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ORIGINAL ARTICLE

Associations between Anemia and Glomerular Filtration Rate and Albuminuria in Korean Adults by Metabolic Syndrome Status: Analysis of KNHNES V-3 Data

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대한민국 성인의 대사증후군 유무에 따른 빈혈과 사구체 여과율 및 알부민뇨의 연관성: 국민건강영양조사 V-3 분석

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ABSTRACT

The present study was conducted to explore relationships between anemia and estimated glomerular filtration rate (eGFR) and urine microalbumin/creatinine ratio (uACR) in Korean adults with or without metabolic syndrome (MetS). The data of 4,943 adults aged ≥20 years who participated in KNHNES V-3 (2012) were analyzed. In the non-MetS group, the odds ratio (OR) for anemia of those with a decreased eGFR {eGFR<60 mL/min/1.73 m^2, 3.85 (95% confidence interval [CI], 2.03~7.30)} was significant as was the OR of those with decreased eGFR plus elevated uACR (eGFR<60 mL/min/1.73 m^2 and uACR≥30 mg/g, 5.81 [95% CI, 2.60~13.02]). In the MetS group, ORs for anemia for those with an elevated uACR (2.18 [95% CI, 1.11~4.27]), a decreased eGFR (3.74 [95% CI, 1.11~12.55]), or a decreased eGFR plus an elevated uACR (16.79 [95% CI, 5.93~47.57]) were significant. In conclusion, in non-MetS, anemia was associated with a low eGFR, whereas in MetS, anemia was associated with a low eGFR and an elevated uACR. In addition, the OR for anemia was greatly increased when eGFR was diminished and uACR was elevated regardless of MetS and MetS status.

INTRODUCTION

The incidence and prevalence of chronic kidney disease (CKD) have rapidly increased worldwide, which is a concerning finding given that CKD significantly increases the risks of all-cause mortality and cardiovascular mortality [1, 2]. Anemia is one of the most common complications in patients with CKD, and an increase in the prevalence of anemia in patients with CKD significantly increases the risk of cardiovascular morbidity and mortality [3, 4]. In addition, anemia is a frequent complication in patients with diabetic nephropathy, and albuminuria is a predictor of diabetic nephropathy [5, 6]. Anemia in patients with CKD and diabetic nephropathy is known to be due to an absolute or relative deficiency in the synthesis of renal erythropoietin [6, 7].

In the progression of CKD, it is important to monitor the estimated glomerular filtration rate (eGFR) and urine

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microalbumin/creatinine ratio (uACR) levels. If albuminuria occurs in patients with CKD, the incidence of the end-stage renal disease (ESRD) and cardiovascular mortality increases at a rapid rate [8, 9]. At present, most research on the association of albuminuria and anemia has been conducted on patients with diabetes [10-13], while research on patients with metabolic syndrome (MetS), which is similar to type 2 diabetes mellitus, is rare. Furthermore, there are only a limited number of studies on the change in the prevalence of anemia when the eGFR decreases and the uACR increases simultaneously. Therefore, our objective in this study was to assess the association between anemia and eGFR and uACR in Korean adults with and without MetS using data from the fifth Korean National Health and Nutrition Examination Survey (KNHNES V-3; 2012), which is representative of the Korean population.

MATERIALS AND METHODS

1. Study Subjects

This study was performed using data from the KNHNES V-3. The KNHNES V-3 was conducted over the course of 2012 using a rolling sampling survey that involved a complex, stratified, multistage, probability cluster survey of a representative sample of the non-institutionalized civilian population in South Korea. The survey comprised three sections: a health interview survey, a health examination survey, and a nutrition survey. Each survey was conducted by specially trained interviewers, who had no prior knowledge of the participants before conducting the interviews. Participants provided written, informed consent to participate in this survey, and the data was received in anonymized form. In the KNHNES V-3 (2012) survey, 8,958 individuals over one year of age were sampled. Limiting the analyses to adults aged ≥20 years left 6,665 participants, who were then further limited by the exclusion of 1,722 subjects whose data was missing for important analytic variables, such as hemoglobin (Hb), urine microalbumin and urine creatinine levels, or various blood chemistry tests. Finally, 4,943 subjects were included in the statistical analysis. The KNHNES V-3 study was conducted according to the principles expressed in the Declaration of Helsinki (Institutional Review Board No, 2010-02CON-21-C). All participants in the survey signed an informed written consent form. Further information can be found in "The KNHNES V-3 (2012) Sample," which is available on the KNHNES website. The official KNHNES website (https://knhanes.kdca.go.kr/knhanes/sub03/sub03_02_05.do) is currently operating an English-language information homepage. The data of the respective year is available to everyone free of charge. If the applicant completes a simple subscription process and registers his/her email address on the official website of KNHNES, the data of the respective year can be downloaded free of charge.

2. General Characteristics and Blood Chemistry

Research subjects were classified by gender (male and female). The set of anthropometric measurements included the measurement of the body mass index (BMI) and waist measurements (WM), as well as the final measurements of systolic blood pressure (SBP) and diastolic blood pressure (DBP). Blood chemistries included the measurements of total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), triglycerides (TGs), fasting blood glucose (FBG), blood urea nitrogen (BUN), serum creatinine, red blood cell (RBC), white blood cell (WBC), Hb, hematocrit (Hct), urine microalbumin, and urine creatinine measurements.

3. Metabolic Syndrome

The MetS was defined using the diagnostic criteria of the National Cholesterol Education Program based on common clinical measures including TGs, HDL-C, blood pressure, FBG, and WM. TGs over 150 mg/dL were set as the criteria for elevated TGs. The criteria for reduced HDL-C were an HDL-C value below 50 mg/dL in men and 40 mg/dL in women. 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 included abdominal circumference measurements of over 90 cm and 80 cm for men and women, respectively, according to the Asia-Pacific criteria [14]. The presence of defined abnormalities in any three of these five measures constitutes a diagnosis of Mets [15].

4. Glomerular Filtration Rate and Urine Microalbumin and Anemia

eGFR was calculated with a simplified equation developed using the Chronic Kidney Disease Epidemiology Collaboration: eGFR = 141 × min (Scr/κ, 1)$^{\alpha}$ × max (Scr/κ,1)$^{-1.209}$ × 0.993^{Age} × 1.018 [if women] × 1.159 [if black], where Scr indicates serum creatinine and κ is a correction factor, defined as follows: → 0.7 if women and → 0.9 if men [16]. A decreased eGFR was classified as eGFR<60 mL/min/1.73 m^2 [17]. Urine microalbumin was measured with a turbidimetric assay (Albumin; Roche) using a Hitachi Automatic Analyzer 7600 (Hitachi). The urine creatinine was measured with a colorimetric assay (CREA; Roche) using a Hitachi Automatic Analyzer 7600. Urinary albumin was assessed based on the uACR. Elevated uACR was classified as uACR ≥30 mg/g [17]. Anemia was classified as Hb of less than 13 mg/dL and 12 mg/dL for men and women, respectively [18].

5. Data Analysis

The collected data was statistically analyzed using SPSS WIN version 18.0 (IBM Corp.). In statistical analyses, continuous variables were reported as mean±standard

Table 1. Clinical characteristics of research subjects

Variable	Overall (N=4,943)	Non-MetS (N=3,653)	MetS (N=1,290)	*P*-value
Age (yr)	51.85±16.01	49.73±16.29	57.85±13.50	<0.001
<40	1,293 (26.2)	1,147 (31.4)	146 (11.3)	<0.001
40~59	1,883 (38.1)	1,379 (37.7)	504 (39.1)	
≥60	1,767 (35.7)	1,127 (30.9)	640 (49.6)	
Gender (women)	2,772 (56.1)	2,012 (55.1)	760 (58.9)	0.017
eGFR (mL/min/1.73 m^2)	91.71±18.03	93.15±17.93	87.61±17.68	<0.001
≥60	4,785 (96.8)	3,559 (97.4)	1,226 (95.0)	<0.001
<60	158 (3.2)	94 (2.6)	64 (5.0)	
uACR (mg/g)	20.06±113.95	13.99±92.20	37.24±159.07	<0.001
<30	4,520 (91.4)	3,460 (94.7)	1,060 (82.2)	<0.001
≥30	423 (8.6)	193 (5.3)	230 (17.8)	
BMI (kg/m^2)	23.84±3.34	23.01±2.97	26.17±3.24	<0.001
WM (cm)	81.50±9.59	78.91±8.73	88.83±7.98	<0.001
SBP (mmHg)	120.07±16.96	116.38±15.42	130.51±7.98	<0.001
DBP (mmHg)	75.91±10.48	74.16±9.71	80.86±10.99	<0.001
TC (mg/dL)	190.50±36.10	187.95±34.19	197.72±40.16	<0.001
TGs (mg/dL)	131.16±87.22	106.27±62.87	201.66±106.01	<0.001
HDL-C (mg/dL)	51.52±12.63	54.35±12.41	43.52±9.41	<0.001
FBG (mg/dL)	98.92±21.79	94.26±16.49	112.13±28.53	<0.001
BUN (mg/dL)	14.65±4.49	14.40±4.31	15.33±4.92	<0.001
Crea (mg/dL)	0.84±0.23	0.84±0.23	0.85±0.24	0.067
RBC (10^6/μL)	4.54±0.45	4.51±0.44	4.60±0.47	<0.001
WBC (10^3/μL)	5.89±1.65	5.74±1.61	6.30±1.68	<0.001
Hb (g/dL)	14.05±1.60	13.97±1.59	14.27±1.60	<0.001
Hct (%)	41.82±4.14	41.63±4.11	42.35±4.18	<0.001
Anemia	395 (8.0)	328 (9.0)	67 (5.2)	<0.001
Urine MA (μg/dL)	23.66±113.75	17.76±90.87	40.34±160.75	<0.001
Urine creatinine (mg/dL)	150.11±84.98	154.29±86.99	138.30±77.84	<0.001

n (%) or mean±SD.
Abbreviations: Non-MetS, non-metabolic syndrome; MetS, metabolic syndrome; eGFR, estimated glomerular filtration rate; uACR, urine microalbumin/creatinine ratio; BMI, body mass index; WM, waist measurement; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TGs, triglycerides; HDL-C, high density lipoprotein cholesterol; FBG, fasting blood glucose; BUN, blood urea nitrogen; Crea, serum creatinine; RBC, red blood cell; WBC, white blood cell; Hb, hemoglobin; Hct, hematocrit; Anemia, men Hb<13 g/dL or women Hb<12 g/dL; Urine MA, urine microalbumin.

deviation. Categorical variables were reported as percentages (%). The distribution and average difference in clinical characteristics between the non-MetS group and MetS group were calculated using a chi-square and an independent t-test (Table 1). The distribution and average difference in clinical characteristics according to the normal, decreased eGFR, elevated uACR, and decreased GFR plus elevated uACR in the non-MetS group (Table 2) and MetS group (Table 3) were calculated using a chi-square test and an analysis of variance. In the case of the logistic regression for the incidence odds ratio (OR) for anemia, the four models constructed were: 1) non-adjusted; 2) adjusted for age; 3) further adjusted for gender; and 4) further adjusted for BMI (Table 4). An analysis of covariance was conducted for Hb, Hct, RBC, and WBC after adjusting for age, gender, and BMI (Table 5). The significance level for all of the statistical data was set as $P<0.05$.

RESULTS

1. Clinical Characteristics of Research Subjects

The clinical characteristics of the research subjects are provided in Table 1. The prevalence rate of the decreased GFR and elevated uACR were 158 (3.2%) and 423 (8.6%), respectively. Age ($P<0.001$), uACR ($P<0.001$), BMI ($P<0.001$), TC ($P<0.001$), BUN ($P<0.001$), Hb ($P<0.001$), Hct ($P<0.001$), and urine microalbumin ($P<0.001$) in the MetS group were significantly higher than those in the non-MetS group. However, eGFR ($P<0.001$), anemia ($P<0.001$), and urine creatinine ($P<0.001$) in the MetS group were significantly lower than those in the non-MetS group.

2. Clinical Characteristics of Subjects According to the Normal, Elevated uACR, Decreased eGFR, and Decreased GFR Plus Elevated uACR in Subjects with and without MetS

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Table 2. Clinical characteristics of subjects according to the normal, elevated uACR, decreased eGFR, and decreased eGFR plus elevated uACR in subjects without MetS (N=3,653)

Variable	Normal (N=3,401)	Elevated uACR (N=158)	Decreased eGFR (N=59)	Decreased eGFR plus elevated uACR (N=35)	*P*-value
Gender (women)	1,884 (55.4)	84 (53.2)	29 (49.2)	15 (42.9)	0.351
Age (yr)	48.77±15.94	58.88±16.21	70.83±9.34	68.37±12.86	<0.001
SBP (mmHg)	115.72±15.01	124.88±18.27	124.51±15.34	129.77±22.39	<0.001
DBP (mmHg)	74.13±9.59	75.13±9.77	72.36±9.89	74.94±17.87	0.275
BMI (kg/m^2)	22.94±2.94	23.58±3.29	23.29±2.77	23.80±3.67	0.024
WM (cm)	78.72±8.67	81.03±9.49	81.27±8.07	83.13±9.46	<0.001
TC (mg/dL)	188.17±34.17	184.66±36.74	187.64±27.64	180.11±33.60	0.328
TGs (mg/dL)	105.96±63.59	112.55±59.63	104.22±34.98	110.06±36.30	0.604
HDL-C (mg/dL)	54.45±12.45	54.00±11.44	51.06±12.25	51.26±11.79	0.082
FBG (mg/dL)	93.47±14.51	106.70±34.06	99.41±14.23	105.94±38.72	<0.001
BUN (mg/dL)	14.14±3.90	15.34±4.50	20.90±6.04	25.00±10.64	<0.001
Crea (mg/dL)	0.82±0.16	0.82±0.17	1.26±0.26	1.77±1.30	<0.001
eGFR (mL/min/1.73 m^2)	94.37±16.58	92.15±18.34	53.42±5.94	45.73±13.65	<0.001
uACR (mg/g)	4.94±5.02	133.38±193.74	9.95±7.51	361.80±733.55	<0.001
RBC (10^6/μL)	4.52±0.44	4.49±0.44	4.24±0.55	4.27±0.61	<0.001
WBC (10^3/μL)	5.73±1.58	5.87±2.08	5.88±1.57	6.06±1.06	0.008
Hb (g/dL)	13.99±1.57	13.98±1.69	13.26±2.00	13.07±1.89	<0.001
Hct (%)	41.69±4.06	41.59±4.27	39.69±5.18	39.49±5.47	<0.001
Anemia	283 (8.3)	16 (10.1)	17 (28.8)	12 (34.3)	<0.001

n (%) or mean±SD.
Abbreviations: uACR, urine microalbumin/creatinine ratio; eGFR, estimated glomerular filtration rate; MetS, metabolic syndrome; Normal, eGFR≥60 mL/min/1.73 m^2 and uACR<30 mg/g; Elevated uACR, uACR≥30 mg/g; Decreased eGFR, eGFR<60 mL/min/1.73 m^2; Decreased eGFR plus elevated uACR, eGFR<60 mL/min/1.73 m^2 and uACR≥30 mg/g; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WM, waist measurement; TC, total cholesterol; TGs, triglycerides; HDL-C, high density lipoprotein cholesterol; FBG, fasting blood glucose; BUN, blood urea nitrogen; Crea, serum creatinine; RBC, red blood cell; WBC, white blood cell; Hb, hemoglobin; Hct, hematocrit; Anemia, men Hb<13 g/dL or women Hb<12 g/dL.

Table 3. Clinical characteristics of subjects according to the normal, elevated uACR, decreased eGFR, and decreased eGFR plus elevated uACR in subjects with MetS (N=1,290)

Variable	Normal (N=1,025)	Elevated uACR (N=201)	Decreased eGFR (N=34)	Decreased eGFR plus elevated uACR (N=30)	*P*-value
Gender (women)	590 (57.6)	132 (65.7)	21 (61.8)	19 (63.3)	0.168
Age (yr)	56.26±13.24	62.22±12.96	72.68±6.60	67.50±12.09	<0.001
SBP (mmHg)	128.75±16.01	138.42±16.51	136.65±16.91	131.27±22.92	<0.001
DBP (mmHg)	81.00±10.35	82.08±12.97	76.00±10.26	73.63±15.18	<0.001
BMI (kg/m^2)	26.16±3.16	26.39±3.51	25.38±3.58	26.11±3.51	0.399
WM (cm)	88.80±7.77	89.12±8.75	87.67±8.89	89.35±8.43	0.770
TC (mg/dL)	198.87±39.29	193.02±41.99	195.18±50.91	195.57±44.01	0.283
TGs (mg/dL)	202.93±103.85	192.20±113.86	190.50±103.04	227.90±125.05	0.266
HDL-C (mg/dL)	43.45±9.45	44.67±9.16	42.09±7.99	40.40±10.64	0.068
FBG (mg/dL)	110.18±26.84	120.02±34.72	110.32±21.23	127.07±33.07	<0.001
BUN (mg/dL)	14.73±3.95	15.80±4.24	21.27±7.97	26.37±12.15	<0.001
Crea (mg/dL)	0.83±0.17	0.80±0.16	1.27±0.36	1.47±0.75	<0.001
eGFR (mL/min/1.73 m^2)	89.56±15.43	89.53±16.96	51.66±7.94	48.16±12.08	<0.001
uACR (mg/g)	7.25±6.41	131.42±212.24	11.12±7.55	470.41±725.60	<0.001
RBC (10^6/μL)	4.63±0.44	4.57±0.47	4.32±0.55	4.60±0.73	<0.001
WBC (10^3/μL)	6.27±1.57	6.28±1.68	6.50±1.84	6.98±2.20	0.132
Hb (g/dL)	14.37±1.54	14.09±1.63	13.5±1.70	13.01±2.38	<0.001
Hct (%)	42.60±4.00	41.95±4.23	40.27±4.56	38.66±6.43	<0.001
Anemia	36 (3.5)	15 (7.5)	4 (11.8)	12 (40.0)	<0.001

n (%) or mean±SD.
Abbreviations: uACR, urine microalbumin/creatinine ratio; eGFR, estimated glomerular filtration rate; MetS, metabolic syndrome; Normal, eGFR≥60 mL/min/1.73 m^2 and uACR<30 mg/g; Elevated uACR, uACR≥30 mg/g; Decreased eGFR, eGFR<60 mL/min/1.73 m^2; Decreased eGFR plus elevated uACR, eGFR<60 mL/min/1.73 m^2 and uACR≥30 mg/g; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WM, waist measurement; TC, total cholesterol; TGs, triglycerides; HDL-C, high density lipoprotein cholesterol; FBG, fasting blood glucose; BUN, blood urea nitrogen; Crea, serum creatinine; RBC, red blood cell; WBC, white blood cell; Hb, hemoglobin; Hct, hematocrit; Anemia, men Hb<13 g/dL or women Hb<12 g/dL.

Table 4. Comparisons of anemia incidence odds ratios according to the normal, the elevated uACR, decreased eGFR, and decreased eGFR plus elevated uACR groups in non-MetS and MetS (N=4,943)

Variable	Anemia (odd ratios [95% confidence interval])			
	Model 1	Model 2	Model 3	Model 4
Non-MetS (N=3,653)				
Normal	1	1	1	1
Elevated uACR	1.21 (0.73~2.11)	11.14 (0.67~1.95)	1.16 (0.68~2.00)	1.14 (0.66~1.97)
Decreased eGFR	4.45 (2.51~7.94)	3.71 (2.05~6.74)	4.06 (2.20~7.51)	3.85 (2.03~7.30)
Decreased eGFR plus elevated uACR	5.75 (2.83~11.67)	4.88 (2.37~10.05)	5.91 (2.79~12.50)	5.81 (2.60~13.02)
MetS (N=1,290)				
Normal	1	1	1	1
Elevated uACR	2.23 (1.20~4.16)	2.19 (1.16~4.13)	2.16 (1.14~4.08)	2.08 (1.09~3.99)
Decreased eGFR	3.67 (1.23~10.96)	3.49 (1.11~10.92)	7.18 (1.30~13.45)	3.74 (1.11~12.55)
Decreased eGFR plus elevated uACR	18.33 (8.22~40.91)	17.71 (7.71~40.70)	22.30 (9.17~54.24)	16.79 (5.93~47.57)

Abbreviations: uACR, urine microalbumin/creatinine ratio; eGFR, estimated glomerular filtration rate; MetS, metabolic syndrome; Anemia, men Hb<13 g/dL or women Hb<12 g/dL; eGFR, estimated glomerular filtration rate; uACR, urine microalbumin/creatinine ratio; Model 1, non-adjusted; Model 2, adjusted for age; Model 3, Model 2 further gender; Model 4, Model 3 further adjusted for body mass index.

eGFR, and elevated uACR in subjects with and without MetS, are provided in Tables 2 and 3. In both subjects with and without MetS, compare with the normal group, RBC, Hb, and Hct levels in the elevated uACR group, decreased eGFR group, and decreased GFR plus elevated uACR group were decreased, in contrast, age, BUN, FBG, WBC, and anemia were increased.

Table 5. Comparisons of Hb, Hct, RBC, and WBC levels according to the normal, elevated uACR, decreased eGFR, and decreased eGFR plus elevated uACR groups in non-MetS and MetS (N=4,943)

	Hb (g/dL)[a]	Hct (%)[a]	RBC (10^6/μL)[a]	WBC (10^3/μL)[a]
Non-MetS (N=3,653)				
Normal	14.04±0.09 (13.86~14.21)	41.74±0.24 (41.28~42.21)	4.53±0.03 (4.48~4.59)	5.72±0.03 (5.66~5.77)
Elevated uACR	13.98±0.02 (13.95~14.02)	41.68±0.05 (41.58~41.78)	4.52±0.01 (4.51~4.53)	5.38±0.13 (5.69~6.18)
Decreased eGFR	13.41±0.15 (13.12~13.71)	40.07±0.40 (39.29~40.84)	4.36±0.04 (4.28~4.45)	6.07±0.21 (5.66~6.48)
Decreased eGFR plus elevated uACR	13.09±0.20 (12.70~13.48)	39.53±0.52 (38.52~40.54)	4.35±0.06 (4.24~4.47)	6.76±0.27 (6.23~7.29)
P-value	<0.001	<0.001	<0.001	<0.001
MetS (N=1,290)				
Normal	14.30±0.04 (14.23~14.37)	42.44±0.10 (42.25~42.63)	4.61±0.01 (4.58~4.63)	6.24±0.05 (6.14~6.34)
Elevated uACR	14.29±0.08 (14.13~14.45)	42.43±0.22 (42.01~42.86)	4.63±0.03 (4.58~4.68)	6.40±0.12 (6.17~6.63)
Decreased eGFR	13.86±0.20 (13.47~14.26)	41.22±0.53 (40.17~42.27)	4.49±0.06 (4.37~4.62)	6.83±0.29 (6.26~7.39)
Decreased eGFR plus elevated uACR	13.47±0.22 (13.03~13.90)	39.92±0.59 (38.76~41.08)	4.35±0.07 (4.22~4.49)	7.18±0.38 (6.55~7.80)
P-value	0.001	<0.001	0.001	0.008

Mean±SD (95% confidence interval).
[a]Adjusted for age, gender, and body mass index.
Abbreviations: Hb, hemoglobin; Hct, hematocrit; RBC, red blood cell; WBC, white blood cell; uACR, urine microalbumin/creatinine ratio; eGFR, estimated glomerular filtration rate; MetS, metabolic syndrome.

3. Comparison of the Anemia-related Index and Anemia Incidence Odds Ratios According to the Normal, Elevated uACR, Decreased eGFR, and Decreased eGFR Plus Elevated uACR Groups

The comparisons of the anemia-related index and ORs of anemia incidence according to the normal, decreased eGFR, elevated uACR, and decreased eGFR plus elevated uACR groups are provided in Tables 4 and 5. In non-MetS subjects, after adjusting for related variables (age, gender, and BMI), the ORs of anemia incidence with a normal group as a reference were significant for the decreased eGFR group {3.85 (95% confidence interval [CI], 2.03~7.30)}, but the elevated uACR group (1.14 [95% CI, 0.66~1.97]) was not significant. In MetS subjects, after adjusting for related variables, the ORs of anemia incidence with a normal group as a reference were significant for the elevated uACR (2.08 [95% CI, 1.09~3.99]) and decreased eGFR group (3.74 [95% CI, 1.11~12.55]). In addition, the ORs of anemia incidence with a normal group as a reference were more significant for the decreased eGFR plus elevated uACR group in both non-MetS (5.81 [95% CI, 2.60~13.02]) and MetS subjects (16.79 [95% CI, 5.93~47.57]) (Table 4). After adjusting for related variables, the Hb, Hct, and RBC levels were significantly decreased according to the normal, elevated uACR, the decreased eGFR, and the decreased GFR plus elevated uACR groups in non-MetS and MetS subjects, while the WBC levels were significantly increased (Table 5).

DISCUSSION

The present study investigated the association between anemia and eGFR and uACR in Korean adults with or without MetS using data from the KNHNES V-3 (2012). Anemia was associated with the decreased eGFR group in non-MetS, but was associated with both the decreased eGFR and the elevated uACR groups in MetS. In addition, in both non-MetS and MetS, the ORs of anemia increased greatly when the decreased eGFR and elevated uACR appeared simultaneously.

Several studies report that the incidence of anemia is increased in CKD [19-21]. Moreover, anemia is associated with cardiovascular events in populations with CKD [4, 22]. In particular, an increase in the prevalence of anemia in ESRD significantly increases cardiovascular morbidity and mortality [23]. Previous studies have suggested that the importance of the early treatment of anemia in CKD should be emphasized because it

can slow the decline in renal function [24, 25]. Anemia in CKD is caused by the relative erythropoietin deficiency and the uremic-induced inhibitors of erythropoiesis and shortened erythrocyte survival [26]. In the progression of CKD, the decline in renal function is determined by the eGFR level; however, it is important to monitor both eGFR and uACR levels in the progression of CKD because in the instance that albuminuria appears in the population with CKD, it demonstrates an accelerated decline in renal function [8, 9].

The association of decreased eGFR and anemia is well established. In the presented study, a decreased eGFR was positively associated with the incidence of anemia in both subjects with or without MetS. However, an elevated uACR was positively associated with the incidence of anemia in the subjects with MetS, and was not subjects in the population without MetS. The mechanism for the relationship between anemia and albuminuria remains ambiguous. However, there are potentially mechanisms linking anemia with albuminuria. Albuminuria in patients with CKD contributes to a significant increase in the prevalence of anemia [27]. Anemia is a frequent complication of diabetic nephropathy and is more frequently present in populations with type 2 diabetes mellitus or MetS with albuminuria compared to those without albuminuria [10, 28]. Albuminuria is an important predictor in the progression of diabetic nephropathy nephropathy in insulin resistance diseases such as type 2 diabetes mellitus and MetS [29, 30], but is unclear in participants without insulin resistance diseases. Dronavalli et al [31] suggested that albuminuria reflects no renal risk, but if the uACR levels continue to increase, then diabetic nephropathy may be present. We consider that this may be due to a continuous increase of the uACR levels in the population with MetS relative to those without MetS. Previous studies have emphasized that the treatment of MetS in the population with diabetic nephropathy is incredibly important because the treatment of MetS slows the progression of diabetic nephropathy [32, 33]. Okada et al [13] reported that a low Hb level is the predictor of the progression or development of albuminuria in those with type 2 diabetes, which is similar to MetS. Prinsen et al [34] suggested that the synthesis of transferrin is increased in the nephrotic syndrome and significant losses of transferrin in severe proteinuria populations may result in iron-deficiency anemia.

Upon examining the incidence of anemia, when the decreased eGFR and elevated uACR occurred simultaneously in non-MetS and MetS, interesting findings emerged. The results indicated that the ORs of anemia in the decreased eGFR plus elevated uACR group (non-MetS, 5.81; MetS, 16.79) were much higher than in the decreased eGFR group (non-MetS, 3.85; MetS, 3.74) or in the elevated uACR group (non-MetS, non-significant; MetS, 2.08) in both non-MetS and MetS. The elevated uACR was positively associated with anemia in MetS but not in non-MetS. However, if the decreased eGFR and elevated uACR occurred simultaneously, an increased incidence of anemia was observed due to their strong interaction in both non-MetS and MetS. Due to the strong synergistic interaction between a decrease in eGFR and an increase in uACR, if albuminuria is present in the population with CKD, the incidence of acute kidney injury (AKI), ESRD, and progressive CKD can be accelerated [8, 9]. Levey et al [8] reported that both AKI and progressive CKD for the decreased eGFR plus elevated uACR group were higher (AKI, at least 5.9 times; progressive CKD, at least 9.4 times) than in the case of the decreased eGFR group (AKI, at least 2.2 times; progressive CKD, at least 3.0 times) or elevated uACR group (AKI, at least 2.4 times; progressive CKD, at least 1.9 times) [8]. In particular, the ESRD for the decreased eGFR plus elevated uACR group was much higher (at least 40 times) than in the case of the decreased eGFR group (at least 5.2 times) or the elevated uACR group (at least 3.8 times).

In the present study, the decreased eGFR plus elevated uACR group of anemia in MetS is higher than in non-MetS. The increase of uACR in MetS, which is characterized by insulin resistance, can accelerate the progression of diabetic nephropathy, which is asso-

ciated with the reduction of erythropoietin [29, 30, 35]. Diabetic nephropathy leads the transformation of peritubular fibroblasts into myofibroblasts, thereby reducing erythropoietin production [36], as well as damaging the tubulo-interstitial and leading endogenous erythropoietin production [37]. The treatment of albuminuria is important for reducing the progression of diabetic nephropathy and ESRD in CKD [38, 39]. In addition, the treatment of albuminuria can block the synergistic interaction between albuminuria and CKD, reducing CKD complications, such as anemia. The present study might be limited by the constraints of a cross-sectional study, compromising the ability to establish a causal relationship between anemia and uACR and GFR. Despite these limitations, this study is the first to report on the relationship between anemia and eGFR and uACR in Korean adults with and without MetS. In the future, conducting a cohort study may yield more accurate results. It's crucial to consider how these findings compare with current data for a comprehensive interpretation, ensuring relevance and precision.

In conclusions, the presented study investigated the association between anemia and eGFR and uACR in Korean adults with or without MetS using data from the KNHNES V-3 conducted in 2012. In non-MetS, anemia was associated with the decreased eGFR but not with the elevated uACR. In MetS, anemia was associated with both the decreased eGFR and elevated uACR. In addition, in both non-MetS and MetS, the ORs of anemia were greatly increased when a decreased eGFR and elevated uACR appeared simultaneously.

요 약

본 연구는 대한민국 성인을 대상으로 대사증후군(metabolic syndrome, MetS) 유·무에 따른 빈혈과 추정 사구체여과율(estimated glomerular filtration rate, eGFR) 및 요 미세알부민/크레아티닌 비율(urine microalbumin/creatinine ratio, uACR)의 관련성을 평가하기 위하여 2012년 국민건강영양조사(KNHNES V-3) 자료를 활용하여 20세 이상 성인 4,943명을 대상으로 데이터를 분석하였다. 본 연구에서 몇 가지 중요한 발견이 있었다. 첫째, 비 MetS 그룹에서는 정상군(eGFR≥60 mL/min/1.73 m^2 및 uACR<30 mg/g)의 빈혈(남성, 헤모글로빈[hemoglobin, Hb]<13 g/dL; 여성, Hb<12 g/dL)의 발생률에 비하여 감소된 eGFR 그룹(eGFR<60 mL/min/1.73 m^2; odds ratio [OR], 3.65; 95% confidence interval [CI], 1.90~7.00) 및 감소된 eGFR+증가된 uACR 그룹(eGFR<60 mL/min/1.73 m^2 및 uACR≥30 mg/g, OR, 6.00; 95% CI, 2.61~13.80)의 빈혈 발생률이 높았다. 둘째, MetS 그룹에서는 정상군에 비하여 증가된 uACR 그룹(OR, 2.18; 95% CI, 1.11~4.27), 감소된 eGFR 그룹(OR, 3.73; 95% CI, 1.09~12.75) 및 감소된 eGFR+증가된 uACR 그룹(OR, 18.17; 95% CI, 6.16~53.63)의 빈혈 발생률이 높았다. 결론적으로, 비 MetS 그룹에서는 빈혈은 eGFR의 감소와 관련이 있었고, MetS 그룹에서는 빈혈은 eGFR 감소 및 uACR 증가와 관련이 있었다. 추가적으로, 비 MetS 그룹과 MetS 그룹 모두에서 eGFR의 감소 및 uACR의 증가가 동시에 나타날 때 빈혈의 발생률이 크게 증가하였다.

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REFERENCES

1. Inker LA, Coresh J, Levey AS, Tonelli M, Muntner P. Estimated GFR, albuminuria, and complications of chronic kidney disease. J Am Soc Nephrol. 2011;22:2322-2331. https://doi.org/10.1681/ASN.2010111181
2. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int. 2020;98(4S):S1-S115. https://doi.org/10.1016/j.kint.2020.06.019
3. Kuo IC, Lin HY, Niu SW, Lee JJ, Chiu YW, Hung CC, et al. Anemia modifies the prognostic value of glycated hemoglobin in patients with diabetic chronic kidney disease. PLoS One. 2018;13:e0199378.

https://doi.org/10.1371/journal.pone.0199378
4. Kubo K, Okamura T, Sugiyama D, Hisamatsu T, Hirata A, Kadota A, et al. Effect of chronic kidney disease or anemia or both on cardiovascular mortality in a 25-year follow-up study of Japanese general population (from NIPPON DATA90). Am J Cardiol. 2022; 184:1-6. https://doi.org/10.1016/j.amjcard.2022.08.027
5. Bajaj S, Makkar BM, Abichandani VK, Talwalkar PG, Saboo B, Srikanta SS, et al. Management of anemia in patients with diabetic kidney disease: a consensus statement. Indian J Endocrinol Metab. 2016;20:268-281. https://doi.org/10.4103/2230-8210.176348
6. Roshan B, Stanton RC. A story of microalbuminuria and diabetic nephropathy. J Nephropathol. 2013;2:234-240. https://doi.org/10.12860/JNP.2013.37
7. Portolés J, Martín L, Broseta JJ, Cases A. Anemia in chronic kidney disease: from pathophysiology and current treatments, to future agents. Front Med (Lausanne). 2021;8:642296. https://doi.org/10.3389/fmed.2021.642296
8. Levey AS, de Jong PE, Coresh J, El Nahas M, Astor BC, Matsushita K, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int. 2011;80:17-28. https://doi.org/10.1038/ki.2010.483
9. Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. Am J Kidney Dis. 2014;63:713-735. https://doi.org/10.1053/j.ajkd.2014.01.416
10. Adetunji OR, Mani H, Olujohungbe A, Abraham KA, Gill GV. 'Microalbuminuric anaemia'--the relationship between haemoglobin levels and albuminuria in diabetes. Diabetes Res Clin Pract. 2009;85:179-182. https://doi.org/10.1016/j.diabres.2009.04.028
11. Jain RB. Perfluoroalkyl acids and their isomers, diabetes, anemia, and albuminuria: variabilities with deteriorating kidney function. Ecotoxicol Environ Saf. 2021;208:111625. https://doi.org/10.1016/j.ecoenv.2020.111625
12. Yang JQ, Ran P, Chen JY, He YT, Li LW, Tan N, et al. Development of contrast-induced acute kidney injury after elective contrast media exposure in patients with type 2 diabetes mellitus: effect of albuminuria. PLoS One. 2014;9:e106454. https://doi.org/10.1371/journal.pone.0106454
13. Okada H, Hasegawa G, Tanaka M, Osaka T, Shiotsu Y, Narumiya H, et al. Association between hemoglobin concentration and the progression or development of albuminuria in diabetic kidney disease. PLoS One. 2015;10:e0129192. https://doi.org/10.1371/journal.pone.0129192
14. Yoon H, Go JS, Kim KU, Lee KW. The association of serum ferritin and metabolic syndrome and metabolic syndrome score in Korean adults. Korean J Clin Lab Sci. 2016;48:287-295. https://doi.org/10.15324/kjcls.2016.48.4.287
15. Yoon H, Jeong DK, Lee KS, Kim HS, Moon AE, Park J. Relationship between metabolic syndrome and metabolic syndrome score and beta cell function by gender in Korean populations with obesity. Endocr J. 2016;63:785-793. https://doi.org/10.1507/endocrj.EJ16-0106
16. Seong JM, Lee JH, Gi MY, Son YH, Moon AE, Park CE, et al. Gender difference in the association of chronic kidney disease with visceral adiposity index and lipid accumulation product index in Korean adults: Korean National Health and Nutrition Examination Survey. Int Urol Nephrol. 2021;53:1417-1425. https://doi.org/10.1007/s11255-020-02735-0
17. Park J, Ryu SY, Han MA, Choi SW. The association of vitamin D with estimated glomerular filtration rate and albuminuria: 5th Korean National Health and Nutritional Examination Survey 2011-2012. J Ren Nutr. 2016;26:360-366. https://doi.org/10.1053/j.jrn.2016.07.003
18. World Health Organization. Iron deficiency anaemia: assessment, prevention and control. A guide for programme managers. World Health Organization: 2001.
19. McClellan W, Aronoff SL, Bolton WK, Hood S, Lorber DL, Tang KL, et al. The prevalence of anemia in patients with chronic kidney disease. Curr Med Res Opin. 2004;20:1501-1510. https://doi.org/10.1185/030079904X2763
20. Ryu SR, Park SK, Jung JY, Kim YH, Oh YK, Yoo TH, et al. The prevalence and management of anemia in chronic kidney disease patients: result from the KoreaN Cohort Study for Outcomes in Patients With Chronic Kidney Disease (KNOW-CKD). J Korean Med Sci. 2017;32:249-256. https://doi.org/10.3346/jkms.2017.32.2.249
21. Guedes M, Muenz DG, Zee J, Bieber B, Stengel B, Massy ZA, et al. Serum biomarkers of iron stores are associated with increased risk of all-cause mortality and cardiovascular events in non-dialysis CKD patients, with or without anemia. J Am Soc Nephrol. 2021;32:2020-2030. https://doi.org/10.1681/ASN.2020101531
22. Jankowski J, Floege J, Fliser D, Böhm M, Marx N. Cardiovascular disease in chronic kidney disease: pathophysiological insights and therapeutic options. Circulation. 2021;143:1157-1172. https://doi.org/10.1161/CIRCULATIONAHA.120.050686
23. Hanna RM, Streja E, Kalantar-Zadeh K. Burden of anemia in chronic kidney disease: beyond erythropoietin. Adv Ther. 2021;38:52-75. https://doi.org/10.1007/s12325-020-01524-6
24. Gouva C, Nikolopoulos P, Ioannidis JP, Siamopoulos KC. Treating anemia early in renal failure patients slows the decline of renal function: a randomized controlled trial. Kidney Int. 2004;66:753-760. https://doi.org/10.1111/j.1523-1755.2004.00797.x
25. Srinivasan R, Fredy IC, Chandrashekar S, Saravanan J, Mohanta GP, Manna PK. Assessment of erythropoietin for treatment of anemia in chronic kidney failure- ESRD patients. Biomed Pharmacother. 2016;82:44-48. https://doi.org/10.1016/j.biopha.2016.04.041
26. Babitt JL, Lin HY. Mechanisms of anemia in CKD. J Am Soc Nephrol. 2012;23:1631-1634. https://doi.org/10.1681/ASN.2011111078
27. Han JS, Lee MJ, Park KS, Han SH, Yoo TH, Oh KH, et al. Albuminuria as a risk factor for anemia in chronic kidney disease: result from the KoreaN Cohort Study for Outcomes in Patients With Chronic Kidney Disease (KNOW-CKD). PLoS One. 2015;10:e0139747. https://doi.org/10.1371/journal.pone.0139747
28. Ritz E, Haxsen V. Diabetic nephropathy and anaemia. Eur J Clin Invest. 2005;35(Suppl 3):66-74. https://doi.org/10.1111/j.1365-2362.2005.01544.x
29. Mutter S, Valo E, Aittomäki V, Nybo K, Raivonen L, Thorn LM, et al. Urinary metabolite profiling and risk of progression of diabetic nephropathy in 2670 individuals with type 1 diabetes. Diabetologia. 2022;65:140-149. https://doi.org/10.1007/s00125-021-05584-3
30. Maric C, Hall JE. Obesity, metabolic syndrome and diabetic

nephropathy. Contrib Nephrol. 2011;170:28-35. https://doi.org/10.1159/000324941
31. Dronavalli S, Duka I, Bakris GL. The pathogenesis of diabetic nephropathy. Nat Clin Pract Endocrinol Metab. 2008;4:444-452. https://doi.org/10.1038/ncpendmet0894
32. Lim AKh. Diabetic nephropathy - complications and treatment. Int J Nephrol Renovasc Dis. 2014;7:361-381. https://doi.org/10.2147/IJNRD.S40172
33. Duran-Perez EG, Almeda-Valdes P, Cuevas-Ramos D, Campos-Barrera E, Muñoz-Hernandez L, Gomez-Perez FJ. Treatment of metabolic syndrome slows progression of diabetic nephropathy. Metab Syndr Relat Disord. 2011;9:483-489. https://doi.org/10.1089/met.2011.0056
34. Prinsen BHCMT, Velden MGMS, Kaysen GA, Straver HWHC, Rijn HJMV, Stellaard F, et al. Transferrin synthesis is increased in nephrotic patients insufficiently to replace urinary losses. J Am Soc Nephrol. 2001;12:1017-1025. https://doi.org/10.1681/ASN.V1251017
35. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes. 1988;37:1595-1607. https://doi.org/10.2337/diab.37.12.1595
36. Cao Y, Lin JH, Hammes HP, Zhang C. Cellular phenotypic transitions in diabetic nephropathy: an update. Front Pharmacol. 2022;13:1038073. https://doi.org/10.3389/fphar.2022.1038073
37. Zhang Y, Zhu X, Huang X, Wei X, Zhao D, Jiang L, et al. Advances in understanding the effects of erythropoietin on renal fibrosis. Front Med (Lausanne). 2020;7:47. https://doi.org/10.3389/fmed.2020.00047
38. McGill JB, Haller H, Roy-Chaudhury P, Cherrington A, Wada T, Wanner C, et al. Making an impact on kidney disease in people with type 2 diabetes: the importance of screening for albuminuria. BMJ Open Diabetes Res Care. 2022;10:e002806. https://doi.org/10.1136/bmjdrc-2022-002806
39. Yamazaki T, Mimura I, Tanaka T, Nangaku M. Treatment of diabetic kidney disease: current and future. Diabetes Metab J. 2021;45:11-26. https://doi.org/10.4093/dmj.2020.0217