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Vitamin D deficiency as risk factor associated with anemia and outcome hemodialysis patients

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***Abstract*---**Background**:** Vitamin D deficiency and anemia are common problems that increased pathophysiology in the chronic kidney disease (CKD) undergoing hemodialysis (HD). This study was conducted to assess the association between vitamin D and anemia status in HD patients. Methods: This was a cross-sectional study of 65 HD patients and EPO therapy were enrolled; compared with 25 age matched healthy individuals as controls. The current study was investigated serum hepcidin, iron status was included serum ferritin and iron levels, anemia hematological indices such as RBC, Hb, MCV, and MCH, in addition to other clinical parameters of kidney function, and C-reactive protein (CRP) as inflammation markers were performed in both HD patients and controls. Results: The mean patient age was (45.65±13.34) years, with dialysis vintage of median (IQR) was (12 (3-36) month. serum hepcidin were highly significantly increase in HD patients than in the control group (622.3±139.6, and 465.16±80.31pg/ml, respectively p = 0.0001). serum hepcidin significantly associated with 37% anemia severity about (692.4±119.8) pg/ml more than patient with 49.2% of moderate about (605.3±117.7) pg/ml, (p=0.007) as compared with 13.8% of mild anemia groups (531.8±99.12) pg/ml, (p=0.001). negative significant correlation between Vt.D levels and age (r = -0.283, p= 0.022), but no correlated with BMI (r= 0.127, p=0.314). A negatively significant between Vt.D with dialysis vintage (r= -0.419, p=0.0001), Urea (r= - 0.422, p=0.0001), and creatinine (r= -0.491, p=0.0001), while its strong positively significant correlated with GFR (r= 0.800, p=0.0001), Ca (r= 0.339, p=0.0001), and serum iron (r= 0.592, p=0.0001), but no with ferritin (r= -0.063, p=0.616). Moreover, vitamin D a negative correlated with blood glucose (r= -0.489, p=0.0001), and CRP (r=--0.598, p=0.0001). The study concluded that Vt.D was associated with risk hemodialysis outcome and anemia severity in HD patients.

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***Keywords*---**Vitamin D, Deficiency, Anemia, Hemodialysis, CKD.

Introduction

Anemia is a frequent symptom of chronic kidney disease (CKD), and its incidence and severity are known to rise as renal function declines. Furthermore, anemia is linked to a variety of clinical symptoms and indicators, resulting in a worse quality of life and a higher risk of morbidity and death in these patients (Shimizu et al; 2014, Kim et al; 2016; Abass and Sharba 2020). Vitamin D (Vt.D) is an essential steroid hormone with properties extending beyond its classical role in bone-mineral disease. Vitamin D deficiency has been defined as 25(OH)D levels < 20 ng/ml and adequacy as levels ≥ 30 ng/ml (Ibrahim et al; 2021; Sharba et al., 2021). As a result, vitamin D deficiency in patients with CKD may increase the likelihood or severity of anemia. However, few research have focused on the impact of vitamin D on CKD-related anemia throughout the world to date. Vitamin D deficiency was found to be strongly and independently related with anemia in patients with CKD who did not require dialysis in previous studies utilizing data from the Study to Evaluate Early Kidney Disease and the Third National Health and Nutrition Examination Survey (Li et al; 2021). The main cause of the development of anemia in patients treated with regular hemodialysis is the deficiency of endogenous erythropoietin, and its main clinical consequences are: progressive decline in residual kidney function. Iron insufficiency, microinflammation, vitamin D deficiency, secondary hyperparathyroidism, vitamin C deficiency, and insufficient hemodialysis are the key risk factors for the development of resistance to the effects of erythropoietin. (Gilbertson et al; 2009, Stauffer and Fan, 2014; Sharba and Al-Zahid, 2016). The current study aimed to determine the association between vitamin D deficiency with anemia severity in hemodialysis patients.

Materials and Methods

Study design

The current cross-sectional study was performed from January 2022 to march 2022. Conducted 65 patients were ≥18 years of age and had a history of CKD recruited from the center kidney diseases at Al-Sadder Teaching Hospital in Al–Najaf City, Iraq, the only inclusion criterion was dialysis from first vintage to two times a week. The exclusion criteria were liver disease, all types of malignancy, kidney transplantation, receiving blood in the last 6 months, history of sustained heart disease, infection, inflammatory disease. The objectives for this investigation, as well as the informed consent form provided from all individuals, were approved by the hospital's institutional review board, and the study was conducted in accordance with the principles of the Helsinki Declaration. The patients were stopped iron supplementation intake for one weeks before the study. Before dialysis, blood samples were taken to avoid interactions between hemodialysis and hepcidin. Five ml of blood samples were drawn from Fasted participant, and put in tubes with anticoagulant and other jell tubes without any anticoagulant for carefully supernatant serum. By centrifugation at temperature

37 c^o for 10 minutes at 3000 rpm, serum was separated, and frizzed at -80 c^o. kidney function parameters, blood glucose, iron indicis (iron and ferritin), RBC indicis (RBCs, Hb, MCV, and MCH), C-reactive protein (CRP) by automated analysis device, and Vt. D was measured with ELISA according kit that supply from (Bioassay technology laboratory company).

Statistical analysis

All data were statistically analyzed with IBM SPSS 28 (SPSS Inc., Chicago, IL). the normal distribution used of Kolmogorov-Smirnov test and independent t-test between two groups, ANOVA test and post hoc for comparison among groups. Median (interquartile range) for continuous variables with non-normal distribution and Kruskal-Wallis test for among groups. Pearson's or Spearman Rho coefficient correlation tests between Vt.D with other studied parameters. Numerical data were expressed as mean ± standard deviation (SD), Nominal data reported by frequencies and percentage with used of chi-square test. The significant level was considered as p-value <0.05.

Results

Demographic and clinical characteristics of Hemodialysis (HD) patients.

The statistical analysis in the Table (1) indicated to 65 samples consisted of HD patients. the mean ages of the HD patients were (45.65±13.34), the distribution of age groups proportion of > 48 year was more than 33(50.8%) compared with group 33-47 year was 18(27.7%), and group 18-31 year was 14(21.5) %, (p=0.010). BMI were (26.88±4.82) kg/m^2, and There were 25(38.4%) patients with Overweight, and 20(30.8%) for each Normal weight and obesity, with non-significant (p=0.681) between these BMI classifications. median (IQR) dialysis vintage was (12 (3-36) month, they were proportion of first D.v. dialysis 11(16.9%), 25(38.5%) were ≤ 1 years, 24(36.9%) ≤ 5 years, and 5(7.7%) were dialysis > 5 years. In the current study, a significant difference (p=0.002) in anemia status proportion of moderate 32(49.2%) and severe anemia 24(37.0%) were more than mild anemia 9(13.8%). The Comorbidity of HD patients with hypertension 30(46.2%), Diabetes & Hypertension 21(32.3%), more than Diabetes 14(21.5%) no significant differences between themes (p=0.051). Furthermore, in the same table were parameters of the kidney function, mean serum Urea levels (173.54±51.23) mg/dl, and Creatinine (10.14±2.47) mg/dl, and GFR (14.52±10.35) ml/min/1.73 m^2, in HD patients. Mean level of Ca (7.08±1.49) mg/dl, PO (4.86±1.26) mg/dl. Means level of B. Glucose (244.47±61.3) mg/dl, AST (12.97±9.77) IU/L, and ALT (13.81±5.98) IU/L. Results of inflammation and iron status in HD patients indicated to means serum of CRP (6.06±1.70) mg/l, (52.25±7.35) mg/l, and Ferritin (310.35±103.45) ng/ml, but Vt.D (12.34±9.41) ng/ml. The results of the anemia status were showed in hematological parameters such as Hb (8.87±1.92) mg/dl, RBCs (3.39±0.55) 10^6/ml, and MCV (86.77±2.39) fL, While the mean of MCH was (31.23±1.89) pg.

Table 1: Demographic and clinical characteristics of Hemodialysis (HD) patients

Variables	HD patients n=65	p-value
Age (year) **18-32** **33-47** **> 48**	45.65±13.34 14(21.5%) 18(27.7%) 33(50.8%)	0.010 *
BMI (kg/m²) **Normal weight** **Over weight** **Obesity**	26.88±4.82 20(30.8%) 25(38.4%) 20(30.8%)	0.681
Dialysis vintage (month) **First D.v.** **≤ 1 years** **≤ 5 years** > 5 years	12 (3-36) # 11(16.9%) 25(38.5%) 24(36.9%) 5(7.7%)	0.0001 *
Vit. D (ng/ml) **Deficiency** **Insufficiency** **Sufficiency**	12.34±9.41 41(63.1%) 15(23.1%) 9(13.8%)	0.0001 *
Mild **Moderate** **Severe**	9 (13.8%) 32 (49.2%) 24 (37.0%)	0.002 *
Diabetes **Hypertension** **Diabetes &Hypertension**	30(46.2%) 14(21.5%) 21(32.3%)	0.051
Urea (mg/dl)	173.54±51.23	
Creatinine (mg/dl)	10.14±2.47	
GFR (ml/min/1.73 m²)	14.52±10.35	
Ca (mg/dl)	7.08±1.49	
PO (mg/dl)	4.86±1.26	
B. Glucose (mg/dl)	244.47±61.3	
AST (IU/L)	12.97±9.77	
ALT (IU/L)	13.81±5.98	
CRP (mg/l)	6.06±1.70	
Ferritin (ng/ml)	310.4±103.45	
Iron (mg/l)	68.03±11.22	
Hb (mg/dl)	8.87±1.92	
RBC (X10⁶/ ml)	3.39±0.55	
MCV (fL)	86.77±2.39	
MCH (pg)	31.23±1.89	

Values are expressed as mean ±SD, or # median (IQR) inter quarter range, nominal data are expressed as frequencies and percentage. Chi-Square test. D.v. Dialysis vintage**. N.A**: non applicated; **BMI**: body max index; **GFR**: glomerular filtration rate; **Ca**: calcium; **PO**: phosphor; AST: aspartate aminotransferase; **ALT**, alanine aminotransferase; **CRP**: C-reactive protein. **Vt.D**: vitamin D; **RBC:** red

blood corpuscular**; Hb**: hemoglobin; **MCV**: mean corpuscular volume; **MCH**: mean concentration hemoglobin.

Comparison of demographic and clinical Characteristics among Vt.D status in anemia HD patients

The demographic and clinical Characteristics were compared for each HD patients according Vt.D status that showed in the Table (2). The mean ages of 9 patients with Sufficiency were lower (39.6±15.25), and 15 with Insufficiency (42.67±15.52) than with 41 patients of Deficiency (48.07±11.68). The difference was not statistically significance (p=0.137). The results of BMI showed no significant difference among HD patients (p=0.184) when the three of Vt.D status compared Sufficiency (27.46±2.96), Insufficiency (28.7±4.16) and Deficiency (26.08±5.23) respectively. The Dialysis vintage in HD patients was a highly significant (p=0.137) increase in deficiency groups the median (IQR) of 36(12-48) month, compared with Insufficiency 8(2.0-12) month and more than in Sufficiency patients 1 (1.0-1.5) month, (p=0.0001). A significant difference between groups of Vt.D status indicated to increase means of serum urea 194.73±51.08, (p=0.0001), creatinine 11.26±2.26, (p=0.0001), and decrease of GFR 9.54±7.12, (p=0.0001) in HD patients with deficiency Vt.D as compared with Insufficiency (urea 139.39±30.3, creatinine 8.56±1.76, and GFR 19.8±8.12), and sufficiency patients (133.9±9.35, 7.74±0.75, and 28.78±9.27). A Significant decline in serum Ca levels (p=0.002), and increased in PO levels (p=0.001), and B. Glucose (p=0.017) were showed in patients with deficiency Vt.D as compared with Insufficiency and sufficiency patients. The AST and ALT have no significant difference (p=0.0756) and (p=0.925) respectively. Results of iron status showed that no significant differences in serum ferritin levels (p=0.258), but these were significant decrease in serum iron levels (p=0.0001) in deficiency Vt.D groups (64.16±10.64), and Insufficiency (71.02±8.33) as compared with sufficiency patients (80.69±6.88). Also, The CRP results showed a significance increase (p=0.031) in deficiency Vt.D (6.98±1.51), and Insufficiency (5.85±2.3) as compared with sufficiency patients (5.14±0.63) respectively. Furthermore, anemia status which involved of hematological tests indicated to significant fall in RBC (p=0.0001), Hb (p=0.0001), and MCH (p=0.020) while increase of MCV (p=0.003) in HD patients with deficiency Vt.D as compared with Insufficiency and sufficiency patients.

Serum Vt.D was associated with anemia status and dialysis vintage HD patients

Statistically analysis showed that HD patients with both severe anemia groups have significantly decrease in serum Vt.D levels were median (IQR) of 7.12(5.38-8.3), and moderate anemia groups were 9(8.0-14.3), when compared with groups of mild anemia 14(8.6-36.5) ng/ml, (p=0.0001), figure (1). In addition, serum Vt.D levels were significantly decrease at long time of dialysis vintage, median (IQR) of 5(4.5-6.8) ng/ml in dialysis vintage > 5 year, 7.8(6.37-8.9) ng/ml in <5 years, 9.9(7.7-14.5) ng/ml at <1year, as compared with 30(11.9-36) ng/ml at first dialysis vintage, (p=0.0001) (Figure 2).

Table 2: Effects of Vt. D status on demographic and clinical parameters in HD patients

Variables	Vt. D status (Mean±SD)			p-value
	Sufficiency n=9	Insufficiency n=15	Deficiency n=41	
Age (year)	39.6±15.25 a	42.67±15.52 a	48.07±11.68 a	0.137
BMI (kg/m²)	27.46±2.96 a	28.7±4.16 a	26.08±5.23 a	0.184
Dialysis vintage (month) #	1(1.0-1.5) c	8(2.0-12) b	36(12-48) a	0.0001
Urea (mg/dl)	133.9±9.35 b	139.39±30.3 b	194.73±51.08 a	0.0001
Creatinine (mg/dl)	7.74±0.75 b	8.56±1.76 b	11.26±2.26 a	0.0001
GFR (ml/min/1.73 m²)	28.78±9.27 a	19.8±8.12 b	9.54±7.12 c	0.0001
Ca (mg/dl)	7.69±1.39 a	8.03±1.04 a	6.61±1.46 b	0.002
PO (mg/dl)	4.28±1.4 b	4.05±1.16 b	5.29±1.07 a	0.001
B. Glucose (mg/dl)	199.7±63.6 b	231.03±46 a	259.2±61 a	0.017
AST (IU/L)	11.75±4.88 a	17.98±16.87 a	11.4±6.0 a	0.075
ALT (IU/L)	13.66±5.38 a	14.35±7.57 a	13.64±5.59 a	0.925
Ferritin (ng/ml)	288.2±75.1 a	348.3±113.3 a	301.33±103.8 a	0.258
Iron (mg/l)	80.69±6.88 a	71.02±8.33 b	64.16±10.64 b	0.0001
CRP (mg/l)	5.14±0.63 b	5.85±2.3 b	6.98±1.51 a	0.031
Vt. D (ng/ml)	31.15±9.36 a	13.15±3.08 b	7.92±4.58 c	0.0001
Hb (mg/dl)	10.59±1.44 a	9.69±1.51 b	8.06±1.92 c	0.0001
RBC (X10^6/ mm^3)	4.06±0.32 a	3.51±0.49 b	3.21±0.49 c	0.0001
MCV (fL)	84.57±1.58 b	86.36±2.59 a	87.41±2.17 a	0.003
MCH (pg)	32.51±1.22 a	31.71±1.76 a	30.77±1.91 b	0.020

Values are expressed as mean ±SD, or # median (IQR) inter quarter range and Kruskal-Wallis test, nominal data are expressed as frequencies and percentage. Chi-Square test. D.v. Dialysis vintage**. N.A**: non applicated; **BMI**: body max index; **GFR**: glomerular filtration rate; **Ca**: calcium; **PO**: phosphor; AST: aspartate aminotransferase; **ALT**, alanine aminotransferase; **CRP**: C-reactive protein. **Vt.D**: vitamin D; **RBC:** red blood corpuscular**; Hb**: hemoglobin; **MCV**: mean corpuscular volume; **MCH**: mean concentration hemoglobin

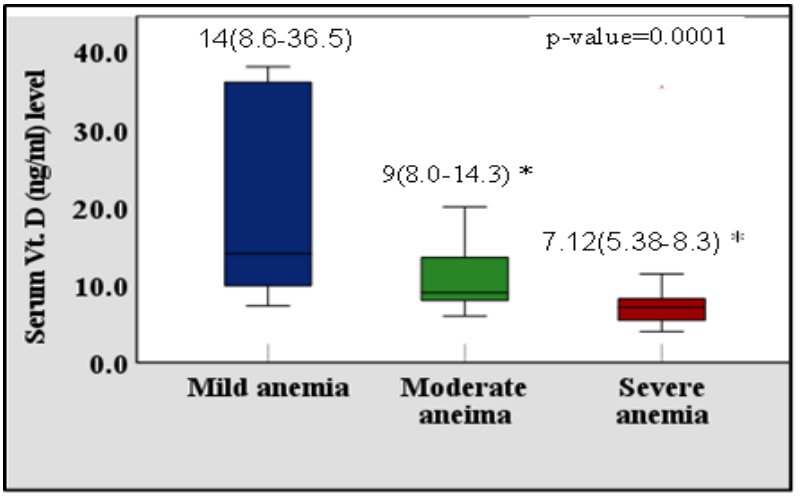

Figure 1: Serum Vt.D levels in HD patients according anemia status. Values are expressed median (IQR) inter quarter range, * significant differences as p-value <0.05.

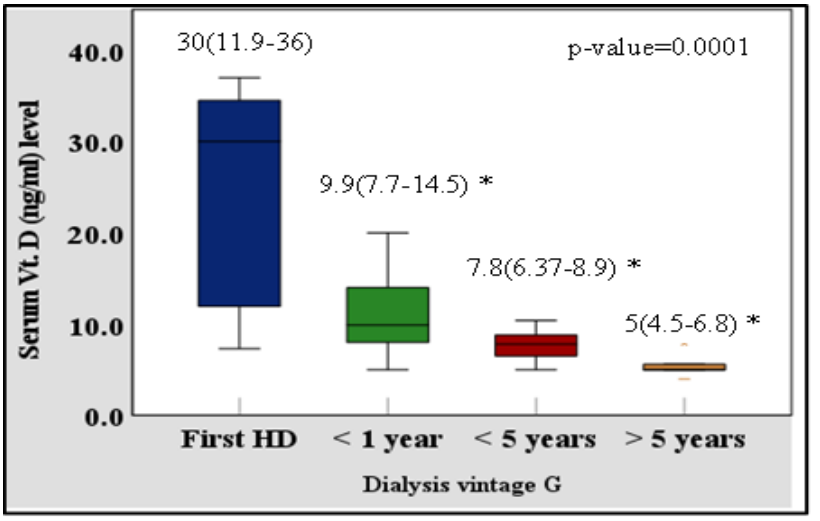

Figure 2. Serum Vt.D levels in HD patients according dialysis vintage. Values are expressed median (IQR) inter quarter range, * significant differences as p-value <0.05.

Correlation between Serum Vt.D levels with demographic and clinical parameters in HD patients

The correlation of serum Vt.D levels with demographic and clinical characteristics that studied in HD patients were observed negative significant correlation between Vt.D levels and age (r = -0.283, p= 0.022), but no correlated with BMI (r= 0.127, p=0.314). A negatively significant between Vt.D with dialysis vintage (r= -0.419, p=0.0001), Urea (r= - 0.422, p=0.0001), and creatinine (r= -0.491, p=0.0001), while its strong positively significant correlated with GFR (r= 0.800, p=0.0001), Ca (r= 0.339, p=0.0001), and serum iron (r= 0.592, p=0.0001), but no

with ferritin (r= -0.063, p=0.616). Moreover, vitamin D a negative correlated with blood glucose (r= -0.489, p=0.0001), and CRP (r=--0.598, p=0.0001), table (3).

Table 3: Correlation of Vt. D with demographic and clinical characteristics in HD patients.

Variables	Vit. D (ng/ml)	
	r	p-value
Age (year)	-0.283*	0.022
BMI (kg/m^2)	0.127	0.314
Dialysis vintage (month)	-0.419**	0.0001
Urea (mg/dl)	-0.422**	0.0001
Creatinine (mg/dl)	-0.491**	0.0001
GFR (ml/min/1.73 m²)	0.800**	0.0001
Ca (mg/dl)	0.339**	0.006
PO (mg/dl)	-0.330**	0.007
B. glucose (mg/dl)	-0.489**	0.0001
Ferritin (ng/ml)	-0.063	0.616
Iron (mg/l)	0.592**	0.0001
CRP (mg/l)	-0.598 **	0.0001

Correlation is significant * at p-value <0.05, ** p-value <0.01. *Significant correlation at p-value <0.05. BMI: body max index; GFR: glomerular filtration rate; CRP: C-reactive protein.

Discussion

The current study provided additional evidence of relationships between vitamin D deficiency and risk of hemodialysis. Vt.D deficiency is prevalent in patients with CKD receiving hemodialysis. The reason for deficiency of vitamin D in these patients is multifactorial; inactivity of patients undergoing replacement therapy and Regardless of whether patients have undergone dialysis, Vt.D deficiency is associated with effects related to frailty and sarcopenia in those with chronic kidney disease (CKD); such effects include low bone density (Pimentel et al; 2021), muscle strength and falls (Gunton and Girgis, 2018), and cognitive and dementia impairment (Chai et al; 2019). Moreover, VT.D deficiency has been many related to many infections, such as tuberculosis, seasonal influenza (Zisi et al; 2019, Grant et al; 2020), and novel COVID 2019, as well as increased mortality (Wang et al; 2022). In this study, most patients on HD were aged 18-65 years, and 46.2% had diabetes. However, most patients were equal proportion of obesity or overweight BMI, at the same time, Vt.D was not associated with BMI. Reported of Nitta, et al. (2019) indicated to that Dialysis patients had an average age of 68.75 years, and diabetic nephropathy has been the most frequent main condition among them (39.0%) according to a national survey conducted by the Japanese Society for Dialysis Therapy, these characteristics are really quite comparable to those we've seen in our patients (Table 1). The present finding confirmed positive associations between Vt.D deficiency (< 20 ng/ml) of mean levels (12.34±9.41 ng/ml), in among our hemodialysis patients by (63.1%) were showed related with most kidney function parameters urea, creatinine, calcium (ca), phosphorus (Po), GFR, and inflammation, Furthermore, these relationship with iron status

and anemia severity was higher than mild anemia. Also Vt.D was highly associated with progressed to have more prolonged dialysis vintage this outcomes agreement with many studied (Kara et al; 2019, Sah et al; 2019, Niculescu et al; 2021). But Vt.D deficiency not related with liver enzymes AST, and ALT, these agrees with (Nazzal, Z. A., Hamdan, Z. 2021). CKD is defined as the existence of kidney impairment and diminished function glomerular filtration rate (GFR) less than <60 mL/min/1.73 m2 or albumin excretion rate ≥ 30 mg/24 h] lasting greater than three months. Defining and staging chronic renal failure is contingent on assessing the GFR, and an estimate is provided by creatinine clearance. Serum creatinine, which is used to determine the creatinine clearance, is not a very sensitive indicator of renal disease and there are a number of limitations associated with obtaining an accurate measurement of the urine creatinine concentration (Tapper, M 2021). Vt.D synthesis depends on the bioavailability of the endogenously in the skin precursor cholecalciferol and the 25-hydroxylation by the liver. Endocrine problems in HD patients a possible explanation for some of these correlations (Muacevic et al; 2021, Christodoulou et al; 2021). Calcitriol deficiency is a crucial factor in secondary hyperparathyroidism development as 1,25 OH2 D3 deficiency induce parathyroid gland growth and increased parathyroid hormone (PTH) production through incapability to upregulate vitamin D receptor (VDR) expression by parathyroid cells (Yamada et al; 2013), The end result is elevated serum PTH and abnormal Ca and Po metabolism (Jacquillet and Unwin, 2019, Nazzal, et al; 2021). Our study confirmed that serum levels of Vt.D associated with severe anemia figure (1), which expressed by decrease RBC indicis and iron status. Many precipitating factors such as poor nutritional status, chronic illness, and inflammation) can be blamed for the relationship between Vt.D deficiency and anemia, previous clinical studies have suggested that vitamin D supplementation can enhance the response to erythropoiesis-stimulating agents (Obi et al; 2020). In several studies vitamin D has been reported to have a direct stimulatory effect on erythroid precursor cells in CKD patients. The burst-forming unit-erythroid (BFU-E) analyze exposed that combined decrease doses of erythropoietin and vitamin D significantly increased proliferation of mononuclear cells isolated from the peripheral blood of patients with CKD compared to low-dose erythropoietin alone (Altemose et al; 2018). Furthermore, high-dose vitamin D increased BFU-E proliferation, but this was not detected in cells obtained from healthy people. These results suggest that vitamin D has a direct impact on the proliferation of erythroid precursors in CKD patients but not in patients with normal kidney function. (Kim et al; 2016). The main cause of the development of anemia in patients treated with regular hemodialysis is the deficiency of endogenous erythropoietin, and its main clinical consequences are: progressive decline in residual kidney function. Iron insufficiency, microinflammation, vitamin D deficiency, secondary hyperparathyroidism, vitamin C deficiency, and insufficient hemodialysis are the key risk factors for the development of resistance to the effects of erythropoietin. (Gilbertson et al; 2009, Stauffer and Fan, 2014). hepcidin, which is a key regulator of circulating iron absorption, has been found to be involved in the etiology of anemia in HD patients (Hong et al; 2022). Its concentrations were demonstrated to be influenced by inflammation, HD patients with increased CRP levels have been shown to have decreased iron absorption than patients with lower CRP levels Iron metabolism, Transferrin saturation (TSAT) and ferritin have typically been utilized as serum iron markers, and

inflammation cusses increased hepcidin has recently been developed as another factor leading to anemia in HD patients (Gluba-Brzózka et al; 2020). Serum vitamin D concentration and Hb concentration in patients with end-stage renal disease, and vitamin D was shown to be an independent risk factor for anaemia in such patients. In addition, Sonkar et al. (2019) showed that patients with CKD and low Hb concentrations had higher circulating PTH concentrations, and noted a positive correlation between their vitamin D and Hb concentrations. These results suggest that a lack of vitamin D and secondary hyperparathyroidism may be closely associated with renal anaemia. Moreover, Vitamin D is associated with anaemia in patients with CKD. A deficiency of vitamin D may increase the risk of anaemia. (Li et al; 2021).

Conclusions

Based on our findings of the current study concluded that serum vitamin D deficiency risk is associated with hemodialysis patients as the majority had anemia severity.

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