“STUDY OF CLINICAL AND BIOCHEMICAL PROFILE OF THYROID ABNORMALITIES IN CHRONIC KIDNEY DISEASE WITH REDUCED GLOMERULAR FILTRATION RATE - A ONE YEAR CROSS SECTIONAL STUDY AT KLE UNIVERSITY, BELGAUM”

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ENDORSEMENT

This is to certify that the dissertation entitled **"STUDY OF CLINICAL AND BIOCHEMICAL PROFILE OF THYROID ABNORMALITIES IN CHRONIC KIDNEY DISEASE WITH REDUCED GLOMERULAR FILTRATION RATE–A ONE YEAR CROSS SECTIONAL STUDY AT KLE UNIVERSITY, BELGAUM"** is a bonafide research work done by **THE CANDIDATE REG. NO. BG0110007.**

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LIST OF ABBREVIATIONS USED

AKI	- Acute kidney injury
ANA	- Antinuclear antibodies
anti GBM	- Anti–glomerular basement membrane
ARIC	- Atherosclerosis Risk in Communities
ART	- Ankle reflex time
ATA	- Anti thyroglobulin assay
BDI	- Beck Depression Inventory
BUN	- Blood urea nitrogen
C-ANCA	- Cytoplasmic pattern antineutrophil cytoplasmic antibody
CBC	- Complete blood count
CKD	- Chronic kidney disease
CRF	- Chronic Renal Failure
eGFR	- Estimated glomerular filtration rate
ESR	- Erythrocyte sedimentation rate
ESRD	- End-stage renal disease
EU	- European union
FNAC	- Fine Needle Aspiration Cytology
FSGS	- Focal and segmental glomerulosclerosis
FT4	- Tetraiodothyronine
HIV	- Human immunodeficiency virus
HUS	- Hemolytic-uremic syndrome
IgA	- Immunoglobulin A
K/DOQI	- The Kidney Disease Outcomes Quality Initiative
LDH	- Lactate dehydrogenase

MDRD	- Modification of Diet in Renal Disease
MI	- Myocardial infarction
NHANES III	- The National Health and Nutrition Examination Survey III
NKF	- National Kidney Foundation
P-ANCA	- Perinuclear pattern antineutrophil cytoplasmic antibody
PTH	- Parathyroid hormone
QIDS-SR	- Quick Inventory of Depressive Symptomatology-Self Report
RAIU	- Radio immune assay
RAS	- Renin angiotensin system
RRT	- Renal replacement therapy
SD	- Standard deviation
SLE	- Systemic lupus erythematous
T3	- Triiodothyronine
T4	- Tetraiodothyronine
TBG	- Thyroid binding globulin
Tg AB	- Antithyroglobulin
TPO Ab	- Thyroperoxidase antibodies
TPO	- Thyroperoxidase
TRH	- Thyrotropin Releasing Hormone
TSH	- Thyroid-stimulating hormone TSH
TTP	- Thrombotic thrombocytopenic purpura
USD	- United States dollars
USRDS	- The United States Renal Data System
VDRL	- Venereal Disease Research Laboratory
WBC	- White blood cells

ABSTRACT

Background and objectives

Chronic kidney disease (CKD) is increasingly recognized as a major public health problem. The kidney normally plays an important role in the metabolism, degradation, and excretion of several thyroid hormones. It is not surprising therefore that impairment in kidney function leads to disturbed thyroid physiology. The present study was undertaken to assess the clinical and biochemical profile of thyroid abnormalities in chronic kidney disease.

Methodology

The present cross-sectional study was carried in Department of Medicine /Nephrology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 91 patients with chronic kidney disease were included in the study based on the definition of The Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation.

Results

Out of 91 patients, 59 (64.84%) were males and 32 patients (35.16%) were females, accounting a male to female ratio of 1.84:1. Majority of patients 58(63.74%) were in the age group of 46 to 60 years. The commonest cause of chronic kidney disease in our study was diabetic nephropathy 46 (50.55%). Majority of patients were in stage IV CKD 42 (46.158%). In all the 91 (100%) patients the commonest symptom was tiredness and weakness. The next common symptom was dry skin in 78(85.71%). In the present study, the commonest sign of thyroid dysfunction was coarse skin (62.64%). Raised TSH was noted in 14

(15.38%) patients, 5 (5.49%) had below normal FT4 and 6 (6.59%) had below normal FT3.

Conclusion and interpretation

Based on the Zulewski's score for the assessment of hypothyroidism considering clinical signs and symptoms 7.69% patients were diagnosed to have clinical hypothyroidism. Of the 91 patients with chronic kidney disease the biochemical profile considering FT3, FT4 and TSH levels 14 (15.38%) patients had thyroid abnormalities of which, 7 (7.69%) each had hypothyroidism and subclinical hypothyroidism.

Keywords

Chronic kidney disease; Hyperthyroidism; Hypothyroidism; Thyroid abnormalities; Zuwelski's score.

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Chapter 1

Introduction

INTRODUCTION

Chronic kidney disease (CKD) is increasingly recognized as a major public health problem. Based on internationally accepted definitions CKD is diagnosed when structural or functional abnormalities of the kidneys persist for more than or equal to three months. The disease is categorized into five stages of increasing severity.[1]

Data derived from the National Health and Nutrition Examination Survey III (NHANES III) show that about 1 out of 10 adult Americans exhibit CKD.[2] Estimates in Asia and Australia[2,3] indicate that the problem is of the same magnitude in these countries. In Europe, several surveys have now been completed;[4-10] these studies indicate that CKD is of concern also in EU countries.

Chronic kidney disease is a dangerous clinical condition for two reasons: first because renal impairment may prelude to the development of end-stage renal disease (ESRD), that is, the disease stage where dialysis and transplantation are needed, second because it amplifies the risk for cardiovascular complications. Independent from other risk factors, patients with stage 4 to 5 CKD have a death risk for cardiovascular complications which is two to four times higher than that of the coeval general population, whilst patients with ESRD have a 100 times higher risk.[11]

The number of patients with CKD and the subsequent need for renal replacement therapy (RRT) has reached epidemic proportion and is anticipated to rise further. Worldwide, it is estimated that over 1.1 million patients with end-stage renal disease (ESRD) currently require maintenance dialysis, and this

number is increasing at a rate of 7% per year.[12] If the trend continues, the number will exceed 2 million by 2010.[13] This figure excludes developing countries, where there is less availability for access to dialysis services, and is therefore an underestimate of the true demand and also there is lack of documentation and economic constraint among patients.

There is coherent, undisputable evidence that treatment can prevent or delay kidney disease progression and the resulting cardiovascular complications,[14-21] but this knowledge has rarely been translated into public health policies. Moreover, early detection can prevent or delay progression to end-stage renal disease (ESRD).

The rise in diagnosis of CKD is multifactorial but associated with the ageing population. As technology and medical interventions are improving, people live longer, which also impacts on chronic disease populations. The incidence of diabetes has reached epidemic proportions throughout the world, with an expected doubling in the number of patients with type 2 diabetes in the next 25 years. This, in turn, will lead to an increased incidence of diabetic nephropathy, with approximately 30% progressing to stage 5 CKD. CKD prevalence increases with age, and men with CKD have a more rapid decline in renal function and progression of their renal disease than women. Some ethnic populations have a higher prevalence of CKD. For example, people from South Asia are at higher risk of CKD linked to diabetes, as there is a higher incidence of diabetes in this community. Afro-Caribbeans and Africans are at greater risk of CKD due to their higher prevalence of hypertension.[22]

Diagnosis of CKD includes a complete blood count (CBC), basic metabolic panel, and urinalysis, with calculation of renal function. Serum phosphate, 25 hydroxy vitamin D, alkaline phosphatase, and intact parathyroid hormone (PTH) levels are obtained to look for evidence of renal bone disease. Renal ultrasound and other imaging studies may be indicated.[23]

The kidney normally plays an important role in the metabolism, degradation, and excretion of several thyroid hormones. It is not surprising therefore that impairment in kidney function leads to disturbed thyroid physiology. All levels of the hypothalamic-pituitary-thyroid axis may be involved, including alterations in hormone production, distribution, and excretion.

The evaluation of thyroid function in systemic illness remains complex because the changes occur at all levels of the hypothalamic-pituitary-thyroid axis. During illness, a decrease in triiodothyronine (T3) and pulsatile thyroid-stimulating hormone (TSH) release and increases in reverse T3 occur. This constellation of findings is termed the low T3 syndrome, the euthyroid sick syndrome or non-thyroid illness.[24]

To date, a variety of alterations in thyroid hormone levels and metabolism have been reported in patients with chronic renal failure and low T3 has been consistently found to be the most common disturbance. Epidemiologic data suggests that predialysis patients with chronic kidney disease have an increased risk of hypothyroidism.[25,26]

Recently, a report[27] described that the prevalence of hypothyroidism in patients with estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2 was 23.1% and those prevalence were increased according to the decrease of eGFR. The reduction in T3 has be related to the decrease production of T3 from T4 in the peripheral tissue. Several lines of evidence suggested that low T3 was an independent predictor of survival in various illness states.

Also, a decreased thyroid function is associated with severe morbidity especially in chronic renal failure patients. Studying the clinical profile may help us understand the condition better and help reduce patient morbidity.[28]

However, previous studies[25-28] have only stressed on the levels of thyroid hormones in chronic renal failure, but have not explored clinical and biochemical profiles of thyroid abnormalities together.

Hence, the present study was undertaken to assess the clinical and biochemical profile of thyroid abnormalities in chronic kidney disease.

Chapter 2

Objectives

OBJECTIVES

The objectives of the present study were to assess the clinical and biochemical profile of thyroid abnormalities in chronic kidney disease.

Chapter 3

Review of Literature

REVIEW OF LITERATURE

Chronic kidney disease (CKD) is a worldwide public health problem. It is recognized as a common condition that is associated with an increased risk of cardiovascular disease and chronic renal failure (CRF). The Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation (NKF) defines chronic kidney disease as either kidney damage or a decreased glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2 for 3 or more months. Whatever the underlying etiology, the destruction of renal mass with irreversible sclerosis and loss of nephrons leads to a progressive decline in GFR.[23]

Epidemiology

Prevalence

Worldwide

Chronic diseases have become a major cause of global morbidity and mortality. Earlier considered to be a health problem only in developed countries, 4 out of 5 chronic disease deaths now occur in low- and middle-income countries.[29]

In India the projected number of deaths due to chronic diseases will rise from 3.78 million in 1990 (40.4% of all deaths) to an expected 7.63 million in 2020 (66.7% of all deaths).[29]

Traditionally, health programs for prevention of chronic diseases have mainly focused on hypertension, diabetes mellitus and cardiovascular disease

(CVD), however, the increase in the prevalence of chronic kidney disease (CKD) progressing to end-stage renal disease (ESRD) and the consequent financial burden of renal replacement therapy (RRT)[30,31] in both developed as well as developing nations has highlighted the importance of CKD and its risk factors. The CKD burden is increasing rapidly worldwide. At the end of 2004, 1,783,000 patients worldwide were receiving treatment for ESRD, of which 77% were on dialysis and 23% had a functioning renal transplant (RT), and this number is increasing at a rate of 7% every year. If the current situation prevails, the global ESRD population will exceed 2 million by the year 2010.[30]

The average incidence of ESRD in developing countries is 150 per million population (pmp), which is lower than what is reported in the developed world. This has been attributed to racial and ethnic diversity and lack of education and non availability of medical facility which is also reflected in the disparity in the incidence of ESRD between different populations within the developed nations.[32]

Kidney disease is the ninth leading cause of death in the United States. The Third National Health and Examination Survey (NHANES III) estimated that the prevalence of chronic kidney disease in adults in the United States was 11% (19.2 million): 3.3% (5.9 million) had stage 1, 3% (5.3 million) had stage 2, 4.3% (7.6 million) had stage 3, 0.2% (400,000) had stage 4, and 0.2% (300,000) had stage 5.[23]

The prevalence of chronic kidney disease stages 1-4 increased from 10% in 1988-1994 to 13.1% in 1999-2004. This increase is partially explained by the

increase in the prevalence of diabetes and hypertension, the two most common causes of chronic kidney disease. Data from the United States Renal Data System (USRDS) indicated that the prevalence of chronic renal failure increased 104% between the years 1990-2001.[33]

Indian scenario

According to the second annual report of the CKD Registry of India by the Indian Society of Nephrology, a total of 25,714 patients are included in the registry. Overall Mean age of the patients was 48.3 ± 16.6 years and constituted 68.9% Males and 31.1% Females. The age ranged between as low as 1 to as high as 98 years. The mean age of paediatric population was 11.5 + 5.2 years. Among the elderly, 68.9% were reported to be males. Among the 30.3% patients diabetic nephropathy was the most common cause of CKD followed by hypertension in 14.5% patients. 23% patients were in stage V, 19.44% patients in stage IV, 18.67% in stage III, 27.26% patients in stage II and 36.06% patients in stage I.[34]

In the most representative population-based study from North India, using a multistage cluster sampling technique in which serum creatinine and urine samples were examined in every subject studied, the prevalence of CKD stage 3 and beyond was found in 0.79% subjects out of 4,972 examined.[35] In this study, CKD diagnosis was based on a repeat sample after 2–3 months to be sure of chronicity of renal disease. However, the diagnosis of renal failure was based on serum creatinine alone (>1.8 mg/dl, upper limit of normal for the laboratory), which is likely to underestimate the magnitude of CKD. This study also evaluated the prevalence of risk factors for CKD, like diabetes, hypertension, renal stone

disease, etc. While extrapolating, the authors concluded that the prevalence of ESRD in India will be 785 pmp and the incidence of ESRD will be 160 pmp.

Another study from South India reported a prevalence of impaired kidney function (defined as eGFR <80 ml/min calculated on the basis of abbreviated MDRD) to be 8.6 per thousand after screening a population of 25,000 and then 13.9 per thousand population when they subsequently screened another 21,500 people in an adjacent area in a new survey. The prevalence of any type of renal disease (not CKD) was seen in 0.68% and CKD was seen in 0.16% in the initial survey.[36,37] This study also evaluated diabetes and hypertension, the two major risk factors for CKD. However, there was a difference when compared to the study from North India[35] in so far as serum creatinine was not done in every subject. Further, there was no mention of whether creatinine was repeated after the first screening to be sure of CKD.

Another recent study in an urban population from the Central India revealed a similar disease burden as in the extrapolated disease burden from a North Indian study[35] with average crude and age-adjusted incidence rates of ESRD of 151 and 232 pmp, respectively.[38] However, this study was limited by the possibility of referral bias and population migration, since it was based on ESRD patients evaluated in a particular hospital and with a premise that all ESRD patients in that population area were coming to this particular hospital. This study had no mention of risk factors for CKD, though the patients were evaluated in the hospital. Further, the primary aim of this study was to assess ESRD and not all CKD patients.

The domiciliary screening program for CKD by a trust in South India has reported the prevalence of CKD stage 5 to be 0.87 per thousand (870 per million),[39] which is also very similar to extrapolation of an earlier study from North India.[35]

Combining all the available literature, both published and unpublished, from various sources, it will not be unwise to comment that the yearly incidence of ESRD in India is approximately 150–200 pmp and diabetes is also an important cause of CKD in approximately 30–40% of the patients. Further, with current life expectancy being 63 years and increasing more so in the future, with time the magnitude of CKD is going to increase even further. Community studies, like screening for CKD, involve huge costs. The Indian Council of Medical Research funded a 3-year study in North India, resulting in costs of USD 30,000, or USD 6 per subject. Any further study to determine the magnitude of the problem of CKD/ESRD in India must therefore be multicentric, involve all regions of India, both rural and urban populations, and follow robust community-based epidemiological strategies, otherwise we are likely to get data which will be no different to what is already known from the above literature.[40]

Racial demographics

A study[41] found that rates of ESRD among black patients exceeded those among white patients at all levels of baseline estimated GFR (eGFR). Risk of ESRD among black patients was highest at an eGFR of 45-59 mL/min/1.73 m^2 (hazard ratio, 3.08), as was the risk of mortality (hazard ratio, 1.32).

Another study[42] found that among black kidney transplant recipients graft loss and acute rejection rates are higher than whites, especially among younger patients.

In another study[43] authors looked at the connection between African Americans with the sickle cell trait and their increased risk for kidney disease; the study found that sickle cell trait is not associated with diabetic or nondiabetic ESRD in a large sample of African Americans.

Sex- and age-related demographics

In NHANES III, the distribution of estimated GFRs for the chronic kidney disease stages was similar in both sexes. Nonetheless, the USRDS 2004 Annual Data Report reveals that the incident rate of ESRD cases is higher for males, with 409 per million population in 2002 compared with 276 for females.[23]

Chronic kidney disease is found in persons of all ages. Nonetheless, in the United States, the highest incidence rate of ESRD occurs in patients older than 65 years. As per NHANES III data, the prevalence of chronic kidney disease was 37.8% among patients older than 70 years. A study of Israeli youth revealed that patients aged 16-25 years with persistent asymptomatic isolated microscopic hematuria had an increased risk of treated ESRD for 22 years; however, the absolute risk and incidence was slight.[44]

Besides diabetes mellitus and hypertension, age is an independent major predictor of chronic kidney disease. The geriatric population is the most rapidly

growing kidney failure (chronic kidney disease stage 5) population in the United States.[23]

The biologic process of aging initiates various structural and functional changes within the kidney. Renal mass progressively declines with advancing age. Glomerulosclerosis leads to a decrease in renal weight. Histologic examination is notable for a decrease in glomerular number of as much as 30-50% by age 70 years. The GFR peaks during the third decade of life at approximately 120 mL/min/1.73 m^2; it shows an annual mean decline of approximately 1 mL/min/y/1.73 m^2, reaching a mean value of 70 mL/min/1.73 m^2 at age 70 years.[23]

Ischemic obsolescence of cortical glomeruli is predominant, with relative sparing of the renal medulla. Juxtamedullary glomeruli see a shunting of blood from the afferent to efferent arterioles, resulting in redistribution of blood flow favoring the renal medulla. These anatomical and functional changes in renal vasculature appear to contribute to an age-related decrease in renal blood flow.[23]

Renal hemodynamic measurements in aged human and animals suggest that altered functional response of the renal vasculature may be an underlying factor in diminished renal blood flow and increased filtration noted with progressive renal aging. The vasodilatory response is blunted in the elderly when compared to younger patients.[23]

However, the vasoconstrictor response to intrarenal angiotensin is identical in both young and older human subjects. A blunted vasodilatory capacity with appropriate vasoconstrictor response may indicate that the aged

kidney is in a state of vasodilatation to compensate for the underlying sclerotic damage.[23]

Given the histologic evidence for nephronal senescence with age, a decline in the GFR is expected. However, a wide variation in the rate of decline in the GFR is reported because of measurement methods, race, gender, genetic variance, and other risk factors for renal dysfunction.[23]

Classification

In 2002, K/DOQI published its classification of the stages of chronic kidney disease,[45] as follows:

- Stage 1: Kidney damage with normal or increased GFR (>90 mL/min/1.73 m^2)
- Stage 2: Mild reduction in GFR (60-89 mL/min/1.73 m^2)
- Stage 3: Moderate reduction in GFR (30-59 mL/min/1.73 m^2)
- Stage 4: Severe reduction in GFR (15-29 mL/min/1.73 m^2)
- Stage 5: Kidney failure (GFR < 15 mL/min/1.73 m^2 or dialysis)

In stage 1 and stage 2 chronic kidney disease, GFR alone does not clinch the diagnosis. Other markers of kidney damage, including abnormalities in the composition of blood or urine or abnormalities on imaging studies, should also be present in establishing a diagnosis of stage 1 and stage 2 chronic kidney disease.

The K/DOQI definition and classification of chronic kidney disease allow better communication among physicians and facilitate intervention at the different stages.

Patients with chronic kidney disease stages 1-3 are generally asymptomatic; clinically manifestations typically appear in stages 4-5 (see Clinical). Early diagnosis and treatment of the underlying cause and/or institution of secondary preventive measures is imperative in patients with chronic kidney disease. These may delay, or possibly halt, progression. The medical care of patients with chronic kidney disease should focus on the following:

- Delaying or halting the progression of chronic kidney disease
- Treating the pathologic manifestations of chronic kidney disease
- Timely planning for long-term renal replacement therapy

Etiology

Causes of chronic kidney disease include the following:[23]

- Diabetic kidney disease
- Hypertension
- Vascular disease
- Glomerular disease (primary or secondary)
- Tubulointerstitial disease
- Urinary tract obstruction

Vascular diseases that can cause chronic kidney disease include the following:[23]

- Renal artery stenosis

- Cytoplasmic pattern antineutrophil cytoplasmic antibody (C-ANCA)–positive and perinuclear pattern antineutrophil cytoplasmic antibody (P-ANCA)–positive vasculitides
- Antineutrophil cytoplasmic antibody (ANCA)–negative vasculitides
- Atheroemboli
- Hypertensive nephrosclerosis
- Renal vein thrombosis
- Unrecovered acute kidney injury

Primary glomerular diseases include the following:[23]

- Membranous nephropathy
- Immunoglobulin A (IgA) nephropathy
- Focal and segmental glomerulosclerosis (FSGS)
- Minimal change disease
- Membranoproliferative glomerulonephritis

Rapidly progressive (crescentic) glomerulonephritis Secondary causes of glomerular disease include the following:[23]

- Diabetes mellitus
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Mixed connective tissue disease
- Scleroderma
- Goodpasture syndrome
- Wegener granulomatosis

- Mixed cryoglobulinemia
- Postinfectious glomerulonephritis
- Endocarditis
- Hepatitis B and C
- Syphilis
- Human immunodeficiency virus (HIV)
- Parasitic infection
- Heroin use
- Gold
- Penicillamine
- Amyloidosis
- Light chain deposition disease
- Neoplasia
- Thrombotic thrombocytopenic purpura (TTP)
- Hemolytic-uremic syndrome (HUS)
- Henoch-Schönlein purpura
- Alport syndrome
- Reflux nephropathy

Causes of tubulointerstitial disease include the following:

- Drugs (eg, sulfa, allopurinol)
- Infection (viral, bacterial, parasitic)
- Sjögren syndrome
- Chronic hypokalemia
- Chronic hypercalcemia

- Sarcoidosis
- Multiple myeloma cast nephropathy
- Heavy metals
- Radiation nephritis
- Polycystic kidneys
- Cystinosis

Urinary tract obstruction may result from any of the following:

- Urolithiasis
- Benign prostatic hypertrophy
- Tumors
- Retroperitoneal fibrosis
- Urethral stricture
- Neurogenic bladder

Findings from the Atherosclerosis Risk in Communities (ARIC) Study,[46] a prospective observational cohort, suggest that inflammation and hemostasis are antecedent pathways for chronic kidney disease. This study used data from 1787 cases of chronic kidney disease that developed between 1987 and 2004.

Another study[47] found that aside from other major risk factors of progression, a strong association between acute kidney injury (AKI) and a cumulative risk for the development of advanced chronic kidney disease was seen in multiply hospitalized patients with diabetes mellitus. After adjustments for various factors, such as demographics, smoking, blood pressure, diabetes, lipid levels, prior myocardial infarction (MI), antihypertensive use, and alcohol use, the above study revealed that the risk for chronic kidney disease rose with

increasing quartiles of white blood cell (WBC) count, fibrinogen, von Willebrand factor, and factor VIIIc. The investigators found a strong inverse association between serum albumin level and chronic kidney disease risk.

Pathophysiology

The Brenner hypothesis[48] postulates that any critical loss of functioning renal mass, irrespective of the nature of the initial injury, leads to glomerular hyperfiltration with an increased single-nephron GFR. According to this hypothesis, which has been established in the rat remnant kidney model and confirmed at least for some human kidney disease conditions (such as congenital and acquired single kidneys),[49] the remaining nephrons lose their ability to autoregulate glomerular pressure, resulting in direct transmission of systemic hypertension to the glomerulus. Elevated intraglomerular pressure induces glomerular and tubular hypertrophy. Endothelial and podocyte cell injury, resulting from disease-specific or nonspecific uremia-associated vasculotoxic and inflammatory insults, are frequently involved in progressive glomerular damage, inducing local inflammation and fibrosis.[50-51]

Furthermore, proteinuria (induced by increased intraglomerular pressure), is considered the pathophysiological link between glomerular, interstitial and tubular damage.[52,53]

The degree of proteinuria in glomerular diseases correlates with the rate of renal-failure progression.[54]

Reabsorption of filtered proteins by the tubuloepithelial cells can induce direct injury to intracellular lysosomal pathways, oxidative stress, increased local expression of growth factors,[55,56] and release of chemotactic factors, which promote tubulointerstitial inflammation and fibrosis through recruitment and activation of macrophages.[57-62]

Macrophages infiltrating the renal parenchyma, in turn, perpetuate the production of further cytokines and growth factors.

In both the glomeruli and tubuli, chronic inflammatory processes result in increased synthesis and reduced degradation of extracellular matrix, with excessive tubulointerstitial collagen accumulation. Consequential glomerular sclerosis, tubulointerstitial fibrosis, and tubular atrophy cause a further loss of functioning renal mass, thereby closing a vicious circle of disease progression by increasing intraglomerular pressure and hypertrophy of the remaining glomeruli.[23]

Angiotensin II is the primary effector of the RAS and is mechanistically involved in most of the pathways described above. Angiotensin II is produced both systemically and locally in the kidney and exerts multiple endocrine, autocrine and paracrine effects. Intrarenal angiotensin II concentrations are three orders of magnitude higher than in the circulation and are maintained by autocrine and paracrine hormone synthesis by tubular, juxtaglomerular and glomerular cells. Most of the intrarenal effects of angiotensin II are mediated via the type-1 angiotensin II receptor.[23]

Angiotensin II is a potent vasoconstrictor that augments the level of intraglomerular pressure by preferentially increasing the efferent arteriolar tone. Angiotensin II also increases intracellular calcium activity in podocytes, inducing cytoskeletal changes and altered podocyte function with induction of protein ultrafiltration even in the absence of structural glomerular damage.[23]

Moreover, angiotensin II increases the proliferation of smooth muscle cells and increases the glomerular and tubular expression of various growth factors, cytokines and chemokines. Angiotensin II stimulates oxidative stress, which perpetuates the upregulation of cytokines, adhesion molecules, and chemoattractants.[23]

Finally, intrarenal angiotensin II stimulates neuronal afferences, which are believed to activate structures of the central nervous system that regulate sympathetic tone. Angiotensin II is, therefore, involved pathophysiologically in the state of sympathetic hyperactivation, which is characteristic of CKD and constitutes another important mechanism of renal-disease progression and cardiovascular morbidity.[63]

Clinical presentation

History

Patients with chronic kidney disease stages 1-3 (glomerular filtration rate [GFR] >30 mL/min) are generally asymptomatic; they do not experience clinically evident disturbances in water or electrolyte balance or

endocrine/metabolic derangements. Generally, these disturbances become clinically manifest with chronic kidney disease stages 4-5 (GFR < 30 mL/min).[23]

Uremic manifestations in patients with chronic kidney disease stage 5 are believed to be primarily secondary to an accumulation of toxins, the identity of which is generally not known. Metabolic acidosis in stage 5 may manifest as protein-energy malnutrition, loss of lean body mass, and muscle weakness. Altered salt and water handling by the kidney in chronic kidney disease can cause peripheral edema and, not uncommonly, pulmonary edema and hypertension.[23]

Anemia is associated with fatigue, reduced exercise capacity, impaired cognitive and immune function, and reduced quality of life. Anemia is also associated with the development of cardiovascular disease, the new onset of heart failure, or the development of more severe heart failure. Anemia is associated with increased cardiovascular mortality.[23]

Other manifestations of uremia in ESRD, many of which are more likely in patients who are inadequately dialyzed, include the following:[23]

- Pericarditis - Can be complicated by cardiac tamponade, possibly resulting in death
- Encephalopathy - Can progress to coma and death
- Peripheral neuropathy
- Restless leg syndrome
- GI symptoms - Anorexia, nausea, vomiting, diarrhea
- Skin manifestations - Dry skin, pruritus, ecchymosis
- Fatigue, increased somnolence, failure to thrive

- Malnutrition
- Erectile dysfunction, decreased libido, amenorrhea
- Platelet dysfunction with tendency to bleeding

Physical Examination

The physical examination often is not very helpful. However, it may reveal findings characteristic of the condition that is underlying chronic kidney disease (eg, lupus, severe arteriosclerosis, hypertension) or complications of chronic kidney disease (eg, anemia, bleeding diathesis, pericarditis).[23]

A study[53] reported that the 16-item Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR[16]) and the Beck Depression Inventory (BDI) are effective screening tools and that scores of 10 and 11, respectively, were the best cutoff scores for identification of a major depressive episode in their study's patient population. The study compared the BDI and QIDS-SR(16) with a gold-standard structured psychiatric interview in 272 patients with stage 2-5 chronic kidney disease who had not been treated with dialysis.

Diagnosis

Testing typically includes a complete blood count (CBC), basic metabolic panel, and urinalysis, with calculation of renal function. Serum phosphate, 25 hydroxy vitamin D, alkaline phosphatase, and intact parathyroid hormone (PTH) levels are obtained to look for evidence of renal bone disease. Renal ultrasound and other imaging studies may be indicated.[23]

Normochromic normocytic anemia is commonly seen in chronic kidney disease. Other underlying causes of anemia should be ruled out. The blood urea nitrogen (BUN) and creatinine levels will be elevated in patients with chronic kidney disease. Hyperkalemia or low bicarbonate levels may be present in patients with chronic kidney disease.[23]

Serum albumin levels may also be measured, as patients may have hypoalbuminemia due to urinary protein loss or malnutrition. A lipid profile should be performed in all patients with chronic kidney disease because of their increased risk of cardiovascular disease. In certain cases, the following tests may be ordered as part of the evaluation of patients with chronic kidney disease:[23]

- Serum and urine protein electrophoresis - Screen for a monoclonal protein possibly representing multiple myeloma
- Antinuclear antibodies (ANA), double-stranded DNA antibody levels - Screen for systemic lupus erythematosus
- Serum complement levels - May be depressed with some glomerulonephritides
- Cytoplasmic and perinuclear pattern antineutrophil cytoplasmic antibody (C-ANCA and P-ANCA) levels - Helpful if positive in diagnosis of Wegener granulomatosis and polyarteritis nodosa
- Perinuclear pattern antineutrophil cytoplasmic antibody (P-ANCA) - Helpful if positive in diagnosis of microscopic polyangiitis
- Anti–glomerular basement membrane (anti-GBM) antibodies - Highly suggestive of underlying Goodpasture syndrome

- Hepatitis B and C, HIV, Venereal Disease Research Laboratory (VDRL) serology - Conditions associated with some glomerulonephritides

THYROID OVERVIEW

Anatomy of Thyroid Gland[64]

In the adult normal thyroid gland weighs about 20-25 gms. It is the largest endocrine gland in man. Two large lateral lobes are connected in the midline by a broad isthmus from which on occasion a pyramid lobe may protrude superiorly.

Embryology

The thyroid gland develops as tubular invagination of the endoderm from the root of the tongue called Foramen caecum about the third week of embryonic life. This endodermal proliferation invaginates and grows downwards to form a diverticulum, the caudal end of which gives rise to median isthmus and two lateral lobes of the thyroid. The ultimobranchial bodies developing from the fourth pharyngeal pouch on each side amalgamates with the development lateral lobes of the thyroid gland and contributes to the parafollicular or C cells of thyroid.

Histology

The functioning unit is the lobule, which contains 20 - 40 variably sized follicles that are lined by regular cuboid cells. Delicate fibrous tissue stroma and small collections of lymphocytes separate these follicles. Dispersed within the follicles are the calcitonins secreting C cells. The resting follicles contain colloid

in which thyroglobulin is stored. In active follicle, with absorption of colloid, cells become more columnar.

Arterial Supply

The arterial supply consists of the superior thyroid arteries arising from the external carotids and inferior thyroid arteries arising from the subclavian artery. Each lobule is supplied by a single arteriole.

Venous Drainage

The venous drainage consists of the superior thyroid veins and the middle thyroid veins draining into the internal jugular vein and inferior thyroid veins draining into brachiocephalic vein.

Lymphatic Drainage

There is an extensive lymphatic network within the gland. The subcapsular plexus drains principally to the juxtathyroid nodes i.e., pretracheal and paratracheal nodes and nodes on the superior and inferior thyroid veins and then to the deep cervical and mediastinal group of nodes.

Physiology[65]

Thyroid secretes two significant hormones thyroxine (T4) and triidothyronine (T3), Iodide a substrate for thyroid hormone synthesis, also plays an auto regulatory role in the metabolism of the thyroid gland.

Iodine Metabolism

A typical daily dietary intake of iodide is about 500µg. Iodide is almost completely absorbed in the gastrointestinal tract, where it enters the inorganic iodide pool in the extracellular fluid. In the presence of normal renal function inorganic iodide in the extracellular fluid is rapidly cleared, with a half-life of about 2 hrs. The only two significant pathways of iodide clearance from the extracellular fluid are the kidneys and the thyroid. When the dietary intake of iodide increases, the fractional uptake of extracellular fluid iodine by the thyroid decreases and the proportionate urinary excretion of iodide increases.

The iodine content of the hormonal pool is about 600µg. Cellular uptake of thyroid hormones from this pool is approximately 75µg of iodine per day in an euthyroid individual. Of this 75 µg of thyroid hormone iodine, about 60µg reenters the extracellular fluid iodide pool following intracellular enzymatic deiodination of the thyroid hormones. The remainder is conjugated in the liver and excreted in the bile and subsequently in the stools.

Synthesis of Thyroid Hormones

The thyroid hormone biosynthesis can be considered as occurring in three sequential stages:

- Active transport of iodide into the gland.
- Organisation of iodide and iodination by the oxidized form of tyrosyl residues within thyroglobulin to yield hormonally inactive iodotyrosines.

- Coupling of iodotyrosines to form the hormonally active iodothyronines namely triiodothyronine (T3) and tetraiodothyronine or thyroxine (T4).

Regulation

Thyroid hormone synthesis and secretion are regulated by thyrotropin and intrathyroidal autoregulatory mechanism. Thyrotropin is the major modulator of thyroid activity. Thyrotropin a glycoprotein with a molecular weight of 28000 kD is secreted by thyrotrophs of anterior pituitary. It consists of alpha and beta chains. Alpha chain is identical to the alpha chain of gonadotrophins. TSH specificity is determined by beta chain.

TSH secretion is modulated by thyroid hormones in a negative feed back mechanism. TSH stimulates thyroid hypertrophy and hyperplasia, accelerates all intermediary metabolisms in the thyroid.

TSH enhances synthesis of thyroglobulin and stimulates synthesis and secretion of thyroid hormones. The actions of TSH are mediated by the binding of TSH to specific receptors on the surface of follicular cells and activation of the plasma membrane enzyme adenylate cyclase. The second messenger cAMP initiates all the responses that characterize the actions of TSH.

Regulation of TSH is affected by two opposing influences at the thyrotrophic cell. Thyrotropin Releasing Hormone (TRH) a peptide of hypothalamic origin stimulates secretion and synthesis of TSH whereas T3 inhibits TSH secretion and antagonize the action of TRH. The homeostatic

control of TSH is mediated via negative feed back control of thyroid hormone the "threshold" thermostat for which is set by TRH.

Intrathyroidal Regulation

In some manner glandular iodine content causes reciprocal changes in thyroid iodide transport activity and regulates growth, amino acid uptake and nucleic acid synthesis. These influences are evident in the absence of TSH, hence termed auto regulation. Their most important role is to modify the response to TSH.

Hormone Transport and Metabolism

Thyroid hormones in the blood are almost entirely bound to plasma proteins. They are bound to a globulin named thyroid binding globulin (TBG), thyroxine binding prealbumin and albumin. Affinity of thyroxine is maximum for thyroid binding globulin and hence TBG is the major determinant of binding. Affinity for T3 and T4 are slightly different because T3 is not bound significantly by thyroxine binding prealbumin and binds to TBG less firmly than T4. The levels of free T3 are 8 to 10 times more than T4. As only the free hormone is available to tissues, metabolic state correlates closely with the concentration of free thyroxine.

Thyroid hormones undergo metabolism mainly through sequential removal of iodine atoms (mono deiodination) Deiodination accounts for 70% of T3 / T4 disposal. In case of T4, 5 mono deiodination yields T3 and 30% of T4 is converted to T3 and virtually all metabolic actions of T4 can be ascribed to T3.

Normally extra glandular T3 accounts for 80% of total T3. 40% of T4 disposal is accounted by its conversion to reverse T3 which has no metabolic function. The second major pathway of T3/T4 metabolism is conjugation with glucuronide in the livers which are deiodinated in the liver and excreted in the bile. 20% of T4 disposal occurs via fecal loss.

Thyroid Hormone Actions

1. Effects on Fetal Development

Thyroid hormones are critically important in fetal development particularly of the neural and skeletal systems. Thus, intrauterine hypothyroidism leads to cretinism.

2. Effects on Oxygen Consumption and Heat Production

Thyroid hormones increase O2 consumption in all tissues except the brain, spleen, and testis. Compared to the effects of TSH on thyroid hormone secretion, most thyroid hormone actions on peripheral tissue are induced relatively slowly over a period of hours or days.

3. Cardiovascular Effects

Thyroid hormones have marked chronotropic and inotropic effects on the heart.

4. Sympathetic Effects

Many thyroid hormone effects, particularly on the cardiovascular system, are similar to those induced by catecholamines. Thyroid hormones increase the

number of catecholamine receptors in heart muscle cells. Thyroid hormones may also amplify catecholamine action at postreceptor.

5. Hematopoietec Effects

Thyroid hormones increase erythropoiesis and also increase 2,3 diphosophoglycreate concentrations in erythrocytes.

6. Endocrine Effects

Thyroid hormones generally increase the metabolism and clearance of various hormones and pharmacologic agents.

Thyroid Function Tests

Thyroid function tests can be classified as:

1. Bio-Chemical

- Those that measure concentration of hormones or biologically inactive products secreted by the thyroid.
- Those that test effects of thyroid hormones on peripheral tissues.
- Those that evaluate hypothalamic-pituitary-thyroid axis.

2. Thyroid Imaging Studies

- Radioactive Iodine uptake
- Radio Iodine I123 Uptake scan - Radionuclide Scan
- Technicium 99mm Pertechnate
- Ultrasound

3. Invasive Studies

- Aspiration Cytology: Fine Needle Aspiration Cytology (FNAC)

4. Immunological Tests

- Thyroid auto antibodies
- Thyroperoxidase antibodies (TPO Ab)
- Antithyroglobulim (Tg AB)

Hypothyroidism

Deficiency of thyroid hormones results in hypothyroidism. It is called primary (Thyroprivic) when caused due to pathology of thyroid gland and secondary (Trophoprivic) when the pituitary or the hypothalamus is the cause. It can affect people of both sexes and all ages, although more common in females. The term myxoedema denotes severe hypothyroidism in which there is accumulation of hydrophilic mucopolysaccharides in the ground substance of the dermis and other tissues leading to thickening and doughy induration of skin.[66]

Aetiology:

Primary hypothyroidism: This accounts for the vast majority of cases, only 5% or less being suprathyroid origin. In this the loss of thyroid tissue leads to inadequate synthesis of thyroid hormones despite maximal stimulation of any thyroid remnant by TSH. The most common cause is surgical or radioiodine ablation of thyroid gland for the treatment of Graves' disease.

Primary hypothyroidism also may occur as a primary idiopathic disorder, which is usually due to autoimmunity and is associated with circulating cytotoxic antithyroid antibodies or in some cases antibodies that block the TSH - receptor. This disorder may co-exist with diabetes mellitus, CRF and other diseases in which circulating auto antibodies are found such as pernicious anaemia, SLE, rheumatoid arthritis, sjogrens syndrome and chronic hepatitis. In addition hypothyroidism can be one manifestation of polyglandular endocrine deficiency state in which auto antibodies cause variable insufficiency of thyroid adrenal, parathyroid and gonadal function. Other causes of hypothyroidism include those due to iodine deficiency in endemic areas and Hashimoto's thyroiditis leading to goitrous hypothyroidism.

Secondary Hypothyroidism: It is caused by pituitary or hypothalamic disorders like tumours, haemorrhage, granulomatous (tuberculosis, histiocytosis) and autoimmune (lymphocytic hypophysitis) disease.

Clinical Features

These depend on the age of the patient, duration and severity of hypothyroidism. Hypothyroidism may be overt or subclinical, among patients with overt hypothyroidism, the severity is variable. At one extreme are patients who have few symptoms and signs at the other extreme are those with myxoedema coma.

As thyroid hormone is required for normal functioning of each and every tissue in the body, the deficiency will manifest as multisystem involvement. The basic metabolic rate is decreased. There is deposition of mucopolysaccharides,

hyaluronic acid and chondroitin sulphate in the dermis and all tissues. This causes accumulation of water and its responsible for the skin and other changes, so characteristic of myxoedema which is the result of long standing hypothyroidism.

The onset and progression of symptoms are very gradual, weakness, malaise, lethargy and weight gain are the early symptoms. This is followed by cold intolerance and loss of hair.

Various systemic manifestations are as follows.

Skin: Dry scaly, loss of hair from scalp and body, generalized Oedema initially pitting, brittle nails, weight gain.

Gastrointestinal: Constipation

Cardiovascular: Mild diastolic hypertension, breathlessness, cold intolerance.

Neurological: Physical and mental slowness, lethargy, somnolencle, delayed tendon reflexes, carpal tunnel syndrome.

Renal: Decreased urine output.

Female reproductive system: Irregular cycles / amenorrhoea, anovulation

Clinical features in the elderly

Hypothyroidism in the elderly is often atypical and elusive and lacks the classical clinical features present in younger patients. This is due to a combination of factors including the insidious onset, the ambiguity of several

signs and symptoms, which may be attributed to normal ageing and to the frequent coexistence of several age associated diseases.

The most relevant findings that lead one to suspect hypothyroidism in the elderly are unexplained increase in serum cholesterol, constipation, congestive heart failure (particularly restrictive cardiomyopathy) and macrocytic anaemia.

Other features include neurological signs like syncope, seizures, impaired cerebellar function, carpal tunnel syndrome and vague arthritic complaints. Dyspnoea in > 50% of cases, neuropsychiatric symptoms occurs in upto 60% of patients and include depression.

Elderly patients are often susceptible to myxoedema coma, a rare but dreadful complication of hypothyroidism.

Effects on carbohydrate metabolism

Absorption of glucose from GIT is slowed and peripheral glucose assimilation is retarded. At the same time glycerol release from adipose tissue is slowed and the availability of aminoacids and glycerol for gluconeogenesis is reduced. Insulin response to glucose is delayed. Degradation of insulin is slow, so that sensitivity to exogenous insulin may be increased.

Hence occurrence of hypothyroidism in a patient with type I diabetes result in decreased exogenous insulin requirement and a greater risk of developing hypoglycemia.

Diagnosis

The single most useful measurement is the serum TSH. In primary hypothyroidism TSH is increased with low T4 (FT4) and T3 (FT3). The thyroid auto - antibodies (anti - TPO, antimicrosomal and anti - thyroglobulin) are usually positive in autoimmune disease.

Other laboratory features

Bradycardia and low voltage on ECG, hyperlipidaemia and normocytic normochromic anaemia, enlarged heart with pericardial fluid on echocardiography.

Secondary hypothyroidism

There is low T4 (and T3) and TSH

Subclinical Hypothyroidism

Sub clinical hypothyroidism is a metabolic disorder characterized by elevated serum Thyroid stimulating hormone (TSH) levels and normal T4 and T3 levels. It can present with different degree of thyroid failure.

Prevalence and incidence

Several epidemiological studies have demonstrated that It is commonly prevalent in almost all population groups throughout the world. It affects 6 to 7.5% of females and 2.5 to 3% males and among these 5 to 10.5% progress to develop overt hypothyroidism.[67,68]

Quantifying thyroid failure

This is done by evaluating the thyroid functions indirectly by measuring the serum concentrations of thyroid hormones. Estimation of serum TSH levels, as it is found to be extremely sensitive (0.1 µIU/ml), cost effective and easily reproducible.[69]

The diagnosis of sub clinical hypothyroidism has been quantified by measuring the free T3, basal TSH, T3 and / or stimulated TSH levels after the oral administration of TRH.

- Sub clinical hypothyroidism TSH level < 20 mu/l
- Overt hypothyroidism TSH level > 20 mu/l

Clinical implications

The term sub clinical hypothyroidism implies that there is no clinical manifestation of this thyroid state. However, several studies indicate that this is not entirely true. Decreased thyroid reserve also describes only one aspect of this condition- the relative inability to increase thyroid hormone production, when there is an increase in demand for it, like the pregnancy. Pre-hypothyroidism is another term suggesting that all individuals with isolated TSH elevation will inevitably progress to overt hypothyroidism which is also not entirely true.

Mild thyroid failure is the recent term used by several authors as it described the biosynthetic deficiency, but maintains neutrality about its consequences.[70]

Subclinical hypothyroidism commonly develops in such patients who have

1. History of autoimmune thyroiditis.
2. Neck Irradiation for head and neck tumours.
3. Who had undergone treatment for thyrotoxicosis with radioactive Iodine or by surgery.
4. In postpartum thyroiditis.
5. Type 1 diabetes mellitus.
6. Drugs-amiodarone, lithium, tricyclic-antidepresants, metaclopramide,
7. Post menopausal women treated for breast cancer receiving tamoxiphen for more than a year.

Hyperthyroidism

The term hyperthyroidism is reserved for disorders that result from over production of hormone by the thyroid gland itself, of which graves disease is the most common.[71] The term thyrotoxicosis refers to the biochemical and physiological manifestations of excessive quantities of the thyroid hormones.

Clinical manifestations

They depend on the severity and the duration of the disease, the age of the patient, presence or absence of extrathyroidal manifestations and the specific disorder producing the thyrotoxicosis.

Systemic effects are as follows:

General Heat intolerance, weight loss, fatigue, insomnia, nervousness, tremulousness

Skin: Fine, Warm, moist, hyperpigmentation, hyperhidrosis, onycholysis, fine and often straight hair, urticaria, pruritus.

Eye: Exophthalmos, lid edema, lid lag, chemosis, ophthalmoplegia.

Mental: Irritability, restlessness, anxiety, inability to concentrate, liability, depression

Neurological: Syncope, delirium, stupor, coma, choreoathetosis.

Cardiovascular: Tachycardia, wide pulse pressure, bounding pulse, signs of CHF, angina pectoris, paroxysmal tachycardia or Arial fibrillation

Respiratory: Dyspnoea

Gastrointestinal: Increased thirst, diarrhea, elevated Liver function tests, and hepatomegaly

Neuromuscular: Tremulousness, brisk reflexes, proximal muscle weakness, muscle atrophy, myopthy, periodic paralysis

Metabolic: Elevated serum calcium, decreased serum magnesium, increased bone alkaline phosphatase

Osseous: Osteopenia or Osteoporosis

Reproductive: Amenorrhoea or irregular menstruations, decreased fertility

Hematopoietic: Anaemia, Lymphocytosis, spleenomegaly, lymphadenopathy, enlarged thymus

Varieties of Thyrotoxicosis

- Sustained Hormone overproduction (Hyperthyroidism).
- Graves' disease
- Toxic multinodular goiter
- Toxic adenoma
- Iodine - induced
- Trophoblastic tumor
- Increased TSH secretion
- No associated hyperthyroidism
- Thyrotoxicosis factitia
- Subacute thyroditis
- Thyroditis with transient thyrotoxicosis
- Ectopic thyroid tissue

Effects on carbohydrate metabolism[72]

Both glucose absorption and production are increased. The oral glucose tolerance test is often abnormal. The most common abnormality is a faster rise is plasma glucose after glucose ingestion, but some patients have delayed peak plasma glucose or a peak value that is higher than in normal subjects. These abnormalities may reflect changes in glucose absorption than glucose metabolism, since many patients who have abnormal oral glucose tolerance have normal response to intravenous glucose administration. In pre - existing diabetes

mellitus aggravated by thyrotoxicosis, one cause being increased degradation of insulin.

Diagnosis

Diagnosis is confirmed by doing total T3/T4 and / or free T4/T3 and TSH assays. Suppressed TSH to <0.1 mu/ml is the first biochemical change that occurs followed by elevation of T3/fT3 and the T4/fT4. The elevation of T3 occurs to a greater extent thanT4. Thyroid peroxidase antibodies are positive in more than 80% of Graves' disease. The radioactive iodine uptake is usually very high showing that the thyroid is producing excessive hormones.

Subclincial Hyperthyroidism[72]

It is defined biologically as the association of a low serum TSH with normal circulating concentration of T4 and T3. The use of the word subclinical implies that subjects should also be asymptomatic but the diagnosis is usually biochemical rather than a clinical one.

Prevalence

There have been relatively few population based studies on the prevalence of subclinical hyperthyroidism. One study done by screening an ambulatory population of subjects aged over 60 yrs found that the prevalence was 6.3% of females and 5.5% of males.[73]

Causes

Causes or associations related to thyroid disease and its treatment

- Thyroxine therapy
- Previous Graves' hyperthyroidism
- Graves' ophthalmopathy
- Nodular goiter

Causes or associations related to 'non thyroidal' illness and drug therapy.

- Any significant illness like myocardial infarction, liver or renal failure, diabetes mellitus.
- Therapy with drugs such as glucocorticoids, dopamine and anti convulsants.
- Drugs - Amiodarone.
- Pregnancy especially in first trimester.

Natural History:

Depends on its cause and severity (in terms of degree of reduction of TSH below the normal range) some patients will progress to overt hyperthyroidism; incidence is relatively low at around 1 to 3% per year.

In patients with non thyroid illness or drug therapy induced sub clinical hyperthyroidism, the biochemical abnormality often disappears after recovery from illness or cessation of drug therapy.

THYROID FUNCTIONS IN CHRONIC RENAL FAILURE

Various studies of thyroid function in uremic patient have been carried out which have shown conflicting results hypothyroidism, hyperthyroidism and euthyroid state have all been reported by various workers.[74]

CKD is associated with a higher prevailed of primary hypothyroidism, both overt and sub clinical, but not with hyperthyroidism.[75] In fact the prevalence of primary hypothyroidism, mainly in the sub clinical form, increases as GFR decreases.[76] Most of the patients are euthyroid because of circulating free thyroid hormone levels.

Thyroid hormone levels in CRF

Serum tri-iodothyronine levels were consistently found to be low without any regard to treatment of CRF.[77] Thyroid function studies conducted is clinically euthyroid uremic dialysis patients demonstrate decrease levels of tri-iodothyronine.[78]

This reduction in T3 concentration has been linked to the decrease in the peripheral synthesis of T3 from T4.[79]

Mean thyroid stimulating hormone (TSH) was not elevated and the TSH response to thyrotrophin releasing hormone (TRH) was distinctly blunted, suggesting possibility of pituitary dysfunction as well.

Effect of Hemodialysis on thyroid function

The thyroid function studies on patients with CRF before and after hemodialysis resulted in only slight increase in TT3 concentration without significant change in other thyroid function.[80]

A study on thyroid function in uremic patients with conservative management and with regular dialysis they found that there is no change in thyroid profile except decrease in TSH in hemodialysates compare to normals.[81]

Effect of Renal transplant on thyroid function

A study reported mean TT3 and TT4 and FT3 levels reduced as the severity of renal damage increased. When the individual values plotted against their respective Sr. creatinine levels, no linear correlationship was observed between those parameters.[81]

Restoration of renal function with renal transplant resulted in normalisation of all parameters of thyroid function with exception of blunted or absent TSH response to TRH. The latter may be a direct consequence of glucocorticoid administration.

Chapter 4

Methodology

METHODOLOGY

The present study was conducted in the Department of Medicine/Nephrology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

Study design

The study design was one year cross-sectional study.

Study period and duration

The present one year cross sectional study was conducted during the period of January 2011 to December 2011.

Place

This study was conducted at Department of Medicine/Nephrology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum a teaching hospital attached to Jawaharlal Nehru Medical College, Belgaum.

Source of Data

Patients with chronic kidney disease (as per the definition of K/DOQI of the National Kidney Foundation)[15] attending Department of Nephrology (In patient department and/or out patients department), KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum were included in the study.

Sample size

A total of 91 patients with chronic kidney disease were selected for the study.

Sampling procedure

The sample size was calculated based on the formula as mentioned below.

$n = 4 \times p \times q / d^2$

Where p = Prevalence 50% (As no hospital statistics available prevalence was considered as 50%).

q = 100 – p

d = Standard error 10%

$n = 4 \times 50 \times 50 / 10^2$

n = 70

By applying the above value in the formula the sample size was calculated as 70. However during the study period 91 patients satisfied the selection criteria and hence 91 patients were included in the study.

Selection criteria

Inclusion Criteria

- Patients with chronic kidney disease.
    - Presence of chronic kidney disease was defined as per the definition of The Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation.[15]

Exclusion Criteria

- Patients who are known cases of hypothyroidism and hyperthyroidism.
- Presence of in infection.

Ethical clearance

Prior to the commencement of the study Ethical Clearance was obtained from the Ethical and Research Committee, Jawaharlal Nehru Medical College, Belgaum.

Informed Consent

All the patients fulfilling selection criteria were explained about the nature of study and a written informed consent was obtained before enrollment (Annexure I).

Method of collection of data

Demographic data such as age and sex were recorded. A thorough physical examination such as anthropometry, vitals and systemic examination was conducted. These findings were recorded on a predesigned and pretested proforma (Annexure II).

Study variables

Clinical signs and symptoms

During the clinical examination the patients were interviewed for the clinical symptoms of thyroid abnormalities such as;

- Tiredness / weakness.
- Dry skin.
- Diminished sweating.
- Weight increase.
- Hair loss.
- Parasthesia.
- Constipation.
- Hoarseness of voice.
- Impairment of hearing.

Further these patients were subjected to the clinical examination and assessed for the following signs of thyroid abnormalities such as;

- Coarse skin.
- Cold skin.
- Periorbital puffiness.
- Slow movements.
- Delayed ankle jerk.

The interpretation of clinical signs and symptoms was done based Zulewski's clinical score for hypothyroidism.[82] The 14 symptoms and signs identified by earlier study[83] were evaluated. Two features, i.e., pulse rate and cold intolerance, had positive and negative predictive values below 70%, and were excluded.

Zulewski's clinical score for hypothyroidism

	Symptoms		New score	
			Present	**Absent**
1	Diminished sweating	Sweating in the warm room or a hot summer day	1	0
2	Hoarseness	Speaking voice, singing voice	1	0
3	Paraesthesia	Subjective sensation	1	0
4	Dry skin	Dryness of skin, noticed spontaneously, requiring treatment	1	0
5	Constipation	Bowel habit, use of laxative	1	0
6	Impairment of hearing	Progressive impairment of Hearing	1	0
7	Weight increase	Recorded weight increase, tightness of clothes	1	0
Physical signs				
1	Slow movements	Observe patient removing his clothes	1	0
2	Delayed ankle reflex	Observe the relaxation of the reflex	1	0
3	Coarse skin	Examine hands, forearms, elbow for roughness and thickening of skin	1	0
4	Periorbital puffiness	This should obscure the curve of the malar bone	1	0
5	Cold skin	Compare temperature of hands with examiner’s	1	0

Sum of all symptoms and signs present

A score >5 points defined hypothyroidism, a score of 3 to 5 was defined as intermediate state while a score of 0-2 points defined euthyroidism.

The most sensitive features were delayed ART (77%) and dry skin (76%), while the most specific were slow movements (98.7%) and diminished hearing (97.5%). A positive predictive value was highest for slow movements (96.5%) and puffiness (94.2%). On the other hand, a negative predictive value was highest for ART (80.3%) and dry skin (72.7%).

Investigations

Routine investigations such as total WBC Count, ESR and liver function test were done.

1. Serum Creatinine (to calculate eGFR by MDRD Formula)

    a. Serum creatinine (by Jaeffe's method)

Based on the MDRD formula eGFR was calculated and patients were staged as below.[84]

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

Multiply by 0.742 for women

Multiply by 1.21 for African Americans

Stages

Stage	eGFR	Extent of kidney damage
I	90+	Normal or minimal kidney damage with normal GFR
II	60-89	Mild decrease in GFR
III	30-59	Moderate decrease in GFR
IV	15-29	Severe decrease in GFR
V	<15	Kidney failure

Thyroid profile

The thyroid profile was assessed by withdrawing venous blood under aseptic precautions and estimation of TSH, FT3 and FT4 was done using a fully automated immunoflorescence immunoassay analyser (Make: Abott Axsym) was used to estimate TSH, FT3 and FT4. The results obtained were interpreted as below;[85,86]

Thyroid stimulating hormone

- Normal range – 0.49 to 4.67 µIU/mL.
- Abnormal - < 0.49 or > 4.67 µIU/mL.

Free Triiodothyronine

- Normal range – 1.45 to 3.48 pg/mL.
- Abnormal - < 1.45 or > 3.48 pg/mL.

Free thyroxine

- Normal range – 0.70 to 1.85 ng/dL.
- Abnormal - < 0.7 or > 1.85 ng/dL.

Statistical analysis

The data obtained was coded and entered into Microsoft Excel Worksheet. The categorical data was expressed as rates, ratios and proportions. The continuous data was expressed as mean ± standard deviation (SD).

Chapter 5

Results

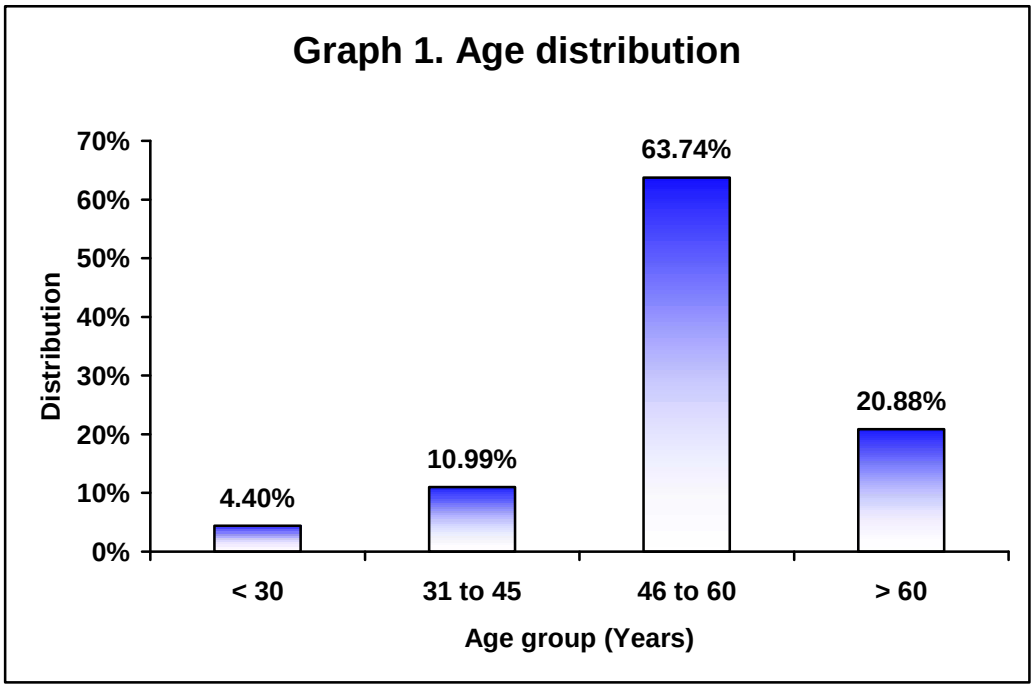
RESULTS

The present cross-sectional study was carried in Department of Medicine /Nephrology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 91 patients with chronic kidney disease were included in the study based on the definition of The Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation.

The results obtained are tabulated as below.

Table 1. Age distribution

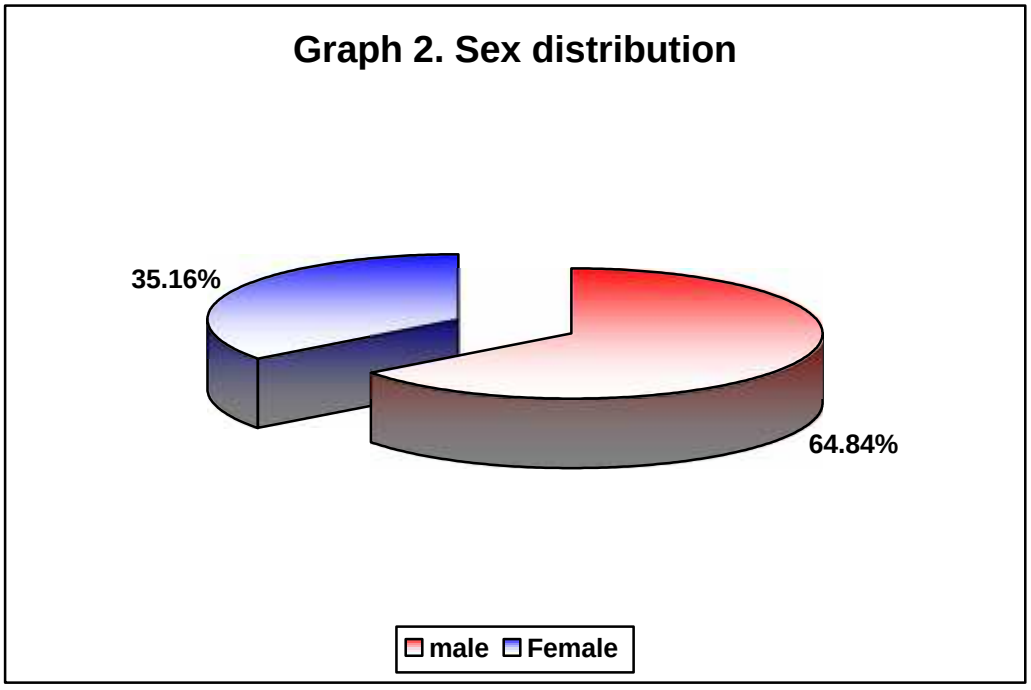
Age (Years)	Patients(n=91)	
	Number n	Percent %
< 30	4	4.40
31 to 45	10	10.99
46 to 60	58	63.74
> 60	19	20.88
Total	**91**	**100.00**



Out of the 91 patients majority of patients 58 (63.74%) were in the age group of 46 to 60 years, followed by 19 (20.88%) patients in the age group greater than 60 years.

Table 2. Sex distribution

Sex	Patients(n=91)	
	Number n	**Percent %**
Male	59	64.84
Female	32	35.16
Total	**91**	**100.00**

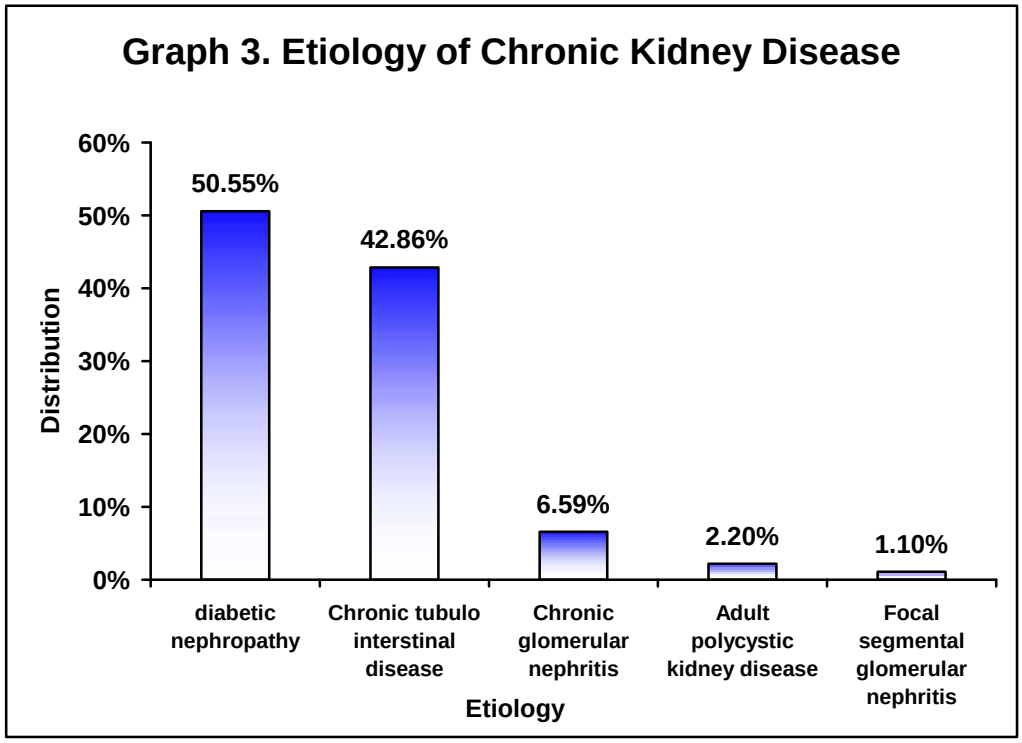


Out of 91 patients 59(64.84%) were males and 32 patients (35.16%) were females, accounting a ratio of male to female was 1.84:1.

Inference: Male preponderance was noted

Table 3. Etiology of Chronic Kidney Disease

Etiology	Patients (n=91)	
	Number (n)	Percent (%)
Diabetic nephropathy	46	50.55
Chronic tubulo interstitial disease	39	42.86
Chronic glomerular nephritis	6	6.59
Adult polycystic kidney disease	2	2.20
Focal segmental glomerular nephritis	1	1.10

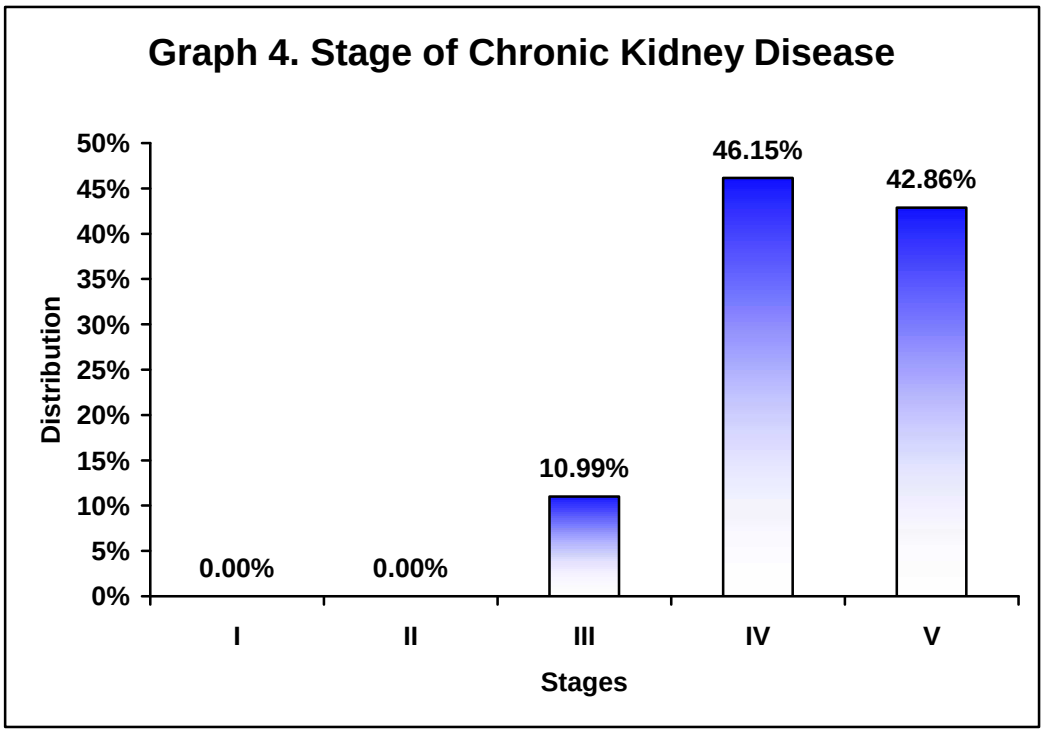


The commonest cause of chronic kidney disease in our study was diabetic nephropathy 46 (50.55%), chronic tubulointertial disease in 39(42.86%),chronic glomerularnephritis in 6 (6.59%), adult polycyctic kidney diease in (2.20%) and focal segmental glomerular nephritis in 1(1.10%).

Inference: The commonest cause of chronic kidney disease was diabetic nephropathy

Table 4. Stage of Chronic Kidney Disease

Stages	Patients (n=91)	
	Number (n)	**Percent (%)**
I	0	0.00
II	0	0.00
III	10	10.99
IV	42	46.15
V	39	42.86
Total	**91**	**100.00**

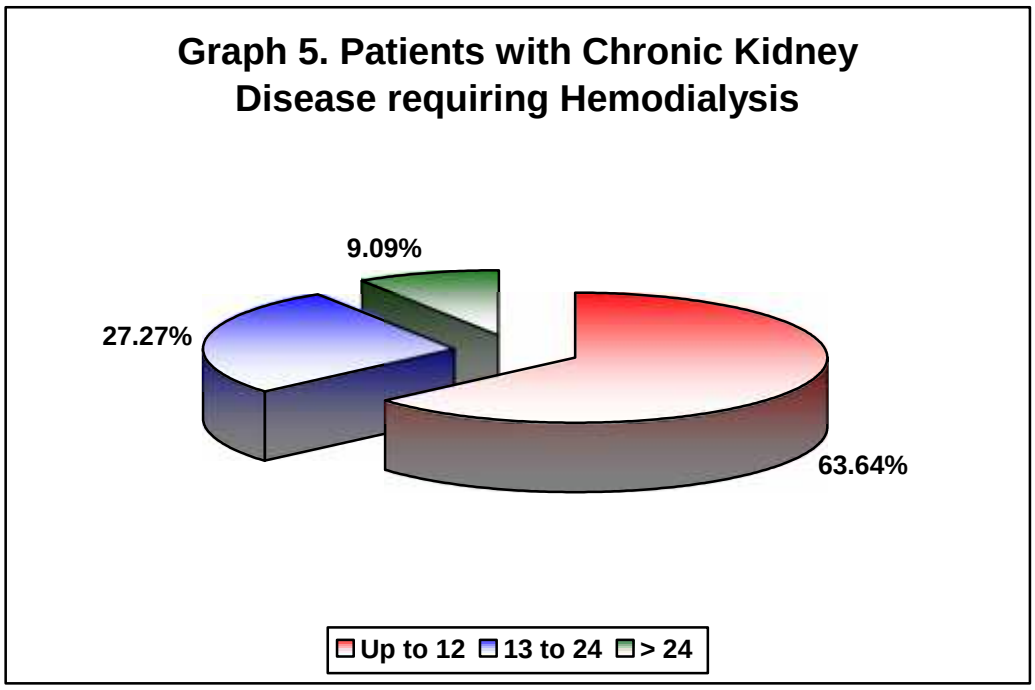


Majority of patients were in stage IV CKD 42 (46.158%), 39 (42.86%,) patients in stage V and 10.99% patients were in stage III CKD.

Inference: Majority of the patients were in stage IV CKD

Table 5. Patients with Chronic Kidney Disease requiring Hemodialysis (Duration in months)

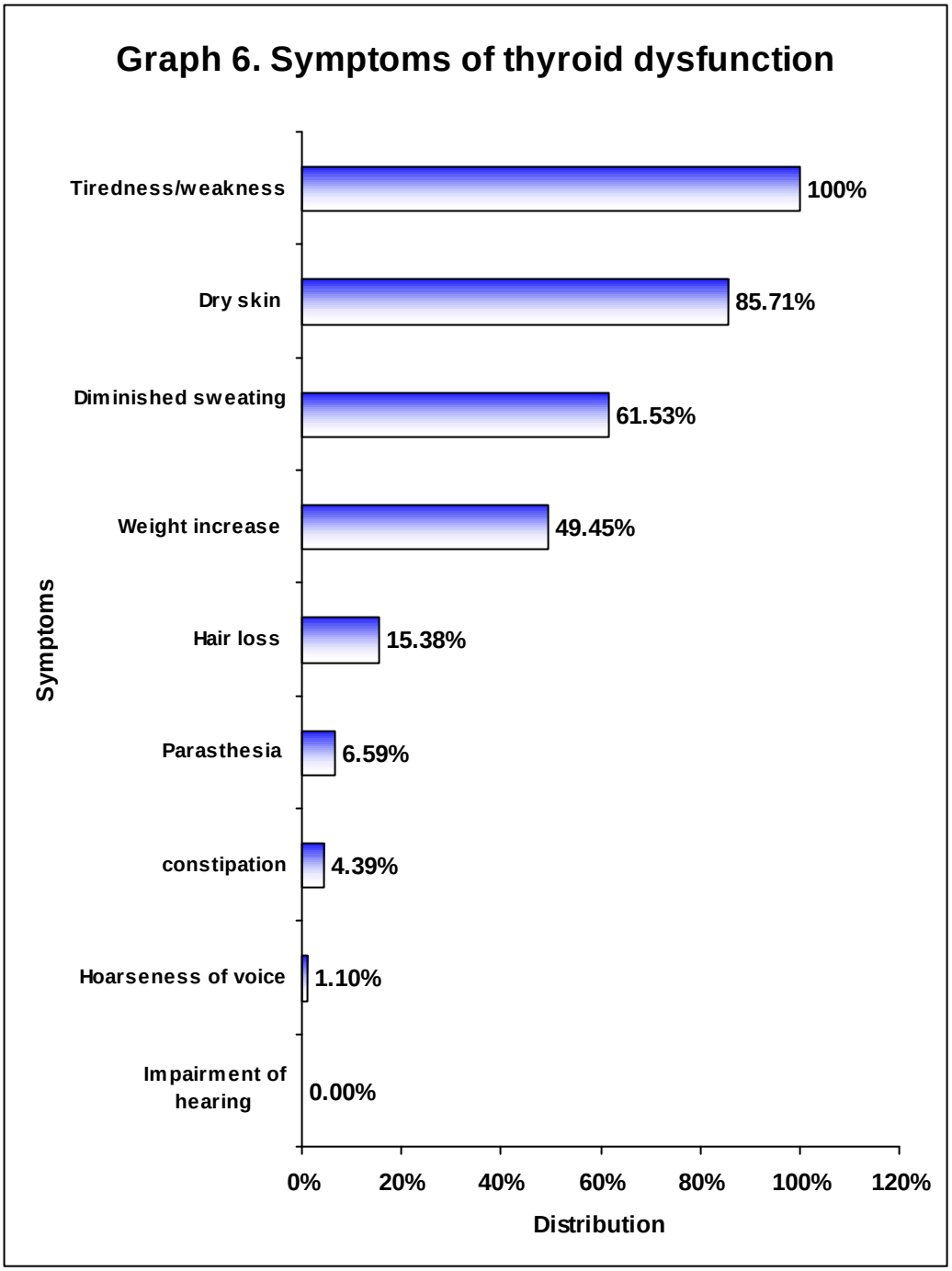
Duration (Months)	Patients(n=91)	
	Number (n)	Percent (%)
Upto 12	14	63.64
13 to 24	6	27.27
> 24	2	9.09
Total	**22**	**100.00**



22 patients were on maintenance hemodialysis. Out of which 14 (63.64%) patients were on hemodialysis upto 12 months, 6 (27.27%) patients were for a period between 13 to 24 months and 2 (9.09%) patients were for a period of >24 months.

Table 6. Symptoms of Thyroid dysfunction

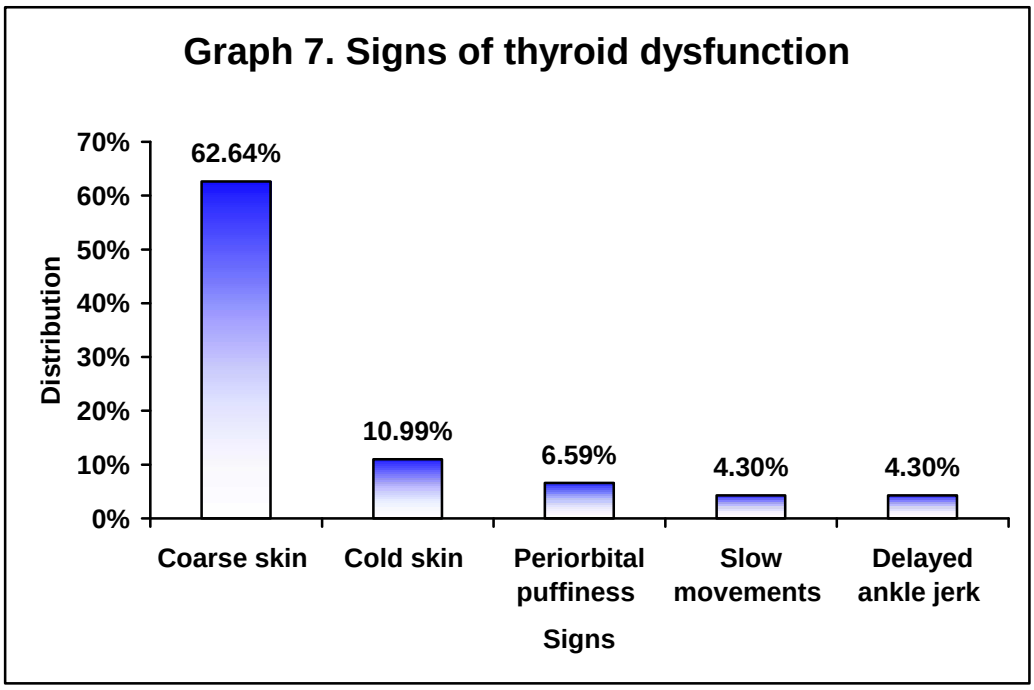
Symptoms	Patients(n=91)	
	Number (n)	**Percent (%)**
Tiredness / weakness	91	100.00
Dry skin	78	85.71
Diminished sweating	56	61.53
Weight increase	45	49.45
Hair loss	14	15.38
Parasthesia	6	6.59
Constipation	4	4.39
Hoarseness of voice	1	1.10
Impairment of hearing	0	0.00



In all the 91 (100%) patients the commonest symptom was tiredness and weakness. The next common symptom was dry skin in 78 (85.71%), diminished sweating in 56 (61.53%), weight increase in 45 (49.45%), hair loss in 14(15.38%), parasthesia in 6 (6.59%), constipation in 4 (4.39%) and hoarseness of voice in 1 (1.10%). However no patients reported impairment of hearing.

Table 7. Signs of thyroid dysfunction

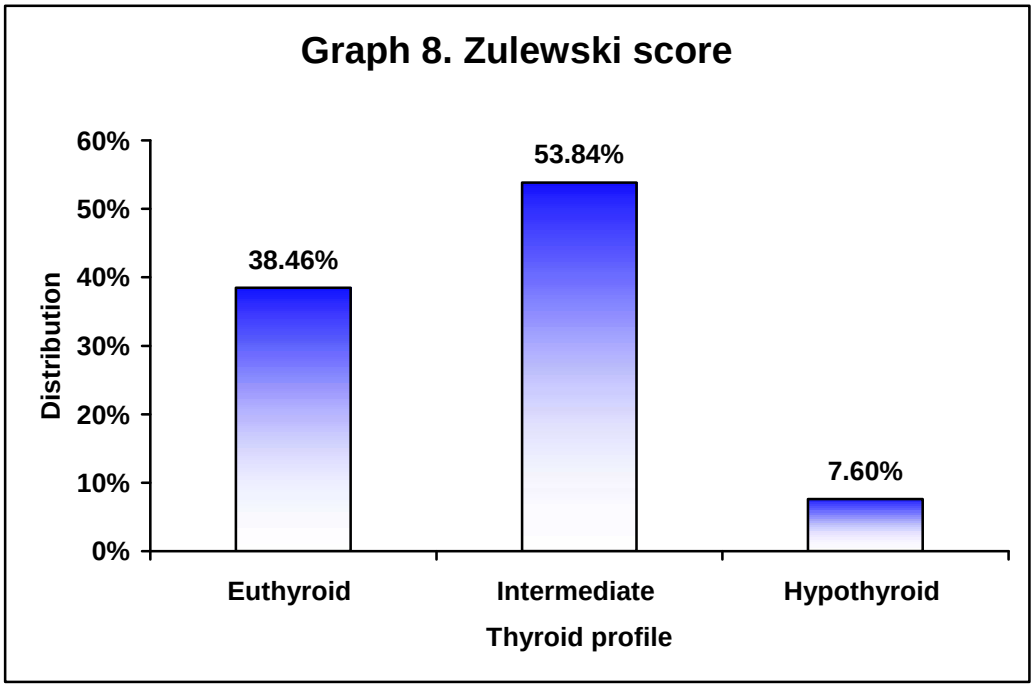
Signs	Patients (n=91)	
	Number (n)	**Percent (%)**
Coarse skin	57	62.64
Cold skin	10	10.99
Periorbital puffiness	6	6.59
Slow movements	4	4.30
Delayed ankle jerk	4	4.30



In the present study, the commonest sign of thyroid dysfunction was coarse skin (62.64%). Cold skin was observed in 10 (10.99%) patients, periorbital puffiness of face in 6 (6.59%), delayed ankle jerk in 4 (4.3%) patients. and slow movements in 4 (4.3%)

Table 8. Zulewski score

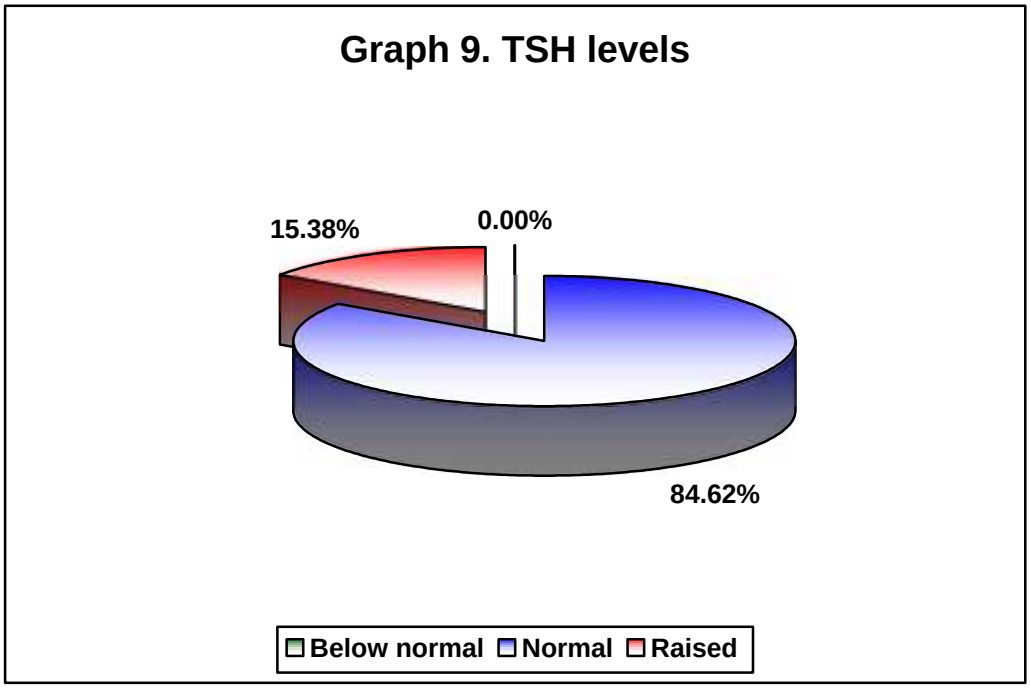
Zulewski score	Patients(n=91)	
	Number (n)	**Percent (%)**
0 to 2 (Euthyroid)	35	38.46
3 to 5 (Intermediate)	49	53.84
>5 (Hypothyroid)	7	7.6
Total	**91**	**100.00**



Using the zulewski score 35 (38.46%) patients had a score between 0 to 2 (euthyroid state), 50 (53.84%) had a score between 03 to 05 (intermediate) and 7 (7.60%) had a score of above 5 (hypothyroid state). No patients were found to have hyperyhyroidism.

Table 9. TSH levels

TSH findings	Patients(n=91)	
	Number (n)	**Percent (%)**
Below normal (<0.49)	0	0.00
Normal (0.49-4.67)	77	84.62
Raised(>4.67)	14	15.38.
Total	**91**	**100.00**



Out of the 91 patients, most of the patients 77 (84.62%) had TSH within normal limits, 14 (15.38%) patients had raised TSH and none of the patients had TSH below normal limits.

Table 10. Free T3 levels

FT3 findings	Patients(n=91)	
	Number (n)	**Percent (%)**
Below normal (<1.452)	6	6.59
Normal (1.45 – 3.48)	85	93.40
Raised (>3.48)	0	0.00
Total	**91**	**100.00**

Out of the 91 patients of chronic kidney disease, most of the patients 85 (93.40%) had FT3 levels within normal limits, 6 (6.59%) patients had below normal FT3 and none of the patients had raised FT3

Table 11. Free T4 levels

FT4 findings	Distribution (n=91)	
	Number (n)	**Percent (%)**
Below normal (<0.7)	5	5.49
Normal (0.7 – 1.85)	86	94.51
Raised (>1.85)	0	0.00
Total	**91**	**100.00**

Out of the 91 patients, most of the patients 86(94.51%) had FT4 within normal limits, 5 (5.49%) patients had below normal FT4 and none of the patients had raised FT4

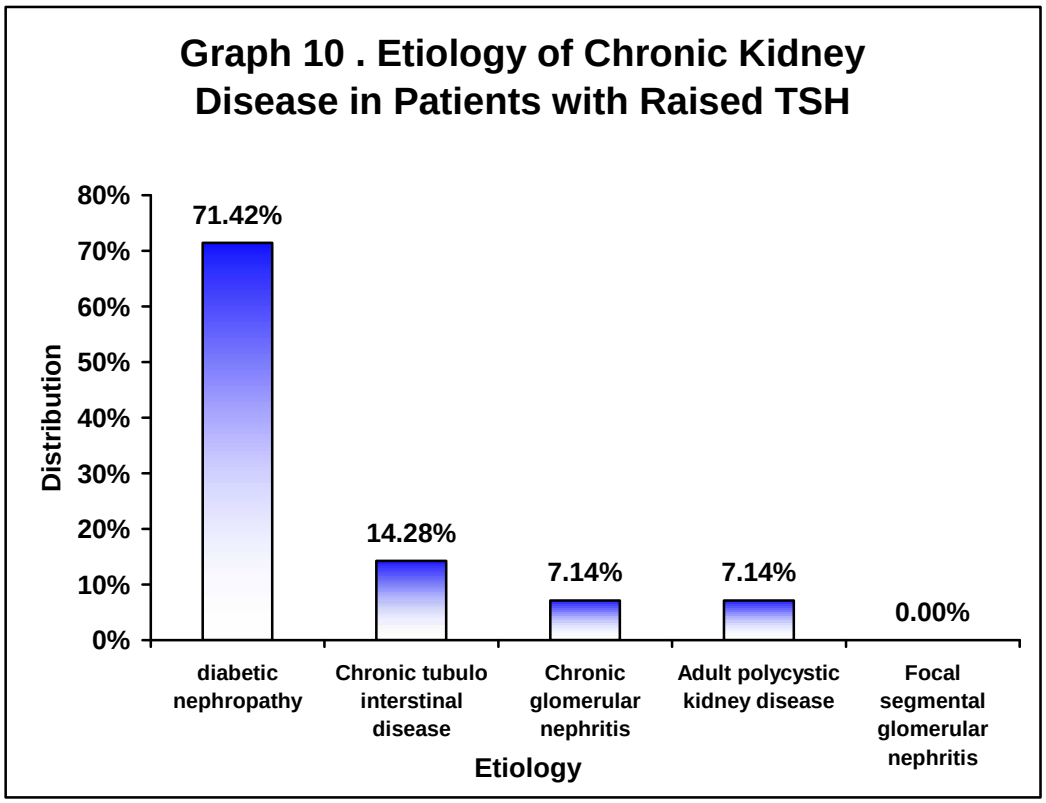
Table 12. Comparison of TSH , FT3 and FT4

FT3 and FT4 below normal	Raised TSH		Normal TSH		Total	
	No	**%**	**No**	**%**	**No**	**%**
FT3	6	6.59	0	00.00	6	6.59
FT4	5	5.49	0	00.00	5	5.49
FT3 and FT4	5	5.49	0	00.00	5	5.49

Out of the 6 (6.59%) patients with below normal FT3 all had raised TSH. Similarly out of the 5(5.49%) patients with raised FT4 all had raised TSH. Also 5 (5.49%) patients had both below normal FT3 and FT4, here too all 5 patients had raised TSH.

Table 13. Etiology of Chronic Kidney Disease in Patients with Raised TSH

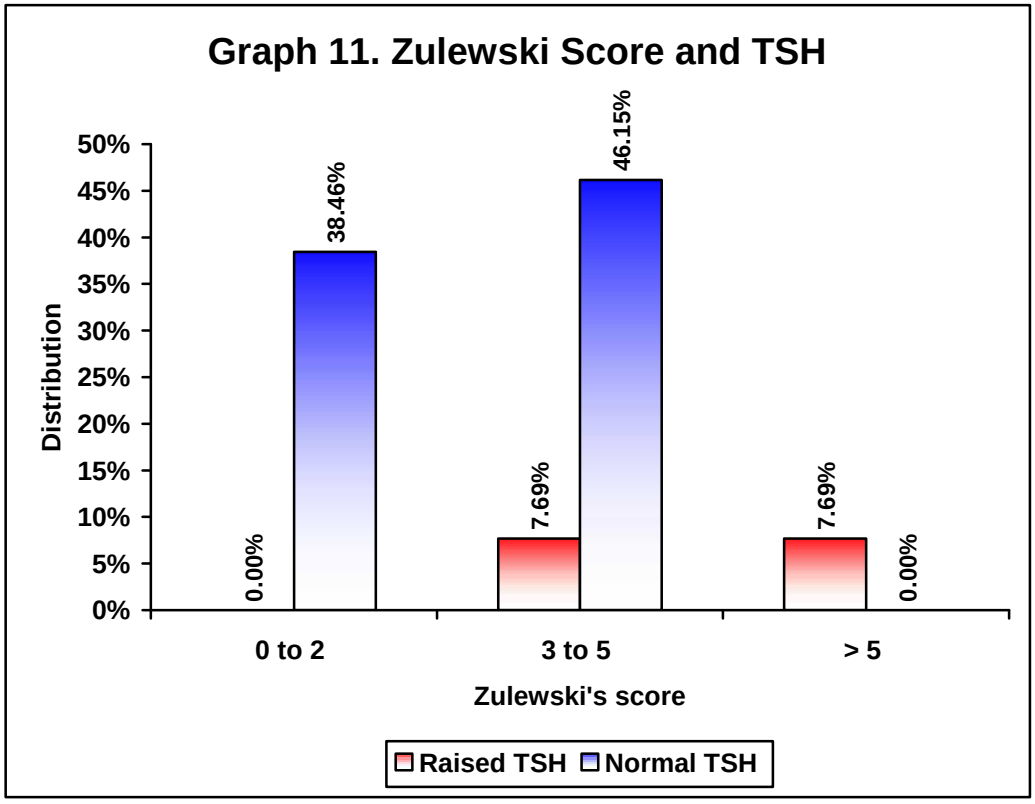
Dysfunction	Patients (n=14)	
	Number (n)	Percent (%)
Diabetic nephropathy	10	71.42
Chronic tubulo interstitial disease	2	14.28
Chronic glomerular nephritis	1	7.14
Adult polycystic kidney disease	1	7.14
Focal segmental glomerular nephritis	0	00.00
Total	14	100



In the 14 patients with raised TSH, diabetic nephropathy was the cause of chronic kidney diease in 10 (71.42%) patients, chronic tubulointertitinal disease in 2(14.28%) patients, chronic glomerular nephritis in 1 (7.14%) patient and adult polycystic kidney disease in 1 (7.14%) patient.

Table 14. Zulewski Score and TSH

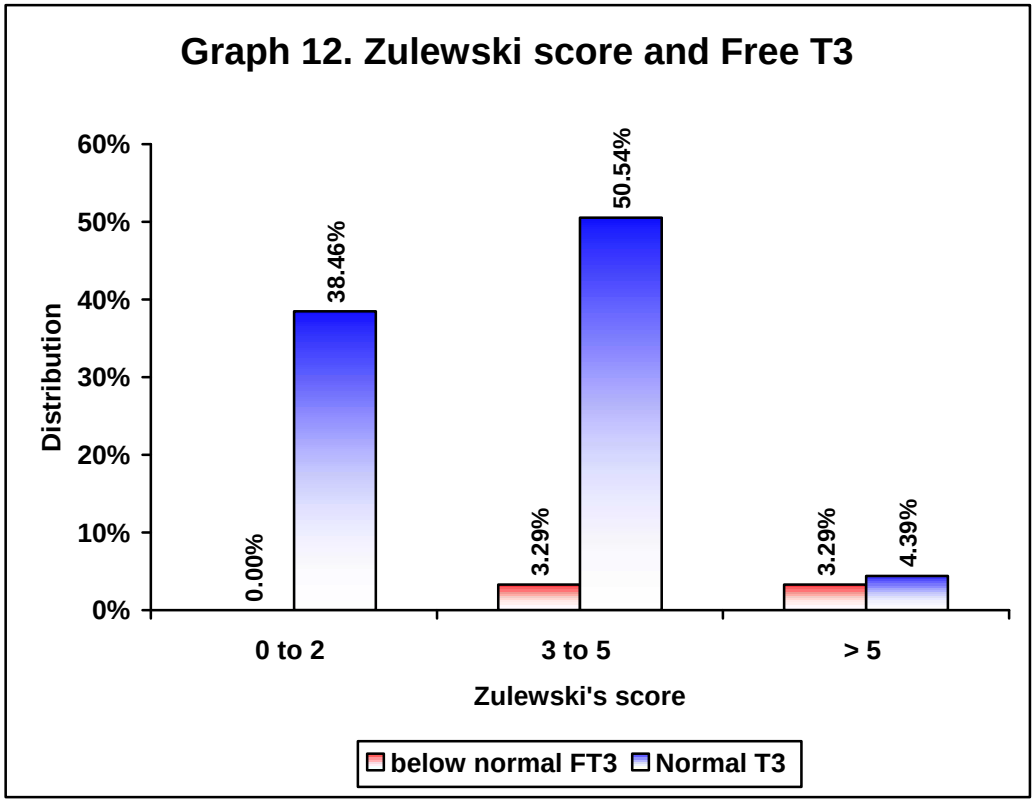
Zulewski score	Raised TSH (n=14)		Normal TSH (n=77)		Total (n=91)	
	No	%	No	%	No	%
0-2	0	0.00	35	38.46	35	38.46
3-5	7	7.69	42	46.15	49	53.84
>5	7	7.69	0	00.00	7	7.69



Out of the 91 patients, among 35(38.46%) patients with a score of 0-2, none had raised TSH. Among the 49 (53.84%) patients with a score of 3-5, 7 (7.69%) patients had raised TSH. In 7 (7.69%) patients with a score of >5, all patients had raised TSH.

Table 15. Zulewski score and Free T3

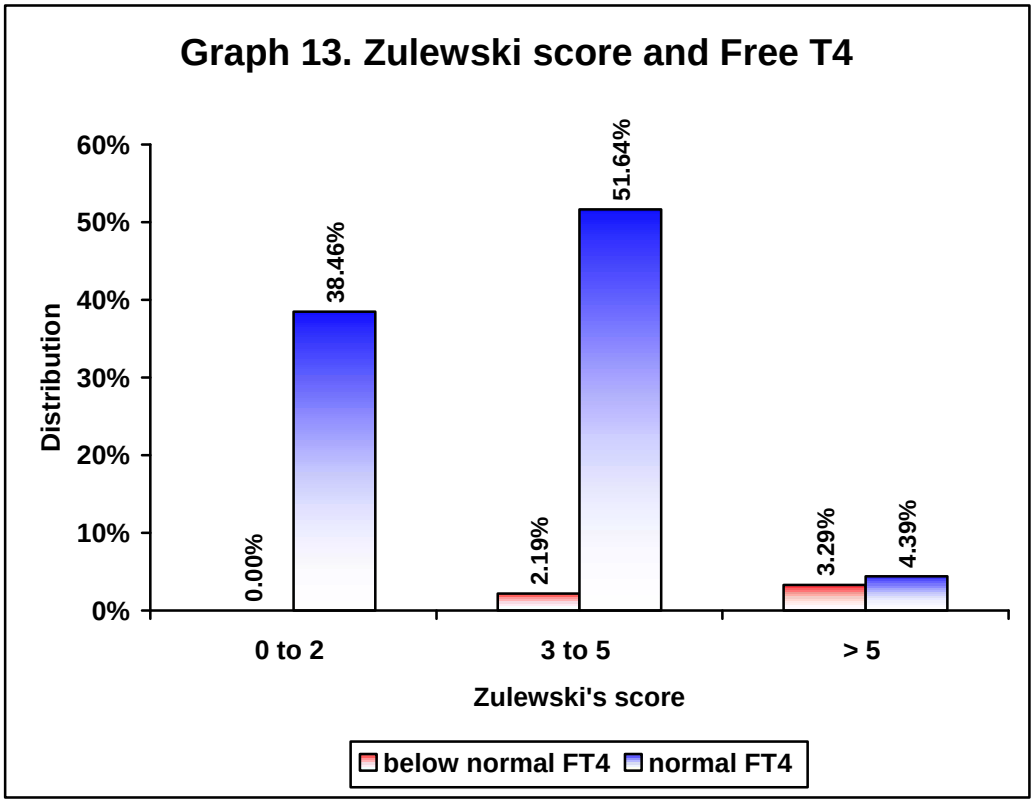
Zulewski score	Below normal FT3 (n=6)		Normal FT3 (n=85)		Total (n=91)	
	No	%	No	%	No	%
0-2	0	0.0	35	38.46	35	38.46
3-5	3	3.29	46	50.54	49	53.84
>5	3	3.29	4	4.39	7	7.69



Out of the 91 patients in patients with a score of 0-2,none had below normal FT3. In patients with a score of 3-5, 3(3.29%) patients had below normal FT3. In patients with a score of >5, 3(3.29%) patients had below normal FT3

Table 16. Zulewski score and Free T4

Zulewski score	Below normal FT4 (n=6)		Normal FT4 (n=85)		Total (n=91)	
	No	%	No	%	No	%
0-2	0	0.0	35	38.46	35	38.46
3-5	2	2.19	47	51.64	49	53.84
>5	3	3.29	4	4.39	7	7.69



Out of the 91 patients in patients with a score of 0-2, none had below normal FT4. In patients with a score of 3-5, 2(2.19%) patients had below normal FT4. In patients with a score of >5, 3(3.29%) patients had below normal FT4

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Table 17. CKD stage and raised TSH

Stages	Patients with raised TSH (n=14)	
	Number	**Percent**
I	0	0.00
II	0	0.00
III	0	0.00
IV	2	14.29
V	12	85.71
Total	**14**	**100.00**

In patients with stage I, II, III none had raised TSH. In patients with stage IV, 2 (14.29%) patient had raised TSH and in stage V, 12 (85.71%) patients had raised TSH.

Table 18. Stage of CKD, Zulewski score and TSH

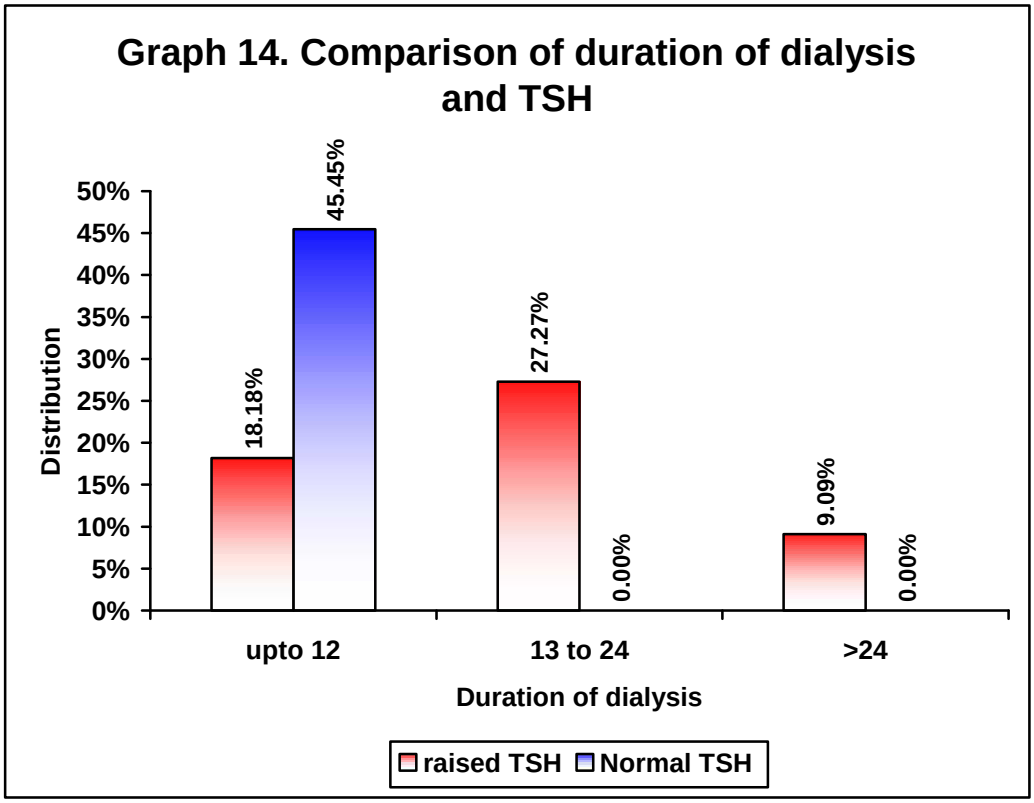
Stage of CKD	Zulewski score	Raised TSH (n=14)		Normal TSH (n=77)	
		Number	**Percent**	**Number**	**Percent**
I	0-2	0	0.00	0	0.00
	3-5	0	0.00	0	0.00
	>5	0	0.00	0	0.00
	Total	0	0.00	0	0.00
II	0-2	0	0.00	0	0.00
	3-5	0	0.00	0	0.00
	>5	0	0.00	0	0.00
	Total	0	0.00	0	0.00
III (n=10)	0-2	0	0.00	5	6.49
	3-5	0	0.00	5	6.49
	>5	0	0.00	0	0.00
	Total	0	0.00	10	12.98
IV (n=42)	0-2	0	0.00	15	19.48
	3-5	1	7.14	25	32.46
	>5	1	7.14	0	0.00
	Total	2	14.28	40	51.94
V (n=39)	0-2	0	0.00	15	19.48
	3-5	6	42.85	12	15.58
	>5	6	42.85	0	0.00
	Total	12	85.71	27	35.06
Total		14	100	77	100

There were no patients in stage I and II in our study. In the patients with stage III none of the patients had either a score of greater then 5 nor did any

patient had raised TSH levels. Among patients with stage IV, 2 (14.28%) had raised TSH levels of which, 1 (7.14%) had a score of between 3 to 5 and 1 (7.14%) had a score greater than 5. In those with stage V, 12 (85.71%) had raised TSH levels. Among these 6 (42.85%) patients had a score between 3 to 5 and 6 (42.85%) had a score more than 5.

Table 19. Comparison of duration of dialysis and TSH

Duration (months)	Raised TSH (n=12)		Normal TSH (n=10)		Total (n=22)	
	No	%	No	%	No	%
Upto 12	4	18.18	10	45.45	14	63.64
13 to 24	6	27.27	0	00.00	6	27.27
>24	2	9.09	0	0	2	9.09
Total	12	54.54	10	45.45	22	100



Out of the 22 patients on hemodialysis, 10 (45.45%) patients had normal TSH. 12 (54.54%) patients had raised TSH. Among 14 (63.64%) patients with diaslysis upto 12 months, 4 (18.18%) patients had raised TSH. Among 6 (27.27%) patients with dialysis for a period between 13 to 24 months, all had raised TSH. Also among 2 (9.09%) patients with dialysis for a period greater 24 months, all had raised TSH.

Table 20. Comparison of duration of dialysis, Zulewski score and TSH

Duration	Zulewski score	Raised TSH (n=12)		Normal TSH (10)		Total (22)	
		No	%	No	%	No	%
Upto 12	0-2	0	0.00	4	0.00	4	18.18
	3-5	3	13.63	6	27.27	9	40.90
	>5	1	0.00	0	0.00	1	4.54
	Total	4	0.00	10	0.00	14	63.64
13 to 24	0-2	0	0.00	0	0.00	0	0.00
	3-5	2	9.09	0	0.00	2	9.09
	>5	4	18.18	0	0.00	4	18.18
	Total	6	0.00	0	0.00	6	27.27
>24	0-2	0	0.00	0	6.49	0	00.00
	3-5	0	0.00	0	6.49	0	00.00
	>5	2	0.00	0	0.00	2	9.09
	Total	2	0.00	0	12.98	2	9.09

Out of the 22 patients on hemodialysis, 10 (45.45%) patients had normal TSH. 12 (54.54%) patients had raised TSH. Among 14 (63.64%) patients with diaslysis upto 12 months, 4 (18.18%) patients had raised TSH out of which only 1 (4.54%) patient had a score of greater than 5. Among 6 (27.27%) patients with dialysis for a period between 13 to 24 months, all had raised TSH out of which 2 (9.09%) patients had a score of 3 to 5 and 4 (18.18%) patients had a score of greater than 5. Also among 2 (9.09%) patients with dialysis for a period greater 24 months, all had raised TSH and a score of greater than 5.

Chapter 6

Discussion

DISCUSSION

The interplay between thyroid and the kidney in each other's functions is known for many years.[87] Thyroid dysfunction affects renal physiology and development, whereas kidney disease could result in thyroid dysfunction. Disorders of the thyroid and kidney may co-exist with common etiological factors. In addition, treatment strategies of one disease may affect those of the other organ.

Thyroid hormones influence protein synthesis and cell growth. Thyroid hormone status affects the functioning renal mass (measured as the kidney to body mass ratio), with hypothyroidism reducing this ratio and hyperthyroidism increasing it.[88] However, severe hyperthyroidism results in protein breakdown and eventual renal atrophy. In addition, children with congenital hypothyroidism have a high incidence of congenital renal anomalies.[89]

Thyroid hormones also influence the neonatal renal function. Perinatal thyroid hormone status affects the mitochondrial energy metabolism enzymes in the cells of the proximal convoluted tubules (PCT). There is an increase in the activity of the Na – P co-transporter (NaPi), Na – H exchanger (NHE), as well as the Na/K ATPase in the PCT. Thus, thyroid hormones play an important role in renal development and early renal function.[90]

Kidney and thyroid function and dysfunction are interrelated through several mechanisms. It is not difficult for physicians to diagnose and treat patients with overt hypothyroidism or hyperthyroidism presenting significant biochemical derangements and clinical symptoms. In the spectrum of subclinical

thyroid dysfunction and nonthyroidal illness syndrome (i.e., alterations in thyroid hormones without any underlying intrinsic thyroid disorder), however, it is not always an easy task. The interpretation of thyroid functions in patients with CKD or ESRD is even more complicated by the declination in GFR, the difference in dialysis modalities, and comorbidities.[91]

Previous studies[25-28] have only stressed on the levels of thyroid hormones in chronic renal failure, but have not explored clinical and biochemical profiles of thyroid abnormalities together. Hence, the present study was undertaken to assess the clinical and biochemical profile of thyroid abnormalities in chronic kidney disease.

The present cross-sectional study was carried in Department of Medicine /Nephrology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 91 patients with chronic kidney disease were included in the study based on the definition of The Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation.

In our study majority of patients 58 (63.74%) were in the age group of 46 to 60. In a similar study[92] done in India most of the patients were in the age group of 38 to 64 years. In a similar study of patients done in Italy majority of patients were in the age group of 40 to 74 years.[26]

In our study we found majority of patients with CKD were males (a male to female ratio of 1.84:1). In a similar study[93] done in Iraq also observed that majority of patients with CKD were male a (male to female ratio of 1.2:1). In a similar Italian study,[26] equal number of patients were found in both sexes.

In our study we found majority of patients with CKD were males (a male to female ratio of 1.84:1) In a similar study[93] done in Iraq also observed that majority of patients with CKD were male a (male to female ratio of 1.2:1). In a similar Italian study[26] equal number of patients were found in both sexes.

In our study the most common etiology of chronic kidney disease was diabetic nephropathy 46 (50.55%), chronic tubulointerstitial disease in 39 (42.86%), chronic glomerulonephritis in 6 (6.59%), adult polycystic kidney disease in (2.20%) and focal segmental glomerular nephritis in 1 (1.10%). In a similar study[92] done in India the commonest etiology of chronic kidney disease was Benign nephrosclerosis in 14 (46.67%), Chronic glomerulonephritis in 9 (30%), Chronic pyelonephritis in 4(13.33%), Obstructive uropathy 2 (6.67%) and Polycystic kidney disease in 1(3.33%). In another study[94] done in Alta the etiology of chronic kidney disease was glomerulonephritis in 38(70.37%), polycystic kidney in 6(11.11%), obstructive pyelonephritis in 2(3.70%), phenacetin nephritis in 2(3.70%), lupus nephritis in 2(3.70%) and other disease in 4(7.40%).

In our study Majority of patients were in stage IV CKD 42(46.158%), 39 (42.86%) patients in stage V and 10.99% patients were in stage III CKD. No patients were in stage II or stage I chronic kidney disease. In a similar study[26] done in Italian population majority of patients were in stage II CKD (57.8%) and (16.0%) were in stage III CKD. In another study[24] done in Korea majority of patients 1042 (45.62%) patients were in stage I, 1025 (44.87%) patients were in stage II, 183 (8.01%) patients were in stage III, 20(0.8%) patients were in stage IV and 14 (0.61%) patients were in stage V.

In our study 22 patients were on maintenance hemodialysis. Out of which 14(63.64%) patients were on hemodialysis for upto 12 months, 6(27.27%) patients were on hemodialysis for a period between 13 to 24 months and 2 (9.09%) patients were on hemodialysis for a period of >24 months. 17 patients with stage V CKD were either on conservative line of treatment or were not on maintenance haemodialysis. In another study[94] done in Alta 31 (57.40%) patients were on hemodialysis fo upto 12 months, 8 (14.81%) patients were on hemodialysis for a period between 13 to 24 months and 13 (24.07%) patients were on hemodialysis for a period of >24 months.

In our study of 91(100%) patients the commonest symptom was tiredness and weakness. The next common symptoms was dry skin in 78(85.71%), diminished sweating in 56 (61.53%), weight increase in 45 (49.45%), hair loss in 14 (15.38%), parasthesia in 6 (6.59%), constipation in 4 (4.39%) and hoarseness of voice in 1(1.10%). However no patients reported impairment of hearing. The commonest sign of thyroid dysfunction was coarse skin (62.64%). Cold skin was observed in 10 (10.99%) patients, periorbital puffiness of face in 6 (6.59%), delayed ankle jerk in 4 (4.3%) patients. and slow movements in 4 (4.3%).

Studies reporting clinical profile of thyroid abnormalities in chronic kidney disease are few. In a study[92] done in Indian population The Billewicz score[83] was used. 2 (6.66%) patients of chronic renal failure had clinical sign symptom index scores suggestive of hypothyroidism. One patient had hypothyroidism index score of +44 and another patient had +32. The Billewicz score[83] utilizes 8 symptoms and 6 signs to assess the thyroid status, and diagnose hypothyroidism.

A new scoring system was proposed by Zulewski and colleugues[82] from Switzerland set out to reevaluate the classical signs and symptoms of hypothyroidism in the light of modern laboratory tests. The 14 symptoms and signs used in the Billewicz score were evaluated. Two features, i.e., pulse rate and cold intolerance, had positive and negative predictive values below 70%, and were excluded.

The most sensitive features were delayed ART (77%) and dry skin (76%), while the most specific were slow movements (98.7%) and diminished hearing (97.5%). A positive predictive value was highest for slow movements (96.5%) and puffiness (94.2%). On the other hand, a negative predictive value was highest for ART (80.3%) and dry skin (72.7%).[82]

As women aged > 55 years also complained of "hypothyroid" symptoms, especially constipation and dry skin, an age-correcting factor was added. One point was added to the sum of symptoms and signs in younger women (aged < 55 years). A score >5 points defined hypothyroidism, while a score of 0-2 points defined euthyroidism. Sixty two percent of all overt hypothyroidism was detected by the new score (as compared to 42% with the Billewicz score).[82]

In our study, using the zulewski score 35 (38.46%) patients and a score between 0 to 2 (euthyroid state), 49 (53.84%) had a score between 03 to 05 (intermediate) and 7 (7.60%) had a score of above 5 (hypothyroid state). No patients were found to have hyperyhyroidism.

Out of the 91 patients ,most of the patients 77(84.62%) had TSH within normal limits, 14 (15.38%) patients had raised TSH and none of the patients had

TSH below normal limits. 6 (6.59%) patients had below normal FT3. 5 (5.49%) patients had below normal FT4 .none of the patients had a FT3 and FT4 above the normal limits.

In a similar study[95] done in Argentina 9 (100%) had low free T4 values 1 (11.11%) had basal TSH levels above the normal range.

In another study[96] it was shown that that in patients on dialysis, mean serum thyroxine and triiodothyronine levels are lower than normal. Patients with chronic renal failure not on dialysis, have mean serum thyroxine levels similar to normal subjects and low mean serum triiodothyronine levels.

In another study[97] from Saudi Arabia significant increase in the serum thyroid stimulating hormone (TSH) level and a significant decrease in serum Triiodo thyronine (T3) levels in patients with CRF as compared to the control ($p<0.001$). No significant difference was found between patients with CRF and controls as regards serum thyroxine (T4) and serum free T4 (FT4) ($p > 0.2$).

In our study out of the 6 (6.59%) patients with below normal FT3 all had raised TSH. Similarly out of the 5 (5.49%) patients with raised FT4 all had raised TSH. Also 5(5.49%) patients had both below normal FT3 and FT4, here too all 5 patients had rasided TSH. In a case control study done in Ludhiana India the mean values of both serum T3 & T4 were significantly low. On studying FT4 concentration in patients of chronic kidney disease, 10 (33%) had low FT4 concentrations compared to none of the controls, 13 (43.33%) patients had high serum TSH levels. 7 (53.84%) of these 13 patients had very low serum T3

concentrations which can be explained by the normal negative feedback regulation of the pituitary thyroid axis.[92]

In another study[96] reported normal levels of serum TSH in patients of CRF inspite of low serum T3 levels. They demonstrated abnormality in the hypophyseal mechanism of TSH Release in uraemic patients as the TSH response to the administration of thyrotropin releasing hormone (TRH) was blunted.

In another study,[98] 127 patients of CKD, who had low T3, T4, FT4 but had high TSH levels suggesting maintenance of pituitary-thyroid axis. The likely explanations for low levels of both T3 and T4 could be defective release in response to TSH.

In our study out of the 14 patients with raised TSH, chronic kidney disease was caused by diabetic nephropathy in 10(71.42%) patients, chronic tubulointertitinal disease in 2(14.28%) patients, chronic glomerular nephritis in 1 (7.14%) patient and adult polycystic kidney disease in 1 (7.14%) patients. Previous studies[99,100] have reported positive association of diabetes with thyroid abnormalities. Hence it is difficult to conclude whether these thyroid abnormalities seen in the present study were due to diabetes per se or due to diabetic nephropathy.

Out of the 91 patients, among 35(37.46%) patients with a score of 0-2, none had raised TSH. Among the 49 (53.84%) patients with a score of 3-5, 7 (7.69%) patients had raised TSH. In 7 (7.69%) patients with a score of >5, all patients had raised TSH. Out of the 14 (15.38%) patients with raised TSH, 7

(7.69%) patients had clinical hypothyroidism and 7 (7.69%) patients had suclinical hypothyroidism.

Out of the 91 patients in patients with a score of 0-2, none had below normal FT3. In patients with a score of 3-5, 3(3.29%) patients had below normal FT3. In patients with a score of >5, 3(3.29%) patients had below normal FT3. Out of the 6(6.54%) patients with below normal FT3, 3(3.29%) patients had clinical hypothyroidism.

Out of the 91 patients in patients with a score of 0-2, none had below normal FT4. In patients with a score of 3-5, 2 (2.19%) patients had below normal FT4. In patients with a score of >5, 3(3.29%) patients had below normal FT4. Out of the 5 (3.57%) patients with below normal FT4, 3 (3.29%) patients had clinical hypothyroidism.

Thus out of the 91 patients, 7 (7.69%) patients with raised TSH had clinical hypothyroidism whereas 3 (3.29%) patients with below normal FT3 and 3 (3.29%) patients with below normal FT4 had clinical hypothyroidism. Thereby suggesting that clinical hypothyroidism is more commonly associated with TSH abnormality.

In patients with stage I, II, III none had raised TSH. In patients with stage IV, 2 (14.29%) patient had raised TSH and in stage V, 12 (85.71%) patients had raised TSH. In a similar study done in Korea of 2284 patients low T3 levels were found in patients with chronic kidney disease. 85 (3.7%) patients in stage I, 112 (4.9%) patients in stage II, 38 (1.6%) patients in stage III, 12 (0.5%) patients in stage IV and 11 (0.4%) patients with stage V were found to have low T3 levels.

There were no patients in stage I and II in our study. In the patients with stage III none of the patients had either a score of greater than 5 nor did any patient had raised TSH levels. Among patients with stage IV, 2 (14.28%) had raised TSH levels of which 1 (7.14%) had a score of between 3 to 5 and 1(7.14%) had a score greater than 5. In those with stage V, 12(85.71%) had raised TSH levels. Among these 6(42.85%) patients had a score between 3 to 5 and 6 (42.85%) had a score more than 5. Thus we can conclude that as the chronic kidney disease worsens the prevalence of clinical hypothyroidism also increases.

Out of the 22 patients on hemodialysis, 10 (45.45%) patients had normal TSH. 12(54.54%) patients had raised TSH. Among 14 (63.64%) patients with dialysis upto 12 months, 4(18.18%) patients had raised TSH. Among 6 (27.27%) patients with dialysis for a period between 13 to 24 months, all had raised TSH. Also among 2 (9.09%) patients with dialysis for a period greater 24 months, all had raised TSH. Thus out of the 14 patients with raised TSH, 12 patients were on hemodialysis. Thus biochemical hypothyroidism was more prevalent in patients with hemodialysis.

Out of the 22 patients on hemodialysis, 10 (45.45%) patients had normal TSH. 12(54.54%) patients had raised TSH. Among 14 (63.64%) patients with dialysis upto 12 months, 4 (18.18%) patients had raised TSH out of which only 1 (4.54%) patient had a score of greater than 5. Among 6 (27.27%) patients with dialysis for a period between 13 to 24 months, all had raised TSH out of which 2 (9.09%) patients had a score of 3 to 5 and 4(18.18%) patients had a score of greater than 5. Also among 2 (9.09%) patients with dialysis for a period greater 24 months, all had raised TSH and a score of greater than 5. Thus as the duration

of dialysis increases the prevalence of clinical hypothyroidism also increases. In a similar study[95] done in Alta the half relaxation time of the ankle jerk was used. In both the patients with dialysis and patients not on dialysis no significant difference was noted in terms of the half relaxation time in both groups.

Chapter 7

Conclusion

CONCLUSION

The present study showed tiredness and weakness as the commonest symptom of thyroid dysfunction followed by dry skin in patients with chronic kidney disease and the most commonest sign was coarse skin. Based on the Zulewski's score for the assessment of hypothyroidism considering clinical signs and symptoms 7.69% patients were diagnosed to have clinical hypothyroidism.

Of the 91 patients with chronic kidney disease the biochemical profile considering FT3, FT4 and TSH levels 14 (15.38%) patients had thyroid abnormalities. Among the 14 patients with thyroid abnormalities, 7 (7.69%) patients each had hypothyroidism and subclinical hypothyroidism. None of the patients had biochemical hyperthyroidism.

Chapter 8

Summary

SUMMARY

Chronic kidney disease (CKD) is increasingly recognized as a major public health problem. The kidney normally plays an important role in the metabolism, degradation, and excretion of several thyroid hormones. It is not surprising therefore that impairment in kidney function leads to disturbed thyroid physiology. The present study was undertaken to assess the clinical and biochemical profile of thyroid abnormalities in chronic kidney disease.

The present cross-sectional study was carried in Department of Medicine /Nephrology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 91 patients with chronic kidney disease were included in the study based on the definition of The Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation.

Out of 91 patients 59(64.84%) were males and 32 patients (35.16%) were females, accounting a ratio of male to female was 1.84:1. Majority of patients 58(63.74%) were in the age group of 46 to 60 years. The commonest cause of chronic kidney disease in our study was diabetic nephropathy 46 (50.55%). Majority of patients were in stage IV CKD 42 (46.158%). In all the 91 (100%) patients the commonest symptom was tiredness and weakness. The next common symptoms was dry skin in 78(85.71%). In the present study, the commonest sign of thyroid dysfunction was coarse skin (62.64%). Raised TSH was noted in 14 (15.38%) patients, 5 (5.49%) had below normal FT4 and 6 (6.59%) had below normal FT3.

Based on the Zulewski's score for the assessment of hypothyroidism considering clinical signs and symptoms 7.69% patients were diagnosed to have clinical hypothyroidism. Of the 91 patients with chronic kidney disease the biochemical profile considering FT3, FT4 and TSH levels 14 (15.38%) patients had thyroid abnormalities of which, 7 (7.69%) each had hypothyroidism and subclinical hypothyroidism.

Chapter 9

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Annexures

Annexure I

ANNEXURE I – CONSENT FORM

"STUDY OF CLINICAL AND BIOCHEMICAL PROFILE OF THYROID ABNORMALITIES IN CHRONIC KIDNEY DISEASE WITH REDUCED GLOMERULAR FILTRATION RATE–A ONE YEAR CROSS SECTIONAL STUDY AT KLE UNIVERSITY, BELGAUM"

Objective and purpose of the study:

This research is intended to study the CLINICAL AND BIOCHEMICAL PROFILE OF THYROID ABNORMALITIES IN CHRONIC KIDNEY DISEASE. The principal investigator of the study is Dr. ***** ****** under the guidance of Dr. ***** ******. My co-operation will be of great help to patients with chronic renal failure in the future.

Procedure:

If you agree to be part of the research study you will be asked the relevant history and will be subjected to relevant clinical examination and investigations. You will also have to give blood and urine samples for the necessary investigations

Risk and Benefits:

The only risk and possible discomfort you might get is while taking blood from your arm for the investigations. It may cause swelling, pain, redness, bruising or infection (rarely happens) at the site from where the blood is drawn.

Alternatives

Taking part in this study is voluntary. You may choose not to take part in this study, or if you decide to take part now, you can later change your mind and withdraw from the study. Your decision will not change the present or future health care or other services that you receive. The study doctor or sponsor may you're your participation in this study any time. If you choose not to take part in the study you will receive the standard treatment for patients with your condition.

Privacy and Confidentiality

All information collected about you during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify you in this research record. Information from this study may be published but your identity will be confidential in any publication.

Institution / Sponsor's policy

Does not apply to this research

Financial incentives for participation

You will not be paid / offered any gifts /incentives for participating in the study.

Authorization to publish the results

The results of the study would be forwarded to the KLE University, Belgaum as part of requirement towards the completion of MS degree, review and publishing.

If I have any questions about your rights as a participant you may call Principal and Chairman, J.N.M.C Ethical Committee for Human Research phone number **** ******.

Consent Statement

I voluntarily agree to take part in this study by signing below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicates that I have read, or it has been read to me, this entire consent form, and have had all my questions answered.

In case of the queries during study or in future you may contact following person

Principal investigator : Dr. ***** *******

Guide : Dr. ***** *******

Name of the Participant: _____ Signature / Thumb print _____

Name of the Witness _____ Signature _____

Name of the investigator _____ Signature _____

Date: Place:

Annexures

Annexure II

ANNEXURE II – PROFORMA

Case No:

Name: Age/Sex:

IP No. Address:

Occupation: Weight:

Height: Pulse:

Blood Pressure Lying Down

History

History Of Renal Dysfunction:

Diaslysis: Yes _____ No_____

If Yes Type Of Dialysis _____

Frequency _____

No of months Dialysis _____

History Pertaining To Thyroid Dysfunction:

1) Do You Feel Tired And Weak

2) How Does Your Skin Feel

A) Does It Feel Dry

B) Does It Feel Sweaty

3) Do You Have Hair Loss?

4) How Are Your Bowel Habits?

Frequency

5) Weight

A) Have You Gained Weight?

B) Have You Lost Weight?

6) How Is Your Appetite?

7) Are You Breathless?

If Yes Hyha Grade

8) Menstrual History

9) Libido

10) Do You Have Hearing Difficulty

Signs

11) Dry Skin

12) Course Skin

13) Cold Skin

14) Ankle Jerks

15) Puffiness Of Face

16) Hoarseness Of Voice

17)Paresthesia

18) Tremors

Remarks:

Investigations:

- Total Wbc Count
- Esr
- Serum Free T3
- Serum Free T4
- Tsh
- Total Bilirubin
- Total Protiens

- Serum Albumin
- Serum Creatinine
- Serum Urea

MASTER CHART

Serial Number	In / Out patient number	Demo-graphy		History													General Physical examination										Zulewski Score	Investigations				
						Dialysis			Thyroid dysfunction symptoms										BP (mm Hg)		Signs									Thyroid profile		
		Sex	Age (Years)	Renal dysfunction	Stage of CKD	Type	Frequency	Duration (months)	Tired / weak	Diminished sweating	Hoarseness	Parasthesia	Dry skin	Bowel (Constipation)	Impairment of hearing	Weight increase	Hair loss	Weight (Kgs)	Pulse rate (bpm)	Systolic	Diastolic	Slow movements	Delayed ankle jerk	Course skin	Periorbital puffiness	Cold skin		Sr. Creatinine (mg/dL)	eGFR (ml/min)	Free T3	Free T4	TSH
1	447721	M	70	DNP	4	HD	2	24	+	+	-	+	+	+	-	-	+	86	86	180	90	+	+	+	+	+	9	18.4	10.0	0.7	0.5	7.6
2	446230	M	36	CGN	4	-	-	-	+	-	-	-	+	-	-	-	-	62	92	140	90	-	-	-	-	-	1	4.8	18.7	2.3	1.0	2.1
3	439596	M	52	DNP	5	-	-	-	+	-	-	+	-	-	-	-	+	62	82	140	90	-	-	-	-	-	2	8.4	9.0	2.7	0.9	4.3
4	448334	F	60	CTID	5	HD	2	6	+	+	-	+	-	-	-	-	+	68	86	150	90	-	-	+	-	-	4	5.4	12.0	2.4	0.9	4.6
5	451427	M	55	CTID	5	HD	2	24	+	+	-	+	+	-	-	-	+	70	82	130	70	-	-	+	+	+	6	20.1	4.1	3.1	1.5	5.8
6	451557	M	29	CGN	5	HD	2	24	+	+	-	-	+	-	-	-	-	68	82	140	90	-	-	+	-	-	3	16.7	6.3	2.2	0.8	5.7
7	452091	M	26	CGN	4	-	-	-	+	-	-	-	-	-	-	-	-	45	82	160	100	-	-	-	-	-	1	7.8	9.1	3.2	1.6	3.5
8	452341	M	49	DNP	5	HD	2	24	+	+	-	-	+	+	-	+	-	56	82	160	90	-	-	+	-	-	5	19.8	3.6	2.4	0.3	4.8
9	451134	M	79	DNP	4	-	-	-	+	+	-	-	+	-	-	+	-	58	82	140	90	-	-	+	-	-	4	30.0	16.4	2.4	0.9	5.0
10	451090	M	46	CTID	5	HD	2	12	+	+	-	-	+	-	-	-	+	52	80	180	90	-	-	+	+	+	5	7.0	9.7	1.4	0.5	4.4
11	451091	M	46	DNP	5	-	-	-	+	-	-	-	+	-	-	+	-	58	83	150	90	-	-	-	-	-	2	7.0	10.8	2.4	0.9	1.3
12	450265	M	43	DNP	3	-	-	-	+	+	-	-	+	-	-	+	-	56	86	140	90	-	-	+	-	-	4	20.0	37.7	3.4	0.9	3.6
13	450461	M	56	DNP	4	-	-	-	+	+	-	-	+	-	-	-	-	82	88	170	100	-	-	+	-	-	3	4.9	19.5	1.8	1.3	1.6
14	450883	M	64	CTID	4	-	-	-	+	-	-	-	+	-	-	+	-	60	90	150	90	-	-	-	-	-	2	4.1	15.5	3.2	0.9	2.6
15	451277	M	58	CTID	4	-	-	-	+	+	-	-	+	-	-	+	-	55	82	140	90	-	-	+	-	-	4	3.2	19.6	2.6	0.9	2.8
16	451278	M	68	DNP	5	-	-	-	+	+	-	-	+	-	-	+	-	65	75	150	100	-	-	+	-	-	4	4.5	14.4	3.0	0.9	3.5
17	451518	F	69	CTID/DNP	4	-	-	-	+	-	-	-	+	-	-	+	-	48	86	130	90	-	-	-	-	-	2	2.6	18.2	3.2	1.5	3.8
18	451491	M	50	DNP	5	-	-	-	+	+	-	-	+	-	-	+	-	58	82	140	90	-	-	+	-	-	5	5.8	12.5	3.4	1.6	3.2
19	451492	M	57	CTID/DNP	5	HD	2	6	+	+	-	-	+	-	-	-	-	76	68	180	70	-	-	+	-	-	3	17.8	4.9	2.8	1.5	3.6

MASTER CHART

Serial Number	In / Out patient number	Demo-graphy		History														General Physical examination											Zulewski Score	Investigations					
						Dialysis			Thyroid dysfunction symptoms											BP (mm Hg)		Signs									Sr. Creatinine (mg/dL)	eGFR (ml/min)	Thyroid profile		
		Sex	Age (Years)	Renal dysfunction	Stage of CKD	Type	Frequency	Duration (months)	Tired / weak	Diminished sweating	Hoarseness	Parasthesia	Dry skin	Bowel (Constipation)	Impairment of hearing	Weight increase	Hair loss	Weight (Kgs)	Pulse rate (bpm)	Systolic	Diastolic	Slow movements	Delayed ankle jerk	Course skin	Periorbital puffiness	Cold skin				Free T3	Free T4	TSH
20	450355	F	52	CTID	4	-	-	-	+	+	-	-	+	-	-	+	-	59	80	140	90	-	-	+	-	-	5	4.0	18.0	3.0	1.2	4.0
21	461292	F	70	CTID/DNP	5	-	-	-	+	+	-	-	+	-	-	-	+	52	82	160	90	-	-	+	-	-	3	6.2	6.9	3.4	0.9	1.9
22	449866	F	62	CTID	4	-	-	-	+	-	-	-	+	-	-	+	-	62	85	150	100	-	-	-	-	-	2	3.0	19.0	2.5	0.9	0.5
23	440227	F	68	CTID	4	-	-	-	+	-	-	-	+	-	-	-	-	46	68	140	90	-	-	-	-	-	1	2.6	15.0	3.1	0.9	4.2
24	449845	M	67	DNP	4	-	-	-	+	+	-	-	+	-	-	-	-	60	83	140	90	-	-	+	-	-	3	2.1	29.0	3.3	0.9	3.5
25	448334	F	52	DNP	4	-	-	-	+	-	-	-	+	-	-	-	-	62	86	160	90	-	-	-	-	-	1	2.3	28.0	3.0	1.8	3.7
26	450439	M	63	CTID	4	-	-	-	+	+	-	-	+	-	-	+	-	60	80	140	90	-	-	+	-	-	4	3.2	20.1	3.2	0.9	1.5
27	448393	M	48	DNP	5	HD	2	9	+	-	-	-	+	+	-	-	-	58	86	160	80	-	-	-	-	-	2	16.5	4.5	2.0	0.7	4.3
28	449757	M	50	CTID	4	-	-	-	+	+	-	-	+	-	-	-	-	58	80	140	90	-	-	+	-	-	4	3.2	22.7	3.4	1.2	2.5
29	448224	M	58	CTID	5	HD	2	2	+	+	-	-	+	-	-	-	-	60	78	140	90	-	-	+	-	+	4	10.7	6.4	2.4	0.9	5.0
30	450455	M	51	DNP	5	HD	2	18	+	+	-	-	+	-	-	+	-	55	80	160	90	-	-	+	-	-	4	5.3	12.8	2.3	0.9	4.8
31	447834	F	60	CTID	4	-	-	-	+	+	-	-	+	-	-	-	-	58	86	174	80	-	-	+	-	-	3	2.8	19.6	3.2	1.3	3.2
32	445724	M	52	DNP	5	HD	2	30	+	+	-	-	+	+	-	+	+	58	80	150	100	+	+	+	+	+	9	8.3	3.8	0.5	1.0	6.5
33	448381	F	50	DNP	4	-	-	-	+	-	-	-	+	-	-	-	-	60	72	160	90	-	-	-	-	-	2	2.6	28.9	3.1	1.5	2.7
34	449767	F	56	CTID	4	-	-	-	+	+	-	-	+	-	-	-	-	57	86	150	90	-	-	+	-	-	3	3.0	18.8	3.2	1.8	3.8
35	447759	M	58	DNP	5	-	-	-	+	-	-	-	+	-	-	-	-	60	68	140	90	-	-	-	-	-	1	4.8	14.2	3.1	1.1	3.1
36	448775	F	55	CTID	4	-	-	-	+	+	-	-	+	-	-	+	-	56	80	140	90	-	-	+	-	-	4	3.2	18.1	3.0	1.2	2.9
37	462212	M	63	CTID	4	-	-	-	+	+	-	-	+	-	-	-	-	76	82	160	90	-	-	+	-	-	3	4.0	18.7	3.0	0.9	3.7
38	449481	M	56	CTID	3	-	-	-	+	-	-	-	+	-	-	-	-	60	82	150	90	-	-	-	-	-	1	2.0	35.0	2.8	1.3	4.2

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Serial Number	In / Out patient number	Demo-graphy		History														General Physical examination											Zulewski Score	Investigations				
						Dialysis			Thyroid dysfunction symptoms											BP (mm Hg)		Signs									Sr. Creatinine (mg/dL)	eGFR (ml/min)	Thyroid profile		
		Sex	Age (Years)	Renal dysfunction	Stage of CKD	Type	Frequency	Duration (months)	Tired / weak	Diminished sweating	Hoarseness	Parasthesia	Dry skin	Bowel (Constipation)	Impairment of hearing	Weight increase	Hair loss	Weight (Kgs)	Pulse rate (bpm)	Systolic	Diastolic	Slow movements	Delayed ankle jerk	Course skin	Periorbital puffiness	Cold skin				Free T3	Free T4	TSH
39	430862	M	56	DNP	3	-	-	-	+	-	-	-	+	-	-	-	-	68	82	160	90	-	-	-	-	-	1	2.3	34.5	3.3	1.8	3.7
40	450089	F	68	DNP	5	HD	2	3	+	+	-	-	+	-	-	+	-	55	78	140	90	-	-	+	-	-	4	19.7	2.4	2.2	1.7	4.2
41	431943	F	41	DNP	4	-	2	-	+	+	-	-	+	-	-	-	-	52	86	140	90	-	-	+	-	-	4	4.7	12.9	2.1	1.4	3.6
42	430862	F	45	CTID	4	-	-	-	+	+	-	-	+	-	-	+	-	53	80	140	90	-	-	+	-	-	5	3.0	19.4	3.2	1.8	0.7
43	436305	M	55	CTID	4	-	-	-	+	+	-	-	+	-	-	-	-	60	79	140	90	-	-	+	-	-	3	3.1	22.9	2.9	0.9	3.2
44	446237	F	65	DNP	5	-	-	-	+	+	-	-	+	-	-	+	-	62	82	150	90	-	-	+	-	-	4	4.5	13.1	3.3	0.9	2.9
45	447521	M	48	CTID	4	-	-	-	+	+	-	-	+	-	-	+	-	60	80	150	100	-	-	+	-	-	4	2.8	27.6	3.1	1.5	3.6
46	446468	M	63	CTID	4	-	-	-	+	+	-	-	+	-	-	+	-	52	80	150	90	-	-	+	-	-	4	2.0	27.8	3.0	0.9	3.9
47	448895	M	50	CTID	3	-	-	-	+	+	-	-	+	-	-	-	-	59	83	150	90	-	-	+	-	-	4	2.0	36.9	1.9	0.9	3.9
48	447660	M	47	DNP	4	-	-	-	+	+	-	-	+	-	-	+	-	58	80	140	90	-	-	+	-	-	4	4.6	16.3	3.2	1.0	3.2
49	449115	M	48	CTID	4	-	-	-	+	+	-	-	+	-	-	-	-	52	80	150	100	-	-	+	-	-	3	3.8	18.1	3.4	1.5	3.9
50	448335	F	50	CTID	4	-	-	-	+	+	-	-	+	-	-	-	-	56	87	150	90	-	-	+	-	-	4	3.9	15.3	3.1	1.8	3.9
51	427675	M	51	DNP	5	-	-	-	+	+	-	-	+	-	-	+	-	60	80	140	90	-	-	+	-	-	4	6.2	12.0	2.7	1.0	4.4
52	433081	M	50	DNP	5	HD	2	4	+	+	-	-	+	-	-	+	-	60	96	140	90	-	-	+	-	-	4	9.0	8.3	3.2	1.0	3.8
53	436196	F	49	CTID	4	-	-	-	+	+	-	-	+	-	-	+	-	57	87	140	80	-	-	+	-	-	5	2.8	21.5	3.1	1.0	0.9
54	436584	M	46	DNP	4	-	-	-	+	+	-	-	+	-	-	+	-	60	80	140	100	-	-	+	-	-	4	4.3	18.2	2.9	1.2	3.5
55	437104	F	42	DNP	4	-	-	-	+	+	-	-	+	-	-	+	-	60	82	150	90	-	-	+	-	-	5	4.3	16.1	2.4	0.8	2.4
56	436661	M	53	DNP	5	HD	2	4	+	+	-	-	+	-	-	+	-	56	80	140	90	-	-	+	-	-	4	16.4	4.1	0.2	1.2	1.8
57	436488	F	52	CTID	4	-	-	-	+	+	-	-	+	-	-	+	-	58	76	150	100	-	-	+	-	-	5	3.3	18.3	1.2	0.9	3.4

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Serial Number	In / Out patient number	Demo-graphy		History														General Physical examination											Zulewski Score	Investigations					
						Dialysis			Thyroid dysfunction symptoms											BP (mm Hg)		Signs									Sr. Creatinine (mg/dL)	eGFR (ml/min)	Thyroid profile		
		Sex	Age (Years)	Renal dysfunction	Stage of CKD	Type	Frequency	Duration (months)	Tired / weak	Diminished sweating	Hoarseness	Parasthesia	Dry skin	Bowel (Constipation)	Impairment of hearing	Weight increase	Hair loss	Weight (Kgs)	Pulse rate (bpm)	Systolic	Diastolic	Slow movements	Delayed ankle jerk	Course skin	Periorbital puffiness	Cold skin				Free T3	Free T4	TSH
58	456457	M	50	CTID	3	-	-	-	+	+	-	-	+	-	-	+	-	60	86	150	90	-	-	+	-	-	5	2.1	35.7	3.2	1.2	3.3
59	439978	F	46	DNP	5	HD	2	2	+	+	-	-	+	-	-	+	-	55	86	140	90	-	-	+	-	-	5	9.2	6.6	1.2	1.1	10.2
60	440084	M	55	CTID	3	-	-	-	+	+	-	-	+	-	-	-	-	60	78	150	100	-	-	+	-	-	3	2.8	35.4	3.2	1.0	0.5
61	438726	M	60	DNP	5	-	-	-	+	+	-	-	+	-	-	+	-	56	82	140	100	-	-	+	-	-	4	6.4	9.9	1.4	0.8	5.4
62	436486	F	62	CTID	4	-	-	-	+	+	-	-	+	-	-	+	-	60	85	150	100	-	-	+	-	-	4	3.3	15.4	3.0	1.2	3.5
63	457157	M	49	CTID/DNP	3	-	-	-	+	-	-	-	-	-	-	+	-	60	80	140	90	-	-	-	-	-	2	2.4	31.6	2.8	0.9	4.0
64	457756	M	52	FFGS	5	-	-	-	+	-	-	-	+	-	-	+	-	70	96	150	90	-	-	-	-	-	2	6.2	13.8	3.3	0.9	3.8
65	458448	F	65	DNP	5	-	-	-	+	-	-	-	+	-	-	-	-	65	88	140	90	-	-	-	-	-	1	7.0	11.6	1.8	0.9	4.2
66	458273	M	56	DNP	5	-	-	-	+	-	-	-	-	-	-	+	-	69	82	150	100	-	-	-	-	-	2	9.0	11.5	3.4	0.9	3.8
67	458275	M	60	CGN	5	-	-	-	+	-	-	-	+	-	-	-	-	70	82	140	90	-	-	-	-	-	1	6.0	13.0	2.8	1.2	3.9
68	459712	M	51	CTID/DNP	4	-	-	-	+	-	-	-	-	-	-	+	-	68	84	150	90	-	-	-	-	-	2	4.0	21.0	2.9	1.1	2.9
69	459715	M	58	DNP	3	-	-	-	+	-	-	-	-	-	-	-	-	55	92	140	80	-	-	-	-	-	0	2.0	31.3	3.0	1.8	3.7
70	459716	M	60	ctid	4	-	-	-	+	-	-	-	-	-	-	-	-	59	87	140	80	-	-	-	-	-	1	2.8	23.4	3.1	0.9	3.7
71	457037	M	66	DNP	5	HD	2	3	+	+	-	-	+	-	-	-	+	69	82	160	90	-	-	+	-	+	4	19.0	3.7	2.2	0.7	5.0
72	454492	M	42	ctid	5	HD	2	4	+	-	-	-	+	-	-	-	-	52	98	150	90	-	-	-	-	-	1	7.8	9.1	3.2	0.8	2.9
73	455767	F	50	ctid	4	-	-	-	+	-	-	-	+	-	-	-	-	53	88	160	90	-	-	-	-	-	2	2.4	27.6	3.2	1.2	2.7
74	456398	F	58	CTID/ADPKD	5	HD	2	15	+	+	-	-	+	-	-	-	-	52	82	140	90	-	-	+	-	-	3	16.0	4.1	2.2	0.9	5.8
75	452946	M	48	DNP	3	-	-	-	+	-	-	-	-	-	-	-	-	68	82	140	90	-	-	-	-	-	0	2.7	32.2	3.0	1.2	4.0
76	452317	F	44	DNP	4	-	-	-	+	+	-	-	+	-	-	+	+	54	82	130	80	-	-	+	-	+	6	3.1	19.7	2.2	1.8	2.2

MASTER CHART

Serial Number	In / Out patient number	Demo-graphy		History													General Physical examination										Zulewski Score	Investigations				
						Dialysis			Thyroid dysfunction symptoms										BP (mm Hg)		Signs									Thyroid profile		
		Sex	Age (Years)	Renal dysfunction	Stage of CKD	Type	Frequency	Duration (months)	Tired / weak	Diminished sweating	Hoarseness	Parasthesia	Dry skin	Bowel (Constipation)	Impairment of hearing	Weight increase	Hair loss	Weight (Kgs)	Pulse rate (bpm)	Systolic	Diastolic	Slow movements	Delayed ankle jerk	Course skin	Periorbital puffiness	Cold skin		Sr. Creatinine (mg/dL)	eGFR (ml/min)	Free T3	Free T4	TSH
77	454046	F	50	DNP	5	HD	2	12	+	+	+	+	+	-	-	+	+	58	82	160	90	+	+	+	+	+	10	16.0	3.9	1.2	0.3	6.0
78	454335	M	62	CTID/DNP	5	HD	2	30	+	+	-	-	+	-	-	+	+	68	82	160	100	+	+	+	+	+	8	14.0	5.9	1.9	0.6	6.7
79	455870	M	66	DNP	5	HD	2	6	+	-	-	-	+	-	-	+	-	68	86	160	90	-	-	-	-	-	2	12.0	5.8	2.4	0.9	4.2
80	386596	F	52	DNP	4	-	-	-	+	-	-	-	+	-	-	-	-	52	82	140	90	-	-	-	-	-	1	2.9	21.9	2.9	1.6	3.7
81	452954	M	56	DNP/ADPKD	4	-	-	-	+	-	-	-	+	-	-	-	-	58	82	160	90	-	-	-	-	-	1	3.1	21.8	2.9	1.3	3.9
82	452181	M	25	CGN	5	-	-	-	+	-	-	-	+	-	-	+	-	56	86	140	90	-	-	-	-	-	2	7.0	12.8	2.6	1.5	3.9
83	452436	M	42	DNP	3	-	-	-	+	+	-	-	+	-	-	-	+	62	86	160	90	-	-	+	-	-	3	2.3	36.7	3.4	1.6	4.0
84	456190	F	60	DNP	5	-	-	-	+	+	-	-	-	-	-	+	-	50	82	170	100	-	-	+	-	-	4	3.2	14.8	3.2	1.6	3.9
85	459565	F	50	DNP	5	HD	2	3	+	-	-	-	+	-	-	-	-	63	86	140	100	-	-	-	-	-	2	8.5	7.9	3.0	0.9	4.2
86	459561	F	55	DNP	5	-	-	-	+	-	-	-	-	-	-	-	-	58	80	150	100	-	-	-	-	-	1	8.9	7.7	2.8	1.1	3.3
87	447451	F	44	CTID/DNP	4	-	-	-	+	-	-	-	-	-	-	+	-	52	82	148	90	-	-	-	-	-	2	2.3	30.1	3.2	1.5	3.2
88	447452	M	25	CGN	5	-	-	-	+	-	-	-	+	-	-	+	-	56	86	140	90	-	-	-	-	-	2	7.0	12.8	2.6	1.5	3.9
89	447453	F	44	DNP	4	-	-	-	+	+	-	-	+	-	-	+	+	54	82	130	80	-	-	+	-	+	6	3.1	19.7	2.2	1.8	2.2
90	447454	M	52	DNP	5	-	-	-	+	-	-	+	-	-	-	-	+	62	82	140	90	-	-	-	-	-	2	8.4	9.0	2.7	0.9	4.3
91	459563	M	56	DNP	4	-	-	-	+	-	-	-	+	-	-	-	-	82	88	170	100	-	-	+	-	-	2	4.9	19.5	1.8	1.3	1.6

Annexures

Annexure III

ANNEXURE III – KEY TO MASTER CHART

-	-	Negative
+	-	Positive
ADPKD	-	Adult polycystic kidney disease
BP	-	Blood pressure
bpm	-	Beats per minute
CGN	-	Chronic glomerular nephritis
CKD	-	Chronic kidney disease
CTID	-	Chronic tubulointerstitial disease
dL	-	Decilitre
DNP	-	Diabetic nephropathy
F	-	Female
FSGS	-	Focal segmental glomerular sclerosis
HD	-	Haemodialysis
Kgs	-	Kilogram
M	-	Male
mg	-	Milligram
min	-	Minute
mL	-	Milli Litre
T3	-	Triiodothyronine
T4	-	Tetraiodothyronine
TSH	-	Thyroid-stimulating hormone TSH