Association between vitamin D deficiency and anemia in patients with end-stage renal disease

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Association between vitamin D deficiency and anemia in patients with end-stage renal disease

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ABSTRACT

Association between vitamin D deficiency and anemia in patients with end-stage renal disease

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Background Despite new treatment strategies, anemia remains the most prevalent complication in patients with end-stage renal disease. We investigated whether 25-hydroxyvitamin D deficiency is associated with anemia in end-stage renal disease patients.

Methods We reviewed the medical records of 410 end-stage renal disease patients who had undergone renal transplantation at Yonsei University Health System, who had 25-hydroxyvitamin D levels measured at renal transplantation. Patients were divided into group 1 (25-hydroxyvitamin D levels < 10 ng/ml) and group 2 (25-hydroxyvitamin D levels ≥ 10 ng/ml).

Results Multivariate linear regression analysis indicated an independent association between serum 25-hydroxyvitamin D and hemoglobin levels, after adjusting age, sex, logarithm (base 10) intact parathyroid hormone, phosphate, alkaline phosphatase, logarithm (base 10) high-sensitivity C-reactive protein, ferritin levels, and erythrocyte-stimulating agent dose ($\beta = 0.035$; $p = 0.039$). Odds ratio for developing anemia (hemoglobin level < 10 g/dl) showed that group 1 had a higher risk (Odds ratio = 3.283; confidence interval, 1.040–10.362; $p = 0.043$) for anemia than group 2, after adjusting for age, sex, log intact parathyroid hormone, phosphate, alkaline phosphatase, logarithm (base 10) high-sensitivity C-reactive protein, ferritin levels, and erythrocyte-stimulating agent use.

Conclusion 25-hydroxyvitamin D deficiency significantly associated with anemia in patients with end-stage renal disease patients. Randomized controlled trials are needed to determine if vitamin D supplementation can improve anemia in these patients.

Key words: vitamin D deficiency; 25-hydroxyvitamin D; anemia; end-stage renal disease; chronic kidney disease

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I. INTRODUCTION

Anemia is a common finding in patients with chronic kidney disease (CKD), and its prevalence and severity are 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.[1] Recently, accumulating evidence indicates that vitamin D has pleiotropic effects in various organ systems based on the distribution of vitamin D receptors in the whole body.[2] In addition to its well-known effect 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.[3] In fact, previous studies using the data of the Study to Evaluate Early Kidney Disease (SEEK) and the Third National Health and Nutrition Examination Survey (NHANES III) showed that vitamin deficiency was significantly and independently associated with anemia in patients with CKD not requiring dialysis.[4,5] However, the relationship between serum 25-hydroxyvitamin D [25(OH)D3] and hemoglobin (Hb) concentrations has not been extensively explored in patients with end-stage renal disease (ESRD). In this study, we attempted to elucidate the correlation of 25(OH)D3 with anemia in relatively healthy patients with ESRD who were admitted to the hospital for renal transplantation (RTx). Moreover, the independent impact of 25(OH)D3 on

anemia was clarified in these patients.

II. MATERIALS AND METHODS

Study population

We reviewed the medical records of 423 patients with ESRD who had undergone RTx at Yonsei University Health System in Seoul, Korea (latitude: 37.5°N; average annual sunshine: 5.8 hours *per* day) between April 2002 and December 2008 and whose 25(OH)D3 levels were measured at the time of RTx. Among these patients, 13 were excluded for being aged < 18 years (n = 6) or > 70 years (n = 7). Thus, the final analysis involved 410 RTx patients. All participants were from an ethnically homogeneous Korean population.

Data collection

Although 1,25-dihydroxyvitamin D is the active form of vitamin D, its half-life is only 4–6 hrs in the circulation. In the clinical field, therefore, 25(OH)D3 is regarded as the best index to assess vitamin D status because of its long half-life of approximately 3 weeks.[6] The serum 25(OH)D3 concentrations were determined at the time of RTx by a radioimmunoassay method using the 25-HYDROXYVITAMIN D ^{125}I RIA KIT (68100E) (DiaSorin Inc., Stillwater, MN, USA).[7] According to the opinion of most experts, vitamin D deficiency is defined as serum 25(OH)D3 levels < 10 ng/ml (25 nmol/l), vitamin D insufficiency as 25(OH)D3 levels 10–29 ng/ml (25–72 nmol/l), and vitamin D sufficiency as 25(OH)D3 levels ≥ 30 ng/ml (73 nmol/l).[6, 8-13] Since there were no patients with vitamin D sufficiency, the patients were divided into two groups for analysis: group 1, 25(OH)D3 < 10 ng/ml and group 2, 25(OH)D3 ≥ 10 ng/ml. Demographic and clinical data at the time of RTx, including age, sex, dialysis modality before RTx, duration of dialysis, comorbidities, season at the time of RTx, and erythrocyte-stimulating agent (ESA) dose, were recorded. To further study the association between 25(OH)D3 levels and ESA requirements,

the ESA dose/Hb index was calculated by dividing the monthly ESA dose (units) by Hb concentration. The results of the following biochemical laboratory tests were also collected: Hb, intact parathyroid hormone (iPTH), serum iron, total iron-binding capacity (TIBC), transferrin saturation (TSAT), ferritin, alkaline phosphatase (ALP), serum phosphate, calcium, albumin, estimated glomerular filtration rate (eGFR), and high-sensitivity C-reactive protein (hs-CRP) levels.

Statistical analysis

Statistical analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation or median ± interquartile range for skewed data. The Kolmogorov-Smirnov test was used to analyze the normality of the distribution of measured parameters, and categorical variables were presented as a number (percentage). 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 by the Student's t test or Mann-Whitney U test for continuous variables and the X^2-method for categorical variables. The relationship between Hb and 25(OH)D3 levels was assessed using Pearson's correlation analysis. The independent association between 25(OH)D3 and Hb levels was evaluated using a multivariate linear regression analysis. A logistic regression analysis was used to estimate odds ratios (ORs) and to identify independent risk factors for anemia. The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guidelines (2012) recommended that Hb targets should be in the range of 10.0–11.5 g/dl, regardless of whether the patients were receiving dialysis.[13] Therefore, we defined anemia as a Hb level < 10 g/dl. In all cases, a p-value < 0.05 was considered statistically significant.

III. RESULTS

Baseline characteristics

Among a total of 410 patients who had undergone RTx, 171 (41.7%) were vitamin D deficient, 239 (58.7%) were vitamin D insufficient, and no patients had normal serum 25(OH)D3 concentrations. Since no patients had normal vitamin D levels, the patients were divided into only two groups: patients with vitamin D deficiency (group 1) or without vitamin D deficiency (group 2). Demographic, clinical, and biochemical data are shown in Table 1. The mean age was 40.7 ± 11.4 years, and 262 patients (63.9%) were male. The mean serum 25(OH)D3 concentration was 11.1 ± 6.4 ng/ml, while the mean 25(OH)D3 level was 6.5 ± 1.8 ng/ml in group 1 and 17.2 ± 5.6 ng/ml in group 2. There were no differences in age, dialysis modality, season at the time of RTx, and comorbidities between the two groups. However, the following factors were significantly different between the two groups. Group 2 had a higher proportion of men than group 1 (69.9%; $p = 0.003$). The proportion of patients who met the criteria for anemia (60.2%; $p < 0.001$) and ESA use (53.8%; $p = 0.013$) was significantly higher in group 1. Moreover, the monthly ESA dose was significantly higher in group 1 (20656.2 ± 17627.7; $p = 0.003$). As seen in Table 1, serum phosphate, calcium, and albumin concentrations were significantly lower in group 1 than in group 2. In contrast, there were no significant differences in serum levels of iPTH, serum iron, TIBC, TSAT, ferritin, ALP, eGFR, and hs-CRP.

Table 1. Baseline clinical characteristics of patients according to 25-hydroxyvitamin D levels

Variable	Total	Group 1 25(OH)D3 < 10 ng/ml	Group 2 25(OH)D3 ≥ 10ng/ml	p-value §
n (%)	410	171 (41.7%)	239 (58.7%)	
Demographic data				
Age (years)	40.7±11.4	40.8±10.5	41.3±11.3	0.662
Male sex, n (%)	262 (63.9%)	95 (55.5%)	167 (69.9%)	0.003
Anemia (Hb < 10g/dl)	175(42.7%)	103 (60.2%)	72 (30.1%)	<0.001
Dialysis (%)				0.395
Hemodialysis	199 (48.5%)	58 (34.0%)	162 (68.8%)	
Peritoneal dialysis	78 (19.0%)	22 (24.5%)	14 (6.3%)	
No dialysis	133 (32.4%)	91 (53.2%)	63 (26.3%)	
Duration of dialysis (mo)	20.4±37.3	16.8±33.1	23.3±40.5	0.236
Season of RTx				0.718
Spring	90 (22.0%)	51 (29.8%)	39 (16.3%)	
Summer	107 (26.1%)	29 (17.0%)	78 (32.6%)	
Autumn	101 (24.6%)	37 (21.6%)	64 (26.8%)	
Winter	112 (27.3%)	54 (31.6%)	58 (24.3%)	
Co-morbidities (%)				
Diabetes	77(18.8%)	38 (22.2%)	39 (16.3%)	0.132
Hypertension	364 (88.8%)	155 (90.6%)	209 (87.4%)	0.313
Medications				
Use of ESA	191 (46.5%)	92 (53.8%)	99 (41.4%)	0.013
ESA dose, units/mo	16956.5±17252.2	20656.2±17627.7	10970.7±16146.2	0.003
ESA dose/Hb index	1842.9±1935.3	2227.5±1929.9	1133.0±1718.4	0.001
Biochemical data				
25(OH)D3 (ng/ml)(median)	11.1±6.4	6.5±1.8	17.2±5.6	<0.001
Hb (g/dl)	9.9±1.9	9.7±2.0	10.5±1.6	<0.001
iPTH (pg/ml)(median)	168.3±164.9	152.3±220.7	225.2±243.0	0.677
Serum iron (ug/dl)	77.1±55.3	77.9±47.1	72.5±58.5	0.814
TIBC (μg/dl)	202.8±85.6	194.1±84.1	209.9±86.7	0.785
TSAT	38.0±86.4	33.3±21.8	41.3±11.6	0.357
Ferritin (ng/ml)	193.2±143.9	190.6±156.2	196.5±128.3	0.391
ALP (IU/l)	60.6±26.1	58.1±23.3	63.7±27.0	0.676
Phosphate (mg/dl)	5.3±1.4	5.0±1.4	5.7±1.3	0.001
Calcium (mg/dl)	7.7±1.0	7.4±0.9	8.1±1.0	0.001
Albumin (g/dl)	3.9±0.4	3.8±0.4	4.0±0.4	0.001
eGFR (ml/min/1.73 m²)	4.9±2.7	4.9±2.2	4.7±1.7	0.567
hs-CRP (mg/l)(median)	0.15±2.2	0.13±2.3	0.19±2.0	0.560

Patients had 25-hydroxyvitamin D levels measured at renal transplantation.
§P-value comparisons between group 1 and group 2.

Results are expressed as x ± SD, median ± interquartile range or n (%)
25(OH)D3, 25-hydroxyvitamin D; Hb, hemoglobin; RTx, renal transplantation; ESA, erythrocyte stimulating agent; iPTH, intact parathyroid hormone; TIBC, total iron binding capacity; TSAT, transferrin saturation; ALP, alkaline phosphatase; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein

Correlation between vitamin D deficiency and anemia

Pearson's correlation analysis revealed a significant correlation between 25(OH)D3 and Hb levels ($r = 0.292$; $p < 0.001$). Hb level also significantly correlated with albumin ($r = 0.267$; $p < 0.001$) and calcium levels ($r = 0.309$; $p = 0.040$). Pearson's correlation analysis revealed a significant negative correlation between ESA dose/Hb index and 25(OH)D3 level ($r = -0.176$ $p < 0.001$). ESA dose/Hb level also negatively correlated with Hb ($r = -0.329$; $p < 0.001$), albumin ($r = -0.172$; $p < 0.001$), and calcium levels ($r = -0.099$; $p = 0.046$).

Effect of vitamin D deficiency on anemia

A multivariate linear regression analysis showed that serum 25(OH)D levels were independently associated with Hb levels after adjusting for age, sex, log iPTH, phosphate, ALP, logarithm (base 10) (log) hs-CRP, ferritin levels, and ESA dose ($\beta = 0.035$; $p= 0.039$) (Table 2). Similarly, serum 25(OH)D3 level was independently associated with the ESA dose/Hb index according to multivariable regression models ($\beta = -0.590$; $p = 0.016$) (Table 3). The ORs for developing anemia using a logistic regression analysis showed that group 1 patients had a higher risk (OR, 3.283; 95% confidence interval [CI], 1.040–10.362; $p = 0.043$) of developing anemia than group 2 patients after adjusting for age, sex, log iPTH, phosphate, ALP, log hs-CRP, ferritin levels, and ESA use (Table 4).

Table 2. Multivariate linear regression analysis with hemoglobin as the dependent variable

	β	p-value
25(OH)D3	0.035	0.039
Age	0.020	0.408
Sex (male/female)	0.202	0.677
Log iPTH	-0.349	0.073
Phosphate	-0.179	0.340
ALP	-0.003	0.689
Log hs-CRP	-0.192	0.283
Ferritin	0.002	0.120
ESA dose	-0.001	0.031

25(OH)D3, 25-hydroxyvitamin D; Log, logarithm; iPTH, intact parathyroid hormone; ALP, alkaline phosphatase; hs-CRP, high-sensitivity C-reactive protein; ESA, erythrocyte stimulating agent

Table 3. Multivariate linear regression analysis with erythrocyte stimulating agent dose/hemoglobin index as the dependent variable

	β	p-value
25(OH)D3	-0.590	0.016
Age	-0.342	0.345
Sex (male/female)	-0.243	0.266
Log iPTH	-0.401	0.073
Phosphate	0.712	0.130
ALP	0.301	0.628
Log hs-CRP	0.401	0.636
Ferritin	0.602	0.899

25(OH)D3, 25-hydroxyvitamin D; Log, logarithm; iPTH, intact parathyroid hormone; ALP, alkaline phosphatase; hs-CRP, high-sensitivity C-reactive protein

Table 4. Odds ratio for developing anemia (hemoglobin < 10g/dl) using logistic regression analysis

Variable	ORs (95% CI)	p-value
25(OH)D3 < 10 vs ≥ 10	3.283 (1.040-10.362)	0.043
Age (per 1 year increase)	0.965 (0.918-1.015)	0.965
Sex (male vs female)	0.436 (0.127-1.495)	0.170
Log iPTH (per 1 pg/ml increase)	1.322 (0.775-2.256)	0.520
Phosphate (per 1 mg/dl increase)	0.874 (0.560-1.363)	0.552
ALP (per 1 IU/l increase)	1.003 (0.981-1.026)	0.762
Log hs-CRP (per 1 mg/l increase)	1.156 (0.743-1.799)	0.520
Ferritin (per 1 ng/ml increase)	1.103 (0.993-1.033)	0.219
ESA use (yes vs no)	2.960 (0.843-10.395)	0.090

ORs, Odds ratio; CI, confidence interval; 25(OH)D3, 25-hydroxyvitamin D; Log, logarithm; iPTH, intact parathyroid hormone; ALP. Alkaline phosphatase; hs-CRP, high-sensitivity C-reactive protein; ESA, erythrocyte stimulating agent

IV. DISCUSSION

Previous studies have demonstrated an association between serum vitamin D and Hb levels in patients with CKD who do not require dialysis[5, 15]; however, the impact of vitamin D deficiency on anemia has not been extensively explored in patients with ESRD.

In this study, we demonstrated that patients with 25(OH)D3 levels < 10 ng/dl had a higher risk of developing anemia than patients with 25(OH)D3 levels ≥ 10 ng/dl. This association remained significant even after adjusting for potentially important risk factors for anemia. These findings are of great clinical significance, as anemia is very common in CKD patients and is associated with negative clinical outcomes.[16-18] The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guidelines (2012) recommended 10g/dl as the lowest Hb level in CKD patients.[14] Hb levels <

10g/dl can increase the need for transfusion and the risks of cardiovascular complications and mortality in CKD patients.[19, 20] Several factors have been identified as risk factors for anemia. Based on our data, we suggest that vitamin D deficiency, a modifiable condition, could be an additional risk factor for anemia in ESRD patients.

Several potential mechanisms could explain the association between vitamin D deficiency and anemia in ESRD patients. Vitamin D was previously shown to directly stimulate erythroid precursor cells in CKD patients, and a burst forming unit-erythroid (BFU-E) assay revealed that combined low doses of erythropoietin and vitamin D significantly increased the proliferation of mononuclear cells isolated from the peripheral blood of CKD patients compared to low-dose erythropoietin alone.[21] Moreover, BFU-E proliferation was further potentiated by high-dose vitamin D,[22] although this was not observed with cells isolated from healthy subjects. Taken together, these findings suggest that vitamin D has a direct effect on erythroid precursor proliferation in CKD patients but not in patients with normal renal function.

In addition, there is growing evidence that inflammatory cytokines influence erythropoiesis in CKD patients.[23] Moreover, vitamin D deficiency was associated with secondary hyperparathyroidism, which is known to induce bone marrow fibrosis and suppress erythropoiesis in CKD patients.[24] Taken together, these findings suggest that vitamin D has multiple effects on erythropoiesis in CKD patients, including the direct stimulation of erythropoietic cell proliferation, inhibition of inflammatory cytokines leading to increased iron availability, and a reduction in parathyroid hormone concentrations.

In this study, vitamin D deficiency was found to be an independent risk factor for anemia in patients with ESRD, which is in agreement with the results of most previous studies of patients with early CKD and patients undergoing hemodialysis. Although no significant differences in serum hs-CRP and iPTH levels were found with respect to vitamin D deficiency, the concentration of

both were lower in patients with vitamin D deficiency. Furthermore, Pearson's correlation analysis revealed no relationships between Hb levels and serum hs-CRP, iPTH, or iron levels. Based on these findings, it seems likely that the weak association between inflammation, hyperparathyroidism, and iron profiles with anemia in the present study was a result of our patients being relatively healthy and stable with minimal inflammation, acceptably controlled secondary hyperparathyroidism, and a good nutritional status.

This study had several limitations. First, the number of patients was relatively small. Second, since the study subjects were all korean patients with ESRD, the associations of vitamin D with anemia and erythropoietin resistance may not be generalizable to other populations. Finally, serum vitamin D concentrations were measured only once at the time of RTx; therefore, it was difficult to conclusively determine whether the changes in serum vitamin D levels had any influence on the changes in Hb concentrations and erythropoietin resistance.

V. CONCLUSION

In conclusion, vitamin D deficiency was prevalent in patients with ESRD undergoing RTx and was found to be independently associated with anemia and erythropoietin resistance. Further studies will be needed to verify the association of vitamin D deficiency with anemia and erythropoietin resistance through evaluating the effect of vitamin D replacement in patients with ESRD.

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ABSTRACT(IN KOREAN)

말기신부전 환자에서 비타민 D 결핍과 빈혈의 연관성

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김 영 리

배경 말기 신부전 환자에서 빈혈의 다양한 치료법이 소개 되었음에도 불구하고 여전히 빈혈은 말기신부전 환자에서 가장 흔한 합병증으로 알려져 있다. 본 연구에서는 말기 신부전 환자에서 빈혈과 비타민 D (25-수산화비타민 D) 결핍과 연관되어 있는지 여부를 알아보고자 연구를 진행하였다.

방법 신촌 세브란스 병원에서 신 이식술을 시행 받았던 410명의 환자를 대상으로 연구를 진행하였다. 이들의 신 이식술 당시 25-수산화 비타민 D 수치를 측정하였다. 이 수치에 따라 25-수산화 비타민 D 수치가 10 ng/ml 미만인 군을 그룹 1 으로, 10 ng/ml 이상인 군을 그룹 2 으로 나누어 분석하였다.

결과 다변량 선형 회귀 분석법을 사용하여 분석하였을 때 혈청 25-수산화 비타민 D 수치는 혈색소 수치와 나이, 성별, 로그 완전한 부갑상선 호르몬, 인산염, 알칼리 인산분해효소, 로그 고감도 C-반응성 단백검사, 페리틴, 적혈구 생성 자극제 사용 여부를 보정하였을때도 의미 있게 연관성이 있는 것으로 분석되었다 ($p = 0.039$). 혈색소 10g/dl 미만의 빈혈이 발생할 오즈비는 나이, 성별, 로그 완전한 부갑상선 호르몬, 인산염, 알칼리 인산분해효소, 로그 고감도 C-반응성 단백검사, 페리틴, 적혈구 생성 자극제 사용 여부를 보정하였을때도 그룹 1 에서 그룹 2 보다 높은 것을 확인 하였다 ($p = 0.039$).

결론 25-수산화 비타민 D 의 결핍은 말기신부전 환자에서 빈혈과 통계적으로 유의하게 연관성이 있음을 확인하였다. 이러한 환자군에서 비타민 D 투약이 빈혈을 호전 시켜줄지 여부에 대해서는 추후 추가적인 전향적인 연구가 필요하리라고 판단 된다.

핵심되는 말: 비타민 D 결핍, 25-수산화 비타민 D, 빈혈, 말기신부전, 만성신부전