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The Correlation between the Biomarkers of Bone and Mineral Disorders in patients with CKD stage 4 and stage 5 patients not on dialysis

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Abstract
Background: *Bone abnormalities are found almost universally in patients with CKD requiring dialysis (stage 5D), and in the majority of patients with CKD stages 3–5 because the mineral and endocrine functions disrupted in CKD are critically important in the regulation of both initial bone formation during growth (bone modeling) and bone structure and function during adulthood (bone remodeling).*
Objectives: *The study was to assess the mineral and bone disorders by investigating biochemical parameter and also with the help of DEXA scan of bone in the patients with CKD stage 4 and stage 5 patients not on dialysis.*
Method: *In this cross-sectional study serum biomarkers of bone turnover: Bone-specific alkaline phosphatase (BAP) along with parathyroid hormone, 25(OH) vitamin D, and bone mineral density (BMD) using dual absorption X-ray absorptiometry in 176 patients who met the inclusion and exclusion criteria for the enrollment were evaluated.*
Results: *Out of 176 patients maximum number of patients belongs to age group 48-57 years (28.41%) and the age group 18-27 years has the lowest number of patients (6.82%). total number of patients having deficient Vit-D level were (75%) and insufficient were (20.45%) and only (4.55%) showed sufficient level of Vit-D among the study population. stage 4 and in stage 5 the Vita-D deficient patients were (68.89%) and (81.4%). In stage 5 the level of Vita-D decreases significantly. It also shows that in CKD stage 5 there was no patient with sufficient level of Vita-D. PTH level more than 2 times the upper limit was found in (71.6%) patients and among them (57.1%) patients had BAP values more than the mean value. significant correlation between PTH and PO4 (p=0.001), between PTH and Vit-D (p=0.007), between Calcium and PO4 (p=0.008). There are negative correlation between PTH and calcium (r=-0.119), PTH and Vita-D (r=-0.394), PTH and BMD (r=-0.081), between calcium and PO4(r=-0.392), PO4 and Vit-D (r=-0.311), and PO4 and BMD (r=-0.147).*
Conclusion: *High turnover could contribute to the development of osteoporosis. Vitamin D deficiency is widespread and seems to have a role in the genesis of hyperparathyroidism and high turnover renal bone disease. 25(OH) vitamin D is now recognized as an important player in maintenance of bone health in CKD*
Keywords: *Biomarkers, Bone and Mineral Disorders, CKD stage 4 and stage 5.*

Introduction

Renal osteodystrophy (ROD) is a segment of the expansive range of mineral and bone issue of CKD Bone disease related with chronic kidney illness is made out of various variations from the abnormalities of bone mineralization. The real issue can be characterized into those related with high bone turnover and high PTH levels (counting osteitis fibrosa, the trademark injury of auxiliary hyperparathyroidism, and blended sore) and low bone turnover and low or typical PTH levels Chronic kidney illness (CKD) is an overall general medical issue influencing 5-10% of the total populace. It has expanding pervasiveness and unfavorable results, including dynamic loss of kidney work, cardiovascular ailment, and untimely death.[1] Disturbances in mineral digestion and bone infection are normal, cause impressive bleakness, and lessening personal satisfaction in patients with incessant kidney illness (CKD).[2-4] A disorder of bone redesigning, the osteodystrophy of CKD, is a typical inconvenience. When patients require dialysis substitution treatment, almost all are influenced. The beginning of the confusion is noticeable about the time half of kidney capacity is lost. [5,6] As kidney capacity decreases; there is a dynamic crumbling in mineral homeostasis, with a disturbance of ordinary serum and tissue convergences of phosphorus and calcium, and changes in circling levels of hormones. These incorporate parathyroid hormone (PTH), 25-hydroxyvitamin D (25(OH)D), 1,25-dihydroxyvitamin D (1,25(OH)2D). Starting in CKD organize 3, the capacity of the kidneys to fittingly discharge a phosphate burden is lessened, prompting hyperphosphatemia, raised PTH, and diminished 1,25(OH)2D.

The mineral and endocrine capacities upset in CKD are fundamentally significant in the guideline of both beginning bone arrangement during development (bone demonstrating) and bone structure and capacity during adulthood (bone renovating). Subsequently, bone variations from the norm are found all around in patients with CKD requiring dialysis (stage 5D), and in most of patients with CKD stages 3–5. The term 'CKD–Mineral and Bone Disorder (CKD–MBD)' is utilized to portray the more extensive clinical disorder including mineral, bone, and calcific cardiovascular variations from the norm that create as an entanglement of CKD. Biochemical variations from the norm are regular in unending kidney illness (CKD) and are the essential markers by which the finding and the executives of CKD–mineral and bone issue (CKD–MBD) is made.[7] The research facility conclusion of CKD–MBD incorporates the utilization of lab testing of serum PTH, calcium and phosphorus. In certain circumstances, estimating serum ALPs (aggregate or bone explicit) and bicarbonate might be useful.

Objectives

General Objectives: To assess the bone-mineral disorders by DEXA scan of bone and biochemical abnormalities by serum markers in stage 4 and stage 5 CKD patients not on dialysis in Nephrology Department of Kurmitola General Hospital Dhaka.

Specific Objectives: To assess any correlation between the markers of MBD (mineral and bone disorder).

Methodology

Type of study: Cross sectional analytical study.

Place of study: Department of Nephrology Private and Public Hospitals, Dhaka.

Period of study: July 2016 to June 2017 one year.

Method of study

Sampling technique was purposive. Patients attending outpatient of as well as the admitted patients in Department of Nephrology, Kurmitola General Hospital, with chronic kidney disease (CKD) stages 4 and stage 5 (predialysis) were included. After proper explanation, written informed consent was obtained from the selected patients. Meticulous history was taken to include inclusion criteria and to exclude exclusion criteria of each patient. Demographic data such as age, sex, height (cm), weight (kg), B.P were measured

and BMI (kg/m2) calculated. Detailed general and systemic examinations were done. e-GFR was calculated by MDRD (Modification of Diet in Renal Disease) formula (Ashman, 2014).eGFR = 186.3 x ((serum creatinine) exp [– 1.154]) x (Age exp[– 0.203]) x (0.742 if ♀) x (1.21 if African American). And according to the e-GFR, patients were grouped into stage 4 and stage 5 of CKD according to K/DOQI 2002 guidelines.

Then the patients were assessed with routine laboratory investigations CBC, renal function tests (serum creatinine, serum calcium, serum inorganic phosphate) with some other specific laboratory tests (serum albumin, serum iPTH, serum Vit-D) as per data sheet. Previous investigation reports were analyzed to appropriately categorize the subjects to stage 4 and stage 5 Serum sample were collected after the observation period needed for the patient who were taking drugs like Vitamin-D, Calcium or Phosphate as supplementation. Serum sample were collected after all aseptic preparation and were stored in -35º C freezer in Kidney Research Lab, Department of Nephrology, Kurmitola General Hospital , Dhaka, before the assay were done for BAP ELISA.

Sample Size Determination

The sample size will be determined by following formula,

n=the desired sample size

z= the standard normal deviate, set at 1.96 at 5% level which corresponded to 95% confidence level

The assumed target population was P to have a particular characteristics andq= 1-p

Here P=0.5 (As prevalence of bone and mineral disorders in CKD patients in Bangladeshi population is not known it will be considered as 50%)

q=1-0.5=0.5; D is the allowable error which is 10% of P i.e. 10% of .5=0.05.

Putting the values in the above equation the sample size n will be estimated as. So, final sample size will be 384. But due to monetary and time constrains and I have included 200 as my sample size. Among 200 patients 2 died, 10 did not returned for the study and 12 had undertaken dialysis as the prescribed treatment during the observation period and were excluded and the final sample became 176.

Selection Criteria

Inclusion Criteria

1) Age over 18 years in both sex
2) Patients diagnosed as a case of stage 4 and stage 5 CKD patents not on dialysis

Exclusion Criteria

1) Subjects with a history of
2) fracture
3) Having received steroids
4) Non-steroidal anti-inflammatory drugs (NSAIDs)
5) Anticoagulants
6) Antiepileptic Agents
7) Androgens taking in the last 3 months

Results

Table-1 shows the stage wise distribution of age in CKD population. Here stage 4 CKD patients were 90 and among them maximum patients 18 (40%) belongs to age group 48-57 years and in stage 5 CKD (n=86) maximum patients 11 (25.58%) belongs to age group 38-47 years. The age distribution among the CKD stages was not statistically significant (p>0.05).

Table-1: Distribution of age in stage 4 and stage 5 CKD

Age (years)	CKD stage 4 (n=90)		CKD stage 5 (n=86)		
	n	%	n	%	
18-27	2	2.22%	10	11.63%	
28-37	10	11.11%	12	13.95%	
38-47	8	8.89%	22	25.58%	
48-57	36	40.00%	14	16.28%	
58-67	22	24.44%	18	20.93%	
>68	12	13.33%	10	11.63%	

Here,
CKD = Chronic Kidney Disease

Figure-1 shows the age distribution among the study population. Out of 176 patients maximum number of patients belongs to age group 48-57 years (28.41%) and the age group 18-27 years has the lowest number of patients (6.82%).

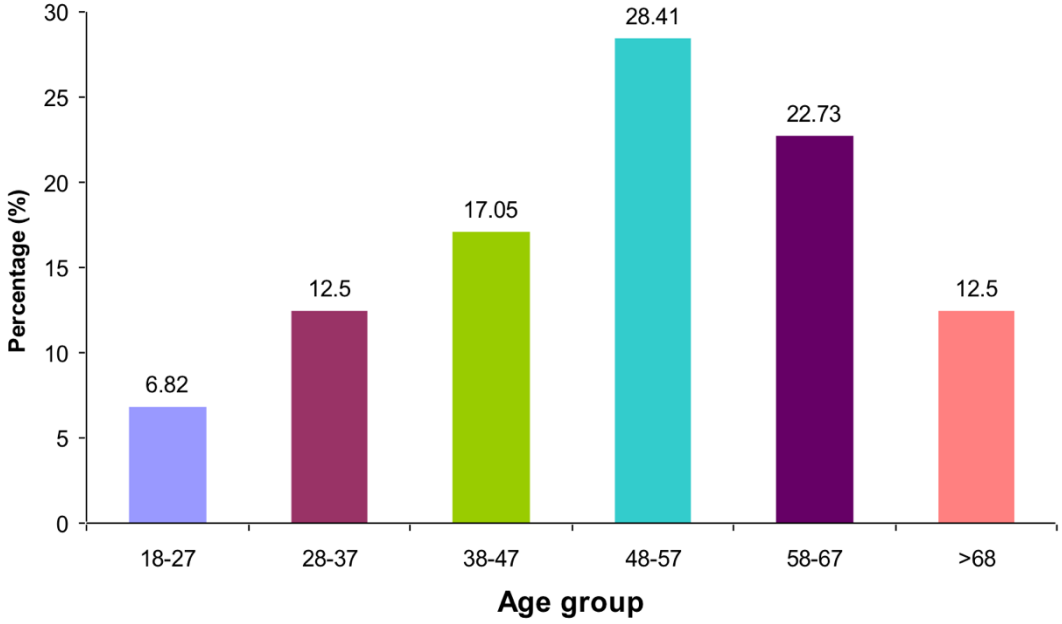

Figure 1: Age distribution of the study population (n=176)

Table-2 shows that in the total patients (n=176) 84were male and 92 were female. The male female ratio in the stages of CKD was 0.95:1 vs. 0.79:1 in stage 4 and stage 5 CKD respectively.

Table-2: Sex distribution among the stage 4 and stage 5 CKD population

Sex	CKD stage 4 (n=90)		CKD stage 5 (n=86)		Total
	n	%	n	%	
Male	44	48.89	40	46.51%	84
Female	46	51.11	46	53.49%	92
Total	90	100	86	100	176
M:F	0.95:1		0.87:1		0.91:1

Table-3: shows the comparison of study parameters between groups of CKD in stage 4 and stage 5. CKD Stage 5 patients showed significantly higher levels of serum PO4 and serum PTH. CKD stage 5 patients also had significantly lower levels of serum albumin and serum Vita-D. No significant differences were noted among the CKD groups of serum calcium, BAP and BMD T-scores.

Table-3: Comparison of measured parameters in chronic kidney disease stage 4 and stage 5 patients

Parameters	CKD stage-IV (n=90) Mean±SD	CKD stage-V (n=86) Mean±SD	P value
PO4 (mmol/L)	1.31±0.28	1.48±0.29	0.006*
Ca (mg/dl)	8.29±0.95	8.31±0.77	0.911
Alb (g/dl)	3.72±0.47	3.46±0.69	0.043*
PTH (pg/ml)	245.80±230.38	485.34±317.22	<0.001*
Vit-D (ng/ml)	19.40±7.60	16.20±5.11	0.024*
BAP (pg/ml)	2883.69±1104.23	3295.08±1135.86	0.089
BMD (T-score)	-2.43±1.11	-2.40±0.91	0.897

Unpaired student t-test was performed to calculate the p value.

Figure-2 shows that according to the operational definition total number of patients having deficient Vit-D level were (75%) and insufficient were (20.45%) and only (4.55%) showed sufficient level of Vit-D among the study population.

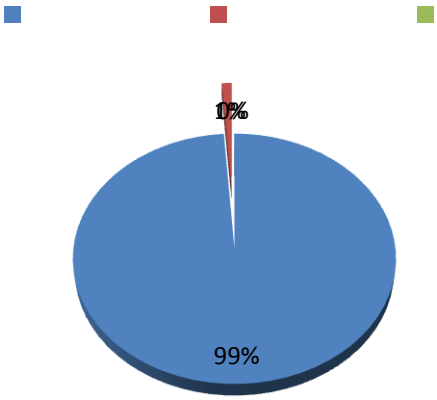

Figure 2: Vitamin-D levels among the study population (n=176)

Figure-3: shows that in stage 4 and in stage 5 the Vita-D deficient patients were (68.89%) and (81.4%). In stage 5 the level of Vita-D decreases significantly. It also shows that in CKD stage 5 there was no patient with sufficient level of Vita-D.

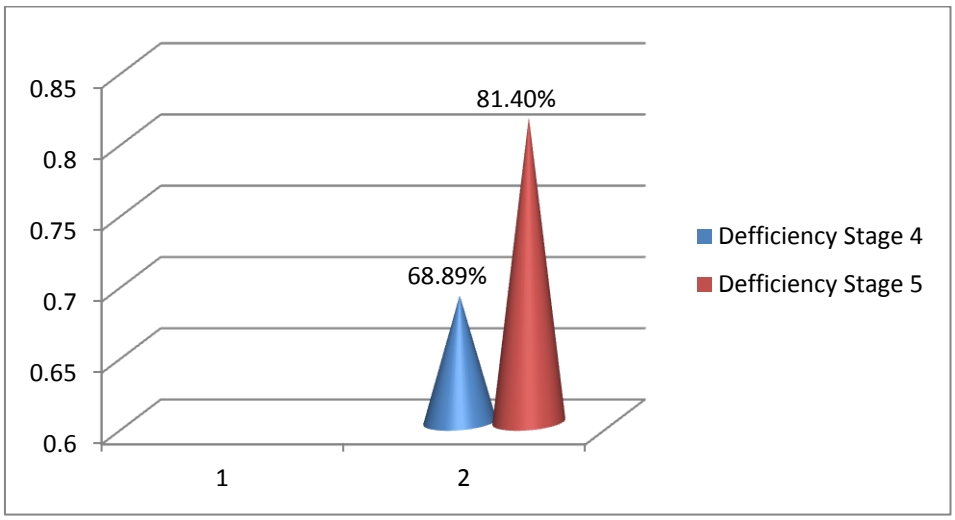

Figure 3: Comparison of Vita-D levels in CKD stage 4 and Stage-5

Table-4 shows that the PTH level more than 2 times the upper limit was found in (71.6%) patients and among them (57.1%) patients had BAP values more than the mean value.

Table 4: Association between BAP and PTH (n=176)

BAP range	PTH	
	< 100 pg/ml	>100 pg/ml
	(n=70)	(n=106)
Lower than mean	(24.0%)	(42.9%)
More than mean	(76.0%)	(57.1%)
Total	(100.0%)	(100.0%)

BAP= Bone alkaline phosphatase
PTH= parathyroid hormone

Table-5 shows that high bone turnover PTH level (>450 pg/ml) was found in 37 (42.9%) patients and among them 41 (57.1%) had BMD value in osteoporotic range (T-score >-2.5).

Table-5: Association between BMD and PTH in the study population (n=176)

BMD	PTH	
	< 450 pg/ml (n=100)	> 450 pg/ml (n=76)
< -2.5	(46.7%)	(57.1%)
> -2.5	(53.3%)	(42.9%)
Total	(100.0%)	(100.0%)

BMD= bone mineral density

Table-6 shows that 2 times higher PTH level (>100 pg/ml) was found in (71.60%) patients and among them (50.79%) had BMD value in osteoporotic range (T-score >-2.5) and all of them (100%) had Vit-D <30 ng/ml that is in insufficient range

Table-6: Association between Vit-D, BMD and PTH in the study population (n=176) with PTH level >/< 100pg/ml.

BMD	Vit-D	PTH		Total
	<30 ng/ml With iPTH >100 pg/ml	< 100 pg/ml (n=76)	> 100 pg/ml (n=100)	
	(100%)			
< -2.5		(46 %)	(49.21%)	(51.14%)
> -2.5		(44%)	(50.79%)	(48.86%)
Total	(100%)	(100.0%)	(100.0%)	(100.0%)

Table-7: Correlation between PTH and Vit. D, Ca, PO4 and BMD

Parameters	**PTH (n=176)**	
	r	**p**
Vitamin D	- .364*	<0.001
Calcium	- .144	0.181
Phosphate	+ .335*	0.001
BMD	-.060	0.582

Pearson's correlation coefficient (r) test was performed to compare relationship between PTH and Vit.-D, Calcium, PO4 and BMD.

The test of significance was calculated and p value < 0.05 was accepted as level of significance.

* = significant

Table-7 shows that the there were significant negative correlation present between PTH with Vit-D and Calcium (p=<0.001 for Vit-D and p=0.181 for calcium respectively). The table also shows that there was a negative correlation between PTH and BMD (p=>0.05). There was a significant and strong positive correlation between PTH and Phosphate level (r=+0.335, p=0.001).

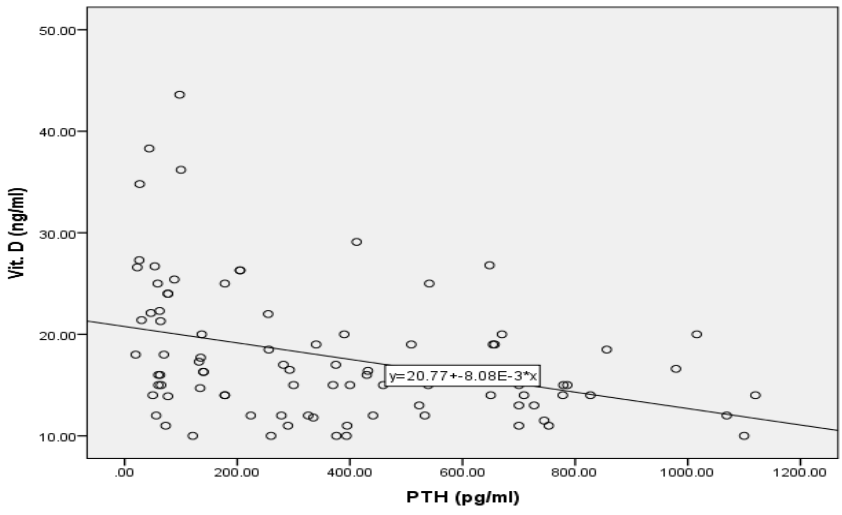

Figure 4: Correlation between Vita-D and PTH

Table-8 describes a significant correlation between PTH and PO4 (p=0.001), between PTH and Vit-D (p=0.007), between Calcium and PO4 (p=0.008). There are negative correlation between PTH and calcium (r=-0.119), PTH and Vita-D (r=-0.394), PTH and BMD (r=-0.081), between calcium and PO4(r=-0.392), PO4 and Vit-D (r=-0.311), and PO4 and BMD (r=-0.147).

Table-8: Correlation of study parameters in CKD stage 4(n=90)

Correlations in stage 4 CKD (n=90)						
		PTH (pg/ml)	PO4 (mmol/L)	Ca (mg/dl)	Vit. D (ng/ml)	BMD (T-score)
PTH (pg/ml)	r		.462**	-.119	-.394**	-.081
	p		.001	.435	.007	.597
PO4 (mmol/L)	r	.462**		-.392**	-.311*	-.147
	p	.001		.008	.038	.337
Ca (mg/dl)	r	-.119	-.392**		.064	.021
	p	.435	.008		.678	.889
Vita. D (ng/ml)	r	-.394**	-.311*	.064		-.190
	p	.007	.038	.678		.211
BMD (T-score)	r	-.081	-.147	.021	-.190	
	p	.597	.337	.889	.211	
**. Correlation is significant at the 0.01 level (2-tailed).						
*. Correlation is significant at the 0.05 level (2-tailed).						

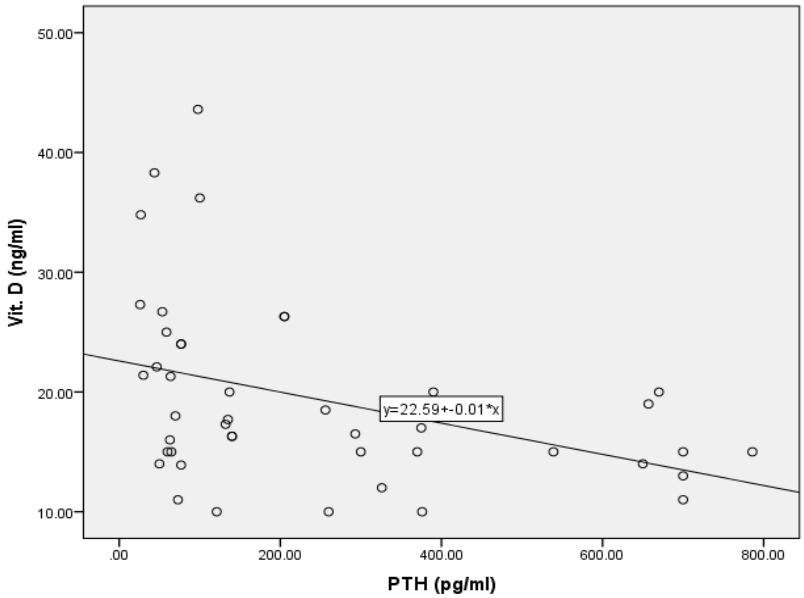

Figure 5: Correlation between PTH and Vita-D in stage 4 CKD (n=90)

Table-9: Correlation of study parameters in CKD Stage 5 (n=93)

Correlations in stage 5 CKD (n=93)						
		PTH (pg/ml)	PO4 (mmol/L)	Ca (mg/dl)	Vit. D (ng/ml)	BMD (T-score)
PTH (pg/ml)	r		.092	-.214	-.236	-.067
	p		.557	.168	.128	.671
PO4 (mmol/L)	r	.092		-.265	-.004	-.003
	p	.557		.086	.981	.983
Ca (mg/dl)	r	-.214	-.265		.059	.253
	p	.168	.086		.706	.101
Vit. D (ng/ml)	r	-.236	-.004	.059		-.074
	p	.128	.981	.706		.638
BMD (T-score)	r	-.067	-.003	.253	-.074	
	p	.671	.983	.101	.638	

Table-9 describes a negative correlation between PTH and calcium (r=-0.214), PTH and Vit-D (r=-0.236), PTH and BMD (r=-0.067), between calcium and PO4(r=-0.265), PO4 and Vit-D (r=-0.004), and PO4 and BMD (r=-0.003).

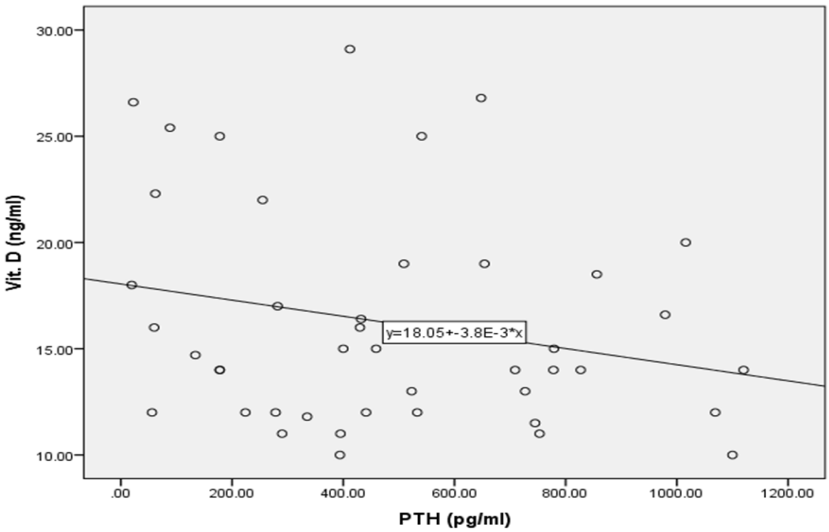

Figure 6: Correlation between PTH and Vit-D in stage 5 CKD (n=86)

Discussion

This is a study to evaluate comprehensively the various indicators of bone disease in patients with CKD stage 4 and stage 5 patents not on dialysis attending to the Department of Nephrology, Kurmitola General Hospital. Our study involved diagnosed or newly diagnosed stable CKD patients who met the inclusion and exclusion criteria.

Total of 200 patients were enrolled and the patients who met the exclusion criteria were studied and investigation reports were analyzed and entered into the datasheet and those who needed observation for their current condition to settle down or who were taking drugs like Vit-D and calcium and Phosphorous containing drugs as supplementation were observed and analyzed after 3 weeks.

Among 200 patients 2 died, 10 did not returned for the study and 12 had undertaken dialysis as the prescribed treatment during the observation period and were excluded and the final sample became 176.

In the age distribution among the study population I found that out of 176 patients maximum number of patients belongs to age group 48-57 years (28.41%) and the age group 18-27 years has the lowest number of patients (6.82%).

The stage wise distribution of age in CKD population were like stage 4 CKD patients were 90 and among them maximum patients (40%) belongs to age group 48-57 years and in stage 5 CKD (n=86) maximum patients (25.58%) belongs to age group 38-47 years. The age distribution among the CKD stages was not statistically significant (p>0.05).

In our study we found that among the total patients (n=176) with M: F of 0.91:1. The male female ratio in the stages of CKD was 0.95:1 vs. 0.87:1 in stage 4 and stage 5 CKD respectively.

In the comparative study of measured parameters in chronic kidney disease stage 4 and stage 5 patients in table-4 it was observed that CKD Stage 5 patients showed significantly higher levels of serum PO4 and serum PTH. CKD stage 5 patients also had significantly lower levels of serum albumin and serum Vit-D. No significant differences were noted among the CKD groups of serum calcium, BAP and BMD T-scores.

Vitamin D levels among the study population were deficient (<20ng/ml) in 66 (75%) patients and the level was insufficient (20-29 ng/ml) in

(20.45%) of patients and only (4.55%) patients showed normal level.

Conclusion

High turnover could contribute to the development of osteoporosis. Vitamin D deficiency is widespread and seems to have a role in the genesis of hyperparathyroidism and high turnover renal bone disease. 25(OH) vitamin D is now recognized as an important player in maintenance of bone health in CKD. Guidelines recommend regular measurement of 25(OH) vitamin D concentration and supplementation if levels fall below 30 ng/ml. Through our research we would like to draw the same inference and would like to recommend Vitamin D supplementation along with richer dietary sources for a better life with a healthy bone.

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