

## Original Research Article

# Renal bone disease in patients on hemodialysis: an observational study focusing on the variation of calcium metabolism

Wajeeha Elahi<sup>1</sup>, Ameen Zubair Syed<sup>1</sup>, Bilal Jamil<sup>2</sup>, Shahid Kamran<sup>3</sup>, Raheela Adil<sup>4</sup>,  
Nazia Qamar<sup>5</sup>, Madiha Ariff<sup>6\*</sup>, Adnan Anwar<sup>4</sup>

<sup>1</sup>Department of Nephrology, <sup>2</sup>Medical Director, Tabba Kidney Institute, Karachi, Sindh, Pakistan

<sup>3</sup>Department of Forensic Medicine, <sup>4</sup>Department of Physiology, <sup>5</sup>Department of Pathology, Altibri Medical College, Karachi, Sindh, Pakistan

<sup>6</sup>MBBS, Dow Medical College, Karachi, Sindh, Pakistan

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### \*Correspondence:

Dr. Madiha Ariff,

E-mail: [madiha.ariff@live.com](mailto:madiha.ariff@live.com)

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## ABSTRACT

**Background:** The aim of this study was to determine the disturbances in the levels of mineral in the body due to hemodialysis at different levels of parathormone levels and to assess its association with the calcium levels.

**Methods:** Study was a cross sectional for the period of 6 months taking ethical approval. Total 255 cases were registered in this study after taking their informed consent. The cases were divided into three groups according to PTH level. Group 1 has 87 subjects with PTH level <250, group 2 has 102 subjects with PTH level 250-650 and group 3 has 66 cases with PTH level >650. The cases were taking hemodialysis for greater than 6 months and have the ages more than 18 years were included in this study. The demographic data includes age, sex dialysis related data like duration of hemodialysis, levels of calcium, phosphorus, albumin, PTH, ALP were observed.

**Results:** Hemodialysis duration were recorded in respective three groups as 7.28±5.71, 6.26±5.56 and 6.15±4.30 days respectively (P=0.319). Calcium was found in group 1, 8.70±0.81, in group 2, 8.39±0.89 and in group 3, 8.76±0.82 (P=0.01). PTH level in three respective group were recorded to be 123.46±74.15, 418.47±115.49 and 1314.67±1188.63 (P<0.001).

**Conclusions:** Present study showed that significant difference was found in mineral levels in patients on hemodialysis with PTH level as well as with alkaline phosphatase level. Nevertheless, no significant difference was found with duration of dialysis and with parameter of albumin.

**Keywords:** Calcium metabolism, Cross sectional study, Developing country, Dialysis duration, Mineral levels

## INTRODUCTION

Mortality and morbidity in subjects receiving hemodialysis are extremely on higher site, when the hemodialysis is associated with marked alteration in

mineral metabolism that causes metabolic bone diseases.<sup>1,2</sup> Minerals as well as bone disorder (MBD) is a predisposing factor to develop post hemodialysis complications like cardiovascular calcification and arterial dysfunction.<sup>3</sup> Subjects on dialysis suffers from

disturbance in renal activity that are accompany with secondary hyperparathyroidism that causes mineral metabolism disturbance and leads to higher levels of phosphorus in blood, hypocalcemia and increase level of parathyroid hormone (PTH).<sup>4,5</sup> Recent investigations reveals that biochemical markers in disturbed mineral metabolism is associated with bad prognosis in subjects with End Stage Renal Disease (ESRD) that needs dialysis.<sup>6</sup> On the beginning of dialysis treatment most of the cases with hyperplastic parathyroid glands along with prominent higher level of PTH indicates long term Renal Replacement Therapy (RRT).<sup>7-10</sup> Several different investigations found that elevated level of PTH could be connected with increase death rate in subjects having renal activity disorder.<sup>11,12</sup> Association of PTH's has not found in previous studies.<sup>13</sup> Current recommendations suggested that achievable level of PTH depends on degree of CKD and GFR, lower the GFR, higher will be the PTH level.<sup>14</sup> Biochemical changes in Chronic Kidney Disease and Metabolic Bone Disease (CKD-MBD) consists of higher fibroblast growth factor-23 (FGF23) and parathyroid hormone (PTH), lesser 1,25-dihydroxyvitamin D (1,25D), higher level of phosphate in blood and lower level of calcium in blood. Although decrease absorption of calcium and lesser excretion of urinary calcium are major hallmarks along with different bone disease and extreme vascular and soft tissue calcification. CKD-MBD is associated to induce fractures as well to cause cardiovascular accidents and may lead to cardiovascular associated mortalities.<sup>15</sup> However, the development of discussed disease is not completely evaluated. Founders of diagnosed abnormalities are undefined and final treatment plans are not sufficient. Negative and positive calcium balance constitutes viable health problems in patients with CKD-MND: negative balance can cause increase hazard to develop osteoporosis and fracture, and positive balance can lead to extra-skeletal calcification and cardiovascular accidents.<sup>16</sup> There is significant association between certain elements that stimulates calcium and phosphate regulation. These influences are more complicated in patients having impaired renal function. Elements that stimulate phosphate homeostasis primarily alters phosphate absorption through gut, reabsorption through the renal system and regulate through and/or uptake by bone. In order to recognize specific etiologies it is very important to assess the relationship regarding Parathyroid Hormone (PTH) and Fibroblast Growth Factor-23 (FGF23).<sup>17</sup> PTH has a key role in the maintenance of calcium and phosphate regulations. Parathyroid glands consist of calcium-sensing receptors which stimulate the extracellular ionised calcium absorption and control PTH production.<sup>13</sup> Reduction in the ionized calcium (with higher phosphate level in blood, causes production of PTH and induces phosphaturic effect straight on the renal system.<sup>6</sup> PTH also excites osteoclasts productions in the bone which secretes calcium and phosphate into the extracellular fluid as well as excites the formation of vitamin D to activate its functions.<sup>8</sup> Additionally PTH causing reduction in the formation of Sodium Phosphate

(Na-Pi) co-transporters in the proximal tubules, leads to reduction in phosphate reabsorption and finally causes higher elimination of phosphate through renal tubules. This concludes lower level of phosphate in blood, lesser excretion of calcium as well as higher concentration of calcium in blood.<sup>18</sup>

The aim of this study was to determine the disturbances in the levels of mineral in the body due to hemodialysis at different levels of parathormone levels and to assess its association with the calcium levels.

## METHODS

Study was a cross sectional observational in which convenient sampling was used. Study was conducted at Tabba Kidney Institute Karachi during the period of 6 months from January to August 2017. The Institutional review board of Tabba Kidney Institute Karachi was given the ethical approval for this study. Total 255 cases were registered in this study after taking their informed consent. The cases were divided into three groups according to PTH level. Group 1 has 87 subjects with PTH level <250, group 2 has 102 subjects with PTH level 250-650 and group 3 has 66 cases with PTH level >650. The cases were taking hemodialysis for greater than 6 months and have the ages more than 18 years were included in this study. Multi-systemic disorder cases, subjects having co morbidities except renal disorder, inadequate record and the cases which were disagreed to provide written consent were excluded from the study. The demographic data includes age, sex dialysis related data like duration of hemodialysis, levels of calcium, phosphorus, albumin, PTH, ALP were observed and documented. 91 subjects had diabetes, 238 had hypertension and 65 were suffering from ischemic heart diseases. Patients having a medical history of fits, fractures, body ache, joint mobility, itching were also noticed. Some had a history of taking mineral supplements as well.

## Data analysis

Coding was done then the data was entered and evaluated by using SPSS version 20.0. Descriptive analysis was performed. ANOVA was applied to assess the difference. The significant p-value was set at  $\leq 0.05$ .

## RESULTS

A total of 255 patients were included in this study. Out of which 126 (49.4%) were male and 129 (50.6%) were females with dominant female to male ratio 1.2:1. Mean age of the subjects were recorded in three respective group as  $47.98 \pm 14.68$ ,  $50.84 \pm 14.51$ ,  $49.16 \pm 14.70$  with p value 0.404. 225 Subjects which were on hemodialysis having comorbidities out of which 95 (37.3%) had diabetes mellitus, 238 (93.3%) had hypertension, 65 (25.5%) had ischemic heart diseases, 173 (67.8%) had hepatitis B and 124 (48.6%) had hepatitis C positive.

Some patients were taking treatment of concomitant drugs and few had surgical treatments like phosphate binders, vitamin D, sensipar, calcium, proton pump inhibitors and parathyroidectomy. Their respective frequency and percentages are 91 (35.7%), 142 (55.7%),

23 (9.0%), 75 (29.4%), 176 (69.0%), 28 (11.0%). Few cases had clinical features which includes 32 (12.5%) had itching, 7 (2.7%) had fits, 18 (7.1%) had history of fractures, 155 (60.8%) had body ache, 4 (1.6%) had tetany and 101 (39%) had reduced mobility (Table 1).

**Table 1: History and clinical features of the patients.**

Variables (n=255)		Yes	No
		N (%)	N (%)
Comorbid	Diabetes mellitus	95 (37.3)	160 (62.7)
	Hypertension	238 (93.3)	17 (6.7)
	Ischemic heart disease	65 (25.5)	190 (74.5)
	Hepatitis B	173 (67.8)	82 (32.2)
	Hepatitis C	124 (48.6)	131 (51.4)
Concomitant drugs and treatment	Phosphate binders	91 (35.7)	164 (64.3)
	Vitamin D	142 (55.7)	113 (44.3)
	Sensipar	23 (9.0)	232 (91.0)
	Calcium	75 (29.4)	180 (70.6)
	Proton pump inhibitors	176 (69.0)	79 (31.0)
	Parathyroidectomy	28 (11.0)	227 (89.0)
Clinical features	Itching	32 (12.5)	223 (87.5)
	Fits	7 (2.7)	248 (97.3)
	Fractures	18 (7.1)	237 (92.9)
	Body ache	155 (60.8)	100 (39.2)
	Tetany	4 (1.6)	251 (98.4)
	Mobility reduced	101 (39.6)	154 (60.4)

**Table 2: Association of calcium and phosphate metabolism in different groups (n=255).**

Variables	Group 1 (n=87)	Group 2 (n=102)	Group 3 (n=66)	P value
	Mean±SD	Mean±SD	Mean±SD	
Age (years)	47.98±14.68	50.84±14.51	49.16±14.70	0.404
Duration (days)	7.28±5.71	6.26±5.56	6.15±4.30	0.319
Calcium (mg/dl)	8.70±0.81	8.39±0.89	8.76±0.82	0.01
Phosphate (mg/dl)	4.67±1.73	5.20±3.17	4.84±1.63	0.30
PTH (pg/ml)	123.46±74.15	418.47±115.49	1314.67±1188.63	<0.001
ALK Phosphatase (IU)	192.50±271.35	178.61±124.20	346.483±377.42	<0.001
Albumin (mg/L)	3.79±0.74	7.25±33.77	3.93±0.55	0.463

Hemodialysis duration were recorded in respective three groups as 7.28±5.71, 6.26±5.56 and 6.15±4.30 days respectively (P=0.319). Calcium was found in group 1, 8.70±0.81, in group 2, 8.39±0.89 and in group 3, 8.76±0.82 (P=0.01). The phosphate level was found to be 4.67±1.73, 5.20±3.17, 4.84±1.63 (P=0.30) in different groups respectively. PTH level in three respective group were recorded to be 123.46±74.15, 418.47±115.49 and 1314.67±1188.63 (p<0.001). Recorded mean standard deviation of enzyme ALK phosphates in three different groups were 192.50±271.35, 178.61±124.20, 346.483±377.42 (P<0.001). The albumin levels were 3.79±0.74, 7.25±33.77 and 3.93±0.55 (P=0.463) (Table 2).

**DISCUSSION**

The present study was conducted to determine the variety of renal bone disease in patients receiving hemodialysis. A study by Tarek A et al, on 100 cases of hemodialysis patients revealed the mean age was in group 136.11±8.59, in group 2 45.42±8.5 and in group 3 52.8±3.93 with P value 0.001. In Current study authors have found the dissimilar results if compare with the Tarek A study with the mean age of the patients in group 1 is 47.98±14.68, in group 2 is 50.84±14.51 and in group 3 is 49.16±12.70 with P value (0.40). In present study mean standard deviation of calcium in three respective group was 8.70±0.81, 8.39±0.89, 8.76±0.82 (0.01). Similar findings were noted in Wang WH et al, study in three respective

groups with p value as  $9.4\pm 0.3$ ,  $9.4\pm 0.3$ ,  $9.4\pm 0.4$  (0.05).<sup>20</sup> Current study reveals the mean standard deviation of Alkaline phosphatase in three representative groups are  $192.50\pm 271.35$ ,  $178.61\pm 124.20$ ,  $346.483\pm 377.42$  with highly most significant difference ( $<0.001$ ).

Similar findings were found in Soleymanian T et al, study with highly significant difference as in group 1 mean standard deviation of ALP  $281\pm 143$ , in group 2,  $331\pm 170$  and in group 3,  $767\pm 826$  ( $<0.001$ ).<sup>21</sup> Similar observations were also reported in 22. Omidvar B et al, study with significant P value as  $272.75\pm 122.58$ ,  $454.16\pm 405.49$ ,  $652.26\pm 735.41$  (0.04).<sup>22</sup>

In present study, authors have found 37.3% cases has diabetes, 93.3% cases has hypertension and 25.5% patients has ischemic heart disease. The study by Gomez AT et al, revealed the similar finding with 30.6% has diabetes, 17.9% has hypertension and 30.6% has ischemic heart diseases.<sup>23</sup> Another study by Zhang Y et al, which was conducted on 34,914 individuals noticed diabetes patients with 48% and hypertensive patients with 31.2%.<sup>24</sup> Current study reported the cases of hepatitis B reactive with 67.8% and hepatitis C reactive with 48.6%. If authors compare with the Alashek WA, study it was observed dissimilar findings having 34.9% hepatitis B reactive cases and 31.1% hepatitis C reactive cases.<sup>25</sup>

The above different could be due to large sample size of study which was on 2382 patients. In study of Kong X et al, Phosphate binders were used by 70.8% patients and vitamin D supplements by 77.5% of patients.<sup>26</sup> If authors compared with the current study, authors have found the patients using phosphate binders was 35.7% and vitamin D supplements was 55.7%. Present study revealed that the patients those were taking PPI inhibitors was 69.0% if authors compared with the Erdem E et al, study found 72% subjects taking PPI inhibitors.<sup>27</sup>

Present study also noticed some clinical signs and symptoms in the cases receiving hemodialysis, clinical features not routinely considered by most of studies. Most of the patients 155 (60.7%) had complains of body ache, along with restricted movements of joints was found in 101 (39.6%) cases. 7 patients (2.7%) having fits, 18 (7.1%) had a history of fractures, 32 (12.5%) had itching and 4 (1.6%) had tetany. Study by Wikstrom B was observed 46% patients have complains of itching.<sup>28</sup> Current study was found 12.5% has history of itching during dialysis treatment. Another study of Bilge K was reported 36.7% patients had bodyache.<sup>29</sup> The reason might be due to poor health associated quality of life in patients taking hemodialysis treatment.

## CONCLUSION

Present study showed that significant difference was found in mineral levels in patients on hemodialysis with PTH level as well as with alkaline phosphatase level.

Nevertheless, no significant difference was found with duration of dialysis and with parameter of albumin.

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