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Original Research

Assessment of vitamin D levels in different stages of chronic kidney disease and its correlation with hemoglobin levels

[1]Zeenat Mahendru, [2]Divya Soin, [3]Shaminder Kaur

[1]M.D.Medicine, Medical Officer, Civil Hospital, Malerkotla, Punjab, India;
[2,3]Associate professor, GGS Medical College and Hospital, Faridkot, Punjab, India

ABSTRACT:

Introduction: Anemia is one of the most common complications of CKD, and it has been suggested that Vitamin D, through its down-regulatory effects on inflammatory cytokines and hepcidin may favorably impact anemia, particularly anemia of inflammation. This study is undertaken to evaluate whether an association exists between 25-hydroxyvitamin D deficiency and anemia in different stages of chronic kidney disease patients. **Methods and material:** It consisted of 150 patients, 30 patients in each study group divided according to different stages of CKD. Patients above 18 years of age of any gender with chronic kidney disease were included in the study. All patients were assessed with complete clinical history, thorough clinical examination and suitable investigations. **Results:** The study consisted of more number of males i.e. 61 % and mean age of the patient was 56.27±8.78. On comparing the mean values of the age, eGFR, Hemoglobin, Urea , Creatinine and Vitamin D levels ($p<0.001$) significant difference was observed among various stages. The prevalence of anemia in in stage III, IV and V was 100% ($p<0.001$). Significant difference was observed between stages and values of vitamin D. The correlation of mean values of Vitamin D with hemoglobin in various stages was statistically significant in in stage IIIA and IIIB, IV, AND V($p<0.0001$). Among anemic patients (Hb<10g/dl) vitamin D deficiency was present in 47.2%, vitamin D insufficiency was seen in 52.8% and none of the patient had adequate vitamin D levels. The difference between them was statistically significant ($p<0.001$). **Conclusion:** Anemia in Chronic kidney disease is due to reduced production of erythropoietin by interstitial fibroblasts. EPO cells also express calcitriol receptors which induces proliferation and maturation of erythroid progenitor cells. Vitamin D deficiency was prevalent in patients with ESRD and was found to be independently associated with anemia.

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Corresponding Author: Divya Soin, Associate professor, GGS Medical College and Hospital, Faridkot, Punjab, India

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INTRODUCTION

Chronic kidney disease (CKD) due to its high prevalence, high rate of complications, high health care costs and poor outcomes is now widely recognized as a global public health issue. More than 850 million people suffer with some form of CKD worldwide, which is approximately double the number of people with diabetes and 20 times than those with cancer (1, 2). Patients with CKD are at increased risk of developing several complications such as infections, anemia, malnutrition, hypoalbuminemia, metabolic acidosis (reduced acid excretion by the kidneys), and Cardiovascular disorder (CVD) (3).

Recent research shows that the progression of CKD may be linked to hypovitaminosis D. Kidneys are a major target organ for both classical and non-classical functions of vitamin D because of the high expression of vitamin D receptors in the kidneys. The classical pathway is regulated by renin-angiotensin system(harmfull effect on Blood Pressure) and the non-classical autocrine actions of vitamin D, regulated by is the NF–kB pathway(inflammatory cascade). (4,5,6,7)

Anemia is one of the most common complications of CKD, and may further complicate chronic diseases including kidney and heart disease. According to the etiology, it can be classified as iron deficiency anemia or anemia of nutrient deficiency, and anemia of inflammation (also called anemia of chronic disease). It has been suggested that Vitamin D, through its down-regulatory effects on inflammatory cytokines

and hepcidin may favorably impact anemia, particularly anemia of inflammation. Patients with CKD have decreased renal function, thus reducing erythropoietin production, erythropoietin resistance, and reduced ability to convert $25(OH)D_3$ to the active hormone. Other than this, there is an increase in inflammatory cytokines that promote hepcidin release. (8)

Hepcidin concentrations are inversely associated with hemoglobin concentrations, thus increasing the risk of anemia. Various studies show that vitamin D decreases the pro-inflammatory cytokines and directly suppresses the hepcidin expression. It is also useful in mobilizing iron stores and promoting erythropoiesis and hemoglobin synthesis (8). This study is undertaken to evaluate whether an association exists between 25-hydroxyvitamin D deficiency and anemia in different stages of chronic kidney disease patients.

METHODS AND MATERIAL

The present study was a hospital based descriptive study performed in OPD and IPD in the Department of Internal Medicine at Guru Gobind Singh Medical College and Hospital Faridkot, Punjab after obtaining approval from the Institutional Ethics Committee. It consisted of 150 patients, 30 patients in each study group divided according to different stages of CKD. Patients above 18 years of age of any gender with chronic kidney disease were included in the study. Patients having blood loss from any site, aplastic and macrocytic anemia, chronic inflammatory disorders, inflammatory bowel disease, and on hemodialysis were excluded from the study.

All patients were assessed with complete clinical history, thorough clinical examination and suitable investigations. The data pertaining to socio-demographic and other clinical variables was entered as a data matrix in Microsoft® Excel® and analysed using IBM® SPSS® V 22.0.0 in the light of suitable statistical tests.

RESULTS

The results of the present study shows that there were more number of males i.e. 61 % and females were 39 %. Male:Female ratio was 1.54:1(fig1). Maximum patients were seen in age group 51 -60 years followed by 61-70 years. Minimum patients were in age group 11-30 and 71-80 years(fig 2). Mean age of the patient was 56.27±8.78. Table 1 shows the mean values of the different parameters observed in the present study. the parameters included age, eGFR, Hemoglobin, Urea , Creatinine and Vitamin D levels ($p<0.001$). It was observed that on comparing these values significant difference was observed among various stages. Table 2 shows the prevalence of anemia in stage I was in 23.3%.It was seen in 90% cases in stage II. Its prevalence was 100% in stage III, IV and V. There was significant change seen in both the groups in different stages($p<0.001$).

Significant difference was observed between stages and values of vitamin D. In stage I, II &III A, all (100%) patients had vitamin D levels between 15-30. Table 3 shows that In stage IIIB, 66.7% patients were deficient of vitamin D, 26.7% were insufficient and 6.7% had sufficient Vitamin D levels. In stage IV, vitamin D deficiency was prevalent in 73.3% patients and in 26.7% patients it was insufficient. In stage V in 86.7% patients, vitamin D was deficient and in 13.3% it was insufficient. In total, 38.7% patients reported deficiency, 60.7% had insufficient and it was adequate in 0.7%($p<0.001$).

Table 4 shows correlation of mean values of Vitamin D with hemoglobin in various stages. It was observed that the value of vitamin D and hemoglobin did not correlate in stage I and stage II($p<0.646$ and $p<0.890$), but there was a highly significant correlation between both in stage IIIA and IIIB, IV, AND V($p<0.0001$). Table 5 shows the correlation between vitamin D and hemoglobin levels. Among anemic patients (Hb<10g/dl) vitamin D deficiency was present in 47.2%, vitamin D insufficiency was seen in 52.8% and none of the patient had adequate vitamin D levels. The difference between them was statistically significant ($p<0.001$).

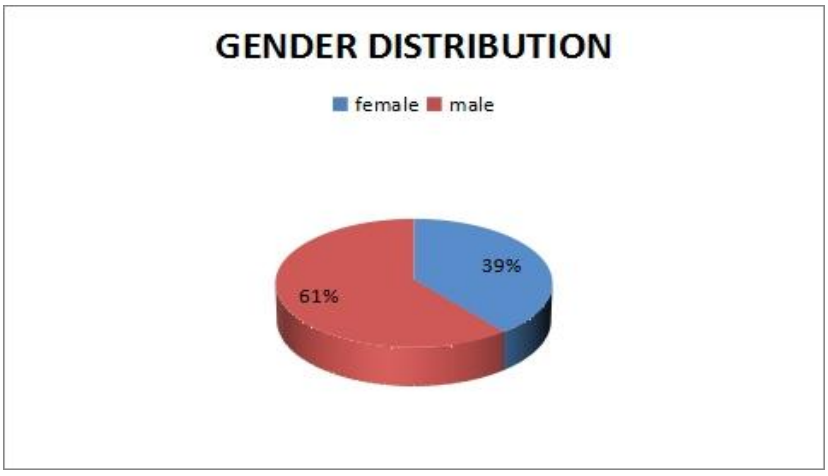

Fig 1: Gender Distribution in CKD patients

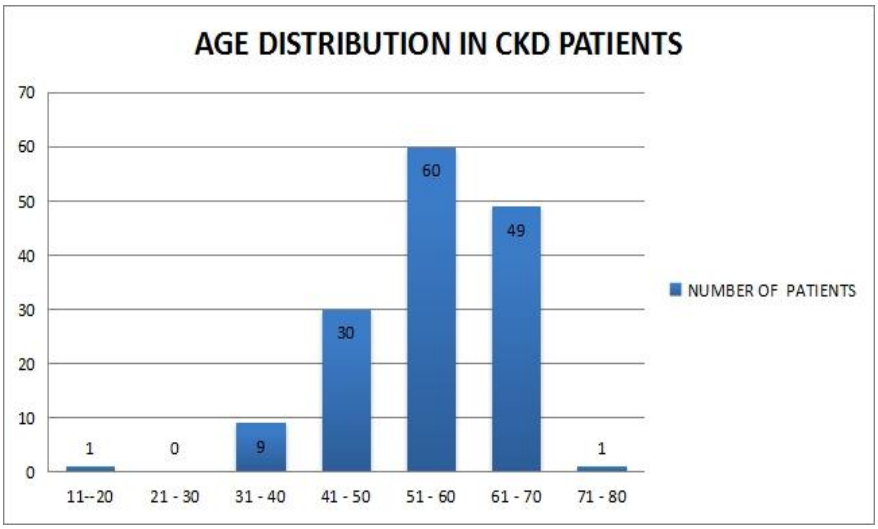

Fig 2: Age Distribution in CKD patients

Table 1: Various baseline parameters of different CKD stages

CKD STAGE	Mean± Std. Deviation age of patients (years)	Mean EGFR ± Std. Deviation (ml/min./1.73m2)	Mean blood urea levels ± Std. Deviation (mg/dl)	Mean serum Creatinine levels± Std. Deviation (mg/dl)	Mean Hemoglobin levels± Std. Deviation (g/dl	Mean Serum Vitamin D(ng/ml)
Stage I	48.10± 7.54	94.78± 4.07	57.83± 18.96	0.84±.11	10.65±.88	26.07±1.44
Stage II	57.10± 8.33	69.80± 7.39	57.90± 18.40	1.04±.16	8.91±.70	22.92±1.89
Stage III(A)	49.53± 7.15	49.59±3.08	85.60±19.55	1.44±.21	7.22±.28	17.07±1.19
Stage III(B)	54.80±9.93	37.15± 5.08	93.46± 22.12	1.86±.24	6.62±1.07	15.60±6.36
Stage IV	64.23± 4.23	21.81± 3.77	89.07± 25.39	2.83±.45	6.38±.90	13.76±2.48
Stage V	59.77± 2.63	8.67± 3.45	112.03± 31.59	7.85±4.44	5.12±1.01	8.54±3.67
ANOVA	.001**	.001**	.001**	.001**	.001**	.001**

Table 2: Prevalence of anemia in different stages

CKD Stage	Hb>10(g/dl) patients (%)	Hb<10(g/dl) patients (%)
Stage I	23 (76.7)	7(23.3)
Stage II	3(10.0)	27(90.0)
Stage III(A)	0(0)	15(100)
Stage III(B)	1(6.7)	14(93.3)
Stage IV	0(0)	30(100)
Stage V	0(0)	30(100)

Table 3: Prevalence of Hypovitaminosis D in different CKD stages

CKD Stage	Vit D value <15ng/ml (%)	Vit D value 15-30ng/ml	Vit D value >30ng/ml
Stage I	0(0)	30(100)	30(100)
Stage II	0(0)	30(100)	30(100)
Stage III(A)	0(0)	15(100)	15(100)
Stage III(B)	10(66.7)	4(26.7)	4(26.7)
Stage IV	22(73.3)	8(26.7)	8(26.7)
Stage V	26(86.7)	4(13.3)	4(13.3)
Total	58(38.7)	91(60.7)	91(60.7)
p value	.001**		

Table 4: correlation of mean S.Vitamin D with mean hemoglobin levels in various CKD stages

Stage	Pearson correlation coefficient	Mean hemoglobin levels(g/dl)	Mean S.vitamin d levels(ng/ml)	p value
STAGE I	.08	10.65	26.07	.646
STAGE II	.02	8.91	22.92	.890

STAGE IIIA	.97	7.22	17.07	.0001**
STAGE IIIB	.97	6.62	15.60	.0001**
STAGEIV	.96	6.38	13.76	.0001**
STAGE V	.95	5.12	8.54	.0001**

Table 5: Correlation between S.Vitamin D and Hemoglobin Levels in Study Population

Vit D (ng/ml)	Hb>10(g/dl) (%)	Hb<10(g/dl) (%)	p-value chi square
<15	0(0)	58(47.2)	.001**
15-30	26(96.3)	65(52.8)	
>30	1(3.7)	0(0)	
Total	27(100)	123(100)	

DISCUSSION

Anemia is a common finding in patients with CKD, and its prevalence and severity is known to increase as renal function decreases. In addition, anemia is closely associated with a wide range of clinical symptoms and signs, resulting in poor quality of life and increased risk of morbidity and mortality in these patients. Recently, accumulating evidence indicates that vitamin D has pleotropic effects in various organ systems based on the distribution of vitamin D receptors in the whole body. In addition to its well-known effects on bone and mineral metabolism, vitamin D has been revealed to play a protective role in a number of chronic diseases, including CKD associated anemia (9).

The present study aimed to assessed if 25-hydroxyvitamin D [25(OH)D3] deficiency was associated with anemia. Our study reported more number of males i.e. 60.7% and females were 39%. Kim and co-workers in their study reported more than 60% males which was similar to the present study as in our study also percentage of males was 61% (9). Maximum patients were seen in age group 51-70 years (72.6%) with mean age of 56.27±8.78. Mohd Rozita et al. in their study showed the mean age of the patients to be 53.3 years.(10) In a study by Yuste C et and al. Ravani et al. the mean age of patients was 67.5 ±15 and 70.1±11.9 years respectively.(11,12)

The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guidelines (2012) recommended that Hb targets should be in the range of 10.0–11.5g/dl, regardless of whether the patients were receiving dialysis or not. Therefore we defined anemia as an Hb level of <10 g/dl (13).

In the present study, the mean value of hemoglobin of the patients of all stages was 7.59 ±2.14. It was observed that with increasing stage of the disease, the mean Hb levels of the patients decreased significantly. Poudel B. and fellow researchers in their study observed high incidence of anemia in overall CKD patients (14).Sathyan and co-workers in their study on Indian population reported the mean Hb in their study was 8.42±2.20 g/dl which was in accordance to our study . Mean Hb in their study was 9.167 g/dl in stage III, 10.195 g/dl in stage IV and 7.993 in stage V. The prevalence of anemia increased from stage III (66.6%) to stage V (94.7%) and this correlation was statistically significant (p<0.005) (15). In the present study also, significant change was seen in hemoglobin levels from stage III to stage V.

Prevalence of anemia in stage I was in 23.3% . It was seen in 90% cases in stage II. Its prevalence was 100% in stage III, IV and V (Table 6). In a study by Stauffer and fellow workers the prevalence of anemia increased with stage of CKD, from 8.4% at stage I to 53.4% at stage V (16). Shaheen et al. in their study observed the hemoglobin levels below 11 g/dl (the minimum hemoglobin level at which therapy should be initiated with erythropoietin), to be 21%, 17%, 31%, 49%, and 72%, respectively from stages I to V (17). Kazmi and co-workers in their study in Boston, USA, showed the prevalence of anemia below 12 g/dl to be 45%, 49%, 58%, 92%, 92% from CKD stages 1 to 5, respectively, and below 11 g/dl as 24%, 34%, 41%, 79%, 74%, from stages I to V respectively (18).

The mean Vit D levels of patients in all stages was 17.52 ± 6.99 and it was observed that with there was significant decrease in the mean vitamin D levels with increasing CKD stage. Chandra and co-workers in their study observed mean baseline vitamin D levels to be 20 ng/dl for stage III and IV (19). Oksa and fellow researchers observed it to be 19.5 from stage II-IV (20).

For the purpose of analysis, $25(OH)D_3$ concentration was categorized based on Current Kidney Disease Outcomes Quality Initiative guidelines (K/DOQI guidelines, 2003 to: Optimal levesl (>30 ng/ml), insufficient (15-30 ng/ml) and deficient (<15 ng/ml) (21).

Our study shows significant association between vitamin D and anemia in CKD patients, as vitamin D was significantly less in anemic patients. Kim and co workers in their study demonstrated that patients with $25(OH)D_3$ levels <10 ng/dl had a higher risk of developing anemia than patients with $25(OH)D_3$ levels ≥10 ng/dl (9). In a study by Patel and co-workers, the value of vitamin D for anemic was 26±13 for patients without anemia, it was 31±12 with a statistically significant difference .Whereas in our study, it was 15.63 for Hb<10gm/dl and 26.7 for and >10gm/dl with statistically significant difference (22).

A secondary analysis of NHANES that included over 19,000 patients revealed increasing prevalence of $25(OH)D_3$ deficiency (<15 ng/ml) from 9% to 14% in CKD stages 1 to 3 to 27% in CKD stages IV to V

(23). In the present study in stage I, II & IIIA all 100% patients had vitamin D levels between 15-30. In stage IIIB 66.7% patients were deficient , 26.7% were insufficient and 6.7% had sufficient vitamin D levels. In stage IV, vitamin D deficiency was prevalent in 73.3% patients and in 26.7% patients it was insufficient. In stage V, vitamin D was deficient and in 13.3% it was insufficient. In total, 38.7% reported deficiency and 60.7% had insufficient and it was adequate in 0.7% patients.

In the present study Vitamin D deficiency was present in 47.2% of anemic patients. vitamin D insufficiency was present in 52.8% of anemic patients. None of the anemic patient had adequate vitamin D levels. The difference between their values were statistically significant. In a study by Altemose done on children suffering from CKD it was reported that mean hemoglobin was higher in $25(OH)D_3$ sufficients as compared to insufficient/deficient children (24). Similar results were obtained in our study where in the deficient group, the hemoglobin was 5.48gm/dl, 8.91gm/dl in sufficient group and 10.10gm/dl in adequate group. Mean hemoglobin in a study by patel NM was obtained to be 11.7±2g/dl in patients with vitamin D less than 10 ng/ml, 12.8±2 for vitamin D in between 10–30 ng/ml and 13.5±2 in vitamin D >30ng/ml (22). The lowest levels of $25(OHD)_3$ were associated with the highest prevalence of anemia. The independent association between vitaminD $[25(OH)D_3]$ and hemoglobin concentrations were consistent across stages III, IV and V of CKD.

Vitamin D deficiency could be one of the risk factors involved in anemia in CKD patients. Vitamin D, through its down-regulatory effects on inflammatory cytokines and hepcidin may favorably impact anemia, particularly anemia of inflammation. Vitamin D Deficiency is defined as <30ng/ml according to WHO (25). The prevalence of Vitamin D deficiency in ESRD patients is much more than in the other populations. Around 75% of these patients suffers from vitamin D deficiency. This could be due to decreased sun exposure, lower renal hydroxylase enzyme, and malnutrition. It is also known that vitamin D and EPO synergistically stimulates the bone marrow precursor cells, resulting in red blood cell formation. Additionally, vitamin D receptors are present in several tissues which are able to transform it into its active form. So, the level of vitamin D could be effective with the functioning of these tissues.

CONCLUSION

Anemia in Chronic kidney disease is due to reduced production of erythropoietin by interstitial fibroblasts. EPO cells also express calcitriol receptors which induces proliferation and maturation of erythroid progenitor cells. Vitamin D deficiency was prevalent in patients with ESRD and was found to be independently associated with anemia. Many studies have shown that the administration of Vitamin D and analogs has been associated with an improvement of anemia and reduction in EPO requirements. Therefore, measurement of serum $25(OH)D_3$ levels and appropriate vitamin D supplementation should be considered in anemic patients in CKD.

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