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Mineral and Bone Disorders in Pre-dialysis Chronic Kidney Disease

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Authors' contributions

This work was carried out in collaboration between the two authors. Author DKC conceptualized the study, collected data, did literature search, collaborated for statistical analysis and prepared the first draft. Author BMC re-analyzed the draft and extracted information to prepare this paper, did sample size calculation, defined sampling technique, analyzed data, prepared some graphs and charts, did literature search to include recent references, reviewed and revised, and prepared manuscript for submission. Both authors read and approved the final manuscript.

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ABSTRACT

Chronic kidney disease (CKD) affects 9.1% of the world population (estimated in 2017). The estimates indicate that globally 1.2 million people died of CKD in 2017. As kidney function declines, there is a progressive deterioration in mineral homeostasis. There are changes in circulating levels of hormones as well including parathyroid hormone (PTH), vitamin D, fibroblast growth factor-23 (FGF-23), and growth hormone. Studies have also found association between MBD and fractures, cardiovascular disease (CVD) and mortality.

It is well established that abnormalities in mineral metabolism are apparent early in the course of chronic kidney disease (CKD). This study was undertaken to assess and compare the biochemical markers of bone mineral disorders in diabetics with early CKD and non-diabetics with early CKD.

Keywords: Mineral and bone disorders; chronic kidney disease; hypocalcemia in CKD; hyperphosphatemia in CKD; alkaline phosphatase in CKD; parathyroid hormone in CKD; vitamin D in CKD.

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1. INTRODUCTION

Richard Bright first suggested the renal origin of cardiovascular disease in 1836 [1]. The cardiovascular disease in CKD includes ischemic heart disease, congestive cardiac failure, arrythmias and peripheral vascular disease [1]. The risk for cardiovascular disease (CVD) increases in a graded fashion as renal function worsens [1].

Chronic kidney disease (CKD) is associated with skeletal abnormalities known as renal osteodystrophy (ROD), including different types of bone tissue abnormalities. Osteopenia is a frequent feature that may lead to fragility fractures late in the course of ROD. Most studies on BMD in patients with renal failure that have been published during the recent years have been performed in patients on dialysis, where several investigators have found reduced bone mass. Studies on BMD in patients with early CKD are few. Cardiovascular mortality is 10–20 times greater in dialysis patients than in non-CKD patients even after adjusting for other factors like age, gender, race, hypertension, and diabetes [1]. Pathogenesis of CVD in patients with CKD is multifactorial, and includes traditional cardiovascular risk factors like dyslipidemia, hypertension, diabetes, obesity, smoking and uremic risk factors including albuminuria, anemia, hyperparathyroidism, metabolic bone disease, hyperphosphatemia, hyper-homocysteinemia, inflammation, endothelial dysfunction, and oxidative stress [1-3].

This study was undertaken to assess and compare the biochemical markers of bone mineral disorders, including serum calcium, phosphorus, alkaline phosphatase, parathyroid hormone and vitamin D level, in diabetics with early CKD and non-diabetics with early CKD.

2. METHODS

2.1 Source and Method of Collecting Data

Sixty patients attending the nephrology out-patient/ in-patient department at St Johns Medical College hospital, Bangalore, were included in the study.

The study duration was 2 years, from July 2010 to July 2012.

2.2 Inclusion Criteria

Diabetics (type 1 or type 2) and non-diabetics with early CKD were included in the study, and formed separate groups for comparison.

Patients with other comorbidities including hypertension, ischemic heart disease, that did not fall in the exclusion criteria, were included in the study.

2.3 Exclusion Criteria

Patients with acute renal failure, those receiving maintenance dialysis, renal transplant recipients, those currently taking or who within the last five years had been taking medication known to influence bone mineral metabolism [such as corticosteroids, other immunosuppressive agents, hormone replacement therapy (HRT), vitamin D analogs, calcium supplements, phosphate binders, anticoagulants or lithium], prolonged bedridden patients, patients with age less than 18 years and more than 60 years, and those with other causes of vascular calcification like tuberculosis, sarcoidosis, multiple myeloma; were excluded from the study.

2.4 Study Design

This study was a prospective, observational, cross sectional survey. The study compared biochemical markers of bone mineral disorders between diabetics with CKD and non-diabetics with CKD. IBM SPSS version 17 was used for data analysis.

2.5 Sample Size Calculation

Sample size was calculated using Raosoft (http://www.raosoft.com/samplesize.html). The input values were:

- Margin of error: 5%
- Confidence level: 95%
- Population size: 70
- Response distribution: 50%

Based on these inputs, the software suggested that required sample size is 60 (output).

2.6 Sampling Technique

The sampling technique used was consecutive sampling, also called total enumerative sampling, (a non-probability sampling method). Following

this sampling technique, every subject meeting the inclusion criteria, and not meeting the exclusion criteria was selected until the required sample size of 60 subjects was achieved.

2.7 Participants

Sixty patients with early *CKD* were included and were divided into 2 groups - group A and group B.

Thirty diabetics with early CKD were assigned to Group Aand 30 non-diabetics with early CKD due to any other cause were assigned to Group B.

2.8 Statistical Analysis

2.8.1 Statistical test

Mean of the continuous data were compared with the student t test. Multivariable data were compared with multivariate analysis.

Null Hypothesis: was used when there was no significant difference in the mean value between two groups i.e. $\mu1=\mu2$

*Alternate Hypothesis:*was used when there was a significant difference in the mean value between two groups i.e. $\mu1\neq\mu2$

Level of Significance:$\alpha=0.05$

*Decision Criterion:*P-Value was compared with the level of significance. If $P < 0.05$, null hypothesis was rejected, and the alternate hypothesis was accepted. If $P \geq 0.05$, null hypothesis was accepted.

3. RESULTS

3.1 BMD Comparison in Diabetic (Group A) and Non-diabetic CKD (Group B)

Group A consisted of 19 males (minimum age 41, maximum age 50, median age 48, mean age 46.47) and 11 females (minimum age 41, maximum age 50, median age 47, mean age 46).

Group B consisted of 23 males (minimum age 41, maximum age 49, median age 46, mean age 45.74) and 7 females (minimum age 45, maximum age 49, median age 47, mean age 46.86). Predominant cause of CKD in this group was chronic interstitial nephritis (53%). Table 1 depicts the distribution of patients according to etiology of CKD in this group.

Mean age among both males (46.47 years versus 45.74 years) and females (46 years versus 46.86 years) in both the groups were comparable. Mean eGFR between group A (58.2 ml/min/1.73 m^2) and group B (62.23 ml/min/1.73 m^2) were comparable.

Mean corrected calcium level was significantly lower in Diabetics (group A) as compared to non-diabetics (group B) with (P= 0.006), as shown in Fig. 1.

Mean phosphorus level was significantly higher in group A as compared to group B ($P < 0.001$) as shown in Fig. 2.

Mean albumin level was lower in diabetic CKD (group A) as compared to non-diabetic CKD (group B) as shown in Fig. 3, however this difference was not significant.

Mean alkaline phosphatase level was significantly lower in diabetics (group A) as compared to non-diabetics (group B) with ($p = 0.002$), as shown in Fig. 4.

Mean parathyroid hormone level was significantly lower in diabetic CKD (group A) as compared to non-diabetic CKD (group B) with ($p = 0.005$), as shown in Fig. 5.

Mean Vitamin D level was significantly lower in diabetics (group A) as compared to non-diabetics (group B) with (p= 0.005), as shown in Fig. 6.

Table 1. Etiology of CKD in non-diabetic CKD group (group B)

Etiology of CKD	Number of patients (percentage)
Chronic interstitial Nephritis (CIN)	53
Chronic Glomerulonephritis (CGN)	27
Hypertensive nephrosclerosis	10
Autosomal Dominant Polycystic Kidney Disease (ADPKD)	3
Human immunodeficiency virus Associated Nephropathy (HIVAN)	7

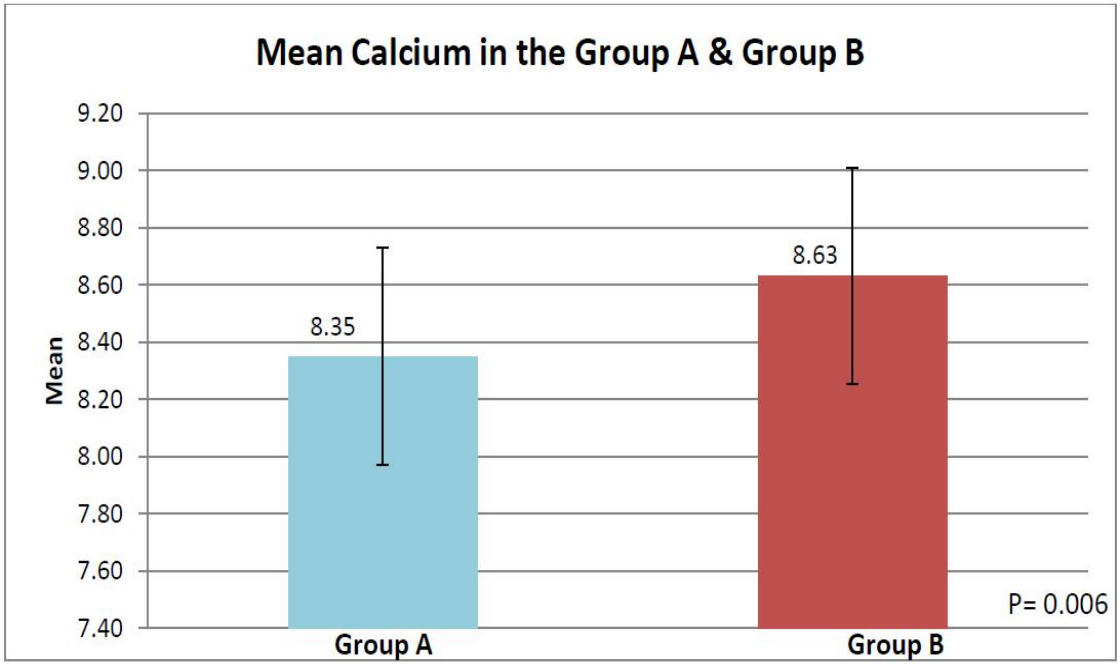

Fig. 1. Mean calcium levels in group A and group B. Serum calcium values are in mg/dl

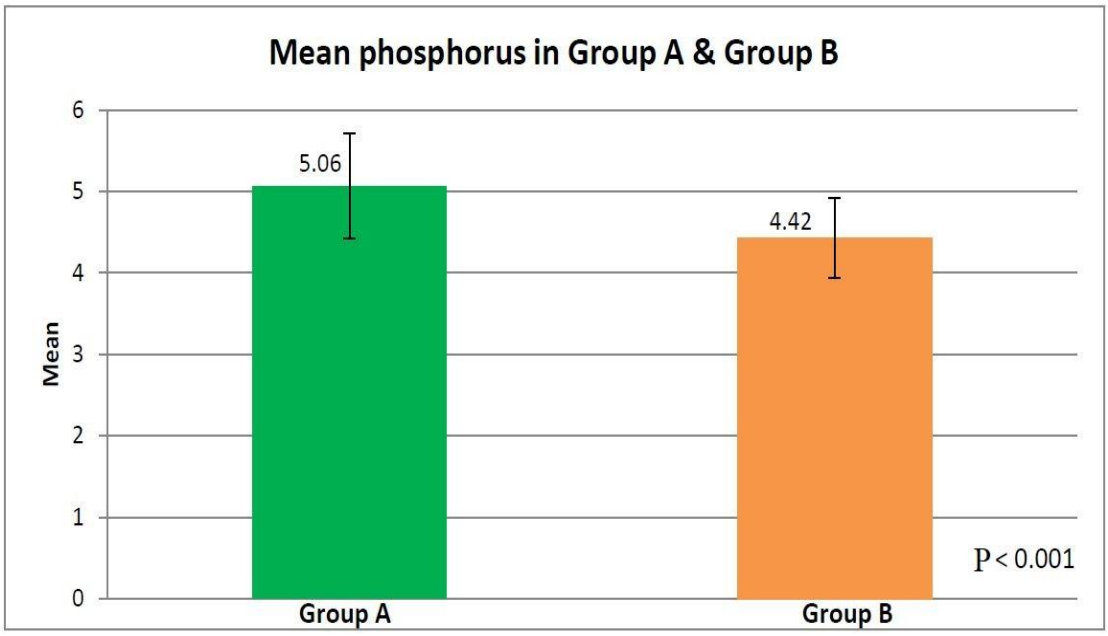

Fig. 2. Mean phosphorus levels in group A (diabetic CKD) and group B (non-diabetic CKD)

The statistical analysis showed that in diabetic CKD group (group A), as eGFR decreases parathyroid hormone level increases andvitamin D level decreases. Decrease in vitamin D level corelates with increase in parathyroid hormone level. The PTH levels andVitamin D levels significantly correlated with eGFR in Group A (P <0.001). This is shown in Fig. 7.

The parathyroid hormone levels and vitamin D levels had no correlation with eGFR in Group B (non-diabetic CKD group) (p = 0.081).

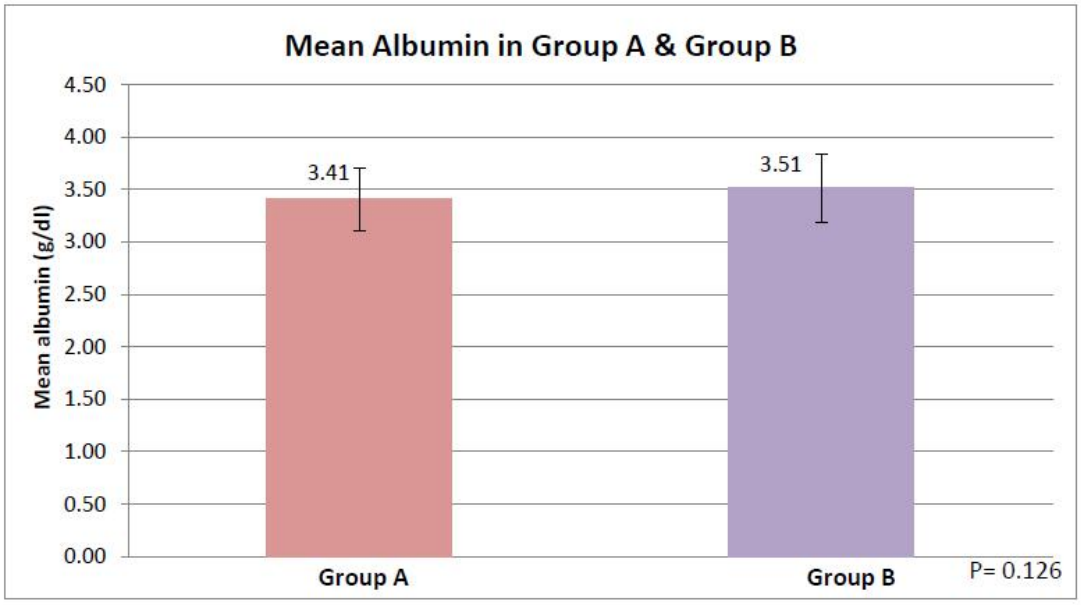

Fig. 3. Mean albumin levels in group A and group B

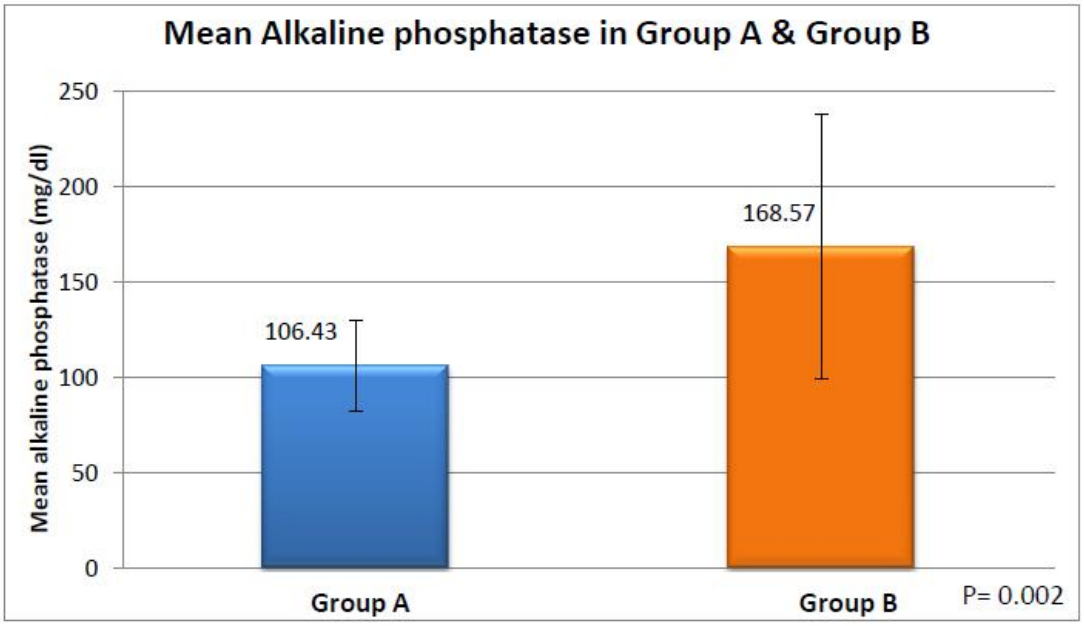

Fig. 4. Mean alkaline phosphatase levels in group A and group B

3.2 Summary of Results

In this study it was observed that:

- Mean corrected calcium levels were significantly lower in Diabetics (group A) as compared to non-diabetics (group B) with (P= 0.006).
- Mean phosphorus level was significantly higher in group A as compared to group B (P < 0.001).
- Mean albumin level was lower in diabetic CKD (group A) as compared to non-diabetic CKD (group B), however this difference was not significant.

- Mean alkaline phosphatase levels were significantly lower in diabetics (group A) as compared to non-diabetics (group B) with (p = 0.002).
- Mean parathyroid hormone levels were significantly lower in diabetic CKD (group A) as compared to non-diabetic CKD (group B) with (p = 0.005).
- Mean Vitamin D levels were significantly lower in diabetics (group A) as compared to non-diabetics (group B) with (p= 0.005).
- The parathyroid hormone (PTH) levels and Vitamin D levels significantly correlated with eGFR in Group A (P <0.001) but not in group B.

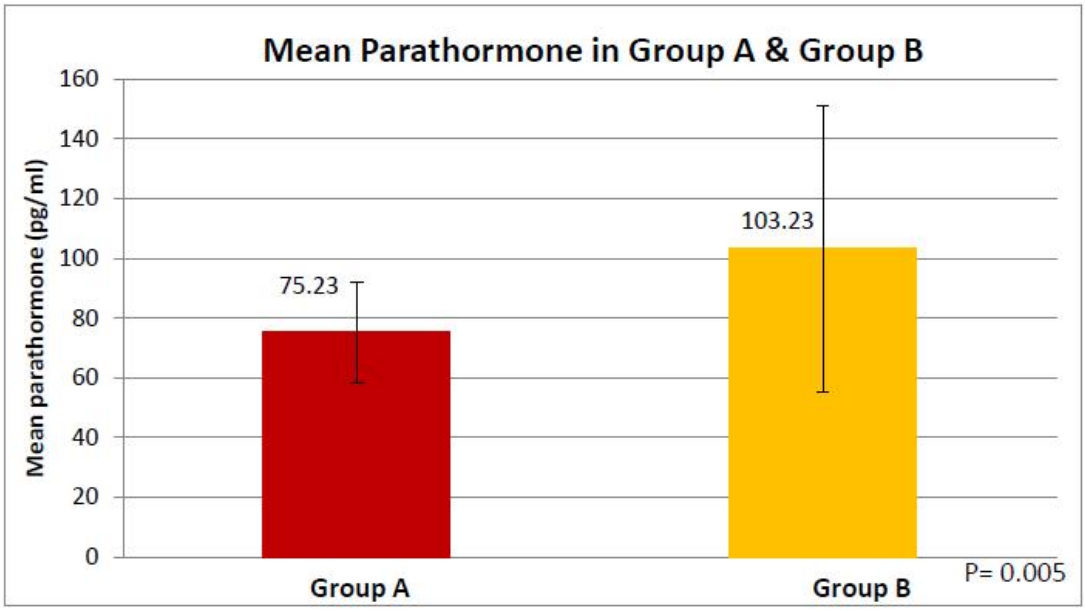

Fig. 5. Mean parathormone levels in group A and group B

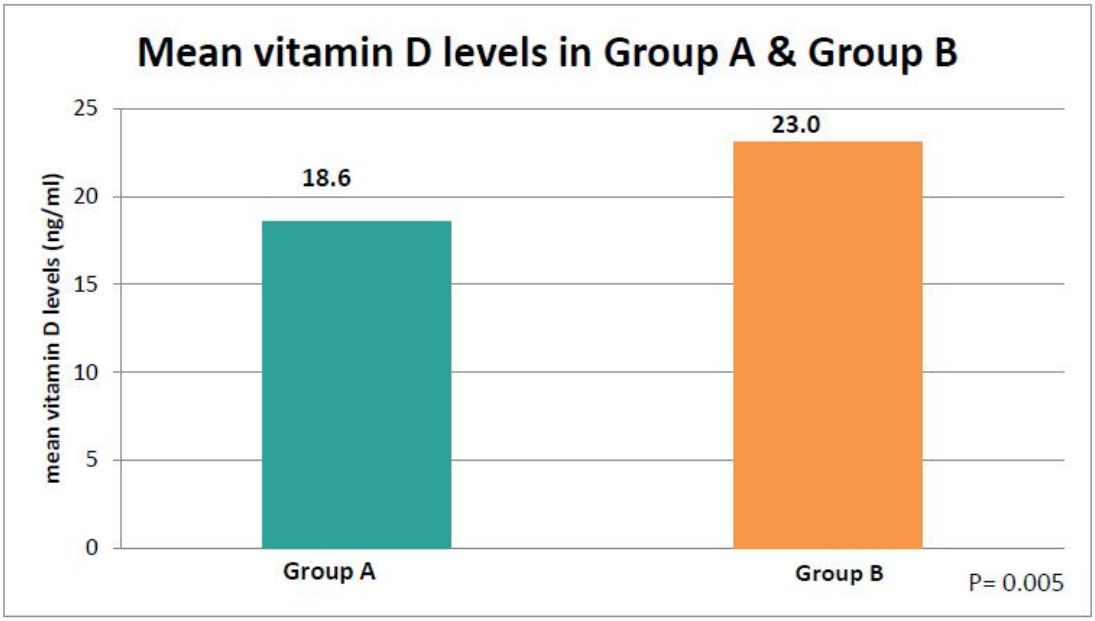

Fig. 6. Mean vitamin D in group A (diabetic CKD) and group B (non-diabetic CKD)

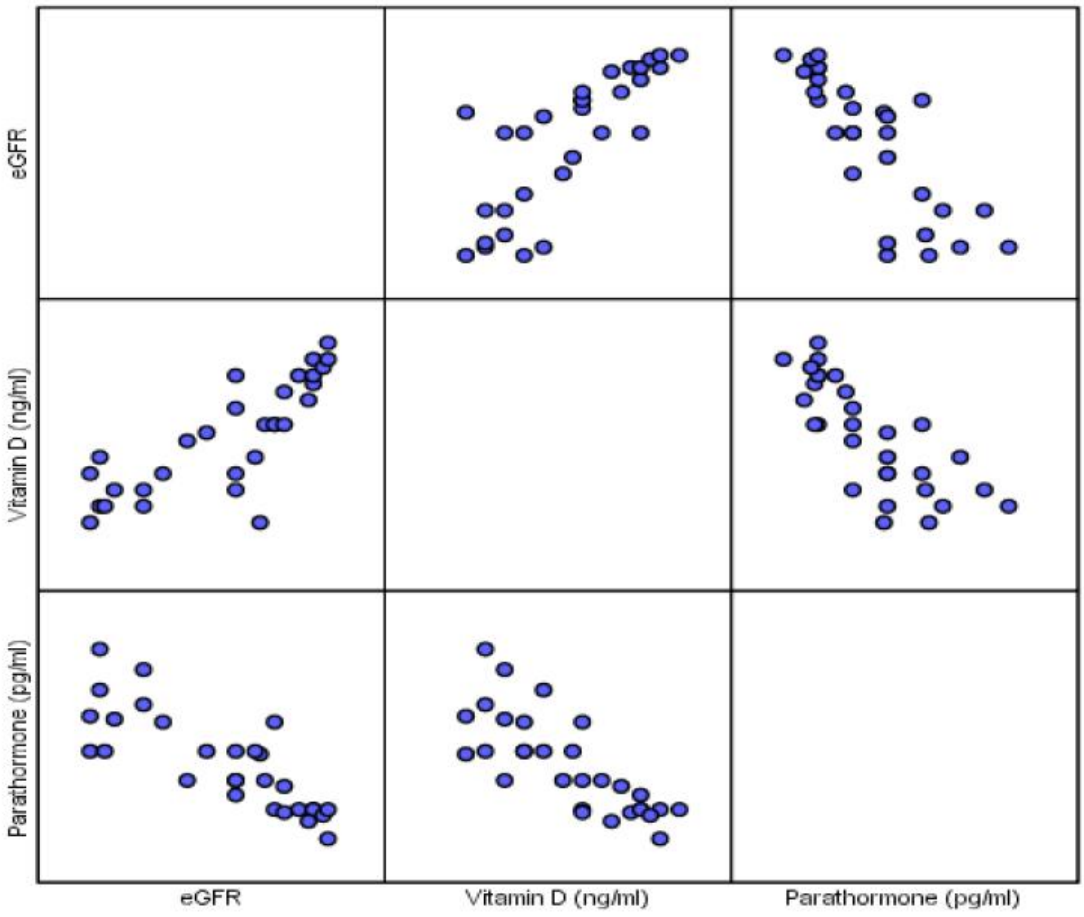

Fig. 7. Co-relation of eGFR with other parameters in group A (diabetic CKD)

This figure shows that as eGFR decreases, parathyroid hormone level increases and vitamin D level decreases. As vitamin D level increases, parathyroid hormone level decreases. The PTH levels and Vitamin D levels significantly correlated with eGFR in Group A (p<0.001)

4. DISCUSSION

The earliest manifestations of CKD-MBD are biochemical abnormalities like deranged calcium and phosphate homeostasis, vitamin D deficiency, secondary elevations of parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23) [4].

These biochemical abnormalities are found to be novel risk factors for cardiovascular disease in CKD and the current K/DOQI clinical practice guidelines advocate screening for and treating these abnormalities as early as eGFR of <60 ml/min/1.73m^2 (beginning in eGFR grade 3a when eGFR is 45-59 ml/min/1.73 m^2)[5].

The biochemical markers of CKD-MBD have been evaluated in advanced CKD and dialysis patients, however its occurrence in early CKD (stage 2 to 3) has not been extensively evaluated. Furthermore, diabetics with advanced CKD are found to have different profile of biochemical parameters as compared to non-diabetics [4].

Hence, we undertook this study to assess biochemical markers of bone mineral disorders in early CKD and compare it between diabetics (Group A) and non-diabetics (Group B).

The two groups in our study had similar age and sex distribution (male predominant). However, when compared to Patricia Wahl et al, Stephan S et al and CRIC study, our study groups had lower mean age and similar sex distribution (refer Table 2).

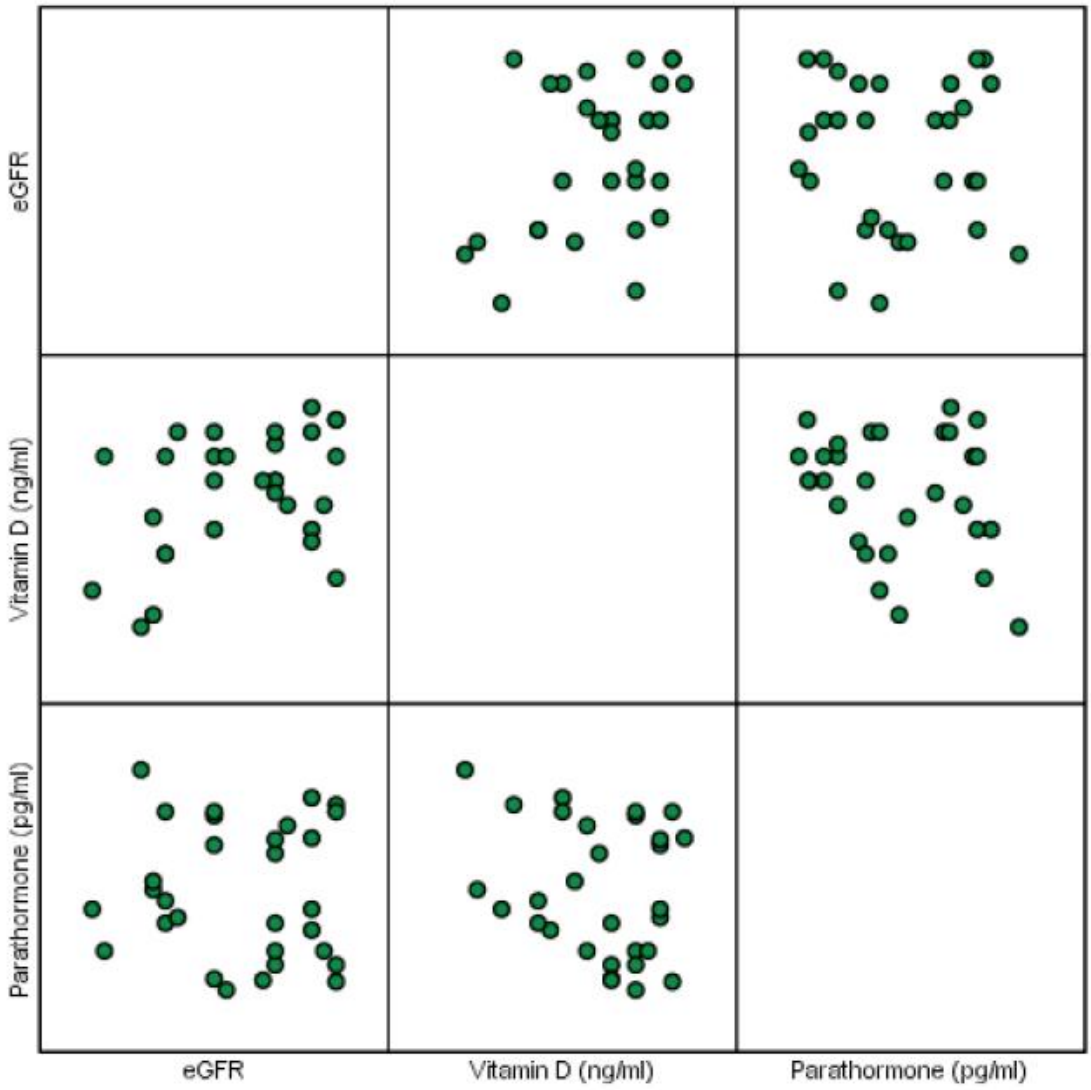

Fig. 8. Co-relation of eGFR with other parameters in group B (non-diabetic CKD)

This figure shows that there is no correlation between eGFR and parathyroid hormone levels, or between parathyroid hormone levels and vitamin D levels in non-diabetic CKD group

Mean eGFR in our study was slightly higher as compared to the other studies (refer- Table 2), the reason being, our groups had lower mean age and earlier stages of CKD (stages 2 to 3) as compared to other studies (CKD stage 2 to 4) [6-8].

Table 2. Demographic characteristics compared with other prominent studies

	Patricia Wahl et al [6]		**CRIC study [7]**		**Stephan S et al [8]**		**Present study**	
Study groups	DM	NDM	DM	NDM	DM	NDM	A (DM)	B (NDM)
Study population	1820	1936	1683	1929	538	590	30	30
Mean age (years)	59.5	57.5	59.5	57.1	68.5	64.1	46±5	45.5±6
Male/female (%)	56/43	54/45	55/45	53/47	51/49	56/44	63/37	77/23
Mean eGFR	40.7	44.7	41.4	45.1	39	35	58.2±16	62.2±18

DM: diabetes mellitus. NDM: non-diabetes mellitus

Table 3. Serum albumin levels found in this compared with other prominent studies

	Patricia Wahl et al [6]		Stephan S et al [8]		Present study	
Study groups	DM	NDM	DM	NDM	A (DM)	B (NDM)
Mean albumin	3.8	4	3.4	3.7	3.4±0.1	3.5±0.1

DM: diabetes mellitus. NDM: non-diabetes mellitus

Table 4. Serum calcium and phosphorus levels in this study compared with other prominent studies

	CRIC study [7]		Stephan S et al [8]		Present study	
Study groups	DM	NDM	DM	NDM	A (DM)	B (NDM)
Mean corrected calcium (mg/dl)	9.1±0.6	9.2±0.5	9.2±0.5	9.7±0.6	8.35±0.1	8.64±0.2
Mean phosphorus (mg/dl)	3.9±0.5	3.6±0.4	4.5±0.4	3.9±0.5	5.0±0.6	4.4±0.4

DM: diabetes mellitus. NDM: non-diabetes mellitus

Table 5. Intact parathyroid hormone levels and vitamin D levels in this study compared with other prominent studies

	CRIC study [7]		Patricia Wahl et al [6]		Present study	
Study groups	DM	NDM	DM	NDM	A (DM)	B (NDM)
Mean iPTH (pg/ml)	60	48.5	60	49.5	75.2±16	103.2±19
Mean vitamin D (ng/ml)	27.2	34.3	25.8	33.5	18.6±7	23.0±9

DM: diabetes mellitus. NDM: non-diabetes mellitus. iPTH: intact parathyroid hormone

4.1 Biochemical Variables

The study groups (A & B), had similar serum albumin levels. However, when compared to the studies by Patricia Wahl et al and Stephan S et al, albumin levels were lower probably because of poor nutritional status in Indian CKD patients (see Table 3).

The mean calcium and mean phosphorus levels differed in both the groups with group A having significantly lower calcium levels as compared to group B (p=0.006) and group A having significantly higher phosphorus levels as compared to group B (p=<0.001).

This difference was probably due to the earlier occurrence and more severe bone disorders observed in diabetic CKD as compared to non-diabetic CKD, even in early stages of CKD [9].

The mean calcium and phosphorus levels in our study were similar, when compared to Stephan S et al and CRIC study, as shown in Table 4.

Mean levels of intact parathyroid hormone (iPTH), vitamin D and alkaline phosphatase differed in both the groups, with group A having lower levels of iPTH, vitamin D and alkaline phosphatase as compared to group B (p=0.005). This variation is probably due to increased tendency of diabetics to have a dynamic bone disease as compared to non-diabetics, a finding seen in advanced CKD patients.

Our study groups (A & B) had lower iPTH levels as compared to Patricia Wahl et al and CRIC study. This difference may be because of the smaller population size in our study (refer Table 5).

The results of vitamin D levels of our groups were in accordance with Patricia Wahl et al and CRIC study. (refer Table 5)

The results of alkaline phosphatase in our groups (refer Fig.4) agreed with study done by S. Banerjee et al [10].

These various biochemical abnormalities of bone mineral disorders discussed above are risk factors for vascular as well as cardiac valvular calcification which predispose to cardiovascular disease [2].

5. CONCLUSION

Thirty diabetics with early CKD (group A) were compared with non-diabetics with early CKD (group B) for biochemical markers of bone mineral disorders. The study showed that subjects in diabetic CKD group had significantly lower calcium, iPTH, vitamin D and alkaline phosphatase levels, while phosphorus levels were significantly higher.

Derangements in biochemical markers of bone mineral disorders are observed in early CKD (stage 2 to 3) and tend to be more severe in diabetic CKD patients than non-diabetic CKD.

6. LIMITATIONS OF THE STUDY

- Bone biopsy was not done in Group A and Group B, because it was not clinically feasible.
- Small sample size.

CONSENT AND ETHICAL APPROVAL

Written informed consent was obtained before enrolling the patients. Hospital ethical committee clearance was obtained. Patients themselves bore the cost of all the investigations. The investigations done are regularly done as per protocol. No patient was asked to do any extra investigation just to satisfy the requirements of the study. All patients, whether a part of this study or not, are advised to do the same investigations.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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