

Research article

Prevalence and biochemical profile of adynamic bone disease in a hemodialysis populationR. Geethanjali¹, M. Ganesh¹, V. Jayaprakash², E. Ramprasad³, A. Manikandan¹, M. Rakchna¹¹Department of Biochemistry, ²Department of Nephrology, Sri Ramachandra Institute of Higher Education and Research (SRIHER), Chennai, Tamil Nadu, India²Department of Nephrology, SRM Medical College Hospital and Research Centre, SRMIST, Chengalpattu, Tamil Nadu, India

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Corresponding author: **M. Ganesh**. Email: ganeshm@sriramachandra.edu.in**ABSTRACT**

Introduction and Aim: The number of patients suffering from end stage renal disease (ESRD) requiring dialysis has increased worldwide. Mineral bone disorders (MBD) commonly occur in ESRD patients. MBD is classified into high turnover bone disease and low turnover bone disease. Biochemical parameters play a key role in classifying MBD. Data on adynamic bone disease (ABD) in hemodialysis (HD) patients is sparse. The aim is to study the prevalence and biochemical profile of ABD in hemodialysis patients.

Materials and Methods: This study was done as a cross sectional study in HD patients of a tertiary care hospital in South India. Baseline demographic data of the study population was collected. Biochemical data such as serum creatinine, blood urea nitrogen (BUN), bone markers for the diagnosis of CKD-MBD including serum calcium, phosphorus, alkaline phosphatase (ALP) and intact parathyroid hormone (iPTH) were collected. Based on the biochemical values, patients who had parameters suggestive of ABD were grouped as a separate cohort. Prevalence of ABD was calculated. Descriptive analysis of ABD cohort was done. Correlation of various bone markers with iPTH was carried out.

Results: The study population (n=150) included 96 male (64%) and 54 female (36%) HD patients. The mean age of the study population is 54.54±14.81 years. 32.7% (n=49) of our study population had ABD. Serum calcium was found to be significantly higher in the ABD group. ALP and phosphorus were significantly lower in the ABD group.

Conclusion: The prevalence of ABD in our HD population was 32.7%. The prevalence of ABD was the same among males and females. There was significant correlation of iPTH levels with ALP, calcium, and phosphorus levels.

Keywords: Adynamic bone disease; hemodialysis; mineral bone disease.

INTRODUCTION

Chronic Kidney Disease (CKD) is defined as kidney damage or an estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73m² persisting for 3 months or more irrespective of the cause. Based on eGFR values, five stages of CKD have been described (1). In CKD, mineral metabolism gets affected more commonly. Chronic kidney disease–mineral and bone disorder (CKD-MBD) is a syndrome characterised by the clinical features, biochemical and imaging abnormalities consequent to disturbances in mineral metabolism. CKD-MBD includes high turnover bone disease and low turnover bone disease. CKD-MBD appears from chronic kidney disease stage 3. As the CKD stages progress to stages 4 and 5, there is increased incidence of MBD (2).

ABD is a form of low turnover renal bone disease. The prevalence of ABD across the world is variable and is dependent on various factors, such as age, gender, diabetes mellitus, intake of calcium + vitamin D supplements and dialysis vintage. Several reports suggest increasing prevalence of ABD in hemodialysis population (3-5). Despite an increase in the global burden of dialysis population worldwide, clinical, and biochemical data of ABD is sparse (6).

MATERIALS AND METHODS

This study was done as a cross sectional study in HD patients of a tertiary care hospital in South India. The study population included the prevalent CKD Stage 5D patients of more than 18 years of age. Cases in the paediatric and adolescent age group, pregnancy, patients who had undergone renal transplantation, and patients with history of liver disease, rheumatologic disorders and bone fractures were excluded in this study.

Baseline demographic data of the study population was collected. Biochemical data such as serum creatinine, blood urea nitrogen and bone markers for the diagnosis of CKD-MBD including serum calcium, phosphorus, alkaline phosphatase (ALP) and intact parathyroid hormone (iPTH) were collected. Based on the biochemical values, patients who had parameters suggestive of ABD were grouped as a separate cohort. Prevalence of ABD was calculated. Descriptive analysis of ABD cohort was done. Correlation of various bone markers with iPTH was carried out.

Biochemical assays

Serum iPTH was measured using the electro chemiluminescent sandwich immuno assay in Roche Cobas e 602 analyser. The other parameters were measured in Beckman Coulter AU 5800 and AU 680.

ALP was measured by the PNPP AMP buffer enzymatic method. Serum calcium was measured by a photometric method using Arsenazo III and corrected for albumin levels. Serum phosphorus was measured by a photometric method using phosphomolybdate. Serum creatinine by modified Jaffe's method and BUN by Urease-GLDH method.

Ethics committee clearance was obtained prior to the study (CSP-MED/21/SEP/71/121). Informed consent was obtained from the HD patients.

Assuming the proportion of ABD as 40%, the sample size required for the study was 144, with a relative precision of 20% and desired confidence interval (1- α) of 95%

Statistical analysis

All statistical analyses were done with the software SPSS 15.0. The Shapiro Wilks test was done as the test for normality. The parameters followed a non-normal distribution. Median and Interquartile range were calculated. Mann Whitney U test and Kruskal Wallis test were used and p value < 0.05 was considered statistically significant. Correlation analysis was done by Spearman correlation in the study cohort and p value < 0.01 was considered statistically significant.

RESULTS

The study population (n=150) included 96 males (64%) and 54 females (36%). The mean age of the study population is 54.54±14.81 years. The mean

hemoglobin (Hb) of the study population was 9.29±1.76 g/dl. The mean BUN and creatinine values were 51.23±19.71 mg/dl and 8.71±2.98 mg/dl, respectively. The mean calcium and phosphorus levels were 8.45±1.29 mg/dl and 5.04±1.87 mg/dl, respectively. The mean ALP level was 123.84±69.18 IU/L. The mean iPTH level was 399±333 pg/ml.

ABD was defined by iPTH < 100 pg /ml. By this definition, 32.7% (n=49) of our study population had ABD. Of them, 32 (65.3%) were male and 17 were female (34.7 %). The prevalence of ABD among males and females were almost the same. Among the male population (n=96), 33.3% (n=32) had ABD and among females (n=54), 31.5% (n=17) had ABD. The median age of patients with ABD was 56 (IQR 45 – 65). The median with interquartile range of biochemical parameters in ABD cohort are as follows: BUN (mg/dl) 45 (38-60), serum creatinine (mg/dl) 8.8 (7.15-10.5), ALP (IU/L) 90 (69.5-115), serum calcium (mg/dl) 9 (8.4-9.65) and serum phosphorus (mg/dl) 3.9 (3.15-5.35). The median Hb (g/dl) with interquartile range was 9.2 (8.15-10.4).

In the ABD cohort, 21 (42.86%) patients had diabetes mellitus. The average dialysis vintage at the time of diagnosis of ABD was 29 months. Four patients (8.16%) had dialysis vintage of less than a year, 21 cases (42.86%) had dialysis vintage of 1 to 2 years, 12 cases (24.49%) had dialysis vintage of 2 to 3 years and 12 cases (24.49%) had vintage of more than 3 years.

Table 1: Comparison of parameters between Group 1 (iPTH < 100 pg/ml) and Group 2 (iPTH >100 pg/ml)

Parameter	Group 1 (n=49)	Group 2 (n=101)	p value
Age (Years)	56 (45-65)	57 (49.5-65.5)	0.915
Blood urea nitrogen (BUN) (mg/dl)	45 (38-60)	48 (38.5-61)	0.482
Creatinine (mg/dl)	8.8 (7.15-10.5)	8.3 (6.5-10.3)	0.359
Alkaline phosphatase (ALP) (IU/L)	90 (69.5-115)	112 (83.5-168.5)	0.002*
Calcium (mg/dl)	9 (8.4-9.65)	8.2 (7.6-8.9)	<0.001**
Phosphorus (mg/dl)	3.9 (3.15-5.35)	5.2 (4.15-6.6)	<0.001**
Hemoglobin (Hb) (g/dl)	9.2 (8.15-10.4)	9.3 (8.15-10.3)	0.787

Data represented as median with interquartile range. Comparison done via Mann Whitney U test.

For statistical analysis, the entire study population was grouped into two based on iPTH values (Group 1 - iPTH < 100 pg/ml; Group 2 - iPTH > 100 pg/ml). Serum calcium was found to be significantly higher in ABD group: 9 (8.4-9.65) vs 8.2 (7.6-8.9) in group 2 (p

<0.001). Serum ALP (IU/L) 90 (69.5-115) vs 112 (83.5-168.5); p 0.002) and phosphorus (mg/dl) 3.9 (3.15-5.35) vs 5.2 (4.15-6.6); p <0.001) were significantly higher in group 2 than in group 1 (Table 1).

Table 2: Correlation analysis between iPTH and age, BUN, creatinine, ALP, calcium, phosphorus and Hb

Parameter	Correlation coefficient (R value) with PTH	p value
Age	-0.073	0.372
BUN	0.018	0.827
Creatinine	-0.015	0.855
ALP	0.423	<0.001**
Calcium	-0.344	<0.001**
Phosphorus	0.252	0.002*
Hb	-0.069	0.399

Spearman correlation; Correlation coefficient expressed as R value
BUN – Blood Urea Nitrogen, ALP – Alkaline phosphatase, Hb – Hemoglobin

Spearman correlation analysis was done between iPTH and age, BUN, creatinine, ALP, calcium, phosphorus and Hb. The analysis revealed significant correlation of iPTH with ALP ($p < 0.001$) and phosphorus ($p = 0.002$) and significant negative correlation between iPTH and serum calcium levels. ($p < 0.001$; Table 2)

The study group was divided into 3 groups for analysis. Group 1 with iPTH < 100 pg/ml, group 3

with iPTH between 100 -500 pg/ml and group 4 with iPTH > 500 pg/ml. Statistical analysis using Kruskal Wallis test yielded similar results. Serum calcium was higher in group 1 - 9 (8.4-9.65) vs 8.4 (7.7-8.9) in group 3 vs 8.1 (7.3-8.775) in group 4 ($p < 0.001$). ALP and phosphorus were higher in group 3 and group 4 (Table 3).

Table 3: Comparison of parameters among Group 1 (iPTH < 100 pg/ml), Group 3 (iPTH 100 - 500 pg/ml) and Group 4 (iPTH > 500 pg/ml)

Parameter	Group 1 (n=49)	Group 3 (n=61)	Group 4 (n=40)	p value
Age (Years)	56 (45-65)	57 (52-65.5)	53.5 (48-65.25)	0.866
BUN (mg/dl)	45 (38-60)	51 (38.5-61)	44.5 (37.5-60.75)	0.56
Creatinine (mg/dl)	8.8 (7.15-10.5)	8.3 (6.35-10.65)	8.1 (6.85-9.775)	0.596
ALP (IU/L)	90 (69.5-115)	107 (69.5-148)	120.5 (92.5-206)	$< 0.001^{**}$
Calcium (mg/dl)	9 (8.4-9.65)	8.4 (7.7-8.9)	8.1 (7.3-8.775)	$< 0.001^{**}$
Phosphorus (mg/dl)	3.9 (3.15-5.35)	5.2 (4-6.1)	5.3 (4.3 -7.175)	$< 0.001^{**}$
Hb(g/dl)	9.2 (8.15-10.4)	9.1 (8.05-10.15)	9.4 (8.45-10.8)	0.645

Data represented as median with interquartile range. Comparison done via Kruskal Wallis test.

BUN – Blood Urea Nitrogen, ALP – Alkaline Phosphatase, Hb – Hemoglobin

Table 4: Comparison of ALP, calcium and phosphorus between the groups - Group 1 (iPTH < 100 pg/ml), Group 3 (iPTH 100 - 500 pg/ml) and Group 4 (iPTH > 500 pg/ml)

Parameter	Significance between Group 1 and Group 3	Significance between Group 1 and Group 4	Significance between Group 3 and Group 4
ALP	0.08	$< 0.001^{**}$	0.023*
Calcium	$< 0.001^{**}$	$< 0.001^{**}$	0.312
Phosphorus	$< 0.001^{**}$	$< 0.001^{**}$	0.389

Comparison done via Mann Whitney U test.

ALP – Alkaline Phosphatase

*Statistically significant ($p < 0.05$)

**Statistically significant ($p < 0.001$)

Comparison done using Mann-Whitney test revealed significant differences in calcium and phosphorus levels between group 1 and 3 and significant differences in calcium, phosphorus and ALP levels between group 1 and group 4. There were no statistically significant differences in any of the parameters between groups 3 and 4 (Table 4).

DISCUSSION

‘Renal osteodystrophy’ is the term that has to be used ideally to define the bone disease associated with CKD. CKD-MBD is a more relevant term because it takes into consideration the clinical features, biochemical and imaging abnormalities that are associated with CKD. Various skeletal abnormalities described in CKD population include: 1. osteitis fibrosa, characterized by increase in bone turnover, osteoclast and osteoblast activity, seen as a manifestation of secondary hyperparathyroidism 2. osteomalacia, which is caused by defects in mineralization of the newly formed osteoid, 3. ABD, which is characterized by very low bone turnover, 4. osteoporosis and combination of the above abnormalities, which is termed as ‘mixed renal osteodystrophy’(2).

With increasing human lifespan and better access to healthcare facilities worldwide, there is an increasing global burden of CKD. (6) Renal replacement therapy, as in dialysis have prevented mortality and have improved life expectancy in end stage renal disease (ESRD) patients, but the quality of life of patients on dialysis is far inferior when compared to the general population (7). CKD-MBD contributes significantly to the morbidity of the dialysis population. MBD has an adverse effect on cardiovascular disease outcomes as well (8-10). Despite a better understanding of etio-pathogenesis of MBD, data on the prevalence of various forms of MBD in dialysis population is sparse.

ABD is characterized by low rates of collagen synthesis and mineralization. In comparison, another low turnover bone disease, osteomalacia is characterized by defective bone mineralization, which exceeds the rate of bone formation. Recent reports have suggested an increasing prevalence of ABD, both in the early stages of CKD and in the dialysis population. Several risk factors that are implicated in the pathogenesis of ABD include older age, diabetes mellitus, treatment with calcimimetics and bisphosphonates, inflammatory states and parathyroidectomy. Principles of management of

ABD include the supplementation of non-calcium-based phosphate binders instead of calcium-based phosphate binders, stopping vitamin D supplementation, restricting dietary calcium intake, lowering dialysate calcium and use of recombinant human parathyroid hormone, such as teriparatide (4, 11, 12).

Because the symptoms of ABD such as bone pains are often vague and non-specific, and can occur in high turnover bone disease also, biochemical tests for bone markers form the 'cornerstone' for the diagnosis of ABD. Regular follow up of CKD patients from CKD stage 3 onwards with necessary biochemical tests such as calcium, phosphorus, ALP, vitamin D levels and intact PTH would help in recognising MBD earlier. Clinical practice guidelines are available for investigating and managing cases of CKD-MBD. Those guidelines suggest clinicians regarding the ideal frequency of patients' visit to the physician and biochemical testing of bone markers, according to the stages of CKD(13).

The demographic characteristics of this study population are like other similar studies on CKD-MBD (5, 14-17). In our study, the prevalence of ABD was 32.7%. Abdu A et al, in their study including 48 HD cases reported that 27% of cases had features suggestive of ABD. (14) Vikrant and Parashar reported ABD prevalence of 31.3% in their study(15). Suman *et al.*, reported a prevalence of 92.7% in their study, which included 109 dialysis cases (5).

In our study, there was significant correlation of iPTH levels with ALP ($p < 0.001$) and phosphorus ($p 0.002$) levels. There was significant negative correlation between iPTH and serum calcium levels. ($p < 0.001$) In a study done by Vikrant and Parashar, there was a significant positive correlation between iPTH levels with ALP, phosphorus and creatinine, and a significant negative correlation with age, Hb and vitamin D levels(15). In a study from Brazil, which included 1134 dialysis patients from 11 nephrology centres, linear regression analysis showed a significant negative correlation between iPTH levels, age, and diabetic status and a significant positive association between dialysis vintage and iPTH levels(16). Suman *et al.*, from their study which included cases from CKD stages 3 to 5, concluded that iPTH was significantly associated with sex, eGFR, serum calcium, and vitamin D levels and no association was found between iPTH levels and age. (5) Ghosh *et al.*, demonstrated significant inverse correlation between hyperparathyroidism and calcium levels in CKD 5D patients, which is similar to our study findings (18).

There are several strengths for this study. This is a single centre study with a good sample size. All the biochemical parameters have been performed by standardized assays. Studies on CKD-MBD available in the literature have included patients with several stages of CKD. This study focussed on prevalence and

biochemical profile of patients with ABD in HD population.

Nevertheless, this study is not without limitations. Most of the cases were followed up with their primary care physicians from pre-dialysis stages of CKD and had been prescribed calcium + vitamin D supplements in different doses for a variable time period. They would have contributed to the pathogenesis of ABD in our study cohort. Hence, statistical correlation with the intake of calcium + vitamin D supplements and prevalence of ABD could not be done. DEXA (Dual-energy X-ray absorptiometry) scans and bone biopsies were not performed in the study cohort to characterize the bone disease and the diagnosis of ABD relied solely upon biochemical parameters. Recent Kidney Diseases: Improving Global Outcomes (KDIGO) guidelines on MBD have recommended clinicians to perform such investigations when those tests could potentially change treatment plan in selected cases (13,19).

CONCLUSION

The prevalence of ABD in our HD population was 32.7%. The prevalence of ABD was the same among males and females. In the ABD cohort, 42.86% of cases had diabetes mellitus. There was significant correlation of iPTH levels with ALP, calcium, and phosphorus levels.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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