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To Study the Altered Calcium Phosphorus Intact Para Thyroid Hormone in Chronic Kidney Disease Patients and Correlate with Bone Denstiometery Analysis

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Abstract: ***Introduction: The prevalence of Chronic Kidney Disease is large and treatment options nowadays can be accounted for. With advancements in management techniques in follow up, researchers have isolated markers to predict the course of disease and even delay or prevent various grave complications related to CKD. However, the work is still in progress as numerous studies are done to correlate markers/parameters with the CKD natural history. This study attempts to assess altered Calcium, Phosphorous, intact PTH in CKD patients and correlate with Bone Densitometry analysis. Bone remodelling is a dynamic process with an average remodelling cycle of 3-6 months for an area of bone. Therefore, the use of multiple bone biopsies as a gold standard for diagnosing and monitoring renal osteodystrophy is impracticable. There is need for reliable biomarkers for assessing and monitoring patients with CKD-MBD. Therefore, the KDIGO guidelines recommended the use of serum PTH in conjunction with total or bone-specific alkaline phosphatase (b-ALP) since high or low levels of these markers correlate with underlying bone turnover. Objective: To study the altered Calcium Phosphorus iPTH and Vitamin D homeostasis in CKD patients and correlate with altered BMD. Materials and Methods: This study was conducted in a tertiary care centre with 100 subjects of CKD was taken as per inclusion/exclusion criteria mentioned, investigated and various statistical analyses were applied to draw intellectual conclusions. We took two groups as Hyperdynamic bone disease (High turnover) and Adynamic Bone disease and evaluated multiple factors, such as age, sex, individual biomarkers; their relationship with the two groups along with an attempt to correlate with BMD done by DEXA scan, a non-invasive method to assess bone mass/health. Results: We drew outcome that Phosphorous, Calcium, IPTH, BMD, had no significant correlation between age and gender in both groups. Hypercalcemia was associated with Adynamic disease whereas hypocalcemia was found in Hyperdynamic disease. IPTH level was higher in the case of hyperdynamic disease and suppressed with the adynamic disease. The bone mineral metabolism abnormality leads to complicated extraskeletal vascular calcification, increases coronary and cerebrovascular accidents along with diseases of bone and joints. Conclusion: We found statistically significant increase in serum urea, creatinine, phosphorus and parathyroid hormone and decreased level in serum calcium in hyperdynamic disease. In adynamic disease, there was a remarkable increase in serum urea, creatinine, phosphorus, calcium and vitamin D3, and a decrease in parathyroid hormone in CKD patients. Thus, it could be concluded that parathyroid level can be used as a marker to identify the bone mineral disturbance in CKD patients even in the early stages. Serial maintenance of IPTH with BMD for maintaining optimal skeletal health is advised for preventing dysregulated mineral metabolism to reduce morbidity and mortality in CKD patients.***

Keywords: Chronic Kidney Disease, Bone Densitometry analysis, renal osteodystrophy, Hyperdynamic bone disease, Adynamic Bone disease, coronary and cerebrovascular accident

1. Introduction

It is a well-known fact that Chronic Kidney Disease (CKD) leads to abnormal homeostasis of Calcium and Parathyroid hormone. We have done a study to assess altered calcium, phosphorus, parathyroid and vitamin D homeostasis in patients of chronic kidney disease (CKD) and to asses altered **Bone Mineral Density** in CKD patients and to co-relate that with 'altered Calcium-Phosphorus Homeostasis' in patient of various stages of Chronic Kidney Disease. With the decline in kidney function, there is an ongoing deterioration in mineral homeostasis with the upsetting of conventional serum concentrations of phosphorus, calcium and changes in circulating levels of hormones like parathyroid hormone (PTH) and Vitamin D3. Beginning in CKD stage 3, the capacity of the kidneys to fittingly eliminate phosphorous load is diminished, leading to hyperphosphatemia. In addition, there is a suppression of vitamin D receptors and resistance to the actions of PTH at the tissue level causing secondary hyperparathyroidism. ([1])

As a consequence, patients are at higher risk of bone disease, extra-osseous calcification, and death. These alterations mostly start early in the course of CKD, where Glomerular Filtration Rate (GFR) falls below 60mL/min per 1.73 m^2 [(2)]. Cardiovascular disease accounts for 70% of all deaths in patients with CKD, with an overall mortality of 20% per year in patients on dialysis. [(3)] Hyperphosphatemia and hypercalcemia have been illustrated to promote calcification of the vasculature, myocardium, and cardiac valves. Vascular calcification manifested in reduced vessel wall elasticity, the increased intima-media layer thickness is linked to Left ventricular hypertrophy, and happens with increased severity in dialysis patients versus non-CKD patients. ([4])

2. Material and Method

100 patients with CKD (determine by eGFR concerning KDIGO Criteria) with written informed consent were taken at SNMC, Agra. Enrolment is done according to inclusion and exclusion criteria mentioned later. Demographic data such as age, sex, address noted, a detailed history general physical examination, vitals (temperature, blood pressure, respiratory rate) and systematic examination performed and noted. Serum samples were withdrawn for haemoglobin, complete blood count, serum creatinine, urea, phosphorus, vitamin 'D' level serum calcium level, serum intact

parathyroid hormone level and bone densitometry done. **Bone DEXA scan is done by GE machine model lunar DPX bone DEXA done with lumbar spine and both hip.** Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Assumptions made in the study are as:

1) Dependent variables should be normally distributed.
2) Samples drawn from the population should be random.,
3) Cases of the samples should be independent. (5) (6) (7) (8)

Analysis of variance (ANOVA) has been used to find the significance of study parameters between three or more groups of patients; Student test (two-tailed, independent) has been used to find the significance of study parameters on a continuous scale between two groups (Intergroup analysis) on metric parameters. Level 1 test for homogeneity of variance has been performed to assess the homogeneity of variance. Chi-square/Fisher Exact test has been used to find the significance of study parameters on a categorical scale between two or more groups.

Inclusion Criteria:

Patients having Chronic Kidney Disease as determined by eGFR with respect to Kidney Disease Improving Global Outcomes (KDIGO) criteria at SN Medical College Agra.

Exclusion Criteria:

- Age < 18 years.
- Patients who deny consent to be a part of the study.
- Patients were not treated with oestrogens.
- Patients on dialysis for less than 6 months.
- Patients who had taken corticosteroids.
- Those who had a parathyroidectomy were excluded from the study.

All females were postmenopausal or permanently amenorrhoeic.

3. Observations

Multivariant Correlations
Hyperdynamic Disease (HBD)

Table 1: Multivariant Correlations Hyperdynamic Bone Disease (HBD) with Age

Age group (yrs.)	No.	PO4		Ca+		IPTH		BMD	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
18-40	37	7.29	1.33	6.82	1.07	592.68	307.4	1.21	0.50
41.60	16	7.34	1.11	6.44	1.10	735.81	358.94	1.18	0.43
>60	11	8.27	1.36	6.90	1.10	735.09	239.56	0.97	0.51
f-value		2.578		0.836		1.826		1.052	
p-value		0.084		0.438		0.170		0.355	

Adynamic Bone Disease (ABD)

Table 2: Multivariant Correlations adynamic Bone Disease (ABD) with Age

Age group (yrs.)	No.	PO4		Ca+		IPTH		BMD	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
18-40	20	6.79	0.97	11.17	0.41	12.03	1.60	3.42	0.33
41-60	3	7.44	0.01	11.40	0.05	14.60	0.04	3.30	0.02
>60	9	7.33	1.49	11.03	0.13	11.83	1.51	3.57	0.50
f-value		0.994		1.413		4.137		0.766	
p-value		0.382		0.260		0.026		0.474	

HBD

Table 3: Multivariant Correlations hyperdynamic Bone Disease (HBD) With Sex

Sex	No.	PO4		Ca+		IPTH		BMD	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
Male	49	7.61	1.38	6.66	1.19	608.71	300.64	1.04	0.39
Female	15	7.03	1.02	6.99	0.52	810.60	322.89	1.55	0.56
t-value		-1.503		1.040		2.237		3.980	
p-value		0.1378		0.3025		0.0289		0.0002	

ABD

Table 4: Multivariant Correlations adynamic Bone Disease (ABD) With Sex

Sex	No.	PO4		Ca+		IPTH		BMD	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
Male	15	7.25	1.15	11.12	0.18	12.56	1.59	3.50	0.39
Female	17	6.79	1.05	11.18	0.44	11.91	1.72	3.41	0.36
t-value		-1.183		0.492		-1.105		-0.679	
p-value		0.2462		0.6261		0.2780		0.5025	

4. Result

In age-wise **distribution**, as per our observation chi-square test applied and p-value 0.14 which was not significantly different between various groups (adynamic and hyperdynamic) when related to age. There was no association with Bone mineral density done by Dexa Scan. **In sex-wise distribution,** as per our observation chi-square test applied and p-value 0.004 which is significantly different in the various groups, showing male gender is associated with hyperdynamic bone disease and female gender associated with adynamic bone disease in CKD patients. There was no association with Bone mineral density done by Dexa Scan.

In phosphorus level distribution, the mean phosphorous level in the hyperdynamic disease is 7.47 with SD 1.32 and p-value 0.0937 while in adynamic disease mean phosphorus level 7.01 and SD 1.11, it is observed the higher serum phosphorous value associated with occurrence of both adynamic and hyperdynamic bone disease in CKD patient. Hence not significantly different. In **calcium level distribution,** as per our observation, there is hypercalcemia in adynamic bone disease and hypocalcaemia in hyperdynamic bone disease. The association was established to be significant with a p-value of 0.0001.

In Ipth distribution, IPTH levels are higher in case of hyperdynamic disease, and suppress with adynamic disease; this observation found to be statistically significant with a p-value<0.0001.

In our study, according to dialysis duration, as per our observation Hyperdynamic bone disease prevalence increases with chronicity of dialysis while no correlation was observed between duration of dialysis and occurrence of adynamic bone disease.

In **multivariant correlations,** including phosphorous, calcium, IPTH, BMD, no significant correlation was observed according to age and gender.

5. Discussion

Many studies and literature have shown that CKD is associated with alterations in calcium and phosphorus metabolism leading to increased mortality and morbidity. These alterations would cause changes in PTH levels in almost all stages of the disease. We have used this in our study to find out the usefulness of the Elevated PTH levels as an early marker of derangements in bone and mineral metabolism associated with CKD. Nephrology guidelines also recommend targets and early treatment strategies to correct serum levels of phosphorus, calcium, and parathyroid hormone, because many data suggested there was a clear association between these potential risk biomarkers and vascular disease and death. ([2] So numerous drugs including phosphorus binders, vitamin D and calcium-mimetic agents have been specifically developed and promoted to decrease these complications.

The pattern of Parathyroid hormone levels in CKD:

Recent observational studies have shown that even a slight elevation in PTH levels have been associated with an increased cardiovascular risk. It is also found that monitoring PTH levels from the early stages of CKD can prevent complications due to mineral disturbances. Elevated serum phosphorus has been associated with the progression of secondary hyperparathyroidism and deposition of calcium in soft tissues. The long-term consequences associated with persistently elevated PTH levels in CKD include high turnover bone disease, anaemia, CVD, and mortality. ([2] As a result, both NKF and Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend that PTH levels should be regularly monitored beginning in stage 3 CKD and that elevated levels should be treated with a combination of dietary phosphorus restriction and therapy with vitamin D and/or calcimimetic. [(10)] In our study, we found a statistically significant increase in PTH levels in Hyperdynamic bone disease as compared to A dynamic bone diseases ($p < 0.0001$).

6. Conclusion

Our study aimed to assess the prevalence of bone disease in CKD patients. In conclusion in our study, we found a statistically significant increase in serum urea, serum creatinine, serum phosphorus and parathyroid hormone and decreased level in serum calcium in hyperdynamic disease. In the case of *adynamic disease,* there was a remarkable increase in serum urea, serum creatinine, serum phosphorus, serum calcium and vitamin D3, and a decrease *in parathyroid hormone in CKD patients*. Thus, it could be concluded that parathyroid level can be used as a marker to identify the bone mineral disturbance in case of CKD patients even in the early stages, like in the standard guidelines which highlight the importance of measuring PTH early in the course of the disease and also recommends an annual measurement of PTH once the diagnosis of CKD is made. If the PTH levels are measured and maintained within the target range, many significant complications can be prevented. This result is supported by previous studies.

The bone mineral metabolism abnormality leads to complicated extra-skeletal vascular calcification increases coronary and cerebrovascular accident events along with diseases of bone and joints. Various guidelines like (KIDGO) have advised serial maintenance of IPTH along with BMD for maintaining optimal skeletal health and advised preventing dysregulated mineral metabolism to reduce morbidity and mortality in CKD stage-V patients. The present study also advocates such measures.

A limiting factor of the study was limited size of the sample size of patients and the economic status of patients and restricting optimal dialysis therapy further study with larger population size is needed to better ascertain and validate these observations.

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