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CLINICAL LABORATORY SCIENCE **ORIGINAL ARTICLE****Relationship between the Estimated Glomerular Filtration Rate and the Urine Microalbumin/Creatinine Ratio and Ferritin in Korean Adults**

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한국 성인에서 사구체여과율 및 요 중 미세알부민/크레아티닌 비율과 페리틴의 관련성

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Accepted April 15, 2019**Key words**Ferritin
Glomerular filtration rate
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This study examined the relationship between the estimated glomerular filtration rate (eGFR) and urine microalbumin/creatinine ratio (uACR) with ferritin in Korean adults. This study included 4,948 adults aged ≥ 20 years from the 2012 Korea National Health and Nutrition Examination Survey (KNHANES) data. A covariance test adjusted for covariates was performed for the ferritin levels in relation to the decreased eGFR ($\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$) and elevated uACR ($\text{uACR} \geq 30 \text{ mg/g}$). Several key findings were made in the present study. First, after adjusting for the related variables, the ferritin level was higher in the decreased eGFR group [$103.04 \pm 6.59 \text{ mL/min/1.73 m}^2$; 95% confidence interval (CI), $90.12 \sim 115.96$] than in the normal eGFR group ($84.87 \pm 1.16 \text{ mL/min/1.73 m}^2$; 95% CI, $82.59 \sim 87.14$; $P=0.007$). Second, after adjusting for the related variables, the ferritin level ($M \pm SE$) was similar in the normal uACR group ($85.70 \pm 1.20 \text{ mg/g}$; 95% CI, $83.35 \sim 88.05$) and elevated uACR group ($82.72 \pm 4.09 \text{ mg/g}$; 95% CI, $74.71 \sim 90.73$) ($P=0.487$). Chronic kidney disease was positively associated with the ferritin level in Korean adults but albuminuria was not.

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INTRODUCTION

Chronic kidney disease (CKD) is a common public health problem, with 10% of the population worldwide affected by it; millions die each year because they do not have access to appropriate treatment [1, 2]. Further, the complications of CKD, such as anemia, hypertension,

diabetes, dyslipidemia, and metabolic syndrome (MetS), have been increasing [3], and these complications further accelerate the progression of severe CKD [4]. In the progression of CKD, diabetic nephropathy, a diabetes-related kidney disease, is a strong risk factor of end-stage renal disease (ESRD) [5]. In particular, it is important to monitor estimated glomerular filtration rate (eGFR) and urine microalbumin/creatinine ratio (uACR) levels. If albuminuria occurs in patients with CKD, the incidence of the ESRD and cardiovascular mortality increase rapidly [6]. Therefore, prevention of diabetes-related kidney disease

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is of prime importance to decrease the socioeconomic burden of illness due to ESRD.

Ferritin, which is regulated by hepcidin [7], is a biomarker of iron stores in the body because ferrous iron combined with apoferritin is stored as ferritin in many organisms [8]. Low serum ferritin levels can be an indicator of iron deficiency anemia (IDA) [9]. Conversely, ferritin is an important biomarker of inflammation and oxidative stress [10, 11] and is increased in diseases that present with insulin resistance, such as type 2 diabetes mellitus (T2DM) and MetS [12, 13].

Regarding the available literature on ferritin, previous studies have mainly focused on anemia, inflammation, oxidative stress, and cardiovascular disease [14–16] and rarely on the relationship between ferritin and CKD. Therefore, the present study aimed to investigate the relationships of ferritin with eGFR and uACR in Korean adults using the fifth Korea National Health and Nutrition Examination Survey (KNHANES V-3) data.

MATERIALS AND METHODS

1. Study subjects

This study was based on data from the KNHANES V-3 (2012), which are the most recent data for ferritin. The KNHANES is a cross-sectional survey conducted nationwide by the Division of Korean National Health and Welfare. The KNHANES V-3 (2012) was performed from January 2012 to December 2012. In the KNHANES V-3 (2012), 8,058 individuals over 1 year of age were sampled for the survey. Among the 6,221 subjects who participated in the KNHANES V-3, we limited the analyses to adults aged ≥ 20 years. We excluded 1,073 subjects whose data were missing for important analytic variables such as serum ferritin level, various blood chemistry tests, and information about lifestyle. In addition, we excluded participants who had liver cancer (57 subjects), hepatitis virus B (126 subjects), and hepatitis virus C (17 subjects). Finally, 4,948 subjects (2,174 men and 2,774 women) were included in the statistical analysis. The KNHANES V-3 (2012) study was conducted according to the principles

expressed in the Declaration of Helsinki. (Institutional Review Board No, 2012-01EXP-01-2C). All participants in the survey provided written informed consent. Further information can be found in “The KNHANES V-3 (2012) Sample,” which is available on the KNHANES website. The data from KNHANES are available on request by email if the applicant logs onto the “Korea National Health and Nutrition Examination Survey” website.

2. General characteristics and blood chemistry

Research subjects were classified by sex (men and women). In the smoking category, participants who smoked more than one cigarette a day, those who was classified into the current smoker. 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 aspartate aminotransferase (AST), alanine aminotransferase (ALT), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), triglycerides (TGs), fasting plasma glucose (FBG) and insulin, serum iron (Fe), transferrin saturation rate (TFS), total iron binding capacity (TIBC), red blood cell (RBC), white blood cell (WBC), hemoglobin (Hb), hematocrit (Hct), blood urea nitrogen (BUN), serum creatinine (Crea), urine microalbumin, and urine creatinine.

3. Glomerular filtration rate and urine microalbumin/creatinine ratio and ferritin

GFR was estimated from the simplified equation developed using MDRD data: $eGFR = 186.3 \times (\text{serum creatinine in mg/dL})^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ for women}) \times (1.212 \text{ if African American})$ [17]. The decreased eGFR was classified as $eGFR < 60 \text{ mL/min/1.73 m}^2$. Urine microalbumin was measured with a turbidimetric assay (Albumin; Roche, Germany) using a Hitachi Automatic Analyzer 7600 (Hitachi, Japan). Urine creatinine was measured with a colorimetric assay (CREA; Roche, USA)

using a Hitachi Automatic Analyzer 7600 (Hitachi, Japan). The elevated urine microalbumin/creatinine ratio (uACR) was classified as $uACR \geq 30 \text{ mg/g}$ [18]. Concentrations of 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).

4. Statistical analysis

The collected data were statistically analyzed using SPSS WIN version 18.0 (SPSS Inc., Chicago, IL, USA). The distributions of the participant characteristics were

Table 1. General clinical characteristics in research subjects

N (%), Mean $\pm$ SD (N=4,948)

Variables	Category	Total (N=4,948)	Men (N=2,174)	Women (N=2,774)	P-value
Age (years)	<40	1,293 (26.1)	590 (27.1)	703 (25.3)	0.360
	40~59	1,883 (38.1)	815 (37.5)	1,068 (38.5)	
	≥ 60	1,772 (35.8)	769 (35.4)	1,003 (36.2)	
Smoking	Current smoker	1,020 (20.6)	902 (41.5)	118 (4.3)	<0.001
Alcohol drinking	Yes	2,495 (50.4)	1,527 (70.2)	968 (34.9)	
Regular exercise	Yes	313 (6.3)	165 (7.6)	148 (5.3)	
eGFR (mL/min/1.73 m ²)		91.70 $\pm$ 18.02	89.46 $\pm$ 16.52	93.46 $\pm$ 18.94	<0.001
	eGFR ≥ 60	4,790 (96.8)	2,100 (96.6)	2,690 (97.0)	
	eGFR < 60	158 (3.2)	74 (3.4)	84 (3.0)	
uACR (mg/g)		20.11 $\pm$ 113.96	18.86 $\pm$ 99.79	21.09 $\pm$ 123.95	0.495
	uACR < 30	4,524 (91.4)	2,000 (92.0)	2,524 (91.0)	
	uACR ≥ 30	424 (8.6)	174 (8.0)	250 (9.0)	
BMI (kg/m ²)		23.84 $\pm$ 3.34	24.12 $\pm$ 3.15	23.62 $\pm$ 3.47	<0.001
WM (cm)		81.50 $\pm$ 9.58	84.56 $\pm$ 8.70	79.10 $\pm$ 9.56	
SBP (mmHg)		120.08 $\pm$ 16.98	121.72 $\pm$ 15.41	118.80 $\pm$ 18.01	
DBP (mmHg)		75.91 $\pm$ 10.49	78.24 $\pm$ 10.85	74.08 $\pm$ 9.82	<0.001
AST (U/L)		22.82 $\pm$ 16.67	24.96 $\pm$ 18.17	21.15 $\pm$ 15.20	
ALT (U/L)		21.84 $\pm$ 22.77	26.35 $\pm$ 29.23	18.32 $\pm$ 15.08	
TC (mg/dL)		190.51 $\pm$ 22.77	187.41 $\pm$ 35.21	192.93 $\pm$ 36.62	<0.001
TGs (mg/dL)		131.13 $\pm$ 87.19	147.87 $\pm$ 99.49	118.00 $\pm$ 73.59	
HDL-C (mg/dL)		51.52 $\pm$ 12.63	48.21 $\pm$ 11.50	54.12 $\pm$ 12.87	
FBG (mg/dL)		98.92 $\pm$ 21.78	100.88 $\pm$ 22.50	97.39 $\pm$ 21.08	<0.001
Ferritin (μ g/L)		85.40 $\pm$ 95.70	126.83 $\pm$ 117.42	52.93 $\pm$ 55.98	
Fe (μ g/dL)		115.58 $\pm$ 47.67	131.03 $\pm$ 50.15	103.47 $\pm$ 41.83	
TFS (%)		37.20 $\pm$ 15.80	42.67 $\pm$ 16.27	32.92 $\pm$ 13.99	<0.001
TIBC (μ g/dL)		317.13 $\pm$ 45.31	310.39 $\pm$ 40.43	322.41 $\pm$ 47.94	
Hemoglobin (g/dL)		14.05 $\pm$ 1.60	15.25 $\pm$ 1.27	13.11 $\pm$ 1.14	
Hematocrit (%)		41.82 $\pm$ 4.14	44.85 $\pm$ 3.36	39.44 $\pm$ 2.98	<0.001
RBC ($10^6/\mu$ L)		4.54 $\pm$ 0.45	4.83 $\pm$ 0.41	4.31 $\pm$ 0.33	
WBC ($10^3/\mu$ L)		5.89 $\pm$ 1.65	6.26 $\pm$ 1.66	5.60 $\pm$ 1.57	
BUN (mg/dL)		14.65 $\pm$ 4.49	15.24 $\pm$ 4.49	14.18 $\pm$ 4.44	<0.001
Crea (mg/dL)		0.84 $\pm$ 0.23	0.98 $\pm$ 0.20	0.73 $\pm$ 0.20	

Abbreviations: eGFR, estimated glomerular filtration rate; uACR, urine microalbumin/urine creatinine; BMI, body mass index; WM, waist measurement; SBP, systolic blood pressure; DBP, diastolic blood pressure; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TC, total cholesterol; TGs, triglycerides; HDL-C, high density lipoprotein cholesterol; FBG, fasting blood glucose; Fe, serum iron; TFS, transferrin saturation rate; TIBC, total iron binding capacity; RBC, red blood cell; WBC, white blood cell; BUN, blood urea nitrogen; Crea, serum creatinine.

converted into percentages, and the successive data were presented as averages with standard deviations. The distribution and average difference in clinical characteristics according to gender, decreased eGFR, and elevated uACR were calculated using chi-squared and an independent t-test. In the case of analysis of covariance test (ANCOVA) for the decreased eGFR and elevated uACR, the 4 models constructed were: 1) age and gender; 2) further adjusted for smoking, drinking, regular exercising, SBP, DBP, BMI, and WM; 3) further adjusted for WBC, AST, and ALT; 4) further adjusted for TC, TGs, HDL-C, and FBG. The significance level for all of the statistical data was set as $P < 0.05$.

RESULTS

1. General clinical characteristics of research subjects

The general clinical characteristics of subjects are shown in Table 1. Among men (2,174 subjects), the prevalence rates of the decreased eGFR and elevated uACR were 74 (3.4%) and 174 (8.0%), respectively. Further, the eGFR, uACR, Fe, TFS, TIBC, and ferritin levels were 89.46 ± 16.52 mL/min/1.73 m², 18.86 ± 99.79 mg/g, 131.03 ± 50.15 µg/dL, $42.67 \pm 16.27\%$, 310.39 ± 40.43 µg/dL, and 126.83 ± 117.42 µg/L, respectively. Among women (2,774 subjects), the prevalence rates of the decreased eGFR and elevated uACR were 84 (3.0%) and 250 (9.0%), respectively. The eGFR, uACR, Fe, TFS, TIBC, and ferritin levels were 93.46 ± 18.94 mL/min/1.73 m², 21.09 ± 123.95 mg/g, 103.47 ± 41.83 µg/dL, $32.92 \pm 13.99\%$, 322.41 ± 47.94

Table 2. Clinical characteristics according to eGFR

N (%), Mean $\pm$ SD (N=4,948)

Variables	Category	Normal eGFR (N=4,790)	Decreased eGFR (N=158)	P-value
Age (years)	<40	1,292 (27.0)	1 (0.6)	<0.001
	40~59	1,857 (38.7)	26 (16.5)	
	≥ 60	1,641 (34.3)	131 (82.9)	
Gender	Men	2,100 (43.8)	74 (46.8)	0.456
Smoking	Current smoker	976 (10.4)	44 (27.8)	0.064
Alcohol drinking	Yes	2,447 (51.1)	48 (30.4)	<0.001
Regular exercise	Yes	301 (6.3)	12 (7.6)	0.505
eGFR (mL/min/1.73 m ²)		93.07 ± 16.55	50.34 ± 10.16	<0.001
uACR (mg/g)		14.98 ± 65.23	175.57 ± 504.47	<0.001
BMI (kg/m ²)		23.82 ± 3.34	24.39 ± 3.47	0.035
WM (cm)		81.40 ± 9.58	84.59 ± 9.18	<0.001
SBP (mmHg)		119.77 ± 16.78	129.57 ± 19.92	<0.001
DBP (mmHg)		75.97 ± 10.38	73.96 ± 13.12	0.017
AST (U/L)		22.81 ± 16.89	23.06 ± 7.72	0.853
ALT (U/L)		21.96 ± 23.08	18.30 ± 8.72	0.047
TC (mg/dL)		190.55 ± 36.04	189.10 ± 38.26	0.619
TGs (mg/dL)		130.59 ± 86.98	147.56 ± 92.25	0.016
HDL-C (mg/dL)		51.67 ± 12.63	47.15 ± 11.98	<0.001
FBG (mg/dL)		98.61 ± 21.47	108.46 ± 28.20	<0.001
Ferritin (µg/L)		84.69 ± 94.57	107.03 ± 123.69	0.004
Fe (µg/dL)		116.17 ± 47.83	97.72 ± 38.54	<0.001
TFS (%)		37.38 ± 15.84	31.78 ± 13.40	<0.001
TIBC (µg/dL)		317.08 ± 44.72	318.71 ± 60.51	0.656
Hemoglobin (g/dL)		14.07 ± 1.58	13.22 ± 1.98	<0.001
Hematocrit (%)		41.89 ± 4.07	39.57 ± 5.35	<0.001
RBC (10 ⁶ /µL)		4.55 ± 0.44	4.25 ± 0.60	<0.001
WBC (10 ³ /µL)		5.87 ± 1.64	6.38 ± 1.71	<0.001
BUN (mg/dL)		14.38 ± 3.97	22.92 ± 9.16	<0.001
Crea (mg/dL)		0.82 ± 0.17	1.42 ± 0.75	<0.001

Abbreviations: See Table 1.

μg/dL, and 52.93 ± 55.98 μg/L, respectively.

(Table 3).

2. Clinical characteristics according to eGFR and uACR

The clinical characteristics according to eGFR and uACR are shown in Tables 2 and 3. In terms of eGFR, uACR, SBP, BMI, WM, WBC, TGs, FBG, BUN, and Crea were higher in the decreased eGFR group than in the normal eGFR group, whereas DBP, Fe, TFS, RBC, Hb, and Hct were lower in the former than in the latter. However, the between-group differences of TC and TIBC were not significant (Table 2). In terms of uACR, BMI, WM, SBP, DBP, WBC, TGs, FBG, BUN, and Crea were higher in elevated uACR group than in normal uACR group, whereas eGFR, HDL, Fe, TFS, RBC, Hb, and Hct were lower in the former than in the latter. However, the between-group differences of TC, ferritin, and TIBC were not significant

3. Comparisons of iron and anemia index and ferritin levels according to eGFR and uACR

Comparisons of iron and anemia index and ferritin levels according to eGFR and uACR are shown in Tables 4, 5, and 6. In terms of eGFR (model 4), after adjustment for the related variables, ferritin level ($M \pm SE$) was higher in the decreased eGFR group [103.04 ± 6.59 mL/min/ 1.73 m^2 ; 95% confidence interval (CI), 90.12~115.96] than in the normal eGFR group (84.87 ± 1.16 mL/min/ 1.73 m^2 ; 95% CI, 82.59~87.14) ($P=0.007$). In terms of uACR, after adjusting for the related variables (model 4), ferritin level ($M \pm SE$) in normal uACR group (85.70 ± 1.20 mg/g; 95% CI, 83.35~88.05) and the elevated uACR group (82.72 ± 4.09 mg/g; 95% CI, 74.71~90.73) did not significantly differ ($P=$

Table 3. Clinical characteristics according to uACR

N (%), Mean $\pm$ SD (N=4,948)

Variables	Category	Normal uACR (N=4,524)	Elevated uACR (N=424)	P-value
Age (years)	<40	1,255 (27.7)	38 (9.0)	<0.001
	40~59	1,769 (39.1)	114 (26.8)	
	≥ 60	1,500 (33.2)	272 (64.2)	
Gender	Men	2,000 (44.2)	174 (41.0)	0.208
Smoking	Current smoker	925 (20.4)	95 (22.4)	0.301
Alcohol drinking	Yes	2,320 (51.3)	175 (41.3)	<0.001
Regular exercise	Yes	275 (6.1)	38 (9.0)	0.020
eGFR (mL/min/ 1.73 m^2)		92.43 ± 17.29	83.97 ± 23.18	<0.001
uACR (mg/g)		5.58 ± 5.55	175.15 ± 353.84	<0.001
BMI (kg/m^2)		23.72 ± 3.28	25.11 ± 3.69	<0.001
WM (cm)		81.11 ± 9.47	85.63 ± 9.84	<0.001
SBP (mmHg)		118.95 ± 16.31	132.14 ± 19.19	<0.001
DBP (mmHg)		75.68 ± 10.19	78.31 ± 13.02	<0.001
AST (U/L)		16.93 ± 16.93	25.24 ± 13.46	0.002
ALT (U/L)		21.61 ± 22.99	24.31 ± 20.09	0.020
TC (mg/dL)		190.65 ± 35.75	189.02 ± 39.78	0.376
TGs (mg/dL)		128.58 ± 85.20	158.26 ± 102.43	<0.001
HDL-C (mg/dL)		51.82 ± 12.70	48.39 ± 11.44	<0.001
FBG (mg/dL)		97.47 ± 19.43	114.39 ± 35.36	<0.001
Ferritin (μg/L)		84.61 ± 94.42	93.86 ± 108.19	0.057
Fe (μg/dL)		116.50 ± 47.86	105.73 ± 44.56	<0.001
TFS (%)		37.52 ± 15.88	33.82 ± 14.47	<0.001
TIBC (μg/dL)		316.89 ± 45.07	319.63 ± 47.72	0.234
Hemoglobin (g/dL)		14.06 ± 1.58	13.89 ± 1.77	0.036
Hematocrit (%)		41.86 ± 4.09	41.38 ± 4.63	0.022
RBC ($10^6/\mu\text{L}$)		4.54 ± 0.44	4.48 ± 0.51	0.012
WBC ($10^3/\mu\text{L}$)		5.86 ± 1.63	6.20 ± 1.82	<0.001
BUN (mg/dL)		14.42 ± 4.11	17.14 ± 6.96	<0.001
Crea (mg/dL)		0.83 ± 0.18	0.94 ± 0.54	<0.001

Abbreviations: See Table 1.

Table 4. Comparisons of ferritin levels according to eGFR and uACR

(N=4,948)

Variables	Category	Ferritin ($\mu\text{g/dL}$)			
		Model 1	Model 2	Model 3	Model 4
eGFR (mL/min/1.73 m^2)					
	Normal eGFR	85.03 $\pm$ 1.27 (82.53~87.52)	84.98 $\pm$ 1.26 (82.51~87.45)	84.83 $\pm$ 1.17 (82.55~87.11)	84.87 $\pm$ 1.16 (82.59~87.14)
	Decreased eGFR	96.79 $\pm$ 7.16 (82.76~110.82)	98.27 $\pm$ 7.11 (84.34~112.21)	104.14 $\pm$ 6.62 (91.16~117.12)	103.04 $\pm$ 6.59 (90.12~115.96)
	P-value	0.106	0.066	0.004	0.007
uACR (mg/g)					
	Normal uACR	84.83 $\pm$ 1.31 (82.26~87.40)	85.20 $\pm$ 1.30 (82.65~87.75)	85.44 $\pm$ 1.20 (83.09~87.80)	85.70 $\pm$ 1.20 (83.35~88.05)
	Elevated uACR	91.53 $\pm$ 4.35 (83.00~100.06)	87.56 $\pm$ 4.38 (78.98~96.14)	85.49 $\pm$ 4.05 (77.54~93.43)	82.72 $\pm$ 4.09 (74.71~90.73)
	P-value	0.142	0.607	0.992	0.487

Normal eGFR, eGFR $\geq$ 60 mL/min/1.73 m²; Decreased eGFR, eGFR<60 mL/min/1.73 m²; Normal uACR, uACR<30 mg/g; Elevated uACR, uACR $\geq$ 30 mg/g.

Model 1 [Mean $\pm$ SE (95% CI)], adjusted for age and gender; Model 2 [Mean $\pm$ SE (95% CI)], Model 1 further adjusted for smoking, drinking, regular exercising, SBP, DBP, BMI, and WM; Model 3 [Mean $\pm$ SE (95% CI)], Model 2 further adjusted for WBC, AST, and ALT; Model 4 [Mean $\pm$ SE (95% CI)], Model 3 further adjusted for TC, TGs, HDL-C, and FBG.

Table 5. Comparisons of iron index according to eGFR and uACR

(N=4,948)

Variables	Category	Fe ($\mu\text{g/dL}$)* [M $\pm$ SE (95% CI)]	TFS (%)* [M $\pm$ SE (95% CI)]	TIBC ($\mu\text{g/dL}$)* [M $\pm$ SE (95% CI)]
eGFR (mL/min/1.73 m^2)				
	Normal eGFR	115.63 $\pm$ 0.60 (114.46~116.80)	37.23 $\pm$ 0.20 (36.84~37.62)	316.99 $\pm$ 0.61 (315.81~318.19)
	Decreased eGFR	113.89 $\pm$ 3.40 (107.22~120.55)	36.28 $\pm$ 1.13 (34.07~38.49)	321.80 $\pm$ 3.46 (315.02~328.58)
	P-value	0.467	0.296	0.166
uACR (mg/g)				
	Normal uACR	115.86 $\pm$ 0.62 (114.65~117.07)	37.30 $\pm$ 0.21 (36.90~37.70)	317.03 $\pm$ 0.63 (315.79~318.26)
	Elevated uACR	112.57 $\pm$ 2.11 (108.45~116.70)	36.11 $\pm$ 0.70 (34.74~37.48)	318.50 $\pm$ 2.14 (314.30~322.70)
	P-value	0.137	0.104	0.511

Normal eGFR, eGFR $\geq$ 60 mL/min/1.73 m²; Decreased eGFR, eGFR<60 mL/min/1.73 m²; Normal uACR, uACR<30 mg/g; Elevated uACR, uACR $\geq$ 30 mg/g.

*Adjusted for age, gender, smoking, drinking, regular exercising, SBP, DBP, BMI, WM, WBC, AST, ALT, TC, TGs, HDL-C, and FBG.

0.487) (Table 4). In terms of eGFR, anemia indices, such as Hb, Hct, and RBC, were significantly lower ($P<0.001$) in the decreased eGFR group than in the normal eGFR group, whereas WBC was significantly higher ($P<0.001$) in the former. In terms of uACR, iron indices, such as Fe, TFS, and TIBC, did not significantly differ between the groups. In addition, WBC ($P=0.029$) was higher in the decreased eGFR group than in the normal eGFR group but anemia indices, such as Hb, Hct, and RBC, did not significantly differ. Further, iron indices, such as Fe, TFS, and TIBC, did not significantly differ between the normal uACR group and the elevated uACR group (Table 5).

DISCUSSION

The present study investigated the relationship of ferritin with eGFR and uACR in Korean adults. The key findings in the present study were that the decreased eGFR was positively associated with ferritin level but the elevated uACR was not significant.

The prevalence of CKD and albuminuria varies by the country and ethnicity and is increased with increasing age [19]. The prevalence of CKD and albuminuria in China [20], Switzerland [21], and the US [18] were 2.9% and 8.5%, 8.5% and 17.1%, and 7.0% and 9.3%, respectively. In the present study, the prevalence of CKD and albuminuria was

Table 6. Comparisons of Hb, Hct, RBC, and WBC according to eGFR and uACR

(N=4,948)

Variables	Category	Hb (g/dL)* [M±SE (95% CI)]	Hct (%)* [M±SE (95% CI)]	RBC (10 ⁶ /μL)* [M±SE (95% CI)]	WBC (10 ³ /μL)* [M±SE (95% CI)]
eGFR (mL/min/1.73 m ²)					
	Normal eGFR	14.06±0.02 (14.03~14.09)	41.87±0.04 (41.78~41.95)	4.54±0.01 (4.53~4.55)	5.87±0.02 (5.83~5.91)
	Decreased eGFR	13.40±0.09 (13.22~13.57)	40.05±0.24 (39.57~40.52)	4.35±0.03 (4.29~4.40)	6.39±0.13 (6.14~6.64)
	<i>P</i> -value	<0.001	<0.001	<0.001	<0.001
uACR (mg/g)					
	Normal uACR	14.05±0.02 (14.02~14.08)	41.83±0.04 (41.75~41.92)	4.54±0.01 (4.53~4.55)	5.86±0.02 (5.82~5.91)
	Elevated uACR	13.94±0.06 (13.82~14.05)	41.54±0.15 (41.25~41.84)	4.52±0.02 (4.49~4.55)	6.05±0.08 (5.89~6.21)
	<i>P</i> -value	0.058	0.066	0.216	0.029

Normal eGFR, eGFR ≥ 60 mL/min/1.73 m²; Decreased eGFR, eGFR < 60 mL/min/1.73 m²; Normal uACR, uACR < 30 mg/g; Elevated uACR, uACR ≥ 30 mg/g.

*Adjusted for age, gender, smoking, drinking, regular exercising, SBP, DBP, BMI, WM, AST, ALT, TC, TGs, HDL-C, and FBG.

3.2% and 8.6%, respectively; it increased with increasing age ($P < 0.001$) and was similar to that reported for China. Currently, research on the relationship of ferritin with eGFR and uACR is being conducted worldwide. Regarding the relationship between ferritin and eGFR, Branten et al. reported that ferritin was inversely associated ($P < 0.001$) with GFR [22]. However, Cases-Amenós et al. reported that the decrease of Fe ($P = 0.0456$) was associated with CKD, but ferritin ($P = 0.1564$) and TFS ($P = 0.3110$) were not [23]. In addition, Kang et al. reported that CKD was associated with ferritin in men (1.573; 95% CI, 1.014~2.441) but not in women (1.061; 95% CI, 0.381~2.955) [24]. Regarding the relationship between ferritin and uACR, some studies reported that ferritin was not associated with albuminuria [25, 26]. Serum ferritin level was associated with microalbuminuria (OR, 1.746; 95% CI, 1.221~2.497) in non-hypertensive, non-diabetic men [27]. Hsu et al. reported that serum ferritin level was positively associated with microalbuminuria ($P_{\text{trend}} < 0.001$) in T2DM [28]. As mentioned above, the prevalence of CKD and albuminuria varies with country and ethnicity, and ferritin levels also vary with ethnicity, gender, and disease status [29]. Thus, the results of the relationship between ferritin and eGFR or ferritin and uACR may vary with country, ethnicity, gender, and disease status. We investigated the relationship of ferritin with both eGFR and uACR in general populations, and there is also a

research similar to ours. Oh et al. studied the relationship of ferritin with both eGFR and uACR in general populations, and consequently, ferritin was not found associated with either [30]. In their study, ferritin levels were positively associated with eGFR in non-adjusted model but there was no significant association with uACR. However, when adjusted for age and gender, the significance disappeared. Our result was also similar. In non-adjusted model, ferritin level was significantly higher in the decreased eGFR group than in the normal eGFR group ($P = 0.004$), but the significance disappeared in a model adjusted for age and gender ($P = 0.106$). However, when after adjusted for all related variables, including age and gender, ferritin level was significantly higher in the decreased eGFR group than in the normal eGFR group ($P = 0.007$).

Serum ferritin is nonspecifically elevated in a wide range of inflammatory conditions, autoimmune disorders, acute infections, and malignancies [31, 32]. Serum ferritin is recognized as a marker of acute and chronic inflammations and is also a marker of iron store [33]. The increase of serum ferritin level is significant in anemia resolution. Compared with healthy subjects, patients with CKD have increased levels of markers of anemia, insulin resistance, oxidative stress, and inflammation [34, 35]. Regarding the relationship of CKD with anemia and inflammation, in terms of anemia, ferritin level has to be

lower in the decreased eGFR group than in the normal eGFR group. However, in terms of inflammation, ferritin level has to be higher in the decreased eGFR group than in the normal eGFR group. In the present study, anemia indices, such as RBC, Hb, and Hct, were lower in the decreased eGFR group than in the normal group; however, inflammation indices, such as WBC, were higher in the former. Further, ferritin level was higher in the decreased eGFR group than in the normal eGFR group. There is currently no consensus on whether ferritin in patients with CKD should be considered as a marker of anemia or inflammation. We believe that an increase of ferritin in patients with CKD should be considered as a marker for inflammation but not for anemia. Kell et al. reported that ferritin is the final product of oxidative stress and inflammation, and serum ferritin can be a better marker of inflammation than of iron status in inflammatory diseases [10]. Some studies suggested that ferritin, which is elevated as a product of oxidative stress and inflammation, cannot be used for haem synthesis [33, 36]. Wish suggested that Hb, percentage of hypochromic red cells, and soluble transferrin receptor should be used rather than ferritin and TSF in diagnosing IDA in CKD patients [37]. In our study, GFR was estimated from the simplified equation developed using MDRD data. In the current guidelines, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation using serum creatinine and cystatin C is recommended [38]. However, since glomerular filtration cannot be measured directly in humans, true GFR cannot be known with certainty in either method [39]. Therefore, there is a requirement for standardization across methods of measuring eGFR, including the development of more accurate eGFR equations.

The present study has some limitations. First, hepcidin is an important determinant of ferritin. However, hepcidin was not employed in the KNHANES V-3 study (2012) and thus the related data are not incorporated in this study. Second, GFR was estimated from the simplified equation developed using MDRD data. In the current guidelines, the use of the CKD-EPI equation using serum creatinine and

cystatin C is recommended. However, since glomerular filtration cannot be measured directly in humans, true GFR cannot be known with certainty in either method. Therefore, there is a requirement for standardization across methods of measuring eGFR, including the development of more accurate eGFR equations. Third, because this study was a cross-sectional study, the scope of establishing a causal relationship between ferritin and CKD was limited. Therefore, more accurate results may be obtained by performing a cohort study.

In conclusion, the present study investigated the relationship between eGFR and uACR and ferritin in Korean adults using data from the KNHANES VI-3 conducted in 2012. Chronic kidney disease was positively associated with ferritin level in Korean adults but albuminuria was not significant.

요약

본 연구는 대한민국 성인에서 eGFR 및 uACR과 Ferritin의 관련성에 대한 연구이다. 2012년 국민건강영양조사자료에서 20세 이상의 4,948명을 대상으로 관련변수를 보정한 후, 만성 신장질환(CKD, $eGFR < 60 \text{ mL/min/1.73 m}^2$) 및 알부민뇨($uACR \geq 30 \text{ mg/g}$)에 따른 페리틴 수준을 분석하였다. 만성신장질환군의 ferritin 수준($M \pm SE$) [$103.04 \pm 6.59 \text{ mL/min/1.73 m}^2$; 95% confidence interval (CI), 90.12~115.96]은 정상군($84.87 \pm 1.16 \text{ mL/min/1.73 m}^2$; 95% CI, 82.59~87.14)에 비하여 유의하게 높았다($P=0.007$). 그러나 정상군($82.72 \pm 4.09 \text{ mg/g}$; 95% CI, 74.71~90.73)과 알부민뇨군($82.72 \pm 4.09 \text{ mg/g}$; 95% CI, 74.71~90.73)의 ferritin 수준은 유의한 차이가 없었다($P=0.487$). 결과적으로, 대한민국 성인에서 만성신장질환과 ferritin수준은 양의 상관관계가 있었지만, 알부민뇨에서는 유의한 차이가 없었다.

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