ORIGINAL RESEARCH PAPER
Volume - 13 | Issue - 03 | March - 2024 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

A COMPREHENSIVE ANALYSIS: PREVALENCE OF METABOLIC BONE DISEASE IN CHRONIC KIDNEY DISEASE THROUGH BIOCHEMICAL PROFILING

Internal Medicine

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ABSTRACT

Introduction: Chronic kidney disease (CKD) is a progressive condition characterized by a gradual loss of kidney function over time. The kidneys play a crucial role in maintaining the balance of minerals, electrolytes, and fluids in the body. Further, they also contribute to the regulation of bone health by producing an active form of vitamin D, which is necessary for calcium absorption in the intestines. CKD-mineral and bone disorder (CKD-MBD) is used to describe the systemic mineral and bone abnormalities associated with CKD. Additionally, metabolic bone disease in CKD includes abnormalities in calcium, phosphorus, parathyroid hormone (PTH), and vitamin D metabolism. The imbalance in mineral metabolism in CKD can result in conditions such as osteoporosis, osteomalacia, and vascular calcification. Therefore, early detection and intervention can help prevent or minimize the impact of metabolic bone disease that further lead to high mortality rates in chronic kidney disease patients. **Materials and methods:** This was cross-sectional observational study conducted on patients of chronic kidney disease in Department of Medicine and Department of Nephrology IGMC Shimla, Himachal Pradesh. The biochemical markers of CKD-MBD, including calcium, phosphorus, alkaline phosphatase, intact parathyroid hormone (iPTH), and 25-hydroxyvitamin D3 (25OHD), were measured in CKD patients. **Results:** A total 80 patients of CKD stages 3, 4 and 5 were enrolled for the study. Out of 80 patients 68 (85%) were anaemic, hypocalcemic 64(80%), hyperphosphatemia 61(77.25%), and raised alkaline phosphatase 58(66.25%). Secondary hyperparathyroidism was present in 55(68.75%) and hypoparathyroidism in 8(10%), vitamin D deficiency present in 48(60%) and insufficiency 26(32.5%). **Conclusion:** This study showed that secondary hyperparathyroidism, hyperphosphatemia, hypocalcemia, increased alkaline phosphatase, and Vitamin D deficiency were quite common in Indian CKD patients

KEYWORDS

CKD-MBD, Secondary hyperparathyroidism and vitamin D deficiency

INTRODUCTION

In the 21st century, chronic kidney disease (CKD) has emerged as one of the most prominent causes of death and suffering. The number of patients affected by CKD has been increasing, due to the rise in risk factors such as diabetes mellitus and hypertension affecting an estimated 843.6 million individuals worldwide in 2017.[1] In addition to this, CKD is associated with numerous complications, like anemia and mineral and bone disorder (CKD-MBD).[2]

According to KDIGO, CKD-MBD is defined as: A systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following: (i) abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism; (ii) abnormalities in bone turnover, mineralization, volume, linear growth, or strength; or (iii) vascular or other soft tissue calcification.

As kidney function declines, there is progressive deterioration in mineral homeostasis manifesting as disruption of serum and tissue concentrations of phosphorus and calcium, as well as changes in circulating levels of hormones such as parathyroid hormone (PTH), 25OHD. Disordered mineral metabolism in CKD patients leads to significant repercussions such as Secondary hyperparathyroidism (SHPTH), renal osteodystrophy, and vascular calcification, which not only contribute to heightened morbidity but also exacerbate the overall health challenges. [3,4,5] The metabolism of minerals and the maintenance of bone health are crucial functions carried out by the kidneys. Acting as the target organ for various hormones like parathormone (PTH), the kidneys also play a role in activating vitamin D. Individuals with chronic kidney disease (CKD) who experience phosphate retention and reduced calcium levels are susceptible to the development of parathyroid gland hyperplasia and renal osteitis fibrosa.[6] The accumulation of phosphate can lead to conditions such as hyperphosphatemia, decreased levels of 1,25(OH)2D3, and hypocalcemia. These imbalances act as stimuli for the secretion of parathyroid hormone (PTH), subsequently enhancing phosphate excretion and playing a role in the advancement of secondary hyperparathyroidism in the later stages of CKD.[7] Throughout the progression of CKD, an array of disturbances in bone turnover or mineralization can occur, such as adynamic, hyperparathyroid, mixed renal bone disease, osteomalacia, and osteoporosis. Additionally, each of these conditions may exhibit decreased bone mineral density (BMD) or be linked to fragility fractures. It also involves Vascular Calcification, which can cause cardiovascular events and other serious complications, ultimately leading to death in CKD patients, including those on dialysis.[9] Hence, detecting and addressing CKD-MBD early is vital, as it significantly contributes to a decline in the quality of life.

Biochemical abnormalities are prevalent in CKD and serve as the key indicators for diagnosing and managing CKD-MBD. It is advised that physicians monitor and regulate these biochemical parameters in the early stages of CKD, well before the necessity for dialysis arises. Consequently, biochemical markers of CKD-MBD, including calcium, phosphorus, alkaline phosphatase, intact parathyroid hormone (iPTH), and 25-hydroxyvitamin D3 (25OHD), were assessed. There are only few studies being done on severity of bone mineral disease in CKD patients therefore, we planned to conduct this study.

MATRIALS AND METHODS

Study Design – A prospective cross sectional observational study.

Setting– Patients of chronic kidney disease in Department of Medicine and Department of Nephrology IGMC Shimla, Himachal Pradesh.

Study Population- Study will be conducted in patients with age 18 years or more with chronic kidney disease.

Study Period- One year from 1st Jan 2021 to 30th july 2021.

Inclusion Criteria:

Patients diagnosed with chronic kidney disease and CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implication for health and requires one of two criteria documented or inferred for >3 months: either GFR<60ml/min/1.72m^2 or markers of kidney damage, including albuminuria. A patient who has age 18yrs or moreand give consent to participate in the study.

Exclusion Criteria:

Previous history of chronic disorders associated with changes in mineral metabolism:

1. Thyroid disorders

2. Cushing's syndrome
3. Prolonged immobilization in the past
4. Liver disease
5. Primary hyperparathyroidism
6. Any medication which might influence bone metabolism (corticosteroids, hormone replacement therapy, calcitonin, bisphosphonates, cytotoxics, antimetabolites anticoagulants, anticonvulsants, thyroxine, interferon or lamivudine) will also be excluded.

METHODOLOGY

All patients were subjected to detailed history and clinical examination. Only routine relevant lab investigations were done, so there was no extra burden on patients.

Categories definition

The definitions for hypocalcemia (cCa < 8.5 mg/dl), hypercalcemia (cCa >10.5 mg/dl),<10 g/dl anemic, hyperphosphatemia (phosphorus >4.5 mg/dl), hypophosphatemia (phosphorus <2.5 mg/dl), elevated alkaline phosphatase level (>120 IU/L), serum iPTH level (iPTH < 150pg/mL, 150–300pg/mL and >300pg/mL).[10,11,12,13,]

Statistical Analysis

The data were coded and entered into Microsoft Excel spreadsheet. Categorical variables were summarized as frequencies and percentages, and continuous variables as means and standard deviation. Analysis was done using SPSS version 17.0 (IBM SPSS Statistics Inc., Chicago, Illinois, USA).Windows software program. Significance of difference in mean in three groups was inferred by "ANOVA test" and the significance of difference in proportion in the groups was inferred by "chi-square test". Correlation among numerical was assessed by pearson correlation test depending on the parametric distribution of data. Statistical significance was assigned at p-value of less than 0.05.

RESULTS

Patient characteristics:

Demographic characterstics has been shown in table:1. A total of 80 patients were included in this study. Mean age of the patients was 56.66 ±14.19 years. There were 80 patients out of which maximum number of patients 23(28.75%) were in age group of 60-69 years, followed by 20 (25%) patients in age group of 50-59 years. There was female predominance with 43(53.75%) male and 37(46.25%) females. Most of patients 54(67.5%) were from rural area and 26 (32.5%) were from urban area.

Etiology:

As shown in table:1, most common etiology for CKD among patients enrolled was diabetes seen in 31 (38.75%) followed by hypertension (HTN) and *Chronic Glomerulonephritis* (CGN) 13(16.25%) patients. Other causes included were obstructive uropathy (7; 8.75%), IgA nephropathy (4; 5%) followed by other.

Biochemical parameters:

Table: 2 showed the frequency of various of mineral metabolism disorders. Mean BUN level in enrolled patients was 37.09±10.23 mg/dl for stage 3, 33.75%±15.67 mg/dl for stage 4 and 123.79±45.77 mg/dl for stage 5 and as chronic kidney disease stage progresses the BUN levels increased significantly. Mean creatinine level observed were 3.03±1.5mg/dl for stage 3, 6.18±2.19mg/dl for stage 4 and 10.75±3.84mg/dl for stage 5.Out of all patients enrolled 68(85%) had Hb levels <10g/dl and 12(15%) had Hb levels ≥10g/dl. Stages of CKD showed a significant difference with hemoglobin.

The distribution of the laboratory parameters in different stages of CKD is shown through bar chart in Figure 1,2,3,4,5,6,7,8 (BUN, Creatinine, hemoglobin ,calcium and phosphorus, alkaline phosphatase (ALP) vitamin D and iPTH. On ANOVA and chi square test a significant difference was found of BUN, creatinine, hemoglobin, calcium, phosphorus, alkaline phosphatase, Vitamin D, serum iPTH in the various CKD stages ($P = 0.001$).

On comparison of biochemical profile among enrolled patients it was seen that 64(80%) had calcium levels <8.5mg/dl and 16(20%) had calcium levels between 8.5-10.5mg/dl. There were no patients who had calcium levels>10.5mg/dl. Similarly, Phosphorus levels in 61(77.25%) patients were >4.5mg/dl and 2-4.5mg/dl in 19(23.75%) patients. There were no patients who had phosphorus levels <2mg/dl. A total of 58(66.25%) patients had ALP ≥120U/l and only 22(33.75%) patients had ALP levels ≤120U/l.

A low proportion 6(7.5%) of patients in various CKD stages had an adequate Vitamin D levels. Out of total 74 (92.5%) patients had inadequate 25OHD levels. The 25OHD levels were suggestive of vitamin D deficiency in 48(60%) and Vitamin D insufficiency in 26(32.5%) patients. There was a significant difference in the mean levels of 25OHD in the different CKD stages.

Serum iPTH levels were <150pg/ml in 8(10%) patients, 150-300pg/ml in 17(21.25%) patients and >300pg/ml in 55(68.75%) patient. A total of 72 (90%) had iPTH level above KDOQI target range suggested for the CKD stages. The prevalence of patients with iPTH levels >300 pg/ml was 16(20%) in CKD Stage 4 and 39(48.75%) in CKD Stage 5.There was no patient >300 ng/dl in CKD stage 3. A percentage of 5(6.25%) and 3(3.75%) respectively, of CKD Stage 3 and 4 patients had iPTH levels of <150 pg/ml. Out of total, 6(7.5%), 8(10%) and 3(3.75%) had iPTH level KDOQI target range suggested for the CKD stages 3, 4 and 5 patients. On Chi square test, a significant difference was found in serum iPTH in the various CKD stages ($P = 0.001$)

Table-4 Statistical correlation between various CKD-MBD biomarkers

The pearson correlation cofficient analysis revealed significant positive correlation between iPTH levels with phosphorus $r = 0.57$, $P = 0.001$ alkaline phosphatase ($r = 0.47$, $P = 0.001$), and a significant negative correlation with hemoglobin ($r = -0.6$, p 0.001) and vitamin D ($r = 0.57$, $P = 0.001$).Vitamin D had a significant positive correlation with calcium ($r = 0.58$, $P = 0.001$) and a significant negative correlation with alkaline phosphatase ($r = -0.44$, $P = 0.001$). Similarly, calcium showed a negatively correlation with phosphorus(r=-0.46, p=0.001) and ALP r= -0.57= p=0.001)

Tables -5 Comparison of laboratory parameters in different chronic kidney disease stages by one way ANOVA

On ANOVA, a significant difference was found in the mean values of hemoglobin, creatinine, calcium, phosphorus, alkaline phosphatase, vitamin D, serum iPTH in the various CKD stages ($P = 0.001$).

Table: 1 Demographic Characterstics

Age Range	Count of Age	%
20-29	4	5%
30-39	7	8.75%
40-49	11	13.75%
50-59	20	25%
60-69	23	28.75%
70-79	13	16.25%
80-90	2	2.5%
Gender		
M	43	53.75%
F	37	46.25%
Address		
Rural	54	67.5%
Urban	26	32.5%
Etiology		
Diabetics mellitus	31	38.75%
CGN	13	16.25%
HTN	13	16.25%
Obstructive uropathy	7	8.75%
1gA nephropathy	4	5%
CIN	4	5%
ADPKD	3	3.75%
LUPUS	3	3.75%
RSD	1	1.25%
FSGS	1	1.25%

Table: 2 Frequency of various of mineral metabolism disorders

	Stages of CKD	Frequency	%	Mean	Median	Std. Deviation	Minimum	Maximum
BUN	5	42	52.5%	123.79	121	45.77	64	244
	4	27	33.75%	69.7	68	15.67	45	112
	3	11	13.75%	37.09	36	10.23	18	53

	Results (p value)				<0.001			
Creatinine	5	42	52.5%	10.75	10.35	3.84	4.1	17.5
	4	27	33.75%	6.18	6.3	2.19	2.7	13.5
	3	11	13.75%	3.03	2.3	1.5	1.4	5.6
	Results (p value)				<0.001			

Table: 3 Frequency of various of mineral metabolism disorders

		Stages of CKD				p value
		3	4	5	Total	
n	Total (80)	11(13.75 %)	27(33.75 %)	42(52.5 %)		
Hb						p<0.001
	<10 g/dl	3 (3.75%)	23(28.75 %)	42(52.5 %)	68(85%)	
	>10 g/dl	8 (10%)	4 (5%)	0 (0%)	12 (15%)	
Calcium						
	<8.5 mg/dl	5(6.25%)	18(22.25 %)	41(51.2) %	64(80%)	p<0.001
	8.5-10.5 mg/dl	6(7.5%)	9(11.25 %)	1 (1.25%)	16(20%)	
	>10.5 mg/dl	0 (0%)	0 (0%)	0 (0%)	0(0%)	
Phosphorus						
	2-4.5 mg/dl	7(8.75%)	10(12.5 %)	2(2.5%)	19 (23.75%)	p<0.001
	>4.5 mg/dl	4 (5% %)	17(21.25 %)	40(50%)	61 (77.25%)	
ALP						
	>120 U/l	5(6.25%)	11(13.75 %)	42(52.5 %)	58 (66.25%)	p<0.001
	<120 U/l	6(7.5 %)	16(20%)	0 (0%)	22 (33.75%)	
Vit D						
	<20 ng/ml	0(0%)	11(13.75 %)	37(46.2 5%)	48(60%)	p<0.001
	20-30 ng/ml	8(10%)	13(16.25 %)	5 (6.25%)	26(32.5%)	
	30-80 ng/ml	3(3.75%)	3 (3.75%)	0(0%)	6(7.5%)	
	>80 ng/ml	0(0%)	0 (0%)	0(0%)	0(0%)	
iPTH						
	<150 pg/ml	5(6.25%)	3 (3.75%)	0 (0%)	8(10%)	p<0.001
	150-300 pg/ml	6(7.5%)	8 (10%)	3 (3.75%)	17 (21.25%)	
	>300 pg/ml	0(0%)	16(20%)	39(48.7 5%)	55 (68.75%)	

Table-4 Statistical correlation between various CKD-MBD biomarkers

Correlation	Pearson coefficient	P value
Calcium and iPTH	-0.58	<.001.
Phosphorus and iPTH	0.57	<.001
iPTH and ALP	0.47	<.001.
Vitamin D & iPTH	-0.57	<.001
Hb %& iPTH	-0.63	<.001
Calcium and Vit D	0.58	<.001
ALP & Vit D	-0.44	<.001
Calcium and phosphorus	-0.46	<.001
Calcium and ALP	-0.57	<.001

Table-4 Comparison of biochemical parameters in different stages of chronic kidney disease by one-way ANOVA

CKD	Stage 3	Stage 4	Stage 5	P value
BUN	37.09± 10.23	69.7± 15.67	123.79 ± 45.77	<0.001
Creatinine	3.03± 1.5	6.18 ±2.19	10.75± 3.84	<0.001
Hb	10.07± 1.16	7.94± 1.67	6.91 ±1.19	<0.001
phosphorus	3.85 ±0.83	4.79 ±0.93	6.34± 1.03	<0.001
Calcium	9.36 ±0.86	7.95 ±1.12	6.74 ±0.94	<0.001
ALP	111.45 ±23.93	117.04 ±32.61	168.19 ±17.67	<0.001
Vitamin D	33.05±12.58	22.16±9.38	12.53±5.46	<0.001
iPTH	153.91± 74.61	317.67± 138.35	467.62 ±143.72	<0.001

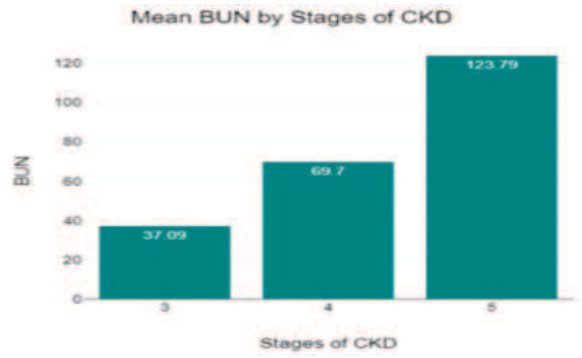


Figure:1

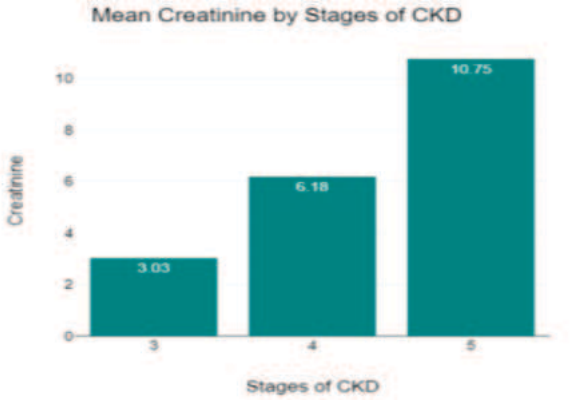
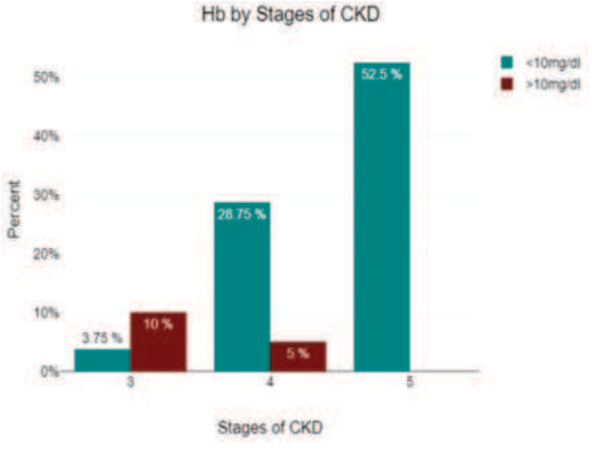


Figure:2



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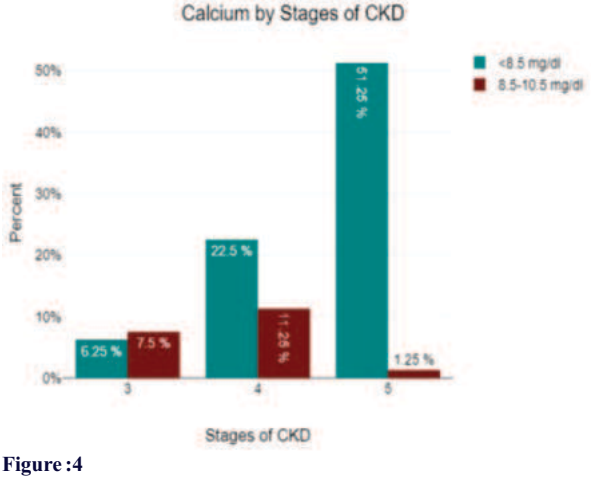
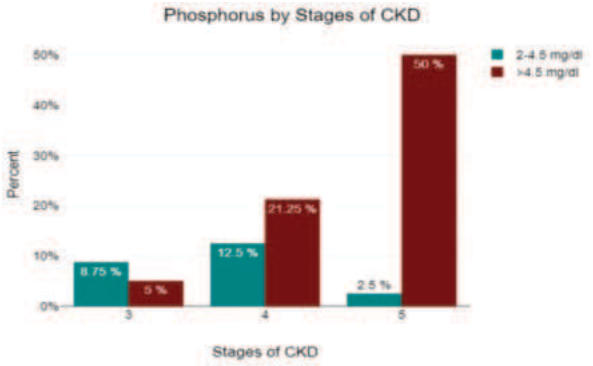


Figure :4

PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr



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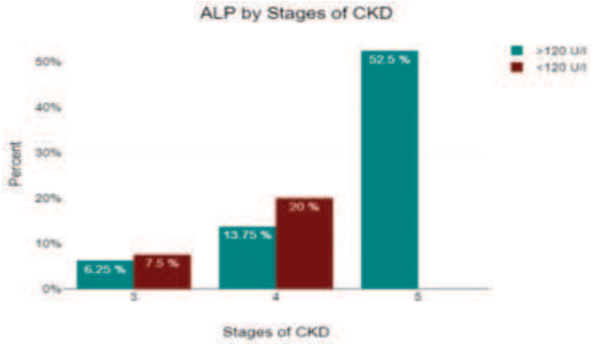

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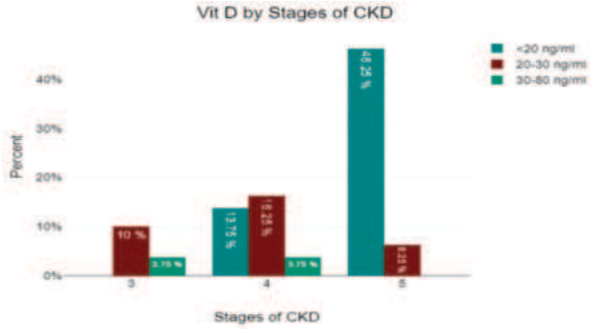

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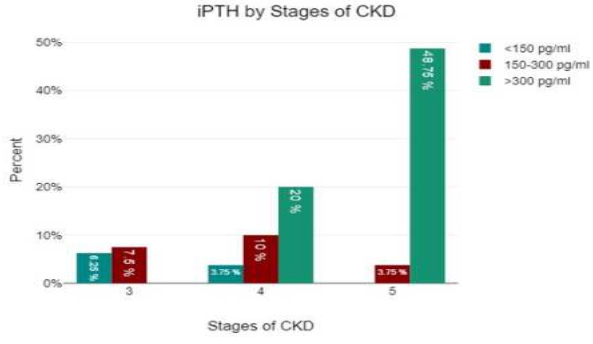

Figure:8

DISCUSSION

This study encompassed a total of 80 participants. The study population comprised predominantly mean age of the patients was 56.66 ±14.19 years in which maximum numbers of patients were in age group of 60-69 years, followed by patients in 50-59 years. Previous research has noted an increased prevalence of CKD among older individuals. Aging is frequently linked to both structural and functional alterations in the kidneys, potentially playing a role in the onset and advancement of CKD.[14] Furthermore, older adults with CKD commonly experience multiple comorbidities like diabetes, hypertension, and cardiovascular disease, contributing to an increased prevalence of CKD. Moreover, considering the higher mortality rates among the elderly population, particularly those aged 75 years and older, the prevalence of CKD tends to decrease. This observation implies a reduction in the occurrence of CKD among individuals in the 70-80 age group.[1516]

A higher predominance of males was observed compared to females, and this disparity may be attributed to lifestyle and behavioral factors, including smoking, alcohol consumption, and dietary habits, which could contribute to the development of CKD.[17] Most of patients were from rural areas as compared to urban area. This is because of geographical distribution of population in this area.In our study most common etiology for CKD among patients enrolled was diabetes seen in followed by hypertension, chronic glomerulonephritis in patients.[1819]

This observational study, which included patients in CKD Stage 3–5, identified a significant occurrence of biochemical abnormalities associated with CKD-MBD. It is well-established that the principal instigator of secondary hyperparathyroidism has traditionally been recognized as phosphate retention resulting from a decrease in renal function. The accumulation of phosphate results in hyper phosphatemia, reduced levels of Vitamin D, and hypocalcemia. These well-recognized factors act as stimuli for the secretion of parathyroid hormone (PTH), subsequently promoting phosphate excretion and contributing to the progression of secondary hyperparathyroidism in advanced stages of CKD. Observed mean levels of phosphorus 3.85 ±0.83, 3.85 ±0.83, 6.34± 1.03 and ALP 111.45 ±23.93, 117.04 ±32.61, 168.19 ±17.67 in CKD stage 3, 4, 5 respectively. There was a significant difference between the various stages of CKD and the mean levels of, phosphorus, and ALP. The current investigation noted the mean ± standard deviation of intact parathyroid hormone (iPTH) in stages 3, 4, and 5 as 153.91 ± 74.61, 317.67 ± 138.35, and 467.62 ± 143.72, respectively. Significant differences in iPTH levels are evident across the various stages of CKD Serum phosphorous and alkaline phosphatase levels were a strong and significant predictor of the serum iPTH level.[21] In our study Phosphorus, ALP and iPTH showed a positive correlation r= 0.57, p=0.001, r= 0.47, p=0.001.

In accordance with the KDOQI (2003) recommended target ranges for various CKD stages, our study revealed that the highest proportion of hyperparathyroidism patients with iPTH levels exceeding 300 pg/ml were in CKD stage 5, followed by stage 4. Additionally, 8 out of 10% had iPTH levels below 150 pg/ml. Given that iPTH levels below 150 pg/ml are linked to a greater incidence of adynamic bone disease, it's worth noting that adynamic bone disease is characterized by minimal or absent bone turnover, a common occurrence in individuals with low PTH and reduced tissue-specific alkaline phosphatase activity. Complications arising from adynamic bone disease involve an elevated occurrence of fractures and bone pain, coupled with a correlation to heightened vascular and cardiac calcification. [22,23]

The levels of 25OHD emerged as the most reliable indicator of Vitamin D status, indicating vitamin D deficiency in 48 (60%) individuals and vitamin D insufficiency in 26 (32.5%) patients. The mean levels of vitamin D in CKD stages 3, 4, 5 are 33.05±12.58, 22.16±9.38 and 12.53±5.46 respectively. There was a significant difference in the mean levels of 25OHD in the different CKD stages. Levels of 25OHD below <20ng/dl are associated with increased PTH levels.[24] In our study, 25OHD had a significant positive correlation with calcium (r=0.58, P = 0.001) and a significant negative correlation with alkaline phosphatase (r = -0.44, P = 0.001) and iPTH (r = -0.57, P = 0.001).

Additionally, calcium exhibited a negative correlation with both phosphorus (r=-0.47, p=0.001) and ALP (r=-0.57, p=0.001). This observation aligns with the understanding that parathyroid hormone (PTH) and vitamin D serve as the primary physiological regulators of calcium and phosphate homeostasis in humans. As the glomerular filtration rate (GFR) decreases, there is a decrease in phosphate excretion, leading to the accumulation of phosphate and an elevated synthesis of parathyroid hormone (PTH).

Additionally, the compromised kidney function suppresses the production of vitamin D, resulting in hypocalcemia. This hypocalcemia leads to heightened levels of parathyroid hormone, further extracting calcium from the bones, resulting in weakened bones with low bone mass and the development of renal osteodystrophy, increasing the risk of fractures.[25]

While bone biopsy remains the gold standard for diagnosing the type of renal osteodystrophy, it is not easily accessible for most patients.

Consequently, assessing bone or total alkaline phosphatase along with intact parathyroid hormone (iPTH) can serve as an alternative to estimate bone turnover. [26]

The primary objective of managing CKD-MBD is to mitigate the adverse outcomes linked to hypocalcemia, hyperphosphatemia, vitamin D deficiency, and hyperparathyroidism. Consequently, addressing all these complications relies on utilizing established measurable surrogate markers of disordered mineral bone metabolism. These markers include serum calcium, phosphate, intact parathyroid hormone, and 25-hydroxyvitamin D. As per the current KDIGO guideline, treatment decisions are recommended based on the serial trends of these biochemical markers.

CONCLUSION

Our research indicated a high prevalence of hyperphosphatemia, hypocalcemia, elevated alkaline phosphatase, Vitamin D deficiency, and hyperparathyroidism in the CKD study population. In light of the correlation analysis findings, any disturbance in these biomarkers should be recognized as a significant warning sign of CKD-MBD. Given the substantial prevalence of metabolic bone disease among CKD patients, it is advisable for these individuals to undergo early-stage CKD monitoring for CKD-MBD, incorporating all recommended biomarkers by KDIGO.

REFERENCES

1. Jager, K. J., Kovesdy, C., Langham, R., Rosenberg, M., Jha, V., & Zoccali, C. (2019). A single number for advocacy and communication-worldwide more than 850 million individuals have kidney diseases. *Kidney international*, *96*(5), 1048–1050.
2. Moschella C. (2016). Chronic kidney disease-mineral and bone disorder: Guidelines for diagnosis, treatment, and management. *JAAPA : official journal of the American Academy of Physician Assistants*, *29*(7), 21–29.
3. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group (2017). KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney international supplements*, *7*(1), 1–59.
4. Raggi, P., Boulay, A., Chasan-Taber, S., Amin, N., Dillon, M., Burke, S. K., & Chertow, G. M. (2002). Cardiac calcification in adult hemodialysis patients. A link between end-stage renal disease and cardiovascular disease? *Journal of the American College of Cardiology*, *39*(4), 695–701.
5. Reddy, Y. N., Abraham, G., Reddy, Y. N., Nagarajan, P., Matthew, M., Jayaseelan, T., & Padma, G. (2014). Mineral bone disease in maintenance hemodialysis patients: Association with morbidity and mortality. *Indian journal of nephrology*, *24*(5), 302–307.
6. Pavlović, D., Katić, D., & Josipović, J. (2012). Kronicna bubrezna bolest--poremećaj metabolizma minerala i kosti: zasto i kako kontrolirati fosfor [Chronic kidney disease--mineral and bone disorder: why and how to control phosphate]. *Acta medica Croatica : casopis Hravatske akademije medicinskih znanosti*, *66 Suppl 2*, 64–67.
7. Block, G. A., Hulbert-Shearon, T. E., Levin, N. W., & Port, F. K. (1998). Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. *American journal of kidney diseases: the official journal of the National Kidney Foundation*, *31*(4), 607–617.
8. Etta, P. K., Sharma, R. K., & Gupta, A. (2017). Study of chronic kidney disease-mineral bone disorders in newly detected advanced renal failure patients: A Hospital-based cross-sectional study. *Saudi journal of kidney diseases and transplantation : an official publication of the Saudi Center for Organ Transplantation, Saudi Arabia*, *28*(4), 874–885.
9. Foley, R. N., Parfrey, P. S., & Sarnak, M. J. (1998). Clinical epidemiology of cardiovascular disease in chronic renal disease. *American journal of kidney diseases : the official journal of the National Kidney Foundation*, *32*(5 Suppl 3), S112–S119.
10. Joanne M, Bargman, Skorecki K. (2008). Disorders of the kidney and urinary tract. In: Harrison's principle and practice of internal medicine. 17th ed. New York: McGraw-Hill; p. 1761-71. vol2
11. National Kidney Foundation (2003). K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *American journal of kidney diseases: the official journal of the National Kidney Foundation*, *42*(4 Suppl 3), S1–S201.
12. Holick M. F. (2007). Vitamin D deficiency. *The New England journal of medicine*, *357*(3), 266–281.
13. Eknoyan G., Levin A., Levin N.W. (2003). Bone metabolism and disease in chronic kidney disease. American. Journal of. Kidney Disease;42:S1–S201.
14. Mallappallil, M., Friedman, E. A., Delano, B. G., McFarlane, S. I., & Salifu, M. O. (2014). Chronic kidney disease in the elderly: evaluation and management. Clinical practice (London, England), 11(5), 525–535.
15. Hill, N. R., Fatoba, S. T., Oke, J. L., Hirst, J. A., O'Callaghan, C. A., Lasserson, D. S., & Hobbs, F. D. (2016). Global Prevalence of Chronic Kidney Disease - A Systematic Review and Meta-Analysis. *PloS one*, *11*(7), e0158765.
16. Vikrant, S., & Parashar, A. (2016). Prevalence and severity of disordered mineral metabolism in patients with chronic kidney disease: A study from a tertiary care hospital in India. *Indian journal of endocrinology and metabolism*, *20*(4), 460–467.
17. Agarwal, S. K., Dash, S. C., Irshad, M., Raju, S., Singh, R., & Pandey, R. M. (2005). Prevalence of chronic renal failure in adults in Delhi, India. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*, *20*(8), 1638–1642.
18. Hadian B, Zafarmohtashami A, Hasanvand A, Hasani M. (2020). Assessment of chronic kidney disease-mineral and bone disorder in hemodialysis patients according to biomarkers value. *Journal of Parathyroid Disease*.8:e05.
19. Sharma, M., Doley, P., & Das, H. J. (2018). Etiological profile of chronic kidney disease: A single-center retrospective hospital-based study. *Saudi journal of kidney diseases and transplantation : an official publication of the Saudi Center for Organ Transplantation, Saudi Arabia*, *29*(2), 409–413.
20. Moe, S. M., Drüeke, T., Lameire, N., & Eknoyan, G. (2007). Chronic kidney disease-mineral-bone disorder: a new paradigm. *Advances in chronic kidney disease*, *14*(1), 3–12.
21. Li, J., Molnar, M. Z., Zaritsky, J. J., Sim, J. J., Streja, E., Kovesdy, C. P., Salusky, I., & Kalantar-Zadeh, K. (2013). Correlates of parathyroid hormone concentration in hemodialysis patients. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*, *28*(6), 1516–1525.
22. Brandenburg, V. M., & Floege, J. (2008). Adynamic bone disease-bone and beyond. *NDT plus*, *1*(3), 135–147.
23. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group (2009). KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney international. Supplement*, (113), S1–S130.
24. Holick, M. F., Binkley, N. C., Bischoff-Ferrari, H. A., Gordon, C. M., Hanley, D. A., Heaney, R. P., Murad, M. H., Weaver, C. M., & Endocrine Society (2011). Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *The Journal of clinical endocrinology and metabolism*, *96*(7), 1911–1930.
25. Martin, K. J., & González, E. A. (2007). Metabolic bone disease in chronic kidney disease. *Journal of the American Society of Nephrology: JASN*, *18*(3), 875–885.
26. Lehmann, G., Ott, U., Kaemmerer, D., Schuetze, J., & Wolf, G. (2008). Bone histomorphometry and biochemical markers of bone turnover in patients with chronic kidney disease Stages 3 - 5. *Clinical nephrology*, *70*(4), 296–305.