"PREVALENCE OF SECONDARY HYPERPARATHYROIDISM IN PATIENTS WITH STAGE 5 CHRONIC KIDNEY DISEASE ON MAINTENANCE HEMODIALYSIS'' – A ONE YEAR HOSPITAL BASED CROSS-SECTIONAL STUDY"

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LIST OF ABBREVIATIONS USED

iPTH	–	Intact Parathyroid Hormone
CKD	–	Chronic Kidney Disease
SHPT	–	Secondary Hyperparathyroidism
NKF	–	National Kidney Foundation
K/DOQI	–	Kidney Disease Outcomes Quality Initiative
KDIGO	–	Kidney Disease: Improving Global Outcomes
SD	–	Standard Deviation
eGFR	–	estimated Glomerular Filtration Rate
ESRD	–	End Stage Renal Disease
MDRD	–	Modification of Diet in Renal Disease
RAAS	–	Renin Angiotensin Aldosterone System
Camp	–	cyclic Adenosine Monophosphate
ATP	–	Adenosine Triphosphate
PKA	–	Protein Kinase A
CKD-MBD	–	Chronic Kidney Disease – Mineral Bone Disease
CVD	–	Cardiovascular Disease
FGF 23	–	Fibroblast Growth Factor 23
ROD	–	Renal Osteodystrophy
Ca R	–	Calcium Receptor
CGN	–	Chronic Glomerulonephritis
CTID	–	Chronic Tubulointerstitial Disease
cCa × P	–	corrected Calcium and Phosphorus product
25OH vitamin D	–	25 Hydroxy Vitamin D
ALP	–	Alkaline Phosphatase

ABSTRACT

BACKGROUND AND OBJECTIVES:

Disturbances in mineral metabolism are commonly seen in patients with chronic renal failure. But there are very few studies on their prevalence in Indian dialysis population. Objective of our study was to know the prevalence of secondary hyperparathyroidism in patients with stage 5 chronic kidney disease on maintenance hemodialysis.

METHODS:

This cross sectional study was done on patients undergoing maintenance hemodialysis. Patients were examined for clinical features of secondary hyperparathyroidism and serum calcium, phosphorus, alkaline phosphatase, 25 hydroxy vitamin D and intact parathyroid hormone levels were measured.

RESULTS:

85 patients were included in our study. Various mineral, bone abnormalities were as follows- hypercalcemia (5.88%), hypocalcemia (36.47%), hyperphosphatemia (30.59%), hypophosphatemia (28.24%), hyperparathyroidism (36.48%), hypoparathyroidism (10.59%), deficiency of vitamin D(52.94%) and insufficiency of vitamin D (20%). iPTH levels had positive correlation with phosphorus and alkaline phosphatase levels, negative correlation was significant between iPTH and calcium levels. iPTH levels did not differ significantly in diabetics, compared to non-diabetics and also between patients undergoing 8 and 12 hours of dialysis.

INTERPRETATION AND CONCLUSION.

Prevalence rate of secondary hyperparathyroidism was 36% in our study and 40% had oversuppresion of iPTH levels. One third of our patients had a risk of adynamic bone disease.

KEY WORDS: Chronic kidney disease, Secondary hyperparathyroidism, hemodialysis.

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INTRODUCTION

Chronic kidney disease (CKD) is a spectrum of pathophysiologic processes associated with abnormal kidney function and progressive fall in glomerular filtration rate. CKD stage 5 is the condition in which accumulated toxins leads to death if they are not removed by renal replacement therapy.[1]

Incidence and prevalence of CKD stage 5 have increased causing social and economic burden to health care system.[2] Type 2 diabetes mellitus and hypertensive nephrosclerosis are the major causes of stage 5 CKD.[3]

Secondary hyperparathyroidism (SHPT) is common complication in patients with chronic renal failure. Phosphorus is mainly present in bones and teeth and is required for cellular metabolism. More than required amount of phosphorus in plasma is cleared by kidneys, which mainly depends on glomerular filtration. Serum phosphate does not get elevated until glomerular filtration rate falls below approximately 30ml/min/1.73m^2 or stage 4 CKD, according to National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) classification.[4] In End Stage Renal Disease (ESRD) reduced urinary excretion of phosphorus cannot keep pace with intestinal phosphate absorption, causing hyperphosphatemia.

Only 70% of absorbed phosphorus is cleared by dialysis, hence hyperphosphatemia is found in majority of patients with ESRD.[5] Hyperphosphatemia is a main factor causing SHPT.[6] A degree of SHPT must exist to maintain normal bone modelling. Optimal intact parathyroid hormone (iPTH) level as per "NKF-K/DOQI guidelines for Bone Metabolism and Disease" in CKD stage 5 patients is

150- 300 pg/ml, which also recommends maintenance of serum phosphorus between 3.5 and 5.5 mg/dl, corrected total calcium between 8.4 and 9.5 mg/dl and serum calcium and phosphorus product below $55mg^2/dl^2$ in these patients.[7]

SHPT induces several forms of renal osteodystrophy. But importance of SHPT and the possibility of its reduction are neglected issues in hemodialysis centers. Evaluation of ESRD patients for SHPT is very important, as early detection and treatment of SHPT reduce the progression of bone, cardiac and other complications. This study aims to determine the prevalence of secondary hyperparathyroidism in CKD stage 5 patients on maintenance hemodialysis.

AIMS AND OBJECTIVES

To study the Prevalence of Secondary Hyperparathyroidism in patients with stage 5 Chronic Kidney Disease on maintenance hemodialysis.

REVIEW OF LITERATURE

Chronic kidney disease (CKD) affects 5-10% of global population.[8,9] Low income countries are unable to afford the cost of care required to manage patients with chronic renal failure.

In renal failure there is significant irreversible reduction in number of nephrons and applies to CKD stages 3-5.

Chronic Kidney Disease is divided into 5 stages based on estimated GFR. To be classified as stage 1 or stage 2, there must be an accompanying structural or functional defect (eg proteinuria, hematuria) as the GFR is normal or near normal in these stages.[10,11]

The term end stage renal disease represents a stage of CKD where the accumulation of toxins, fluids and electrolytes that are normally excreted by the kidneys, results in uremic syndrome. This syndrome leads to death unless the toxins are removed by renal replacement therapy, using dialysis or kidney transplantation.

DEFINITION.

National kidney foundation has defined CKD as,

CRITERIA:

1. Kidney damage for > 3 months, either structural or functional abnormality with or without decreased GFR, manifested by either pathologic abnormalities or markers of kidney damage in blood, urine or in imaging studies.[11]

2. GFR <60 ml/min/1.73 sq m for > 3 months with or without kidney damage.

The risk of CKD progression is closely linked to both the GFR and the amount of albuminuria. Figure 3.1 shows staging of CKD, classified by measurement of both of these parameters.[12]

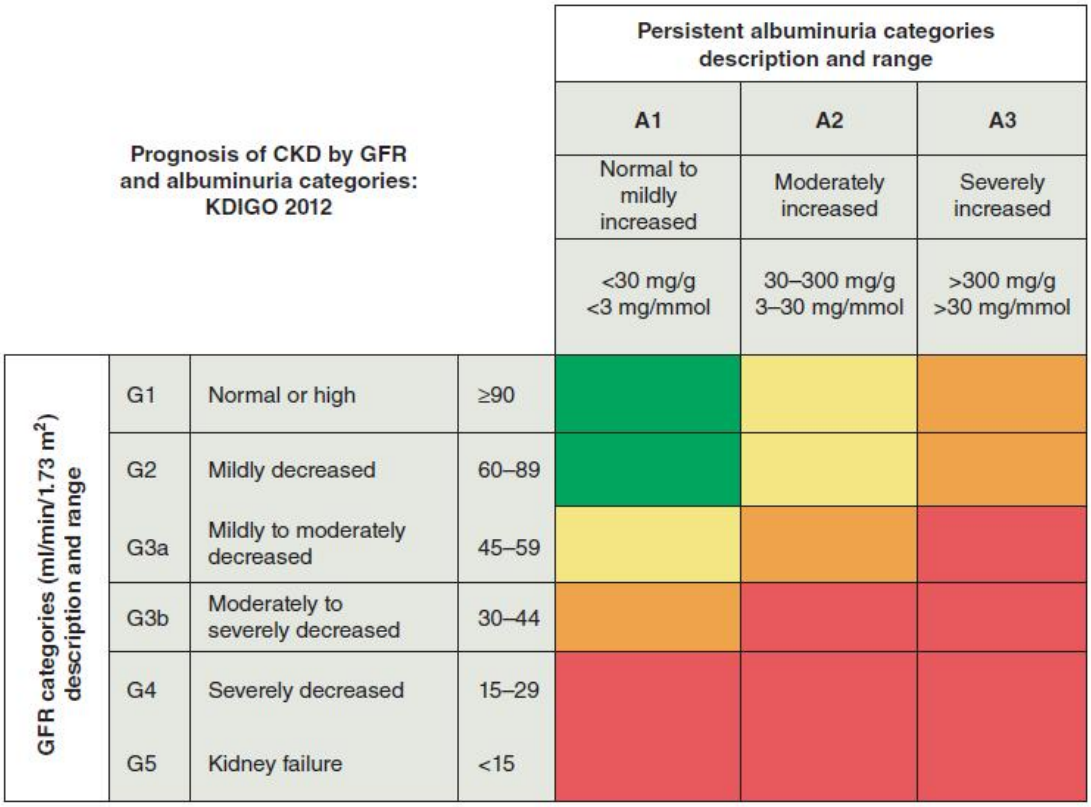


Figure 3.1: Kidney disease improving global outcome (KDIGO) classfication of Chronic kidney disease. Gradation of color from green to red corresponds to increasing risk and progression of CKD

Two formulas are used widely to estimate kidney function from serum creatinine.[1,10]

1. Cockcroft-Gault: Creatinine Clearance (ml/min) = 140-age(years) x weight(kg)x0.85 if female /72x sCr(mg/dl) .
2. MDRD: eGFR (ml/min/1.73m^2 = 186.3 x Serum Creatinine(e- 1.154) x age(e-0.203)x 0.742 if female x 1.21 if black.

PATHOPHYSIOLOGY OF CKD

Long term reduction in renal mass

↓

Activation of RAAS

↓

Hyperfiltration and hypertrophy of nephrons to maintain GFR

↓

Distortion of glomerular architecture, abnormal podocyte function

↓

Disruption of filtration barrier

↓

Sclerosis and Loss of remaining nephrons

↓

Progressive decline in renal function over many years

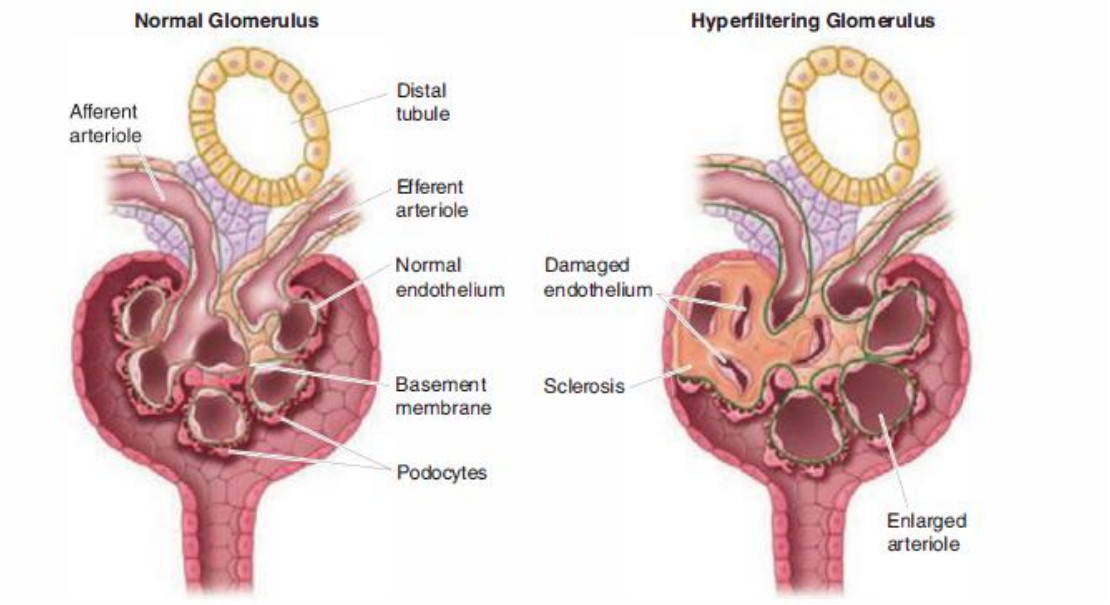


Figure 3.2 Left: Schema of the normal glomerular architecture. Right: Secondary glomerular changes associated with reduction in nephron number, including enlargement of capillary lumens and focal adhesions, which are thought to occur consequent to compensatory hyperfiltration and hypertrophy in remaining nephrons.

In early stages, basal GFR may be normal or elevated but expected rise in response to protein challenge is reduced and this early stage is commonly seen in Diabetic nephropathy. It is detected by estimating GFR, using creatinine concentration. When these parameters are mildly elevated, significant chronic nephron injury has occurred. When GFR is 30% of normal, patient may remain asymptomatic with rise in serum urea and creatinine concentrations. Detailed examination reveals nocturia, mild anemia, malnutrition and abnormalities in serum calcium and phosphorus levels.

When GFR is less than 30% of normal, there will be uremic manifestations with severe biochemical abnormalities. In mild to moderate renal failure, clinical conditions such as infection, hypovolumia, uncontrolled hypertension, drug or radiocontrast nephrotoxicity, compromise renal function and cause overt uremia. As GFR falls below 5-10% of normal, patient requires renal replacement therapy for survival.

ETIOLOGY AND EPIDEMIOLOGY

CKD affects more than 10% of global population and the prevalence has increased in recent years. Cardiovascular disease is the primary cause of death in these patients. Five most common causes of CKD are shown in table 3.1.[12]

Table 3.1 – Causes of CKD

- Diabetic nephropathy
- Glomerulonephritis
- Hypertension-associated CKD (includes vascular and ischemic kidney disease and primary glomerular disease with associated hypertension)
- Autosomal dominant polycystic kidney disease
- Other cystic and tubulointerstitial nephropathy

Common cause of CKD in India is Diabetic nephropathy.[12] Patients with newly diagnosed CKD often have hypertension. When no evidence for primary disease process is present, CKD is attributed to hypertension.

UREMIA

Azotemia is a term used for retention of nitrogenous waste products. Uremia is a clinical condition due to multiorgan system derangement in advanced stages of renal insufficiency and is caused by nitrogen containing nonvolatile products of metabolism normally excreted by kidney.

Manifestations of uremia:

1. **Nervous system.**

   Headache, malaise, insomnia, fatigue and cramps.

   Restless legs, Motor weakness, polyneuritis, Irritability.

   Dementia, Drowsiness, Flapping tremors, Convulsion, Stupor.

2. **Gastrointestinal system.**

   Anorexia, vomiting, gastritis, gastrointestinal ulcer with bleeding, pancreatitis.

3. **Cardiovascular system:**

   Pericarditis, hypertension, hypotension, cardiomyopathy, decreased diastolic compliance, edema, atheromatosis, cardiomyopathy.

4. **Hematological system:** Anemia, thrombocytopenia, bleeding manifestations.
5. **Pulmonary system:** Pleuritis, uremic lung, pulmonary edema.
6. **Skin:** Pruritus, retarded wound healing, melanosis, nail atrophy.
7. **Bone disease:** Osteodystrophy, hyperparathyroidism, osteomalacia, adynamic bone disease.
8. **Others:** Thirst, weight loss, impotence, uremic foetor, hypothermia.

In CKD patients, management of secondary hyperparathyroidism is most often neglected leading to cardiovascular disease and renal osteodystrophy.[13-17] CKD patients are usually detected at stage 3 or 4, during which extra renal manifestations begin. Thus, many patients at diagnosis are vitamin D deficient, hypocalcemic and have elevated levels of iPTH, serum phosphorus and present with skeletal, cardiovascular complications.[18-21]

Our study focuses on prevalence and manifestations of elevated parathyroid hormone levels in patients on maintenance hemodialysis.

CALCIUM AND PHOSPHATE BALANCE: ROLE OF PARATHYROID HORMONE AND VITAMIN D

In calcium handling in the body 3 organ systems and 3 hormones play a major role.

Table 3.2.Organ Systems and Hormones involved in calcium metabolism

ORGAN SYSTEMS	HORMONES
Gastrointestinal system	Parathyroid hormone
Bone	calcitriol
Renal system	calcitonin

Organ systems:

1. **Bone**: 99% of body calcium is present in bone. Calcium gets deposited in bone along with phosphate and can be mobilized when needed.

2. **Gastrointestinal system:** Calcium and phosphate is absorbed from intestine by the action of calcitriol.

3. **Renal system:** Fine tuning of handling of serum calcium is by renal tubules. In physiological states, excess calcium is excreted into urine and during calcium deficiency more calcium is reabsorbed from tubular fluid.

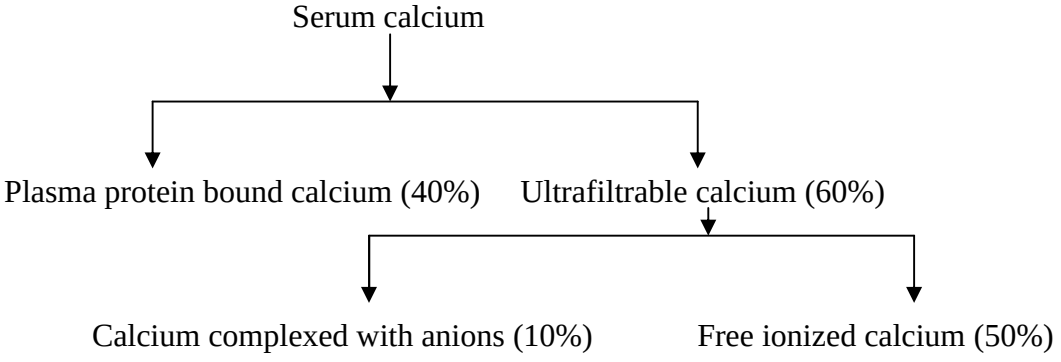
Hormones:

1. **Parathyroid hormone:** It is secreted from chief cells of 4 parathyroid glands situated behind thyroid gland.

2. **Calcitriol:** It is secreted from proximal convoluted tubular cells of kidney.

3. **Calcitonin:** It is secreted from Parafollicular C cells of thyroid gland

Major function of parathyroid hormone is to stabilize the ionized calcium levels in blood, which is the biologically active form of calcium.



Functions of calcium:

1. Calcium influx into cells is responsible for cardiac, skeletal and smooth muscle cell contractility.

2. Calcium is responsible for neurotransmitter release, hormone release.

3. Calcium is necessary for normal coagulation cascade.

4. Calcium and phosphate deposit in bone as hydroxyapatite crystals and add to compressional strength of bone.

Functions of parathyroid hormone: Chief cells of parathyroid gland have calcium receptors- G protein coupled receptors which sense ionized calcium and accordingly release PTH.[22] Transient hypocalcemia activate these receptors and release stored PTH and chronic hypocalcemia give intracellular signals for increased synthesis and release of PTH, normal level of serum calcium being 8-10mg/dl.

Action of PTH on bone: Calcium complexed with phosphate is present in bone in 2 forms.

1. Calcium and phosphate tightly deposited on collagen in mineralized form which cannot be released rapidly.

2. Calcium and phosphate loosely present in interstitial fluid covered by sheet of osteocyte membrane which can be rapidly mobilized. PTH receptors are present on the osteocyte membrane which gives intracellular signaling to pump out both calcium and phosphate from interstitial fluid within minutes.

In bone there are 2 types of cells – bone forming osteoclasts and osteocytes which breakdown the collagen. PTH receptors are present on osteoblasts and osteocytes which are G protein coupled receptors and act on adenylyl cyclase to form cAMP which activates protein kinase A (PKA). PKA phosphorylate certain proteins which act as transcription factors to synthesize cytokines like IL-6. These cytokines activate osteoclasts and these cells start destroying the collagen and release calcium, phosphate and hydroxyproline which freely filter into glomerular structure.[23]

Action of PTH on kidney:

PTH receptors on proximal convoluted tubular cells on activation, inhibit sodium phosphate co transporter and hence reabsorption of phosphate. PTH acts on receptors present on distal convoluted tubular cells and activate calcium ATPases and sodium calcium co- transporter on basolateral membrane so that so that more calcium is shifted into interstitium and then into vascular system. So, as intracellular calcium becomes less more of it is efficiently reabsorbed into the cells from tubular lumen.

PTH is released in response to reduced ionized calcium and it mobilizes calcium and phosphate from the bone and uncouples it in the kidney – it excretes phosphates and reabsorbs calcium. PTH also activates 1 alpha hydroxylase and increase calcitriol which acts on intestine and increase calcium and phosphate absorption.

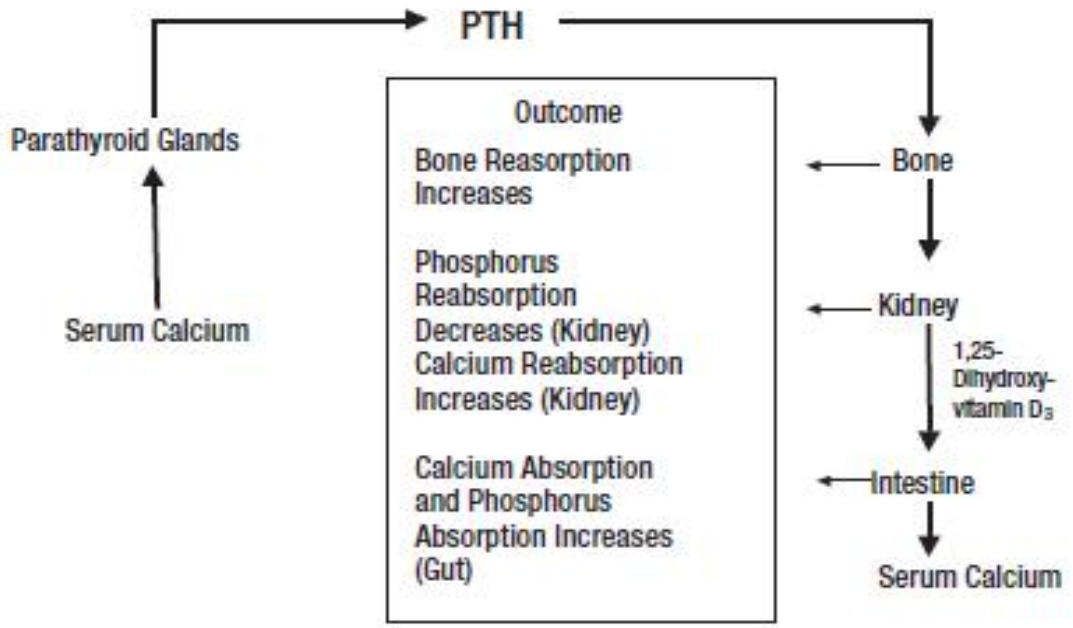
Calcitriol (vitamin D) : Cholecalciferol produced in skin under the influence of sunlight and that from the diet, is converted to 25 hydroxycholecalciferol in hepatocytes, which is storage form of vitamin D. 1 alpha hydroxylase present in

proximal convoluted tubular cells of kidney convert 25 hydroxycholecalciferol into 1, 25 dihydroxycholecalciferol which is active form of vitamin D.

1 alpha hydroxylase is under tight regulation as it converts inactive vitamin D active form. Low calcium, low phosphorous and PTH stimulate it.[24] 33 % of dietary calcium is absorbed from small intestinal cells under the influence of calcitriol. Calcium transporter 1(Ca-T1) on luminal membrane of small intestinal cells take up calcium into the cell and then calcium binds with calbindin and hence intracellular calcium remains low. Calcium then is actively transported into interstitium by calcium ATPases present on basolateral membrane of small intestinal cells.

Vitamin D binds with its receptors which are transcriptional factors and increases the synthesis of calbindin and hence there is more absorption of calcium and phosphate from the intestine.[25] When calcium and phosphate are in appropriate ratio, they precipitate as hydroxyapatite calcium phosphate crystals. Vitamin D by increasing the levels of both calcium and phosphorus favors mineralization and PTH by uncoupling them favors demineralization.

PARATHYROID HORMONE REGULATION



The relationship between the circulating serum calcium concentrations and physiological feedback with the parathyroid glands, bone, intestine, and kidney is depicted. The physiological response to hypocalcemia is to enhance bone resorption and calcium reabsorption from the renal tubules and gastrointestinal tract in order to normalize the serum calcium concentration, while minimizing the potential increases in serum phosphorus concentrations.

Figure 3.3: PTH-Vitamin D – Mineral feedback system- PTH regulation

Hypercalcemia by decreasing PTH activity favors loss of calcium into urine and increases reabsorption of phosphate to bind excess calcium, suppress the release of calcium and phosphate from the bone and 1 alpha hydroxylase is less active and hence reduced absorption of calcium and phosphate from intestine.

`High levels of serum calcium and calcitriol, reduce PTH secretion. calcitriol suppress PTH secretion at transcriptional level where as calcium regulation is post-transcriptional.[26] Mineral abnormalities result from disturbance in the above feedback loop causing hyperparathyroidism.

SECONDARY HYPERPARATHYROIDISM.

In secondary hyperparathyroidism primary defect is not in the gland. Due to some other pathology in the body, patient has chronically low levels of ionized calcium which, over- stimulates parathyroid gland chronically, to produce excess parathyroid hormone. This type of hyperparathyroidism is secondary to low ionized calcium levels and chronic renal failure is the most common cause of chronically low calcium levels.

Secondary hyperparathyroidism, defined by elevated levels of parathyroid hormone (PTH) is a complex alteration in bone and mineral metabolism caused by changes that occur as a result of decreased kidney function.

Abnormalities of serum calcium, phosphorus and PTH levels are common in CKD patients and are known to cause cardiovascular calcification, arterial dysfunction and increased morbidity and mortality. These biochemical changes along with abnormalities in vitamin D metabolism and bone turnover, constitute a systemic syndrome known as CKD mineral bone disorder (CKD-MBD)

Definition of mineral bone disorder in CKD

A systemic manifestation of mineral and bone metabolism as a result of CKD leading to one or more of the following abnormalities:

1. Abnormalities in the metabolism of calcium, phosphorus, PTH or vitamin D.
2. Disturbances in bone turnover, mineralization, volume, linear growth or strength.
3. Calcification in blood vessels and other soft tissues.[27]

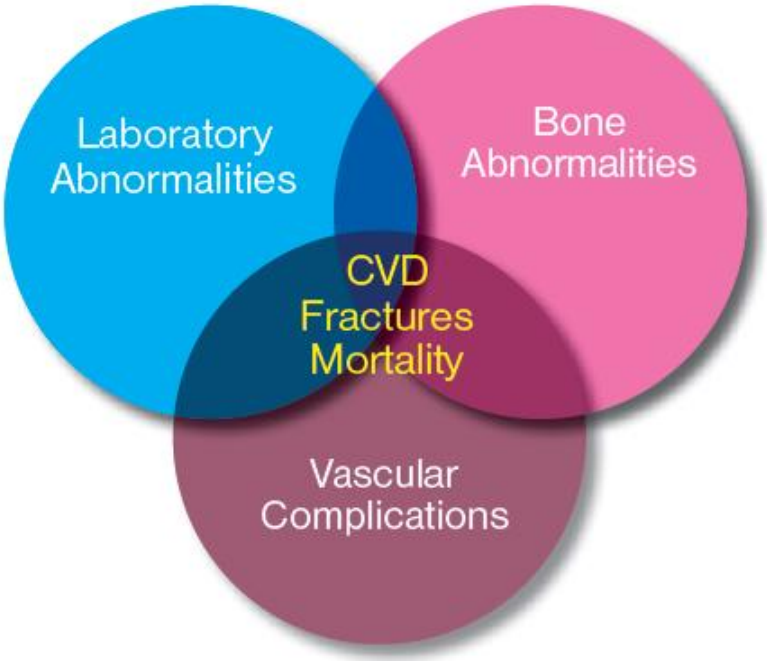


Figure 3.4: Chronic Kidney Disease – Mineral Bone Disorder[28]

SECONDARY HYPERPARATHYROIDISM: PATHOPHYSIOLOGY

In Chronic Renal Failure glomerular filtration is reduced. Phosphorus is important component of bones and teeth and is required for intracellular metabolism and production of energy. Our body is loaded constantly with nutritive substances rich in phosphates. Clearance of phosphate from blood is mainly dependent on filtration. Hence in patients with chronic renal failure, as there is reduced GFR, there is reduced phosphate filtration and clearance, leading to phosphate retention and hyperphosphatemia.[6,29]

Retained phosphate, complexes with more ionized calcium and free ionized calcium in blood is reduced.[30] Reduced free ionized calcium stimulates chief cells of parathyroid gland and will produce chronically increased levels of PTH.[31,32] Other mechanisms of secondary hyperparathyroidism in CKD are:

1. Retained phosphate stimulates increased synthesis of FGF-23 by osteocytes which will stimulate the growth of parathyroid gland mass.

2. Decreased levels of ionized calcium resulting from the suppression of calcitriol production by FGF- 23, also stimulates PTH production.[33]

3. Low calcitriol levels cause hyperparathyroidism both by leading to hypocalcemia and also by directly increasing PTH gene transcription. These changes occur when GFR falls below 60ml/min.[34-37]

4. Most of patients on dialysis have vitamin D deficiency, altering PTH-Vitamin D feedback loop.[38] Hyperplastic tissue of parathyroid gland in SHPT is less sensitive to calcium, altering calcium level feedback loop.[39]

5. Hyperglycemia suppresses serum PTH, hence Diabetic CKD patients have lesser PTH levels and a reduced risk of SHPT.[40]

COMPLICATIONS OF SECONDARY HYPERPARATHYROIDISM:

Table 3.3 – Complications of Secondary hyperparathyroidism[41,42]

Renal Osteodystrophy	Cardiovascular Disease
Osteitis fibrosa Adynamic bone disease Osteomalacia	Left ventricular hypertrophy Vascular calcification Visceral calcification Peripheral artery disease Hypertension Congestive heart failure

1. SKELETAL COMPLICATIONS OF SHPT:

Patients present with- bone pain especially on weight bearing or standing, disability due to stiffness of joint and periarticular pain, muscle pain with weakness.[43,44]

Patients on dialysis for long time are more prone for skeletal fracture.[45] Bone fractures, particularly hip fractures, have high mortality. In CKD patients bone mass varies inversely with serum PTH levels.[46]

Action of PTH on Bone in patients with SHPT:

In healthy person, at multiple points bones are being destroyed and bones are being rebuilt which is physiological bone turn over. Bone remodelling and skeletal turnover is regulated mainly by PTH in CKD patients.[47]

Osteoclasts increase in number along with increased activity under the influence of high serum PTH levels destroying both organic and inorganic component of bone.[48-50] PTH causes bone formation by directly acting on its receptors on osteoblasts, increasing their number and activity which in turn produce type I collagen forming collagenous bone matrix.[51]

Renal osteodystrophy

Renal osteodystrophy is an alteration of bone morphology in patients with CKD.[27] It is one measure of the skeletal component of the systemic disorder of CKD-MBD that is quantifiable by histomorphometry of bone.

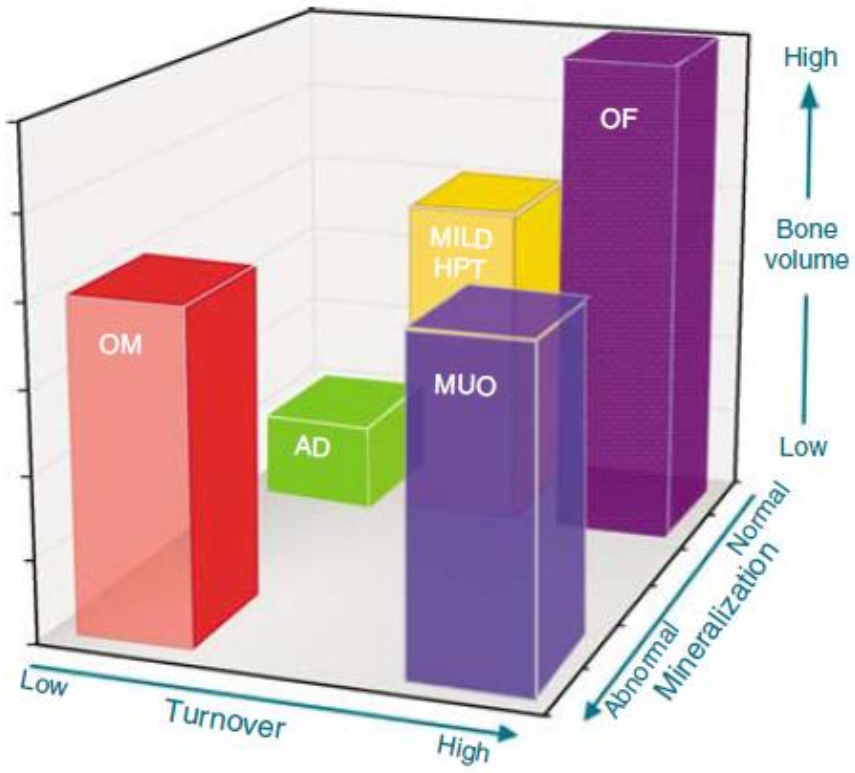


Figure 3.5 – Renal Osteodystrophy[27]

AD = adynamic bone disease; Mild HPT = Mild hyperparathyroid-related disease; MUO = mixed uremic osteodystrophy; OF = osteitis fibrosa or advanced hyperparathyroid-related disease; OM = osteomalacia.

High-Turnover Bone Disease:

With increase in bone formation, lamellar bone is replaced by woven bone in which collagen fibrils are abnormally arranged leading to loss of strength in skeletal tissue.[52] Severe SHPT with increased bone formation causes fibrous tissue deposition in bone marrow, hence the term osteitis fibrosa cystica and it can worsen anemia of CKD.[53]

Osteomalacia was more common before calcitriol use due to persistently reduced calcium and phosphorous levels.

Patients with Mixed renal osteodystrophy present with features of both osteitis fibrosa cystica and osteomalacia.[54] In these patients, formation and turnover of bone may be low, normal, or high. Mixed renal osteodystrophy is less frequent due to widespread use of calcitriol.[55, 56]

Low-Turnover disease of bone:

In these adynamic states of renal osteodystrophy, the activity of both osteoblasts and osteoclasts are reduced and hence bone formation and turnover are less than normal.[57] Adynamic bone disease is not a feature of SHPT, but it arises after calcitriol and calcium supplementation.[58] Calcitriol directly inhibits bone cells and indirectly by lowering PTH levels reduces formation of osteoblasts from precursor cells and inhibits their activity decreasing the collagen synthesis.

Combined oral therapy with larger doses of calcium and vitamin D, suppress bone formation by increasing serum calcium levels and by reducing serum PTH levels.[59] Complications of adynamic bone in patients with ESRD include hypercalcemia and skeletal fracture.[60,61] As adynamic bone has less remodeling sites, it has reduced ability to buffer fluctuations in serum calcium levels. Adynamic bone disease patients have higher serum calcium levels and hypercalcemic episodes compared to patients with high turnover bone disease. These changes increase calcium and phosphorous deposition in soft tissues, causing vascular calcification and increased risk of calciphylaxis.[62]

Table 3.4: Prevalence of Renal osteodystrophy in CKD

	Stage 3	Stage 4	Stage 5 (ESRD)
High bone turnover	90%	90%	25%-40%
Low bone turnover	10%	10%	60% (20%-40% ADB; 4%-12% OM)*

ADB=adynamic bone disease; ESRD=end-stage renal disease; OM=osteomalacia.

As depicted in above table, low or high-bone turnover ROD prevalence, varies with CKD staging. Majority of CKD stage 3 and 4 patients (90%) have high bone turn over ROD. Low-bone turnover disease is more common in stage 5 patients due to over-suppression of PTH, aluminum toxicity and high calcium concentration in dialysate.[67] 25% to 40% of ROD in ESRD patients is Osteitis fibrosa and 60% have low-bone turnover disease. 20% to 40% of low-bone turnover patients have adynamic bone and 4% to 12% have osteomalacia.[65, 66]

2. NONSKELETAL COMPLICATIONS OF SHPT:

Patients with high calcium phosphorous product are more prone for calcification of soft tissues which occur mainly due to hyperphosphatemic episodes in dialysis patients. Hyperphosphatemia in these patients is due to imbalance between ingested phosphorus and that removed during weekly dialysis.

As dialysis removes small amounts of phosphorus, patients on dialysis will have positive phosphorus balance every week and will have retention of phosphorus even after taking medications. Phosphorus levels are better controlled with nightly hemodialysis or hemodialysis of short duration for 6 days in a week.[53]

Hyperphosphatemia is more common in CKD stage 5 patients with advanced SHPT. High PTH levels lead to resorption of phosphorus from the bone into the extracellular fluid. High oral doses of calcium cause hypercalcemia leading to calcification of arterial walls in dialysis patients.[64]

Excessive retention of phosphorus and calcium, with recurrent episodes of hyperphosphatemic and hypercalcemic episodes causes calcification of soft tissue in CKD stage 5 patients. Despite high levels of calcium and phosphorus, crystal formation in plasma is inhibited by plasma citrate. These crystals tend to deposit in alkaline interstitium such as of stomach walls, lungs, arterial walls and kidney leading to nephrolithiasis and nephrocalcinosis.

Vitamin D therapy by increasing serum calcium and phosphorus levels causes soft tissue calcification in subcutaneous tissue, conjunctiva, cornea, muscle, blood vessels,myocardium, lung and gastrointestinal tract.[65-70]Adynamic bone disease patients with low or normal PTH levels also present with soft tissue calcification.[71]

Calciphylaxis is a condition in which there is calcification of small and medium sized arteries of subcutaneous tissue causing skin ulceration with gangrene which resolves after parathyroidectomy.[72-74] Proximal calciphylaxis presents as skin ulceration on abdominal wall, buttocks and thighs. Mortality rate in patients with calciphylaxis is 39% within 6 months after diagnosis increasing up to 80% with ulcerative lesions of skin and its incidence in hemodialysis patients is 4.5%.[75] The widespread use of calcium and vitamin D sterols has contributed to the increased incidence of calciphylaxis which can be prevented.

Complications involving cardiovascular system:

40% of deaths in CKD stage 5 patients are mainly caused by cardiovascular disease (CVD) and mortality due to CVD is 10 to 70 times more in people on dialysis compared to age-matched controls.[76]

SHPT with high levels of phosphorus, calcium phosphorus product and its treatment with large doses of vitamin D lead to cardiovascular manifestations in patients on long-term dialysis.

PTH disturbs energy metabolism in myocardium by increasing its calcium content.[77] According to U.S. Renal Data System registry, patients with PTH levels of > 495 pg/ml have greater risk of sudden cardiac death when compared to patients with PTH levels of 91–197 pg/ml.[78] CKD stage 5 patients with very low iPTH levels also have high mortality.[79]

In patients on dialysis, hypercalcemia impairs myocardial function. Left ventricular ejection fraction is inversely related with plasma iPTH levels. Patients with serum phosphorus level of > 6.5mg/dl have greater risk of sudden cardiac death compared to those with normal serum phosphorus levels.[78]

Aortic and mitral valve calcification is more common in patients on regular hemodialysis leading to congestive cardiac failure.[80] Older age and longer hemodialysis duration have been associated with calcification of cardiac valves in CKD stage 5 patients.[81] Patients with calcium phosphorus product of about 55 mg^2/dl^2 are at risk of calcification of myocardium leading to fibrosis, dysfunction and arrhythmias when it involves conduction system.[82]

Other Complications of Uncontrolled SHPT:

Disturbed calcium metabolism has been associated with abnormalities of glucose and lipid metabolism. Most patients with secondary hyperparathyroidism have pruritus due to chronic elevations in serum iPTH and phosphorus levels and they also have anemia due to marrow fibrosis and increased erythrocyte fragility caused by high PTH levels.[83-85]

CLINICAL FEATURES OF HYPOCALCEMIA:

Sodium channels in cell membrane are guarded by calcium. During hypocalcemia, calcium detaches from them and hence more sodium enters sodium channels causing more depolarization. So neuronal system is hyperexcitable and tetany develops.

Tetany is clinicopathological situation in which due to low levels of ionized calcium, neuromuscular system becomes irritable, which manifests as sensory disturbances such as circumoral numbness and tingling sensation in fingers due to undue action potential in sensory nerve endings and in severe deficiency patient develops generalized seizures and laryngospasm.

Motor abnormalities of hypocalcemia include Chvostek's sign in which tapping of hyperexcitable facial nerve causes hemifacial contraction and trousseau's sign in which ischemia caused by inflating the cuff will hyperexcite the nerves causing carpopedal spasm.

Mental state changes of hypocalcemia include emotional instability,irritability, anxiety, confusional state, hallucination and frank psychosis.

COMPLICATIONS OF HYPERCALCEMIA:

1. Metastatic calcification.
2. Nephrolithiasis – Renal stones sometimes leading to obstructive complications.
3. Nephrocalcinosis- Calcium precipitation in interstitium- may lead to dysfunction of distal part of nephron causing diabetes insipidus.
4. Peptic ulcer,constipation, gall bladder stones and pancreatitis.
5. Since sodium channels are over guarded by calcium, neuronal excitability is reduced making the patient lethargic with severe fatigability and depression.

GUIDELINES: K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease.[7]

Table 3.5 – Guideline 1

Target Range of Intact Plasma PTH by Stage of CKD

CKD Stage	GFR Range (mL/min/1.73 m²)	Target "intact" PTH (pg/mL [pmol/L])
3	30-59	35-70 [3.85-7.7 pmol/L] (OPINION)
4	15-29	70-110 [7.7-12.1 pmol/L] (OPINION)
5	<15 or dialysis	150-300 [16.5-33.0 pmol/L] (EVIDENCE)

Guideline 3: Serum phosphorus levels

In CKD patients with kidney failure (Stage 5) and those treated with hemodialysis or peritoneal dialysis, the serum levels of phosphorus should be maintained between 3.5 to 5.5mg/dl.

Guideline 6: Serum calcium and calcium-phosphorus product.

In CKD stage 5 patients, serum levels of corrected total calcium should be maintained within the normal range for the laboratory used, preferably toward the lower end (8.4 to 9.5 mg/dl).

If hypercalcemia (serum levels of corrected total calcium >10.2 mg/dl) develops, therapies that cause serum calcium to rise should be adjusted.

Guideline 8B. Vitamin D therapy in patients on dialysis (CKD stage 5)

Patients treated with hemodialysis or peritoneal dialysis with serum levels of intact PTH levels >300 pg/mL should receive an active vitamin D sterol (such as calcitriol, alfacalcidol, paricalcitol, or doxercalciferol) to reduce the serum levels of PTH to a target range of 150 to 300 pg/mL.

- The intermittent, intravenous administration of calcitriol is more effective than daily oral calcitriol in lowering serum PTH levels.
- In patients with corrected serum calcium and/or phosphorus levels above the target range, a trial of alternative vitamin D analogs, such as paricalcitol or doxercalciferol may be warranted.

- When therapy with vitamin D sterols is initiated or the dose is increased, serum levels of calcium and phosphorus should be monitored at least every 2 weeks for 1 month and then monthly thereafter. The plasma PTH should be measured monthly for at least 3 months and then every 3 months once target levels of PTH are achieved.

Guideline 13C. Adynamic bone disease

Adynamic bone disease in Stage 5 CKD (as determined either by bone biopsy or intact PTH <100 pg/mL [11.0 pmol/L]) should be treated by allowing plasma levels of intact PTH to rise in order to increase bone turnover, by decreasing doses of calcium-based phosphate binders and vitamin D or eliminating such therapy.

Guideline 14. Parathyroidectomy in patients with CKD

Parathyroidectomy should be recommended in patients with severe hyperparathyroidism (persistent serum levels of intact PTH>800 pg/ml), associated with hypercalcemia and/or hyperphosphatemia that are refractory to medical therapy.

Secondary Hyperparathyroidism:- Treatment

Regulation of iPTH, calcium, phosphorus and cCa × P product decreases mortality and morbidity in SHPT patients.[86] Vitamin D should be supplemented in deficient patients and in those with iPTH values above the acceptable levels. Calcimimetics are also given in SHPT patients. PTH-calcium-vitamin D feedback loop has to be restored in these patients.[87]

Both intravenous and oral Calcitriol is approved in dialysis patients to treat hypocalcemia and secondary hyperparathyroidism and it acts by inhibiting the

synthesis of PTH. But there is increased prevalence of hypercalcemia and hyperphosphatemia with this therapy leading to soft tissue calcification.[88] Doxercalciferol and paricalcitol are vitamin D analogues which are approved to reduce PTH levels.

Cinacalcet

Cinacalcet is a calcimimetic. Calcium receptors (CaR) present in parathyroid gland are made more sensitive to calcium by calcimimetics.[89] Cinacalcet binds to CaR at its transmembrane domain and change its conformation thereby reducing its threshold for activation by serum calcium levels.[90] So it decreases PTH secretion even at lower serum calcium levels. Cinacalcet is approved by FDA to treat secondary hyperparathyroidism in patients on regular hemodialysis.

Studies on prevalence of SHPT

In a hospital based cross-sectional study by B. Ghosh et al at Varanasi, it was shown that in CKD stage 5 patients on dialysis, the most common mineral bone disorder is hyperparathyroidism with prevalence of 88.29% followed by elevated alkaline phosphatase(76.66%), hyperphosphatemia(70.27%) and hypocalcemia (54.95%). Significant inverse correlation was found between serum calcium, vitamin D and Parathyroid harmone.[91]

Sanjay Vinkrant and Anupam Parashar conducted a prospective observational study of CKD-mineral bone disorder (CKD-MBD) over a period of 3 years. The biochemical markers of CKD-MBD were measured in newly diagnosed CKD stage 3-5 patients and in prevalent stage 5 patients on dialysis. They showed that secondary hyperparathyroidism, hyperphosphatemia, hypocalcemia, increased alkaline

phosphatase were common in Indian CKD patients. The most common type of MBD was secondary hyperparathyroidism with prevalence of 82.75% in patients on dialysis.[92]

In a study by Fatemeh Hayati et al in Khuzesthan Iran, on 112 hemodialysis patients, with the aim to determine the prevalence of secondary hyperparathyroidism, it was found that 69.6% had PTH levels above 300pg/ml, all patients had hyperphosphatemia and 37.5% had hypocalcemia. This study showed that significant percent of hemodialysis patients had secondary hyperparathyroidism.[94]

In a survey carried out in Argentina including 1210 patients from different dialysis centers to study prevalence of Bone and Mineral Metabolism disorders, it was found that 51.6% had adequate calcium, 51.6% had adequate phosphorus and 21.1% had intact PTH levels between 150-300pg/ml. 24% of patients had intact PTH levels less than 150pg/ml and in 54.5% of patients iPTH levels were more than300pg/ml. 28.3% of patients had iPTH levels of ≥600pg/ml and in 13.3% of patients, iPTH levels of ≥ 1000pg/ml were found. They concluded that secondary hyperparathyroidism was more prevalent in CKD stage 5 patients on dialysis.[95]

In a study by Owda A et al, 122 patients who were receiving maintenance hemodialysis for at least 12 months in 2 dialysis centers in mid Michigan were evaluated to study the prevalence of secondary hyperparathyroidism. It was found that 78% of patients had iPTH above 200pg/ml, 19% had iPTH within the accepted normal range, while 3% had iPTH level below 100pg/ml.[96]

METHODOLOGY

STUDY SITE: This study was conducted in the General Medicine Department and Department of Nephrology, Dr.Prabhakar Kore Hospital, KLE University, Belagavi.

STUDY POPULATION: Patients with stage 5 Chronic Kidney Disease on maintenance hemodialysis for ≥ 6 months at Dialysis Unit, Department of Nephrology in KLE's Dr Prabhakar Kore Hospital and Medical Research Centre, Belagavi

STUDY DESIGN: The study was a Cross-sectional study.

SAMPLE SIZE(n): Based on the study by Ghosh B et al, in which prevalence of secondary hyperparathyroidism in CKD stage 5 patients on dialysis was 88.29%, sample size is calculated as follows, formula being:

$$n = \frac{4Pq}{d^2}$$

= 83.03

n – sample size

P- Prevalence = 0.8829

q= 1-P= 0.1171

d= 8% of prevalence =0.007

So, the Sample size is 85

SAMPLING METHOD: All the eligible patients were included in the study by convenient sampling till the sample size was reached.

STUDY DURATION: The data for the present study was collected between January 2018 and December 2018, for a period of one year.

INCLUSION CRITERIA:

- Chronic Kidney Disease stage 5 patients of 18 years and above, on maintenance hemodialysis for ≥ 6months in KLE's Dr Prabhakar Kore Hospital and Medical Research Center, Belagavi, willing to participate in the study.

EXCLUSION CRITERIA:

- Patients on glucocorticoids, bisphosphanates, nonsteroidal anti-inflammatory drugs, phenytoin or warfarin.
- Patients with rheumatologic diseases
- Patients with primary Parathyroid disorder
- Patients with history of liver disease.
- Patients with history of bone fracture in last 6 months prior to enrollment.

ETHICAL CONSIDERATIONS: The present study was approved by the Institutional Committee of Human Ethics. Informed written consent was obtained from all the subjects included in the study. All the subjects participating in the study were informed about the risks and benefits of the study. We maintained the study participant's confidentiality.

DATA COLLECTION TOOLS: All the data that was collected was documented in a study proforma.

METHODOLOGY:

- Stage of Chronic kidney disease was defined according to K/DOQI criteria.[4] eGFR was calculated by using Cockcroft-Gault formula. After taking informed consent, patient's details and a detailed clinical history was obtained for symptoms suggestive of secondary hyperparathyroidism.

- All patients were clinically examined including general physical examination, careful examination of the Joints, examination of cardiovascular system, respiratory system, per abdomen and nervous system for the signs of secondary hyperparathyroidism.

- After taking the informed consent, about 6ml of blood was drawn at start of hemodialysis session to measure serum calcium, phosphorus, alkaline phosphatase, calcitriol and intact Parathyroid hormone.

- Serum intact parathyroid hormone was measured by electrochemiluminescence immunoassay, but not the fragments of it, which will also be increased in renal failure.

- Serum calcitriol was measured by chemiluminescence immunoassay, Alkaline phosphatase by King and Amstrong method, serum calcium by 5-nitro -5 methyl BAPTA method and serum phosphorus by phosphomolybdate UV Kinetic method.

FOLLOW UP: No follow-up was done as the present study was a cross sectional study.

INVESTIGATIONS :

Patients were subjected to following blood investigations:

1. Serum intact Parathyroid hormone
2. Serum Vitamin D
3. Serum Alkaline phosphatase.
4. Serum calcium
5. Serum phosphorus
6. Serum creatinine
7. Serum albumin

STATISTICAL METHODS :

The information collected from the patients was noted in master chart. Analysis of data was done using statistical software version SPSS 20.00, Descriptive statistics including frequency, percentage, mean and SD, Chi-square for independence, Karl Pearson's correlation coefficient for relationship were used and statistical significance was set at 5% level with $p<0.05$ considering significant.

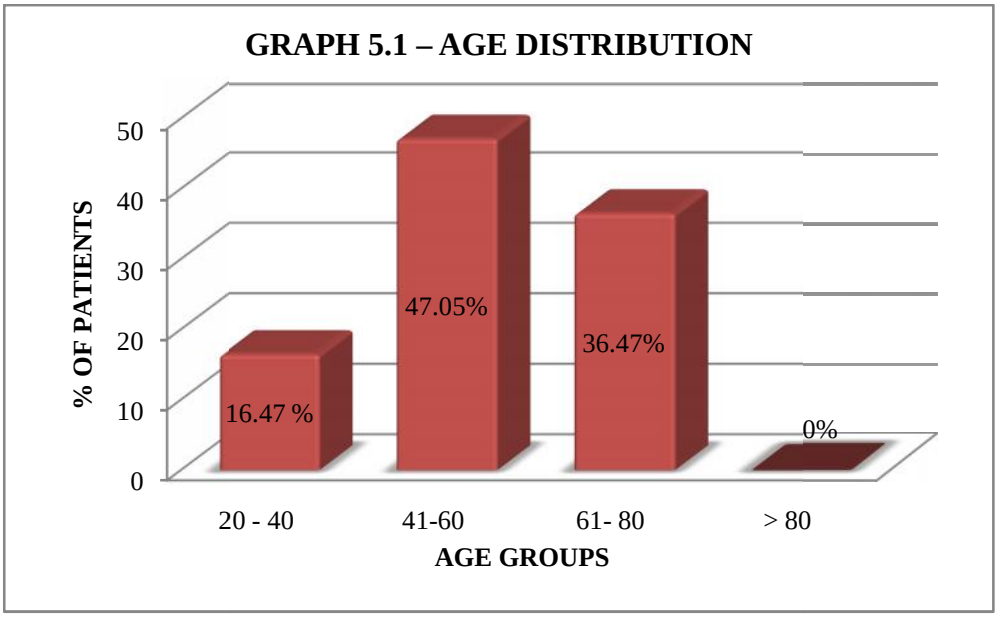
RESULTS

A total of 85 patients on maintenance hemodialysis were included in this study the results obtained were as follows -

TABLE 5.1 – AGE DISTRIBUTION

AGE GROUP	NO. OF PATIENTS	%
20 TO 40	14	16.47
41 TO 60	40	47.05
61 TO 80	31	36.47
>80	0	0
TOTAL	85	100
MEAN ± SD = 54.68± 12.46		

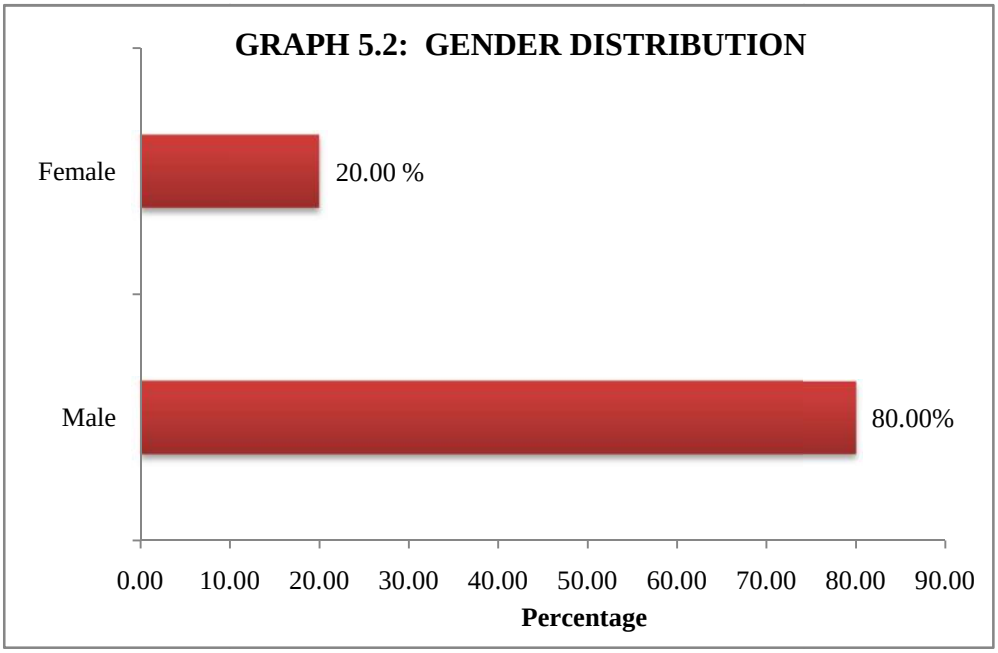
GRAPH 5.1 – AGE DISTRIBUTION



The mean age of the study population was 54.68 ±12.46 years and ranged from 23 years to 76 years. Table 1 depicts the age distribution of the patients and it can be concluded that majority of the patients were in the age group of 41- 60 years (47.05%).

TABLE 5.2 – GENDER DISTRIBUTION

GENDER	NUMBER	PERCENTAGE
FEMALE	17	20
MALE	68	80
TOTAL	85	100.00

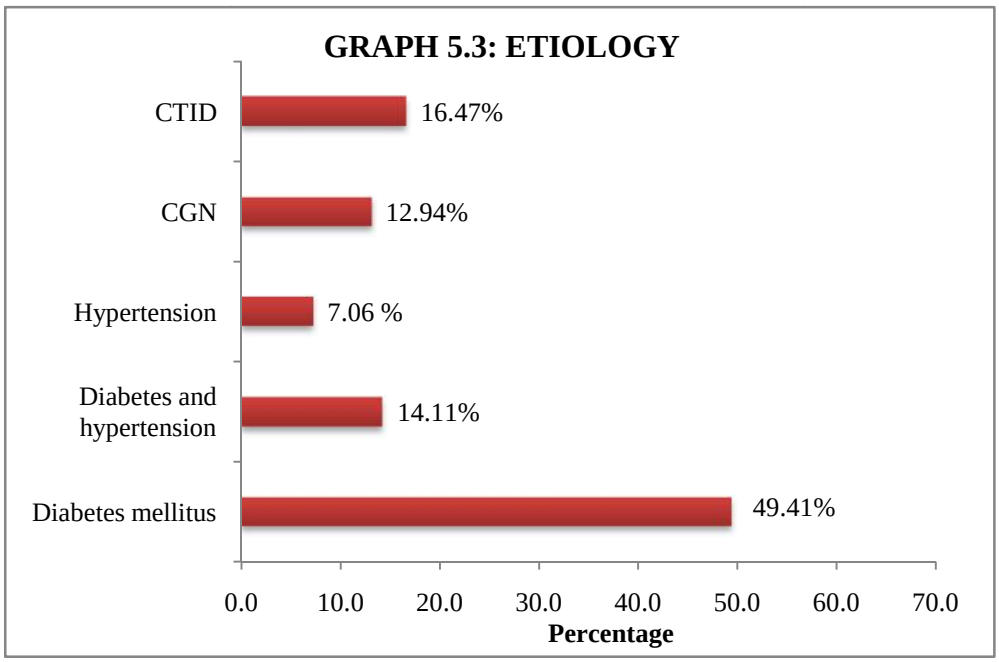


Males formed majority of the study population. Table 2 depicts that 80 % of the population were males as compared to females (20%)

ETIOLOGY OF CHRONIC KIDNEY DISEASE

TABLE 5.3 - ETIOLOGY

ETIOLOGY	NUMBER	PERCENTAGE
DIABETIC MELLITUS	42	49.41
DIABETES AND HYPERTENSION	12	14.11
HYPERTENSION	6	7.06
CGN	11	12.94
CTID	14	16.47
TOTAL	85	100.00

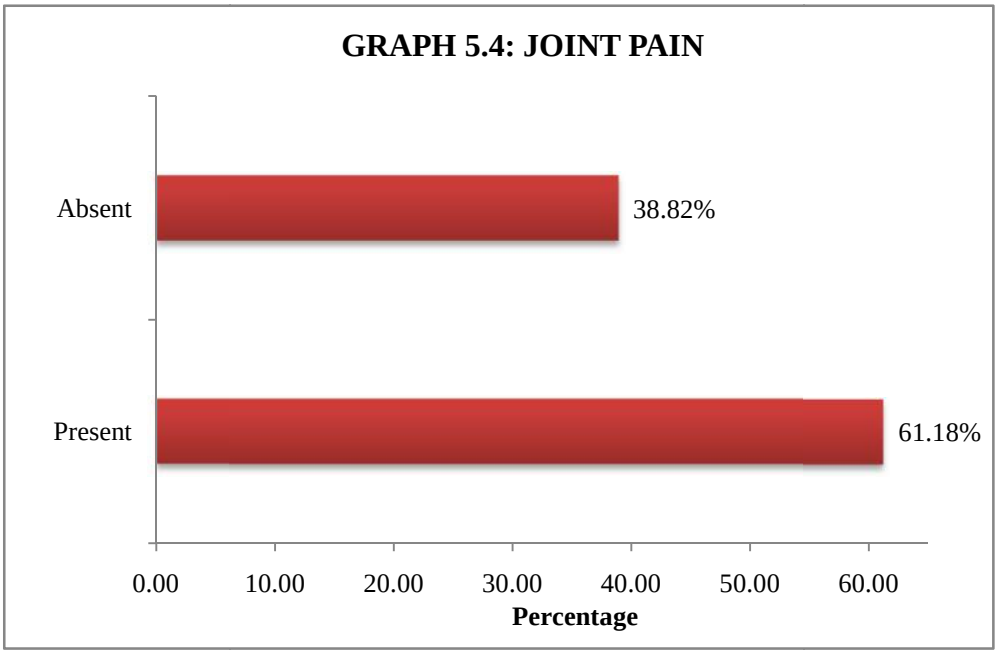


Diabetes Mellitus was the major cause of CKD in 49.41 % of patients. Other causes of CKD included Hypertension, chronic glomerulonephritis and CTID.

CLINICAL SYMPTOMS OF SECONDARY HYPERPARATHYROIDISM

TABLE 5.4 –JOINT PAIN

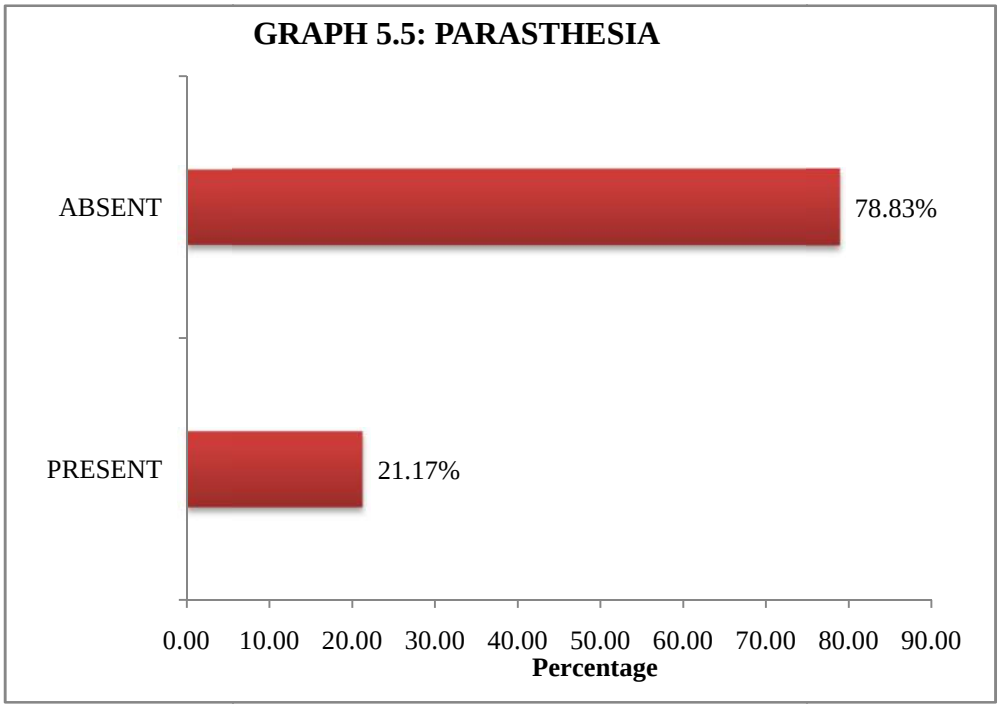
JOINT PAIN	NUMBER	PERCENTAGE
ABSENCE	33	38.82
PRESENCE	52	61.18
TOTAL	85	100



The above table depicts that among the 85 patients, 52 of them (68.87 %) had joint pain.

TABLE 5.5– PARASTHESIA

PARASTHESIA	NUMBER	PERCENTAGE
ABSENCE	67	21.17
PRESENCE	18	78.83
TOTAL	85	100

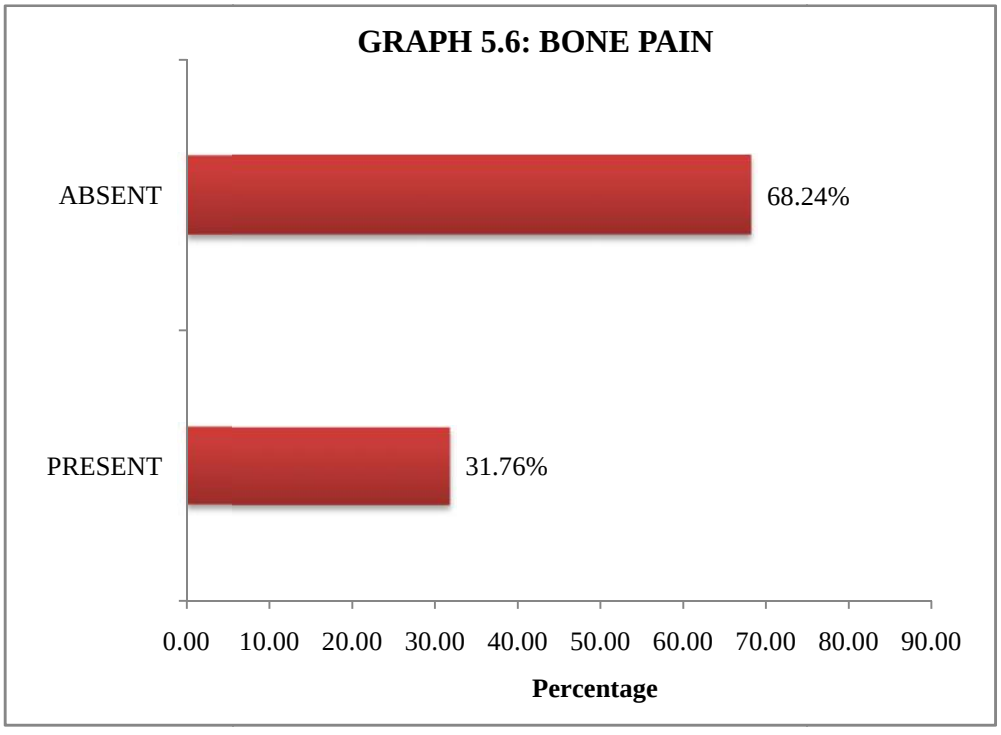


As seen in the above table, 21 % of the patients had parasthesia.

BONE PAIN

TABLE 5.6- BONE PAIN

BONE PAIN	NUMBER	PERCENTAGE
NO	61	68.24
YES	27	31.76
TOTAL	85	100.00

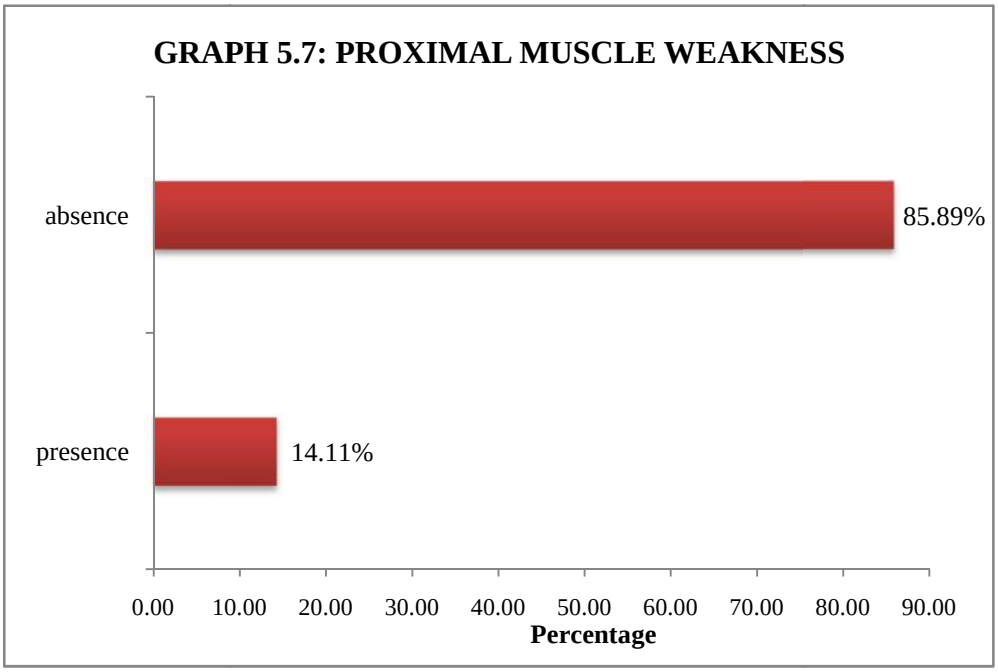


Above table depicts that 31.76% of patients, had bone pain.

PROXIMAL MUSCLE WEAKNESS

TABLE 5.7 –

PROXIMAL MUSCLE WEAKNESS	NUMBER	PERCENTAGE
PRESENT	12	14.11
ABSENT	73	85.89
TOTAL	85	100.00

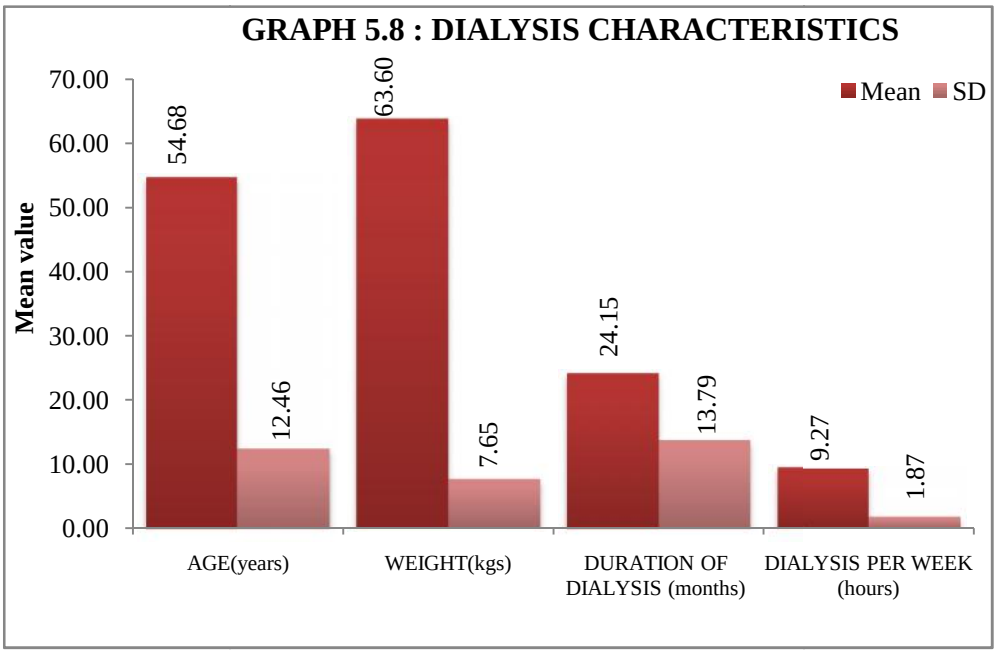


As per the above graph, 12 out of 85 patients (14.11 %) had proximal muscle weakness.

DIALYSIS CHARACTERISTICS

TABLE 5.8

Variables	Min	Max	Mean	SD
Age (years)	23	76	54.68	12.46
Weight (in kg)	40.00	78.00	63.60	7.65
Duration of dialysis (months)	7.00	72.00	24.15	13.79
Hemodialysis per week (hours)	8.00	12.00	9.27	1.87

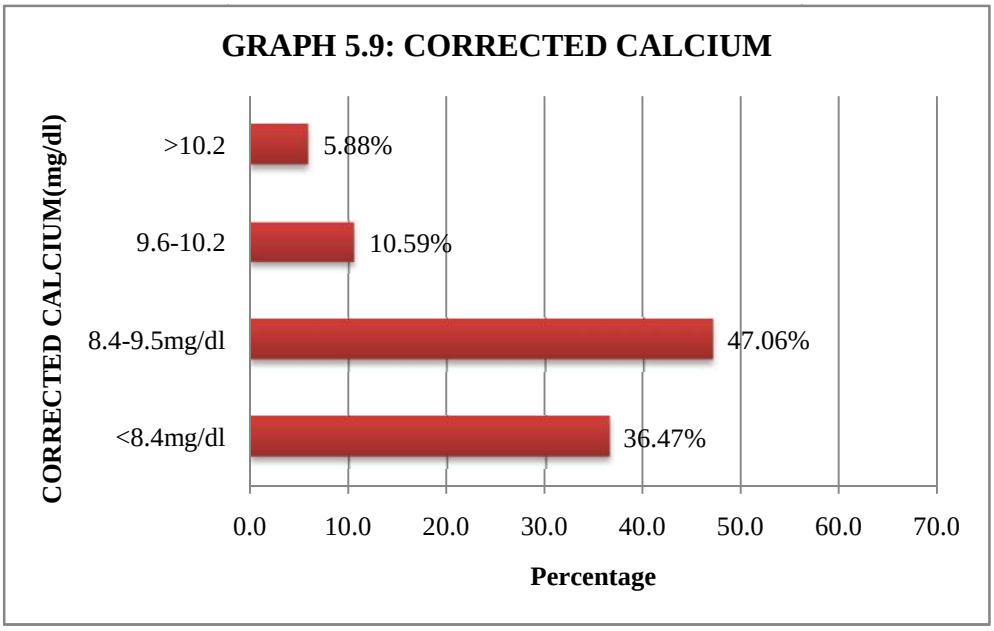


Dialysis characteristics of the study population are shown in above table. Patients underwent maintenance hemodialysis for an average of 24±13 months and 9.27 hours per week as depicted in graph 5.8.

LABORATORY FINDINGS: CORRECTED CALCIUM

TABLE 5.9 – VALUES OF CORRECTED CALCIUM

CORRECTED CALCIUM(in mg/dl)	NUMBER	PERCENTAGE
<8.4	31	36.47
8.4-9.5	40	47.06
9.6-10.2	9	10.59
>10.2	**5**	**5.88**
TOTAL	85	100
MEAN ±SD= 8.71 ± 1.09		

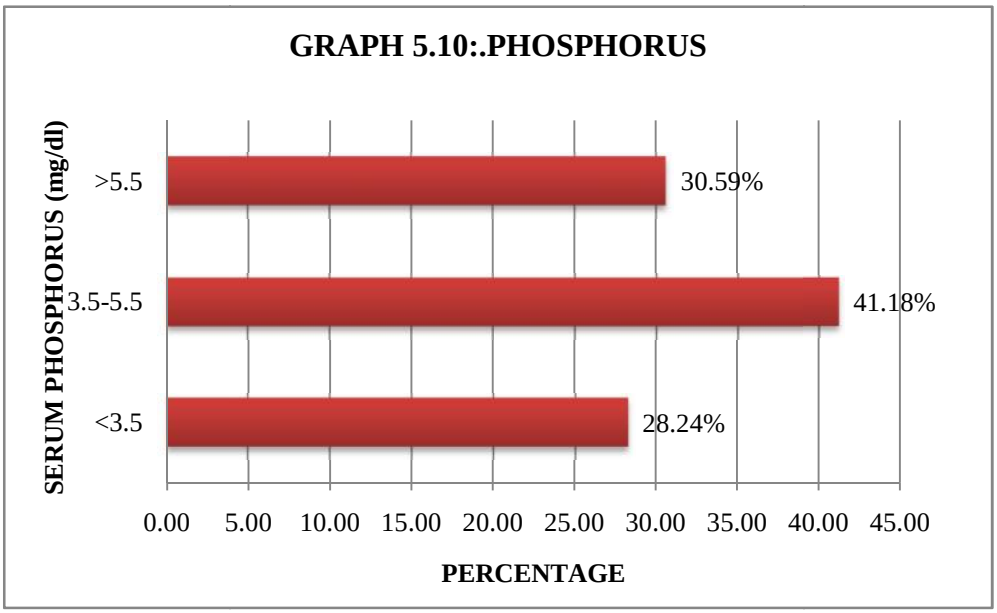


The above table shows that among the 85 patients in our study, 47.06 % of them had acceptable levels of serum corrected calcium in the range of 8.4 mg/dl to 9.5 mg/dl, 36.47 % of patients had values below and 16.47% of patients above the accepted range. 5.88% of patients had hypercalcemia with serum calcium > 10.2mg/dl. The mean value of corrected serum calcium was 8.71 ± 1.09 mg/dl.

PHOSPHORUS

TABLE 5.10- SERUM PHOSPHORUS CONCENTRATION

PHOSPHORUS (in mg/dl)	NUMBER	PERCENTAGE
<3.5	24	28.24
3.5-5.5	35	41.18
>5.5	26	30.59
TOTAL	85	100
MEAN ±SD= 4.50± 2.16		

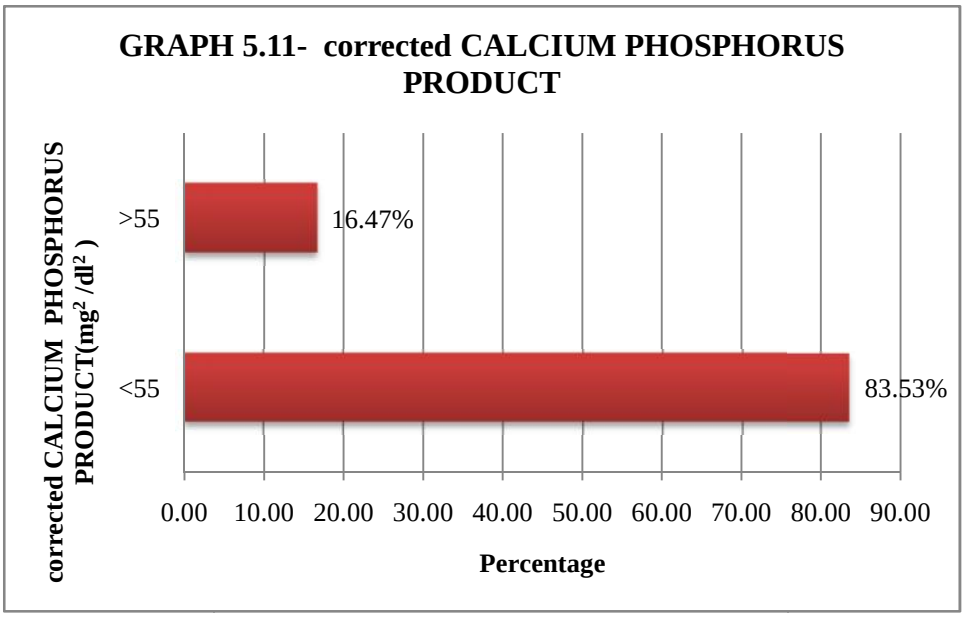


As per the above table, 24 out of 85 patients had serum phosphorus value of < 3.5 mg/dl, 35 of them had serum phosphorus between 3.5mg/dl and 5.5mg/dl and in 26 patients phosphorus was more than 5.5mg/dl. Mean value of phosphorus was 4.5±2.16 mg/dl.

Corrected CALCIUM PHOSPHORUS PRODUCT

TABLE 5.11– VALUE OF corrected CALCIUM PHOSPHORUS PRODUCT (cCaxP)

(cCaxP)	NUMBER	PERCENTAGE
<55	71	83.53
>55	14	16.47
TOTAL	106	100
MEAN ±SD =39.84±21.52		

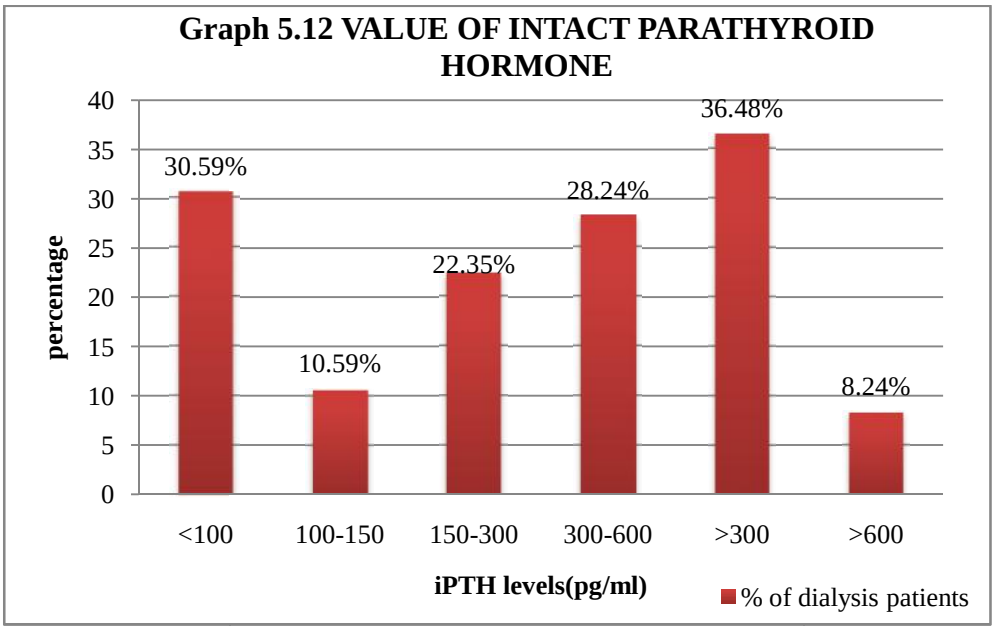


In our patients the values of corrected calcium phosphorus product ranged from 6.12 mg^2/dl^2 to 157mg^2/dl^2 with a mean of 39.84±21.52 mg^2/dl^2. 83.53% of patients had corrected calcium phosphorus product of less than 55mg^2/dl^2

PARATHYROID HORMONE

TABLE 5.12 – VALUE OF INTACT PARATHYROID HORMONE (iPTH)

iPTH (in pg/ml)	NUMBER	PERCENTAGE
<100	26	30.59
100-150	9	10.59
150-300	19	22.35
300-600	24	28.24
>600	7	8.24
TOTAL	85	100
MEAN ±SD=255.12±231.75pg/ml		

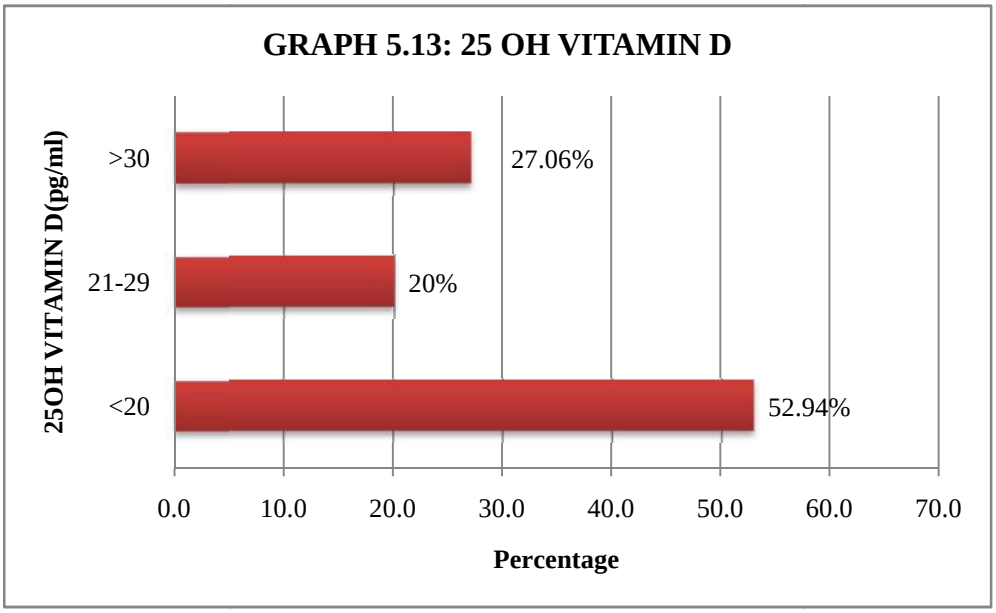


Mean level of iPTH was 255.12±231.75 pg/ml with a range from 4.3 to 987.60pg/l. The above table and graph depicts that 36.48% of patients had intact PTH levels above 300pg/ml suggesting hyperparathyroidism as per K/DOQI guidelines. 22.35% of patients had accepted range of intact PTH levels between 150-300 pg/ml and 41.18% of patients had intact PTH levels below 150pg/ml. 8.24% of patients had iPTH values > 600pg/ml and 30.59% of patients had iPTH levels less than 100pg/ml.

VITAMIN D

TABLE 5.13 – VALUES OF 25-OH VITAMIN D

25 OH VITAMIN D(ng/ml)	NUMBER	PERCENTAGE
≤20	45	52.94
21-29	17	20.00
≥30	23	27.06
TOTAL	85	100.00
MEAN ±SD = 25.83±19.52		

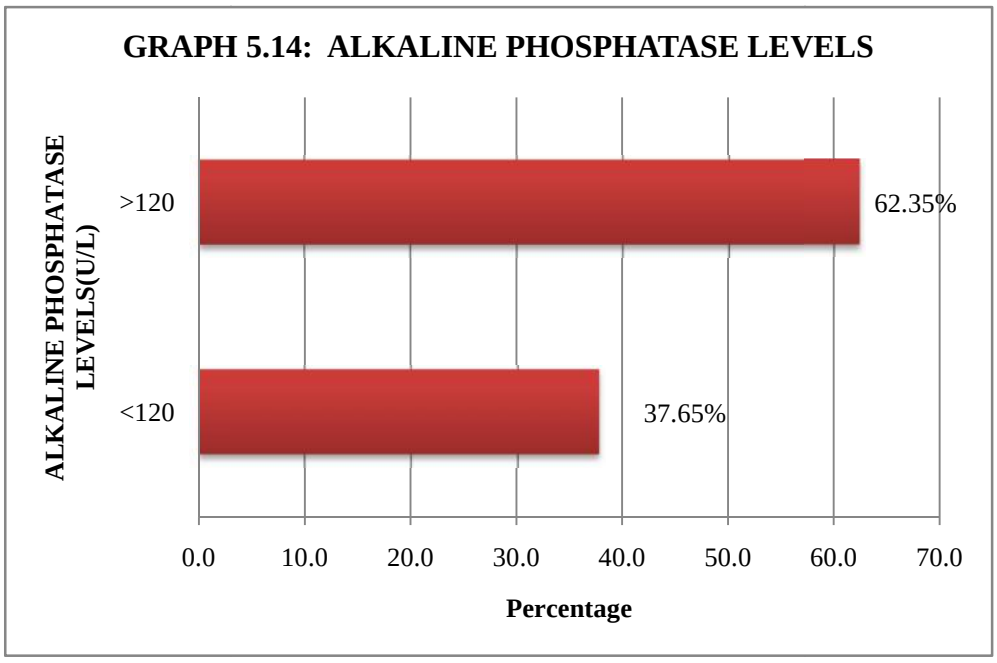


The above table depicts that 27.06 % of the patients had adequate levels of vitamin D with 25OH vitamin D levels of ≥ 30ng/ml, 52.94% of patients had vitamin D deficiency with 25OH vitamin D levels ≤20ng/ml and 20% of patients had vitamin D insufficiency with values between 21-29ng/ml. Mean levels of 25OH Vitamin D were 25.83 ± 19.52ng/ml.

ALKALINE PHOSPHATASE

TABLE 5.14- SERUM ALKALINE PHOSPHATASE LEVEL

ALKALINE PHOSPHATASE (U/L)	NUMBER	PERCENTAGE
<120	32	37.65
≥120	53	62.35
TOTAL	85	100
MEAN±SD=137.79±59.34		

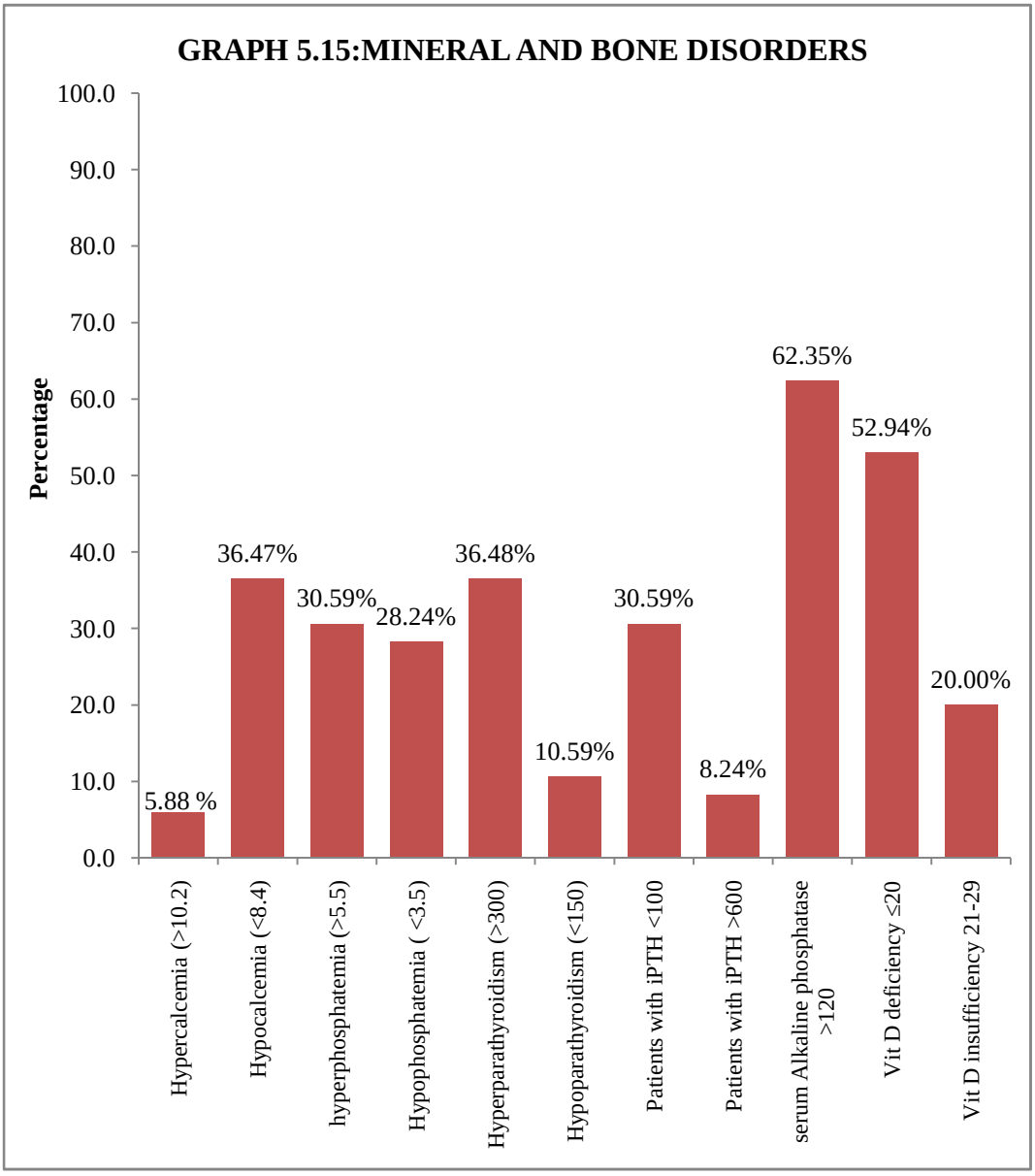


The mean level of alkaline phosphatase was 137.79±59.34 U/L. 37.65 % of the patients had serum alkaline phosphatase level of less than 120U/L and the rest 62.35 % had value of ≥120U/L.

BONE MINERAL DISORDERS

TABLE 5.15– BONE MINERAL DISORDERS

DISORDERS	NUMBER	PERCENTAGE
Hypercalcemia (>10.2mg/dl)	5	5.88
Hypocalcemia (<8.4 mg/dl)	31	36.47
Hyperphosphatemia (>5.5mg/dl)	26	30.59
Hypophosphatemia (<3.5mg/dl)	24	28.24
Hyperparathyroidism (>300pg/ml)	31	36.48
Hypoparathyroidism (<150pg/ml)	9	10.59
Patients with iPTH<100pg/ml	26	30.59
Patients with iPTH>600pg/ml	7	8.24
Serum alkaline phosphatase>120U/L	53	62.35
Vitamin D deficiency (≤ 20ng/ml)	45	52.94
Vitamin D insufficiency (21-29ng/ml)	17	20.00

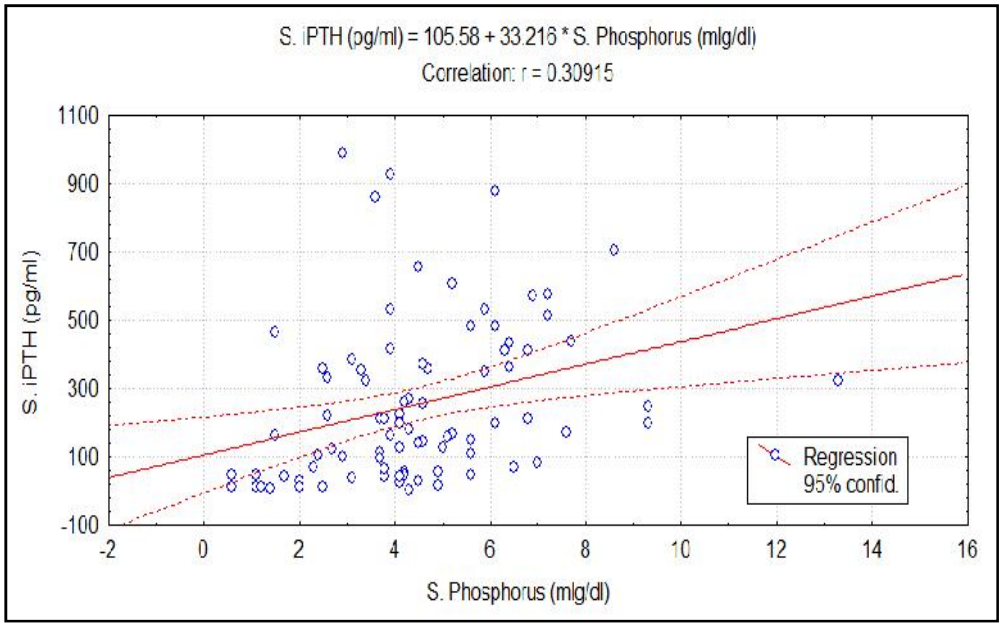


The various mineral and bone disorders in study population are shown in above table and graph. The most was common mineral bone disorder was elevated serum alkaline phosphatase levels in 62.35% of patients, followed by vitamin D deficiency in 52.94%, hyperparathyroidism in 36.48%, hypocalcemia in 36.47%, hyperphosphatemia in 30.59% of patients. iPTH levels were < 100pg/ml in 30.59% of our patients.

Table 5.16 - CORELATION OF iPTH WITH OTHER VARIABLES

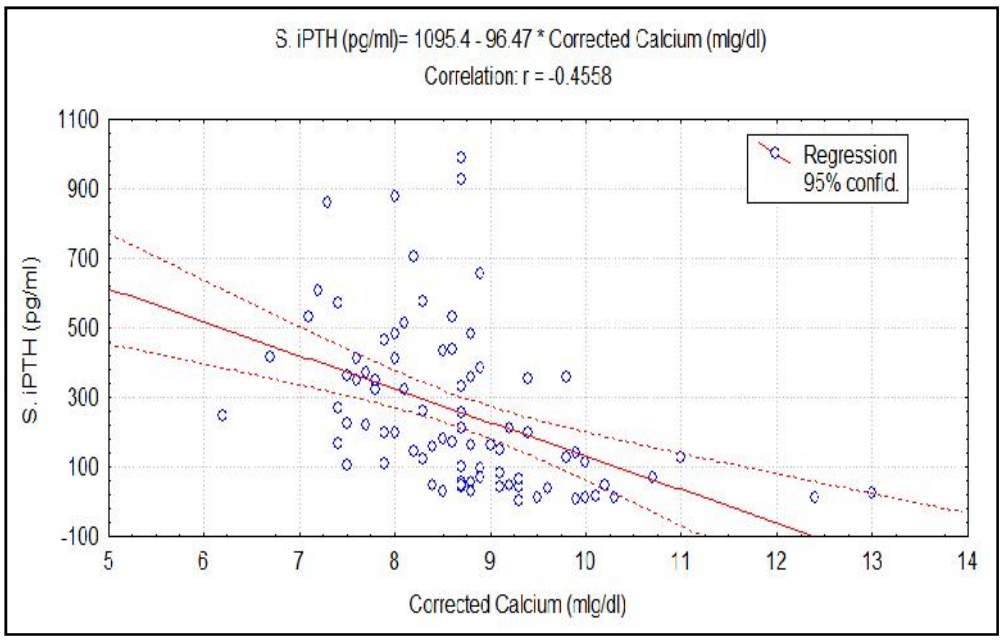
Variables	Correlation of iPTH with		
	r-value	t-value	p-value
S. Phosphorus (mg/dl)	0.3091	2.9615	0.0040*
Corrected Calcium (mg/dl)	-0.4558	-4.6649	0.0001*
Calcium Phosphorus product(mg^2/dl^2)	0.2059	1.9569	0.0500*
25 OH Vitamin D(ng/ml)	0.0089	0.0811	0.9356
Serum Alkaline Phosphatase(U/L)	0.2770	2.6267	0.0103*

a) GRAPH 5.16-CORRELATION OF iPTH WITH PHOSPHORUS



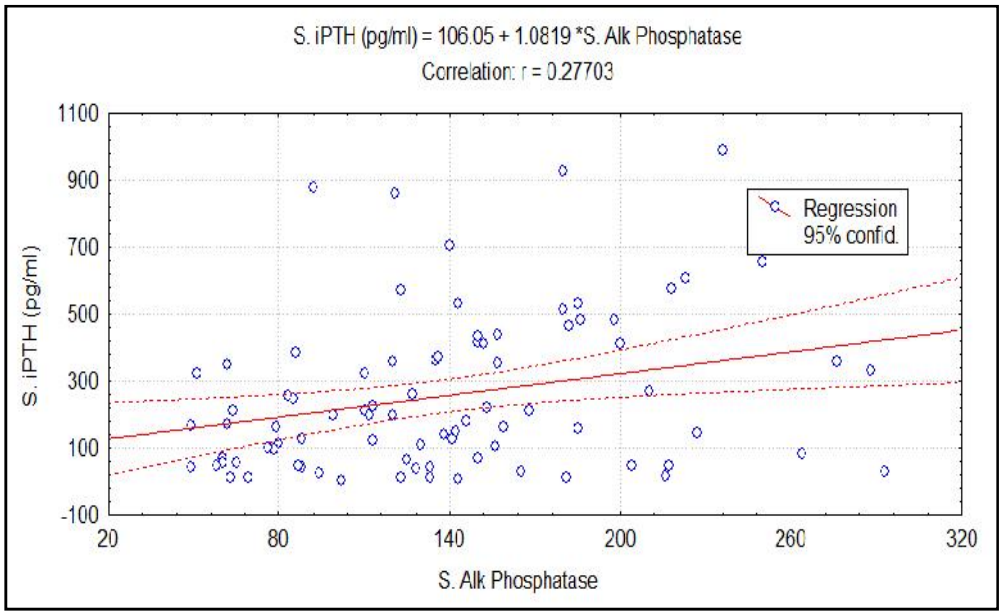
The study of correlation between serum iPTH levels and serum phosphorus levels revealed that there was a positive correlation(r = 0.3091) between the two. Hence, it can be inferred that, as serum phosphorus increases, the level of iPTH increases. This correlation is statistically significant (p value-0.004). Therefore with worsening of renal function as phosphate level increases; there is rise in serum iPTH levels.

b) GRAPH 5.17-CORRELATION OF iPTH WITH CORRECTED CALCIUM



The above graph depicts that there is a negative correlation between value of iPTH with corrected calcium levels (r = -0.4558) and this correlation was statistically significant (p value - 0.0001). This implies that with decrease in serum calcium, there is rise in serum iPTH levels.

c) GRAPH 5.18 – CORRELATION OF iPTH WITH ALKALINE PHOSPHATASE LEVELS



The above graph shows that there is a positive correlation of iPTH with alkaline phosphatase levels (r=0.2770) and this correlation was statistically significant (p value-0.01).

COMPARISION BETWEEN DIABETIC AND NON DIABETIC PATIENTS

Different parameters were compared between those with and without diabetes mellitus and results are as shown below.

Table 5.17-COMPARISON OF PARAMETERS BETWEEN DIABETIC AND NON-DIABETIC PATIENTS

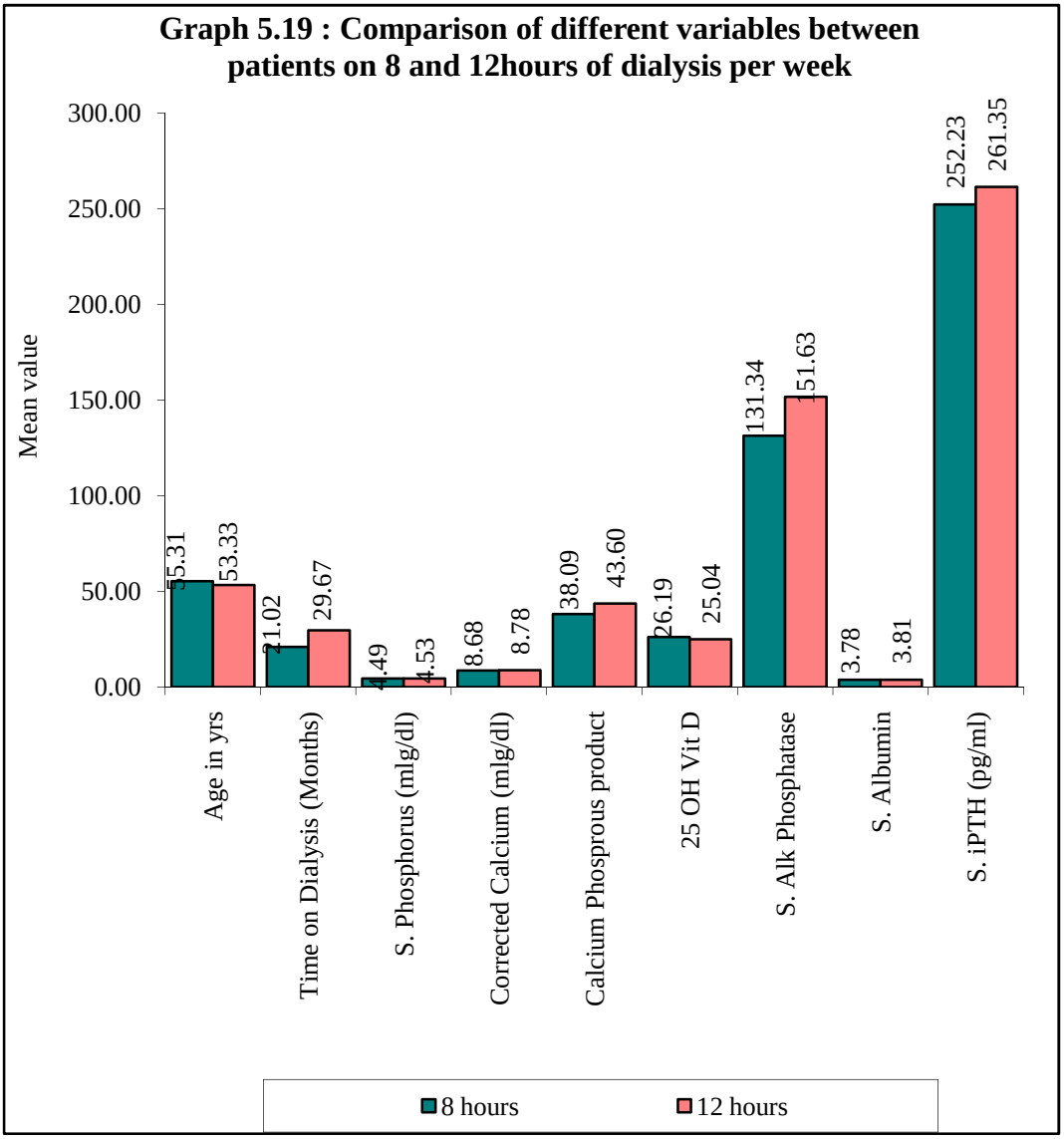
Variables	Diabetic group		Non-diabetic group		t-value	p-value
	Mean	SD	Mean	SD		
Age in years	60.46	8.38	44.61	12.07	7.1217	0.0001*
Duration of Dialysis (Months)	24.19	13.30	23.03	16.09	0.3561	0.7227
S. Phosphorus (mg/dl)	4.40	1.93	4.68	2.53	-0.5647	0.5738
Corrected Calcium (mg/dl)	8.72	1.16	8.69	1.00	0.1081	0.9142
Calcium Phosprous product(mg^2/dl^2)	39.74	22.20	40.01	20.65	-0.0560	0.9554
25 OH Vitamin D(ng/ml)	24.28	15.42	28.52	25.19	-0.9625	0.3386
S. Alkaline Phosphatase(U/L)	150.61	61.31	115.45	49.07	2.7284	0.0078*
S. Albumin(gm/dl)	3.79	0.66	3.78	0.63	0.1164	0.9076
S. iPTH (pg/ml)	271.16	224.13	227.20	245.69	0.8402	0.4032

Patients with diabetes had lower serum phosphate and higher corrected calcium levels but were not statistically significant. There was no significant difference in iPTH levels between diabetic and non-diabetic patients with mean iPTH of 270 pg/ml and 227pg/ml respectively.

Table 5.18- COMPARISON OF DIFFERENT VARIABLES BETWEEN PATIENTS ON 8 AND 12 HOURS OF DIALYSIS.

Variables	8 hours/week		12 hours/week		t-value	p-value
	Mean	Std.Dev.	Mean	Std.Dev.		
Age in years	55.31	12.49	53.33	12.52	0.6788	0.4992
Duration of Dialysis (Months)	21.02	12.61	29.67	16.08	-2.6919	0.0086*
S. Phosphorus (mg/dl)	4.49	2.07	4.53	2.37	-0.0791	0.9372
Corrected Calcium (mg/dl)	8.68	1.10	8.78	1.11	-0.3841	0.7019
Calcium Phosprous product	38.09	16.87	43.60	29.18	-1.1004	0.2743
25 OH Vitamin D(ng/ml)	26.19	21.15	25.04	15.76	0.2510	0.8025
S. Alkaline Phosphatase(U/L)	131.34	54.51	151.63	67.61	-1.4776	0.1433
S. Albumin(g/dl)	3.78	0.62	3.81	0.71	-0.1858	0.8530
S. iPTH (pg/ml)	252.23	226.26	261.35	247.43	-0.1681	0.8670

Graph 5.19 : Comparison of different variables between patients on 8 and 12hours of dialysis per week



Different parameters were compared between patients on hemodialysis for 8 hours and 12hours per week as shown in above table. There was no significant difference in iPTH levels between the 2 groups with mean iPTH of 252.23 pg/ml in patients on 8 hours/week and 261.35pg/ml in patients on 12 hours/week of dialysis.

DISCUSSION

A total of 85 patients with chronic kidney disease stage 5 on maintenance hemodialysis, in Department of nephrology, KLES Dr. Prabhakar Kore Hospital and Medical research centre were studied during the period January 2018 to December 2018. The study was done to evaluate the prevalence of secondary hyperparathyroidism in maintenance hemodialysis patients.

AGE DISTRIBUTION

The mean age of our study population was 54.68 ± 12.46 years. This was in concordance with a study conducted by Sanjay Vikrant et al., where in the age group affected was 56.8±13years.[92] In a study by Suresh Sankarasubbaiyyan et al., mean age of study population was 47.31± 14.66 years.[93] Similarly, in another study done by Walter G. Douthat et al., the mean age was found to be 55.3 ±17.6 years.[95]

GENDER DISTRIBUTION

In the present study, 80% of the patients on maintenance hemodialysis were males which is similar to a study done by B.Ghosh et al., in which 78 % of the subjects were males.[91] Also in Suresh Sankarasubbaiyyan et al., study 78% were men.[93]In a study done by Sanjay Vikrant et al., there were 77.3% males as compared to 22.7% of females.[92] Males are more than females in CKD population in most studies.

ETIOLOGY OF CHRONIC KIDNEY DISEASE

Diabetes Mellitus was the most common etiology for chronic kidney disease in our study, i.e. 49.41%. This is in concordance with the study done by Salim Lim et al., in which majority of the patients (67%) had diabetes mellitus as the cause of CKD.[97] In Suresh Sankarasubbaiyyan et al., study diabetes was the cause of stage 5 CKD in 29.5% of patients.[93] However in another study by B.Ghosh et al., chronic glomerulonephritis was the most common cause in 41.44% of patients.[91]

DIALYSIS CHARACTERISTICS

a) Duration of dialysis.

Patients in our study population were on maintenance hemodialysis for a mean duration of 24.15±13.79 months before enrollment into the study. This was similar to the study done by Salim Lim et al., in which patients were on dialysis for a mean duration of 23± 17 months.[97] In another study by Gallieni et al., patient underwent dialysis for about 72.2 months which was longer compared to our study population.[98]

b) Hemodialysis session/week.

Our patients had shorter dialysis session with mean of 9.27 ± 1.87 hours/week compared to study of Salim Lim et al., in which patients underwent 13.5± 1.2 hours of dialysis per week.[97]

BIOCHEMICAL PARAMETERS

CALCIUM

In our study the mean levels of serum corrected calcium was 8.71±1.09mg/dl. In a study by Ghosh et al., mean serum corrected calcium was 8.24±1.26mg/dl.[91] The Walter G. Douthat et al., showed that mean level of serum calcium was 8.9±0.9mg/dl in their study population.[95] In Salim Lim et al. study mean level of serum corrected calcium was 9.4±0.6mg/dl.[97]

The results of our study showed that only 47.06 % of patients had acceptable levels of serum corrected calcium, 36.47% had below and 16.47% had values above the acceptable levels. In the study done by Fatemeh Hayati et al., 55.4% had acceptable levels (8.4-9.5mg/dl), while 7.1% had above and 37.5% had values below acceptable levels, which is similar to our study.[94] In study by Salim et al., 58% of the patients had serum calcium between 8.4 to 9.5 mg/dl.[97]

PHOSPHORUS

In our study the mean level of serum phosphorus was 4.5±2.16mg/dl. In Salim et al. study, mean level of serum phosphorus was 5±1.4mg/dl.[97] In Walter G. Douthat et al. study, mean levels of serum phosphorus was 5.2±1.5mg/dl.[95] In Ghosh et al. study, mean levels of phosphorus was about 5.7mg/dl.[91]

41.18% of patients in our study had acceptable levels of serum phosphorus between 3.5-5.5 mg/dl. Majority of patients had the values outside the acceptable levels, with 28.24% below and 30.59% above the acceptable levels. In the study by Fatemeh Hayati et al., all the patients had serum phosphorus levels >5.5 mg/dl.[94] In

the study by Salim Lim et al., 67% of patients had serum phosphorus levels between 3.5 to 5.5 mg/dl.[97]

PARATHYROID HORMONE

In our study mean iPTH value was 255.12±231.75mg/dl. In Ghosh et al. study, mean level of iPTH was about 288pg/ml.[91] In Suresh Sankarasubbaiyyan et al.study, iPTH level was 124.6±174.9 pg/ml.[93] In Fatemeh Hayati et al. study, mean iPTH levels were 483.3±285.8pg/ml.[94] In Walter G. et al. study, mean levels of iPTH was 529±567pg/ml.[95]

41.8% of our patients had intact PTH levels <150pg/ml, 22.35% had between 150 to 300pg/ml and 36.48% of patients had more than 300pg/ml. Majority of our patients (77.66%) had iPTH levels outside the acceptable levels.

36.48% of patients had hyperparathyroidism with iPTH levels of >300pg/ml. Walter G Douthat et al., found that 54.5% of patients had iPTH > 300pg/ml.[95] In a study by Fatemeh Hayati et al., 69.6% of patients had iPTH >300pg/ml which is very high compared to our results.[94] In an Indian Study by Sanjay Vikrant et al., 53.1% of patients had hyperparathyroidism with iPTH levels >300pg/ml.[92]

In Dialysis Outcomes and Practice Patterns Study (DOPPS), which is one of the largest multinational observational study about bone and mineral disorders in dialysis patients, only 26.7% of patients had hyperparathyroidism with iPTH >300pg/ml.[99,100] Our study shows the results which are approximately similar to DOPPS study.

In our study 41.18% of patients had iPTH levels less than 150pg/ml, 22.35% had iPTH levels between 150 -300pg/ml and 36.48% had iPTH levels more than 300pg/ml. In DOPPS study the percentages of patients on dialysis with iPTH levels below 150 pg/ml and iPTH greater than 300pg/ml in Japan, European countries and United States were 58.6% and 19.0%, 50.1% and 26.9%, and 48.2% and 30.3%, respectively.[99,100]

In our study, only 8.24 % of patients had serum iPTH levels >600pg/dl, which is more than the accepted range set by K/DIGO guidelines.[101] In an Indian study by B Ghosh et al., 20.72% of patients had iPTH more that 600pg/ml.[91]

In contrast to other Indian studies, prevalence of secondary hyperparathyroidism in our study was lower. Only 36.48% in our study population developed secondary hyperparathyroidism (defined as iPTH > 300pg/ml) due to higher reference range of iPTH levels in our study.

In our study 30.59% of patients had serum iPTH levels <100pg/ml which is similar to study done by Salim Lim et al., in which 30% of patients had iPTH<100pg/ml.[97] In a study by Moriniere et al, it was observed that most of the cases of adynamic bone disease were found in patients with serum iPTH levels of less than 100pg/ml.[102] In Suresh Sankarasubbaiyyan et al. study, 69.5% of patients had iPTH levels less than twice the normal range(<130pg/ml).[93]

VITAMIN D

The mean levels of 25OH Vitamin D in our study was 25.83±19.52ng/ml. In Walter G. Douthat et al. study, mean levels 25OH Vitamin D was 24.6±6.7ng/ml.[95] In Ghosh et al. study, mean level of Vitamin D was about 18.4ng/ml.[91]

In our study, majority of patients (52%) had vitamin D deficiency. The study by Sanjay Vikrant et al., showed that 87% of patients had vitamin D deficiency.[92] In a study by B.Ghosh et al., 58% of patients had vitamin D insufficiency, which is similar to our study.[91]

CALCIUM PHOSPHORUS PRODUCT

The mean level of corrected calcium phosphorus product, in our study was 39.84± 21.52 mg^2/dl^2. In Douthat et al. study, mean level of corrected calcium phosphorus product was 46± 13.8 mg^2/dl^2.[95] In Hayati et al. study, mean levels were 63.6±8 mg^2/dl^2.[94]

Our study found that 83.53% of patients had corrected calcium phosphorus product of less than $55mg^2/dl^2$ similar to study done by Salim Lim et al. in which 81% of patients had corrected calcium phosphorus product <$55mg^2/dl^2$.[97] In contrast, study by Fatemeh Hayati et al., showed that 81% of patients had corrected calcium phosphorus product more than $55mg^2/dl^2$.[94]

ALKALINE PHOSPHATASE LEVELS

The mean level of serum alkaline phosphatase in our study was 137.79±59.34 U/L. In Ghosh et al. study, mean levels of alkaline phosphatase were about 180U/L.[91]

In our study 62.35% of patients had ALP levels ≥120 U/L. Sanjay Vikrant et al. found that 78% of patients had ALP levels more than 120U/L which is more than our study.[92] In study by B.Ghosh et al., 76.66% had serum ALP levels of more than 112U/L.[91]

MINERAL AND BONE DISORDERS

A high prevalence of biochemical abnormalities of bone mineral metabolism was found in our study. 62.35% of patients had elevated alkaline phosphatase levels, 52.94% of patients had vitamin D deficiency, 41.18% of patients had iPTH levels <150pg/ml, 36.48% of patients had Secondary hyperparathyroidism with iPTH > 300pg/ml, 36.47% of patients had hypocalcemia, 30.59% of patients had iPTH levels <100pg/ml, 30.59% of patients had hyperphosphatemia, 5.88% of patients had hypercalcemia.

Agarwal et al. found hypocalcemia in 49.6% of patients.[103] Ghosh et al. showed that 54.95% of patients had hypocalcemia, 2.7% had hypercalcemia and 70.27% had hyperphosphatemia(>4.5mg/dl).[91] Sanjay Vikrant et al. found that 15% of patients had hypercalcemia, 15% had hypocalcemia and 78% had hyperphosphatemia(>4.5 mg/dl).[92] Compared to these Indian data our study population had less prevalence of hypocalcemia and hyperphosphatemia as in Suresh Sankarasubbaiyyan et al. study, in which 16.5% had hypocalcemia and 35.7% of patients had hyperphosphatemia.[93] LaClair et al. found hypocalcemia in 28% and hyperphosphatemia (phosphorus>4.5mg/dl) in 50% of patients.[104] Thus western data showed lower prevalence as in our study.

Prevalence of secondary hyperparathyroidism in our study was 36.48%. Agarwal et al. found hyperparathyroidism in 39.4% of patients similar to our study.[103] DOPPS study also found prevalence of secondary hyperparathyroidism to be 26.7%.[99,100] Fatemeh Hayati et al. found a prevalence rate of 69.6% and Salim Lim et al. found prevalence rate of 17%.[94,97]

In B.Ghosh et al. study, prevalence of secondary hyperparathyroidism was 88.29% which was very high compared to other studies as they defined hyperparathyroidism as iPTH value of >69pg/ml.[91] Sanjay Vikrant et al. also found a prevalence of SHPT of 82.7% considering iPTH levels of >65pg/ml as hyperparathyroidism.[92] Owda A et al. found a prevalence rate of SHPT to be 78% at a cutoff of 200pg/ml of serum iPTH and with the same cutoff level, Salem et al. found 50% of prevalence.[96,105] As we used higher cutoff range of 300pg/ml, compared to these studies, lower prevalence was found in our study population.

Only 8.24% of our study population had iPTH of > 600pg/ml whereas B.Ghosh et al. found 26.13% of patients with iPTH>600pg/ml.[91] Walter G Douthat et al. found 28.3% of patients with iPTH values of >600pg/ml.[95]

30.59% of our patients had iPTH < 100pg/ml with more predilection for adynamic bone disease. In Suresh Sankarasubbaiyyan et al., study, 69.5% of patients had iPTH levels less than twice the normal range (<130pg/ml).[93]

There was no significant difference in mean iPTH levels between diabetic and non diabetic patients and also between patients on 8 and 12 hours of dialysis as found in Suresh Sankarasubbaiyyan et al., study.[93]

CONCLUSION

To conclude, our study found a spectrum of mineral and bone disorders in patients with chronic kidney disease stage 5 on maintenance hemodialysis. Mean levels of phosphate, corrected calcium and calcium phosphorus product were in the acceptable levels in our study population. We also found many patients with vitamin D deficiency, secondary hyperparathyroidism, oversupression of iPTH, hypocalcemia, hyperphosphatemia in our dialysis patients.

Two fifth of patients (40%) had over-suppression of iPTH levels and a third of our patients on maintenance hemodialysis were at risk of developing adynamic bone disease.

We found a lower prevalence rate (36%) of secondary hyperparathyroidism in our study population, with no significant difference in parathyroid hormone levels between diabetic and non-diabetic patients and also between patients on 8 and 12 hours of hemodialysis per week.

SUMMARY

The study population consisted of 85 patients diagnosed to have stage 5 chronic kidney disease and were on maintenance hemodialysis for more than 6 months. The mean age of the study population was 54.68±12.46 years and 80% of them were males. Among 85 patients, 42 (49.41%) had Diabetes Mellitus as the etiology of chronic kidney disease.

The patients coming to the hospital for maintenance hemodialysis had various symptoms of secondary hyperparathyroidism like joint pain, parasthesia, bone pain and proximal muscle weakness. Joint pain was present in 61.18% of the patients, 21.17% had parasthesia, 31.76% had bone pain and 14.11 % had proximal muscle weakness. Mean duration of hemodialysis of our study population before enrollment was 24±13.79 months.

Laboratory evaluation showed that 47.06% of patients had acceptable levels of serum corrected calcium (8.4-9.5 mg/dl), 36.47% had hypocalcemia (serum corrected calcium < 8.4mg/dl) and 16.47% had values above the acceptable levels (>9.5mg/dl). 5.88% of patients had hypercalcemia (corrected calcium > 10.2mg/dl). 41.18% of patient had acceptable levels of serum phosphorus between 3.5-5.5 mg/dl, 28.24% had hypophosphatemia (<3.5mg/dl) and 30.59% had hyperphosphatemia(>5.5mg/dl).

41.8% of our patients had intact PTH levels <150pg/ml, 22.35% had between 150 to 300pg/ml and 36.48% of patients had more than 300pg/ml. 36.48% of patients had Secondary hyperparathyroidism with iPTH > 300pg/ml, 41.18% had hypoparathyroidism with iPTH levels of less than 150pg/ml and 30.59% of patients had iPTH levels of less than 100pg/ml who are at risk of adynamic bone disease.

52% of patients had vitamin D deficiency(25OH vitamin D ≤20 ng/ml) and 20% had vitamin D insufficiency with values between 21 to 29 ng/ml. Elevated alkaline phosphatase levels (>120U/L) was seen in 62.35% and was the most common mineral bone disorder.

On further evaluation, there was significant positive correlation between serum iPTH and serum phosphorus and alkaline phosphatase levels. iPTH levels had significant negative correlation with serum calcium levels. Different laboratory parameters were compared between diabetic and non-diabetic patients. There was no significant difference in iPTH, calcium and phosphorus levels between the two groups. Different laboratory parameters were also compared between patients on hemodialysis on 8hours and 12 hours per week but there was no statistically significant difference in iPTH, calcium and phosphorus levels between the two groups.

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ANNEXURE I – CONSENT FORM

INFORMED CONSENT

"Prevalence of Secondary hyperparathyroidism in patients with stage 5 Chronic Kidney Disease on Maintenance hemodialysis'' – A one year hospital based Cross-sectional study

PRINCIPAL INVESTIGATOR:

DR. _____

Post Graduate student

Department of General Medicine

GUIDE :

DR._____

Professor

Department of General Medicine

J.N. Medical College, KLE, KAHER, Belgaum

CO-GUIDE:DR. _____

Professor, Department of Nephrology J.N. Medical College, KAHER,, Belgaum

INTRODUCTION AND PURPOSE:

The present study is being conducted among patients with stage 5 chronic kidney disease patients on maintenance hemodialysis attending dialysis unit, department of Nephrology in KLE's Dr.Prabhakar Kore Charitable Hospital and Medical Research Centre, Belgaum and will be investigated for the presence of secondary hyperparathyroidism. You are requested to participate in the study and your participation is completely voluntary.

PROCEDURE:

If you agree to participate in this 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 sample for the necessary investigations.

RISKS 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 (rarely happens) at the site from where the blood is drawn. You may be benefitted by these investigations and you will be part of this study which is going to be useful to others in future.

Alternatives:

Taking part in this study is voluntary. You may choose not to take part in this study. If you decide to take part 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 stop your participation in this study at 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 MD degree, review and publishing.

QUERIES AND CONTACT:

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

1. Dr.RoopaBellad, Chairman, J.N.M.C Ethical Committee for Human Research 9448113403

CONSENT FORM

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 this consent form, or it has been read to me and have had all the questions answered.

Signature / Left Thumb print of the Participant or legally authorized representative

Participant's name :……...

Signature / Left thumb impression:……...of the participant

Name of the legally authorized :……...

representative / guardian

Signature / Left thumb impression :……...

Witness' name :……...

Signature / Left thumb impression :……...

Investigator's name and signature :……...

Date:

Place:

ANNEXURE-II

PROFORMA

"Prevalence of Secondary hyperparathyroidism in patients with stage 5 Chronic Kidney Disease on Maintenance hemodialysis'' – A one year hospital based Cross-sectional study

Name:

Age/Sex:

IP /OP No:

Occupation:

Date of Admission:

Address:

CHIEF COMPLAINTS:

Joint pain- site, duration, type and severity of pain

Limited range of movement of joints (shoulder, elbow, small joints of hands, hip, ankle)

Irritation and redness of eye

Dyspnea

Fatigue

Palpitation

Chest pain

Syncope

Epigastric pain/Discomfort: relieved or precipitated by food

Nausea, weight loss

Parasthesias of fingers, toes and circumoral region

Seizures

Symptoms of proximal muscle weakness

Pruritus

Psychosis

Diffuse bone pain

Pain due to fractures

Symptoms of Renal Failure:Hiccups/ Puffiness of

face/Headache/Drowsiness/Distension of abdomen/ others…..

Any other……..

PAST HISTORY:

1. Diabetes Mellitus
2. Hypertension
3. HIV/ HBsAg infection
4. Others

FAMILY HISTORY:

PERSONAL HISTORY :

Diet: Appetite: Sleep:

Bowel/Bladder: Habits: Alcohol/smoking

GENERAL EXAMINATION

Temperature	Pulse	Respiratory Rate	B.P

Chvostek's Sign: Carpopedal spasm: Laryngeal spasm:

Trousseau's Sign: Facial grimacing:

Pallor Oedema Icterus

Lymphadenopathy Cyanosis Clubbing

JVP:

Ophthalmic examination:

1. Inflammation and redness of conjunctiva
2. White plaques/ punctate deposits in conjunctiva
3. Slit-lamp examination showing corneal band keratopathy 4. Papilledema

Skin ulcerations/ small macules or papules:

Palpable subcutaneous nodules or masses:

Tumoral mass adjacent to joints: Tendonitis:

SYSTEMIC EXAMINATION:

Respiratory system :

Breath sounds

Crepitations

Rales

Cardiovascular system :

Apical impulse

Parasternal impulse

Heart sounds

Murmurs

Per abdomen:

Hepatomegaly

Splenomegaly

Ascites

Central nervous system:

Higher Mental Functions:

Cranial Nerves:

Motor system:

Sensory system:

Musculo Skeletal system:

Skeletal fracture

Tendonitis/avulsion of tendon: Rupture of patella

INVESTIGATIONS:

Serum calcium	
Serum phosphorus	
Serum intact parathyroid hormone	
Serum Alkaline Phosphatase	
Serum Vitamin D	

Hb

Serum Creatinine

Serum Albumin

GFR

ECG

ECHO

X-Ray

Other imaging modalities

Other investigations

Diagnosis:

Treatment given:

Signature of the guide: **Date:**

Signature of the co-guide:

ANNEXURE-III- ETHICAL CLEARANCE LETTER

K.L.E.UNIVERSITY'S
JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRU NAGAR, BELAGAVI-590010 (KARNATAKA-INDIA)
(Accredited 'A' Grade by NAAC)

Website: http://www.jnmc.edu
E-Mail : dome@jnmc.edu

Phone: (+ 91-(0)831 Office : 2471350
Principal: 2471701
Fax No. +91 (0)831 – 2470759

Ref: MDC/DOME/ 34 **Date: 22/11/2017**

To.

PG student in Medicine.
J.N.Medical College.
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"PREVALENCE OF SECONDARY HYPERPARATHYROIDISM IN PATIENTS WITH STAGE 5 CHRONIC KIDNEY DISEASE ON MAINTENANCE HEMODIALYSIS – A ONE YEAR HOSPITAL BASED CROSS SECTIONAL STUDY",** is ethical and justifiable.

The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr. Arathi Darshan)
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research.
J.N.Medical College. Belagavi.

(Dr. Roopa M Bellad)
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

ANNEXURES IV - MASTER CHART

S. No.	Name	IP/OP No.	Gender	age	Etiology of CKD	JOINT PAIN	BONE PAIN	PARESTHESIA	PROXIMAL MUSCLE WEAKNESS	Weight (Kg)	S. Creatinine(mg/dl)	eGFR (ml/min)	Time on Dialysis (Months)	Length of Dialysis per week (Hours)	S. Phosphorus (mlg/dl)	Corrected Calcium (mg/dl)	Calcium Phosprous product(mg2/dl2)	S. iPTH (pg/ml)	25 OH Vit D(ng/ml)	S. ALP(U/L)	S. Albumin(gm/dl)	Hb(gm/dl)
1	Sambaji	4329343	M	34	T1 DM	PRESENT	PRESENT	ABSENT	ABSENT	50	11.99	6.14	14	12	4.1	7.5	30.75	225.6	14.6	113	3.5	9.5
2	kalpana	3148786	F	46	T2 DM	PRESENT	PRESENT	ABSENT	ABSENT	62	8.76	7.85	36	8	6.4	7.5	48	361	17.66	135	3.7	9.8
3	Subhadra	900091	F	64	T2DM	PRESENT	PRESENT	PRESENT	PRESENT	65	8.92	6.54	8	8	6.1	8	48.8	879.7	18.24	92	3.5	9.6
4	vasudev	2001850	M	36	HTN	PRESENT	PRESENT	ABSENT	ABSENT	70	14.54	4.97	60	8	3.9	7.1	27.69	530	30.69	185	4.6	11.3
5	Prabhakar	3878545	M	75	T2DM, HTN	PRESENT	PRESENT	ABSENT	ABSENT	70	9.4	6.72	7	4	9.3	6.2	57.66	245	16.62	85	4.2	11.6
6	Satteppa	4033716	M	60	T2DM	PRESENT	PRESENT	PRESENT	PRESENT	68	11	5	24	8	4.6	8.2	37.72	144.7	46.77	227	3.9	10.4
7	Shivarayappa	5036009	M	72	CGN	PRESENT	PRESENT	ABSENT	PRESENT	68	7.2	8.79	8	8	4.2	8.7	36.54	55.8	70	65	4	10
8	Riyaz	924886	M	58	HTN	PRESENT	ABSENT	ABSENT	ABSENT	71	9.62	8.41	24	8	7	9.1	63.7	82.3	16.14	264	2.5	7.9
9	Sharada	920876	F	50	CTID	PRESENT	ABSENT	ABSENT	ABSENT	60	22.64	2.82	8	8	6.8	8.7	59.16	213	6.67	110	2.9	6.9
10	Appayya	920725	M	65	T2DM,HTN	PRESENT	ABSENT	PRESENT	ABSENT	50	6.61	8	36	12	4.5	9.9	44.55	138.9	18.33	138	2.4	8
11	Kusta	4207371	M	68	T2DM	PRESENT	PRESENT	PRESENT	ABSENT	70	9.37	7.37	30	8	5.9	8.6	50.74	530	70	143	3.9	11.8
12	Chandrakanth	871842	M	64	T2DM	PRESENT	PRESENT	PRESENT	PRESENT	62	6.61	9.77	40	8	3.9	9	35.1	163.8	6.76	79	3.7	7.4
13	Dilawar	923775	M	64	T2DM,HTN	ABSENT	ABSENT	ABSENT	ABSENT	70	8	9.24	12	8	3.4	8.1	27.54	324	18.93	110	3.4	9.4
14	Raju	2464481	M	37	CTID	PRESENT	ABSENT	ABSENT	ABSENT	72	10.52	9.79	24	8	3.9	8.7	33.93	925.2	17.21	180	3.2	7.6
15	vilas	936779	M	50	HTN	ABSENT	ABSENT	ABSENT	PRESENT	50	12.92	4.84	12	8	3.7	8.7	32.19	210	20.03	64	4.1	10.8
16	Radha	4140469	F	66	T2DM, HTN	PRESENT	ABSENT	ABSENT	PRESENT	66	6.9	8.21	24	8	3.8	9.2	34.96	209.9	14.48	168	4.2	9.7
17	Shivaleela	3500826	F	46	CGN	ABSENT	ABSENT	ABSENT	ABSENT	58	6.23	10	24	12	3.8	9.3	35.34	40.6	21.87	49	3.1	11
18	Sadashiv	5031532	M	56	CGN	PRESENT	PRESENT	PRESENT	ABSENT	60	9.75	6	8	8	5.9	7.6	44.84	349.3	13.89	62	3.8	11.1
19	Jayashree	3523250	F	49	HTN	ABSENT	ABSENT	ABSENT	PRESENT	65	10.3	8	12	8	4.1	9.8	40.18	125	23.3	141	4	8.3
20	Kiran	915849	M	23	CTID	ABSENT	ABSENT	ABSENT	PRESENT	50	9.18	8.85	12	8	6.5	10.7	69.55	68.2	33.49	60	3.2	10.1
21	Pavananjay	913230	M	58	T2DM,HTN	ABSENT	ABSENT	ABSENT	ABSENT	65	8.45	8.76	8	8	4.1	8	32.8	198	12.54	112	2.1	8.4
22	Hiralal	896961	M	61	T2DM,	ABSENT	ABSENT	ABSENT	ABSENT	56	8.65	7.1	30	12	2	8.5	17	29.3	24.21	293	3.5	9.1
23	Suresh	4068180	M	62	T2DM	ABSENT	ABSENT	PRESENT	ABSENT	62	7.9	8.61	50	8	3.7	10	37	114.2	11.42	80	4.6	10.3
24	Adinath	3470227	M	54	T2DM	PRESENT	PRESENT	ABSENT	ABSENT	60	14.58	2.23	36	12	4.1	13	53.3	26.4	20	94	3.4	13
25	Fakira	2953143	M	62	T2DM,HTN	ABSENT	ABSENT	ABSENT	PRESENT	62	6.22	10	36	12	1.1	9.5	10.45	9.7	47.72	181	3.7	9.7
26	Namdev	4763844	M	42	CGN	ABSENT	ABSENT	PRESENT	ABSENT	71	20.92	4.19	18	8	8.6	8.2	70.52	704.6	42.89	140	4.2	12.1

27	Sandeep	3814512	M	33	CGN	PRESENT	PRESENT	ABSENT	ABSENT	70	9.85	9.72	8	4	4.9	8.8	43.12	54.9	21.28	60	3.3	7.2
28	Premakumari	934971	F	48	T2DM	PRESENT	PRESENT	PRESENT	ABSENT	50	14.4	4.44	7	8	2.4	7.5	18	104.7	10.48	156	2.7	9.3
29	Arjun	4679963	M	62	HTN	ABSENT	ABSENT	PRESENT	PRESENT	68	10.63	6.93	12	12	4.3	9.3	39.99	4.3	42.23	102	3.9	10.6
30	Gundu	4642423	M	73	CGN	PRESENT	PRESENT	PRESENT	ABSENT	72	11.89	5.48	12	8	5.2	7.4	38.48	167	26.31	49	3.9	11.1
31	Satish	921494	M	59	T2DM,HTN	PRESENT	ABSENT	ABSENT	ABSENT	58	11.56	5.64	12	8	7.6	8.6	65.36	171.1	40.66	62	4	7.8
32	anumati	3515701	F	50	HTN	PRESENT	PRESENT	ABSENT	ABSENT	60	10.34	6.17	24	8	9.3	7.9	73.47	199.1	27.04	99	4	11.9
33	KEDARNATH	4437192	M	31	CTID	PRESENT	PRESENT	ABSENT	PRESENT	45	7.23	9.42	36	12	4.5	8.8	39.6	29.4	14.19	165	3.9	9.5
34	BABURAO	2819082	M	59	T2DM,HTN	PRESENT	PRESENT	ABSENT	PRESENT	70	13.86	5.68	12	8	4.7	8.8	41.36	357.7	38.55	276	3.9	10.5
35	Mukhtyarbe	1987868	F	74	T2DM	PRESENT	PRESENT	PRESENT	ABSENT	75	11.85	4.93	72	12	4.5	8.9	40.05	655.3	31.4	501	4.4	10.3
36	Charles	4954014	M	58	T2DM	ABSENT	ABSENT	PRESENT	ABSENT	75	12	7.12	24	8	2.5	9.8	24.5	358.2	19	120	3.9	11
37	karuna	2824428	F	30	CTID	ABSENT	ABSENT	ABSENT	ABSENT	56.87	7.32	9.93	72	12	2.6	7.7	20.02	220.3	32.29	153	4.4	14
38	Durdundi	880540	M	31	CTID	PRESENT	PRESENT	ABSENT	ABSENT	52	11.3	6.97	24	12	1.4	9.9	13.86	7.9	14.36	143	1.5	5.9
39	Afiya	1155813	F	35	CTID	PRESENT	PRESENT	PRESENT	ABSENT	40	11.7	4.81	24	8	3.6	7.3	26.28	859.4	15.89	121	4.4	10.7
40	Basappa	4612518	M	53	T2DM	ABSENT	ABSENT	PRESENT	ABSENT	55	7.79	8.53	36	8	1.7	8.7	14.79	41	20.5	133	2.8	9.4
41	Dsai raveendra	887727	M	39	CGN	ABSENT	ABSENT	PRESENT	ABSENT	65	17.82	5.17	24	8	2.7	8.3	22.41	120.9	20.54	113	3.8	12.3
42	Kapeel	4907828	M	34	CTID	PRESENT	ABSENT	ABSENT	ABSENT	56	11	7.49	24	12	3.7	8.9	32.93	95.3	70	78	4.5	8.9
43	Maruti pol	3962088	M	52	T2DM	PRESENT	PRESENT	ABSENT	ABSENT	67	12.21	6.71	48	12	2.6	8.7	22.62	330.1	34.25	288	4.4	11.4
44	kallappa	3276197	M	59	T2DM	PRESENT	PRESENT	ABSENT	ABSENT	62	8.9	7.84	36	12	5.1	8.4	42.84	160	14.07	185	3.8	11.3
45	Kasturibai	872126	F	72	T2DM	PRESENT	PRESENT	PRESENT	ABSENT	60	5.81	9.75	20	8	4.3	7.4	31.82	269.4	45.87	210	3.5	10.6
46	Shivaputra	3755432	M	57	T2DM	PRESENT	ABSENT	ABSENT	ABSENT	70	8.16	9.89	36	8	1.2	10	12	10.9	6.9	63	3.4	9.9
47	Ramesh	933949	M	52	T2DM	PRESENT	ABSENT	ABSENT	ABSENT	62	18.3	4.14	24	12	6.9	7.4	51.06	570	11.52	123	4.4	5.9
48	Laxmibai	2176102	F	68	T2DM	PRESENT	PRESENT	PRESENT	ABSENT	60	6.8	7.5	18	8	5.6	7.9	44.24	108.9	60.14	130	4	9.5
49	Gurupad	4241772	M	52	CGN	PRESENT	PRESENT	ABSENT	ABSENT	49	5.14	9.9	16	8	4.9	10.1	49.49	16.1	26.57	216	3.5	15.8
50	Ramachandra	3945419	M	55	T2DM	PRESENT	PRESENT	ABSENT	ABSENT	44	5.28	9.84	12	8	6.1	9.4	57.34	197	5.51	120	2.3	9.9
51	uttam	896634	M	51	CTID	PRESENT	PRESENT	ABSENT	ABSENT	56	25.81	2.68	16	12	13.3	7.8	103.74	323.6	10.76	51	4	7.4
52	Sopamma	923898	M	61	T2DM	PRESENT	ABSENT	ABSENT	ABSENT	60	7.1	9.27	48	12	3.3	9.4	157	353.7	12.17	157	3.1	10.9
53	Daryl	3077516	M	45	T2DM	ABSENT	ABSENT	ABSENT	ABSENT	65	9.81	8.74	36	12	5.2	7.2	37.44	606.9	20.78	223	3.6	12.2
54	Mashnu	4657928	M	63	T2DM	PRESENT	ABSENT	ABSENT	ABSENT	66	9.46	7.46	24	8	1.5	7.9	11.85	463.6	10.89	182	3.8	13.9
55	Rudrappa	4574759	M	64	T2DM	PRESENT	ABSENT	ABSENT	ABSENT	70	11.59	6.38	24	12	5.6	8.4	47.04	47.9	35.54	204	4.2	10.1
56	Prema patil	5034211	F	56	T2DM	ABSENT	ABSENT	ABSENT	ABSENT	68	8.78	7.68	8	12	4.2	8.7	36.54	45.9	23.49	58	4.2	7.2
57	Sham kadam	924993	M	65	T2DM	PRESENT	ABSENT	ABSENT	ABSENT	63	6.95	9.44	16	12	4.6	8.7	40.02	253.6	10.06	83	4.3	9.6
58	Revsab	1072114	M	60	T2DM	ABSENT	ABSENT	ABSENT	ABSENT	66	9.23	7.95	24	8	3.8	9.3	35.34	62.5	29.18	125	4.2	10.2
59	Madhav	5178409	M	54	CTID	ABSENT	ABSENT	ABSENT	ABSENT	65	9.03	8.6	12	8	4.6	7.7	35.42	370	136	136	3.9	10.6
60	Angad	4207127	M	54	T2DM	ABSENT	ABSENT	ABSENT	ABSENT	58	6.94	9.98	24	8	2.3	8.9	20.47	70	26.12	150	4.4	14.4
61	Daniel	1114305	M	39	CTID	ABSENT	ABSENT	ABSENT	ABSENT	65	12.38	7.37	36	8	1.1	9.2	10.12	46.9	28.36	217	3.9	9.2
62	Agnel	4171308	M	63	T2DM	ABSENT	ABSENT	ABSENT	ABSENT	70	7.61	9.84	36	8	5	11	55	127.2	18.2	88	3.5	10.5
63	Kashappa	2471176	M	42	CGN	ABSENT	ABSENT	ABSENT	ABSENT	62	16.59	5.09	36	8	5.6	9.1	50.96	150.5	8.2	142	3.4	1O.8
64	Shankar j	948572	M	63	T2DM, HTN	PRESENT	ABSENT	ABSENT	ABSENT	68	10.18	7.14	16	12	4.3	8.5	36.55	178.4	13.01	146	3.1	8.2
65	Mallikrjun iti	4254754	M	54	T2DM	ABSENT	ABSENT	ABSENT	ABSENT	68	10.27	7.91	36	8	2	9.5	19	11	48.91	69	3.9	9.4
66	Sanjeev R	929334	M	41	CTID	PRESENT	ABSENT	ABSENT	ABSENT	70	13.41	7.18	40	8	3.9	6.7	26.13	417.5	4.97	150	3	7.8

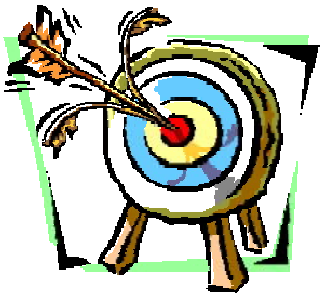
67	Sanjeev B	5098513	M	76	T2DM	ABSENT	ABSENT	ABSENT	ABSENT	74	12	5.48	18	8	4.1	9.1	37.31	42.2	47.52	88	3.7	8.3
68	Pundalik C	1884413	M	50	T2DM	PRESENT	ABSENT	ABSENT	ABSENT	70	12.3	7.11	29	12	6.8	7.6	51.68	412.8	18.28	152	4.8	12.4
69	Mohammed	3337109	M	59	T2DM, HTN	ABSENT	ABSENT	ABSENT	ABSENT	78	9.84	7.77	36	8	7.2	8.3	59.76	575.9	20.09	218	4.5	11.8
70	shivaraj	3756150	M	64	T2DM	PRESENT	ABSENT	ABSENT	ABSENT	68	7.27	4.61	24	12	3.1	8.9	27.59	384.8	18.56	86	4.3	9.7
71	Prahlad	2676710	M	75	T2DM	ABSENT	ABSENT	ABSENT	ABSENT	65	9.29	6.32	18	8	1.5	8.8	13.2	163.2	6.18	159	2.9	9.3
72	Vandana	5137099	F	47	T1DM	PRESENT	ABSENT	ABSENT	ABSENT	68	12.34	6.05	28	8	6.3	8	50.4	411.8	18.2	200	4.8	12
73	Ayesha	3654524	F	48	CGN	PRESENT	ABSENT	ABSENT	ABSENT	64	12.54	5.54	30	12	7.7	8.6	66.22	437.2	19.42	157	4.2	10.4
74	shivanand	5210174	M	35	CGN	ABSENT	ABSENT	ABSENT	ABSENT	60	10.08	8.68	16	8	0.6	10.2	6.12	47.1	37.71	87	3.8	8.4
75	basappa B	4997454	M	67	T2DM	PRESENT	ABSENT	ABSENT	ABSENT	72	7.7	9.48	12	8	2.5	10.3	25.75	9.8	16.39	133	3.4	13
76	Santosh T	4762692	M	36	CTID	ABSENT	ABSENT	ABSENT	ABSENT	70	11.92	8.48	12	8	2.9	8.7	25.23	100	18	76	4.3	9.5
77	Bhima	4479406	M	65	T2DM	PRESENT	ABSENT	ABSENT	ABSENT	68	7.1	9.98	24	8	4.2	8.3	34.86	257.9	15.98	127	4	12
78	Sadashiv	5031532	M	56	T2DM, HTN	ABSENT	ABSENT	ABSENT	ABSENT	71	11.2	7.4	12	8	5.9	7.8	46.02	349.3	13.89	62	4.8	9.5
79	Venkatesh	2326553	M	59	T2DM	ABSENT	ABSENT	ABSENT	ABSENT	60	8.95	7.54	10	8	7.2	8.1	58.32	512	22.3	180	4.9	12
80	Vinayak naik	2200905	M	70	T2DM	PRESENT	ABSENT	ABSENT	ABSENT	73	12.08	5.88	18	12	6.1	8.8	53.68	481	17.08	186	4	11
81	pandurang	876365	M	70	T2DM	PRESENT	ABSENT	ABSENT	ABSENT	67	13.29	4.9	10	8	6.4	8.5	54.4	434.1	17.43	150	4	8.6
82	Hanumanth	5051419	M	65	T2DM	ABSENT	ABSENT	ABSENT	ABSENT	70	9.68	7.53	36	8	0.6	12.4	7.44	12.6	44.93	123	4.4	11
83	Shankar K	941903	M	73	T2DM	PRESENT	ABSENT	ABSENT	ABSENT	65	10.46	5.78	24	8	5.6	8	44.8	484.1	18.2	198	4.8	8.8
84	laxmi G	4489093	F	56	T2DM,HTN	PRESENT	ABSENT	ABSENT	ABSENT	68	11.78	5.72	12	12	2.9	8.7	25.23	987.6	65.96	236	4.2	6.6
85	Maruti M	5246996	M	44	CTID	ABSENT	ABSENT	ABSENT	ABSENT	60	8.64	9.26	18	8	3.1	9.6	29.76	39.9	18.4	128	3.8	10.4

ANNEXURE-V

KEY TO MASTER CHART

Gender	**-**	**M- Male F- Female**
T1DM	**-**	**Type 1 Diabetes Mellitus**
T2DM	**-**	**Type 2 Diabetes Mellitus**
HTN	**-**	**Hypertension**
CGN	**-**	**Chronic Glomerulonephritis**
CTID	**-**	**Chronic Tubulo Insterstitial Disease**
S.iPTH	**-**	**Serum intact Parathyroid Hormone**
Hb	**-**	**Hemoglobin**
25 OH Vit D	**-**	**25 Hydroxy Vitamin D**
eGFR	**-**	**estimated Glomerular Filtration Rate**

Introduction



Objectives

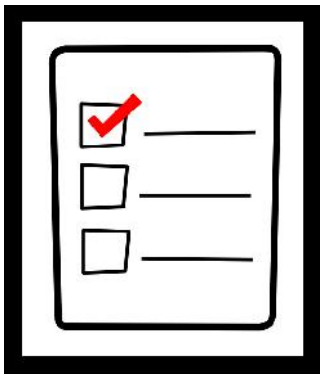
Review of Literature

Methodology

Results

Discussion

Conclusion

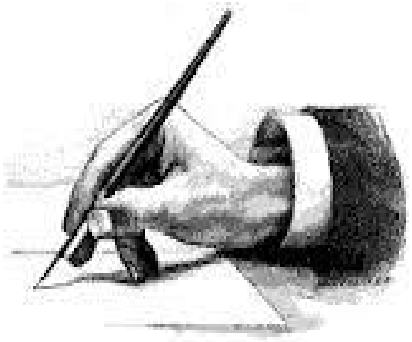


Limitations

Recommendations

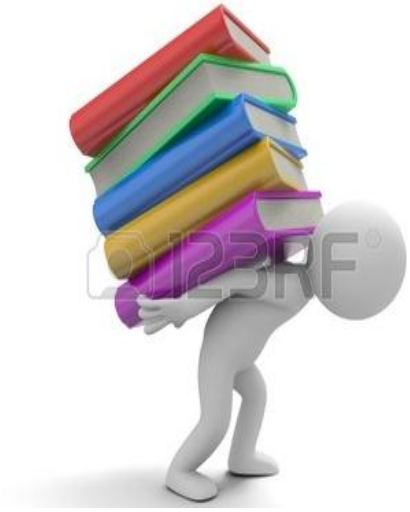
Summary

Bibliography



Annexure-I

Annexure-II



Annexure-III

Annexure-IV

Annexure-V