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RESEARCH ARTICLE

Study of Vitamin D, Parathormone, calcium and phosphorus levels in patients with End Stage Renal Disease undergoing haemodialysis and their interpretation.

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Abstract

Background: Chronic Kidney Disease (CKD) is an international public health affecting 5-10% of world population. As kidney function declines, there is progressive deterioration in body homeostasis. Impaired metabolism of Vitamin-D is among the most recognized disorders associated with CKD. The end result of which is elevated serum Parathyroid Hormone (PTH) and abnormal Calcium (Ca) and Phosphorus balance. The objective of the study was to interpret the Vitamin-D levels with PTH, Ca and phosphorus.

INTRODUCTION

Chronic Kidney Disease (CKD) refers to an irreversible deterioration in renal function which classically develops over a period of years. CKD is defined as kidney damage with or without decreased GFR, manifested as either pathologic abnormalities or markers of kidney damage, including abnormalities in composition of blood or urine, abnormalities renal imaging findings, and a GFR less than 60 ml/min/ 1.73m2. For operational purposes, CKD is defined as the presence, for at least three months, of evidence of kidney damage with an abnormal GFR (glomerular filtration rate) or, alternatively, by a GFR below 60ml/min/1.73 m2 body surface area. A cut off of 60ml/min/1.73 m2 body surface area is selected because it represents a decrement to approximately half of normal renal function and because its use avoids the classification of many older individuals who may have mild reductions in their GFR. Whether such reductions truly represent a physiologic alteration or are the consequence of occult pathology is unknown. The prevalence of CKD as per the National Kidney Foundation Kidney Disease Outcomes Quality Initiative are – Stage 1 CKD 3.3 %, Stage 2 CKD 3.0 %, Stage 3 CKD 4.3 %, Stage 4 CKD 0.2 %, Stage 5 CKD 0.1 %. As the kidney function declines, there is a progressive deterioration in mineral homeostasis, with a disruption of normal serum and tissue concentration of phosphorus and calcium, and changes in circulating levels of hormone. Derangements in calcium and phosphorus metabolism that develop during the course of CKD are caused by multiple mechanisms, including alteration in dietry intake, development of secondary hyperparathyroidism and hypovitaminosis-D, and alteration in calcium sensing receptor and bone-associated proteins. Impaired metabolism of Vitamin-D is among the most recognized disorders associated with CKD. The end result of which is elevated serum

Parathyroid Hormone (PTH) and abnormal Calcium (Ca) and Phosphorus balance, wherein there is drop in serum calcium levels and rise in serum phosphorus levels. There are three organs involved in phosphorus homeostasis: intestine, kidney and bone. The major hormones controlling phosphorus levels are vitamin D and PTH. Phosphorus absorption is dependent on both passive transport related to the concentration in the intestinal lumen and active transport stimulated by 1,25,dihydroxy-D (calcitriol) and PTH. Most inorganic phosphorus is freely filtered by the glomerulus. Factors that increase inorganic phosphorus excretion are primarily increased plasma phosphorus concentration and PTH. Serum levels of calcium are maintained in the normal range by inducing increases in the secretion of PTH. PTH acts to increase bone resorption, increase renal calcium resorption, and increase the conversion of 25(OH)-D to 1,25(OH)2- D in the kidney, thereby increasing gastrointestinal calcium absorption. In individuals with normal homeostatic mechanisms, these interactions of PTH and Vitamin D metabolites at target organs, including kidney, maintain the serum ionized calcium levels within the normal range to ensure proper cellular function. The physiologic effect of calcitriol is to facilitate uptake of calcium in intestinal and renal epithelium by increasing the activity of the voltage dependent calcium channels. Elevated serum levels of PTH increases 1 alpha hydroxylase activity in the kidney, thereby increasing the levels of 1,25 dihydroxy-D levels. This results in a rise in serum calcium, and then 1,25 dihydroxy –D feeds back on the parathyroid gland, decreasing PTH secretion, thus completing the typical endocrine feedback loop. PTH does not directly inhibit its own synthesis, which is one reason why PTH levels increase in presence of renal failure, in which 1,25 dihydroxy –D is no longer synthesized in sufficient amounts. Hypocalcemia and hyperphosphatemia stimulate PTH, whereas 1,25 dihydroxy – D inhibit PTH. The primary function of PTH is to maintain calcium homeostasis by increasing bone mineral dissolution, increasing renal absorption of calcium and excretion of phosphorus, increasing the activity of renal 1-alpha hydroxylase and enhancing the gastrointestinal absorption of both calcium an phosphorus indirectly through its effects on the synthesis of 1,25 dihydroxy-D. PTH secretion occurs in response to hypocalcemia, hyperphosphatemia, and 1,25 dihydroxy –D deficiency. Based on available literature it appears that calcium is more important in stimulating PTH release, whereas calcitriol is more important in inhibiting PTH release.

Subjects and Methods:

A hospital based cross sectional study was carried out in the department of medicine, central referral hospital, Gangtok, East Sikkim. A total of 45 CKD patients undergoing hemodialysis were recruited. Levels of Vitamin- D, PTH, Ca and phosphorus was estimated. Estimation of serum vitamin D was done with vitamin D estimation kit, a solid phase enzyme-linked immun0-ssay (ELISA) based on the principle of competitive binding. Reference range for vitamin D in ng/ml were : <10- severly deficient, 10-20 - deficient, 21-30 - insufficient, 31-100 - sufficient, > 100 – intoxication. Estimation of PTH was done by the intact PTH immunoassay, a two-site ELISA (enzyme linked immunosorbant assay). One antibody is prepared to bind only the mid-region and C-terminal PTH 39-84 and this is biotinylated. The other antibody is prepared to bind only the N-terminal PTH 1-34 and this antibody is labeled with horseradish peroxidase (HRP) for detection. Reference range for PTH : 10-65 pg/ml. Estimation of calcium was done by Arsemazo III (BeneSphere). Reference range for calcium : 8.8-10.2 mg/dl. Estimation of phosphorus was done by Ammonium Molybdate (BeneSphere). Referene range for phosphorus : 2.5-4.8 mg/dl.

Results:

A total of 45 CKD patients undergoing hemodialysis (HD) in Central Referral Hospital (CRH), Sikkim, were included in the study. A majority of these patients were between the age o 40 to 60 years with the mean age of 50 +/- 12. Among these, 15 patients were female and 30 patients were male.

In the present study, 68.43% of the CKD patients had Vitamin-D deficiency (20ng/ml). Only 11.11% of patients had sufficient (> 30ng/ml) levels of Vitamin-D. The remaining were found to be Vitamin-D insufficient (21-30ng/ml). The mean value of Vitamin-D levels in CKD patients was 19.01 +/-9.19.

The mean value of intact PTH in these patients were 266.96+/-243.75. The study documented hyperparathyroidism in 73.33% of CKD patients.

The mean value of calcium in CKD patients was 8.40+/-0.96. The mean value of phosphorus in CKD patients was 5.16+/-1.22. The mean value of serum alkaline phosphatase in CKD patients was 189+/-77.15. Serum alkaline phosphatase is a biochemical marker of bone turnover and is used to monitor the metabolic bone disease associated with renal insufficiency.

Discussion:

In our study 88.89% of the CKD patients had hypovitaminosis D. Most of the patients in our study were on calcitriol supplements but we did not measure 1,25(OH)D. From our study we found that 1,25(OH)D has not role in maintaining viatamin-D status in CKD patients. The identification of extra-renal 1-alfa-hydroxylase suggests that 25 (OH) D status is an important consideration in patients with CKD. Gonzalez et al, showed a positive correlation between 25 (OH) D and calcitriol suggesting that the later was dependent on 25 (OH) D levels in CKD individuals. Levin et al, showed low levels of the 25 (OH) D itself may contribute to decreased levels of 1,25(OH)D3 production, particularly in CKD patients with nephritic range proteinuria.

The mean value of intact PTH in these patients were 266.96+/-243.75. The study documented hyperparathyroidism in 73.33% of CKD patients. The correlation between the two variables, Vitamin-D and parathormone was calculated by Karl Pearson Correlation and was found to be statistically significant ($p < 0.05$). The present study found the negative correlation between 25 (OH) D and PTH levels. Ghazali et al, had too observed that the levels of 25 (OH) D and PTH and PTH was negatively correlated. Most of our patients in our study were prescribed calcitriol supplement. Despite taking calcitriol the levels of PTH were found to be elevated in these patients. On the basis of this observation we postulate that 25 (OH) D supplement along with calcitriol may have a greater impact on pTH regulation in CKD patients undergoing hemodialysis. Whether the elevated level of PTH decreased the serum 25 (OH) D level or low serum 25 (OH) D have direct or indirect effect on PTH secretion was beyond the scope of our study.

The mean value of calcium in CKD patients was 8.40+/-0.96. The study noted that the level of calcium was low in CKD patients. Bayard et al, who first reported plasma level in uremic patients prior to and while on maintainance dialysis, pointed a positive correlation between plasma 25 (OH) D and calcium levels. Several studies showed the association between the low serum 25 (OH) D levels and lower serum calcium.

The mean value of phosphorus in CKD patients was 5.16+/-1.22. Hyperphosphatemia in CKD patients is associated with low serum levels of 25 (OH) D and secondary hyperparathyroidism. Secondary hyperparathyroidism , reduced absorption of calcium from intestine and hyperphosphatemia leads to bone disease in CKD patients.

The mean value of serum alkaline phosphatase in CKD patients was 189+/-77.15, which is significantly high. Serum alkaline phosphatase is a biochemical marker of bone turnover and is used to monitor the metabolic bone disease associated with renal insufficiency.

CONCLUSION

In this hospital based cross sectional study, it was observed that majority of the CKD patients had hypovitaminosis D. The study documented hyperparathyroidism in most of CKD the patients. The correlation between the two variables, Vitamin-D and parathormone was calculated by Karl Pearson Correlation and was found to be statistically significant ($p < 0.05$). The present study found the negative correlation between 25 (OH) D and PTH levels. Hyperphosphatemia in CKD patients is associated with low serum levels of 25 (OH) D and secondary hyperparathyroidism. Serum alkaline phosphatase, was significantly high in CKD patients, which is a biochemical marker of bone turnover and is used to monitor the metabolic bone disease associated with renal insufficiency.

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