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한국 여성에서 혈청 ferritin과 25-hydroxyvitamin D 및 대사 증후군의 관련성

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The association of vitamin D and urine microalbumin/creatinine and obesity in Korean adults

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요약 본 연구는 한국 여성에서 혈청 ferritin과 25-hydroxyvitamin D [25 (OH) D]와 대사 증후군 (MetS)의 관련성을 평가하기 위해 시행되었다. 다섯 번째 국민 건강 영양 조사 (KNHANES V) (2,010- 2,012)에서 ≥ 20세 이상 성인 9,256명(4,196 폐경 전 여성과 폐경 후 여성 4,340)의 데이터를 분석 하였다. 주요 연구 결과는 다음과 같다. 첫째, MetS가 없는 여성의 경우 관련 변수 (연령, 흡연, 음주, 규칙적인 운동, SBP, DBP, WM, TC, TG, HDL-C, FPG, Hb, Hct)를 조정 한 후, 비타민 D 상태는 혈청 ferritin 수치와 관련이 있었다 (폐경 전, p <0.001, 폐경 후, p = 0.027). 둘째, MetS를 가진 여성에서 비타민 D 상태는 혈청 ferritin 수치와 관련이 없었다 (폐경 전, p = 0.739, 폐경 후, p = 0.278). 결론적으로, 비타민 D 상태는 MetS가 없는 여성에서는 혈청 ferritin 수준과 양의 상관 관계가 있었지만 MetS가 있는 여성에서는 그렇지 않았다.

Abstract The present study was conducted to assess the association between serum ferritin and 25-hydroxyvitamin D [25(OH)D] and metabolic syndrome (MetS) in Korean women. The data of a total of 9,256 adults (4,196 premenopausal women and 4,340 postmenopausal women) aged ≥ 20 years from the Fifth Korean National Health and Nutrition Examination Survey (KNHANES V) (2010-2012) were analyzed. The key study results were as follows: First, in women without MetS, after adjusting for related variables (age, smoking, alcohol consumption, regular exercise, SBP, DBP, WM, TC, TGs, HDL-C, FPG, Hb, Hct, and Fe), vitamin D status was positively associated with serum ferritin levels (premenopausal, $p < 0.001$; postmenopausal, $p = 0.027$). Second, in women with MetS, after adjusting for related variables, vitamin D status was not associated with serum ferritin levels (premenopausal, $p = 0.739$; postmenopausal, $p = 0.278$). In conclusions, vitamin D status was positively associated with serum ferritin levels in women without MetS but not in women with MetS.

Key Words Ferritin, Vitamin D, Metabolic syndrome, Korean women

1. Introduction

The serum ferritin level reflects iron stores

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in the body, since ferrous iron combined with apoferritin is stored by ferritin in many organisms [1]. Low serum ferritin levels are associated with diseases such as telogen effluvium, iron deficiency anemia, and bone mineral density [2-4], while high serum ferritin levels are associated with cardiovascular disease, insulin resistance, and metabolic syndrome (MetS) [5-7].

In the past, the main role of vitamin D was understood to be controlling the calcium levels and bone metabolism by its involvement in calcium and phosphate absorption in the intestines [8]. However, recently, vitamin D has also received attention regarding additional functions concerning its effects on the prevention of diseases, such as telogen effluvium, cardiovascular disease, MetS, and anemia [9-12].

Among the research on the association between vitamin D and ferritin in women, some studies have reported that increases in vitamin D increase ferritin levels [13-14]. However, these results may vary depending on whether the subjects have diseases such as MetS and diabetes mellitus, because ferritin levels are associated with insulin resistance diseases. Therefore, our objective in this work was to assess the association between vitamin D status and ferritin levels in Korean women with and without MetS using data from the fifth Korean National Health and Nutrition Examination Survey (KNHANES V; 2010 - 2012), which is representative of the population of Korea.

2. Body

2.1 methods

2.1.1 Study subjects

This study was performed using data from the fifth Korean National Health and Nutrition Examination Survey (KNHANES V). Participants provided written informed consent to participate in this survey, and we received the data in anonymized form. In the KNHANES V (2010 - 2012), 25,534 individuals over age 1 were sampled for the survey. Among them, of the 19,392 subjects who participated in the KNHANES V, we limited the analyses to adults aged ≥ 20 years. We excluded participants 2,138 subjects whose data were missing for important analytic variables, such as serum ferritin level, 25(OH)D level, various blood chemistry tests, and information about lifestyle. We excluded participants who had cancer (650 subjects) or hepatitis virus B (259 subjects) or hepatitis virus C (38 subjects) or 211 subjects that participants are suspected hemochromatosis (serum ferritin > 300 ng/mL). In addition, we excluded participants were excluded 6,840 men. Finally, 9,256 subjects (4,916 premenopausal and 4,340 postmenopausal women) were included in the statistical analysis. All participants in the survey signed an informed written consent form. Further information can be found in “The KNHANES V Sample”, which is available on the KNHANES website.

2.1.2 General characteristics and Blood chemistry

Research subjects were classified by sex (men or women), smoking (non-smoker or ex-smoker or current smoker), alcohol drinking (yes or no), and regular exercise (yes or no). In the smoking category, participants who smoked more than one cigarette a day, those who had previously smoked but do not presently smoke, and

those who never smoked were classified into the current smoker, ex-smoker, and non-smoker groups, respectively. Alcohol drinking was indicated as “yes” for participants who had consumed at least one glass of alcohol every month over the last year. Regular exercise was indicated as “yes” for participants who had exercised on a regular basis regardless of indoor or outdoor exercise. (Regular exercises was defined as 30 min at a time and 5 times/wk in the case of moderate exercise, such as swimming slowly, doubles tennis, volleyball, badminton, table tennis, and carrying light objects; and for 20 min at a time and 3 times/wk in the case of vigorous exercise, such as running, climbing, cycling fast, swimming fast, football, basketball, jump rope, squash, singles tennis, and carrying heavy objects). Anthropometric measurements included measurement of body mass index (BMI) and waist measurement (WM), as well as final measurements of systolic blood pressure (SBP) and diastolic blood pressure (DBP). Blood chemistries included measurements of total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), triglycerides (TGs), fasting plasma glucose (FPG), 25-hydroxyvitamin D [25(OH)D], serum iron (Fe), total iron binding capacity (TIBC), transferrin saturation (TFS), hemoglobin (Hb), and hematocrit (Hct).

2.1.3 Metabolic syndrome

Metabolic syndrome was defined using the diagnostic criteria of the National Cholesterol Education Program (NCEP) based on common clinical measures including TGs, HDL-C, blood pressure, FBG, and WM. TGs over 150 mg/dL was set as the criteria for elevated TGs. The criteria for reduced HDL-C were HDL-C of less than 50 mg/dL. FBG over 100 mg/dL was set as the criteria for elevated FBG. SBP over 130 mmHg or DBP over 85 mmHg or medication were set as the criteria for elevated blood pressure. The criteria for abdominal obesity were abdominal measurements of over 80 cm, according to the Asia-Pacific criteria [15]. The presence of defined abnormalities in any three of these five measures constitutes a diagnosis of metabolic syndrome.

2.1.4 Serum 25(OH)D and ferritin assessments

Blood samples were collected through an antecubital vein after 10 - 12 h of fasting to assess serum levels of biochemical markers. Serum levels of 25(OH)D were measured with a radioimmunoassay (25-hydroxy-vitamin D ^{125}I RIA Kit; DiaSorin, Still Water, MN, USA) using a 1470 Wizard Gamma Counter (Perkin Elmer, Turku, Finland). To minimize the analytical variation, serum 25(OH)D levels were analyzed by the same institute, which carried out a quality assurance program through the analysis period. Serum 25(OH)D levels were classified as either vitamin D deficiency [25(OH)D $<$ 10.0 ng/dL], vitamin D insufficiency [25(OH)D $\geq$ 10.0, $<$ 20.0 ng/dL], or vitamin D sufficiency [25(OH)D $\geq$ 20.0 ng/dL] [16]. Concentrations of serum ferritin were measured using an immunoturbidimetric Assay (IRMA-mat Ferritin; DiaSorin, Still Water, MN, USA) using a 1470 Wizard Gamma Counter (Perkin Elmer, Turku, Finland).

2.1.5 Data analysis

The collected data were statistically analyzed using SPSS WIN (ver. 18.0). In the case of analysis of covariance test (ANCOVA), the 2 models constructed were:

1) no adjustment; 2) adjusted for age, smoking, alcohol drinking, regular exercise, SBP, DBP, WC, BMI, TC, TGs, HDL-C, FPG, Hb, Hct, and Fe. The significance level for all of the statistical data was set as $p < 0.05$.

3. Result

3.1 Comparisons of serum ferritin levels according to vitamin D status in premenopausal and postmenopausal women with and without MetS

Comparisons of serum ferritin levels according to vitamin D status are shown in [Table 1]. In premenopausal women without MetS, in terms of serum ferritin levels by vitamin D status after adjusting for related variables (i.e., age, smoking, alcohol drinking, regular exercise, SBP, DBP, WM, TC, TGs, HDL-C, FPG, Hb, Hct, and Fe), serum ferritin levels (M ± SE) were 28.10 ± 1.06 ng/dL (95% CI, 26.03 - 30.17) for vitamin D deficiency, 30.60 ± 0.42 ng/dL (95% CI, 29.77 - 31.43) for vitamin D insufficiency, and 33.69 ± 0.94 ng/dL (95% CI, 31.85 - 35.52) for vitamin D sufficiency. This shows that serum ferritin levels were significantly increased with the increasing of vitamin D status ($p < 0.001$). In postmenopausal women without MetS, in terms of serum ferritin levels by vitamin D status after adjusting for related variables, serum ferritin levels (M ± SE) were 55.72 ± 2.99 ng/dL (95% CI, 49.86 - 61.60) for vitamin D deficiency, 63.99 ± 0.97 ng/dL (95% CI, 62.08 - 65.90) for vitamin D insufficiency, and 64.11 ± 1.32 ng/dL (95% CI, 61.52 - 66.71) for vitamin D sufficiency, showing that serum ferritin levels were significantly increased with the increasing of vitamin D status ($p = 0.027$). However, in women with MetS, after adjusting for related variables, serum ferritin levels were not increased with the increasing of vitamin D status (premenopausal, $p = 0.739$; postmenopausal, $p = 0.278$).

[table 1] Supplement Clinical characteristics of subjects according to MetS in premenopausal and postmenopausal women

n (%), Mean ± SD

Variables	Premenopausal women			Postmenopausal women		
	Non-MetS (n =4,368)	MetS (n =548)	p-value	Non-MetS (n =2,592)	MetS (n =1,748)	p-value
Age (years)	36.95 ± 10.04	44.97 ± 12.21	< 0.001	62.18 ± 9.34	65.59 ± 8.85	< 0.001
FPG (mg/dL)	89.08 ± 11.62	109.47 ± 31.52	< 0.001	94.28 ± 16.35	110.07 ± 27.37	< 0.001
Ferritin (μg/L)	31.33 ± 27.86	41.88 ± 39.24	< 0.001	63.53 ± 41.11	73.56 ± 49.32	< 0.001
Fe (μg/dL)	100.94 ± 48.03	94.92 ± 41.39	0.002	104.56 ± 34.57	98.78 ± 32.53	< 0.001
TIBC (μg/dL)	328.76 ± 50.82	345.66 ± 49.91	< 0.001	309.21 ± 40.52	316.13 ± 41.84	< 0.001
TFS (%)	31.80 ± 15.91	28.23 ± 12.83	< 0.001	34.28 ± 11.73	31.72 ± 10.95	< 0.001
Hb (g/dL)	12.84 ± 1.20	13.16 ± 1.26	< 0.001	13.13 ± 1.01	13.35 ± 1.05	< 0.001
Hct (%)	38.72 ± 2.99	39.54 ± 3.13	< 0.001	39.43 ± 2.81	39.94 ± 2.94	< 0.001
25(OH)D (ng/dL)	15.31 ± 5.07	15.52 ± 5.32	0.369	18.15 ± 6.31	17.62 ± 6.25	0.007

FPG: fasting plasma glucose, Fe: serum iron, TIBC: total iron binding capacity, TFS: transferrin saturation, Hb: hemoglobin, Hct: hematocrit, 25(OH)D: 25-hydroxyvitamin D

4. Discussion and Conclusion

The present study investigated the association between serum ferritin and 25(OH)D levels in Korean women with and without MetS using data from the fifth KNHANES conducted in 2010–2012. Vitamin D status was positively associated with serum ferritin levels in women without MetS but not in women with MetS.

Ferritin is decreased in patients with anemia but increased in patients with insulin resistance diseases, such as MetS [17-18]. In subjects with MetS, despite the increase of hepcidin, which is a negative regulator of ferritin, ferritin levels were increased, and both hepcidin and ferritin levels were increased with increases in MetS components [19-20]. Vitamin D plays an important role in the prevention of anemia, and it decreases insulin resistance, inflammation, and oxidative stress [21-22]. The relationship between vitamin D and ferritin differs between non-MetS and MetS subjects, because ferritin is a marker of iron stores but also an important biomarker of insulin resistance, inflammation, and oxidative stress [23-24]. In the present study, in both premenopausal and postmenopausal women with MetS, vitamin D status was not associated with ferritin levels (Supplemental table). In addition, vitamin D status was not associated with any of the anemia-related variables (e.g., Fe, TIBC, TFS, Hb, Hct). In the advanced state of insulin resistance, such as diabetes or MetS, whether ferritin is a marker of insulin resistance and inflammation or a marker of anemia is not yet clear. In terms of anemia, this process has a positive effect; in contrast, in terms of inflammation markers, insulin resistance, and oxidative stress, this process may have negative effects. As described above, both vitamin D and ferritin are associated with anemia, insulin resistance, inflammation, and oxidative stress. The mechanism of association of vitamin D and ferritin in subjects with MetS is not clear. In terms of anemia, vitamin D may increase ferritin levels. In contrast, in terms of insulin resistance, inflammation, and oxidative stress, vitamin D may decrease ferritin levels. In addition, both processes may occur at the same time. In the present study, we could not demonstrate the mechanisms behind these processes, but we were able to determine that vitamin D was not associated with ferritin in Korean women with MetS.

The present study investigated the association between serum ferritin and 25(OH)D levels in Korean women with and without MetS using data from the fifth KNHANES conducted in 2010–2012. Vitamin D status was found to increase with serum ferritin levels in Korean women without MetS but not in those with MetS.

This is the first reported study to determine the relationship between ferritin and vitamin D in Korean adults with and with MetS. Therefore, more accurate results might be obtained by performing a cohort study by adding these variables.

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