

# Relationship between anemia and biochemical parameters of mineral bone disorders in chronic kidney disease stages 3-5 pre-dialysis patients

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## Abstract

**Background:** Anemia and mineral bone disorders (MBD) accompany chronic kidney disease (CKD) and worsen as CKD progresses. Different biochemical parameters of CKD-MBD have been associated with anemia of CKD but are less well evaluated in low resource settings. In this study, we evaluated the role CKD-MBD disorders as a cause of anemia in CKD non-dialysis patients.

**Methods:** This cross-sectional study recruited 115 patients with CKD who attended outpatient department (OPD) of Nephrology in BIRDEM General Hospital between January and June 2019. Patients, who were on iron, erythropoietin, calcium or vitamin D therapy in any form within the preceding 3 months and patients with known parathyroid disorders, metabolic bone diseases or anemia with definite etiology were excluded. Each patient's demographic, clinical and biochemical parameters were recorded. Associations between anemia and serum levels of calcium (corrected), phosphate, parathyroid hormone (PTH), 25-hydroxy vitamin D [25(OH)D] and alkaline phosphatase were evaluated.

**Results:** Total patients were 115 including 71 (61.7%) females. Mean age was 57.8 years. Most patients were in CKD stage 4 (43, 37.4%) and 5 (45, 39.1%). Mean duration of diabetes and hypertension were 12.7 and 7.2 years respectively. Mean serum creatinine (mg/dL), hemoglobin (gm/dL), calcium (mg/dL), albumin (gm/L), phosphate (mg/dL), alkaline phosphatase (U/L), PTH (pg/mL) and 25(OH)D (ng/mL) were 3.1, 10.5, 8.7, 37.9, 4.0, 119.1, 211.1 and 15.1 respectively. Hemoglobin in CKD stages 3-5 pre-dialysis patients had positive correlation with calcium and 25(OH)D and negative correlation with phosphate, alkaline phosphatase and PTH. Among these parameters of CKD-MBD, correlation with alkaline phosphatase was significant ( $r=-0.352$ ,  $p=0.001$ )

**Conclusion:** Anemia in CKD patients is multifactorial and this study concludes that CKD-MBD is yet another entity contributing to anemia in such pre-dialysis patients.

**Key words:** anemia, chronic kidney disease, chronic kidney disease-mineral bone disorders, correlation.

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## Introduction

Anemia is a common feature of chronic kidney disease (CKD) and is associated with numerous adverse outcomes including reduced quality of life, cognitive impairment, cardiovascular disease and mortality.<sup>1</sup> Relative erythropoietin deficiency and disturbed iron homeostasis are the major causes of anemia in CKD patients, although other different mechanisms could be involved such as circulating uremia induced inhibitors of erythropoiesis, shorter lifespan of red blood cells as well as nutritional and vitamin deficiencies.<sup>2</sup>

CKD-mineral bone disorders (CKD-MBD) is an important but unrecognized factor contributing to anemia in advanced CKD. Secondary hyperparathyroidism is a contributing factor for erythropoietin resistance in patients with CKD.<sup>3</sup> High levels of parathyroid hormone (PTH) decrease endogenous erythropoietin production, cause inhibition of bone marrow erythroid progenitors, induce bone marrow fibrosis and reduce red cell survival.<sup>4</sup> Vitamin D and its analogues lead to improvement of anemia by reducing erythropoietin requirements in CKD patients.<sup>5-7</sup> Vitamin D also helps in erythropoiesis by directly inhibiting PTH and reducing the production of inflammatory cytokine.<sup>8</sup> In addition, vitamin D diminishes the expression of hepcidin, an acute phase protein associated with decreased iron absorption and impaired mobilization of iron stores in CKD patients.<sup>9</sup> Lower calcium and/or greater phosphorus values have been found to be independent predictors of hypo-responsiveness to erythropoietin stimulating agents.<sup>10</sup> There is also a significant correlation between higher serum phosphorus levels and presence of anemia in CKD patients.<sup>11</sup> This study was done to evaluate the correlations between hemoglobin levels and CKD-MBD parameters as possible contributors to cause anemia in CKD non-dialysis patients.

## Methods

### Study design and subjects

This cross-sectional study recruited 115 patients with CKD who attended outpatient department (OPD) of Nephrology in BIRDEM General Hospital between January and June 2019. The patients completed a survey questionnaire, covering medical history and medication use and then underwent a physical examination. Those who were on iron, erythropoietin, calcium or vitamin D therapy in any form within last 3 months and patients with known parathyroid disorder, metabolic bone diseases or anemia with definite etiology were excluded from study. Patients' demographic, clinical and biochemical parameters were recorded. Associations between anemia and serum levels of calcium (corrected), phosphate, PTH, 25-hydroxy vitamin D [25(OH)D] and alkaline phosphatase were evaluated.

### Laboratory measures

Hemoglobin was measured by flow cytometry. Intact PTH and 25(OH)D<sub>3</sub> were measured by

Chemiluminescent Microparticle Immuno Assay (CMIA). Estimated GFR (eGFR) was calculated by using the CKD-EPI Creatinine 2009 Equation. According to the Kidney Disease Improving Global Outcomes Guideline for anemia in CKD, anemia was defined as serum hemoglobin <13 g/dl in men and <12 g/dl in women.

### Statistical analyses

Continuous variables were summarized as mean  $\pm$  SD. One way ANOVA has been performed to see correlations between anemia and CKD-MBD biochemical parameters. The data were analyzed with the statistical software SPSS 11.5.0. Statistical significance was set at  $p < 0.05$ .

## Results

Total patients were 115 including 71 (61.7%) females. Mean age was 57.8 years (Table I). Most patients were in CKD stage 4 (43, 37.4%) and 5 (45, 39.1%) (Table II). Mean duration of diabetes and hypertension were 12.7 and 7.2 years respectively. Mean serum creatinine (mg/dL), hemoglobin (gm/dL), calcium (mg/dL), albumin (gm/L), phosphate (mg/dL), alkaline phosphatase (U/L), PTH (pg/mL) and 25(OH)D (ng/mL) were 3.1, 10.5, 8.7, 37.9, 4.0, 119.1, 211.1 and 15.1 respectively (Table III). Hemoglobin in CKD stages 3-5 pre-dialysis patients had positive correlation with calcium (Figure 1) and 25(OH)D (Figure 2); and negative correlation with phosphate (Figure 3), alkaline phosphatase (Figure 4) and PTH (Figure 5). Among these parameters of CKD-MBD, correlation with alkaline phosphatase was significant ( $r = -0.352$ ,  $p = 0.001$ )

**Table I** Base-line characteristics of study subjects (N=115)

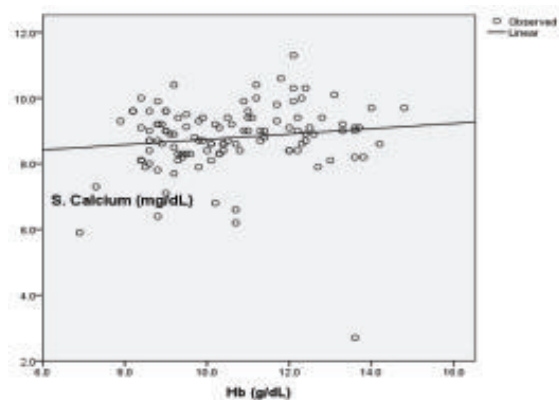
Parameter	Mean $\pm$ SD
Age (years)	57.82 $\pm$ 11.73
Duration of diabetes (years)	12.78 $\pm$ 6.21
Duration of hypertension (years)	7.24 $\pm$ 6.57
Serum creatinine (mg/dl)	3.16 $\pm$ 1.67
Hemoglobin (gm/dl)	10.53 $\pm$ 1.74

**Table II** Stages of CKD of study population (N=115)

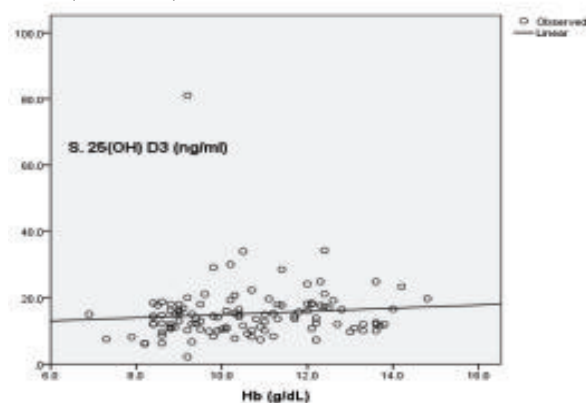
CKD Stage	Frequency	Percentage
1	3	2.6%
2	2	1.7%
3	22	19.1%
4	43	37.4%
5	45	39.1%

**Table III** Biochemical parameters of CKD-MBD (N=115)

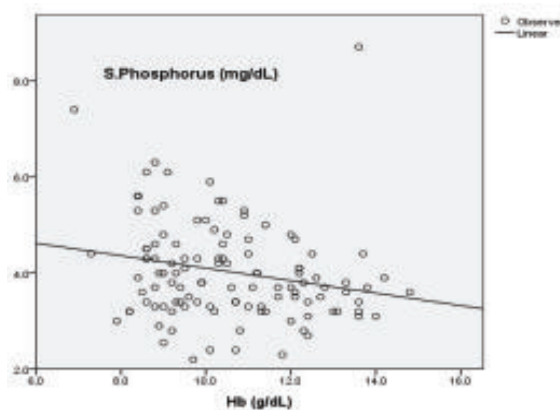
Parameter	Mean ± SD
Corrected serum calcium (mg/dl)	9.04 ±0.79
Serum phosphorus (mg/dl)	4.03±1.031
Serum alkaline phosphatase (U/L)	119.15±56.15
Serum PTH (pg/mL)	211.19±276.92
Serum 25(OH)D3 (ng/ml)	15.13±8.36



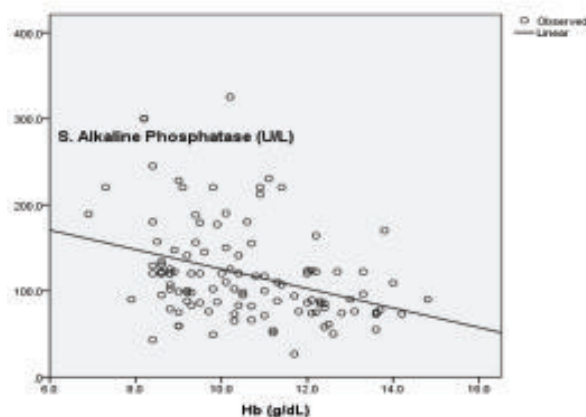
**Figure 1** Correlation of hemoglobin with serum calcium level ( $r = 0.152$ )



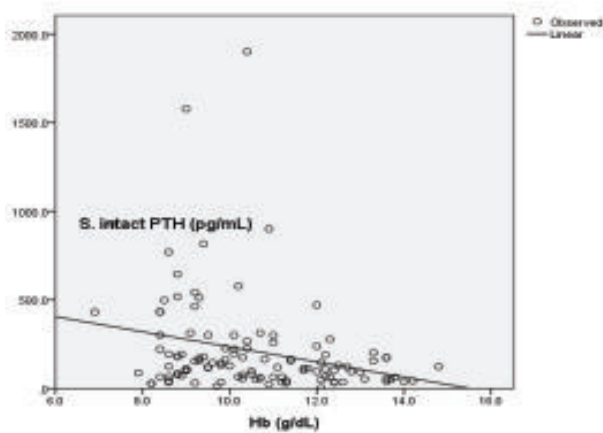
**Figure 2** Correlation of hemoglobin with vitamin D level ( $r = 0.287$ )



**Figure 3** Correlation of hemoglobin with serum phosphorus level ( $r = - 0.220$ )



**Figure 4** Correlation of hemoglobin with serum alkaline phosphatase level ( $r = - 0.352$ )



**Figure 5** Correlation of hemoglobin with serum PTH level ( $r = - 0.268$ )

## Discussion

Patel et al. showed that 25(OH)D and 1,25(OH)D deficiency are independently associated with decreased hemoglobin levels and anemia in CKD. They measured the concentrations of 25-hydroxyvitamin D (25(OH)D), 1,25-dihydroxyvitamin D (1,25(OH)D) and hemoglobin in a cross-sectional study of 1661 subjects in a multicenter cohort study of CKD patients in the United States, of whom 41% met the criteria for anemia. Similar to our study, the mean hemoglobin concentrations significantly decreased with decreasing 25(OH)D and 1,25(OH)D.<sup>12</sup> These linear trends remained significant after adjustment for age, gender, ethnicity, eGFR, diabetes and PTH. Recent clinical observations suggest a possible role of vitamin D in erythropoiesis.<sup>13</sup> In CKD patients, the administration of either nutritional or active vitamin D has been associated with an improvement of anemia and reduction in erythropoiesis stimulating agent (ESA) requirements.<sup>14</sup>

A reverse correlation has also been found to exist between PTH and hemoglobin level in studies similar to our one.<sup>15</sup> Possible causes of low hemoglobin level or anemia due to secondary hyperparathyroidism may be because of increased bone marrow fibrosis, which may lead to decreased erythropoietin and increased resistance to erythropoietin.<sup>16</sup> There are also some studies, which support an increase in erythrocyte osmotic fragility due to high concentration of PTH in patients on dialysis, leading to low hemoglobin level.<sup>17</sup> There is also indirect evidence of restoration of the hematocrit after parathyroidectomy in uremic patients.<sup>18</sup>

As regards the relationship between calcium and phosphorus with anemia, according to data collected from cohort studies of hemodialysis patients, hemoglobin levels are independently associated with serum concentrations of calcium and phosphorus. Data obtained from more than 8,000 hemodialysis patients participating in the Dialysis Outcomes and Practice Patterns Study revealed that higher serum calcium levels were associated with hemoglobin levels  $e^{-11}$  g/dl, just like in our study and this association was found to be independent of vitamin D supplementation and PTH levels.<sup>19</sup>

In addition, analogous to our study, two population based studies and a third one in kidney transplant recipients had also demonstrated a significant

correlation between higher serum phosphorus levels and presence of anemia among subjects with normal to moderately decreased glomerular filtration rate (GFR).<sup>20-22</sup> Lower calcium and/or greater phosphorus values have been found to be independent predictors of hypo-responsiveness to erythropoiesis stimulating agents in some studies.<sup>23-25</sup>

## Conclusion

Anemia in CKD patients is multifactorial and this study concludes that CKD-MBD is yet another entity contributing to anemia in such pre-dialysis patients. Deficiency of 1,25-dihydroxy vitamin D and calcium with resulting secondary hyperparathyroidism, raised alkaline phosphatase and serum phosphate all seem to be associated with anemia via a variety of mechanisms.

**Conflicts of interest:** Nothing to declare.

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