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Research Article

Interrelation of Vitamin D, Parathyroid Hormone, Calcium and Phosphorus in Stage 3 To Stage 5 Chronic Kidney Disease

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Abstract: The Kidneys maintains filtration, endocrine function and excretory function. In CKD, the said functions get impaired, that leads to changes in biochemical parameters such as increased concentration of urea and creatinine. Chronic kidney disease also causes hypocalcemia, hyperkalemia, hyperphosphatemia and secondary hyperparathyroidism. The aim of the present study was to assess the interrelationship of vitamin D, Parathyroid hormone, Calcium and phosphorus in Stage 3 to Stage 5 chronic kidney disease. The study contains 180 patients in which 45 in control group and 135 will be CKD individuals with stage 3 to stage 5 each stage consisting of 45 each. In all the subjects, serum sample was estimated for blood urea, creatinine, serum calcium and serum phosphorus by using fully automatic chemistry analyzer. Serum Vitamin D and parathyroid hormone are estimated by ELISA. GFR was estimated by the MDRD formula. Data was expressed by Mean ±SD. In the present study, the mean serum calcium and Vitamin D were decreased in stage 3, stage 4 and stage 5 compared with the control and it is statistically significant. The mean phosphorus and parathyroid hormone were increased in stage 3, stage 4 and stage 5 compared with control and it is statistically significant. There was a positive correlation between vitamin D and calcium, and also between parathyroid and Phosphorus. Whereas it showed a negative correlation between vitamin D and Phosphorus and also between Parathyroid and calcium. The assessment of these parameters will be helpful in preventing future risk and also helpful in better life and outcome.

Keywords: Chronic kidney Disease, Calcium, Phosphorus, Vitamin D and Parathyroid hormone

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1. INTRODUCTION

Chronic Kidney Disease (CKD) is characterized by irreversible sclerosis and loss of nephrons.[1] It affects 10-16% of the adult population worldwide. [2] In India, the recent estimate is found to be 229 per million populations.[3] The National Kidney Foundation (NKF) Task Force on Cardiovascular Disease in CKD, demonstrated the prevalence of cardiovascular disease in CKD and its associated high death rate.[4] People with high blood pressure, diabetics and people with a family history of kidney failure are at the highest risk of developing CKD. These inflammations mediated alterations can induce irreversible tubular injury and nephron failure leading to decreased filtration.[5,6]CKD (chronic kidney disease) is one of the major health problems which is the last stage event in the disease of renal parenchyma caused by various etiologic factors associated with significant morbidity and mortality. These effects of changed kidney functioning affect every organ in the body of the affected individual. The confirmation of kidney damage can be done by various methods including abnormality in renal imaging modality, abnormal urine or blood composition, and histologic kidney disease evidence.[7]Chronic kidney disease is a global health issue affecting a large population globally of all ethnicity and race. One of the leading causes of CKD is diabetes mellitus. With the rapid and significant increase in diabetic subjects globally, the exponential rise in chronic kidney disease is seen. It is estimated that a large increase will continue with an increase in diabetes. As of 2000 data, nearly 4 lakh subjects having the end-stage renal disease was maintained on dialysis in the United States and Japan. In India, the prevalence of chronic kidney disease is seen in nearly 1% of the subjects with the estimation of 8 million of 1 billion populations. [8] NHANES (National Health and Nutrition Education Survey) reported a nearly 30% increase in subjects with End-stage renal disease in the United States from 1992 to 2008. Mortality in subjects with chronic kidney disease in more than half of the subjects is secondary to cardiovascular complications with dyslipidemia being the major risk factor for coronary artery disease. [9] In subjects of CKD, decreased HDL and hypertriglyceridemia are seen with normal or increased LDL levels. Also, chemical modifications including oxidation and lipoprotein clearance is not seen with normal mechanisms triggering an inflammatory response with the formation of foam cells from macrophages initiating the atherosclerotic process. [10] Vitamin D is a well-known factor, that regulates bone and mineral metabolism by promoting calcium, phosphate absorption and suppressing Parathyroid hormone (PTH) secretion.[11] It is Reno protective with suppression of the renin–angiotensin–aldosterone system, and with antiproteinuric as well as anti-inflammatory effects.[12] It has anti-atherosclerotic role that includes inhibition of macrophage to foam cell formation, downregulation of vascular smooth muscle cell proliferation and migration and suppression of inflammation triggered expression of endothelial adhesion molecules. Besides, vitamin D also prevents vascular calcification by inhibiting bone morphogenetic protein-2 expression. Decreased vitamin D can cause low calcium and hyperparathyroidism. PTH normally causes absorption of calcium and excretion of phosphorous.[13] In CKD the most common feature is hypovitaminosis D leading to secondary hyperparathyroidism. This would have caused an increase in calcium and a decrease in phosphate levels. But due to the declined renal mass, this does not happen and PTH secretion is further stimulated.[14] All the abnormal metabolism increases mortality and morbidity. Hence, the present study was aimed to assess the serum calcium, phosphorus, vitamin D and parathyroid hormone levels in control and test groups and also to study the correlation of these parameters.

2. MATERIAL AND METHODS

2.1 Study population

The study was a Case-Control study. The study was carried out in the Department of Biochemistry, Saveetha Medical College & Hospital. with the Nephrology Department association. The Study consists of 180 subjects in which normal healthy individuals are 45 and 135 are CKD patients which contain stage 3 to stage 5 each stage contains 45 subjects. The study was carried out at the Nephrology Department after obtaining clearance from the concerned Ethical committee. The study protocol was approved by the Ethical Committee of the Institute. All procedures performed in the study were in accordance with the ethical standard of the Saveetha Medical College Review Board (002/06/2018/IEC/SMCH). After explaining the detailed study design, written informed consent was taken from all the study subjects.

2.2 Inclusion and Exclusion criteria

The patients included are diagnosed with chronic kidney disease individuals who are attending the Nephrology Department, Saveetha Medical College. The inclusion criteria for the study were CKD cases, those who have reduced GFR to less than 60 mL/min/1.73ml. Controls: Age and sex matched healthy individuals. The age group of 30-70 years for both cases and controls. The exclusion criteria for the study were patients with Viral hepatitis and HIV positive, Patients with a history of malignancy or suffering from other life-threatening illnesses, and Cerebrovascular disease such as stroke or transient ischemic episodes. Patient history of liver diseases, Patients with age less than 30 and greater than 70 are excluded. Ethical committee approval was obtained by the Institutional Ethical committee from the patients and controls groups. Demographic data was collected

2.3 Biochemistry

From the control and patient, serum samples blood urea, serum creatinine, serum calcium and serum phosphorus were estimated by a fully automatic chemistry analyzer. Serum Vitamin D and Parathyroid hormone were estimated by the ELISA method. Based on serum creatinine using MDRD formula estimated GFR was measured.[15]

2.4 Statistical Analysis

The collected datas were subjected to the statistical evaluation using SPSS software version 21 (Chicago, IL, USA) and one-way ANOVA and t-test for results formulation Post hoc analysis was performed using Least significance difference. The data were expressed in percentage and number, and mean and standard deviation. The level of significance was kept at $p<0.05$.

3. RESULTS

Patient's Characteristics

The characteristics of the study subjects were listed in Table 1. The Majority of the study subjects were in the age of >40 years with 80.07% (n=109) subjects. There were 53.3% (n=72) males and 47% (n=63) females in the study. The most common etiology of CKD was diabetic nephropathy in 47.4 % (n=64) subjects followed by hypertensive nephropathy in 35.5% (n=48) subjects followed by Glomerulonephritis in 12.5% (n=17) subjects.

Table 1: Characteistics data inControlanddifferent stages of CKD

Parameter	Stage 3 of CKD (n=45)	Stage 4 of CKD (n=45)	Stage 5 of CKD (n=45)
1. Age (Mean± SD)	47.7±11.4	45.2±7.7	47.0±9.7
<40	12 (27%)	9 (20%)	5 (11%)
>40	33 (73%)	36 (80%)	40 (89%)
2. Gender			
a) Male	25 (55.5%)	24 (53%)	23 (51%)
b) Female	20 (44.5%)	21 (47%)	22 (49%)
Smokers (%) Yes : NO	(15.5%) 7:38	(22.2%) 10:35	(20%) 9:36
Alcoholic (%) Yes: No	(20%) 9:36	(20%) 9:36	(20%) 9:36
Etiology			
a. Diabetic nephropathy (%)	24 (53.3%)	21(46.7%)	19 (35.6%)
b. Glomerulonephritis(%)	5 (11.1%)	7 (15.6%)	5 (11.1%)
c. Hypertensive nephropathy (%)	13 (28.9%)	15 (33.3%)	20 (44.4%)
d. Poly cystic Kidney Disease (%)	3 (6.7%)	2 (4.4%)	1 (2.2%)

Table 2: Blood urea, Creatinine and eGFR between Control and different stages of CKD (*=statistical significance)

Parameter	Control (n=45)	Stage 3 of CKD (n=45)	Stage 4 of CKD (n=45)	Stage 5 of CKD (n=45)	One way ANOVA
Blood Urea (mg/dL) Mean ± SD	27.31±6.44	45.57±11.31*	65.0±11.94*	81.20±14.35*	F=190.09 p<0.0001
Creatinine (mg/dL) Mean ± SD	0.83±0.07	1.83±0.25*	3.01±0.44*	5.38±0.66*	F=965.49 p<0.0001
eGFR (mL/min) Mean ± SD	95.58±10.80	38.06±7.40*	21.62±4.25*	10.74±2.36*	F=1313.86 p<0.0001

The above table shows the mean blood urea and serum creatinine significantly higher in CKD patients when compared with Control. The mean eGFR was significantly lower in CKD patients when compared with control. The blood urea in controls was 27.31±6.44 mg/dl which increased significantly to stage 3, 4, and 5 chronic kidney disease subjects to 45.57±11.31, 65.0±11.94, and 81.20±14.35mg/dl respectively with p<0.001. Similar findings were also seen for creatinine and GFR which significantly increased from controls to stage 3, 4, and 5 chronic kidney disease subjects with p<0.001 (Table 2).

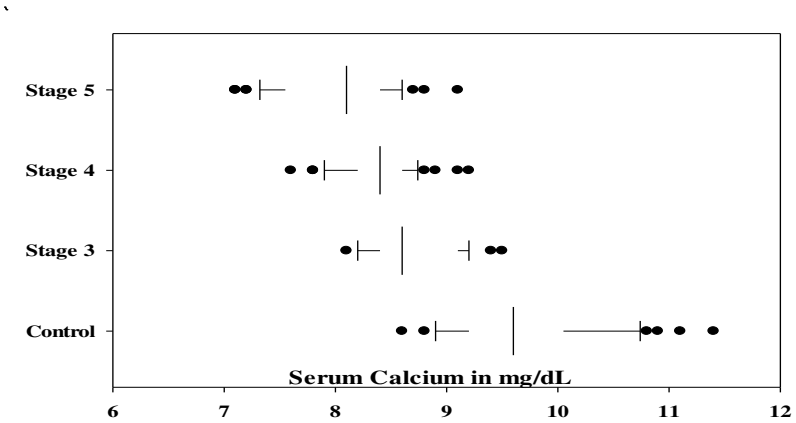

Fig 1: Serum calcium level in control and different stages of CKD (one way Anova F value 110.773; p<0.0001)

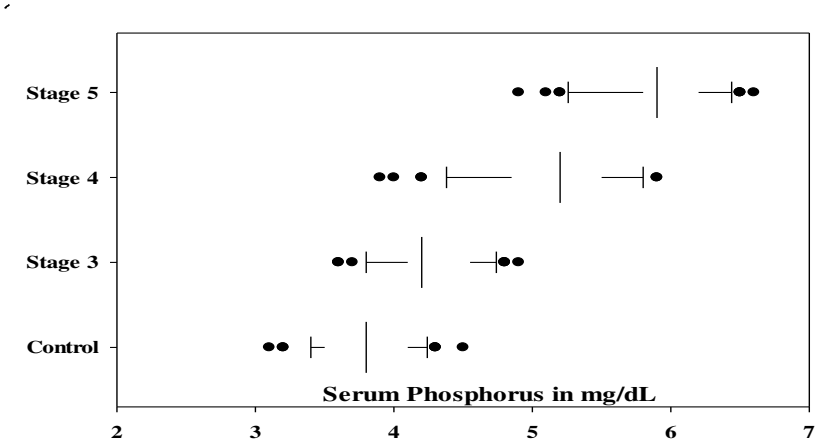

Fig 2: Serum Phosphorus level in control and different stages of CKD (one way Anova F value 248.388; p<0.0001)

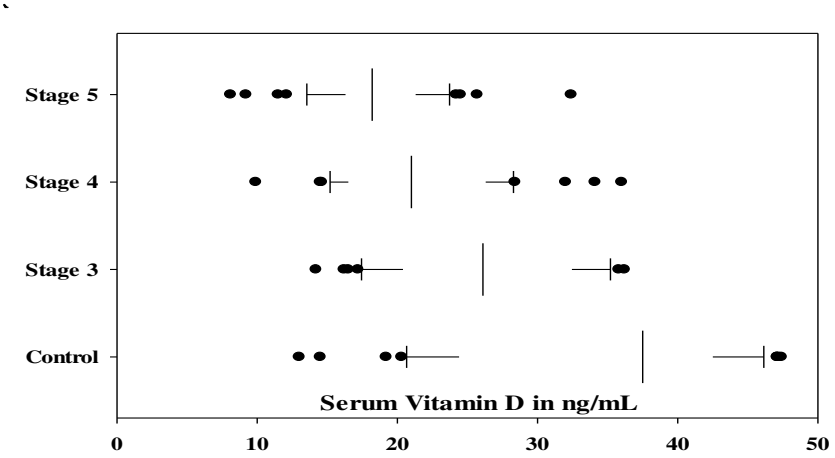

Fig 3: Serum Vitamin D level in control and different stages of CKD (one way Anova F value 38.74; p<0.0001)

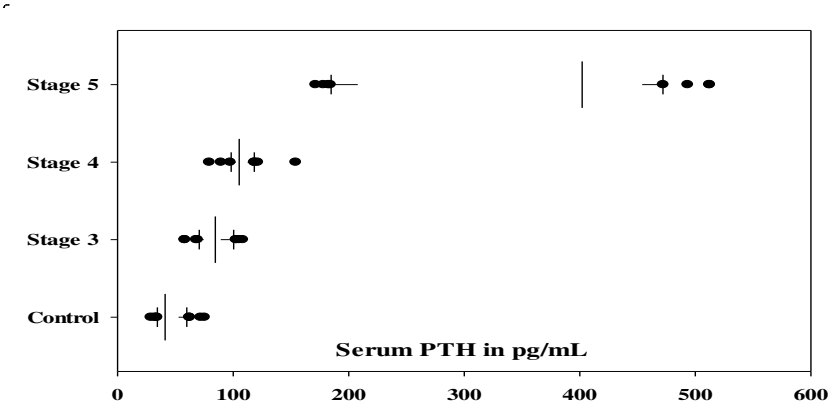

Fig 4: Serum Parathyroid hormone level in control and different stages of CKD (One way Anova F value 213.96; p<0.0001)

Table 3: Post hoc analysis of Serum Calcium, Phosphorus, Vitamin D and PTH level in control and different stages of CKD

	Serum calcium (95 CI) (p value)	Serum Phosphorus (95 CI) (p value)	Serum VitaminD (95 CI) (p value)	Serum PTH (95 CI) (p value)
Control vs. Stage 3	(0.814-1.208) <0.0001	(0.638-0.3037) <0.0001	(4.539-10.451) <0.0001	(63.886-13.007) <0.005
Control vs. Stage 4	(1.143-1.537) <0.0001	(1.496-1.161) <0.0001	(9.248-15.160) <0.0001	(87.339-36.460) <0.0001
Control vs. Stage 5	(1.538-1.932) <0.0001	(2.305-1.970) <0.0001	(12.144-18.055) <0.0001	(320.61-269.73) <0.0001

Stage 3 vs. Stage 4	(0.131-0.525) <0.005	(1.025-0.690) <0.0001	(1.753-7.664) <0.005	(48.892-1.986) >0.05(N.S)
Stage 3 vs. Stage 5	(0.527-0.921) <0.0001	(1.834-1.499) <0.0001	(4.648-10.560) <0.0001	(282.16-231.28) <0.0001
Stage 4 vs. Stage 5	(0.592-0.198) <0.0001	(0.976-0.641) <0.0001	(0.060-5.851) >0.05 (NS)	(258.71-207.83) <0.0001

(95CI): 95 % Confidence Interval (Lower bound – Upper Bound) NS: Not significant

The above table shows posthoc analysis and there was no statistical significant differences of vitamin D between stage 4 and stage 5 of CKD. The mean serum PTH was significant also not showed significant difference between Stage 3 and stage 4 CKD reaming all are shown statistical significant.

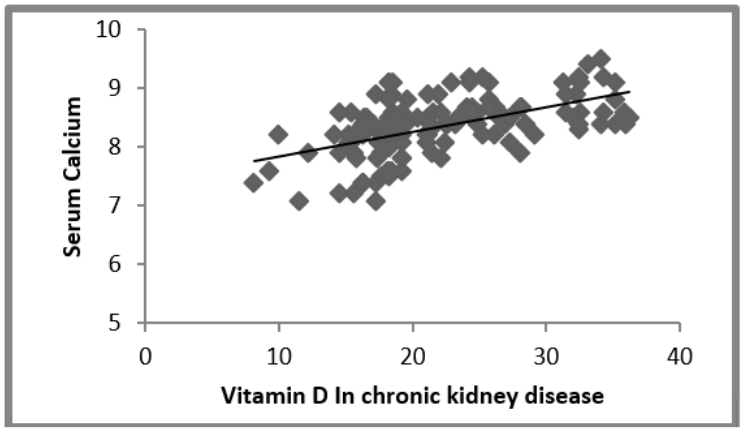

Fig 5: Correlation between Vitamin D and serum calcium (R value 0.5469)

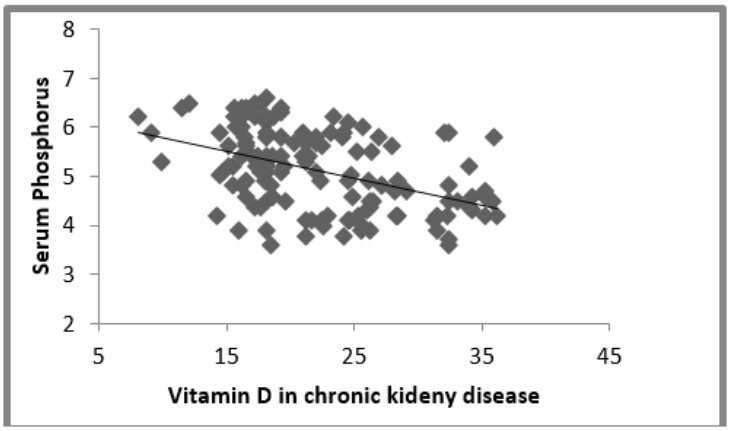

Fig 6: Correlation between Vitamin D and serum phosphorus (R value -0.4462)

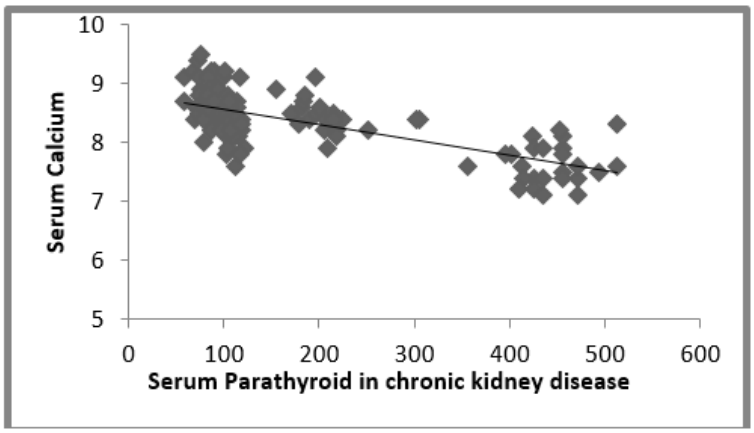

Fig 7: Correlation between Serum Parathyroid and serum calcium (R value -0.7036)

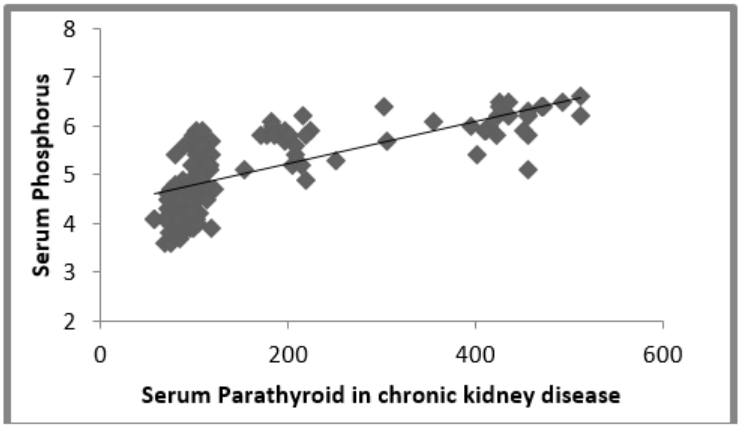

Fig 8: Correlation between Serum Parathyroid and serum phosphorus (R value 0.7358)

4. DISCUSSION

The present study consists of 180 subjects in which 45 are controls and 135 are chronic kidney disease patients. In all the individual blood urea, serum creatinine was estimated. Based on serum creatinine using MDRD formula, GFR was estimated. Based on estimated GFR, chronic kidney disease individuals are further classified into stage 3 of CKD, stage 4 of CKD and stage 5 of CKD, each stage consisting of 45 patients each. The blood urea and serum creatinine are increasing gradually from stage 3 of CKD to stage 5 of CKD due to decreased GFR. In the present study estimated GFR by MDRD showed decline in CKD stages when compared with control this decrease is statistically significant (Table-2;). ($p<0.0001$) In the present study the mean serum calcium in control, stage 3, stage 4 and stage 5 were 9.72±0.63, 8.71±0.35, 8.32±0.32 and 7.98±0.50 respectively and the decreased level of serum calcium is statistically significant (Figure 1; $F=110.773$; $p<0.0001$). The mean phosphorus in control, stage 3, stage 4 and stage 5 were 3.80±0.34, 4.27±0.33, 5.13±0.49 and 5.94±0.40 respectively and the increased levels of serum phosphorus is statistically significant (Figure 2; $F=248.388$; $p<0.0001$). Serum calcium level declined as CKD progressed due to the retention of phosphate and declined calcitriol and decreased to the calcaemic action of parathyroid hormone on bone. Calcium is a key molecule for regulation of PTH secretion via specific membrane receptors, which is present in chief cells of the parathyroid gland surface as depicted by the previous study of Llach et al in 1995.[16] Also, Martin KJ et al in 2007 favored the present study by describing that, as CKD progresses the serum calcium level will decrease due to retention of phosphate. Decreased vitamin D promotes resistance to the action of PTH on bone. PTH secretion inversely proportion with calcium. In CKD, decreased calcium receptors causes inadequate suppression of PTH secretion resulting in high PTH and will also causes increased level of phosphorus.[17]In the present study, the mean serum Vitamin D in control, stage 3, stage 4 and stage 5 were 33.78±10.27, 26.28±6.61, 21.57±5.87 and 18.68±4.25 respectively and the decreased level of serum vitamin D is statistically significant (Figure 3; $F=38.74$; $p<0.0001$). The mean parathyroid hormone in control, stage 3, stage 4 and stage 5 were 45.30±10.41, 83.75±11.17, 107.20±10.67 and 340.48±120.86 respectively and the increased level of serum parathyroid hormone is statistically significant (Figure 4; $F=248.388$; $p<0.0001$). The correlation between serum vitamin D and serum calcium showed a moderate positive correlation (Figure 5; $R= 0.5469$). Whereas the correlation between serum vitamin D and phosphorus showed a moderate negative correlation (Figure 6; $R= -0.4462$). The correlation between serum parathyroid hormone and serum calcium showed a moderate negative correlation (Figure 7; $R= -0.7036$). Whereas the correlation between serum parathyroid hormone and phosphorus showed a moderate positive correlation (Figure 8; $R= 0.7358$). As CKD progresses, glomerular filtration rate decreases which leads to declined phosphate filtration. It plays main role in development of secondary hyperparathyroidism. In posthoc analysis, there was no statistical significant of vitamin D between stage 4 and stage 5 of CKD. The mean Serum PTH was significant, but not showed significant difference between Stage 3 and stage 4 CKD reaming all showed statistical significant.(Table 3) These findings were comparable to the studies of Kates DM et al in 1997 and Hruska KA in 1995 studies, where decreased phosphate filtration was seen with GFR reduction.[18,19] Various theories explained how retention of phosphate causes release of PTH that includes induction of hypocalcemia, declined formation of active calcitriol and directly increased phosphate causes raise gene expression of PTH. Fournier A et al in 1992 and Silver J et al in 2005 also testified these results.[20,21] Based on above theory, decreased free calcium and calcitriol and phosphate retention in early CKD contribute hyperparathyroidism as suggested by Slatopolsky et al in 1996 and Fire A et al in 1993.[22, 23] Calcitriol level decreases below the normal if GFR is less than 30ml/min. In previous study by Van holder R et al., in 1993 also reported that calcitriol level decreased below the normal in mild to moderate CKD. [24] In addition to declined renal mass, several other factors contributed to decreased calcitriol, which includes phosphate retention that may directly suppress calcitriol synthesis. Experimental studies also revealed that calcitriol synthesis from calcidiol is inhibited by uremic toxins, which are retained in CKD as shown in the studies of Tentori F et al in 2008 and Block GA et al in 1998.[25,26] In the kidney FGF23 (fibroblast growth factor) inhibits reabsorption of phosphate and inhibits synthesis of calcitriol by decreasing activity of 1 alpha hydroxylase. The calcitriol level increases PTH directly or indirectly. This finding was consistent with the previous study of Andress DL in 2008.[27] Also, Hruska KA et al., in 2008 depicted that, indirect effects on PTH are decreased absorption of calcium from the intestine, which causes hypocalcemia and in turn causes PTH stimulation. The direct response to calcitriol develops hyperparathyroidism. In CKD, increased level of Phosphaturic hormone FGF 23 (fibroblast growth factor) will contributes low calcitriol.[28]

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5. CONCLUSION

This study helpful to label an early alarming marker to prevent the worst progression of CKD by estimating Vitamin D and PTH. The progression and complications of CKD, especially the cardiovascular complications can be prevented or at least postponed to some extent. Supplementation of vitamin D along with calcium would be more beneficial. A chelating phosphate molecule would be a challenge in the coming years to add to the benefits of the treatment for CKD. The quality of life can be improved for the CKD patients to a near normal condition.

6. ACKNOWLEDGEMENTS

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7. AUTHOR'S CONTRIBUTION STATEMENT

Raju DSSK and Dr Kedari GSR designed and conceptualized the study along with collecting the data. Raju DSSK and Dr Kedari GSR discussed methodology and assessed data to formulate the results. Also, the manuscript was designed by both Raju DSSK and Dr Kedari GSR. The final version of the manuscript was approved by both the authors.

8. CONFLICT OF INTEREST

Conflict of interest declared none.

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