International Journal of Life Sciences, Biotechnology and Pharma Research Vol. 14, No. 2, February 2025 Online ISSN: 2250-3137
Print ISSN: 2977-0122

DOI: 10.69605/ijlbpr_14.2.2025.138

ORIGINAL RESEARCH

Parathyroid hormone and cardiac dysfunction in ESRD – A reterospective analysis

[1]Dr. Rajesh Kannan G., [2]Dr. Geetha J.

[1]Assistant Professor, [2]Associate Professor, Department of Anesthesialogy, Dhanalakshmi Srinivasan Medical College and Hospital, Siruvachur, Perambalur, Tamil Nadu, India

Corresponding Author
Dr. Geetha J.
Associate Professor, Department of Anesthesialogy, Dhanalakshmi Srinivasan Medical College and Hospital, Siruvachur, Perambalur, Tamil Nadu, India

Received: 25 January, 2024 Accepted: 10 February, 2025 Published: 25 February, 2025

ABSTRACT

Introduction: Chronic kidney disease has a progressive impairment of kidney functions which enrols bone, mineral and endocrine involvement into its pathophysiology. Secondary hyperparathyroidism is awell-recognised common complication of CKD potentially contributing to impaired left ventricular functionprimarily due to mechanisms such as vascular calcification, myocardial fibrosis anddirect effects on cardiac muscle cells caused by elevated parathyroid hormone (PTH) levels.This article involves retrospective analysis of 56 patients with end stage renal disease for renal transplantation to our institution where high PTH levels were found to be correlating with severity of cardiac involvement.

Aims and objectives

1. To evaluate secondary hyperparathyroidism and correlate with ejection fraction of left ventricle in patients with ESRD presenting for renal transplantation.
2. To infer the range of serum PTH contributing to poor ejection fraction of left ventricle.
3. To examine serum Calcium and Phosphorus levels that trigger secondary hyperparathyroidism.
4. To analyse right ventricular systolic pressure as second factor of cardiac involvement due to PTH in ESRD

Materials and methods: All patients with ESRD who were evaluated by nephrologist and referred to preanaesthetic evaluation for renal transplantation were included in the study.Study period: June 2024 to December 2024.The pre anaesthetic charts were examined retrospectively and parameters includingpatient demographics, parathormone (serum PTH) levels, Ejection fraction, right ventricular systolicpressure were noted, tabulated and analysed.All patients have undergone successfulrenal transplantationand have stable kidney functions in the post-operative period. **Results:** The serum parathormone (PTH) levels ranged from 30 to 1200 pg/dl while serum Calcium levels between 6 to 8 mg/dl. The high PTHshowed a p-value of 0.08 with RVSP 0.4 with EF and 0.5 with Serum calcium.Negative correlation was noted between PTH levels and serum Calcium and ejection fraction. **Conclusion:** Parathyroid hormone has been labelled as one of the uremic toxin causing cardiovascular effects in ESRD. The serum PTH levels may be considered as an indicator of severity of left ventricular dysfunction and pulmonary hypertension in ESRD.

Keywords: Parathyroid hormone, end stage renal disease, Uremic toxins, ejection fraction.

INTRODUCTION

Renal transplantation has proved to be the most successful organ transplant with 90-95% of five-year survival rate. Severity ofthe renal failure which is proportional to progression of the disease and duration of hemodialysis have all been well documented. Advances in biochemical diagnostic techniques have identified several uremic toxins which contribute to as well as allow identification of renal failure. Parathyroid hormone(PTH) has been branded as a uremic toxin and process of secondary hyperparathyroidism in renal failure has been studied.

Several patients with End Stage Renal Disease(ESRD) presenting for a pre anaesthetic evaluation prior to renal transplantation were found to have serum PTH values of 800-1000 pg/ml against the normal values of 15-65 pg/ml these were found to be associated with borderline hypocalcemia and normal or slightly raised phosphorus values.

This biochemistry pattern triggered us to analyse the relationship between parathormone and the systolic dysfunction and raised pulmonary pressures also noted in these patients.

DOI: 10.69605/ijlbpr_14.2.2025.138

The intention was to evaluate the application of parathyroid hormone levels to cardiac dysfunction would be helpful in the perioperative preparation to manage anaesthesia for the renal transplant recipients with poor cardiac indices.

In this retrospective analysis, data were gathered to substantiate and answer the above research questions.

The levels of urea were usually above 100mg and serum creatinine were around 7-10 mg/dl in all patients. All were on hemodialysis though all the patients did not reveal reduced left ventricular ejection fraction.

This study is asolo centric study of 56 patients which may throw some light on markers and indicators of cardiac involvement inrenal failure progressing to end stage renal disease.

AIMS AND OBJECTIVES

1. To evaluate secondary hyperparathyroidism and correlate with ejection fraction of left ventricle in patients with ESRD presenting for renal transplantation.
2. To infer the range of serum PTH contributing to poor ejection fraction(EF) of left ventricle.
3. To examine serum Calcium and Phosphorus levels that trigger secondary hyperparathyroidism.
4. To analyse right ventricular systolic pressure(RVSP) as second factor of cardiac involvement due to PTH in ESRD

Materials and methods

Study: Retrospective analysis
Study period: June 2024 to December2024
Study sample: 56 patients
Study place: DSMCH Siruvachur

Inclusion criteria

All ESRD patients referred by Nephrologist for pre anaesthetic evaluation prior to renal transplantation.

Methods

All ESRD patients had a thorough evaluation aspreanesthetic examination along with written audio and video consent as per nephrologist's protocol.

All patients had undergone successful renal transplant surgery under general anaesthesia. The preoperative charts of the patients under the study period were examined and data collected. Parameters such as Age, gender, Serum phosphorus, Serum Calcium and serum PTH were noted, tabulated and analysed.

The distribution of individual parameter,correlation matrix across the parameters, p values, Scatter plots and KDE density plots between EF and PTH, between RVSP and PTH were plotted to evaluate a clear picture of correlation. A lattice 3-D scatter plot between PTH, calcium and Phosphorus was also prepared to analyse the data.

Ejection fraction of left ventricle was chosen to correlate systolic dysfunction of left ventriclewith serum parathormoneand the vascular changes contributed byanemia and Parathormoneneeded aparameter for which right ventricular systolic pressure that indirectly indicated pulmonary pressures were taken up in every patient and data were plotted down for imaginary representation and analysis.

RESULTS

Gender distribution in our study was 73.9% males and 26.1% females.(Fig.1)incidentally diabetic nephropathywas the commonest cause in males and pregnancy induced hypertension was the commonest cause in females within the reproductive age group. IgA nephropathy had no gender discrimination which was another biopsy proven common cause of ESRD.

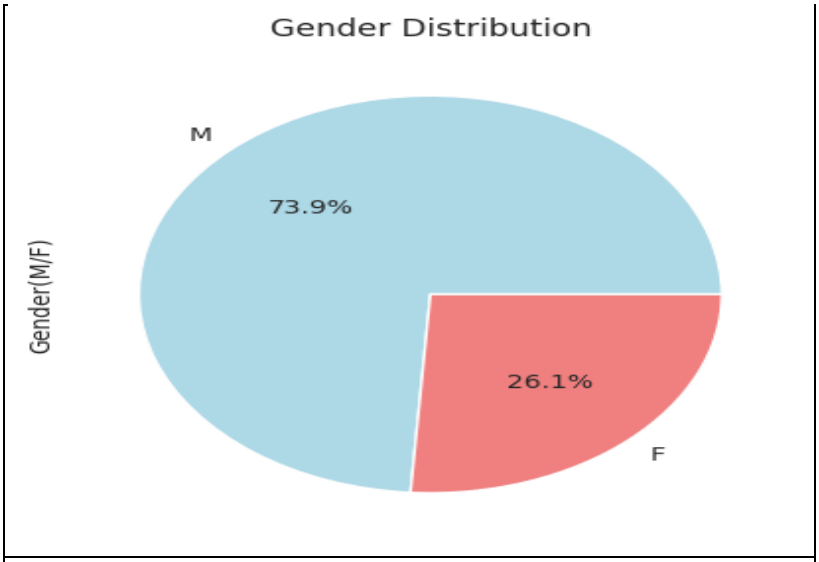


Figure 1: Pie chart showing gender distribution

Most patients were between 40-50 years of age and the age group varied from 18 to 56 years.(Fig.2)

DOI: 10.69605/ijlbpr_14.2.2025.138

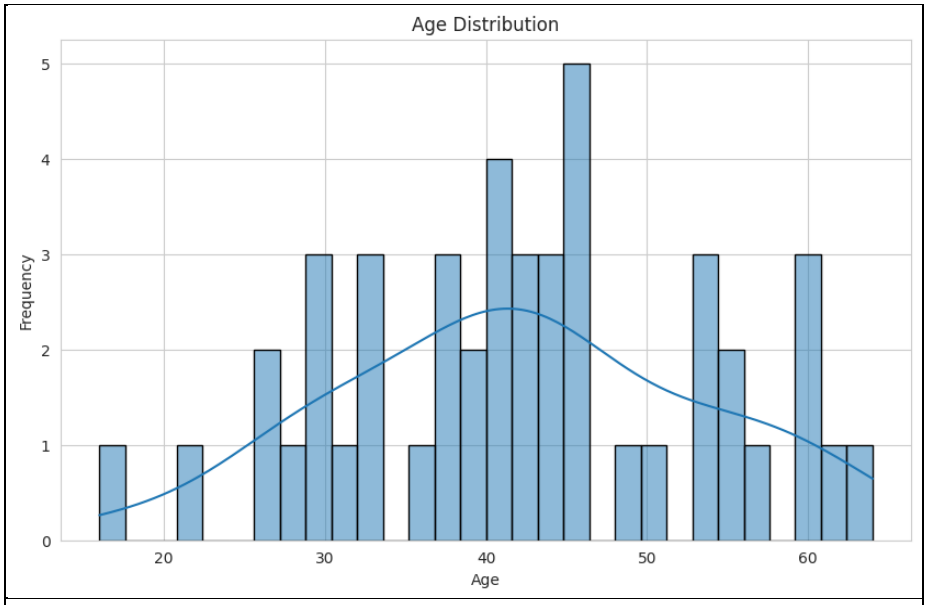


Figure 2: Distribution of Age groups

The scatter plot diagram between the parameters discussed.(Fig.3) Calcium levels ranged from 7.5 to 9.5mg/dl, PTH from 250 to 1600 pg/ml, Phosphorus between 3.5 to 9 mg/dl and Ejection fraction varied from 40 to 65%.

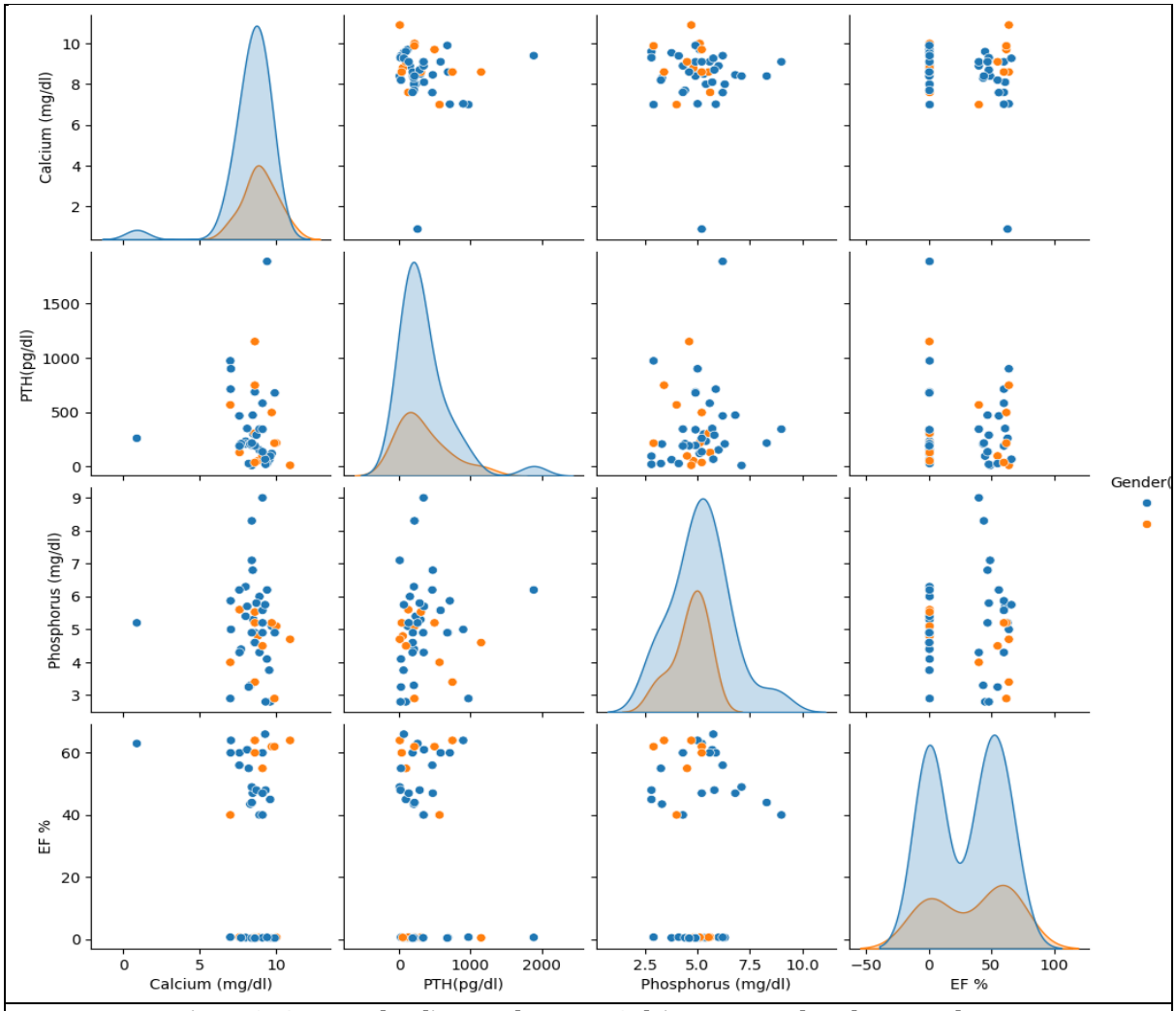


Figure 3: Scatter plot diagram between Calcium, PTH, Phosphorus and EF

DOI: 10.69605/ijlbpr_14.2.2025.138

PTH plot against EF showed increased density of dots around 800-900 pg/ml PTH values for EF of 50-55%. Serum Calcium had more patients within the values of 8 to 9mg/dl with lowest of 7.5 mg/dl.(Fig.4) The serum phosphorus levels in our study showed maximum of6mg/dl.(Fig.5)Serum PTH and calcium known to cause vascular modifications were noted to increase pulmonary pressures as indirectly measured by Right ventricular systolic pressure.(Fig.6)

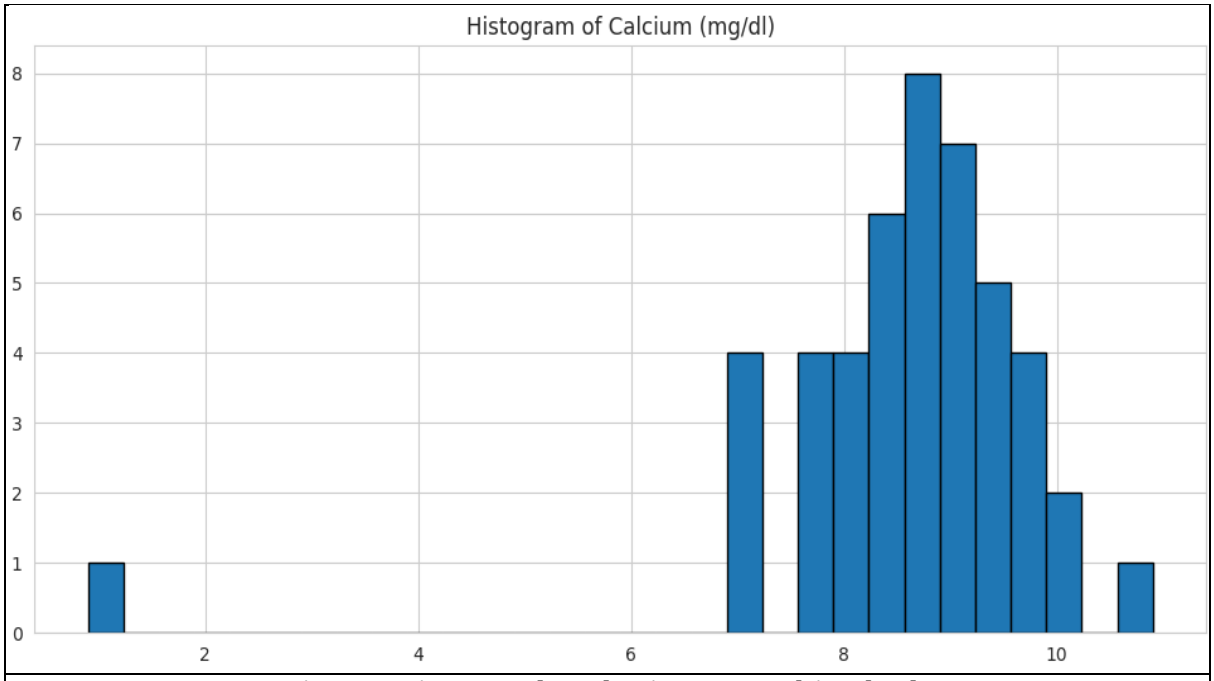


Figure 4: Histogram chart showing serum calcium levels

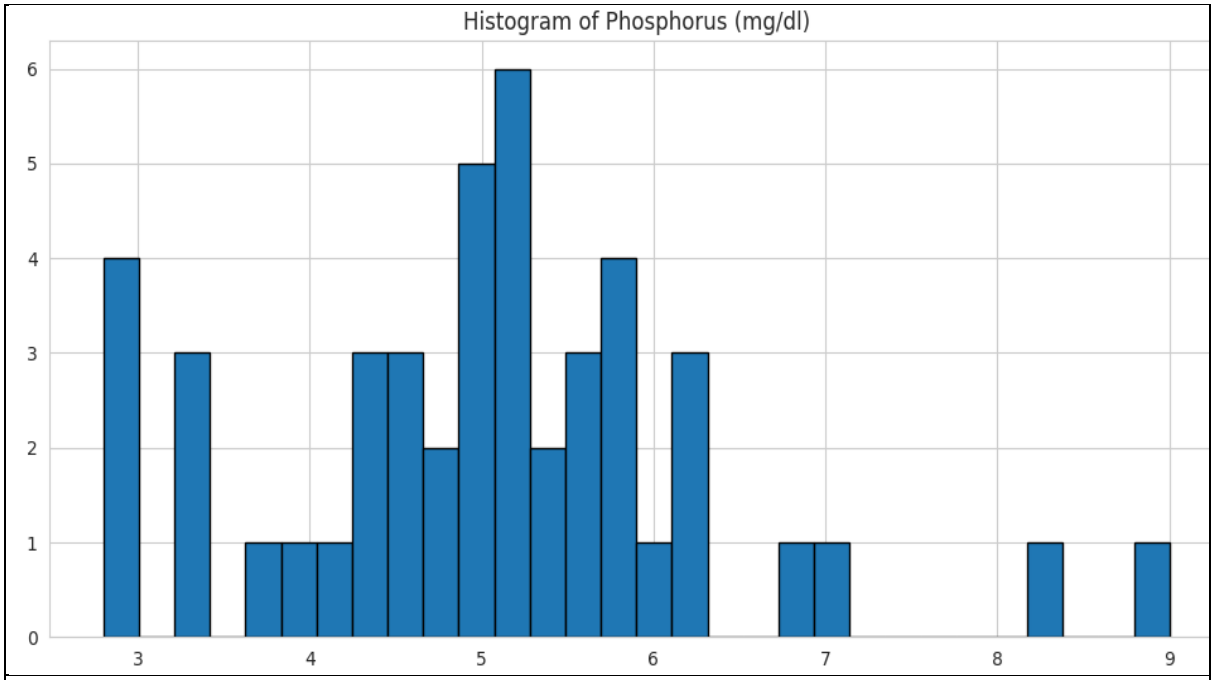


Figure 5: Histogram chart showing serum phosphorus levels

DOI: 10.69605/ijlbpr_14.2.2025.138

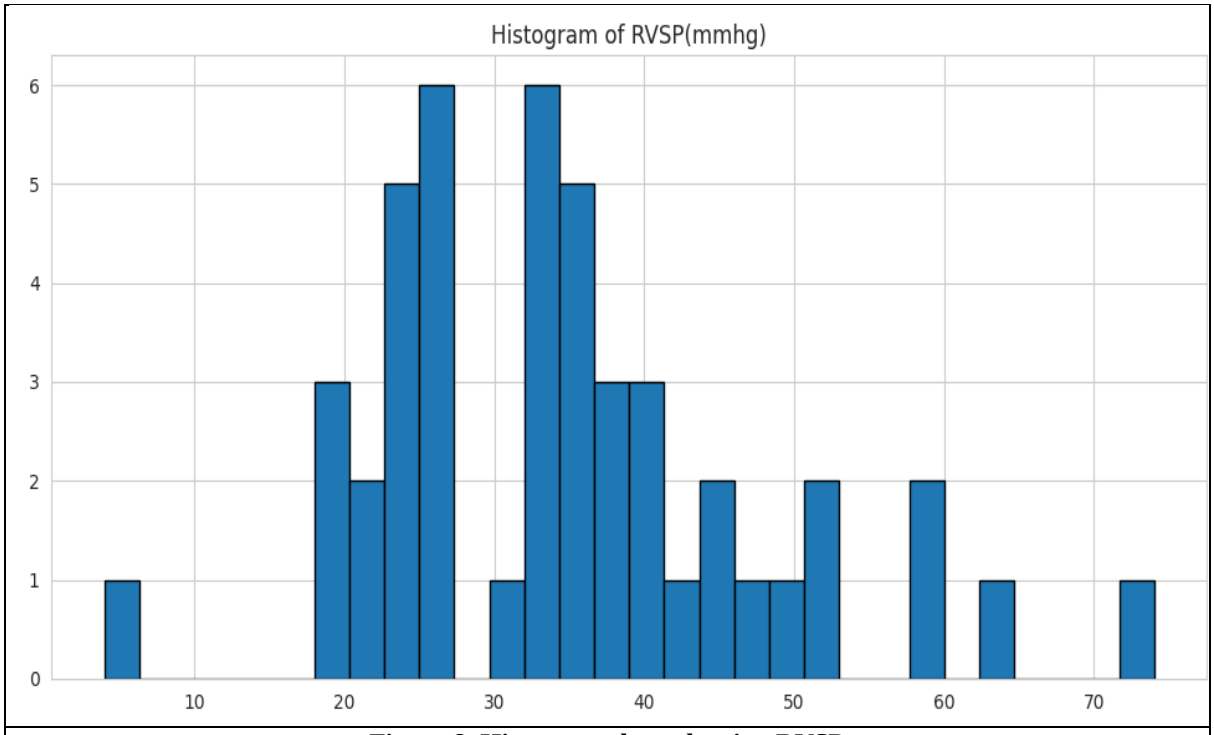


Figure 6: Histogram chart showing RVSP

The rising RVSP with rising PTH showed a pvalue of 0.08 PTH and rising RVSPshowed a p value of 0.13with serum phosphorus.(Fig.7)

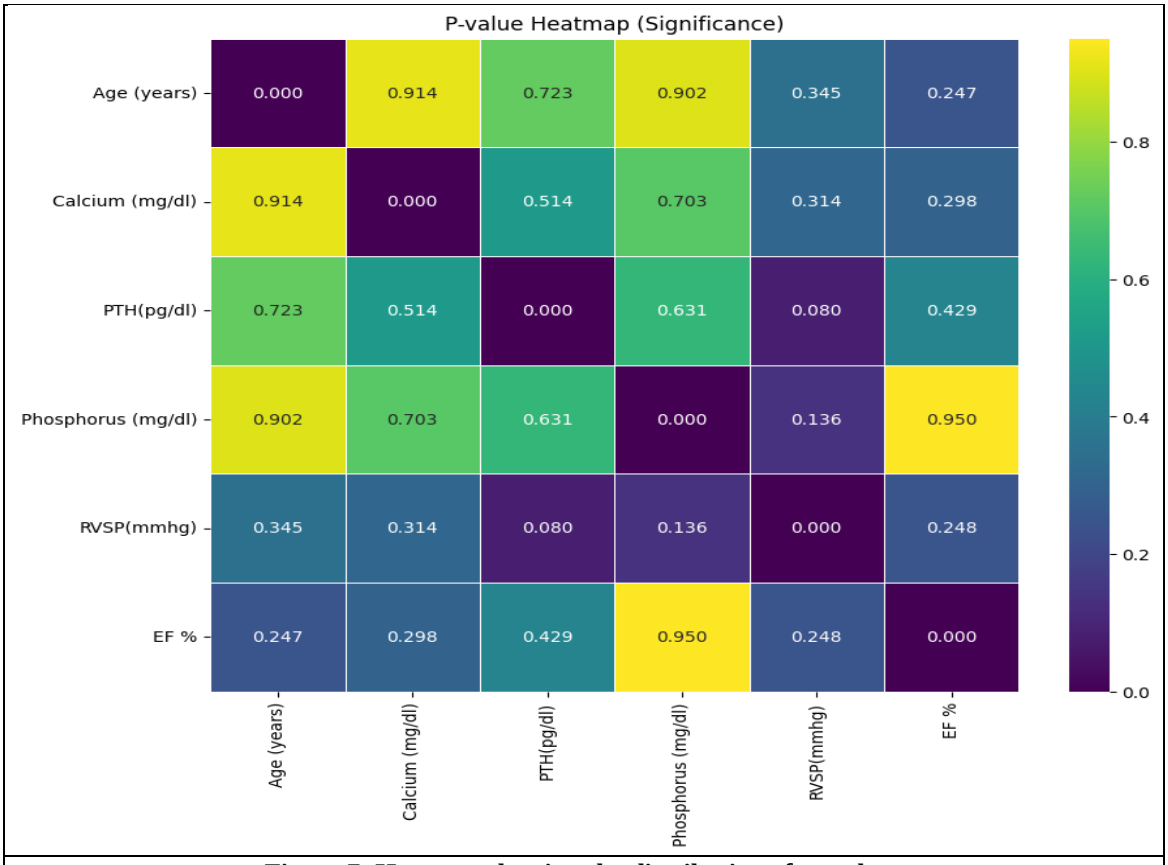


Figure 7: Heatmap showing the distribution of p -values

PTH had a negative correlation of -0.1 with EF depicting an inverse proportionrelationship of Falling EF with rising PTH levels.(Fig.8)

DOI: 10.69605/ijlbpr_14.2.2025.138

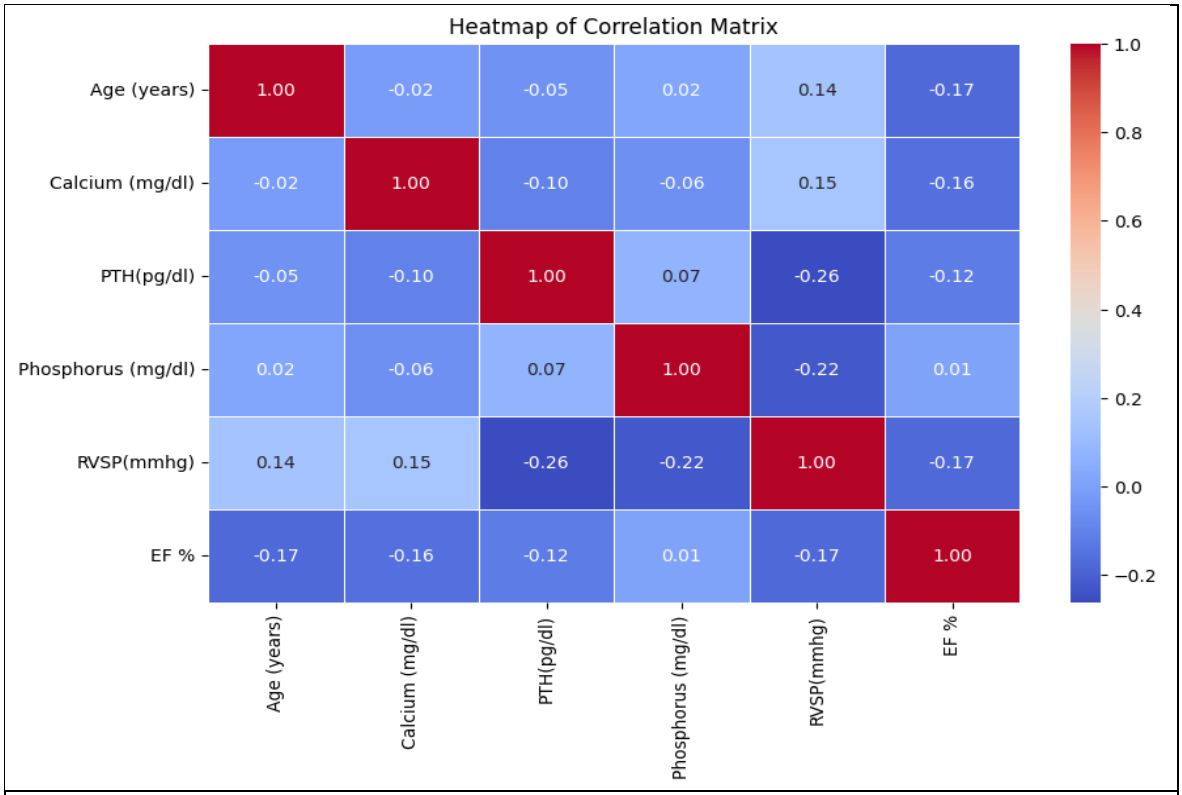


Figure 8: Heatmap showing correlation matrix between variables

One patient had maximum PTH of 1750 pg/ml whose RVSPwas 40 and EF was also was around 40%.(Fig.9&10)

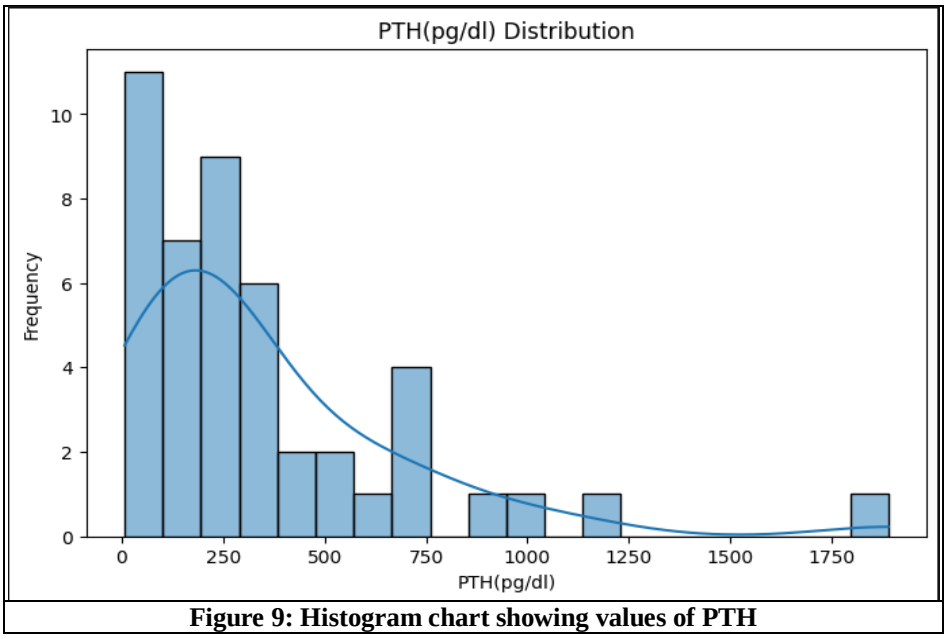


Figure 9: Histogram chart showing values of PTH

DOI: 10.69605/ijlbpr_14.2.2025.138

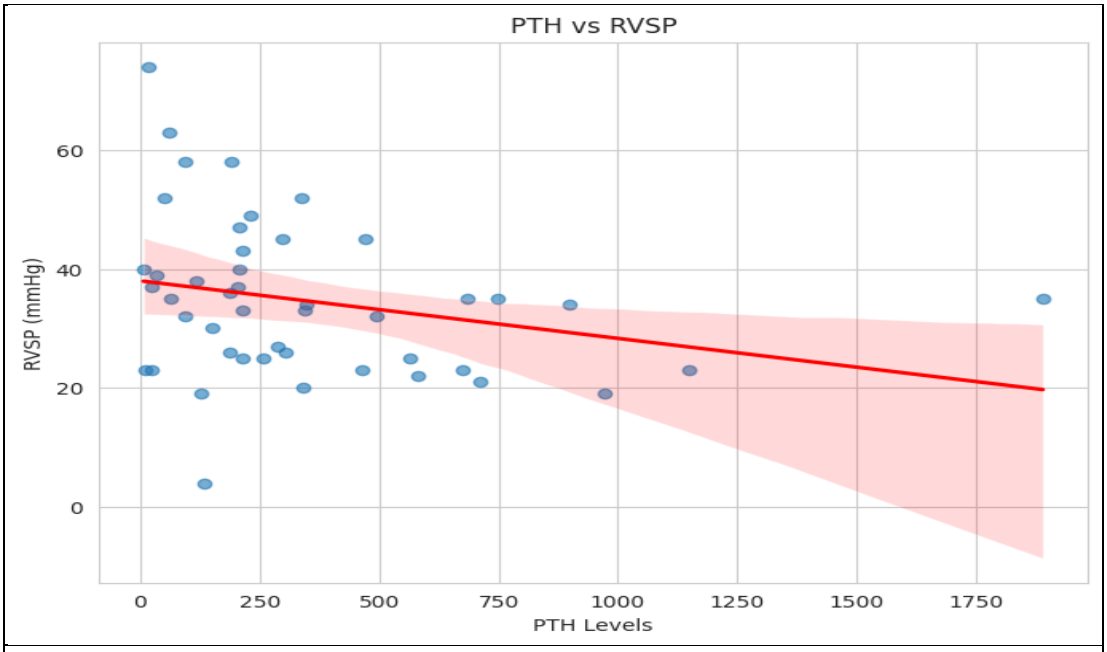


Figure 10: Distribution of PTH vs RVSP

PTHvsEF2DKDE density plot or kernel density estimation gives the pictorial representation of PTH against ejection fraction and the spatial distribution of PTH. The density of PTH values exists around 500-800 pg/ml and EF percentage around 40-60%.(Fig.11)

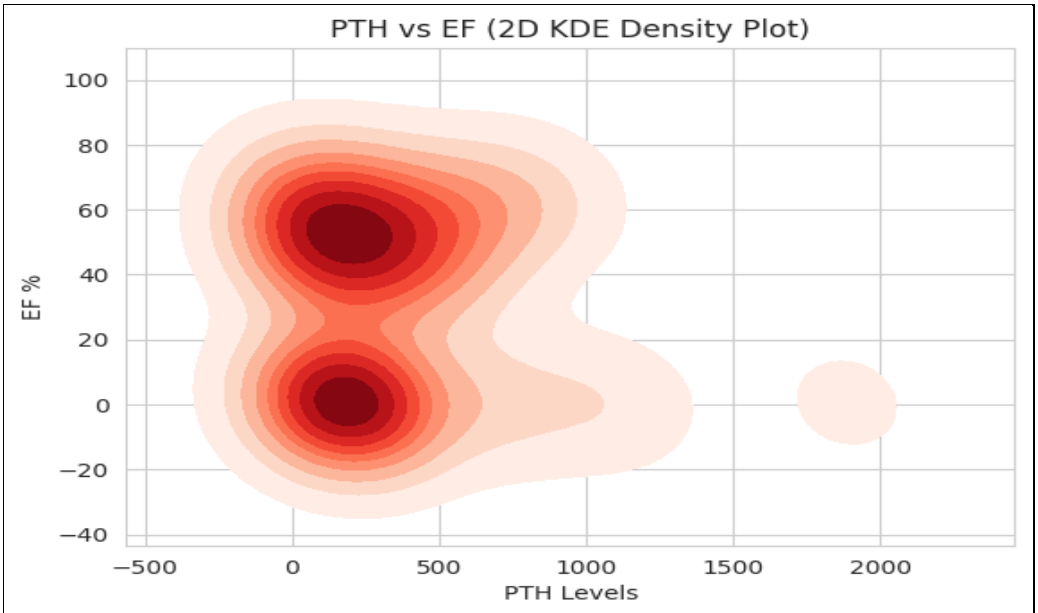


Figure 11: 2D KDE density plot showing PTH versus EF

Lattice 3D correlation diagram between Calcium, Phosphorus and PTHdepicts a low calcium levels correlating with borderline increase in phosphorus levels with PTH levels rising from 500 to the maximum of 1750 pg/ml.(Fiig.12)

DOI: 10.69605/ijlbpr_14.2.2025.138

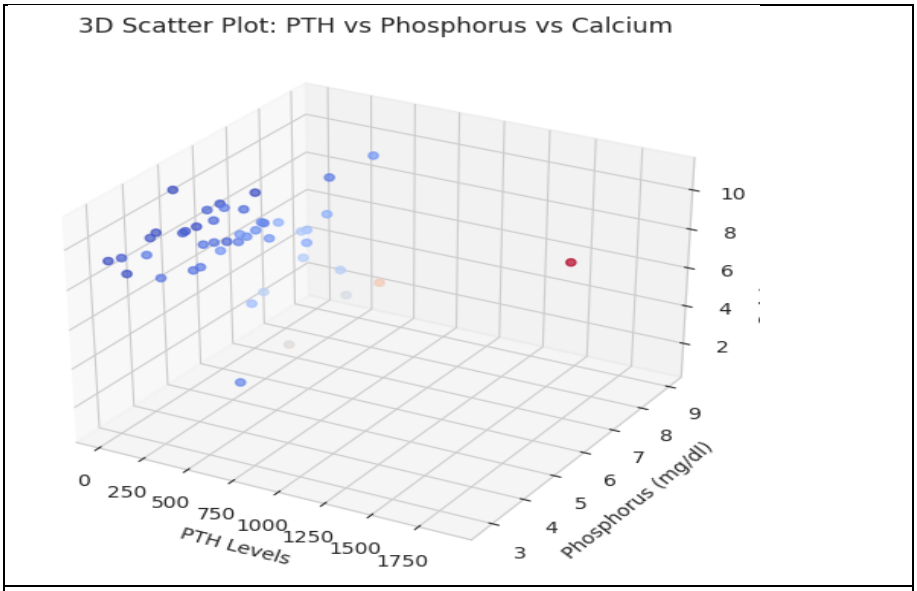


Figure 12: Lattice 3D correlation plot between calcium, phosphorus and PTH

DISCUSSION

PTH: Chemistry & Effects

Parathyroid glands are located immediately behind the thyroid one behind each pole of the thyroid.Their Dimensions are 6*3*2 mm.They contain chief cells and oxyphil cells of which chief cells are functional and secrete parathyroid hormone.[1]

PTH is a polypeptide, its prohormone has been synthesised from ribosomes with 110 aminoacids. ER and Golgi cleave this to a prohormone with 90 aminoacids and then to the hormone itself with 84 Aminoacids and the rest are fragmented. The fragments take many hours to be cleared by the kidney forming major hormonal activity while the 84 aminoacids are cleared by kidney within minutes.

A chronic fall in serum calcium cause greater increase in parathormone rather than acute fall of the same level of calcium.

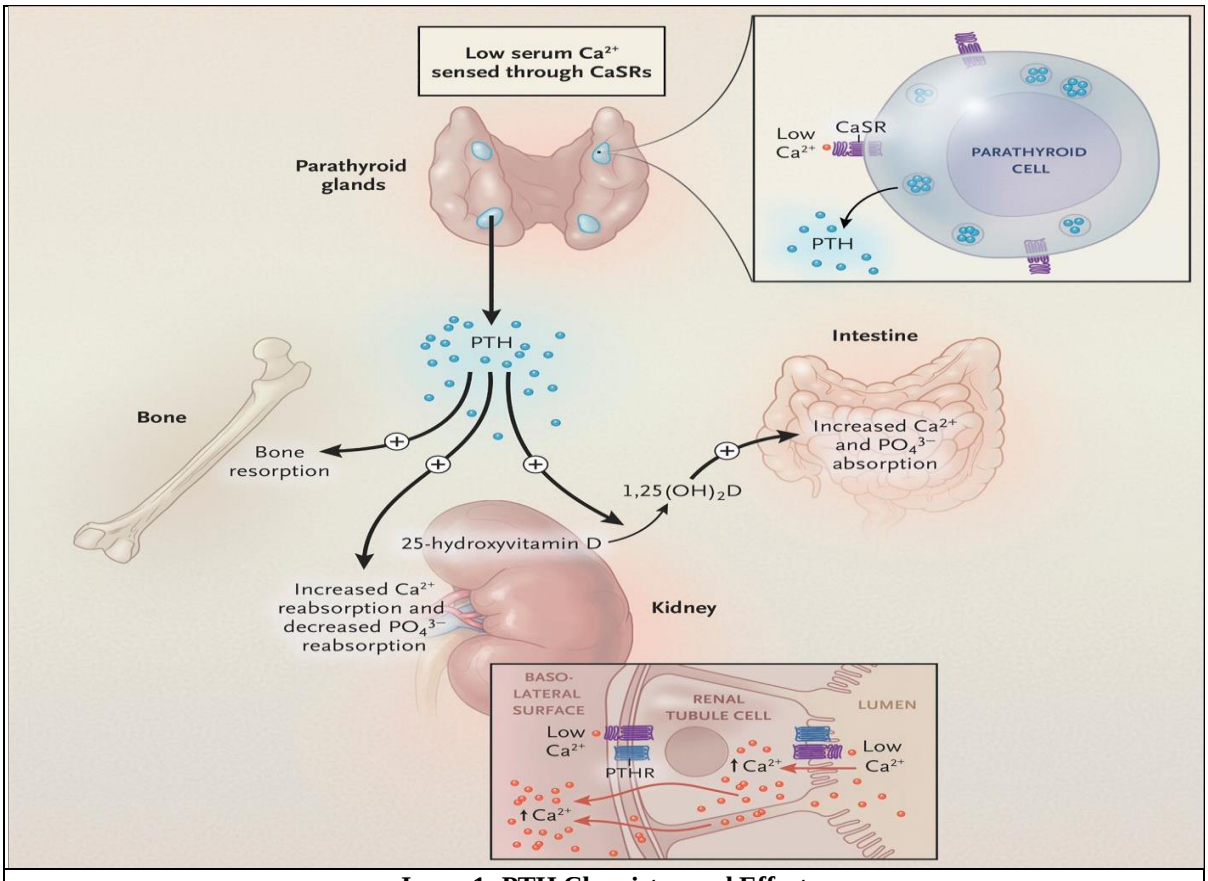


Image1: PTH Chemistry and Effect

DOI: 10.69605/ijlbpr_14.2.2025.138

In secondary hyperparathyroidism, high levels of PTH occurs as a compensation for hypocalcemia rather than as a primary abnormality of parathyroid glands. This contrast with Primary Hyperparathyroidism which is associated with hypercalcemia.[2]

Secondary Hyperparathyroidism can be caused by Vitamin D deficiency or chronic renal disease in which the damaged kidneys are unable to produce sufficient amounts of active form of Vitamin D3,1,25-dihydroxycholecalciferol. vitamin D deficiency leads to osteomalacia (that is inadequate mineralisation of bones) and high levels of PTH cause absorption of bones.[3]

Healthy kidneys maintain normal serum levels of Calcium and Phosphorus through interaction of 3 hormones namely (PTH) Parathyroid hormone, Calcitriol[1,25, ($0H_2$) D3]an active metabolite of Vitamin D and fibroblast growth Factor 23. (FGF-23) Circulating or soluble Klotho is a protein, which is Primarily expressed in the kidneys act as hormone and found in blood, urine and cerebrospinal fluid.[4]This protein is a potential biomarker of chronic kidney disease(CKD). The deficiency of Klotho is caused by hyperphosphatemia, inflammatory cytokines and uremic toxin.Klotho deficiency leads to vascular calcification, bone disease and muscle wasting.Abnormalities in mineral homeostasis begin early in courseof CKD and universally observed when GFR falls to less than 30ml/min. As CKD progresses calcium and phosphorus levels are maintained through altered production of PTH, FGF-23 and klotho with calcitriol.

A triad of biochemical measures, skeletal abnormalities and extraskeletal calcification was termed CKD-MBD or chronic kidney disease mineral and bone disorder[5] in 2006, The biochemical measures included altered serum concentration of Calcium, phosphorus, PTH, calcitriol, FGF-23 and klotho. The skeletal abnormalties involved disturbances in bone remodeling and mineralisation and impaired growth in children. The extraskeletal calcification occurs in soft tissues and arteries.

Phosphorus balance

The normal serum phosphorus measures between 2.5-4.5 mg/dl.During early phase of CKD,Phopshate balance is well maintained in neutral as PTH and FGF: 23 have compensatory phosphaturic effects. As these mechanisms begin to fail CKD progressing to ESRD, positive phosphorus balance ensues. About 60-70% of phosphate in diet is absorbed by the GI tract in the ileum. Of this 50% is sodium dependent and the rest is independent paracellular or transcellular transport of phosphates.[6]

Calcium balance and homeostasis

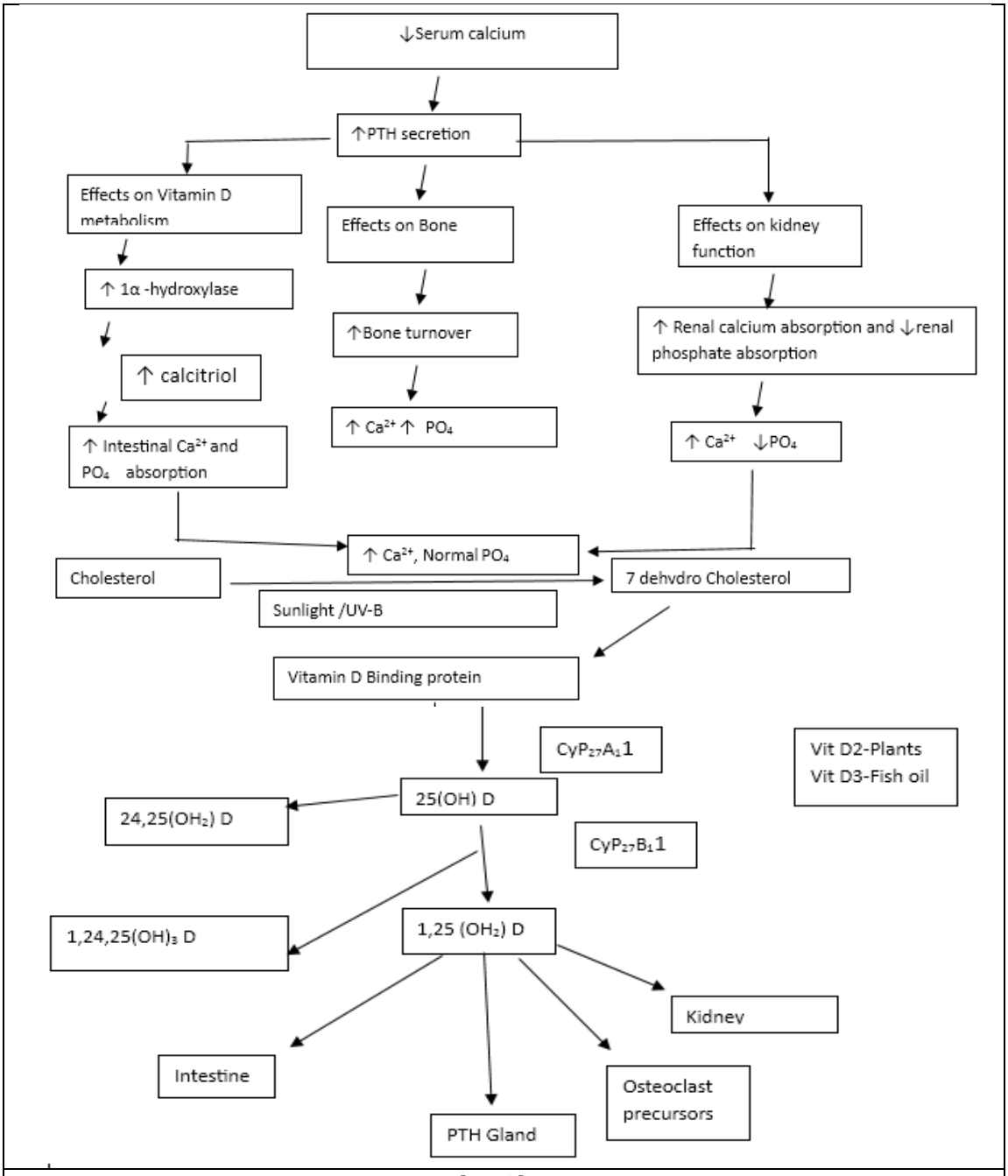
Children and young adults have slightly calcium Balance and when bone stops growing Calcium balance becomes neutral. Calcium overload is prevented in normal individuals due to renal excretion of Calcium and reduced intestinal absorption of calcium through actions of PTH and calcitriol. In CKD this ability is diminished.

Calcium absorption intestinal epithelium occurs by vitamin D dependent and vitamin D independent nonsaturableParacellularpathway.[7]

Serum Calcium normalisation by PTH

Serum levels of ionised calcium are maintained by induction of increases in secretion of PTH. PTH acts to increase bone resorption, renal calcium reabsorption and conversion of 25 (OH)D to Calcitriol in the kidney thus increasing gastrointestinal calcium absorption.

DOI: 10.69605/ijlbpr_14.2.2025.138



Flow Chart

Vitamin D plays an essential role incalcium metabolism. In vitamin D knock out animals, parathyroid hyperplasia is consistently observed despite normalisation of serum Calcium levels. Calcitriol has been proved to regulate growth of parathyroid gland growth. Hence it is used to treat especially secondary Hyperparathyroidism.

Solutes cleared by kidney and retained in uremia:[8]

- Urea
- D AminoAcids
- Peptides & proteins
- Guanidines
- Phenols and aromatic compound
- Indoles and tryptophan melabolites
- Aliphatic amines namely methyl amines
- Myoinositol
- Low molecular weight proteins and protein fragments
- Alpha 1 microglobulin
- Beta microglobulin
- Beta trace protein
- Cystatin c
- Natriuretic peptides
- Leptin
- Troponin I
- Retinal Binding Protein
- Procalcitonin

DOI: 10.69605/ijlbpr_14.2.2025.138

CONCLUSION

Serum PTH levels have been found remarkably high in patients with ESRD more than 100 times by calculation. This is triggered by hypocalcemia with Calcium levels as low as 7.5mg/dl. The associated impairment of phosphates metabolism has been inferred as borderline increase in serum phosphorus levels.

Left ventricular ejection function has been reduced with rise in PTH levels and pulmonary vascular pressure or pulmonary hypertension as recorded by echocardiogram in the form of right ventricular systolic pressure has significant correlation (p=0.08) with serum PTH levels.

Secondary hyperparathyroidism estimated by serum parathyroid hormone levels may indicate the severity of cardiovascular Involvement end stage renal disease with reduced left ventricular systolic function(r=-0.1) and increased right ventricular systolic pressure(p=0.08).

However larger studies are needed to substantiate and brand PTH as a biomarker for cardiorenal syndrome.

REFERENCES

1. Hannan FM, Kallay E, Chang W, et al: The calcium--sensing receptor in physiology and in calcitropic and noncalcitropic diseases. Nat Rev Endocrinol 15:33, 2018.
2. Habas E Sr, Eledrisi M, Khan F, Elzouki AY. Secondary Hyperparathyroidism in Chronic Kidney Disease: Pathophysiology and Management. Cureus. 2021;13(7)
3. Davenport A. Chronic kidney failure: renal replacement therapy. In: Morris PJ, KnechtleSJ, editors. Kidney Transplantation: Principles and Practice. 8th ed. Philadelphia: Elsevier; 2020. p. 40.
4. Christor M, Sprague SM. Chronic kidney disease: mineral bone disorder. In: AlansLiyu et al., editors. Brenner and Rector's The Kidney. Vol. 1.Edition 11, Philadelphia: Elsevier; p. 1806.
5. Chande S, Bergwitz C: Role of phosphate sensing in bone and mineral metabolism. Nat Rev Endocrinol 14:637, 2018. Christakos S, Dhawan P, Verstuyf A, et al: Vitamin D: metabolism, molecular mechanism of action, and pleiotropic effects. Physiol Rev 96:365, 2016.
6. Hernando N, Wagner CA: Mechanisms and regulation of intestinal phosphate absorption. ComprPhysiol 8:1065, 2018
7. Moe SM: Calcium homeostasis in health and in kidney disease. ComprPhysiol 6:1781, 2016.
8. Meyor T, Hostetter T. Pathophysiology of uremia. In: Yu ASL, Chertow GM, Marsden PA, Luyckx V, Taal MW, Skorecki K, editors. Brenner & Rector's The Kidney. 11th ed. Vol. 2. Philadelphia: Elsevier; 2019. p. 1793