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Prevalence of 25-Hydroxyvitamin D Deficiency in Korean Patients With Anemia

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Background: We investigated the prevalence and risk factors for vitamin D deficiency in Korean patients with anemia. *Methods:* We included 200 anemic patients and 300 controls. Anemia was defined according to the WHO criteria. Serum 25-hydroxyvitamin D [25(OH)D] was measured using an electrochemiluminescence immunoassay. We compared serum 25(OH)D levels based on the presence and subtypes of anemia. *Results:* We found that 91% (182/200) and 87.3% (262/300) of patients exhibited 25(OH)D inadequacies (<20 ng/ml) in the anemic (median hemoglobin (Hb), 9.6 g/dl) and control groups (median Hb 13.8 g/dl), respectively. The prevalence of 25(OH)D deficiency (<12 ng/ml) was significantly higher in the anemic group than in the control group (52.5% (105/200) vs. 25% (75/300), $P < 0.0001$), with an odds ratio of 3.316 (95% CI, 2.265–4.854; $P < 0.0001$). The prevalence of 25(OH)D deficiency was not different among anemia subtypes. Female gender and high C-reactive protein (CRP) were associated with vitamin D deficiency in anemic group. *Conclusions:* This study demonstrates that vitamin D deficiency is associated with anemia. Therefore, the measurement of serum 25(OH)D levels and appropriate vitamin D supplementation should be considered in anemic patients, particularly in females and patients with high CRP level. J. Clin. Lab. Anal. 29:129–134, 2015.

Key words: anemia; vitamin D deficiency; 25-hydroxyvitamin D [25(OH)D]

INTRODUCTION

The classic role of vitamin D is to regulate calcium and phosphorus homeostasis in bone and mineral metabolism. The major circulating form of vitamin D, 25-hydroxyvitamin D [25(OH)D], is produced via hydroxylation of vitamin D that is either ingested or synthesized in the liver. Biologically active 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] is then formed via a second hydroxylation of 25(OH)D in the kidney. Serum 25(OH)D is a more accurate marker for evaluation of vitamin D status than $1,25(OH)_2D$ due to its longer half-life, more limited dietary intake, greater concentration, and ease of measurement (1).

Recently, vitamin D has been suggested to have an additional role in nonskeletal functions including cellular proliferation and differentiation, muscle function, immunity, and erythropoiesis. Vitamin D deficiency has also been shown to be associated with disease processes such as diabetes mellitus, chronic kidney disease (CKD), hypertension, cancer, aortic aneurysms, and anemia (2–6).

Several studies have reported a role for vitamin D in erythropoiesis due to its presence in the bone marrow (7, 8). Levels of $1,25(OH)_2D$ in the bone marrow are several hundred fold higher than in the plasma (9). Furthermore, vitamin D deficiency is associated with various types of anemia including iron deficiency anemia (IDA), anemia of CKD (ACKD), and anemia of inflammation (AI). In patients with CKD not requiring dialysis, lower 25(OH)D levels are associated with lower hemoglobin (Hb) concentrations (10). In hemodialysis patients, vitamin D repletion has resulted in dose reductions of

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erythrocyte-stimulating agents and increased reticulocytosis (11–13). Vitamin D deficiency is also independently associated with anemia in end-stage heart failure (14). Other studies have shown that vitamin D deficiency has a high prevalence in children with IDA (15), in elderly patients with AI (6), and in cardiac surgical patients with ACKD (16).

Both vitamin D deficiency and anemia are very common health problems in Korean patients (17,18). According to the Fourth Korea National Health And Nutrition Examination Survey (KNHANES IV) of 2008, vitamin D inadequacy with serum 25(OH)D levels <20 ng/ml was found in 47.3% of males and 64.5% of females (17). The prevalence of anemia in Korea was reported to be 9.0% in patients >10 years old, and rose rapidly with advancing age (18).

In this study, we investigated the prevalence of vitamin D deficiency in Korean patients with anemia. In addition, although vitamin D deficiency is an independent risk factor for anemia, not all anemic patients have vitamin D deficiency. Therefore, we also analyzed risk factors associated with vitamin D deficiency state among anemic patients.

MATERIALS AND METHODS

Study Subjects and Data Collection

The study subjects included 200 Korean patients (median age, 66 years; range, 19–91 years) diagnosed with anemia based on the World Health Organization (WHO) criteria and referred for anemia workup testing to our laboratory between September 2011 and August 2012. Three hundred nonanemic controls (median age, 65 years; range, 23–91 years) were also enrolled from health promotion center. After obtaining written informed consent, blood samples were drawn. Serum 25(OH)D was measured using a COBAS E411 analyzer (Roche Diagnostics, Indianapolis, IN) with an electrochemiluminescence immunoassay according to the manufacturer's instructions. We collected clinical and laboratory data including complete blood count (CBC), ferritin, serum iron, total iron-binding capacity (TIBC), unsaturated iron-binding capacity (UIBC), transferrin saturation, folate, vitamin B12, creatinine (Cr), estimated glomerular filtration rate (eGFR) by the Modification of Diet in Renal Disease (MDRD) formula, and C-reactive protein (CRP). This study was approved by the Institutional Review Board of the Konyang University Hospital.

Definitions of Anemia and Vitamin D Deficiency

Anemia was defined according to the WHO criteria as having an Hb level of <13 g/dl in men and <12 g/dl in women. Anemia subtypes were determined based on clinical and laboratory data. IDA was diagnosed when serum ferritin was <30 ng/ml and transferrin saturation was <16%. ACKD was defined as an eGFR <60 ml/min/1.73 m^2. AI was defined as serum iron levels <60 μg/dl in the absence of iron deficiency, or ferritin >100 ng/ml. The remaining patients were categorized as having unexplained anemia. A deficiency of 25(OH)D was defined as <12 ng/ml, and inadequacy was defined as <20 ng/ml based on North American Institute of Medicine (19).

Statistical Analyses

Statistical analyses were carried out using PASW 22 software (IBM Corporation, Somers, NY). Mann–Whitney *U* tests were used to compare the median values of serum 25(OH)D between anemic patients and the control group. For the analysis of serum 25(OH)D status based on anemia subtypes, Kruskal–Wallis tests were used. Multivariable logistic regression was performed to evaluate associations between risk factors and serum 25(OH)D status in anemic patients. *P*-values <0.05 were considered to be statistically significant.

RESULTS

Baseline Characteristics of Patients

Baseline characteristics of the patients are shown in Table 1. A total of 200 anemic patients (86 males and

TABLE 1. Clinical Characteristics and Laboratory Data for Korean Patients With Anemia

Characteristics	$N = 200$
Age (years)	62.96 ± 16.43
Gender (male:female)	86:114
Hb (g/dl)	9.38 ± 1.61
Hematocrit (%)	28.18 ± 5.31
Mean corpuscular volume (fl)	87.96 ± 11.01
White blood cells (/mm^3)	7.57 ± 5.09
Platelets (/mm^3)	248.5 ± 98.45
Ferritin (ng/ml)	265.9 ± 388.1
Iron (μg/dl)	40.25 ± 31.34
TIBC (μg/dl)	272.9 ± 100.5
Transferrin saturation (%)	16.4 ± 14.09
Creatinine (mg/dl)	1.58 ± 2.11
eGFR (ml/min/1.73 m^2)	68.14 ± 32.48
CRP (mg/dl)	5.24 ± 8.57
IDA (*n* (%))	60 (30%)
ACD (*n* (%))	123 (61.5%)
ACKD (*n* (%))	63 (31.5%)
AI (*n* (%))	60 (30%)
Unexplained anemia (*n* (%))	17 (8.5%)

Descriptive data are expressed as means ± SDs or numbers (%).
ACD, anemia of chronic disease.

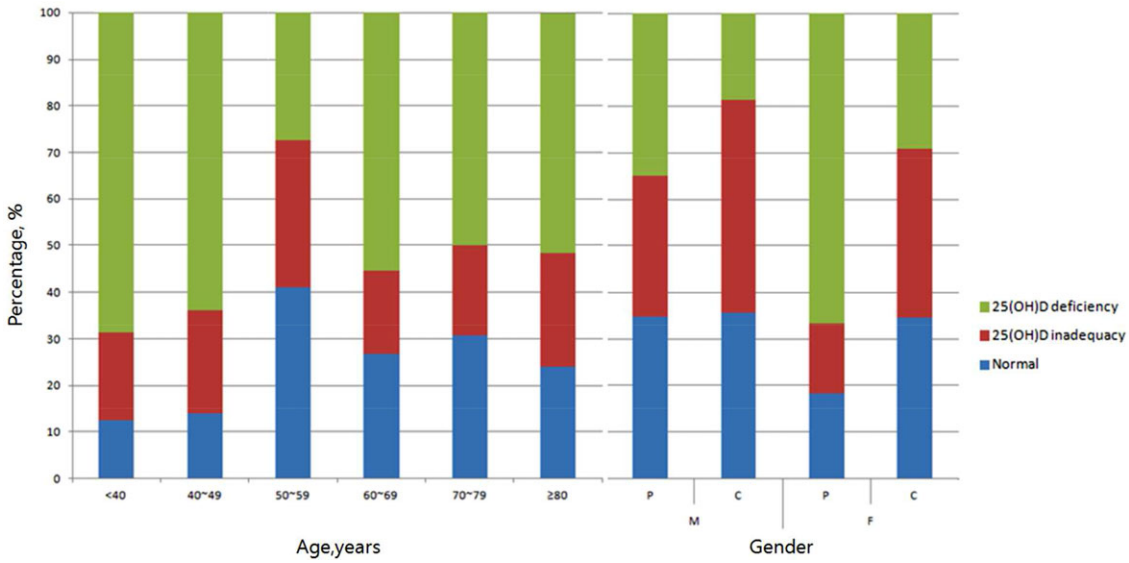

Fig. 1. The distribution of vitamin D status according to age or gender in Korean anemic patients. P, patients; C, controls; M, male; F, female.

114 females) and 300 controls (118 males and 182 females) were included in this study. The distributions of age ($P = 0.12$) and gender ($P = 0.17$) were not different between groups. Sixty (30%) anemic patients were diagnosed with IDA, while sixty-three (31.5%) and sixty (30%) were diagnosed with ACD and AI, respectively. The median Hb level was 9.6 g/dl (range, 5.5–12.3 g/dl) in anemic patients and 13.8 g/dl (range, 12.0–17.2 g/dl) in controls ($P < 0.0001$).

Serum 25(OH)D Levels and the Prevalence of Vitamin D Deficiency

The median serum level of 25(OH)D was 11.21 ng/ml in anemic patients and 16.35 ng/ml in controls ($P < 0.0001$). The prevalence of 25(OH)D inadequacy was 91% (182/200) in the anemic group and 87.3% (262/300) in the control group ($P = 0.247$). Serum 25(OH)D deficiency was significantly more common in the anemic group than in the control group (52.5% (105/200) vs. 25% (75/300), $P < 0.0001$). The odds ratio for 25(OH)D deficiency in anemic patients was 3.316 (95% CI, 2.265–4.854; $P < 0.0001$). The levels of 25(OH)D in 18 anemic patients (9%) were below the minimum detection limit of 3.0 ng/ml. Figure 1 shows the distribution of 25(OH)D deficiencies in anemic patients stratified by age and gender. More than 60% of anemic patients <50 years of age exhibited vitamin D deficiencies. Additionally, nearly half of the patients ≥60 years of age had vitamin D deficiencies. The distribution of vitamin D levels was different according to gender ($P < 0.0001$). The median 25(OH)D levels in anemic patients and controls were 16.24 and 17.31 ng/ml in males, and 9.61 and 13.3 ng/ml in females, respectively. Vitamin D deficiencies were significantly more common in both male and female anemic patients than in controls; 34.9 versus 18.6% in male ($P = 0.0097$) and 66.7 versus 29.1% in female ($P < 0.0001$).

Association of Vitamin D Deficiency With Anemia Subtypes

Table 2 depicts the prevalence of vitamin D deficiency with respect to anemia subtype as well as in controls. The distribution of 25(OH)D levels ($P = 0.169$) and the prevalence of 25(OH)D deficiency ($P = 0.730$) were not different among anemia subtypes.

Risk Factors for Vitamin D Deficiency in Anemic Patients

Table 3 shows the adjusted odds ratios for vitamin D deficiency according to variable factors in anemic patients. Female gender and high CRP were statistically significant risk factors for vitamin D deficiency in anemic patients.

DISCUSSION

In this study, Korean anemic patients had a higher prevalence of vitamin D deficiency and significantly lower 25(OH)D levels compared with controls. In the KNHANES IV study (17), the prevalence of vitamin D inadequacy was slightly less than 70% in both healthy male and female patients who were 40–49 years of age. They also reported mean 25(OH)D levels of 21.4 ng/ml in males and 17.4 ng/ml in females in this same age group. Mean vitamin D levels were found to be highest in patients

TABLE 2. The Distribution of Vitamin D Deficiency Among Anemia Subtypes and the Control Group

25(OH)D level (ng/ml)	Anemic group ($n = 200$)	IDA ($n = 60$)	ACKD ($n = 63$)	AI ($n = 60$)	Unexplained anemia ($n = 17$)	Control group ($n = 300$)
≥20 (*n* (%))	51 (26)	14 (23)	16 (25)	15 (25)	6 (35)	105 (35)
13–19 (*n* (%))	43 (22)	14 (23)	11 (18)	15 (25)	3 (18)	120 (40)
<12 (*n* (%))	106 (53)	32 (53)	36 (57)	30 (50)	8 (47)	75 (25)
Median value	11.21	11.9	9.8	11.8	13.5	16.4

n, number; ACD, anemia of chronic disease.

TABLE 3. Odds Ratios for Vitamin D Deficiency Using Multiple Logistic Regression Analysis

Independent variables	Odds ratio (95% CI)	*P*-value
Age (≥60 years)	1.061 (0.528–2.133)	0.867
Gender (female)	5.769 (2.824–11.785)	<0.001
Hb (<7 g/dl)	1.514 (0.790–2.900)	0.211
Ferritin (<30 ng/ml)	0.659 (0.234–1.851)	0.428
(≥100 ng/ml)	1.020 (0.391–2.662)	0.968
Transferrin saturation (<16 %)	1.862 (0.866–4.006)	0.112
eGFR (<60 ml/min/1.73m$^{2)}$	2.389 (0.936–6.099)	0.069
CRP (≥1.0 mg/dl)	2.751 (1.161–6.519)	0.021

who were 60–69 years of age, at 23.8 ng/ml in males and 20.0 ng/ml in females. In this study, however, the prevalence of vitamin D inadequacy was 86.1% in anemic patients with a mean vitamin D level of 11.69 ng/ml at 40–49 years of age. Anemic patients at age 60–69 years had significantly lower 25(OH)D levels of 14.41 ng/ml.

Vitamin D deficiency was found to be associated with an increased risk of anemia independent of age, gender, and ethnicity. In a previous population-based study, the odds ratio for anemia was increased by approximately 60% in the presence of vitamin D deficiency (20). Anemia may also be an influencing factor for vitamin D deficiency. Anemia can be caused by a number of factors such as nutritional deficiencies including iron, vitamin B12, and folate, chronic inflammation, and CKD. It has been suggested that anemia may predispose patients to vitamin D deficiency because of inadequate sun exposure as a result of decreased outdoor activity (11).

Although endogenous synthetic vitamin D from exposure of sunlight may be the primary contributor to the maintenance of serum vitamin D levels, the role of dietary intake cannot be disregarded. Young females have several risk factors for vitamin D deficiency including poor nutritional status and limited sun exposure due to decreased outdoor activity and excessive use of sun block. IDA is the most common nutritional deficiency worldwide, and is frequently observed in women of reproductive age. Half of the IDA patients enrolled in this study were females younger than 50 years of age. Therefore, IDA patients in this study likely exhibited a high prevalence of vitamin D deficiency. The correlation between IDA and vitamin D deficiency has also been reported in Korean children (15). While there are differences in these studies including study population characteristics, causes of IDA, and risk factors for vitamin D deficiency, all suggest that vitamin D deficiency should be considered in IDA patients regardless of age.

An increased risk of vitamin D deficiency in patients with AI has also been reported. AI, which has historically been known as anemia of chronic disease, is associated with infection, rheumatologic disorders, malignancy, and other chronic diseases. Perlstein et al. previously reported that vitamin D deficiency was strongly associated with AI, particularly in elderly persons ≥60 years of age (6). Additionally, Shin et al. reported that pre- and postmenopausal Korean women with low levels of 25(OH)D are at higher risk of IDA and AI (21).

This study found no statistically significant differences in the prevalence or distribution of vitamin D deficiency among anemia subtypes. Potential reasons for this include differences in characteristics of the study population, prevalence of anemia, criteria for anemia subtypes, distribution of anemia subtypes and sample size. Above all, ethnicity of the enrolled patients was likely the primary cause of this difference. Skin color is an adaptive trait that has evolved in part to regulate 25(OH)D (22). Non-Hispanic blacks were previously shown to have a sevenfold greater risk of having AI, and their vitamin D levels were also lower than those seen in white patients (6). Since only Koreans were enrolled in this study, the association of vitamin D deficiency with AI was not as strong as that reported by Perlstein et al. The basic physical condition of enrolled anemic patients might be different. Compared to the national health survey based studies by Perlstein et al. and Shin et al., all anemic patients in this study had health problems. In addition, relatively higher prevalence of AI and small sample size are also considered as other reasons of different result. A larger dataset from multi-institutional studies is needed to draw any definitive conclusions.

Vitamin D may also have a potential role in the regulation of hepcidin synthesis and inflammatory pathways. Vitamin D increases anti-inflammatory cytokines (23) and suppresses pro-inflammatory cytokines such as IL-6, thereby inducing hepcidin synthesis (24). Decreased levels

of vitamin D may contribute to increases in hepcidin expression, resulting in an increased risk for AI (25). Thus, analysis of hepcidin levels in anemic patients may offer additional information about the correlation between vitamin D metabolism and erythropoiesis. In this study, we instead assessed the correlation between high CRP levels and anemia. Although CRP was not associated with urinary hepcidin levels (26), it is the most commonly used acute-phase reactant for measuring the degree of inflammation (27). A CRP level >1.0 ng/ml in anemic patients was found to be a risk factor for vitamin D deficiency after controlling for other confounding factors such as age, gender, eGFR, and transferrin saturation.

Kendrick et al. previously reported that lower vitamin D and higher CRP levels were independently associated with lower Hb in patients with kidney disease not requiring dialysis (10). Kidney disease is also an inflammatory process, and CRP levels may reflect the degree of inflammation. The median serum 25(OH)D level was the lowest in patients with ACKD, although the distribution of serum 25(OH)D level was not statistically significant in this study.

ACKD is a multifactorial disease, and anemia is a common complication of CKD due to low erythropoietin (EPO) levels, chronic inflammation, iron deficiency, and reduced RBC lifespan. In CKD, vitamin D deficiency may cause immune activation and cytokine production, thereby inducing impaired erythropoiesis in the bone marrow microenvironment. Consequences of this inflammatory cascade are EPO resistance and anemia (28). Hepcidin may contribute to impaired erythropoiesis in ACKD as well (28, 29). As a result, these combined underlying factors may contribute to more severe vitamin D deficiency in ACKD patients.

Vitamin D deficiency has been observed even in the early stages of CKD (30). Both serum 25(OH)D and $1,25(OH)_2D$ levels are decreased in CKD patients, and vitamin D deficiency is a known risk factor for mortality in this population. Moderate renal dysfunction (eGFR <45 ml/min/1.73 m^2) is an important predictor of vitamin D deficiency, as serum 25(OH)D levels begin to decrease at an eGFR of 60 ml/min/1.73 m^2 independent of other risk factors (31). The adjusted odds ratio of eGFR <60 ml/min/1.73 m^2 for vitamin D deficiency was 2.389; however, it was not statistically significant in this study.

Although there are several limitations to this study including small sample size, seasonal variation, and unanalyzed hepcidin levels, we clearly demonstrate that vitamin D deficiency was much more prevalent in anemic patients regardless of age, gender, or anemia subtype. Therefore, serum vitamin D measurement should be considered in the management of anemia, particularly in females and patients with high CRP level.

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