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Assessment of Biochemical Markers and Bone Mineral Density in Patients of Chronic Kidney Disease Undergoing Haemodialysis: A Cross Sectional Study

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Abstract

Introduction With a global surge in patients of diabetes mellitus and hypertension the incidence of chronic kidney disease is increasing exponentially. Irrespective of aetiology of chronic kidney disease the management of end stage renal disease is some or the other kind of replacement therapy that may include renal transplantation of haemodialysis. Various metabolic derangement take place in patients of chronic kidney disease that include hypocalcaemia and hyperparathyroidism which consequently is responsible for osteoporosis in these patients. Early diagnosis of osteoporosis and appropriate intervention is essential in these patients for proper management.

Aims and Objective:-

1) To study the pattern of various mineral abnormalities and biochemical markers like Sr Ca,Sr P, iPTH, 25(OH)vitamin D and FGF23 in patients having chronic kidney disease undergoing haemodialysis.

2) To elucidate the relationship between biochemical markers and correlate DEXA findings with biochemical markers.

Materials and Methods

This was a cross sectional study conducted in the department of nephrology of Osmania medical college Hyderabad India institute. The study was conducted over a period of 2 years (Jan 2019 to Jan 2021). In this study 50 patients having chronic renal dialysis and who were being treated by haemodialysis were included on the basis of a predefined inclusion and exclusion criteria. plasma samples were analysed for 25OH-vit D and iPTH and serum for all other biochemical parameters. Bone mineral density was assessed at femoral neck, distal radius and lumbar spine. Presence of osteoporosis or osteopenia was noted. P value less than 0.05 was taken as significant for statistical purposes.

Results: -

Out of 50 patients having chronic kidney diseases there were 35 males and 15 females with a M:F ratio of 1:0.42. The mean age of affected male and female patients was found to be 49.4 +/- 7.79 and 47.8 +/- 7.74 years respectively. Diabetic Nephropathy was the most common cause of chronic kidney disease which was seen in 27 (54%) patients. Amongst 50 studied cases 15 (30%) patients were normocalcemic whereas hypocalcaemia and hypercalcemia were seen in 33 (66%) and 2 (4%) patients respectively. Estimation of bone mineral density showed that a total of 39 (78%) patient were either osteoporotic or

osteopenic and 11 (22%) patients were having normal bone mineral density. There was a negative correlation between parathyroid hormone and 25 (OH) vitamin D and the correlation was found to be statistically significant (P<0.05).

Conclusion: -

Patients with chronic kidney disease on haemodialysis are predisposed for development of osteoporosis and its consequences such as pathological fractures. Assessment of Bone mineral density and its proper management by anti-resorptive therapy is essential part of optimum management of these patients.

Keywords: - Chronic Kidney Disease, Hypocalcaemia, Haemodialysis, Osteoporosis.

Introduction

Chronic kidney disease (CKD) is spectrum of renal involvement that encompasses various degrees of impaired renal function. With advances in medical facilities and gradual increase in life expectancy of individuals there is steady increase in prevalence of patients with CKD. Increase sedentary lifestyle leading to a pandemic of type II diabetes mellitus with its consequent effects on kidneys is also one of the important contributing factors to increasing prevalence of chronic kidney disease.[1]

Longstanding hypertension and diabetes mellitus or a combination of these two systemic diseases is one of the common causes of CKD. The other causes include glomerular diseases, tubulointerstitial diseases, obstructive uropathy, polycystic kidney disease, autoimmune disorders such as IgA nephropathy, systemic lupus erythematosus and certain drugs such as sulphonamides, allopurinol and non-steroidal anti-inflammatory drugs.[2] The less common causes of chronic kidney disease include autoimmune vasculitis, renal vein thrombosis, human immunodeficiency virus nephropathy and Amyloidosis.[3]

Irrespective of the etiological cause CKD advancing to end stage renal disease require renal replacement therapy such as renal transplantation or haemodialysis. Since scope of renal transplantation is limited given scarcity of donors as well as complexity of procedure including HLA matching and financial aspects of renal transplant most of the patients landing up in end renal stage disease are either managed by continuous ambulatory peritoneal dialysis (CAPD) or haemodialysis.[4]

Since kidneys are important organs involved in metabolic pathway of vitamin D the natural consequence of end stage renal disease is problems with vitamin D metabolism and hypocalcaemia, hyperparathyroidism and consequent osteoporosis is commonly accompany chronic kidney disease.[5] One of the important contributing factors for osteoporosis in CKD patients is many of these patients are on long term steroid therapy either for native diseases (autoimmune diseases such as SLE, IgA nephropathy and nephrotic syndrome) or post renal transplantation. The other factors which include propensity of patients with CKD for developing vitamin D deficiency is that most of these patients are confined to home or hospitals and consequently they are not adequately exposed to sunlight thereby inefficient conversion of 7-dehydrocholesterol to *vitamin D* in the skin.[6]

It is important to diagnose osteoporosis as well as osteopenia in these patients along with its severity. Failure to diagnose and treat osteoporosis may result in pathological fracture following trivial trauma particularly femoral neck fracture.[7] Renal osteodystrophy is different from other bone diseases in that, Bone volume/Trabecular volume ratio is lower in those patients who are undergoing dialysis than in patients who are not undergoing dialysis. Also, in patients undergoing dialysis secondary hyperparathyroidism and cortical bone volume

is low, but the cancellous bone volume is high which is in contrary to osteoporosis where both volumes are decreased.[8]

Vitamin D deficiency not only causes increase parathyroid hormone secretion thereby causing mobilisation of calcium from bones but also it induces upregulation of renin-angiotensin system thereby causing uncontrolled or accelerated hypertension thereby further compromising cardiovascular status of patients having CKD.[9]

We conducted this study to analyse metabolic derangements such as hypocalcaemia, hyperparathyroidism as well as bone mineral density and to find out correlation of osteoporosis with various demographic and biochemical variables in patients having chronic kidney disease and undergoing haemodialysis.

Aims and Objectives:-

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2) To elucidate the relationship between biochemical markers and correlate DEXA findings with biochemical markers.

Materials and Methods:

This was a cross sectional study conducted in the department of nephrology of Osmania medical college Hyderabad India institute. The study was conducted over a period of 2 years (Jan 2019 to Jan 2021). In this study 50 patients having chronic renal dialysis and who were being treated by haemodialysis were included on the basis of a predefined inclusion and exclusion criteria. Study was approved by institutional ethical committee and written informed consent was obtained from all the participants. A detailed history was obtained from all the patients particularly to elicit the history of cause of chronic kidney disease. Duration of diabetes, hypertension or any other significant illness and its duration were noted. Previous investigation including renal function tests and imaging findings were also analysed.

8 ml of venous blood was obtained from median cubital vein without applying tourniquet. All the samples were collected as per recommendations. 3ml of blood was collected in k2 EDTA tube for separating plasma.5 ml of blood was collected in red topped standard serum separating tube. After allowing the sample to clot at room temperature for about 1 hour, samples were centrifuged, and serum/plasma was separated. Serum /plasma samples was stored at -20 centigrade in ice lined refrigerators. All samples were analysed within 3 hours of collection. plasma samples were analysed for 25OH-vit D and iPTH and serum for all other biochemical parameters. Bone mineral density was assessed at femoral neck, distal radius and lumbar spine. Presence of osteoporosis or osteopenia was noted.

All the data collected were coded and entered in Microsoft Excel sheet which were rechecked and analysed using SPSS statistical software version 18. Quantitative variables were presented as mean and standard deviation. Categorical variables were summarized using frequency and percentage. Statistical testing of association of various factors were done using Pearson Chi-square test, independent sample t test and Pearson Correlation. $P< 0.05$ was considered as statistically significant.

Inclusion Criteria: -

1. Patients of chronic kidney disease on dialysis for a minimum 2 times a week for at least 6 months were enrolled.
2. Those who gave written Informed Consent.
3. Age Above 18 years.

Exclusion criteria:

1. Those who refused consent.
2. Those patients who had pre-existing primary parathyroid abnormalities, already on NSAIDS, known liver disease, received steroids

or those on anti-epileptic drugs.

3. Patients having CKD but on continuous ambulatory peritoneal dialysis.
4. Non dialysis dependent CKD patients.

Results:

Total 50 patients with chronic kidney disease and who were on dialysis were included in this study on the basis of a predefined inclusion and exclusion criteria. Out of 50 studied cases there were 35 males and 15 females with a M:F ratio of 1:0.42.

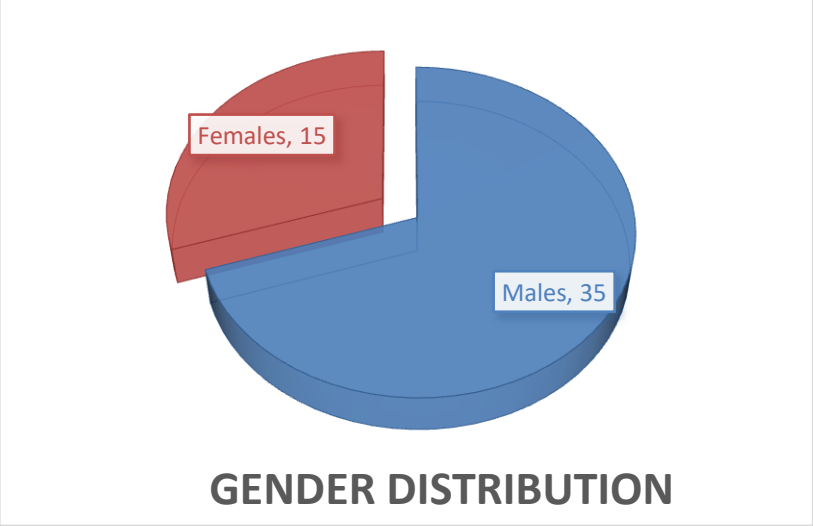

Figure 1: Gender Distribution of the studied cases.

The analysis of age groups of the studied cases showed that the most common affected age group was between 41-50 () years of age, followed by 51-60 () and above 60 years (). Only patients were seen below the age of 40 years. The mean age of affected male and female patients was found to be 49.4 +/- 7.79 and 47.8 +/- 7.74 years respectively. The mean age amongst male and female patients was found to be comparable with no statistically significant difference.

Table 1: Comparison of mean age in Male and Female patients.

	Males		Females	
	No of patients	Percentage	No of patients	Percentage
Below 40 years	3	6.00%	1	2.00%
41-50 years	16	32.00%	8	16.00%
51-60 years	9	18.00%	3	6.00%
Above 60 years	7	14.00%	3	6.00%
Total	35	70%	15	30%
Mean Age	49.4 +/- 7.79 years		47.8 +/- 7.74 years	
P=0.5081 (Not Significant)				

The analysis of patients on the basis of etiological factors for chronic kidney diseases showed that the most common etiological factor in studied cases was diabetic nephropathy which was seen in 27 (54%) patients. The other common causes included, Glomerulonephritis (22%), hypertensive or vascular nephropathy (16%). Amyloidosis, polycystic kidney disease, tubulointerstitial nephropathy and haemolytic uremic syndrome was found to be responsible for CKS in 1 (2%) patient each.

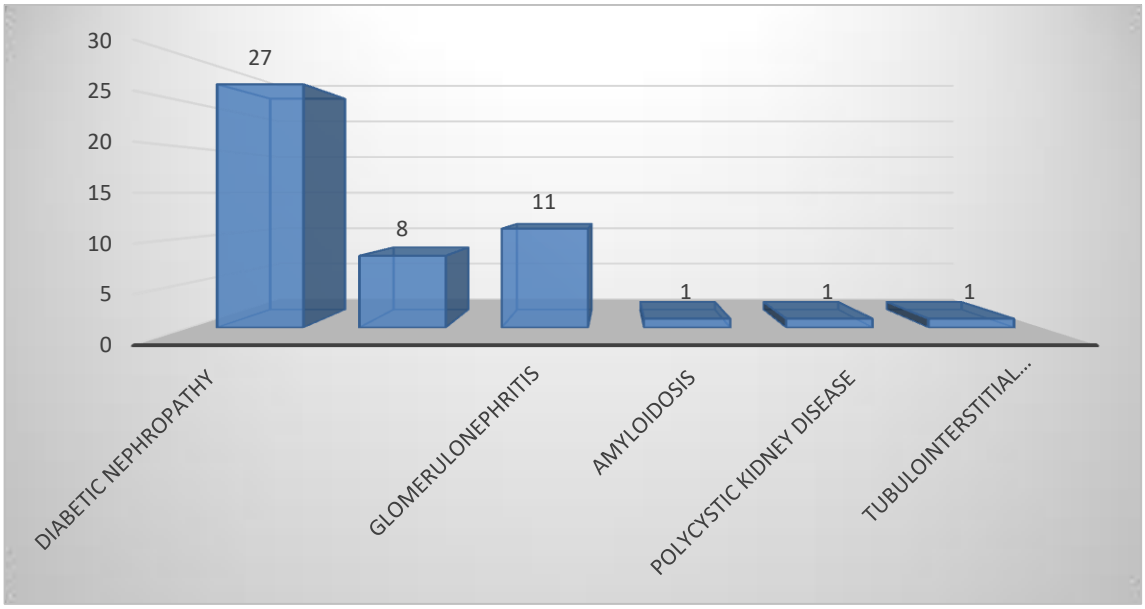

Figure 2: Aetiology of chronic kidney disease in studied cases.

Serum calcium, phosphate, parathyroid hormone, *Fibroblast growth factor-23* (*FGF23*, 25 (OH) cholecalciferol were estimated in all the cases. The mean serum calcium levels in studied cases were found to be 8.23 +/- 1.05 mg/dl whereas mean phosphate levels were found to be 6.56 +/- 2.28 mg/dl. Mean parathyroid and *FGF23* levels were found to be 304.20 +/- 113.18 pg/mL and 1877.36 +/- 1378.67 pg/mL respectively.

Table 2: Mean Calcium, Phosphate, PTH, FGF 23 and 25 (OH) cholecalciferol levels in studied cases.

Serum Levels	**Mean**	**Median**
Serum Calcium	8.23 +/- 1.05	8.05
Serum Phosphate	6.56 +/- 2.28	6.85
Parathyroid Hormone	304.20 +/- 113.18	290.50
Fibroblast growth factor-23 (*FGF23*	1877.36 +/- 1378.67	1782.50
25 (OH) cholecalciferol	19.68 +/- 7.49	21

Amongst 50 studied cases 15 (30%) patients were normocalcemic whereas hypocalcaemia and hypercalcemia were seen in 33 (66%) and 2 (4%) patients respectively.

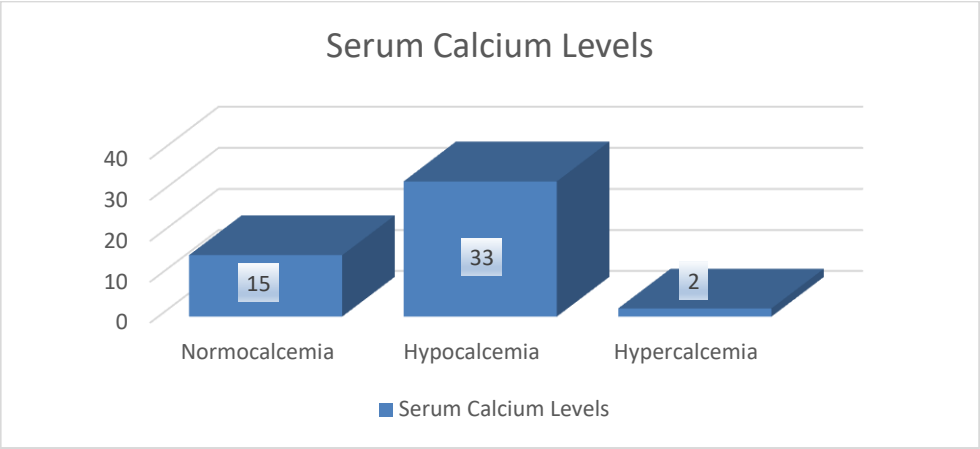

Figure 3: Serum calcium levels in studied cases.

DEXA Scan was done in all cases and femoral neck, Lumbar spine (L1, L2) and Distal Radius were assessed. At femoral neck 15 (30%) patients were found to be osteoporotic and 24 (48%) patients were found to be osteopenic. In 11 (22%) patients bone density was found to be normal. At lumbar spine and distal radius 14 (28%) patients were found to be osteoporotic whereas 21 (42%) and 20 (40%) patients were osteopenic. Bone mineral density was found to be normal in lumbar spine and distal radius in 15 (30%) and 16 (32%) patients respectively.

Table 3: Bone Mineral Density at femoral Neck, Lumbar Spine and Distal Radius.

DEXA Scan	**Osteoporosis**		**Osteopenia**		**Normal**	
	N	%	N	%	N	%
Femoral Neck	15	30 %	24	48 %	11	22 %
Lumbar Spine	14	28 %	21	42 %	15	30 %
Distal Radius	14	28 %	20	40 %	16	32 %

Pearson's analysis was done to find out correlation between parathyroid hormone and 25 (OH) vitamin D and FGF 23. There was a negative correlation between parathyroid hormone and 25 (OH) vitamin D and the correlation was found to be statistically significant (P<0.05). whereas positive correlation existed between parathyroid hormone and FGF23 although it was not found to be statistically significant (P=0.119). Similarly, though a negative correlation existed between FGF23 and 25 (OH) vitamin D the correlation was not statistically significant (P=0.641).

Table 4: Pearson's analysis showing correlation between PTH, FGF23 and 25 (OH) Vitamin D.

Correlation between variables		**Pearson Coefficient (r value)**	**P value**
parathyroid hormone	25 (OH) vitamin D	-0.280	Significant (0.049)
parathyroid hormone	*Fibroblast growth factor*	0.223	Not significant (0.119)
Fibroblast growth factor	25 (OH) vitamin D	-0.067	Not significant (0.641)

The analysis of patients on the basis of whether osteoporosis was present with various demographic and biochemical variables shoed that a lower Bone mineral density and osteoporosis at spine (L2) was associated with higher mean age, higher mean serum phosphate, parathyroid hormone and FGF23 levees and lower mean serum calcium and 25 (OH) Vit D. However, none of these factors were statistically significant.

Table 5: correlation of osteoporosis with various demographic and biochemical variables

Variables		**Osteoporosis**		P Value
		Present	**Absent**	
Age		41.54 +/-15.48	38.35+/-11.91	0.509 (Not Significant)
Gender	Males	7 (14 %)	28 (56%)	0.140 (Not Significant)
	Females	6 (12%)	9 (18%)	
Calcium		8 +/- 0.78	8.30 + 1.13	0.303 (Not Significant)
Phosphate		6.74 +/- 2.10	6.50 +/- 2.36	0.729 (Not Significant)
Parathyroid Hormone		329.54 +/- 90.84	295.30+/119.88	0.294 (Not Significant)
FGF23		1908 +/- 1714.82	1866 +/- 1267.44	0.936(Not Significant)
25 (OH) Vit D		18.92 +/-8.02	19.95 +/- 7.39	0.691

Discussion:

We studied 50 patients with chronic kidney diseases who were on haemodialysis. Out of these 50 cases there were 35 males and 15 were females with a mean age of 39.18 ±12.84 and a median age of 39 years. Mean dialysis duration was 8 months.

Despite dialysis dependent chronic kidney disease only 58%(n=29) of our patients were hyperphosphatemia and 42%(n=21) were normophosphataemic. In a study by Valson AT et al hyperphosphatemia was seen in 59% of patients, which was quite like our study, lower percentage of hyperphosphatemia in our study population could possibly be linked to poor nutrition and incredibly low protein intake in our population. With a mean serum calcium of 8.23 mg/dl ±1.05mg/dl, 66%% (n=33) patients were found to have hypocalcaemia, 30%(n=15) were Normocalcemic and 4%(n=2) were hypercalcaemic in our patient population. The study carried out by Valson AT et al in advanced CKD 66.3% were having hypocalcaemia which was not quite different from our study.[10]

With a mean iPTH of 304.20 pg./ml ± 113.18, secondary hyperparathyroidism was common abnormality in this group of patients and was consistent with other studies. 14%(n=7) of patients in our study group had PTH > 450 pg/ml surrogate of a high turnover disease and 4% (n=2) had low PTH values <100pg/ml being surrogate of low turnover bone disease. Rest 82% (n=41) of patients in study group had PTH values between 100 to 450pg/ml where we could not comment on underlying state of turnover. In a similar study Du J et al in a cross-sectional study that included patients with chronic renal disease undergoing maintenance haemodialysis treatment found hyperparathyroidism to be present in 82.9 % patients which was quite similar to our study.[11] Similar findings were also reported by the authors such Eidman KE as et al[12] and Chandran M et al[13].

With a mean serum 25(OH) vit D of 19.68 ± 7.49ng/ml, vitamin D deficiency was rampant in study population as is true with general population as well. 46%(n=23) were vitamin D deficient (<20ng/ml) 44%(n=22) were vitamin D insufficient (20-30ng/ml) and only 10% (n=5) had normal vitamin D(>30ng/ml), overall, around 90% (n=45) were vitamin D deficient or

insufficient. In a similar prospective observational study of 115 dialysis patients Gracia-Iguacel C found that 25(OH)D deficiency and insufficiency was present in 51% and 42% of the patients, respectively.[14] Only 7% of the patients showed normal 25(OH)D levels. The findings of this study were also found to be similar to our study. Similar findings were also reported by Bansal B et al[15] and El-Arbagy AR et al[16].

The mean serum FGF23 were 1877.36 pg./ml.±1378.67pg/ml, around 18% had values up to 5-fold above normal and 82% had levels above 5-to-10-fold normal values. As FGF23 levels start rising early in CKD as a compensation to prevent hyperphosphatemia, these high values of FGF23 were consistent with other studies. A study by Anandh et al[17] in haemodialysis patients (n=91) with mean dialysis duration 47.2 months had a mean FGF23 levels of 1152.7 pg./ml. In another study in haemodialysis patients by Torres et al[18] (n=99) with a mean haemodialysis duration of 6.8 years the mean FGF23 was >30000pg/ml. In a study by Zheng S et al[19] (n=125) mean dialysis duration of 65 months the mean FGF23 values were 1020 pg/ml. So by and large our results were consistent with these studies.

BMD done by DEXA at femoral neck revealed a remarkably high prevalence of low BMD, around 78% of patients had low BMD at femoral neck, of which 30% were osteoporotic and 48% were osteopenic and only 22% patients had a normal BMD. BMD at distal radius similarly showed low BMD in 70% of patients with 28% being osteoporotic ,42% osteopenic and 30% had a normal BMD at distal radius. At lumbar spine 68% patients had a low BMD, of which 28% were osteoporotic and 40% were osteopenic and 32% had a normal BMD. Similar findings were also reported by the authors such as Slouma et al[20]

Conclusion:

The biochemical abnormalities in chronic kidney disease include high phosphorus, low calcium, high PTH, and low vitamin D. 25(OH) vitamin D deficiency is widespread in these patients and seems to have a role in the genesis of hyperparathyroidism and high turnover renal bone disease. FGF23 levels rise exponentially in these patients. All these factors predispose an individual for development of osteoporosis and consequent pathological fractures. Assessment of bone mineral density is essential to assess the risk of pathological fracture. With introduction of safer and more tolerable anti resorptive therapy. BMD measurements may have therapeutic implications in chronic kidney diseases patients including patients on haemodialysis.

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