Original Article

Gender difference in the relationship between anemia and vitamin D in Korean adults: the fifth Korea National Health and Nutrition Examination Survey

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This study was conducted to assess the relationship between vitamin D deficiency and anemia, by gender, in Korean adults. The data of 16,060 adults were analyzed (men, 6,840; premenopausal women, 4,916; postmenopausal women, 4,340) from the fifth Korean National Health and Nutrition Examination Survey (KNHANES V) (2010–2012). There were several key findings. First, after adjusting for related variables, the odds ratio (OR) of anemia [hemoglobin (Hb) <13 g/dl in men or Hb <12 g/dl in women] using the vitamin D normal group {25-hydroxyvitamin [25(OH)D] ≥15.0 ng/ml} as reference, was significant for the vitamin D deficient group [25(OH)D <15.0 ng/ml] in the overall population [OR, 1.310; 95% confidence interval (CI), 1.168–1.470]. Second, the OR of anemia, using the vitamin D normal group as reference, was significant for the vitamin D deficient group in premenopausal women (OR, 1.293; 95% CI, 1.105–1.513). However, vitamin D deficiency in the vitamin D normal group in men (OR, 1.093; 95% CI, 0.806–1.484) and postmenopausal women (OR, 1.130; 95% CI, 0.906–1.409) was not significant. In conclusion, Vitamin D deficiency is positively associated with anemia in premenopausal women, but not in men and postmenopausal women.

Key Words: anemia, vitamin D, 25(OH)D, gender difference, Korean women

A nemia affects around 33% of the world population and is one of the most common disorders worldwide.[1] In particular, women have a higher risk of anemia than men in most age groups and almost all geographic regions.[2] The disorder is defined as a red blood cell (RBC) count and/or hemoglobin (Hb) concentration that is lower than normal. Anemia may further complicate chronic diseases, such as chronic kidney disease and chronic heart disease, and, if severe enough, cardiovascular morbidity and mortality.[3,4] Several factors may contribute to anemia, including deficiencies in nutrients such as iron, vitamin B_{12}, and folate, as well as infection, blood loss, and inflammation.[5]

Vitamin D plays a major role in the metabolism of the skeletal system (e.g., osteoporosis prevention and treatment, skeletal growth and maintenance, and calcium homeostasis maintenance),

as well as in tissue (e.g., regulation of cellular differentiation/proliferation, anticancer actions, immune function, and prevention of chronic diseases).[6–9] Vitamin D can promote erythropoiesis by decreasing pro-inflammatory cytokines and increasing erythroid progenitor proliferation.[10] It can also affect the synthesis of hemoglobin because vitamin D suppresses hepcidin mRNA expression and increases ferroportin mRNA expression.[11] Vitamin D may be more important in premenopausal women than in men or postmenopausal women because premenopausal women experience blood loss due to menstruation.

Research on vitamin D and anemia have been conducted worldwide; however, as far as we know, studies analyzing gender differences in the relationship between vitamin D and anemia are rare, and no studies have yet analyzed differences in this relationship between premenopausal and postmenopausal women. Therefore, this study assesses the association between anemia and vitamin D and anemia by gender, in Korean adults, using data from the fifth Korea National Health and Nutrition Examination Survey (KNHANES V; 2010–2012), which is representative of the Korean population.

Methods

Study subjects. This study was performed using data from the Korea National Health and Nutrition Examination Survey (KNHANES V); conducted for the three years 2010–2012 using a rolling sample method that involved a complex, multistage, stratified, probability cluster survey of a representative sample of the non-institutionalized civilian population in the Republic of Korea. The survey was composed of three parts: a health examination survey; a health interview survey; and a nutrition survey. Participants provided written informed consent to participate in the study survey, and the survey results were received in anonymized form. KNHANES V sampled 25,534 individuals over the age of one, and we included the 19,392 subjects aged

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≥20 years in our analysis. We also excluded 3,332 participant subjects whose data were missing for important analytic variables such as Hb, Hct, 25-hydroxyvitamin [25(OH)D], and various blood chemistry tests. Finally, we analyzed the results of the remaining 16,060 subjects using statistical analysis. The KNHANES study was conducted according to the principles expressed in the Declaration of Helsinki (Institutional Review Board No. 2010-02CON-21-C; 2011-02CON-06-C; 2012-01EXP-01-2C). All participants of the survey signed an informed written consent form. Further information can be found in "The KNHANES V Sample," available on the KNHANES website. Data from KNHANES can be requested free of charge, by e-mail, once applicants log in to the "National Health and Nutrition Survey" website.

General characteristics and blood chemistry. Research subjects were classified by sex (men, premenopausal women, and postmenopausal women), smoking (non-smoker or current smoker), regular exercise (yes or no), and alcohol drinking (yes or no). In the smoking category, participants who smoked more than one cigarette a day and those who had never smoked were classified into "current smoker" and "non-smoker" groups, respectively. Regular exercise was indicated as "yes" for participants who exercised regularly regardless of whether they did so indoors or outdoors (regular exercise is defined as 30 min at a time and 5 times per week in the case of moderate exercise such as swimming slowly, table tennis, doubles tennis, volleyball, badminton, and carrying light objects; and 20 min at a time and 3 times per week in the case of vigorous exercise such as running, cycling fast, swimming fast, climbing, football, basketball, jump rope, singles tennis, squash, and carrying heavy objects). Alcohol drinking was indicated as "yes" for participants who had consumed at least one glass of alcohol per month during the prior year. Anthropometric measurements included measurement of systolic blood pressure (SBP) and diastolic blood pressure (DBP). Blood chemistries included measurement of 25(OH)D, Hb, Hct, blood urea nitrogen (BUN), serum creatinine (Crea), fasting blood glucose (FBG), serum iron (Fe), total iron-binding capacity (TIBC), and ferritin.

Anemia and vitamin D deficiency. Anemia was classified as Hb <13 mg/dl for men and <12 mg/dl for women.[12] Serum levels of 25(OH)D were measured with a radioimmunoassay (25-hydroxy-vitamin D ^{125}I RIA Kit; DiaSorin, Stillwater, MN) using a 1470 Wizard Gamma Counter (PerkinElmer, Turku, Finland). To minimize analytical variations, serum 25(OH)D levels were analyzed by the same institute, which conducted a quality assurance program throughout the period of analysis. Serum 25(OH)D levels were classified as vitamin D deficient [25(OH)D <15 ng/dl] and vitamin D normal groups [25(OH)D ≥15 ng/dl].[13]

Statistical analysis. The data collected were statistically analyzed using SPSS WIN ver. 18.0 (SPSS Inc., Chicago, IL). The distributions of participant characteristics were converted into percentages, and the successive data were presented as averages with SD.

In the statistical analysis, continuous variables were reported as mean ± SD, and categorical variables were reported as percentages (%). Clinical characteristics by men, premenopausal women, postmenopausal women, and overall, were analyzed using a chi-square test and independent t test (see Table 1). The distribution and average difference in clinical characteristics and iron-related indices by vitamin D deficiency and vitamin D normal group were calculated using an independent t test and chi-square test (see Table 2). We conducted a covariance test (ANCOVA) of the anemia and iron indices after adjusting for age, smoking, drinking, regular exercise, SBP, DBP, BUN, Crea, FBG, and gender (see Table 3). In the case of logistic regression for an odds ratio of anemia, the four models constructed were: 1) non-adjusted; 2) adjusted for age, smoking, drinking, regular exercise, and gender; 3) further adjusted for SBP, DBP, BUN, Crea, and FBG (see Table 4). The significance level for all statistical data was set as $p<0.05$.

Table 1. Clinical characteristics of research subjects [Mean ± SD, n (%)]

Variables	Total (n = 16,096)	Men (n = 6,840)	Women (n = 9,256)		p value
			Premenopausal (n = 4,916)	Postmenopausal (n = 4,340)	
Age (years)	50.07 ± 16.14	50.29 ± 15.96	37.85 ± 10.61	63.55 ± 9.32	<0.001
Current smoker	8,312 (51.6)	4,915 (71.9)	2,273 (46.2)	1,124 (25.9)	<0.001
Alcohol drinker	3,256 (20.2)	2,764 (40.4)	321 (6.5)	171 (3.9)	<0.001
Regular exerciser	1,362 (8.5)	616 (9.0)	348 (7.1)	398 (9.2)	<0.001
SBP (mmHg)	119.81 ± 17.34	122.43 ± 15.88	109.61 ± 13.76	127.22 ± 17.89	<0.001
DBP (mmHg)	76.28 ± 10.48	79.16 ± 10.57	72.12 ± 9.40	76.47 ± 9.94	<0.001
BUN (mg/dl)	14.32 ± 4.39	15.09 ± 4.44	12.13 ± 3.52	15.56 ± 4.31	<0.001
Crea (mg/dl)	0.83 ± 0.20	0.97 ± 0.18	0.70 ± 0.13	0.74 ± 0.15	<0.001
FBG (mg/dl)	97.78 ± 22.19	100.58 ± 24.30	91.35 ± 16.49	100.64 ± 22.83	<0.001
Ferritin (μg/L)	77.40 ± 65.50	115.89 ± 72.12	32.50 ± 29.53	67.57 ± 44.86	<0.001
Fe (μg/dl)	112.83 ± 47.32	128.59 ± 49.95	100.27 ± 47.37	102.23 ± 33.88	<0.001
TIBC (μg/dl)	316.47 ± 44.91	309.11 ± 39.88	330.64 ± 50.98	312.00 ± 41.20	<0.001
Hb (g/dl)	13.96 ± 1.59	15.21 ± 1.21	12.87 ± 1.21	13.22 ± 1.03	<0.001
Hct (%)	41.53 ± 4.11	44.68 ± 3.25	38.81 ± 3.02	39.63 ± 2.86	<0.001
Anemia	1,402 (8.7)	245 (3.6)	776 (15.8)	381 (8.8)	<0.001
25(OH)D (ng/ml)	17.46 ± 6.03	18.68 ± 6.07	15.33 ± 5.10	17.94 ± 6.29	<0.001
≥15.0	9,997 (62.1)	4,879 (71.3)	2,313 (47.1)	2,805 (64.6)	<0.001
<15.0	6,099 (37.9)	1,961 (28.7)	2,603 (52.9)	1,535 (35.4)	

SBP, systolic blood pressure; DBP, diastolic blood pressure; BUN, blood urea nitrogen; Crea, serum creatinine; FBG: fasting blood glucose; Fe, serum iron; TIBC, total iron binding capacity; TFS, transferrin saturation; Hb, hemoglobin; Hct, hematocrit; Anemia, Hb <13.0 g/dl in men or Hb <12.0 g/dl in women; 25(OH)D, 25-hydroxyvitamin.

Table 2. Clinical characteristics according to vitamin D status in men, premenopausal women, and postmenopausal women [Mean ± SD, n (%)]

Variables	Men (n = 6,840)			Premenopausal women (n = 4,916)			Postmenopausal women (n = 4,340)		
	Vitamin D normal (n = 4,879)	Vitamin D deficiency (n = 1,961)	p value	Vitamin D normal (n = 2,313)	Vitamin D deficiency (n = 2,603)	p value	Vitamin D normal (n = 2,805)	Vitamin D deficiency (n = 1,535)	p value
25(OH)D (ng/ml)	21.32 ± 5.07	12.14 ± 2.08	<0.001	19.47 ± 4.15	11.66 ± 2.25	<0.001	21.24 ± 5.27	11.90 ± 2.16	<0.001
Age (years)	51.80 ± 15.54	46.55 ± 16.37	<0.001	38.80 ± 10.95	37.00 ± 10.23	<0.001	63.69 ± 9.23	63.31 ± 9.42	0.207
Current smoker	1,870 (38.3)	894 (45.6)	<0.001	137 (5.9)	184 (7.1)	0.212	100 (3.6)	71 (4.6)	0.206
Alcohol drinker	3,546 (72.7)	1,369 (69.8)	0.009	1,096 (47.4)	1,177 (45.2)	0.129	761 (27.1)	363 (23.6)	0.012
Regular exerciser	486 (10.0)	130 (6.6)	<0.001	186 (8.0)	162 (6.2)	0.014	287 (10.2)	111 (7.2)	0.001
SBP (mmHg)	122.90 ± 15.85	121.28 ± 15.88	<0.001	109.89 ± 14.33	109.37 ± 13.23	0.182	126.59 ± 17.79	128.37 ± 18.02	0.002
DBP (mmHg)	79.22 ± 10.52	79.03 ± 10.70	0.519	72.23 ± 9.37	72.02 ± 9.43	0.452	76.18 ± 9.95	76.98 ± 9.90	0.012
BUN (mg/dl)	15.55 ± 4.52	13.95 ± 4.00	<0.001	12.54 ± 3.53	11.77 ± 3.47	<0.001	15.89 ± 4.40	14.96 ± 4.05	<0.001
Crea (mg/dl)	0.98 ± 0.18	0.97 ± 0.17	0.101	0.71 ± 0.11	0.70 ± 0.14	<0.001	0.74 ± 0.15	0.73 ± 0.15	0.221
FBG (mg/dl)	100.97 ± 24.33	99.61 ± 24.21	0.037	91.75 ± 18.09	91.01 ± 14.91	0.114	100.09 ± 21.89	101.63 ± 24.43	0.035
Ferritin (μg/L)	115.45 ± 71.80	117.00 ± 72.91	0.421	35.86 ± 32.17	29.52 ± 26.62	<0.001	68.91 ± 44.55	65.12 ± 45.34	0.008
Fe (μg/dl)	128.97 ± 50.71	127.65 ± 48.01	0.324	102.72 ± 47.02	98.08 ± 47.59	0.001	103.22 ± 33.86	100.43 ± 33.85	0.01
TIBC (μg/dl)	309.22 ± 40.02	308.84 ± 39.55	0.718	328.25 ± 49.55	332.77 ± 52.13	0.002	311.79 ± 40.67	312.37 ± 42.14	0.654
Hb (g/dl)	15.18 ± 1.22	15.27 ± 1.20	0.065	12.94 ± 1.18	12.81 ± 1.23	<0.001	13.22 ± 1.02	13.22 ± 1.05	0.838
Hct (%)	44.64 ± 3.27	44.78 ± 3.19	0.106	38.98 ± 2.97	38.67 ± 3.06	<0.001	39.66 ± 2.84	39.59 ± 2.89	0.495
Anemia	183 (3.8)	62 (3.2)	0.133	331 (14.3)	445 (17.1)	0.004	238 (8.5)	143 (9.3)	0.201

Vitamin D normal, 25(OH)D ≥15.0 ng/ml; Vitamin D deficiency, 25(OH)D <15.0 ng/ml.

Table 3. Comparisons of Hb, Hct, and iron indices according to vitamin D status

Variables	Hb (g/dl) [Mean ± SE (95% CI)]	Hct (%) [Mean ± SE (95% CI)]	Fe (μg/dl) [Mean ± SE (95% CI)]	Ferritin (μg/L) [Mean ± SE (95% CI)]	TIBC (μg/dl) [Mean ± SE (95% CI)]
Overall (n = 16,096)					
25(OH)D ≥15.0 ng/ml	14.05 ± 0.01 (14.03–14.08)	41.77 ± 0.03 (41.70–41.83)	114.72 ± 0.45 (113.83–115.61)	80.82 ± 0.58 (79.68–81.96)	315.16 ± 0.44 (314.31–316.02)
25(OH)D <15.0 ng/ml	13.81 ± 0.02 (13.78–13.85)	41.14 ± 0.04 (41.06–41.23)	109.77 ± 0.59 (108.62–110.92)	71.91 ± 0.75 (70.44–73.38)	318.41 ± 0.56 (317.30–319.51)
p value	<0.001	<0.001	<0.001	<0.001	<0.001
Men (n = 6,840)					
25(OH)D ≥15.0 ng/ml	15.22 ± 0.02 (15.19–15.25)	44.71 ± 0.04 (44.63–44.79)	128.97 ± 0.70 (127.60–130.34)	115.98 ± 1.00 (114.01–117.94)	309.22 ± 0.55 (308.14–310.30)
25(OH)D <15.0 ng/ml	15.18 ± 0.03 (15.14–15.23)	44.58 ± 0.07 (44.45–44.71)	127.69 ± 1.11 (125.50–129.87)	115.89 ± 1.60 (112.77–119.02)	308.67 ± 0.88 (306.95–310.40)
p value	0.272	0.099	0.334	0.965	0.559
Premenopausal women (n = 4,916)					
25(OH)D ≥15.0 ng/ml	12.95 ± 0.02 (12.90–13.00)	39.00 ± 0.06 (38.88–39.12)	102.75 ± 0.98 (100.83–104.66)	35.63 ± 0.61 (34.45–36.82)	327.90 ± 1.02 (325.90–329.90)
25(OH)D <15.0 ng/ml	12.81 ± 0.02 (12.77–12.86)	38.67 ± 0.06 (38.56–38.78)	98.14 ± 0.92 (96.34–99.95)	29.76 ± 0.57 (28.64–30.88)	332.78 ± 0.96 (330.89–334.66)
p value	<0.001	<0.001	0.001	<0.001	0.001
Postmenopausal women (n = 4,340)					
25(OH)D ≥15.0 ng/ml	13.24 ± 0.02 (13.20–13.27)	39.69 ± 0.05 (39.59–39.79)	103.15 ± 0.62 (101.94–104.36)	69.19 ± 0.84 (67.55–70.83)	312.18 ± 0.76 (310.69–313.68)
25(OH)D <15.0 ng/ml	13.19 ± 0.03 (13.15–13.24)	39.53 ± 0.07 (39.40–39.67)	100.54 ± 0.84 (98.90–102.19)	64.68 ± 1.13 (62.45–66.90)	311.72 ± 1.03 (309.69–313.74)
p value	0.16	0.07	0.013	0.001	0.717

Adjusted for age, smoking, alcohol drinking, regular exercise, SBP, DBP, BUN, Crea, and FBG or gender.

Results

Clinical characteristics of research subjects. The clinical characteristics of the research subjects are shown in Table 1. Among the 16,060 subjects, the mean ferritin, Fe, TIBC, Hb, and Hct were 77.40 ± 65.50 μg/L, 112.83 ± 47.32 μg/dl, 316.47 ± 44.91 μg/dl, 13.96 ± 1.59 g/dl, and 41.53 ± 4.11%, respectively. The incidence of anemia and vitamin D deficiency was 1,402 (8.7%) and 6,099 (37.9%), respectively. The incidence of anemia in men, premenopausal women, and postmenopausal women

Table 4. Comparisons of odds ratio of anemia according to vitamin D status

Variables	Anemia		
	Model 1	Model 2	Model 3
Overall (*n* = 16,096)			
25(OH)D ≥15.0 ng/ml	1	1	1
25(OH)D <15.0 ng/ml	1.474 (1.320–1.646)	1.310 (1.168–1.470)	1.325 (1.177–1.492)
Men (*n* = 6,840)			
25(OH)D ≥15.0 ng/ml	1	1	1
25(OH)D <15.0 ng/ml	0.847 (0.632–1.135)	1.093 (0.806–1.484)	1.122 (0.811–1.552)
Premenopausal women (*n* = 4,916)			
25(OH)D ≥15.0 ng/ml	1	1	1
25(OH)D <15.0 ng/ml	1.242 (1.063–1.450)	1.293 (1.105–1.513)	1.290 (1.098–1.516)
Postmenopausal women (*n* = 4,340)			
25(OH)D ≥15.0 ng/ml	1	1	1
25(OH)D <15.0 ng/ml	1.108 (0.891–1.378)	1.130 (0.906–1.409)	1.182 (0.941–1.484)

Anemia, Hb <13.0 g/dl in men or Hb <12.0 g/dl in women. Model 1 [ORs (95% CI)], non-adjusted; Model 2 [ORs (95% CI)], adjusted for age, smoking, alcohol drinking, and regular exercise or gender; Model 3 [ORs (95% CI)], Model 2 further adjusted for SBP, DBP, BUN, Crea, and FBG or gender.

was 245 (3.6%), 776 (15.8%), and 381 (8.8%), respectively. The incidence of vitamin D deficiency in men, premenopausal women, and postmenopausal women was 1,961 (28.7%), 2,603 (52.9%), and 1,535 (35.4%), respectively.

Clinical characteristics of subjects according to vitamin D status. The clinical features of individuals according to vitamin D status in men, premenopausal women, and postmenopausal women, and the overall population are shown in Supplemental Table 1* and Table 2. In the overall population, ferritin (*p*<0.001), Fe (*p*<0.001), Hb (*p*<0.001), and Hct (*p*<0.001) levels in the vitamin D deficient group were lower than those in the vitamin D normal group, but TIBC (*p*<0.001) and prevalence of anemia (*p*<0.001) were higher (Supplemental Table 1*). In men, ferritin (*p* = 0.421), Fe (*p* = 0.324), TIBC (*p* = 0.718), Hb (*p* = 0.065), Hct (*p* = 0.106), and the prevalence of anemia (*p* = 0.133) in the vitamin D deficient and vitamin D normal groups, were not significant. In premenopausal women, ferritin (*p*<0.001), Fe (*p* = 0.001), Hb (*p*<0.001), and Hct (*p*<0.001) in the vitamin D deficient group were lower than those in the vitamin D normal group; however, TIBC (*p* = 0.002) and prevalence of anemia (*p* = 0.004) were higher. In postmenopausal women, ferritin (*p* = 0.008) and Fe (*p* = 0.010) in the vitamin D deficient group were lower than those in the vitamin D normal group; however, TIBC (*p* = 0.654), Hb (*p* = 0.838), Hct (*p* = 0.495), and the prevalence of anemia (*p* = 0.201), were not significant (Table 2).

Comparisons of Hb, Hct, and iron indices according to vitamin D status. Comparisons of Hb, Hct, ferritin, Fe, and TIBC according to Vitamin D status in men, premenopausal women, postmenopausal women, and the overall population are shown in Table 3. In the overall population, after adjusting for related variables (age, gender, smoking, alcohol drinking, regular exercise, SBP, DBP, BUN, Crea, and FBG), Hb (*p*<0.001), Hct (*p*<0.001), ferritin (*p*<0.001), and Fe (*p*<0.001) in the vitamin D deficient group were lower than in the vitamin D normal group, but TIBC (*p*<0.001) was higher. In men, after adjusting for related variables, Hb (*p* = 0.272), Hct (*p* = 0.099), Fe (*p* = 0.344), ferritin (*p* = 0.965), and TIBC (*p* = 0.599) in the vitamin D deficient and vitamin D normal groups were not significant. In premenopausal women, after adjusting for related variables, Hb (*p*<0.001), Hct (*p*<0.001), Fe (*p* = 0.001), and ferritin (*p*<0.001) in the vitamin D deficient group were lower than in the vitamin D normal group, but TIBC (*p*<0.001) was higher. In premenopausal women, after adjusting for related variables, Fe

(*p* = 0.013) and ferritin (*p* = 0.001) in the vitamin D deficient group were lower than in the vitamin D normal group; however, Hb (*p* = 0.160), Hct (*p* = 0.070), and TIBC (*p* = 0.717) were not significant.

Comparisons of odds ratio of anemia according to vitamin D status. Comparisons of the odds ratios of anemia according to vitamin D status in men, premenopausal women, postmenopausal women, and overall population are shown in Table 4. In the overall population [odds ratio (OR), 1.325; 95% confidence interval (CI), 1.177–1.492] and premenopausal women (OR, 1.290; 95% CI, 1.098–1.516), after adjusting for related variables and with the vitamin D normal group as the reference, the OR of anemia in the vitamin D deficient group was significantly higher. However, in men (OR, 1.122; 95% CI, 0.811–1.516) and postmenopausal women (OR, 1.182; 95% CI, 0.941–1.584), differences between the vitamin D deficient and vitamin D normal groups were not significant.

Discussion

This study investigates the association between vitamin D deficiency and anemia, by gender, in Korean adults, using data from KNHANES V (2010–2012). Vitamin D deficiency is positively associated with anemia in premenopausal women but is not significantly associated in men and postmenopausal women.

The prevalence of vitamin D deficiency varies by ethnic group and country. The Republic of Korea is a country with severe vitamin D deficiency, which is steadily increasing.[14] The prevalence of vitamin D deficiency in our results (62.1%) is lower than in Scotland (78%) and higher than in Germany (58%).[15,16] Research on vitamin D and iron metabolism have been conducted worldwide. Vitamin D increases iron bioavailability for erythropoiesis and Hb synthesis by regulating the hepcidin-ferroportin axis in macrophages and removing impairments to iron absorption.[12,17] In addition, vitamin D can promote erythropoiesis by decreasing pro-inflammatory cytokines. Vitamin D inhibits the expression of inflammatory cytokines, such as interleukin 6 (IL-6) and interleukin 1 beta (IL-1β) in stromal cells, and upregulates lymphocyte release of interleukin-10 (IL-10) which is an inflammatory-suppressing factor, modulating signal transducer and activator of transcription 3 (STAT3) signal pathway.[18,19] Hepcidin plays an important role in iron metabolism in the body. Hepcidin inhibits iron export from the cells of the reticuloen-

dothelial system, including macrophages and intestinal cells; vitamin D can downregulate hepcidin expression.[17] Vitamin D deficiency can cause anemia by stimulating immune cells in the microenvironment of bone marrow to produce inflammatory cytokines, such as IL-6 which inhibits erythropoietin involved in the production of red blood cells.[18] IL-6 directly upregulates hepcidin, which is the iron-regulating hormone, through induction and subsequent binding promotor of STAT3.[20]

In a study of vitamin D and anemia, Malczewska-Lenczowska et al.[21] reported that the vitamin D deficient group had lower levels of Fe ($p = 0.004$) and ferritin ($p = 0.043$), and higher levels of TIBC ($p = 0.016$) and transferrin receptor ($p = 0.001$) in healthy female athletes ($n = 219$). In a meta-analysis of seven studies, vitamin D deficiency was found to increase the incidence of anemia (OR, 2.25; 95% CI, 1.47–3.44).[22] In our study, vitamin D deficiency in the overall population was positively associated with anemia (OR, 1.325; 95% CI, 1.177–1.492). In addition, vitamin D deficiency was significantly associated with all anemia and iron indices. However, some research have suggested that there is no link between vitamin D and anemia. Coutard et al.[23] reported that vitamin D deficiency is not significantly associated with anemia in a hospitalized geriatric French population ($n = 226$) (OR, 1.37; 95% CI, 0.72–2.6). Yoo et al.[24] reported that vitamin D deficiency is not significantly associated with Hb ($p = 0.211$), ferritin ($p = 0.428$), and transferrin saturation ($p = 0.111$) in Korean adults ($n = 500$) enrolled at a health promotion center. Furthermore, research suggests that the relationship between vitamin D and anemia differs by ethnic group; in a generally healthy adult US cohort, Smith et al.[25] revealed that vitamin deficiency is positively associated with the prevalence of anemia in black people but not in white people.

In this study, as well as the overall population, we separately analyzed men, premenopausal women, and postmenopausal women and found that the results differ by gender. Vitamin D deficiency is positively associated with anemia in premenopausal women (OR, 1.290; 95% CI, 1.098–1.516), but not in men (OR, 1.122; 95% CI, 0.811–1.516) or postmenopausal women (OR, 1.182; 95% CI, 0.941–1.584). We believe that gender difference in the relationship between vitamin D and anemia is due to estrogen levels; given secondary sexual characteristics and the menopause, estrogen levels in men and postmenopausal women are significantly lower than in premenopausal women. Kinuta et al.[26] suggested that vitamin D plays an important role in the estrogen biosynthesis mechanism, because it directly regulates the CYP19 gene to maintain extracellular calcium homeostasis. In a mouse model study, estradiol increased iron uptake into the intestine and iron release from storage cells, due to a decrease in hepcidin by a functional estrogen response element located in the promotor region of the hepcidin gene.[27,28] Hepcidin inhibition by 17β-estradiol (E2) can increase the availability of iron for erythropoiesis and compensate for iron loss during menstruation in premenopausal women.[29] Moreover, in premenopausal women, vitamin D deficiency is significantly associated with all anemia and iron indices, such as Hb, Hct, Fe, ferritin, and TIBC. However, vitamin D deficiency is associated with only Fe and ferritin in postmenopausal women, and is not associated with any anemia or iron indices in men. Even in men, estradiol plays an important role in anemia. Lewerin et al.[30] suggested that a decrease in Hb levels in elderly men is due to a decrease in estradiol. In our study, vitamin D deficiency in premenopausal women were found to be associated with reduced Fe and ferritin, and decreased iron can be associated with heavy menstrual bleeding. In premenopausal women, vitamin D and menstrual irregularities may be related. In a cohort study, Jukic et al.[31] revealed that vitamin D deficiency is associated with a longer menstrual cycle. They suggested that vitamin D deficiency is associated with a longer follicular phase and short luteal phase. Several researchers have argued that vitamin D supplements are needed to treat irregular menstruation in premenopausal women.[32,33]

This study has several limitations. First, season is an important determinant of serum 25(OH)D concentrations. However, we could not use season as an adjustment variable because the KNHANES V (2010–2012) study did not measure serum 25(OH)D concentrations according to season. Second, daily intake volumes of vitamin D and serum calcium levels are important determinants of serum 25(OH)D concentrations. However, we could not use these variables as an adjustment variable because the KNHANES V (2010–2012) did not measure the daily intake volume of vitamin D and serum calcium levels. Third, parathyroid hormone is an important determinant of serum vitamin D concentrations. Increased parathyroid hormone promotes calcium influx into adipocytes, where intracellular calcium enhances lipogenesis.[34] Therefore, serum vitamin D concentrations can change depending on the serum parathyroid hormone. However, the KNHANES V (2010–2012) data also failed to measure the serum parathyroid hormone of the participants. Thus, serum 25(OH)D concentrations for each season, along with serum calcium and parathyroid hormone, should be included as variables of vitamin D in future studies. Although the present study has limitations, this is the first study to report on the relationship between anemia and vitamin D, by gender, in Korean adults. More accurate results might be obtained by performing a cohort study.

In conclusions, this study investigated the association between anemia and vitamin D, by gender, in Korean adults, using data from the KNHANES V survey conducted in 2010–2012. Vitamin D deficiency was positively associated with anemia in premenopausal women, but not in men and postmenopausal women.

Conflict of Interest

No potential conflicts of interest were disclosed.

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