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Research Article

Decreased 25-Hydroxyvitamin D Level Is Linked to Anemia in Peritoneal Dialysis Patients

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Abstract

Background: 25-Hydroxyvitamin D (25(OH)D) deficiency is the most common complication of kidney disease. Previous studies have suggested that 25(OH)D deficiency is involved in the pathogenesis of anemia in kidney disease subjects not requiring dialysis. However, these associations have not been investigated in peritoneal dialysis (PD) patients.

Objectives: The aim of this study was to elucidate the prospective relationship between 25-Hydroxyvitamin D insufficiency and anemia in PD Patients.

Materials and Methods: In a cross-sectional study, 80 PD participants were included. Participants were divided into two groups based on baseline 25(OH)D3 concentrations: group 1, 25(OH)D3 levels <10 ng/mL; and group 2, 25(OH)D3 levels ≥ 10 ng/mL. We recorded basic data of subjects. Peripheral blood samples were collected to determine the level of 25(OH)D and hepcidin by the competitive ELISA method.

Results: Pearson's correlation analysis and multivariate linear regression analysis showed that hemoglobin concentration was positively correlated with serum 25(OH)D3 level, $p<0.01$). Even after adjusting for potential risk factors for anemia, serum 25(OH)D were found to be still associated with anemia ($\beta=1.264$; 95% CI=0.992-1.612, $P=0.048$). Meanwhile, Pearson's correlation analysis revealed that serum 25(OH)D3 level negatively affect the level of Hepcidin and hs-CRP ($p<0.001$). We also observed that Hepcidin and hs-CRP negatively regulates Hb level ($p<0.001$).

Conclusions: These findings indicate that 25(OH)D insufficiency was significantly associated with anemia in patients with PD, which, at least in part, was related with the hepcidin level and inflammation.

Keywords: 25-Hydroxyvitamin D; Hepcidin; Anemia; Peritoneal Dialysis; Inflammation

1. Introduction

Anemia is a common complication among patients with peritoneal dialysis, which is associated with adverse outcomes, including cardiovascular disease, increased hospitalization rates, and all-cause mortality [1, 2]. Generally, it is thought that the primary causes of anemia include low erythropoietin levels, iron deficiency, chronic inflammation, and malnutrition. Moreover, recent studies have suggested that vitamin D deficiency is involved in the prevalence of anemia in kidney disease subjects not requiring dialysis [3] and in patients on maintenance hemodialysis [4]. However, the association between vitamin D deficiency and anemia in peritoneal dialysis patients is still elusive. Vitamin D deficiency is the most common complication in chronic kidney disease (CKD) [5]. Although previously studies on vitamin D deficiency in CKD focused on secondary hyperparathyroidism and skeletal dysfunction [6], more and more evidence has shown that treatment with vitamin D compounds appear to improve the anemia in hemodialysis patients [4, 7-9], and the level of 25(OH)D might be particularly important in vitamin D3 supplementation [10]. It is interesting that 25(OH)D deficiency is associated with hemoglobin levels in CKD patients [11]. However, the relationship between 25(OH)D deficiency and anemia has not been extensively elucidated in PD patients. In addition, a few studies have shown that 25(OH)D deficiency causes interventricular septal hypertrophy [12], predicts the risk for peritoneal dialysis-associated peritonitis [13], and is related with metabolic syndrome in PD [14]. In the general population, 25(OH)D deficiency had been shown to be associated with levels of pro-inflammatory cytokines. Therefore, we investigated cross-sectional associations among serum 25(OH)D levels, inflammatory markers, iron status, and hemoglobin concentration in 80 PD patients to test the hypothesis that: (1) 25(OH)D level affected anemia in PD patients, (2) 25(OH)D insufficient increased the level of C-reactive protein (CRP) and hepcidin, and (3) higher levels of CRP and hepcidin may affect anemia.

2. Materials and Methods

2.1 Study design and demographic data

This study is a cross-sectional study of participants who were on PD at a single dialysis unit associated with the Second Affiliated Hospital, Harbin Medical University, Harbin, China. 80 participants from January 2016 to January 2018 were enrolled in the study. Each PD patient received conventional glucose-based, lactate-buffered PD solutions (Ultrabag, Baxter Healthcare, Guangzhou, China). All patients in our study could visit a physician at least once every 3 months. We recorded general information on age, gender, body weight, height, duration of dialysis, and PD prescription for each patient. Dialysis adequacy was evaluated with total Kt/V. The ethics committees of the hospitals approved the study. Exclusion criteria were: age ≤ 18 years, duration of PD <3 months, any cardiovascular event, liver dysfunction, thrombosis, systemic or local infection within 3 months of peritonitis, autoimmune disease, uncontrolled hypertension (above 160/90 mmHg), parathyroidectomy, surgery, and cancer. All patients provided written informed consent for their information to be

collected. Primary diseases: glomerulonephritis (n=44), chronic interstitial nephritis (n=14), diabetic nephropathy (n=9), hypertensive nephropathy (n=11), polycystic kidney disease (n=1), and obstructive nephropathy (n=1).

2.2 Variables and data sources

Participants were requested to stop taking oral vitamin D supplements and oral iron supplement at least 3 days before giving venous blood samples. After overnight fasting while continuing PD therapy, venous blood samples were collected in all participants, then centrifuged, and the supernatant was stored at -80°C before being assayed. Baseline laboratory parameters, including serum creatinine, calcium, phosphorus, albumin, hemoglobin, iron, total iron binding capacity (TIBC), ferritin, parathyroid hormone (iPTH), CRP, and Kt/V were determined by standard commercial assays in the clinical laboratory and biochemistry department. All samples for 25(OH)D (Zcibio, China) and hepcidin (Elabscience, China) were measured by ELISA. The assay was performed strictly according to the instructions.

2.3 Statistical methods

Continuous variables are expressed as mean±standard deviation and categorical variables are presented as a number. The patients were divided into two groups based on serum 25(OH)D3 concentrations (<10 ng/mL and ≥ 10 ng/mL). The differences between the two groups were determined using Student's t test and the chi-square test for categorical variables. Correlation analysis was assessed using Pearson's correlation analysis. Multivariate linear regression analyses were performed to determine the independent correlates of anemia or 25(OH)D3. A logistic regression analysis was used to estimate odds ratios (OR) and to identify independent risk factors for anemia or 25(OH)D3. All probabilities were two-tailed and the level of significance was set at 0.05. Statistical analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1 Clinical characteristics and biochemical parameters

Basal clinical characteristics of the studied groups are presented in Table 1. The mean age was 51 ± 12.9 years, and there were 44 males and 36 females. The mean serum 25(OH)D3 concentration was 12.29 ± 13.37 ng/mL, while the mean 25(OH)D3 level was 21.37 ± 15.99 ng/mL in group 1 and 5.025 ± 2.814 ng/mL in group 2. As seen in Table 1, there were statistical significance in the level of BUN, albumin, hemoglobin, iPTH, hepcidin, and hs-CRP between group 1 and group 2. However, there were no significant differences in age, sex, BMI, duration of dialysis, serum iron, TIBC, ferritin, creatinine, phosphate, calcium, and total kt/v between the two groups.

Variable	**Total**	**Group1**	**Group2**	***p* value**
		25(OH)D3 ≥ 10 ng/mL	**25(OH)D3 <10 ng/mL**	
n (%)	80	35 (43.7%)	45 (56.2%)	-
Demographic data				
Age (years)	51 ± 12.9	48.6 ± 12.47	52.87 ± 13.06	0.1433
Male/Female	44/36	20/15	24/21	0.8

BMI	22.78 ± 2.671	22.73 ± 3.8	22.82 ± 3.611	0.913
Duration of dialysis (months)	19.93 ± 12.17	20.00 ± 12.156	19.87 ± 12	0.916
Biochemical data				
25(OH)D3 (ng/mL)	12.29 ± 13.37	21.37 ± 15.99	5.025 ± 2.814	0.0001
BUN	18.88 ± 6.455	16.82 ± 6.615	20.48 ± 5.919	0.0112
Creatinine (µmol/L)	890.7 ± 211.5	873.1 ± 204.3	904.5 ± 218.3	0.5139
Albumin (g/L)	38.37 ± 4.264	39.69 ± 3,912	37.34 ± 4.224	0.0138
Hemoglobin (g/L)	101.2 ± 17.67	114.6 ± 13.08	90.8 ± 13.25	0.0001
PTH (pg/mL)	355.2 ± 243.1	243.0 ± 169.3	442.4 ± 257.3	0.0002
Phosphate (mg/dL)	1.882 ± 0.525	1.775 ± 0.4618	1.966 ± 0.5602	0.1062
Calcium (mg/dL)	2.172 ± 0.3172	2.223 ± 0.3019	2.132 ± 0.3264	0.2341
Serum iron (µg/dL)	12.44 ± 4.941	12.5 ± 5.285	12.39 ± 4.717	0.9230
TIBC (µg/dL)	43.92 ± 7.031	44.85 ± 6.984	43.2 ± 7.062	0.3026
Hepcidin (ng/mL)	4.325 ± 3.754	1.982 ± 1.286	6.147 ± 4.032	0.0001
Ferritin (ng/mL)	190.3 ± 167	150.6 ± 168.8	221.2 ± 160.7	0.0605
hs-CRP (mg/L）	3.113 ± 3.647	1.66 ± 1.443	4.242 ± 4.392	0.0013
Total Kt/v	1.906 ± 0.8451	2.081 ± 0.9115	1.707 ± 0.8332	0.1177
Medications				
Vitamin D supplement	73 (91.25%)	31 (88.57%)	42 (93.33%)	>0.1
Oral iron supplement	62 (77.5%)	29 (82.85%)	33 (73.33%)	>0.1

Table 1: Baseline Characteristics of Patients with PD According to 25(OH)D3 Levels.

3.2 Association between biochemical parameters and anemia

According to the criteria for anemia (The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guidelines recommended that hemoglobin targets should be in the range of (100-115 g/L) [15]. In this study, 42.5% of participants were anemic. As seen in Table 2, Pearson's correlation analysis show that Hb level positively correlated with albumin and total kt/v ($p<0.05$). In contrast, the level of BUN, iPTH, Phosphorus, Hepcidin and hs-CRP negatively affects Hb level ($p<0.05$). Multivariate linear regression analysis (Table 3) revealed that Hb concentration was significantly correlated with Hepcidin ($\beta=-0.226$, $p=0.024$), hs-CRP ($\beta=-0.281$, $p=0.003$), total kt/v ($\beta=0.281$, $p=0.020$). These results showed that inflammation, Hepcidin, and dialysis adequacy affect anemia developing in PD patients.

Variable	**25(OH)D3**		**Hemoglobin**		**CRP**		**Hepcidin**	
	r	**p**	**r**	**p**	**r**	**p**	**r**	**p**
Age (years)	0.01328	0.9070	-0.1940	0.0864	-0.1228	0.2778	0.0252	0.8238

BMI (kg/m2)	0.01479	0.8964	0.05099	0.6533	-0.2263	0.0435	0.0160	0.8875
Duration of dialysis (months)	0.3117	0.0049	0.0052	0.9631	0.0318	0.7789	0.0842	0.4576
Hemoglobin (g/L)	0.4965	0.0001	-	-	-	-	-	-
BUN (mmol/L)	-0.3077	0.0055	-0.3289	0.0029	0.1999	0.0755	0.1556	0.1683
Creatinine (µmol/L)	-0.1387	0.2198	-0.1472	0.1927	-0.0647	0.5682	0.0529	0.6406
Albumin (g/L)	0.3080	0.0054	0.5379	0.0001	-0.1897	0.0918	-0.2786	0.0123
PTH (pg/L)	-0.3748	0.0006	-0.3511	0.0014	0.4690	0.0001	0.2113	0.0600
Calcium (mol/L)	0.2432	0.0297	0.1249	0.2696	-0.1582	0.1611	0.0414	0.7150
Phosphorus (mol/L)	-0.2647	0.0177	-0.3425	0.0019	0.3211	0.0037	0.2039	0.0697
Iron (µmol/L)	-0.01791	0.8747	0.0072	0.9491	-0.05337	0.5382	-0.0994	0.3804
TIBC (µmmol/L)	0.1238	0.2738	0.1978	0.0786	-0.09063	0.4240	-0.1670	0.1388
Ferritin (ng/mL)	-0.1914	0.0890	-0.2897	0.0091	0.02534	0.8235	0.0628	0.5798
Hepcidin (ng/mL)	-0.4343	0.0001	-0.4386	0.0001	0.2134	0.0474	-	-
hs-CRP (mg/L)	-0.2673	0.0165	-0.4001	0.0002	-	-	-	-
Total Kt/v	0.2471	0.0292	0.3693	0.0009	-0.1320	0.2493	-0.1702	0.1363

Table 2: Association between biochemical parameters.

Variable	**β**	**t**	**p**
Age (years)	-0.177	-1.921	0.059
Iron (µmol/L)	-0.003	-0.036	0.972
TIBC (µmmol/L)	0.007	0.071	0.943
Ferritin (ng/mL)	-0.152	-1.482	0.143
Hepcidin (ng/mL)	-0.226	-2.315	0.024
hs-CRP (mg/L)	-0.281	-3.093	0.003
25(OH)D3 (ng/mL)	0.241	2.382	0.020
Total Kt/v	0.281	2.382	0.020

Table 3: Multivariate linear regression analysis the association between Hemoglobin and Biochemical.

3.3 Association between serum 25(OH)D level and anemia

Pearson's correlation analysis (Table 2) revealed that Hb level positively correlated with 25(OH)D3($r=0.4965$, $p<0.001$), and multivariate linear regression analysis (Table 2) also showed the same result ($\beta=0.241$; $p=0.02$). After adjusting for age, Duration of dialysis, iPTH, BUN, Creatinine, Calcium, Hepcidin, Total Kt/v, phosphate, hs-CRP, ferritin, serum iron, TIBC, TSAT, Table 4 showed that serum 25(OH)D was found to be still associated with anemia ($\beta=1.264$; 95% CI= 0.992-1.612, $P=0.048$). Take these into together, serum 25(OH)D level associated with anemia in PD patients.

Variable	OR (95% CI)	P value
Age (years)	0.995 (0.917-1.080)	0.905
Duration of dialysis (months)	1.080 (0.995-1.173)	0.066
BUN (mmol/L)	1.001 (0.844-1.187)	0.989
Creatinine (μmol/L)	0.996 (0.991-1.000)	0.079
Albumin (g/L)	1.479 (1.124-1.948)	0.005**
Calcium (mol/L)	0.281 (0.010-8.122)	0.460
Phosphorus (mol/L)	0.469 (0.068-3.236)	0.442
Iron (μmol/L)	0.883 (0.731-1.067)	0.198
TIBC (μmmol/L)	0.957 (0.834-1.099)	0.537
Ferritin (ng/mL)	0.997 (0.991-1.002)	0.207
PTH (pg/L)	1.001 (0.996-1.006)	0.791
hs-CRP (mg/L)	0.828 (0.616-1.113)	0.212
25(OH)D3 (ng/mL)	1.264 (0.992-1.612)	0.048*
Hepcidin (ng/mL)	0.956 (0.773-1.181)	0.674
Total Kt/v	1.453 (0.313-6.737)	0.633

Table 4: Risk Factors for Developing Anemia.

3.4 Association between serum 25(OH)D level and biochemical parameters

As seen in Table 2, pearson's correlation analysis revealed that serum 25(OH)D level significantly correlated with duration of dialysis (r=0.3117, p=0.0049), calcium (r=0.2432, p=0.0297), albumin (r=0.3080, p=0.0054), Hepcidin (r=-0.4343, p=0.0001), hs-CRP (r=-0.2673, p=0.0165), total kt/v (r=0.2471, p=0.0292). However, multivariate linear regression analysis (Table 5) showed that serum 25(OH)D only associated with Hepcidin (β=-0.320, p=0.002). These results indicated that serum 25(OH)D level negatively correlated with Hepcidin.

Variable	β	t	p
Age (years)	0.020	0.185	0.854
Calcium (mol/L)	0.239	2.461	0.016
Phosphorus (mol/L)	-0.017	-0.157	0.875
Ferritin (ng/mL)	-0.186	-1.828	0.072
Hepcidin (ng/mL)	-0.320	-3.145	0.002
hs-CRP (mg/L)	0.011	0.103	0.918
Albumin (g/L)	0.154	1.517	0.134

Total Kt/v	0.062	0.609	0.545

Table 5: Multivariate linear regression analysis the association between serum 25(OH)D and Biochemical Parameters.

4. Discussion

In this cross-sectional study, our results showed that 25(OH)D insufficiency was prevalent in PD patients and the proportion of 25(OH)D insufficiency(25(OH)D concentration above 30 ng/mL in 5cases) was 93.75%, which is consistent with a previous study [16]. The possible causes of 25(OH)D deficiency include chronic pathogenesis of renal failure, lack of intake, vitamin D loss from the peritoneal effluent [16]. The prevalence of vitamin D insufficiency may also correlate with the northern location of our study area, as well as and inadequate amount of sun exposure [17, 18] and dietary habits.

It is generally accepted that anemia is a common complication in PD patients, and its pathogenesis is multifactorial. The primary causes of anemia in PD patients, just as in CKD, include low erythropoietin levels, iron and protein deficiency, and decreased half-life of circulating red blood cells. Moreover, malnutrition, inflammation, and atherosclerosis are additional causes of anemia. As described by previous reports, our results also indicated that albumin, hs-CRP, phosphorus, iPTH, BUN, hepcidin, and dialysis adequacy influenced hemoglobin concentration in PD patients. Interesting, accumulating evidence shows that 25(OH)D deficiency is associated with a reduction in circulating levels of hemoglobin concentrations in the non-uremic population [11], and a few studies have shown that treatment with vitamin D compounds appeared to improve anemia in hemodialysis patients [7, 8]. In the present cross-sectional study, our results also showed a stepwise increase in hemoglobin concentration with increasing 25(OH)D levels ($p<0.01$). Previously, a few reports demonstrated that 25(OH)D suppresses pro-inflammatory cytokines and increases anti-inflammatory cytokines [10], and treatment with vitamin D3 significantly decreased levels of the pro-inflammatory cytokine TNF-α and significantly increased levels of the anti-inflammatory cytokine interleukin-10 in a study of healthy non-CKD patients [19]. However, we did not detect the level of TNF-α and anti-inflammatory cytokines. Fortunately, a previous study showed that CRP is the most generally used acute-phase protein and represents the degree of inflammation [20]. In this study, Pearson's correlation analysis and multivariate linear regression analysis a revealed that Hb concentration was also negatively correlated with hs-CRP and Pearson's correlation analysis showed that serum 25(OH)D level significantly correlated with hs-CRP ($r=-0.2673$, $p=0.0165$). When these former studies are considered in the context of the present findings, it is intriguing to speculate that 25(OH)D level may affect hemoglobin levels, at least in part, through its regulation of inflammatory marker. This speculation is also supported by a report that in PD patients, vitamin D supplementation in vitro and in vivo promotes innate immune responses that may enhance macrophage antibacterial responses and prevent infection-related complications [21], and 25(OH)D deficiency increased levels of inflammatory factor and results in a decreased response to erythropoietin [22].

More recently, a report has shown that 25(OH)D can suppress the expression of an antibacterial protein (hepcidin) [23] in dialysis patients. Hepcidin, a recently discovered small, cysteine-rich cationic peptide hormone produced in the liver, is the key regulator of iron homeostasis [24], and is regulated in response to anemia, hypoxia, and inflammation [25]. Just as in

hemodialysis patients [26], our results show that serum hepcidin was markedly increased in PD patients and was inversely associated with hemoglobin level. A possible mechanism is that increased hepcidin was involved in elimination of hepcidin from the kidney [27] and endogenous erythropoietin deficiency [25]. We also found that increased hepcidin levels were inversely related with 25(OH)D levels, supporting a previous report that disorders of mineral metabolism may promote increased hepcidin secretion in CKD not yet requiring dialysis [28]. The mechanism may involve direct transcriptional suppression of hepcidin gene expression mediated by1,25-dihydroxyvitamin D binding to the vitamin D receptor, caused by the decrease in hepcidin mRNA levels. Previous studies indicated that 25(OH)D-induced suppression of hepcidin is associated with changes in ferritin expression, and 25(OH)D is a potent regulator of the hepcidin-ferroportin axis in humans [23], which suppressed intracellular iron transport and then cause the anemia developing [29]. However, in our study there was no significant correlation between hepcidin, and serum iron and ferritin, which was inconsistent with a previously published paper [30], which was perhaps due to a small sample. Take these results together, we speculated that 25(OH)D insufficiency may promote hepcidin secretion, which impede utilization of iron, and result in the development of anemia in PD patients. If so, supplementary vitamin D could be a novel method for decreasing hepcidin levels and thereby improving anemia in PD patients.

Nevertheless, a few limitations in the current study should be noted. First, the cross-sectional design makes it difficult to establish a causal relationship between vitamin D deficiency and anemia. Second, this was a single-center study and the sample in our study was not large enough, so additional studies with larger numbers of participants are needed to further establish the potential relationships between vitamin D deficiency and anemia. In addition, all participants in this study residents of northeastern China, which may affect generalizability of the results to other regions because the prevalence of 25(OH)D deficiency varies with latitude [18].

In summary, 25(OH)D insufficient and anemia are a common problem in PD patients. Our study has shown that lower 25(OH)D levels affect the hemoglobin level, which may be involved in hepcidin and inflammation in PD patients. Future studies should be designed for cohort study and increase the number of samples, and regional issues should be considered.

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Author Contributions

Fanwu Kong and Yeping Ren wrote the main manuscript text; Hongda Li, Wei Zhang, Baoyun Xia, Guojian Liu and Shijian Liu collected data; Hongda Li and Xiaowen Kang detected samples; Xiaowen Kang and Tianrong Ji analyzed the data; and Yeping Ren and Fanwu Kong conceived and designed the experiments. All authors reviewed the manuscript.

Competing Interests

The authors declare that they have no conflicts of interests.

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