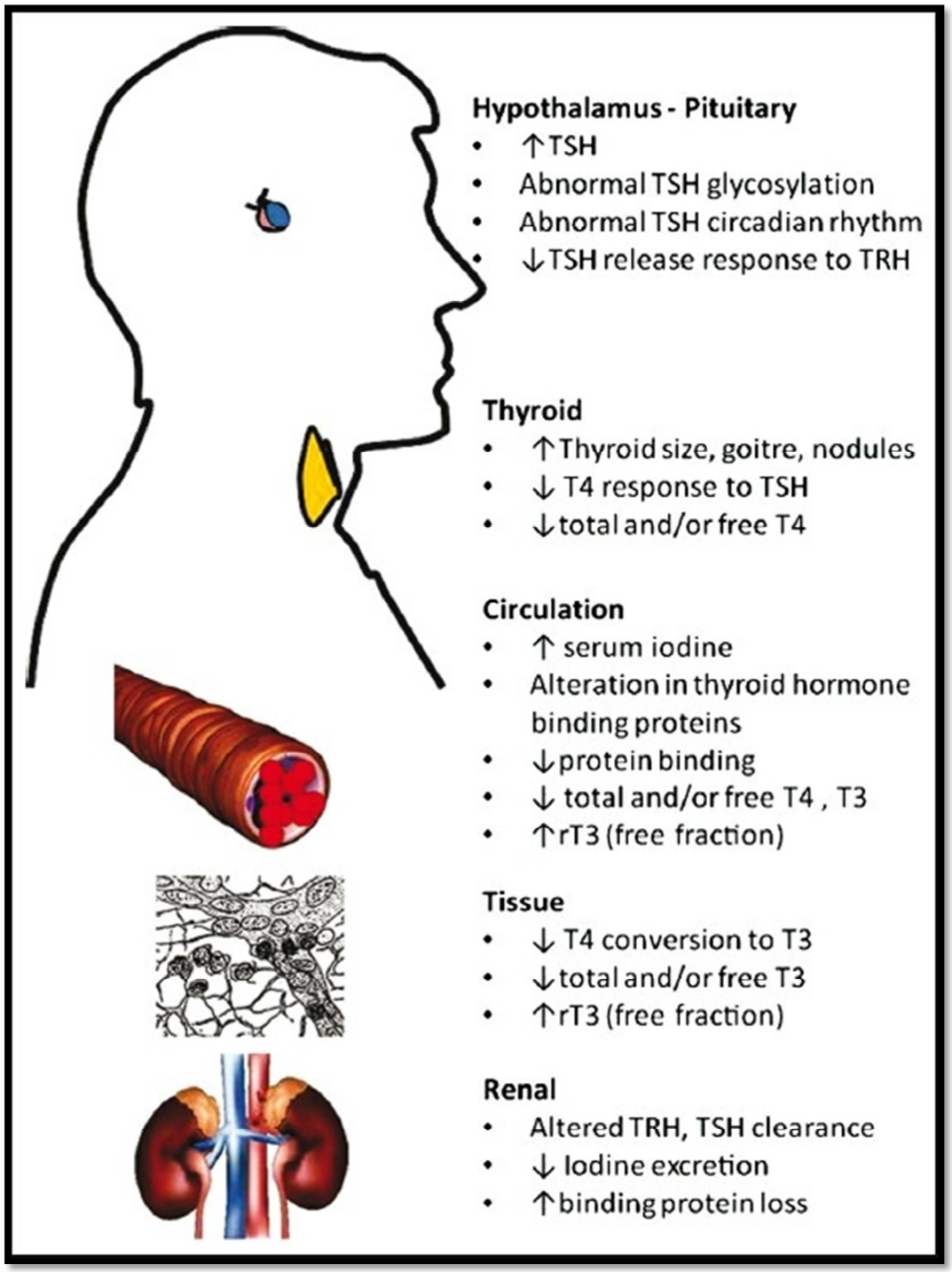

Figure 5 shows the Different consequences of CKD on thyroid profile.

THYROID DYSFUNCTION IN DIALYSIS AND KIDNEY TRANSPLANTATION

Individuals with CKD undergoing hemodialysis (HD) had increased TSH and low thyroid hormone levels. About 20% of uremic patients have slight elevations in TSH levels, however these increases are typically not interpreted as indicative of "hypothyroidism" in this particular patient subset. Patients with chronic kidney disease (CKD) who undergo heparin dialysis have an increased free T4 fraction, even if their total T4 levels are low, since heparin prevents T4 from binding to proteins. Even if thyroid hormone levels in the blood are lower in CKD patients with HD, the euthyroid state can be maintained due to compensatory effect on the cellular transit of thyroid hormones. [(67).] These considerations highlight the need for a substantial increase in TSH levels before beginning thyroid hormone supplementation, regardless of how low the blood thyroid hormone profile may be.

Patients on peritoneal dialysis (PD) are at much higher risk for hypothyroidism and low T3 levels, particularly in its subclinical forms. [68] Thyroid-3, thyroid-4, and lost thyroid-binding globulin (TBG) are all components of the PD effluent. In spite of persistent and considerable protein loss, TBG levels remain normal. The T3 and T4 losses are 1% and 10 %, respectively, and may be readily be compensated for. There is no need for thyroid hormone supplementation in individuals with PD and chronic kidney disease.

Transplanting kidneys can correct abnormal thyroid profiles brought on by chronic kidney disease (CKD). In the three or four months following a transplant, low T3 as well as T4 levels start to rise. T4 levels in kidney transplant recipients often fall below their pre-transplant levels in the months immediately following the procedure and gradually rise back up to normal levels. [69] There is typically a robust relationship between graft function and free T3 levels as well as post-transplant thyroid volume.

[70] The risk of graft loss following transplantation is increased in patients with low pre-transplant T3 levels. [71] The lack of improvement in graft survival after T3 supplementation treatment disproves the existence of a causal link. [72] The Renal transplant patients often experience low T3 levels following the first few months after surgery, but this is not an indication that thyroid hormone replacement therapy is necessary. Thyroid cancer is the seventh most frequently found malignancy among people who have received a kidney transplant. [73]

THYROID DYSFUNCTION AND ASSOCIATION WITH OTHER KIDNEY DISEASES

Several glomerulonephritides may be associated with thyroid disorders. Minimum change disease, membranoproliferative glomerulonephritis, IgA nephropathy, membrane nephropathy, and minimal change nephropathy are the most common associations [76, 77, 78]. Several mechanisms account for these correlations. There are a number of autoimmune diseases that can coexist with thyroid and renal disease, like type 1 diabetes mellitus. Patients with thyroid disease also tend to have circulating immune complexes. Some cases, such as Hashimoto's thyroiditis as well as membranous nephropathy, are associated with deposition of immune complex in the thyroid-epithelial basement membrane and glomerular basement membrane. Additionally, there is evidence to suggest that autoimmune diseases like lupus and vasculitis can cause both thyroid and renal problems. Hypothyroidism is associated with minimal change illness and the sleep disorder obstructive sleep apnea.

Proteinuria, especially in nephrotic syndrome, causes the loss of thyroid hormones that are bound to several proteins, including albumin, transthyretin, prealbumin, and thyroid hormone-binding protein (TBG). [82] Total thyroid hormone levels in the bloodstream fall because of this. Increasing free fraction of hormones, the thyroid compensates for this and keeps the euthyroid state in check. Hypothyroidism,

however, can occur in those who have a low thyroid reserve due to this urine loss. Patients taking extra thyroxine may require more than recommended to keep their thyroids in a healthy state if they experience proteinuria. [83] A further association between primary hypothyroidism and congenital nephrotic syndrome has been found; in this condition, increased TSH levels during pregnancy are caused by urine thyroid hormone loss. Along with the glomerulonephritides listed above, tubulointerstitial nephritis and uveitis (TINU) syndrome has been associated with isolated cases of hyperthyroidism. (84)To treat the disease, steroid treatment is beneficial [85].

Patients with acute renal impairment can develop NTIs (euthyroid sick syndrome), ibut reverse-T3 level do not seem to be increased. [86] Hypothyroidism can lead to acute kidney injury associated with rhabdomyolysis. [87]

Thyroid and renal malignancy

The risk of renal cell carcinoma (RCC) in patients with thyroid cancer is increased due to both genetic predisposition and treatment toxicity [88]. In addition, renal cell carcinoma (RCC) is among the most common cancers to metastasize to the thyroid, and kidney cancer can also develop from thyroid cancer [89].Although clear cell carcinoma of the thyroid is known to resemble RCC, some RCC can physically bear a resemblance to thyroid follicular carcinoma [90].Thyroid tumours expressing EPO receptors have a good prognosis, in contrast to RCC expressing deviant thyroid hormone receptors, which might cause cancer [91,92,93] .

DRUGS IN THYROID AND RENAL DISEASE

It is possible for the other organ's function to be adversely affected by medication used to treat issues with the kidneys or thyroid. Thionamides, such as propylthiouracil, carbimazole, and methimazole cause hypothyroidism and renal

failure by means of immune systems. Numerous glomerular illnesses, such as lupus nephritis, vasculitis, and necrotizing glomerulonephritis complicated by pulmonary haemorrhage, might develop as a result of these problems. [96] In patients who have received a kidney transplant, allezumab has been associated with an autoimmune thyroid disease. [97] The risk of hyperthyroidism is increased when interferon-α is used to treat hepatitis B and C virus infections before transplantation. [98] The anticancer and antiangiogenic properties of lenalidomide make it an effective treatment for renal cell carcinoma. But this medication can lead to short-lived thyrotoxicosis and subacute thyroiditis. [99] Sunitinib, a new drug for renal cell carcinoma, induces hypothyroidism, which some researchers believe is associated with an improved prognosis. Lithium use is related with hypothyroidism, nephrogenic diabetic insipidus, and chronic kidney disease [100]. Acute renal damage, hypo- and hyperthyroidism, and other side effects have all been associated with amiodarone. [101] Hyperthyroidism and tubulointerstitial nephritis are side effects of rifampicin. Important considerations for hyperthyroid CKD patients include treatment. [102] Smaller doses of 131I are often necessary to treat Grave's disease in people with CKD. The usual therapeutic dosage of 131I must be administered to hyperthyroid persons on HD since the radioactive isotope is removed by dialysis. As a precaution against radiation exposure, individuals on PD undergoing treatment for thyroid cancer should have their 131I dose halved [103,104] . Medication interactions with thyroid and renal diseases are detailed in Figure 6.

Drug	Thyroid	Kidney
Thionamide	Hypothyroidism	Glomerulonephritis, vasculitis, lupus nephritis
Alemtuzumab	Autoimmune thyroiditis	Used as induction agent in renal transplantation
Interferon-α	Transient hyperthyroidism	Used for treatment of hepatitis B or C pre-transplant Used in therapy of renal cell carcinoma (RCC) Can accelerate rejection in renal transplant Can precipitate glomerulonephritis/vasculitis
Lenalidomide	Subacute thyroiditis with hyperthyroidism	Used in therapy of RCC
Sunitnib	Hypothyroidism	Used in therapy of RCC
Lithium	Hypothyroidism	Nephrogenic diabetes insipidus Chronic kidney disease (CKD)
^{131}I treatment	Used in therapy of Grave's disease and thyroid carcinoma	Needs dose reduction in CKD and in patients on peritoneal dialysis

Figure 6: Drugs used in kidney and thyroid diseases CKD and Thyroid Disorders

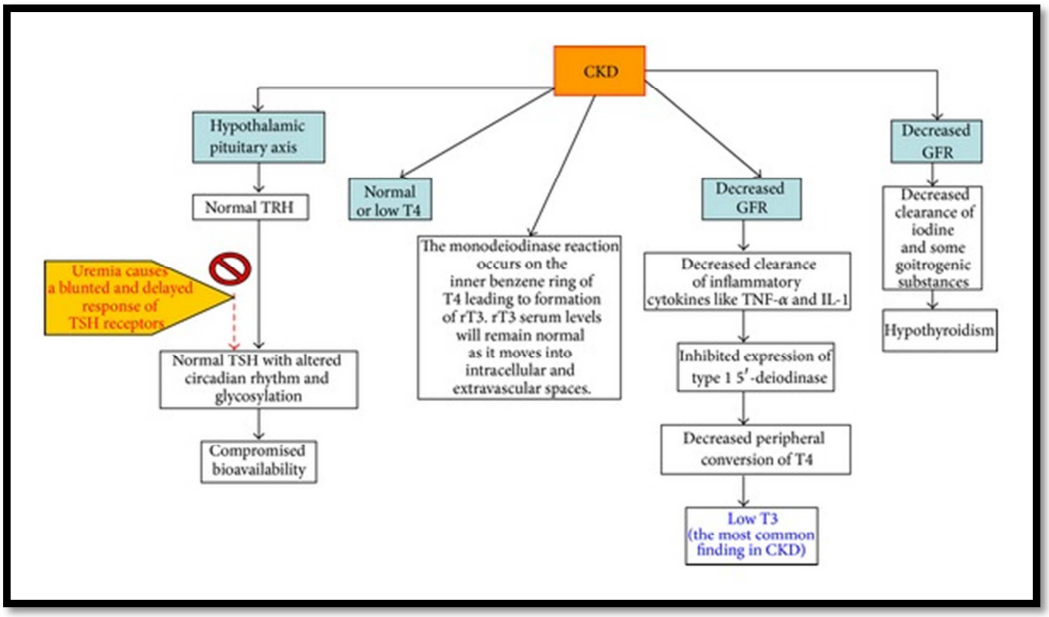

Figure 7: CKD and thyroid disorder

Figure 7 It has already been mentioned that chronic kidney disease affects the hypothalamus-pituitary-thyroid axis and peripheral thyroid hormone metabolism. The most prevalent thyroid issue in individuals with CKD is subclinical hypothyroidism, and the commonest test result for this condition is low T3 [7] . Normal TSH levels (including TSH bioactivity) are common in patients with altered circadian cycles. Uremia reduces TSH secretion because it mutes the pituitary-receptor response to TRH. A delayed response of TSH to TRH is caused by an increase in TSH half-life and a reduction in clearance [7] . Furthermore, in uremic conditions, aberrant serum components might deplete T3 and T4 of their appropriate protein binding sites. If monodeiodinase activity occurs in the inner benzene-ring of T4, rather than the outer ring, the generation of reverse T3 might explain normal or low levels of T4. Reverse T3 levels are seen to be normal in patients with CKD, nonetheless, since this hormone moves from the vascular area to the extravascular and intracellular regions. [7]. Following hemodialysis, transient elevations in the T4 levels are typically observed. The primary cause of this action is the anticoagulant heparin, which prevents T4 from binding to proteins and raises T4 levels [7].

Iodothyronine deiodinase is affected by fasting, chronic metabolic acidosis, and chronic protein insufficiency; this may explain why CKD patients have low T3 levels. Synthesis of T3 begins with T4. These factors influence the protein-T3 binding mechanism [7] . Low T3 levels in chronic kidney disease (CKD) may be due to poor clearance of inflammatory cytokines including TNF-alpha and IL-1, which reduces the peripheral conversion of T4 to T3. The aforementioned cytokines inhibit the expression of 1 5′-deiodinase, an enzyme that helps in conversion of T4 to T3. [8]. Research has shown that low free T3 levels are a strong indicator of mortality in hemodialysis patients. [9]. Prior to a kidney transplant, low T3 levels are linked to

posttransplant chances of graft loss [7]. It is recommended that all clinicians examine T3 levels prior to performing a kidney transplant. It's possible that low T3 levels in CKD prevent TSH levels from rising. Thyrotrophs may be more sensitive in uremia, according to experimental data. This could explain the central thyrostat's reset, which shows a decrease in thyroid hormone levels in the blood and, consequently, influences the inhibition of negative feedback [10]. In chronic kidney disease (CKD), protein catabolism is slowed because the body increases the nitrogen waste surplus as a physiological correction for low T3/T4 levels (when TSH levels are normal).

Goiter and CKD

The prevalence of goitre was greater (0-9%) in patients with CKD. Reduced excretion of inorganic iodides can have hypertrophic effects on thyroid gland tissue, which can lead to goitre [7]. A third factor that might be at play is the reduced clearance of goitrogenic substances such aryl acid caused by chronic kidney disease [8]. Extending the Wolff-Chaikoff effect may be possible with higher serum iodine levels, according to studies.

Subclinical Hypothyroidism

In subclinical hypothyroidism, there is an increase in serum levels of TSH (5-10 μIU/mL) together with normal serum free T4 . With a decrease in GFR, the incidence of subclinical hypothyroidism rises at a steady rate. About 18% of chronic kidney disease (CKD) patients who do not need dialysis also have subclinical primary hypothyroidism, according to one research. This observation is independently linked with a decreasing EGFR. The incidence of subclinical primary hypothyroidism rose up from 7% to 17.9% in individuals whose GFR decreased from ≥90 mL/min to 60 mL/min [11]. Research suggests that cutting back on dietary iodine consumption helps

alleviate hypothyroidism in uremic dialysis patients, making hormone replacement therapy less necessary for these individuals. Thyroid hormone therapy significantly improved estimated glomerular filtration rate (GFR) in a clinical experiment compared to non-treated subjects.

Hyperthyroidism

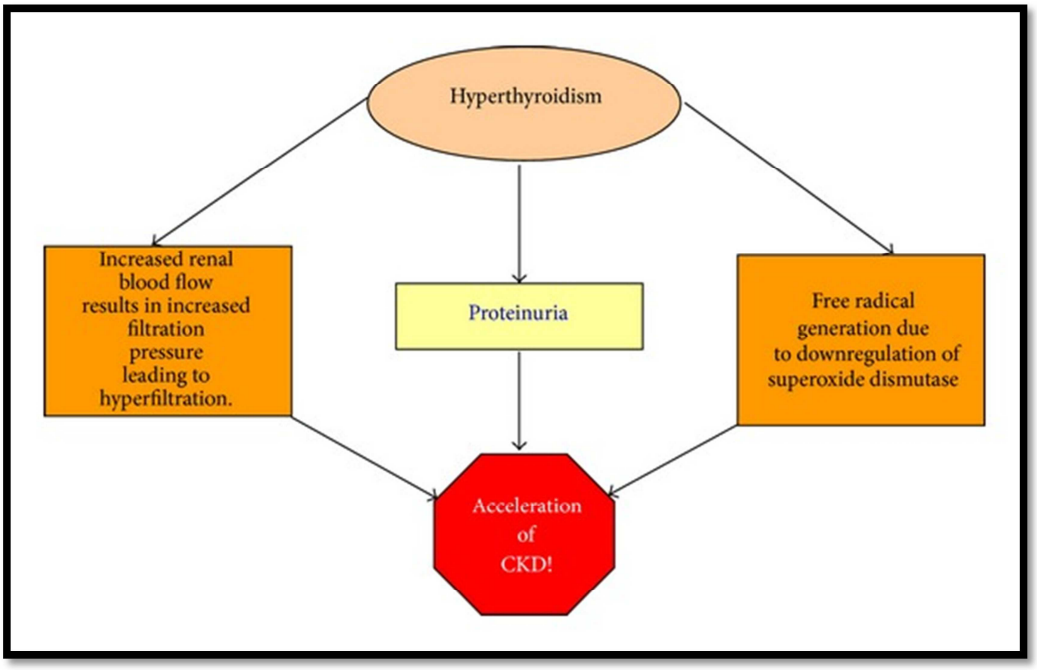

Figure 8: Hyperthyroidism and CKD

Hyperthyroidism is just as common in people with CKD as it is in the general population, hence there is no obvious association between the two (Figure 8). Importantly, several hyperthyroidism-related diseases can speed up CKD. Here are the components of these systems:

Hyperfiltration results from an increase in filtration pressure caused by intraglomerular hypertension, which is caused by hyperthyroidism's elevated renal blood flow. It is well-known that proteinuria, a symptom of hyperthyroidism, causes direct damage to the kidneys. Free radical generation increases due to hyperthyroidism-related increases in mitochondrial energy metabolism and

downregulation of superoxide dismutase. Blood pressure rises due to oxidative stress, another symptom of hyperthyroidism, which advances chronic kidney disease.[7].

Thyroid Disorders in Glomerular Diseases

Numerous forms of glomerulonephritis are linked to thyroid disorders, including both hypo- and hyperthyroidism. The glomerulonephritis forms that are associated with thyroid disease include little change, membranous, IgA, mesangiocapillary, and membranoproliferative glomerulonephritis. Membranous glomerulonephritis is the most common of these. [12] The two primary histological alterations observed are an increase in mesangial and endocapillary cellularity and a thicker glomerular basement membrane (GBM) as a result of immune complex deposition. [13] The development of immune complexes and proteinuria are the pathophysiologic connections between thyroid dysfunction and glomerulonephritis. [12] These complexes, which deposit on the glomeruli's basement membrane, are mostly to blame for the modification of renal function. Thyroglobulin has also been found to be deposited in the glomeruli's basement membrane, according to certain investigations. Similar outcomes are observed not just in thyroid problems but also in other autoimmune illnesses as diabetes and systemic lupus erythematosus (SLE). [12]

Nephrotic Syndrome

Nephrotic syndrome can be impacted by variations in thyroid hormone levels in the serum in a number of ways. Proteinuria causes the loss of many binding proteins, including albumin, transthyretin, prealbumin, and thyroxine-binding globulin (TBG). [12] The loss of the aforementioned proteins causes a drop in serum as well as total T3 levels. It is generally believed that most people are euthyroid because their thyroids can normalise their free T3 and T4 levels and compensate for

proteinuria. [14] The efficacy of levothyroxine as a replacement for thyroid hormone is controversial.

Thyroid Cancer association with Kidney Disease

Thyroid cancer diagnoses are three times higher in women. [12] Individuals who have thyroid cancer are also more likely to get renal cell carcinoma or another cancer. The connection between thyroid hormones and malignancies of the reproductive system is the subject of numerous investigations. Renal sarcoma, oncocytoma, collecting duct tumours, and parenchymal epithelial tumours are some more forms. There are three distinct pathways that thyroid carcinomas can take that lead to kidney metastasis: papillary, follicular, and anaplastic. One further place where kidney tumours might metastasize is to thyroid gland.

Dialysis Effects on Thyroid Hormones Homeostasis

Hypothyroidism is prevalent in hemodialysis (HD) patients. [12] Endothelial damage markers, HD-related inflammation, systemic acidosis, and dialysis duration are all linked with low T3 levels. [12] Patients with low total- T4 levels and increased fT4 levels have heparin-induced increases in the free T4 fraction due to an inhibition of T4 binding to proteins. Twenty percent of HD patients have elevated TSH levels. [7] It is possible that HD's effect on TSH cellular transit is a compensating mechanism that maintains a healthy thyroid [12].

Peritoneal Dialysis

Low thyroid function (T3) and subclinical hypothyroidism are typically linked to peritoneal dialysis (PD). [8] Low T3 levels in Parkinson's disease may be caused by inflammation and malnutrition, considering the link between free T3, CRP, and serum

albumin. [28] In cases of subclinical hypothyroidism, the excretion of iodide may be diminished. In severe chronic kidney disease (CKD), glomerular filtration is impaired, leading to a rise in plasma inorganic iodide content and a reduction in iodide excretion. Such elevations in total-body inorganic-iodide, which inhibit production of thyroid hormone, may account for the high prevalence of subclinical hypothyroidism in CKD population. The PD-related decreases in T4 and T3 are so small (1% and 10%, respectively) that they are easily compensable [7]. Thyroid hormone supplements are unnecessary for people with PD.

Thyroxine-binding globulin (TBG) levels are normal, but TBG, along with T4 and T3, is depleted in Parkinson's disease (PD). There is evidence that subclinical hypothyroidism increases mortality in those with chronic renal disease and is associated with an increased risk of cardiovascular disease.

Renal Transplant

Thyroid hormone levels are known to return to normal after renal transplantation. In individuals undergoing kidney transplantation, low T3 and T4 gradually revert to normal within 3–4 months. T4 decreases less than it did prior to transplantation over the first few months of the procedure and progressively returns to normal. [8] Graft function is positively correlated with free T3 and thyroid volume in transplant patients. Since low T3 levels prior to transplant are associated with a future risk of loss of graft and thyroid hormone supplementation has not shown to be beneficial, these patients do not need to be treated with thyroid hormones. [8]

After obtaining full informed permission, 200 patients met the inclusion criteria and included in the prospective cross-sectional observational study by Nikhil Gupta et al.; 100 patients served as cases and 100 as controls. Patients without CKD

had an average age of 47.74 years, while those with the disease were 52 years old and those in the control group were 43 years old. There was a notable disparity ($p < 0.05$) in the average levels of triglycerides (TGs) and high-density lipoprotein (HDL) when comparing the patients and controls. According to Pearson's correlation analysis, there was a modest but statistically significant positive association between TSH and creatinine ($r = 0.200$; $p < 0.05$). Researchers found that dyslipidemia and abnormal thyroid profiles were more common in CKD patients compared to control subjects. It is recommended that patients with chronic renal disease have regular screenings for hypothyroidism and dyslipidemia. The relationship between thyroid hormone levels and the development of chronic kidney disease (CKD) has not been well studied in all its facets.

Subclinical hypothyroidism accounted for 27.2% of instances, overt hypothyroidism for 8.1%, and subclinical hyperthyroidism for 3.3% of patients with CKD, out of 36.6% of patients with CKD who had thyroid dysfunction, according to research by Saroj Khatiwada et al. The following cholesterol abnormalities were present in 36% of patients: hypertriglyceridemia, low HDL cholesterol, undesirable LDL cholesterol, and hypercholesterolemia. Compared to patients with stage 3, the likelihood of thyroid dysfunction was significantly higher in patients with stage 4 and stage 5 CKD. Heart disease was more common in individuals with chronic kidney disease (CKD) who also had diabetes mellitus, high cholesterol, undesirable low-density lipoprotein cholesterol, and who were in stages 4 or 5 of the illness rather than stage 3.

MATERIALS AND METHODS

Source of Data: Patients being treated in department of medicine at KLE Dr. Prabhakar Kore Hospital and Research Center, Belagavi

Study Design: Cross-sectional study

Study Period: 1 year from January 2023- December 2023

Sample Size: 87

According to the study done by **Mills et al.**[6] entitled "**A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010**".So, for the sample calculation we considered the prevalence of CKD stages 1-5 to be 12%.

In our institute, we get around 10-12 patients with CKD stages 1-5 in a month. And the study duration is of 12 months, so we are expecting to get around 120-150 CKD stages 1-5 patients during the study period.

So, considering an incidence rate of 12% (CKD stages 1-5 patients), and population size of 150, we used the following incidence formula for calculating the sample size.

The sample size n and margin of error E are given by:

$x = Z(c/100)^2 r(100-r)$

$n = N\,x/((N-1)E^2 + x)$

$E = Sqrt[(N - n)x/n(N-1)]$

where N is the population size (N=150), r is the fraction of responses that you are interested in (r=12%), and Z(c/100) is the critical value for the confidence level c (Z=1.96).

Putting the above values in the above formula, the sample size obtained is 79 CKD stages 1-5 patients in our study, at a confidence interval of 95% and 80% power of the study.

Considering an attrition rate of 10%, we intend to include 87 CKD stages 1-5 patients in our study.

Sampling technique: All consecutive patients fulfilling the inclusion criteria will be included in the study

Inclusion Criteria:

- Patients diagnosed with CKD
- Patients who are on conservative management of CKD

Exclusion Criteria: Patients who are undergoing peritoneal or hemodialysis

- Age < 18 years
- Patient on anti-thyroid or thyroid replacement therapy
- Other conditions like
- Acute illness
- Recent surgery, burns or trauma
- Hepatorenal Syndrome
- Hemolytic Uremic Syndrome
- All Acute Kidney Disease patients

- Drugs altering thyroid profile like amiodarone, dopamine, thalidomide, phenytoin, oestrogen pills, iodine-containing drugs, steroids, , anti-psychotic drugs, potassium iodide
- Known thyroid disease before the development of chronic kidney disease

Methodology

All patients meeting the inclusion criteria were considered for the study, after which informed consent was obtained and the patient was enrolled for the study.

All patients fulfilling inclusion criteria were subjected to a questionnaire and thorough clinical examination. Routine workup for chronic kidney disease was done.

Laboratory investigations included Complete blood counts, renal function tests including serum calcium and serum phosphorus, liver function tests including serum proteins.

Along with Serum TSH, free T3 and freeT4.

The following cut off values were considered normal in the study.

- TSH= 0.27 to 4.2 mIU/ml
- Free T3= 2.0 to 4.4 pg/ml
- Free T4= 0.93 to 1.7 ng/ml

Any value above or below was considered decreased and increased, respectively

The patients were graded based on eGFR according to the KIDGO guidelines for Chronic kidney Disease into Stage 1, Stage 2, Stage 3, Stage 4 or Stage 5.

i. Stage 1- GFR of >90 mL/min/1.73m^2
ii. Stage 2- GFR of 60 to 89 mL/min/1.73m^2

iii. Stage 3- GFR of 30 to 59 mL/min/1.73m^2

iv. Stage 4- GFR of 15 to 29 mL/min/1.73m^2

v. Stage 5- GFR <15 mL/min/1.73m^2

Data collection

The following data were collected for the purpose of the study.

- Demographics such as age, gender
- Comorbidities
- Investigations such as Free T3, Free T4 and TSH levels
- Complete Blood Count
- Renal function including creatinine and urea
- Liver function tests
- Urine analysis
- USG abdomen

Ethical considerations

Institutional ethical clearance was obtained prior to initiation of the study. The details of the study were explained to the patients and an informed consent was obtained from all patients

Data handling

The collected data were entered in Microsoft excel and the related records were stored safety with no access to other study personnel.

Statistical Analysis

Data is analysed using statistical software R version 4.4.0. and Microsoft Excel. Categorical variables given in the form of frequency tables. Continuous variables given in Mean ± SD /Median (Min, Max) form. Chi square test is used to check the association of categorical variables with groups. Normality of variable is checked by Shapiro Wilk test and QQ plot. If data follows normal distribution, parametric tests will be used. Otherwise, non-parametric tests will be used. One way ANOVA is used to compare the mean of variables over stage of CKD. Tukey's HSD is used as post hoc analysis. Kruskal Wallis test is used to compare the distribution of variables over stage of CKD. Dunn test is used as post hoc analysis. Spearman's rank correlation test is used to check the correlation of eGFR with thyroid parameters. P-value less than or equal to 0.05 indicates statistical significance.

RESULTS

Data contains measurements on 87 subjects.

Table 1: Distribution of subjects according to demographic details.

Variables	Sub Category	Number of subjects (%)
Age (years)	18-40 years	20 (22.99%)
	41-60 years	43 (49.43%)
	61-80 years	24 (27.59%)
	Mean ± SD	50.86 ± 14.23
	Median (Min, Max)	54 (18, 76)
Sex	Female	30 (34.48%)
	Male	57 (65.52%)

The mean age of the subjects is 50.86 ± 14.23 years. The median age is 54 years, with the minimum and maximum ages being 18 and 76 years, respectively.

Majority subjects belonged to 41 to 60 years, comprising 43 (49.43%) subjects. This is followed by the 61 to 80 years age group, which includes 24 (27.59%). The smallest group is the 18 to 40 years age group, consisting of 20 (22.99%) subjects.

Regarding sex distribution, there are 57 (65.52%) male subjects and 30 (34.48%) female subjects.

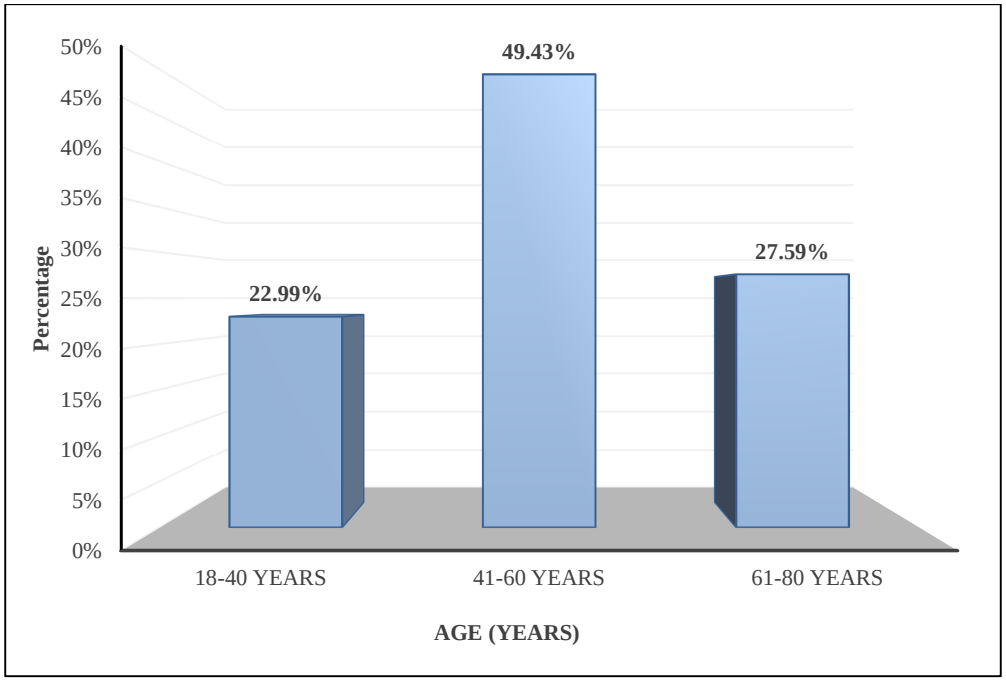

Figure 9: Distribution of subjects according to age.

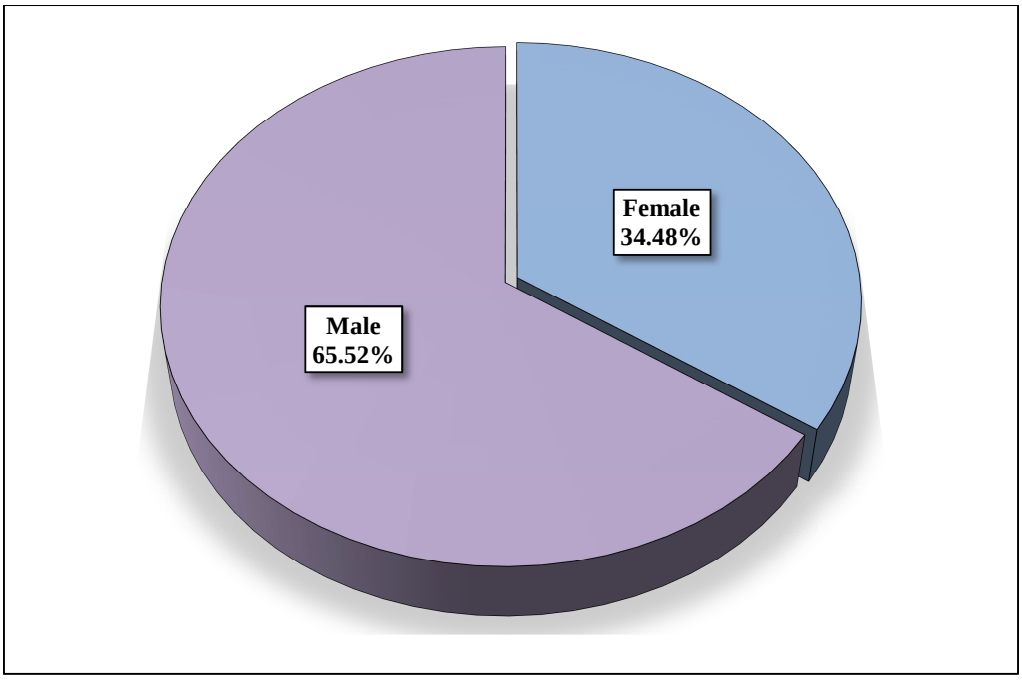

Figure 10: Distribution of subjects according to sex.

Table 2: Distribution of subjects according to comorbidities.

Variables	Sub Category	Number of subjects (%)
Hypertension	No	32 (36.78%)
	Yes	55 (63.22%)
Diabetes Mellitus	No	25 (28.74%)
	Yes	62 (71.26%)
CVD	No	60 (68.97%)
	Yes	27 (31.03%)

The majority of subjects, 55 (63.22%) have hypertension, while 32 (36.78%) do not. In terms of diabetes mellitus, 62 (71.26%) are affected, whereas 25 (28.74%), do not have diabetes mellitus. CVD is observed in 27 (31.03%) subjects, while 60 (68.97%) subjects are free from this condition.

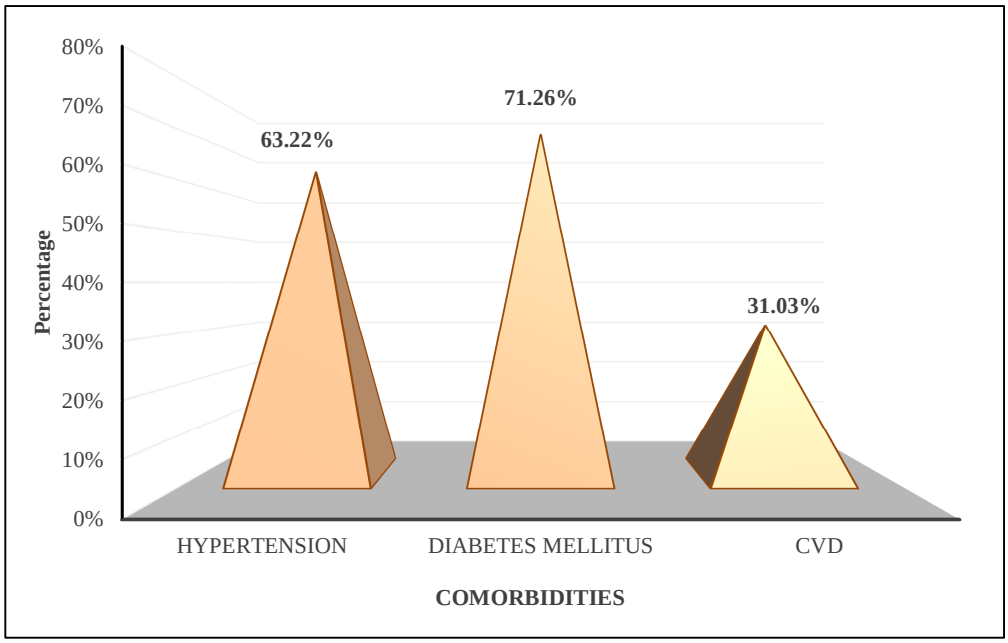

Figure 11: Distribution of subjects according to comorbidities.

Table 3: Distribution of subjects according to blood pressure.

Variables	Mean ± SD	Median (Min, Max)
SBP	155.66 ± 18.61	158 (120, 190)
DBP	97.31 ± 10.47	98 (80, 128)

The mean systolic blood pressure (SBP) among the subjects is 155.66 ± 18.61, while the median SBP is 158 mmHg, ranging from a minimum of 120 mmHg to a maximum of 190 mmHg. For diastolic blood pressure (DBP), the mean is 97.31 ± 10.47 mmHg, and the median is 98 mmHg, varying from a minimum of 80 mmHg to a maximum of 128 mmHg.

The following table gives the distribution of subjects according to laboratory parameters.

Table 4: Distribution of subjects according to laboratory parameters.

Variables	Mean ± SD	Median (Min, Max)
Haemoglobin	8.11 ± 1.22	7.9 (5.6, 10.5)
TLC	6362.53 ± 2316.34	5800 (2310, 13650)
Platelets	175011.49 ± 35320.29	174000 (121000, 294000)
Serum Albumin	3.39 ± 0.49	3.3 (2.78, 4.3)
BUN	46.11 ± 11.35	44.3 (23.3, 67.8)
Urea	98.45 ± 27.14	96 (50, 142)
eGFR	19.44 ± 11.85	17 (6, 59)
Creatinine	4.49 ± 2.42	3.9 (1.4, 11.6)
Sodium	139.51 ± 5.91	138 (132, 151)
Potassium	4.73 ± 0.78	4.7 (3.4, 7.4)
Phosphorous	6.2 ± 6.2	5 (3, 45)
Calcium	8.55 ± 0.97	8.6 (6.5, 11)

The mean haemoglobin level among the subjects is 8.11 ± 1.22 g/dL, and the median is 7.9 g/dL, ranging from a minimum of 5.6 g/dL to a maximum of 10.5 g/dL. Total leukocyte count (TLC) has a mean of 6362.53 ± 2316.34 cells/mm^3, and a median of 5800 cells/mm^3, ranging from a minimum of 2310 cells/mm^3 to a maximum of 13650 cells/mm^3. Platelet count has a mean of 175011.49 ± 35320.29 cells/mm^3, and a median of 174000 cells/mm^3, ranging from a minimum of 121000 cells/mm^3 to a maximum of 294000 cells/mm^3. The mean serum albumin level is 3.39 ± 0.49 g/dL, and a median of 3.3 g/dL, ranging from a minimum of 2.78 g/dL to a maximum of 4.3

g/dL. Other parameters such as blood urea nitrogen (BUN), urea, estimated glomerular filtration rate (eGFR), creatinine, sodium, potassium, phosphorus, and calcium are also provided with their respective mean, standard deviation, median, and range values.

The following table shows distribution of subjects as per CKD stage.

Table 5: Distribution of subjects according to stage.

STAGE	Number of subjects (%)
Stage 3	15 (17.24%)
Stage 4	38 (43.68%)
Stage 5	34 (39.08%)

The majority of subjects fall into Stage 4, comprising 38 (43.68%) subjects, followed closely by Stage 5, with 34 (39.08%) subjects. Stage 3 has the smallest representation, with 15 (17.24%) subjects.

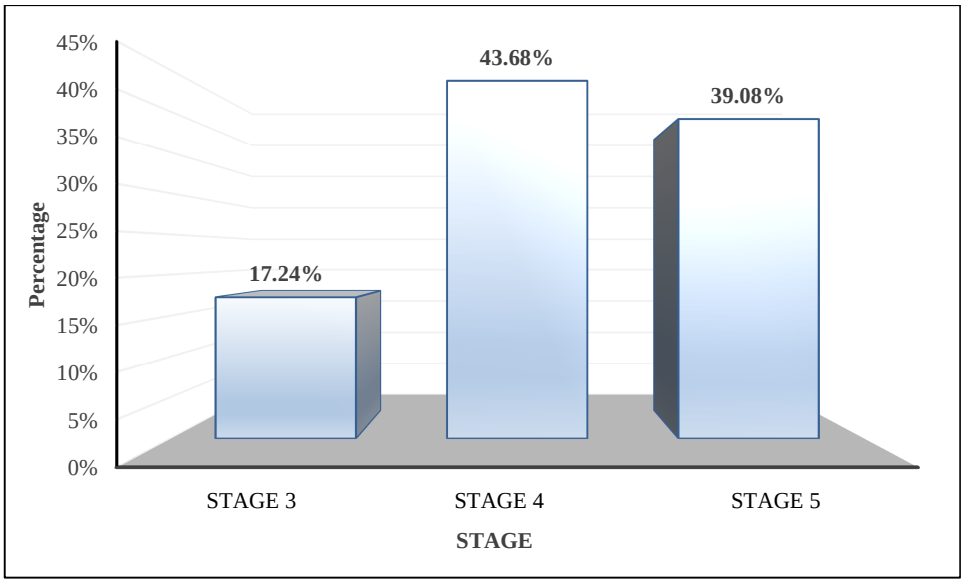

Figure 12: Distribution of subjects according to stage.

Table 6: Distribution of subjects according to thyroid function.

Variables	Sub Category	Number of subjects (%)
TSH	Low	1 (1.15%)
	Normal	67 (77.01%)
	High	19 (21.84%)
	Mean ± SD	2.54 ± 2.11
	Median (Min, Max)	1.73 (0.01, 10.07)
Free T3	Low	52 (59.77%)
	Normal	34 (39.08%)
	High	1 (1.15%)
	Mean ± SD	1.98 ± 0.81
	Median (Min, Max)	1.8 (0.52, 5.12)
Free T4	Low	18 (20.69%)
	Normal	63 (72.41%)
	High	6 (6.9%)
	Mean ± SD	1.22 ± 0.46
	Median (Min, Max)	1.24 (0.2, 3.82)

For TSH, 67 (77.01%) of subjects fall within the normal range, while 19 (21.84%) have high levels, and only 1 (1.15%) have low levels. The mean TSH level is 2.54 ± 2.11 mIU/L, with a median of 1.73 mIU/L, ranging from 0.01 to 10.07 mIU/L. Regarding Free T3, a majority of 52 (59.77%) have low levels, 34 (39.08%) are within the normal range, and 1 (1.15%) have high levels. The mean Free T3 level is

1.98 ± 0.81 pg/mL, with a median of 1.8 pg/mL, and values ranging from 0.52 to 5.12 pg/mL. For Free T4, 63 (72.41%) of subjects have normal levels, 18 (20.69%) have low levels, and 6 (6.9%) have high levels. The mean Free T4 level is 1.22 ± 0.46 ng/dL, with a median of 1.24 ng/dL, and a range of 0.2 to 3.82 ng/dL.

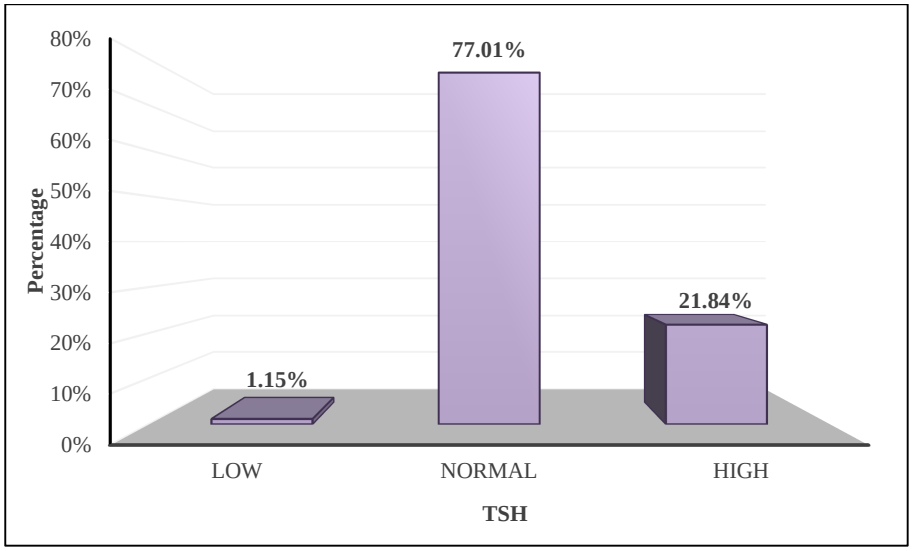

Figure 13: Distribution of subjects according to TSH.

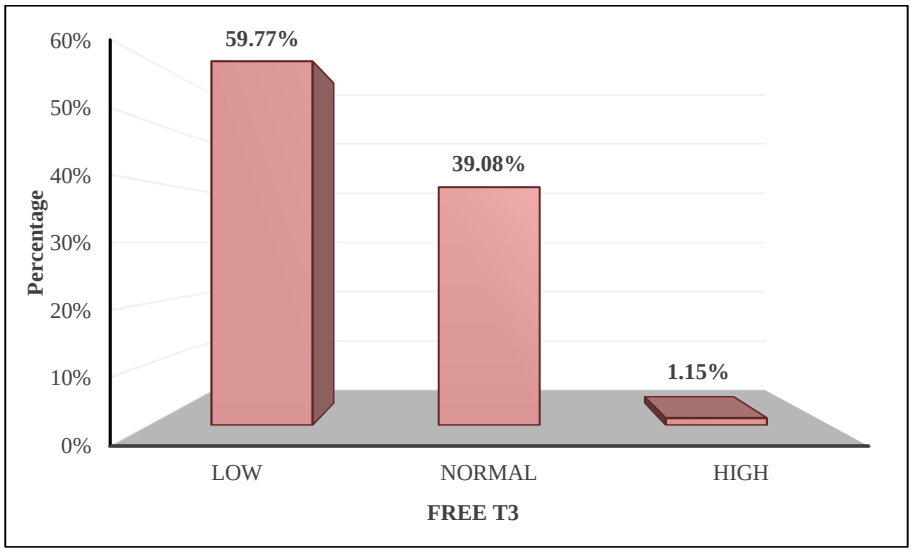

Figure 14: Distribution of subjects according to Free T3.

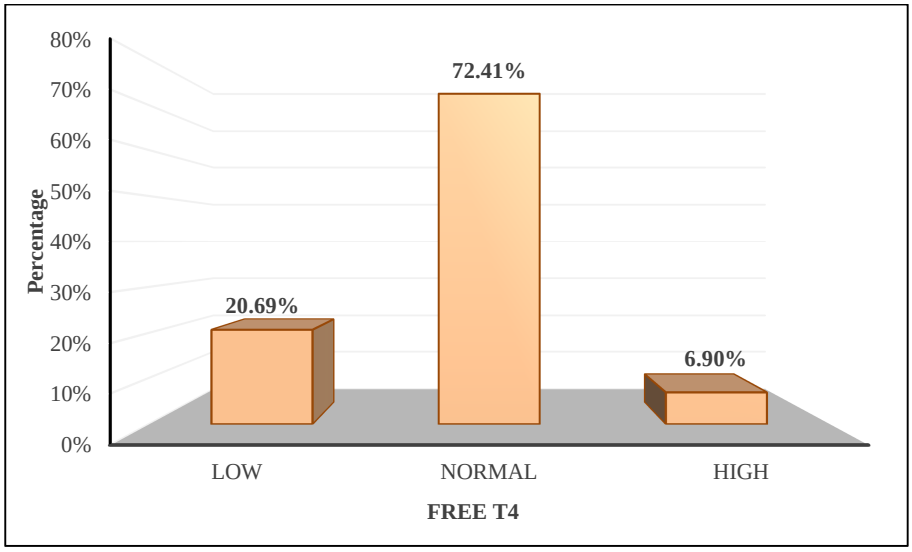

Figure 15: Distribution of subjects according to Free T4.

Table 7: Distribution of subjects according to thyroid abnormalities.

Thyroid abnormalities	Number of subjects (%)
Hypothyroidism	8 (9.20%)
Subclinical Hypothyroidism	11 (12.64%)
Low Free T3	52 (59.77%)
Low Free T4	18 (20.69%)

Out of the subjects, 8 (9.20%) have hypothyroidism, 11 (12.64%) have subclinical hypothyroidism, 52 (59.77%) have low Free T3 levels, and 18 (20.69%) have low Free T4 levels.

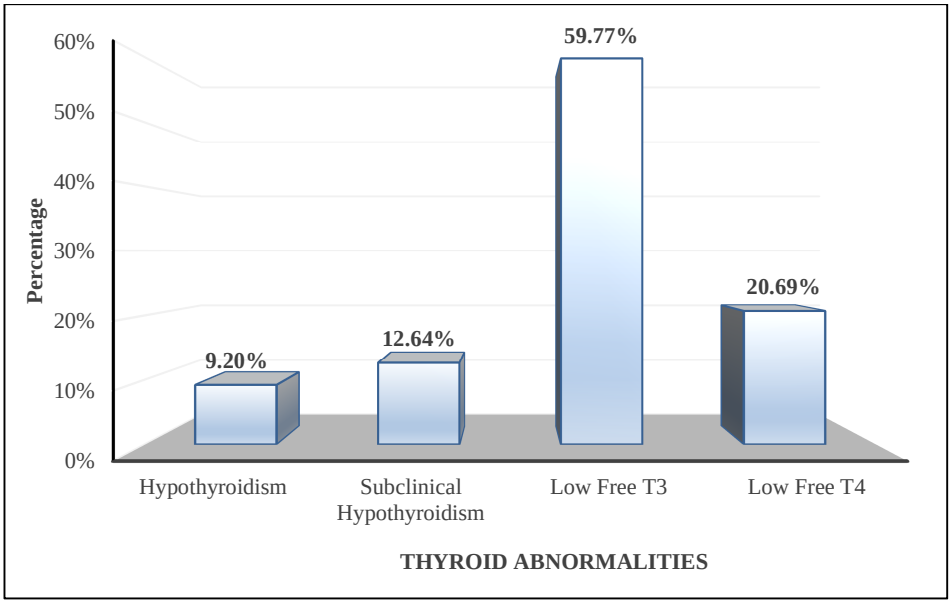

Figure 16: Distribution of subjects according to thyroid abnormalities.

The following table gives the comparison of demographical details over stage of CKD.

Table 8: Comparison of demographical details over stage of CKD.

Variables	Sub Category	Stage 3	Stage 4	Stage 5	p-value
Age (years)	18-40 years	5 (33.33%)	9 (23.68%)	6 (17.65%)	0.6322[MC]
	41-60 years	8 (53.33%)	18 (47.37%)	17 (50%)	
	61-80 years	2 (13.33%)	11 (28.95%)	11 (32.35%)	
	Mean ± SD Median (Min, Max)	46.67 ± 14.59 54 (26, 75)	51.5 ± 13.32 48.5 (30, 76)	52 ± 15.13 54.5 (18, 75)	0.4550[A]
Sex	Female	0 (0%)	16 (42.11%)	14 (41.18%)	**0.0084[C]***
	Male	15 (100%)	22 (57.89%)	20 (58.82%)	

*Abbreviation: C – Chi square test, MC – Chi square test with Monte Carlo simulation, A – One-way ANOVA, * indicates statistical significance.*

Regarding age distribution, there is no statistically significant difference observed among the age groups across stage of CKD (p-value = 0.6322).

The mean age across Stage 3, Stage 4, and Stage 5 CKD is 46.67 ± 14.59 years, 51.5 ± 13.32 years, and 52 ± 15.13 years, respectively, but the difference is not statistically significant (p-value = 0.4550).

Among individuals with Stage 3 CKD, all subjects are male, while in Stages 4 and 5, there is a higher proportion of female subjects. Specifically, 42.11% of Stage 4 and 41.18% of Stage 5 CKD patients are female, contrasting with 0% of females in Stage 3. In terms of sex, a statistically significant association is observed over stage of CKD (p-value = 0.0084).

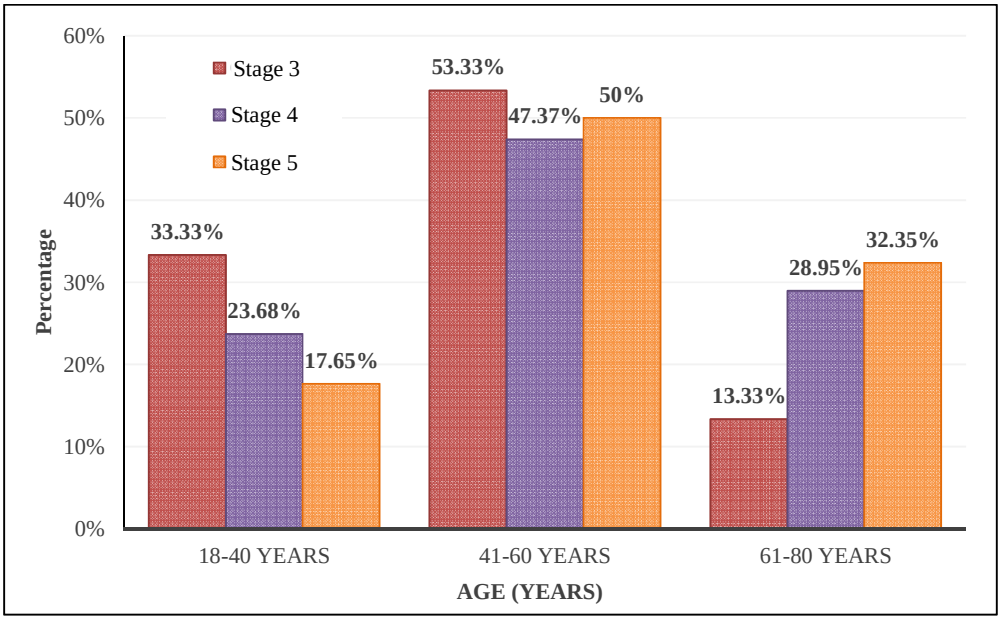

Figure 17: Distribution of age over stage of CKD.

The following table gives the comparison of comorbidities over stage of CKD.

Table 9: Comparison of comorbidities over stage of CKD.

Variables	Sub Category	Stage 3	Stage 4	Stage 5	p-value
Hypertension	No	5 (33.33%)	14 (36.84%)	13 (38.24%)	0.9476[C]
	Yes	10 (66.67%)	24 (63.16%)	21 (61.76%)	
Diabetes Mellitus	No	3 (20%)	19 (50%)	3 (8.82%)	< **0.001**[MC]*
	Yes	12 (80%)	19 (50%)	31 (91.18%)	
CVD	No	13 (86.67%)	33 (86.84%)	14 (41.18%)	**< 0.001**[MC] *
	Yes	2 (13.33%)	5 (13.16%)	20 (58.82%)	

*Abbreviation: C – Chi square test, MC – Chi square test with Monte Carlo simulation, * indicates statistical significance.*

The proportions of subjects with and without hypertension are relatively consistent across the CKD stages. There is no statistically significant difference in distribution of hypertension over stage of CKD (p-value = 0.9476).

The prevalence of diabetes mellitus varies significantly as per CKD stage. It affects 80% of subjects in Stage 3, 50% in Stage 4, and 91.18% in Stage 5 (p-value < 0.001).

Similarly, CVD prevalence also shows a significant association with CKD stage. In Stage 3, 13.33% of subjects have CVD, compared to 13.16% in Stage 4, and a notable increase to 58.82% in Stage 5 (p-value < 0.001).

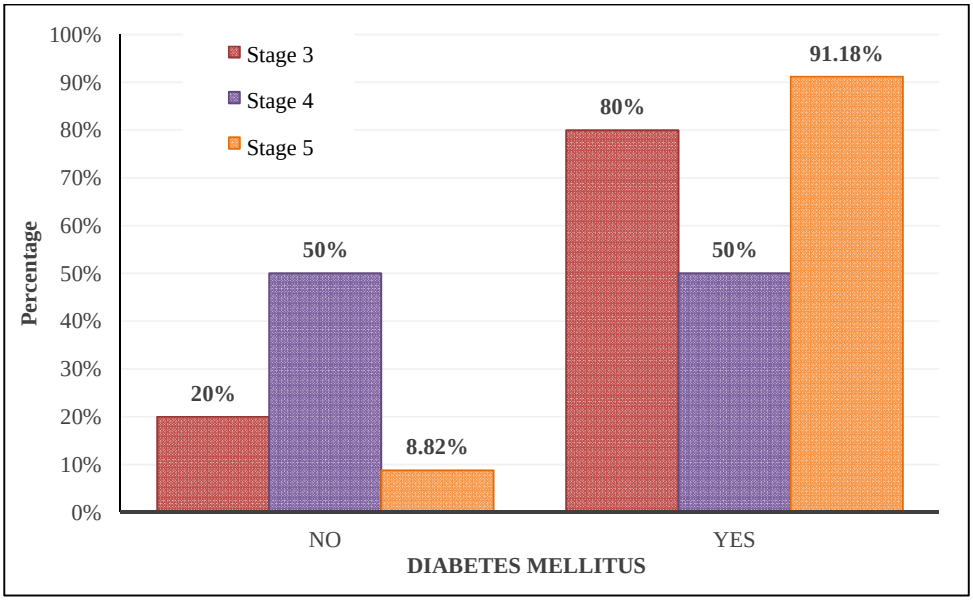

Figure 18: Distribution of diabetes mellitus over stage of CKD.

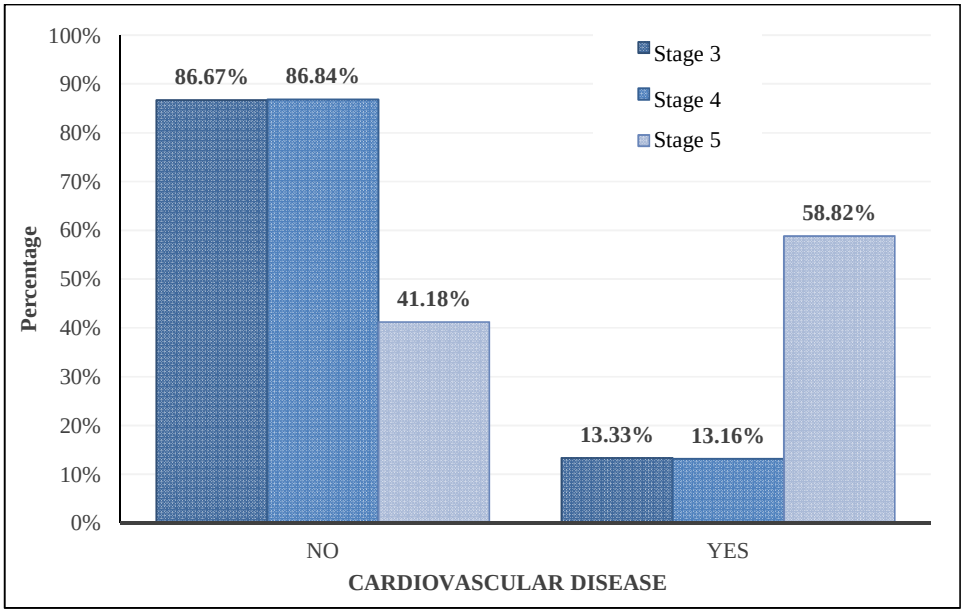

Figure 19: Distribution of cardiovascular disease over stage of CKD.

The following table gives the comparison of laboratory parameters over stage of CKD.

Table 10: Comparison of laboratory parameters over stage of CKD.

Variables	Stage 3	Stage 4	Stage 5	p-value
Haemoglobin	9.03 ± 1.4 9.4 (5.6, 10.5)	8.03 ± 1.15 7.85 (5.6, 10.5)	7.8 ± 1.03 7.9 (6.2, 10.5)	0.0032^{A}*
TLC	5903 ± 1867.8 5670 (3450, 8790)	6951.97 ± 2711.78 6750 (3120, 13650)	5906.47 ± 1883.38 5550 (2310, 9870)	0.3305^{K}
Platelets	173400 ± 44918.66 156000 (132000, 247000)	173210.53 ± 34768.08 174000 (121000, 294000)	177735.29 ± 32050.44 178000 (127000, 241000)	0.6282^{K}
Serum Albumin	3.16 ± 0.34 3.2 (2.8, 4)	3.42 ± 0.51 3.31 (2.8, 4.21)	3.47 ± 0.5 3.5 (2.78, 4.3)	0.1574^{K}
BUN	54.53 ± 8.02 54.6 (43.4, 67.8)	47.14 ± 12.75 45.1 (23.3, 66.9)	41.23 ± 8.25 40.8 (23.5, 64)	0.0003^{K}*
Urea	83.13 ± 23.8 80 (53, 141)	94.74 ± 27.93 93.5 (50, 141)	109.35 ± 23.65 113.5 (60, 142)	0.0032^{A}*
Creatinine	2.05 ± 0.38 2.1 (1.4, 2.7)	3.37 ± 0.73 3.26 (1.9, 5.1)	6.81 ± 2.22 5.85 (3.9, 11.6)	**< 0.001^{K}***
Sodium	140.2 ± 5.89 138 (132, 148)	138.63 ± 5.7 137 (132, 151)	140.18 ± 6.2 139 (132, 151)	0.4638^{K}
Potassium	4.42 ± 0.68 4.7 (3.4, 5.4)	4.77 ± 0.86 4.75 (3.6, 7.4)	4.82 ± 0.71 5 (3.6, 6)	0.1855^{K}
Phosphorous	4.87 ± 1.42 4.6 (3, 6.8)	6.5 ± 6.64 5 (3.2, 45)	6.46 ± 6.99 5 (3.5, 45)	0.5011^{K}
Calcium	8.64 ± 1.24 9 (6.5, 10)	8.67 ± 0.99 8.7 (7, 11)	8.38 ± 0.82 8.6 (7, 10)	0.4310^{A}

*Abbreviation: K – Kruskal Wallis test, A – One-way ANOVA, * indicates statistical significance.*

For TLC, platelets, serum albumin, sodium, potassium, phosphorous and calcium levels, no statistically significant differences are observed over stage of CKD (p-values > 0.05). However, from one-way ANOVA, it is observed that, there is significant difference in the mean haemoglobin over stage of CKD (p-value = 0.0032). Further from Tukey's HSD, it is observed that there is significant difference in haemoglobin between Stage 4 and Stage 3 (p-value = 0.0145) and Stage 5 and Stage 3 (p-value = 0.0024). There is significant difference in the mean urea over stage of CKD (p-value = 0.0032). Further from Tukey's HSD, it is observed that there is significant difference in urea between Stage 5 and Stage 3 (p-value = 0.0040) and Stage 5 and Stage 3 (p-value = 0.0467).

From Kruskal Wallis test, it is observed that there is significant difference in the distribution of BUN, and Creatinine over stage of CKD (p-value < 0.05). Further analysis using the Dunn test reveals significant differences between specific CKD stages for these parameters. For BUN, significant differences are observed between Stage 4 and Stage 3 (p-value = 0.0392), Stage 5 and Stage 3 (p-value = 0.0002), and Stage 5 and Stage 4 (p-value = 0.0392).

Moreover, for creatinine, significant differences are found between Stage 4 and Stage 3 (p-value < 0.001), Stage 5 and Stage 3 (p-value < 0.001), and Stage 5 and Stage 4 (p-value < 0.001).

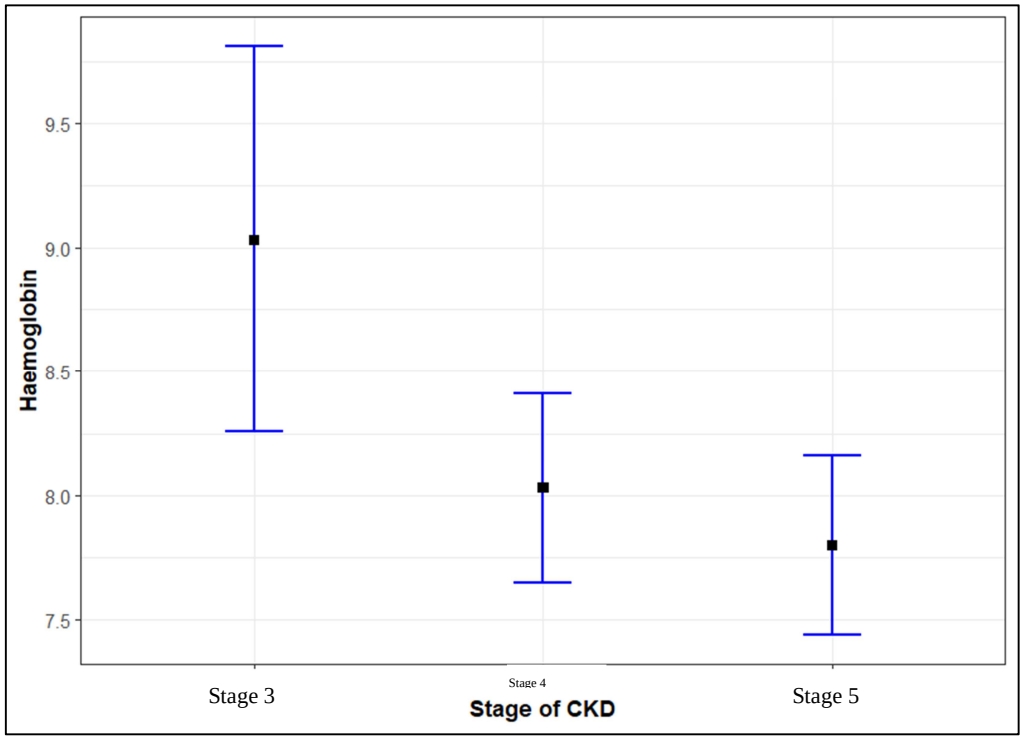

Figure 20: Mean plot of haemoglobin over stage of CKD.

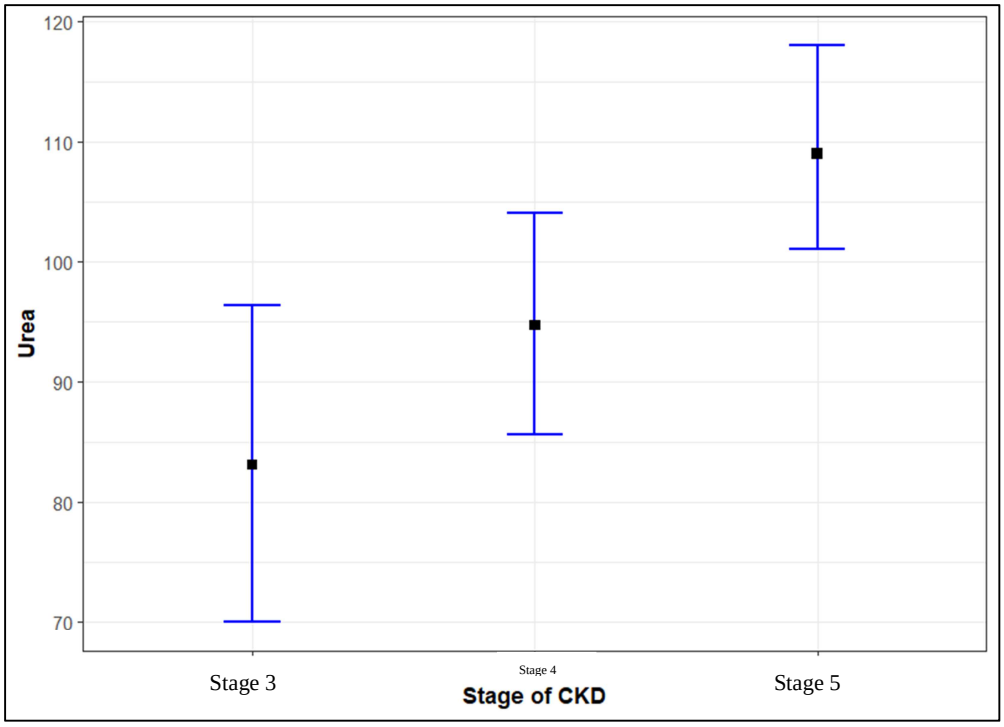

Figure 21: Mean plot of urea over stage of CKD.

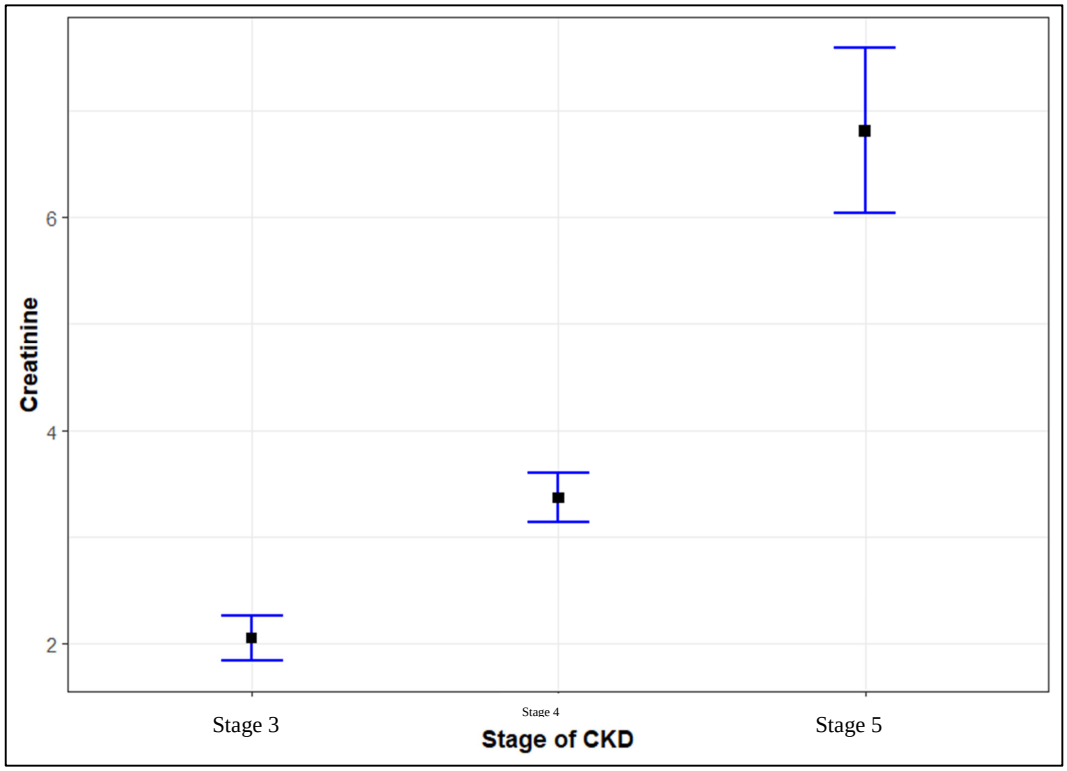

Figure 22: Mean plot of creatinine over stage of CKD.

The following table gives the comparison of thyroid function over stage of CKD.

Table 11: Comparison of thyroid function over stage of CKD.

Variables	Sub Category	Stage 3	Stage 4	Stage 5	p-value
TSH	Low	0 (0%)	0 (0%)	1 (2.94%)	0.5842[MC]
	Normal	10 (66.67%)	30 (78.95%)	27 (79.41%)	
	High	5 (33.33%)	8 (21.05%)	6 (17.65%)	
	Mean ± SD	2.03 ± 1.84	1.95 ± 1.96	2.05 ± 1.71	0.3370[K]
	Median (Min, Max)	1.23 (0.08, 5.31)	1.23 (0.02, 9.43)	1.62 (0.01, 6.7)	
Free T3	Low	7 (46.67%)	22 (57.89%)	23 (67.65%)	0.1644[MC]
	Normal	7 (46.67%)	16 (42.11%)	11 (32.35%)	
	High	1 (6.67%)	0 (0%)	0 (0%)	
	Mean ± SD	2.37 ± 1.12	1.91 ± 0.72	1.94 ± 0.7	0.1310[A]
	Median (Min, Max)	2.14 (1.1, 5.12)	1.8 (0.79, 3.8)	1.81 (0.52, 3.43)	
Free T4	Low	3 (20%)	7 (18.42%)	8 (23.53%)	0.9940[MC]
	Normal	11 (73.33%)	28 (73.68%)	24 (70.59%)	
	High	1 (6.67%)	3 (7.89%)	2 (5.88%)	
	Mean ± SD	1.33 ± 0.36	1.24 ± 0.35	1.31 ± 0.56	0.8808[K]
	Median (Min, Max)	1.32 (0.6, 2.22)	1.27 (0.34, 2.01)	1.3 (0.2, 3.82)	

Abbreviation: MC – Chi square test with Monte Carlo simulation, A – One-way ANOVA, K – Kruskal Wallis test.

For TSH, Free T3, and Free T4 levels, there is no statistically significant differences over stage of CKD (p-values > 0.05). In other words, there is no significant association between thyroid function parameters and CKD stage.

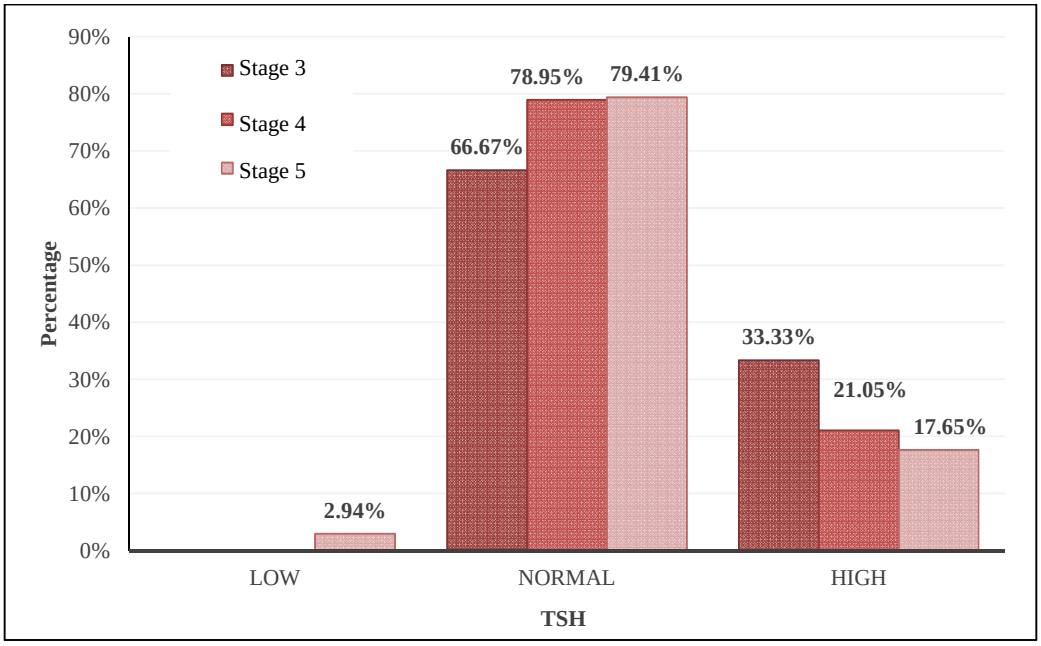

Figure 23: Distribution of TSH over stage of CKD.

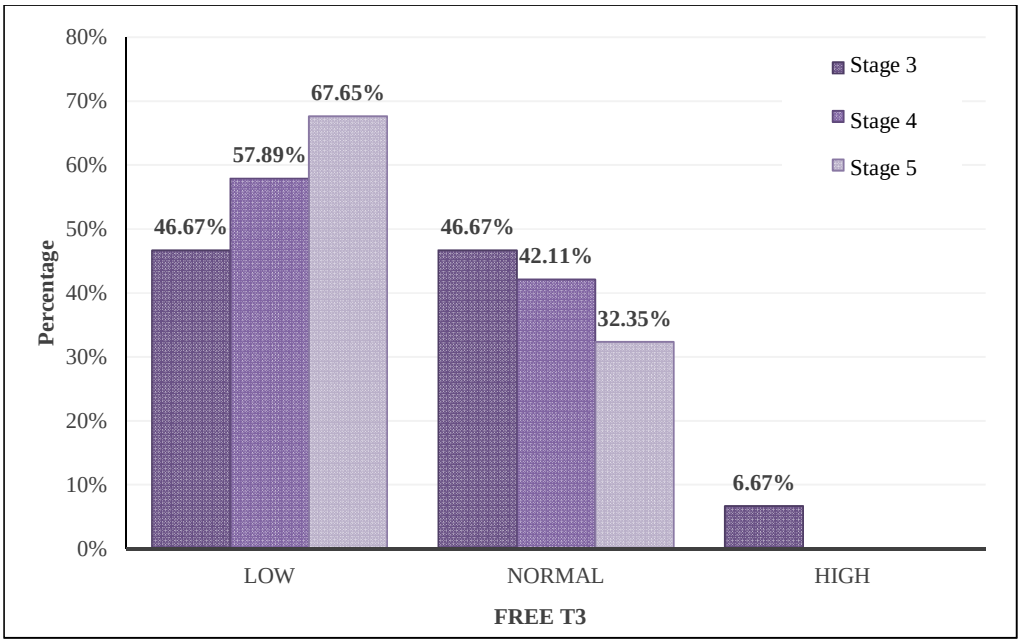

Figure 24: Distribution of Free T3 over stage of CKD.

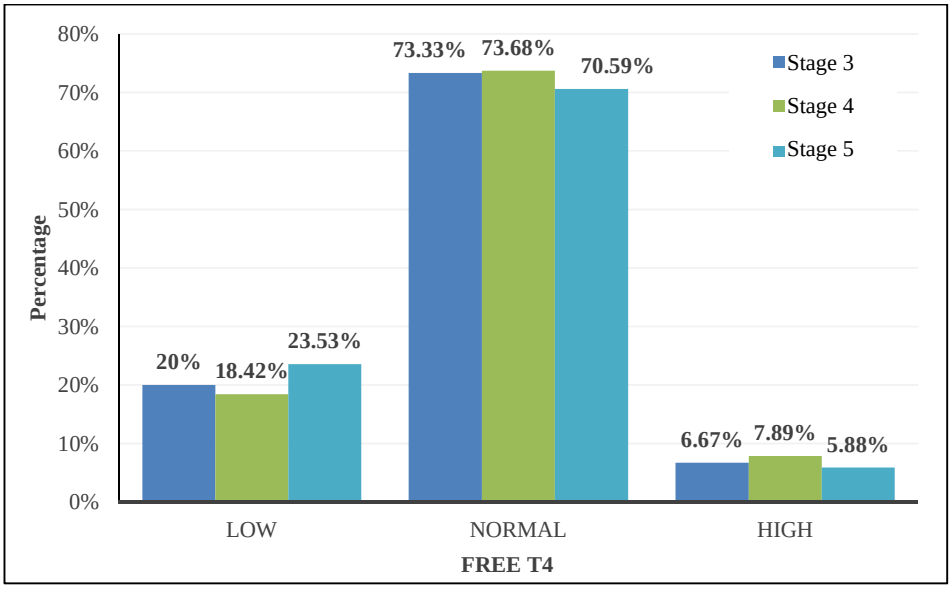

Figure 25: Distribution of Free T4 over stage of CKD.

The following table gives the comparison of thyroid abnormalities over stage of CKD.

Table 12: Comparison of thyroid abnormalities over stage of CKD.

Variables	Sub Category	Stage 3	Stage 4	Stage 5	p-value
Hypothyroidism	No	13 (86.67%)	35 (92.11%)	31 (91.18%)	0.8876[MC]
	Yes	2 (13.33%)	3 (7.89%)	3 (8.82%)	
Subclinical hypothyroidism	No	12 (80%)	33 (86.84%)	31 (91.18%)	0.5937[MC]
	Yes	3 (20%)	5 (13.16%)	3 (8.82%)	
Low free T3	No	8 (53.33%)	16 (42.11%)	11 (32.35%)	0.3671[C]
	Yes	7 (46.67%)	22 (57.89%)	23 (67.65%)	
Low free T4	No	12 (80%)	31 (81.58%)	26 (76.47%)	0.9445[MC]
	Yes	3 (20%)	7 (18.42%)	8 (23.53%)	

Abbreviation: C – Chi square test, MC – Chi square test with Monte Carlo simulation.

Hypothyroidism is present in 13.33% of Stage 3 subjects, 7.89% of Stage 4 subjects, and 8.82% of Stage 5 subjects (p-value = 0.8876). Subclinical hypothyroidism is observed in 20% of Stage 3 subjects, 13.16% of Stage 4 subjects, and 8.82% of Stage 5 subjects (p-value = 0.5937).

For low Free T3 levels, 46.67% of Stage 3 subjects, 57.89% of Stage 4 subjects, and 67.65% of Stage 5 subjects are affected (p-value = 0.3671). Low Free T4 levels are seen in 20% of Stage 3 subjects, 18.42% of Stage 4 subjects, and 23.53% of Stage 5 subjects (p-value = 0.9445).

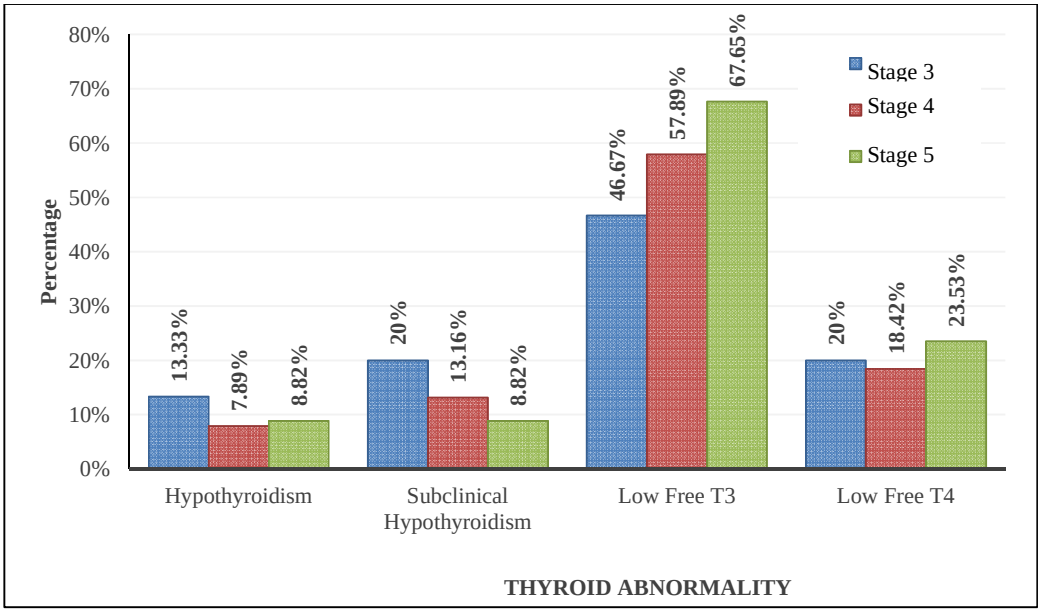

Figure 26: Distribution of thyroid abnormalities over stage of CKD.

The following table gives the correlation of eGFR with thyroid parameters.

Table 13: Correlation of eGFR with thyroid parameters.

Thyroid parameter	Correlation coefficient	p-value
TSH	-0.0078	0.9426
Free T3	0.0558	0.6077
Free T4	0.0529	0.6268

Abbreviation: SP – Spearman's rank correlation test.

From Spearman's rank correlation test, it is observed that, there is weak and non-significant correlation between eGFR and thyroid function parameters (p-values > 0.05).

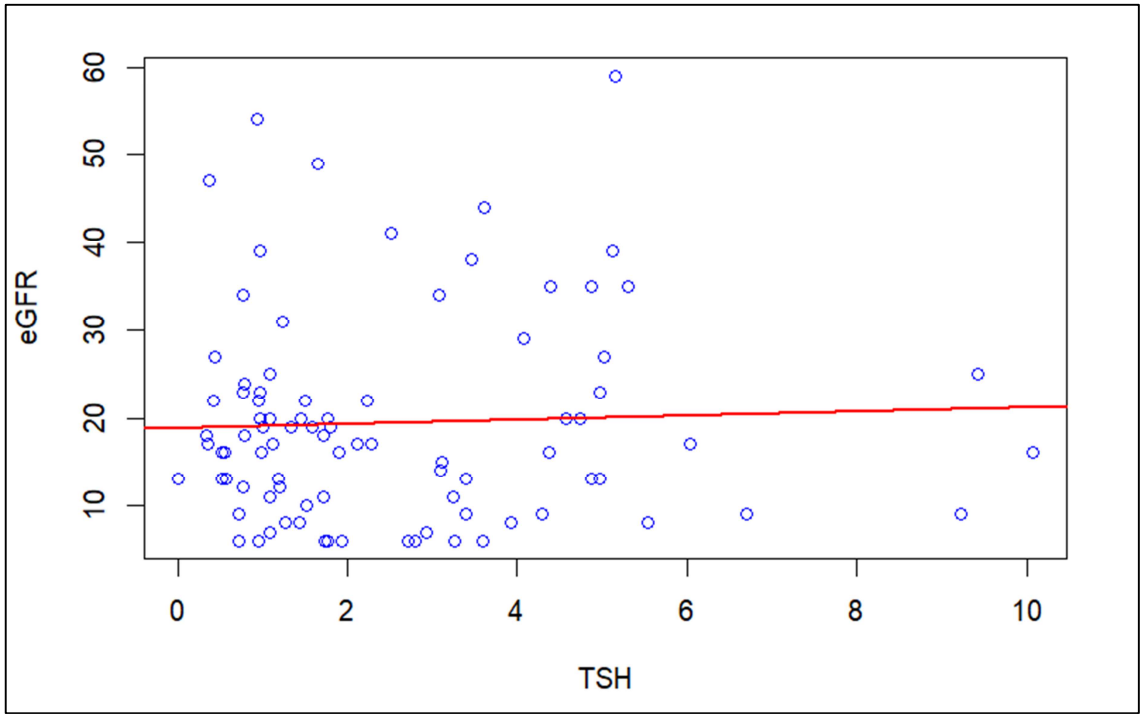

Figure 27: Scatter plot of eGFR with TSH.

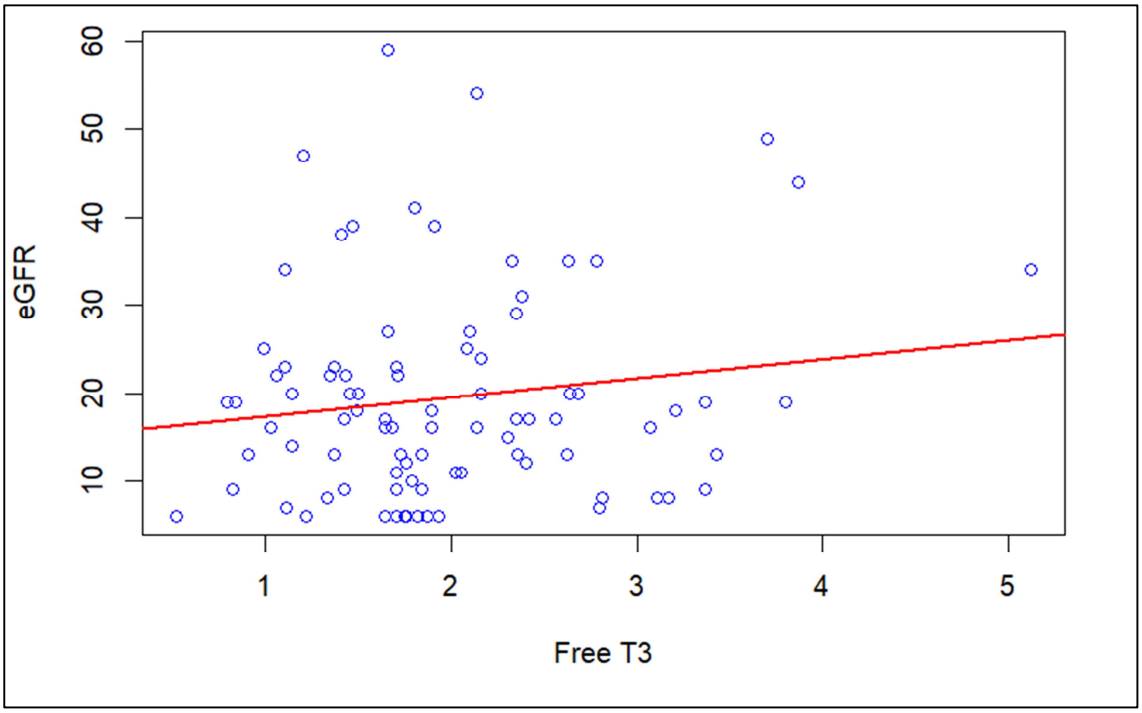

Figure 28: Scatter plot of eGFR with Free T3.

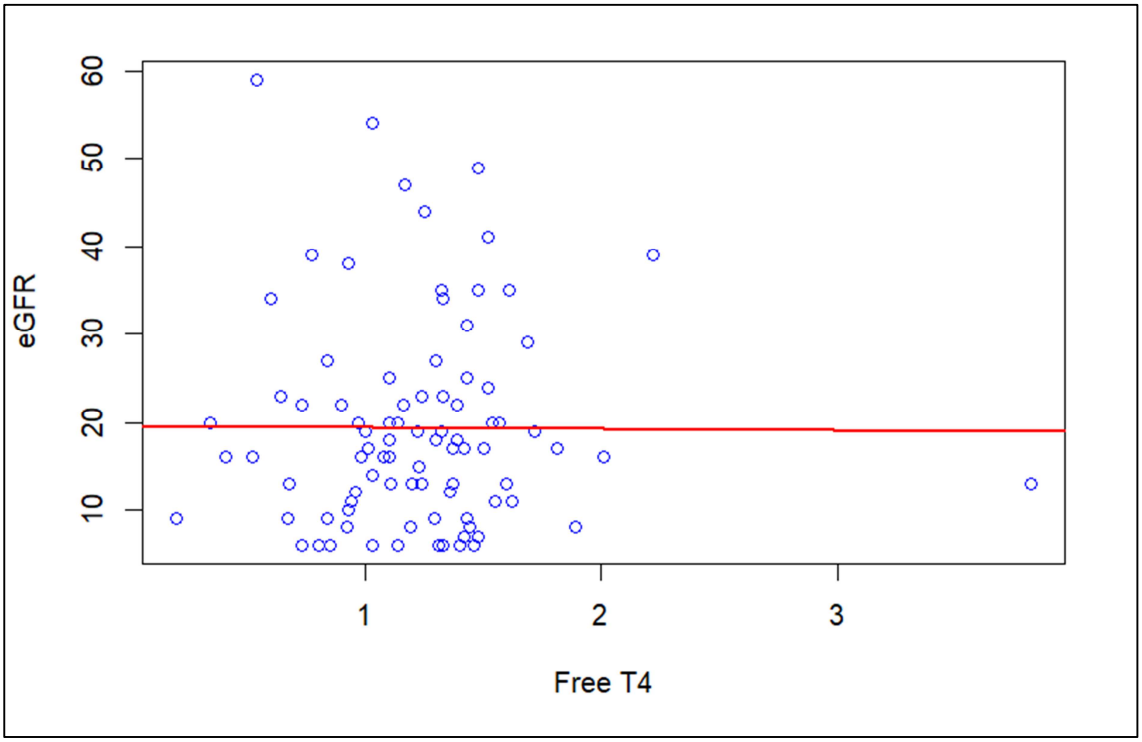

Figure 29: Scatter plot of eGFR with Free T4.

DISCUSSION

Thyroid dysfunction is significantly altered by renal illness and vice versa. Thyroid hormones (TH) are required, on the one hand, for kidney growth and development, as well as for the preservation of electrolyte and water homeostasis [123,124]. In contrast, TH metabolism and excretion are influenced by the kidney. Consequently, thyroid dysfunction and renal function loss are caused due to changes in TH production, metabolism, secretion, and clearance. [125]. CKD is associated with a bigger risk of overt plus subclinical hypothyroidism (HT), but not hyperthyroidism. With decreasing GFR, primary HT becomes more common, with most cases being asymptomatic. [126] The frequency of sub-clinical HT rose to 17.9% in individuals with a GFR less than 60 ml/min per1.73 m2, as reported in a recent study by Chonchol M et al., compared to 7% in patients who had an EGFR higher than 90 ml/min/1.73 m2. [127]. Despite much investigation, the thyroid status in uremia still not obvious because of the complexity of system being studied. Researchers have discovered conflicting results when looking at thyroid hormone levels in patients with uremic symptoms. [128] The free and total T3, T4 readings of patients with chronic kidney disease are frequently normal or low. [129] Among these patients, a drop in T3 levels(low T3 syndrome)is the most prevalent thyroid abnormality. [126,129,130]. Acute kidney injury and chronic kidney disease (CKD) have a major influence on the hypothalamus-pituitary-thyroid axis. The release of pituitary thyrotropin is hindered by uricemia. [131] Serum TSH levels in CKD patients tend to be normal or slightly elevated, with a poor response from the hormone to its releasing hormone (TRH). [129,130] Additionally, current research shows that TH, and particularly T3, might be a survivorship metric for individuals with renal illness. [131].

There are 87 individuals in total included in this study, 30 (34.48%) of whom are female and 57 (65.52%) of whom are male. The maximum age group of 43 patients (49.43%) is 41-60 years old, and the lowest age group is 18–40 years old. Similarly, the study population's mean age was 50.86 ± 14.23 years. These results are in good agreement with the research done by Fernanda Ismaela Rolim Teixeira et al., 2015, where 55.56% of the sample population is male. [69] There were 50 patients in the study by Swaminathan K et al. , of which nine were under 30 years old, 35 were between 31 and 60 years old, and six were above 60 years old. [132] These patient ages were remarkably similar to those in our study.

Co-morbidities are also common in the current study, with 31% having CVD, 71.26% having diabetes, and 63.22% having hypertension. A research conducted by Fernanda Ismaela Rolim Teixeira et al., 2015, found that cardiovascular disease was present in 7.41% of the participants, arterial hypertension in 41.36% of the participants, and arterial hypertension plus diabetes mellitus in 25.93% of the participants. [69]

The patients in the current study had mean SBPs of 156 mm Hg and mean DBPs of 97 mm Hg, respectively, indicating variability in blood pressure. A maximal SBP of 190 mm Hg and a maximum DBP of 128 mm Hg are recorded. As a result, the majority of SBP and DBP values were marginally above upper bounds.

The average haemoglobin level in the study population was found to be low in this investigation (i.e., 8.11).

Patients in this research tended to be in later stages of chronic kidney disease (CKD), with lower proportions in earlier stages, 17.24% in stage 3, 43.68% in Stage 4, and 39.08% in Stage 5.

There has been much research done in the past on the relationship between severity of CKD and thyroid abnormalities, but the results are not always consistent. We found that SCH and hypothyroidism were far more common in our study than subclinical or hyperthyroidism. This result is consistent with earlier research showing a significantly higher prevalence of hypothyroidism and SCH in CKD patients prior to dialysis [20, 21]. According to a research by Kaptein et al. , decreased iodide excretion in CKD leads to increased thyroid gland iodide absorption. [70] This process could account for the increased incidence of SCH and hypothyroidism that has been noted.

Thyroid function impairments in the current study differ significantly between CKD stages. Hypothyroidism, low free thyroxine, low free triiodothyronine, and subclinical hypothyroidism are all present in Stage 3. Hypothyroidism is present in 13.33% of Stage 3 subject, subclinical hypothyroidism is observed in 20% of Stage 3 subject, low Free T3 levels, 46.67% of Stage 3 subjects and low Free T4 levels are seen in 20% of Stage 3 subjects.

The following conditions are most common in stage 4: subclinical hypothyroidism (13.16%), low free triiodothyronine (57.89%), low free thyroxine (18.42%), and hypothyroidism (7.89%). Ultimately, in Stage 5, subclinical hypothyroidism is observed in 8.82% of patients, hypothyroidism, low free thyroxine, and low free triiodothyronine, respectively, in 8.82%, 23.53%, and 67.65% of cases. In general, as CKD advances, thyroid dysfunction becomes more common.

A big proportion of CKD patient had hypothyroidism, as reported by Alshammari et al. [22] Patients with CKD must be promptly diagnosed and treated for hypothyroidism if they are to avoid the elevated mortality risk and poor health related quality of life associated with this condition [23]. The mean TSH level in the present study was 2.54 mIU/ml, which is within the recommended range of 0.27 to 4.2 mIU/ml.

The mean free thyroxine (T4) level of 1.22 ng/ml (SD = 0.46) and the mean free triiodothyronine (T3) level of 1.98 pg/ml (SD = 0.81). A sizable fraction of the study population had thyroid abnormalities, with 9.20% being diagnosed with hypothyroidism, 59.77% having low free triiodothyronine levels, and 20.69% having low free thyroxine levels. Of the patients 12.64% had subclinical hypothyroidism.

We found that low FT3 levels, as the most frequent thyroid malfunction. Reverse triiodothyronine (rT3) levels in plasma have been shown to typically stay normal in these patients. This implies that the elevated conversion of T4 to metabolically inert rT3—a mechanism frequently observed in euthyroid-sick syndrome, when type 2 and type 3 deiodinases are upregulated—is not the cause of low FT3 levels. Rather, the reduced peripheral T4 to T3 conversion is probably the cause of low FT3 levels. This sets patients with chronic illnesses apart from uremic patients, as the latter usually have elevated rT3 levels, acting as a defence mechanism for protein conservation.

Pituitary and intrathyroidal functions may be impacted by these anomalies. The circadian-rhythm and TSH's glycosylation-are both changed in CKD, which may reduce the hormone's bioactivity. Although majority of the participants in this study had TSH levels in the normal range, this may account for the low FT4 levels that were seen.

LIMITATIONS OF THE STUDY

- Ours was a single centre, cross sectional study with a relatively smaller sample size which could limit the generalizability of the results. Further prospective studies with multicentre study designs are warranted to evaluate the role of thyroid hormones in chronic kidney disease.

- In this study, thyroid dysfunction was examined irrespective of the etiology of CKD, thus correlation between etiology of thyroid dysfunction and CKD could not be carried out.

- Patients who were on dialysis were excluded, since dialysis itself can independently influence thyroid-profile. So the study findings could not be applied to patients requiring dialysis.

CONCLUSION

The present study reveals associations between thyroid abnormalities and chronic kidney disease (CKD) stages among the patient population. Thyroid dysfunction is prevalent, with 59.77% of patients having low free triiodothyronine levels, 20.69% with low free thyroxine levels, and 9.20% diagnosed with hypothyroidism. Subclinical hypothyroidism is noted in 12.64% of patients. The majority of patients are in the advanced stages of CKD, with 43.68% in Stage 4 and 39.08% in stage 5, indicating a predominance of late-stage CKD. These findings suggest that thyroid dysfunction is common in patients with CKD, particularly in the more advanced stages of the disease, highlighting the need for regular thyroid function monitoring in CKD patients to manage and mitigate potential complications effectively. The analysis indicates that the prevalence of thyroid function abnormalities increases with the progression of CKD. While early stages show minimal thyroid dysfunction, significant increases are observed in later stages, particularly in low free triiodothyronine and subclinical hypothyroidism. Thus highlighting the need for vigilant thyroid function monitoring in advanced CKD.

SUMMARY

- The present study included 87 patients, of which 30 (34.48%) were female and 57 (65.52%) were male, with the majority being aged 41-60 years and the fewest in the 18-40 years category.

- Co-morbidities were prevalent, with 63.22% of patients having hypertension, 71.26% diabetes, and 31.03% ischemic heart disease.

- Blood pressure readings showed a mean systolic BP of 156 mm Hg and a mean diastolic BP of 97 mm Hg, with maximum values of 190 mm Hg and 128 mm Hg, indicating that most values were slightly above the higher limits.

- Routine investigations revealed an average hemoglobin level of 8.11, which is very low. Other relevant parameters included urea (98.45), creatinine (4.47), sodium (139.51), potassium (4.73), calcium (8.55), phosphorus (6.2).

- The highest prevalence of CKD, was in Stage 4, with 43.68%.
- The reference range for thyroid-stimulating hormone (TSH) is 0.27 to 4.2 mIU/ml, and the biochemical parameters demonstrated an average level of 2.54 mIU/ml (SD = 2.11). Some aberrant thyroid functions were indicated by the mean free thyroxine (T4) level of 1.22 ng/ml (SD = 0.46) and the mean free triiodothyronine (T3) level of 1.98 pg/ml (SD = 0.81).

- Thyroid abnormalities were substantial, with 59.77% having low free triiodothyronine levels, 20.69% with low free thyroxine levels, and 9.20% diagnosed with hypothyroidism. Subclinical hypothyroidism was observed in 12.64% of patients.

- Thyroid function abnormalities vary significantly across CKD stages. In Stage 3 shows, with 13.33% cases with hypothyroidism, low free thyroxine at 20%, low free triiodothyronine at 46.67%, subclinical hypothyroidism at 20%. For Stage 4 the occurrences are: hypothyroidism (7.89%), low free thyroxine (18.42%), low free triiodothyronine (57.89%), subclinical hypothyroidism (13.16%). Finally, in Stage 5, hypothyroidism, low free thyroxine, and low free triiodothyronine are seen in 8.82%, 23.53%, and 67.56% of cases, respectively, with subclinical hypothyroidism at 8.82% .Overall, the prevalence of thyroid dysfunction increases with the progression of CKD.

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ANNEXURES

ANNEXURE I: CONSENT FORM

KAHER's JNMC, BELAGAVI

INFORMED CONSENT FORM

"STUDY OF THYROID FUNCTION IN PATIENTS OF CHRONIC KIDNEY DISEASE"

Name of Student/Principal Investigator:

Name of Guide/Co Investigators:

Objective:

- To study thyroid function in patients of chronic kidney disease
- To study the correlation between thyroid dysfunction and severity of chronic kidney disease in patients

Introduction: Chronic kidney disease (CKD) is a global health problem that has reached epidemic proportions, with an estimated prevalence rate of 8–16%.[3] Patients with chronic renal failure often have signs & symptoms suggestive of thyroid dysfunction. These findings include dry skin, sallow complexion, low temperature, cold intolerance, decreased basal metabolic rate, lethargy, fatigue, edema & hyporeflexia.[1] CKD patients may experience alterations in regulation of the hypothalamic-pituitary-thyroid axis.[2] In addition, as the kidney is involved in the metabolism, degradation, and excretion of certain thyroid hormones and their metabolites, various thyroid functional test alterations may occur in CKD. Various studies of thyroid functions in uremic patients have been carried out which have

shown conflicting results. Hyperthyroidism, hypothyroidism & euthyroid state have all been reported by various workers.

Literature shows significant alteration in thyroid hormone function tests in CKD patients who are receiving long-standing dialysis treatment.[4] However, not much is described in those receiving conservative management without dialysis. Hence it was decided to undertake a study to establish a correlation, if any between thyroid dysfunction and severity of renal disease.

Explanation of procedure:

- Informed consent will be obtained and then patient will be enrolled for the study.
- All patients fulfilling inclusion criteria are subjected to a questionnaire and thorough clinical examination.
- Routine workup for chronic kidney disease is done. Complete blood counts, renal function tests including serum calcium and serum phosphorus will be done. Liver function tests including serum proteins. USG abdomen will be done.
- Serum TSH, free T3 and freeT4 blood samples will be done.
- The patients are then graded according to the KIDGO guidelines for chronic kidney disease into Grade 1, Grade2, Grade 3, Grade 4 or Grade 5.
- Data will be analysed and tabulated.

Withdrawal from participation in the study: Participation in this study is voluntary. You will be free to decide whether to participate in this study or continue participation once enrolled. In case you decide to withdraw your participation, you are free to do so. However, please convey the decision to the principal investigator.

Possible benefits from participating in the study: You will/will not have nor get any benefits by participating in this study. The data gathered will help the population at large.

Possible risks from participating in the study: There are no risks involved in participating in this study.

Privacy and confidentiality: The information collected from you will be coded, to prevent any person from identifying you. Your identity will never be revealed. The data collected from you will be kept confidential and only processed or aggregated data will be used for publication.

Financial incentives: You will not receive any payment for participating in this study.

Authorization for publication of aggregated data: Results obtained after processing of the aggregated data will be published for scientific purposes and or presented to scientific groups. However, your identity will never be revealed.

Questions: In case of any questions with regard to this study, you are free to contact: "Name of student/PI, mobile number, email ID" If you have any question or complaints with regard to your right as study participant you may contact Dr Harsha Hegde, Chairperson, Ethical committee of JNMC, 0831-2473777 Extension 4052.

Legal rights: By signing this consent form, we are not waving any of your legal rights.

ANNEXURE II: PROFORMA

CASE NO:

NAME:

AGE/SEX:

IP NO.:

ADDRESS:

OCCUPATION:

CHIEF COMPLAINTS AT PRESENTATION:

Past history:

Family history:

Personal history:

Treatment history:

PHYSICAL EXAMINATION:

GENERAL CONDITION:

- PALLOR- YES/NO
- ICTERUS-YES/NO
- LYMPHADENOPATHY-YES/NO
- CYANOSIS- YES/NO
- CLUBBING-YES/NO
- EDEMA-YES/NO

VITALS:

- TEMPERATURE:
- PULSE:
- RESPIRATORY RATE:
- BLOOD PRESSURE:

SIGNS OF UREMIA:

- Cognitive dysfunction
- Fatigue
- Shortness of breath
- Loss of appetite
- Muscle cramps
- Nausea and vomiting
- Itching
- Unexplained weight loss

SIGNS OF THYROID DYSFUNCTION:

- Fatigue
- Increased sensitivity to cold
- Constipation
- Dry skin
- Weight gain
- Puffy face
- Hoarseness
- Muscle weakness

- Elevated blood cholesterol level
- Muscle aches, tenderness and stiffness
- Pain, stiffness or swelling in your joints
- Changes in menstrual pattern
- Thinning hair
- Slowed heart rate
- Depression
- Impaired memory
- Goitre
- Unintentional weight loss
- Tachycardia, arrythmia
- Palpitations
- Increased appetite
- Nervousness, anxiety and irritability
- Tremor
- Sweating
- Increased sensitivity to heat
- Changes in bowel patterns
- Difficulty sleeping
- Skin thinning
- Fine, brittle hair

SYSTEMIC EXAMINATION:

R. S.:

C.V.S.:

C.N.S.:

P.A.:

INVESTIGATIONS

- CBC
- LFT, including SERUM PROTEINS
- RFT INCLUDING BLOOD GLUCOSE AND SERUM ELECTROLYTES
- SERUM CALCIUM AND SERUM PHOSPHORUS
- COMPLETE URINE ANALYSIS
- SERUM TSH
- FREE T3
- FREE T4
- USG ABDOMEN AND PELVIS

ANNEXURE III: MASTERCHART

Sr No.	Age	Sex	Hypertension	DiabetisMellitus	IHD	BP	SBP	DBP	Hb	TLC	Plt	SrAlbumin	BUN	Sr.Urea	Creatinine	EGFR	CKD Stage	Na	K	PO4	Ca	TSH	FREET3	FREET4
1	41	Male	No	Yes	No	140/90	140	90	6.4	7830	220000	3	37.38	80	10.6	6	stage 5	135	5.4	3.5	7.5	3.26	1.82	0.8
2	41	Male	Yes	No	No	150/100	150	100	8.5	7890	190000	2.9	57.4	123	11	6	stage 5	138	5.6	4	7.5	1.73	1.93	1.33
3	30	Female	Yes	No	No	160/90	160	90	10.2	7760	294000	4	44.9	96	2.9	22	stage 4	139	5.1	4.5	7.5	1.51	1.71	0.9
4	65	Female	Yes	Yes	No	180/110	180	110	8.5	6250	150000	3.1	53.7	115	4.2	11	stage 5	133	4.2	5	8	3.24	2.02	1.62
5	64	Male	Yes	Yes	No	170/90	170	90	7.3	3710	132000	2.8	31.3	67	3.7	17	stage 4	137	4.5	3.2	10	6.04	2.35	1.01
6	61	Male	Yes	Yes	No	160/110	160	110	6.8	6150	144000	2.8	65.88	141	2.1	35	stage 3	136	4.5	4.5	8	5.31	2.33	1.32
7	57	Male	Yes	Yes	No	150/100	150	100	8.3	5800	159000	3.4	37.8	80	11.6	6	stage 5	140	5.2	3.5	9	3.59	0.52	1.31
8	40	Female	Yes	Yes	No	150/90	150	90	7.3	5450	163000	3.8	61.6	132	2.9	20	stage 4	138	7.4	10	11	4.74	2.68	1.14
9	74	Male	No	Yes	No	160/90	160	90	5.9	7230	191000	3.1	23.3	50	3.8	16	stage 4	133	3.7	5	7.8	10.07	1.64	0.41
10	35	Female	No	Yes	No	190/120	190	120	9.6	5650	189000	2.89	48.1	103	3.11	19	stage 4	137	5.2	6.9	11	1	0.79	1.32
11	64	Female	No	Yes	No	168/106	168	106	7.4	4790	142000	2.9	34.8	80	6.98	6	stage 5	134	5	7.8	8.9	2.8	1.76	1.4
12	55	Male	No	Yes	No	176/112	176	112	7.3	5600	247000	2.87	54.6	117	1.4	59	stage 3	138	3.8	6.8	9.5	5.16	1.66	0.54
13	68	Female	No	Yes	No	160/100	160	100	9.2	5100	165000	2.89	64	137	2.5	20	stage 4	151	5.5	8	10	1.46	1.5	1.57
14	61	Male	No	Yes	No	150/100	150	100	8.3	13650	193000	3.3	45.6	86	3.5	19	stage 4	142	3.7	6.5	8	1.8	3.8	1.72
15	34	Male	No	Yes	No	120/90	120	90	8.3	4120	157000	3.98	34.6	76	5.6	13	stage 5	132	4	4.6	7	0.01	2.62	3.82
16	48	Male	No	Yes	No	138/88	138	88	5.6	4325	145000	4	43.7	90	3.9	18	stage 4	147	5.4	3.5	8	0.34	1.89	1.3
17	26	Male	Yes	Yes	No	178/96	178	96	7.8	5670	132000	3.21	67.8	109	2.3	39	stage 3	137	3.4	3	9	5.13	1.91	0.77
18	73	Male	Yes	Yes	Yes	180/100	180	100	6.7	4560	222000	2.9	54.6	123	8.9	6	stage 5	132	3.6	45	7.5	0.95	1.87	1.03
19	54	Female	Yes	Yes	No	176/100	176	100	7.7	3120	232000	3.89	44.3	80	2.7	20	stage 4	136	4	5	7.8	1.08	1.14	0.34
20	50	Female	Yes	Yes	No	186/116	186	116	7.9	4560	191000	3.32	23.5	60	5.61	9	stage 5	142	5.5	6.4	8.6	9.23	1.7	0.67
21	60	Female	Yes	Yes	No	160/90	160	90	8.3	4350	180000	2.78	43.7	90	3.9	13	stage 5	147	5.1	3.7	8.9	1.19	1.84	1.37
22	39	Female	Yes	No	No	130/80	130	80	7.9	8570	121000	2.8	65.8	134	2.76	22	stage 4	151	5.7	5.4	9	0.96	1.06	0.73
23	32	Male	Yes	No	No	128/86	128	86	8.4	8790	213000	2.9	54.6	109	1.7	54	stage 3	148	5.2	6.5	10	0.93	2.14	1.03
24	55	Male	Yes	Yes	No	136/84	136	84	9.4	7680	132000	3.56	56.4	116	2.2	35	stage 3	146	4.7	3.5	6.5	4.87	2.63	1.48
25	32	Female	Yes	No	No	176/98	176	98	7.3	4120	146000	3.89	55.9	126	3.6	17	stage 4	134	4.8	4.7	7.7	2.28	2.42	1.37
26	55	Male	Yes	No	No	174/104	174	104	8.2	9870	136000	4.1	45.3	100	8.64	7	stage 5	138	5.9	8.6	8.6	2.93	2.8	1.48
27	66	Male	Yes	Yes	No	166/88	166	88	6.4	8970	167000	3.4	34.7	82	2.96	23	stage 4	136	6	6	8.9	0.97	1.7	0.64
28	45	Male	Yes	Yes	Yes	148/96	148	96	6.2	9080	143000	3.8	36.3	86	5.61	12	stage 5	143	5.3	5.3	8.8	0.78	2.4	0.96
29	60	Male	Yes	No	No	164/104	164	104	7.3	8880	147000	4	65.7	134	3.9	17	stage 4	143	3.6	6.6	9.8	0.35	2.56	1.5
30	54	Male	Yes	Yes	No	150/100	150	100	7.7	3450	156000	3.2	48.7	112	1.9	41	stage 3	132	4.7	5	9.9	2.52	1.8	1.52
31	45	Male	No	No	No	150/90	150	90	9.8	6750	154000	3.8	44	101	3.89	19	stage 4	138	5.8	7.6	8.8	1.34	0.84	1
32	65	Female	No	Yes	No	130/80	130	80	6.8	5460	198000	4.3	45.7	105	4.9	9	stage 5	136	4.8	8.7	7.8	3.4	1.42	1.43
33	26	Female	Yes	Yes	No	188/128	188	128	8.9	5640	222000	3.5	33.5	77	5.32	11	stage 5	143	3.8	4.6	8.5	1.72	1.7	0.94
34	75	Male	No	Yes	No	120/80	120	80	7.6	4560	232000	2.9	44.5	102	6.48	8	stage 5	146	4.7	6.4	8.4	1.27	2.81	0.92
35	44	Male	Yes	Yes	No	140/90	140	90	10.5	3470	241000	3.1	35.4	82	4.3	17	stage 4	144	5	3.5	7.7	2.11	1.64	1.42
36	55	Male	No	Yes	No	150/100	150	100	6.9	6540	189000	3.5	37.4	87	8.41	7	stage 5	136	4.2	4.5	8.9	1.09	1.11	1.42
37	44	Female	Yes	Yes	No	150/104	150	104	7.2	6750	189000	4.2	57.7	133	2.5	24	stage 4	134	3.8	3.5	7	0.79	2.16	1.52
38	47	Female	No	Yes	No	140/90	140	90	8.4	7450	127000	4	43.3	101	11	6	stage 5	132	5	5	9.8	1.93	1.7	1.14
39	64	Male	Yes	Yes	No	164/98	164	98	6.8	7870	165000	3.8	33.5	78	3.5	19	stage 4	137	4.4	4.3	9.5	1.59	3.37	1.22
40	45	Male	Yes	No	No	158/100	158	100	8.9	12090	174000	2.9	32.4	74	4.43	16	stage 4	136	4.8	7.8	7.9	0.52	2.14	1.08
41	76	Female	Yes	No	No	160/100	160	100	7.4	6780	174000	3	36.5	89	1.9	27	stage 4	134	4.7	3.5	8.8	5.02	1.66	0.84
42	54	Male	No	Yes	No	152/108	152	108	7.2	4560	185000	3.6	42.8	96	4.9	13	stage 5	145	3.8	5	8.7	0.58	2.36	1.6
43	42	Male	No	No	No	140/90	140	90	8.9	3450	186000	2.9	43.4	98	5.1	18	stage 4	136	4.7	4.4	8.4	1.72	3.21	1.39
44	20	Male	Yes	Yes	No	130/90	130	90	9	7120	147000	4	40.8	84	5.8	13	stage 5	151	5.9	4.4	7	0.53	1.73	1.2
45	60	Male	Yes	No	No	146/98	146	98	8.6	7680	143000	4.21	53.2	110	9.87	6	stage 5	151	5.3	5	9.7	2.71	1.75	1.46
46	70	Female	Yes	Yes	No	184/112	184	112	6.5	6750	176000	2.9	33.9	74	3.1	16	stage 4	143	4.6	3.5	8.6	1.9	1.89	1.1
47	49	Male	No	No	No	176/108	176	108	7.8	5460	189000	2.8	66.9	143	4.5	15	stage 4	132	4.3	4.3	9	3.12	2.3	1.23
48	30	Male	Yes	Yes	No	160/98	160	98	8.9	7680	134000	3.3	56.34	124	2.5	35	stage 3	136	3.4	4.6	7	4.4	2.78	1.61
49	46	Male	No	No	No	158/80	158	80	7.3	4560	154000	3.1	50.9	106	2.7	29	stage 4	135	3.8	4.8	8	4.08	2.35	1.69
50	49	Male	Yes	Yes	No	130/90	130	90	7.9	2310	190000	2.9	43.6	94	6.7	9	stage 5	134	4.3	4.3	7.7	0.72	3.37	0.84
51	64	Female	No	Yes	No	168/106	168	106	7.4	4790	142000	2.9	34.8	80	5.9	8	stage 5	134	5	7.8	8.9	3.92	3.11	1.89

52	55	Male	No	Yes	No	176/112	176	112	7.3	5600	247000	2.87	54.6	117	1.7	47	stage 3	138	3.8	6.8	9.5	0.37	1.2	1.17
53	68	Female	No	Yes	No	160/100	160	100	9.2	5100	165000	2.89	64	137	4.7	10	stage 5	151	5.5	8	10	1.52	1.79	0.93
54	61	Male	No	Yes	No	150/100	150	100	8.3	13650	193000	3.3	45.6	86	2.8	25	stage 4	142	3.7	6.5	8	9.43	0.99	1.1
55	34	Male	No	Yes	No	120/90	120	90	8.3	4120	157000	3.98	34.6	76	5.6	13	stage 5	132	4	4.6	7	4.97	1.37	1.24
56	48	Male	No	Yes	No	138/88	138	88	5.6	4325	145000	4	43.7	90	2.1	38	stage 3	147	5.4	3.5	8	3.46	1.41	0.93
57	26	Male	Yes	Yes	No	178/96	178	96	7.8	5670	132000	3.21	67.8	109	2.3	39	stage 3	137	3.4	3	9	0.97	1.47	2.22
58	73	Male	Yes	Yes	Yes	180/100	180	100	6.7	4560	222000	2.9	54.6	123	2.9	22	stage 4	132	3.6	45	7.5	0.42	1.35	1.39
59	54	Female	Yes	Yes	No	176/100	176	100	7.7	3120	232000	3.89	44.3	80	7.8	6	stage 5	136	4	5	7.8	0.73	1.22	0.85
60	50	Female	Yes	Yes	No	186/116	186	116	7.9	4560	191000	3.32	23.5	60	2.61	22	stage 4	142	5.5	6.4	8.6	2.23	1.43	1.16
61	60	Female	Yes	Yes	No	160/90	160	90	8.3	4350	180000	2.78	43.7	90	3.9	13	stage 5	147	5.1	3.7	8.9	4.88	0.91	0.68
62	39	Female	Yes	No	No	130/80	130	80	7.9	8570	121000	2.8	65.8	134	2.6	23	stage 4	151	5.7	5.4	9	0.78	1.1	1.33
63	32	Male	Yes	No	No	128/86	128	86	8.4	8790	213000	2.9	54.6	109	2.7	31	stage 3	148	5.2	6.5	10	1.23	2.38	1.43
64	55	Male	Yes	Yes	No	136/84	136	84	9.4	7680	132000	3.56	56.4	116	2.21	34	stage 3	146	4.7	3.5	6.5	0.78	1.1	1.33
65	32	Female	Yes	No	No	176/98	176	98	7.3	4120	146000	3.89	55.9	126	3.65	16	stage 4	134	4.8	4.7	7.7	0.56	1.68	0.98
66	55	Male	Yes	No	No	174/104	174	104	8.2	9870	136000	4.1	45.3	100	4	17	stage 4	138	5.9	8.6	8.6	1.12	1.42	1.81
67	66	Male	Yes	Yes	No	166/88	166	88	6.4	8970	167000	3.4	34.7	82	6.98	8	stage 5	136	6	6	8.9	1.44	1.33	1.19
68	45	Male	Yes	Yes	Yes	148/96	148	96	6.2	9080	143000	3.8	36.3	86	5.61	12	stage 5	143	5.3	5.3	8.8	1.21	1.76	1.36
69	30	Male	Yes	No	No	164/104	164	104	7.3	8880	147000	4	65.7	134	3.9	20	stage 4	143	3.6	6.6	9.8	1.76	2.16	1.54
70	54	Male	Yes	Yes	No	150/100	150	100	7.7	3450	156000	3.2	48.7	112	1.8	44	stage 3	132	4.7	5	9.9	3.62	3.87	1.25
71	45	Male	No	No	No	150/90	150	90	9.8	6750	154000	3.8	44	101	2.89	27	stage 4	138	5.8	7.6	8.8	0.44	2.1	1.3
72	65	Female	No	Yes	No	130/80	130	80	6.8	5460	198000	4.3	45.7	105	9.9	6	stage 5	136	4.8	8.7	7.8	1.76	1.64	0.73
73	26	Female	Yes	Yes	No	188/128	188	128	8.9	5640	222000	3.5	33.5	77	5.32	11	stage 5	143	3.8	4.6	8.5	1.09	2.05	1.55
74	75	Male	No	Yes	No	120/80	120	80	7.6	4560	232000	2.9	44.5	102	1.48	49	stage 3	146	4.7	6.4	8.4	1.66	3.7	1.48
75	44	Male	Yes	Yes	No	140/90	140	90	10.5	3470	241000	3.1	35.4	82	7.9	8	stage 5	144	5	3.5	7.7	5.53	3.17	1.44
76	55	Male	No	Yes	No	150/100	150	100	6.9	6540	189000	3.5	37.4	87	3.41	20	stage 4	136	4.2	4.5	8.9	0.97	1.45	0.97
77	44	Female	Yes	Yes	No	150/104	150	104	7.2	6750	189000	4.2	57.7	133	2.4	25	stage 4	134	3.8	3.5	7	1.09	2.08	1.43
78	47	Female	No	Yes	No	140/90	140	90	8.4	7450	127000	4	43.3	101	3.1	18	stage 4	132	5	5	9.8	0.79	1.49	1.1
79	64	Male	Yes	Yes	No	164/98	164	98	6.8	7870	165000	3.8	33.5	78	6.54	9	stage 5	137	4.4	4.3	9.5	4.3	1.84	1.29
80	45	Male	Yes	No	No	158/100	158	100	8.9	12090	174000	2.9	32.4	74	4.43	16	stage 4	136	4.8	7.8	7.9	0.98	3.07	2.01
81	76	Female	Yes	No	No	160/100	160	100	7.4	6780	174000	3	36.5	89	3.6	20	stage 4	134	4.7	3.5	8.8	4.57	2.64	1.1
82	54	Male	No	Yes	No	152/108	152	108	7.2	4560	185000	3.6	42.8	96	4.9	13	stage 5	145	3.8	5	8.7	3.4	3.43	1.11
83	42	Male	No	No	No	140/90	140	90	8.9	3450	186000	2.9	43.4	98	2.4	34	stage 3	136	4.7	4.4	8.4	3.08	5.12	0.6
84	18	Male	Yes	Yes	No	130/90	130	90	9	7120	147000	4	40.8	84	5.8	14	stage 5	151	5.9	4.4	7	3.1	1.14	1.03
85	60	Male	Yes	No	No	146/98	146	98	8.6	7680	143000	4.21	53.2	110	2.98	23	stage 4	151	5.3	5	9.7	4.97	1.37	1.24
86	70	Female	Yes	Yes	No	184/112	184	112	6.5	6750	176000	2.9	33.9	74	4.76	9	stage 5	143	4.6	3.5	8.6	6.7	0.82	0.2
87	49	Male	No	No	No	176/108	176	108	7.8	5460	189000	2.8	66.9	143	4.5	16	stage 4	132	4.3	4.3	9	4.37	1.03	0.52