EnM
ENDOCRINOLOGY AND METABOLISM

Original Article

Endocrinol Metab 2016;31:537-546
https://doi.org/10.3803/EnM.2016.31.4.537
pISSN 2093-596X · eISSN 2093-5978

Urinary Albumin Excretion Reflects Cardiovascular Risk in Postmenopausal Women without Diabetes: The 2011 to 2013 Korean National Health and Nutrition Examination Survey

Hee Jung Ahn, Do Sik Moon, Da Yeong Kang, Jung In Lee, Da Young Kim, Jin Hwa Kim, Sang Yong Kim, Hak Yeon Bae

Division of Endocrinology and Metabolism, Department of Internal Medicine, Chosun University Hospital, Chosun University School of Medicine, Gwangju, Korea

Background: The objective of the current study was to determine whether there was an association between urinary albumin excretion and cardiovascular disease (CVD) risk by estimating the Framingham Risk Score (FRS) in postmenopausal women without diabetes.

Methods: This study was based on data from the Korea National Health and Nutrition Examination Survey, which was conducted by the Korean Ministry of Health and Welfare in 2011 to 2013. Data on 2,316 postmenopausal women from a total of 24,594 participants was included in the analysis.

Results: The mean FRS was significantly different in each of the urinary albumin to creatinine ratio (UACR) subgroups, and it increased with UACR. The FRS was 12.69±0.12 in the optimal group, 14.30±0.19 in the intermediate normal group, 14.62±0.26 in the high normal group, and 15.86±0.36 in the microalbuminuria group. After fully adjusting for potential confounding factors, high normal levels and microalbuminuria were significantly associated with the highest tertile of FRS ([odds ratio (OR), 1.642; 95% confidence interval (CI), 1.124 to 2.400] and [OR, 3.385; 95% CI, 2.088 to 5.488], respectively) compared with the optimal subgroup. High normal levels and microalbuminuria were also significantly associated with a ≥10% 10-year risk of CVD ([OR, 1.853; 95% CI, 1.122 to 3.060] and [OR, 2.831; 95% CI, 1.327 to 6.037], respectively) after adjusting for potential confounding covariates.

Conclusion: Urinary albumin excretion reflects CVD risk in postmenopausal women without diabetes, and high normal levels and microalbuminuria were independently associated with a higher risk of CVD.

Keywords: Urinary albumin excretion; Cardiovascular risk; Postmenopause

INTRODUCTION

Microalbuminuria, which is defined as a urinary albumin to creatinine ratio (UACR) between 30 to 300 mg/g, is a known predictive marker of cardiovascular disease (CVD) and mortality in individuals with [1-3] and without diabetes [4-7]. The Pre-

Received: 19 May 2016, **Revised**: 28 July 2016, **Accepted:** 4 August 2016
Corresponding author: Sang Yong Kim
Division of Endocrinology and Metabolism, Department of Internal Medicine, Chosun University Hospital, Chosun University School of Medicine, 365 Pilmun-daero, Dong-gu, Gwangju 61453, Korea
Tel: +82-62-220-3011, **Fax:** +82-62-223-3316, **E-mail:** diabetes@chosun.ac.kr

vention of Renal and Vascular End Stage Disease (PREVEND) study [8] showed that elevated excretion of albumin in the urine could also be used as a metabolic syndrome component to more reliably predict the development of CVD.

Recent studies have suggested that patients with high-normal albuminuria levels (i.e., less than the current cutoff value of microalbuminuria) also have an increased risk of CVD [9-16]. However, it is unclear whether albuminuria and its association with CVD risk appear in all individuals regardless of demographics, such as race/ethnicity, sex, and population. To our knowledge, no studies have focused on postmenopausal women without diabetes, particularly in a large national representative population.

Postmenopause is a period related to unfavorable metabolic changes and is associated with an increased risk of CVD [17,18]. This high burden of CVD during postmenopause enhances the need to identify its surrogate markers to ensure that patients may benefit from personalized interventions to prevent CVD. Moreover, a possible influence of postmenopause on urinary albumin excretion has been suggested [19-21].

The objective of the current study was to determine whether there was an association between urinary albumin excretion and CVD risk by estimating the Framingham Risk Score (FRS) in postmenopausal women without diabetes.

METHODS

Study population

This study was based on data from the Korea National Health and Nutrition Examination Survey (KNHANES), which was conducted by the Korean Ministry of Health and Welfare in 2011 to 2013. This cross-sectional and nationally representative survey of non-institutionalized civilians used a stratified, multistage, clustered probability sampling design. The sampling units are defined based on data from household registries, including the geographic area, sex, and age groups. KNHANES is composed of a health interview survey, a nutrition survey, and a health examination survey conducted by trained investigators. All participants in this survey provided signed informed consent. Out of the 24,594 participants in the 2011 to 2013 survey, we used data collected from 4,327 women who were naturally postmenopausal. Menopause was defined as the absence of menses for 12 consecutive months. We excluded women 80 years of age and older (n=267), women who experienced the onset of menopause when they were younger than 40 years (n=130), and women who had fasted for <8 hours (n=140). We also excluded women with diabetes (n=732). Diabetes was defined as having a fasting plasma glucose (FPG) level ≥126 mg/dL, an glycated hemoglobin (HbA1c) level ≥6.5%, the use of insulin or anti-diabetic medication, or being diagnosed with diabetes by a physician. Women with missing or incomplete data required for the analysis (n=279) were excluded. Women were also excluded if they had myocardial infarction, angina, or stroke (n=144), were undergoing lipid lowering treatment (n=294), or if they had overt macroalbuminuria (UACR ≥300 mg/g; n=25). Finally, data from 2,316 postmenopausal women were retained for the analysis.

Measurement and classification of variables

Height was measured to the nearest 0.1 cm using a portable stadiometer, with the participants in the upright position. Body weight was measured to the nearest 0.1 kg on a balanced scale. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Waist circumference (WC) was measured midway between the costal margin and the iliac crest at the end of a normal expiration. Blood pressure (BP) was measured from the right arm using a standard mercury sphygmomanometer after 5 minutes of rest in the sitting position. The mean value of two separate BP measurements was used for the analysis. Venous blood samples were obtained after a minimum fasting time of 8 hours. Plasma glucose, total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and triglyceride levels were measured using a Hitachi Automatic Analyzer 7600 (Hitachi, Tokyo, Japan) from 2011 to 2012 and using the COBAS 8000 C702 (Roche, Mannheim, Germany) in 2013. HbA1c was measured using high-performance liquid chromatography (HLC-723G7, Tosoh, Tokyo, Japan) from 2011 to 2012 and the Tosoh G8 (Tosoh) in 2013. Spot urine albumin concentrations were measured with a turbidimetric assay (Hitachi Automatic Analyzer 7600). Serum and spot urine creatinine levels were measured with a colorimetric assay (Hitachi Automatic Analyzer 7600) from 2011 to 2012 using the Jaffe rate-blanked and compensated method (COBAS 8000 C702).

Estimated glomerular filtration rate (eGFR) was calculated using the abbreviated equation from the Modification of Diet in Renal Disease study: eGFR (mL/min/1.73 m^2)=175×(serum creatinine)$^{-1.154}$×(age)$^{-0.203}$×0.742 [22].

The FRS for each subject was calculated using the National Cholesterol Education Program Adult Treatment Panel III algorithm, which is based on six risk factors: sex, age, total cholesterol, HDL-C, systolic BP, and smoking status [23].

The UACR was calculated as the ratio of urine albumin to creatinine, expressed in milligrams per gram.

Self-reported questionnaires were administered to determine smoking status, alcohol use, family income, education level, residential area, and regular exercise habits. The residential area was categorized (according to the Korean administrative district) as urban or rural. Regular exercise was recorded as 'yes' when the subject performed moderate exercise on a regular basis (more than 30 minutes at a time and more than five times per week). Known hypertension was defined as being treated or diagnosed by a physician. The subjects were also asked to recall certain reproductive issues, including age at menarche, age at menopause, lactation history, and oral contraceptive use.

Statistical analysis

Complex sample analysis was applied to the KNHANES data to weigh all values, following the recommendations from the Korea Centers for Disease Control and Prevention. Continuous variables are reported as mean±SD, and categorical variables are reported as weighted percentages. Comparisons among groups were performed using the complex samples general linear model for continuous variables, and the chi-square test was used for categorical variables. To further analyze significant differences between each subgroup, we compared each set of two subgroups using the *t* test.

For data analysis, albuminuria was categorized according to the UACR into optimal (≤5.0 mg/g), intermediate normal (5.1 to 9.9 mg/g), high normal (10.0 to 29.9 mg/g), and microalbuminuria (30.0 to 299.9 mg/g) groups [16,24]. The subjects were also subdivided into three tertile groups based on FRS as follows: tertile 1, FRS ≤12; tertile 2, 12 <FRS<16; and tertile 3, FRS ≥16.

Multivariate logistic regression analyses were used to measure the association between urinary albumin excretion and CVD risk (estimated by FRS) by evaluating the odds ratio (OR), after adjusting for confounding factors that were associated with an increased risk of CVD and their influence on urinary albumin excretion. The analyses were adjusted for potential confounders in a series of models. Covariates were added to the model. First, we added lifestyle behaviors (alcohol drinking and regular exercise) and sociodemographic factors (residential area, family income, and education), and then we added known CVD risk factors (diastolic BP, BMI, WC, FPG, triglyceride, and LDL-C), reproductive factors (age at menarche, age at menopause, oral contraceptive use, and lactation history), eGFR level and hypertension history.

Statistical analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA), and a $P<0.05$ was considered to be statistically significant.

RESULTS

The subjects' clinical and biochemical characteristics are presented in Table 1. The mean patient age was 60.35±0.21 years, and the mean FRS was 13.60±0.10. As expected, the subjects with higher FRS had less favorable cardiometabolic profiles (e.g., higher BMI, WC, BP, FPG, total cholesterol, LDL-C, and triglyceride levels and lower HDL-C levels) and hypertension histories compared to those with lower FRS. Lower family income, education level, and residence in a rural area were more common among the subjects with a higher FRS. Reproductive factors, such as age at menarche, age at menopause, lactation history, and oral contraceptive use, differed between the FRS subgroups. Lifestyle behaviors (smoking and alcohol drinking) and eGFR levels also differed among the FRS subgroups.

The mean UACR was 11.29±0.66 mg/g. The mean value of UACR differed significantly between the FRS subgroups and increased with increased FRS (tertile 1, 7.19±1.01 mg/g; tertile 2, 9.34±0.71 mg/g; and tertile 3, 18.75±1.51 mg/g).

Comparison of clinical characteristics and FRS among the UACR subgroups

Table 2 shows the characteristics of the subjects stratified into four groups by UACR. Subjects with a higher UACR had higher BMI, WC, BP, FPG, HbA1c, and triglyceride levels but lower HDL-C levels; they also had a longer history of hypertension and were more likely to have lower family income and education levels. Alcohol drinking and reproductive factors, such as age at menarche and lactation history, differed between the UACR subgroups.

The mean FRS differed significantly in each of the UACR subgroups, and it increased as the UACR increased. The FRS was 12.69±0.12 in the optimal albuminuria group, 14.30±0.19 in the intermediate normal albuminuria group, 14.62±0.26 in the high normal albuminuria group, and 15.86±0.36 in the microalbuminuria group. The distribution of the 10-year risk of CVD differed significantly between the UACR subgroups, and the proportion of patients with a higher 10-year risk of CVD increased with higher albuminuria levels.

Relationship between FRS and UACR

Table 3 shows the multivariate adjusted relationship between

Table 1. Characteristics of the Study Population according to Framingham Risk Score Tertile

Characteristic	Total	Tertile 1 (FRS ≤12)	Tertile 2 (12<FRS<16)	Tertile 3 (FRS ≥16)	*P* value
Number	2,316	844	670	802	
Age, yr	60.35±0.21	54.46±0.17	60.16±0.27[a]	68.59±0.33[a,b]	<0.001
BMI, kg/m^2	23.92±0.08	23.41±0.12	24.30±0.15[a]	24.25±0.13[a]	<0.001
WC, cm	80.48±0.26	78.06±0.37	81.19±0.42[a]	83.10±0.39[a,b]	<0.001
SBP, mm Hg	122.65±0.49	113.54±0.57	122.64±0.75[a]	135.13±0.78[a,b]	<0.001
DBP, mm Hg	76.19±0.26	74.44±0.35	77.08±0.46[a]	77.73±0.47[a]	<0.001
FPG, mg/dL	93.95±0.26	92.07±0.37	95.18±0.47[a]	95.35±0.40[a]	<0.001
HbA1c, %	5.71±0.00	5.62±0.01	5.77±0.01[a]	5.78±0.01[a]	<0.001
TC, mg/dL	207.40±0.87	197.34±1.23	214.59±1.53[a]	214.30±1.45[a]	<0.001
TG, mg/dL	130.22±2.14	107.84±2.59	135.43±4.04[a]	155.83±4.37[a,b]	<0.001
LDL-C, mg/dL	127.50±0.78	118.87±1.10	134.06±1.44[a]	133.02±1.35[a]	<0.001
HDL-C, mg/dL	53.86±0.32	56.90±0.53	53.43±0.57[a]	50.11±0.49[a,b]	<0.001
Serum Cr, mg/dL	0.72±0.00	0.72±0.00	0.71±0.00	0.73±0.00	0.072
Smoking, %					<0.001
None	93.2	98.9	91.9[a]	86.6[a,b]	
Ex-smoking	2.6	0.3	2.8[a]	5.5[a,b]	
Current	4.2	0.8	5.3[a]	7.9[a,b]	
Alcohol drinking, %					<0.001
None	45.6	38.6	46.5[a]	54.5[a,b]	
≤1/week	47.9	54.5	46.2[a]	40.7[a,b]	
2–3/weeks	4.5	5.7	4.4[a]	2.8[a,b]	
≥4/weeks	2.0	1.2	3.0[a]	2.0[a,b]	
Family income, %[c]					<0.001
<100	23.5	8.1	22.1[a]	45.8[a,b]	
100–199	18.0	15.3	20.3[a]	19.5[a,b]	
200–299	16.2	16.6	18.4[a]	13.5[a,b]	
≥300	42.4	60.0	39.2[a]	21.1[a,b]	
Less than high school education, %	67.9	51.1	73.3[a]	85.7[a,b]	<0.001
Residence in urban area, %	64.6	70.2	63.4[a]	58.0[a,b]	<0.001
Regular exercise, yes, %[d]	6.8	7.2	6.8	6.2	0.769
HTN history, %	26.3	10.0	21.2[a]	53.4[a,b]	<0.001
Age at menarche, yr	15.89±0.05	15.52±0.08	16.01±0.09[a]	16.27±0.08[a]	<0.001
Age at menopause, yr	50.14±0.09	49.96±0.12	50.50±0.16[a]	50.05±0.22	0.036
Lactation, ever, %	87.9	83.5	88.7[a]	93.3[a,b]	<0.001
OC, ever, %	19.8	12.7	23.2[a]	26.1[a,b]	<0.001
eGFR, mL/min/1.73 m^2	84.60±0.40	86.66±0.60	85.27±0.72	81.45±0.67[a,b]	<0.001
FRS	13.60±0.10	10.03±0.07	13.91±0.04[a]	18.18±0.08[a,b]	<0.001
UACR, mg/g	11.29±0.66	7.19±1.01	9.34±0.71[a]	18.75±1.51[a,b]	<0.001
Log UACR, mg/g[e]	1.40±0.04	0.99±0.06	1.45±0.06[a]	1.09±0.07[a,b]	<0.001
UACR, %					<0.001
≤5.0 mg/g	54.2	67.8	52.0[a]	37.7[a,b]	
5.1–9.9 mg/g	21.8	17.8	24.2[a]	25.0[a,b]	
10.0–29.9 mg/g	16.6	10.7	18.4[a]	22.8[a,b]	
30.0–299.9 mg/g	7.4	3.6	5.5[a]	14.4[a,b]	

Values are expressed as mean±SD.
FRS, Framingham Risk Score; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; Cr, creatinine; HTN, hypertension; OC, oral contraceptive; eGFR, estimated glomerular filtration rate; UACR, urinary albumin to creatinine ratio.
[a]P<0.05 for tertile 1 vs. tertile 2 and tertile 1 vs. tertile 3; [b]P<0.05 for tertile 2 vs. tertile 3; [c]Unit is 10,000 Korean won/month; [d]Regular exercise is indicated as 'yes' when the subject performs moderate exercise on a regular basis (more than 30 minutes at a time and more than five times per week); [e]UACR was logarithmically transformed for analysis to ensure a normal distribution.

Table 2. Characteristics of the Study Population according to the Urinary Albumin to Creatinine Ratio

Characteristic	Optimal (≤5.0 mg/g)	Intermediate normal (5.1–9.9 mg/g)	High normal (10.0–29.9 mg/g)	Microalbuminuria (30.0–299.9 mg/g)	*P* value
Number	1,261	515	370	170	
Age, yr	58.72±0.26	61.85±0.43[a]	62.04±0.56[a]	64.11±0.95[a]	<0.001
BMI, kg/m^2	23.71±0.10	23.97±0.16	24.32±0.23[a]	24.41±0.29[a]	0.019
WC, cm	79.67±0.34	80.91±0.47	81.54±0.65[a]	82.72±0.92[a]	0.002
SBP, mm Hg	118.45±0.54	124.45±0.81[a]	128.42±1.36[a,b]	135.24±1.75[a,b,c]	<0.001
DBP, mm Hg	74.79±0.31	76.75±0.54[a]	77.84±0.68[a]	81.13±1.02[a,b,c]	<0.001
FPG, mg/dL	92.73±0.32	94.36±0.47[a]	96.05±0.68[a,b]	96.96±0.85[a,b]	<0.001
HbA1c, %	5.68±0.01	5.73±0.01	5.77±0.20[a]	5.75±0.03	<0.001
TC, mg/dL	207.08±1.16	208.37±1.65	206.80±2.22	208.29±3.46	0.903
TG, mg/dL	123.93±2.53	131.75±4.19	136.34±6.91	158.09±11.07[a]	0.009
LDL-C, mg/dL	127.65±1.03	128.61±1.49	126.83±2.15	124.55±2.88	0.652
HDL-C, mg/dL	54.64±0.46	53.40±0.65	52.70±0.73	52.12±0.98[a]	0.033
Serum Cr, mg/dL	0.72±0.00	0.71±0.00	0.71±0.00	0.72±0.01	0.576
Smoking, %					0.165
None	93.2	93.6	92.4	94.2	
Ex-smoking	2.0	3.6	2.2	4.4	
Current	4.8	2.8	5.4	1.3	
Alcohol drinking, %					0.031
None	41.7	50.6[a]	51.5[a]	46.9	
≤1/week	52.3	42.8[a]	42.8[a]	42.6	
2–3/weeks	4.1	4.4[a]	3.7[a]	9.0	
≥4/weeks	1.9	2.2[a]	2.0[a]	1.6	
Family income, %[d]					<0.001
<100	18.4	27.0[a]	33.2[a,b]	28.7[a,c]	
100–199	17.9	20.1[a]	13.6[a,b]	22.4[a,c]	
200–299	16.1	14.8[a]	19.4[a,b]	13.7[a,c]	
≥300	47.6	38.1[a]	33.8[a,b]	35.2[a,c]	
Less than high school education, %	61.0	74.0[a]	79.0[a]	75.9[a]	<0.001
Residence in urban area, %	65.2	64.3	64.3	61.3	0.876
Regular exercise, yes, %[e]	7.7	5.9	4.9	6.7	0.369
HTN history, %	18.5	31.7[a]	37.2[a]	43.4[a,b]	<0.001
Age at menarche, yr	15.76±0.06	15.91±0.11	16.14±0.14[a]	16.25±0.16[a]	0.011
Age at menopause, yr	50.22±0.10	50.01±0.21	50.23±0.28	49.76±0.41	0.566
Lactation, ever, %	85.4	90.9[a]	90.7[a]	91.4[a]	0.021
OC, ever, %	18.2	20.1	21.6	26.3	0.144
eGFR, mL/min/1.73 m^2	84.35±0.47	85.15±0.86	84.91±1.02	84.12±1.68	0.837
UACR	2.24±0.05	6.96±0.07[a]	16.36±0.35[a,b]	79.24±5.6[a,b,c]	<0.001
Log UACR[f]	0.40±0.04	1.92±0.01[a]	2.74±0.02[a,b]	4.17±0.05[a,b,c]	<0.001
FRS	12.69±0.12	14.30±0.19[a]	14.62±0.26[a]	15.86±0.36[a,b,c]	<0.001
10-Year risk of CVD, %					<0.001
<10%	96.1	91.6[a]	88.8[a]	82.6[a,b,c]	
10–19%	3.1	7.8[a]	10.0[a]	16.4[a,b,c]	
≥20.0%	0.8	0.6[a]	1.1[a]	1.0[a,b,c]	

Values are expressed as mean±SD.
BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; Cr, creatinine; HTN, hypertension; OC, oral contraceptive; eGFR, estimated glomerular filtration rate; UACR, urinary albumin to creatinine ratio; FRS, Framingham Risk Score; CVD, cardiovascular disease.
[a]$P<0.05$ for optimal vs. intermediate normal, optimal vs. high normal, and optimal vs. microalbuminuria; [b]$P<0.05$ for intermediate normal vs. high normal and intermediate normal vs. microalbuminuria; [c]$P<0.05$ for high normal vs. microalbuminuria; [d]Unit is 10,000 Korean won/month; [e]Regular exercise is indicated as 'yes' when the subject performs moderate exercise on a regular basis (more than 30 minutes at a time and more than five times per week); [f]UACR was logarithmically transformed for analysis to ensure a normal distribution.

Table 3. Odds Ratio (95% Confidence Interval) for the Highest Framingham Risk Score Tertile, according to the Urinary Albumin to Creatinine Ratio

	Optimal (≤5.0 mg/g, reference)	Intermediate normal (5.1–9.9 mg/g)	High normal (10.0–29.9 mg/g)	Microalbuminuria (30.0–299.9 mg/g)
Model 1	1.00	1.673 (1.267–2.210)[a]	2.083 (1.497–2.898)[a]	5.279 (3.392–8.216)[a]
Model 2	1.00	1.555 (1.163–2.078)[a]	1.915 (1.340–2.736)[a]	4.227 (2.667–6.700)[a]
Model 3	1.00	1.532 (1.144–2.051)[a]	1.872 (1.305–2.684)[a]	4.004 (2.522–6.357)[a]
Model 4	1.00	1.543 (1.149–2.071)[a]	1.878 (1.309–2.695)[a]	3.929 (2.444–6.314)[a]
Model 5	1.00	1.351 (0.981–1.859)	1.642 (1.124–2.400)[a]	3.385 (2.088–5.488)[a]

Model 1: adjusted for lifestyle behaviors (alcohol drinking and regular exercise) and sociodemographic factors (residential area, family income, and education); Model 2: model 1 plus known cardiovascular risk factors (diastolic blood pressure, body mass index, waist circumference, fasting plasma glucose, triglyceride, and low density lipoprotein cholesterol); Model 3: model 2 plus reproductive factors (age at menarche, age at menopause, oral contraceptive use, and lactation); Model 4: model 3 plus estimated glomerular filtration rate; Model 5: model 4 plus hypertension history.
[a]$P<0.05$.

Table 4. Odds Ratio (95% Confidence Interval) for ≥10% 10-Year Risk of Cardiovascular Disease, according to the Urinary Albumin to Creatinine Ratio

	Optimal (≤5.0 mg/g, reference)	Intermediate normal (5.1–9.9 mg/g)	High normal (10.0–29.9 mg/g)	Microalbuminuria (30.0–299.9 mg/g)
Model 1	1.00	1.829 (1.123–2.980)[a]	2.281 (1.398–3.724)[a]	4.224 (2.288–7.800)[a]
Model 2	1.00	1.768 (1.075–2.908)[a]	2.103 (1.285–3.443)[a]	3.825 (1.987–7.366)[a]
Model 3	1.00	1.669 (1.027–2.713)[a]	2.050 (1.270–3.309)[a]	3.449 (1.682–7.075)[a]
Model 4	1.00	1.654 (0.997–2.743)	2.134 (1.323–3.444)[a]	3.389 (1.642–6.994)[a]
Model 5	1.00	1.390 (0.798–2.424)	1.853 (1.122–3.060)[a]	2.831 (1.327–6.037)[a]

Model 1: adjusted for lifestyle behaviors (alcohol drinking and regular exercise) and sociodemographic factors (residential area, family income, and education); Model 2: model 1 plus known cardiovascular risk factors (diastolic blood pressure, body mass index, waist circumference, fasting plasma glucose, triglyceride, and low density lipoprotein cholesterol); Model 3: model 2 plus reproductive factors (age at menarche, age at menopause, oral contraceptive use, and lactation); Model 4: model 3 plus estimated glomerular filtration rate; Model 5: model 4 plus hypertension history.
[a]$P<0.05$.

the highest tertiles of the FRS and the UACR range. After adjusting for lifestyle behaviors and sociodemographic factors, intermediate normal, high normal, and microalbuminuria levels were significantly associated with the highest tertile of FRS ([OR, 1.673; 95% confidence interval (CI), 1.267 to 2.210], [OR, 2.083; 95% CI, 1.497 to 2.898], and [OR, 5.279; 95% CI, 3.392 to 8.216], respectively) compared to the optimal subgroup. After further adjustments for known CVD risk factors, the ORs were attenuated but remained significant ([intermediate normal: OR, 1.555; 95% CI, 1.163 to 2.078], [high normal: OR, 1.915; 95% CI, 1.340 to 2.736], and [microalbuminuria: OR, 4.227; 95% CI, 2.667 to 6.700]). These independent associations remained after adjusting for reproductive factors, in addition to the above factors ([intermediate normal: OR, 1.532; 95% CI, 1.144 to 2.051], [high normal: OR, 1.872; 95% CI, 1.305 to 2.684], and [microalbuminuria: OR, 4.004; 95% CI, 2.522 to 6.357]). After adjusting for the previous factors, as well as for eGFR level, the association remained significant ([intermediate normal: OR, 1.543; 95% CI, 1.149 to 2.071], [high normal: OR, 1.878; 95% CI, 1.309 to 2.695], and [microalbuminuria: OR, 3.929; 95% CI, 2.444 to 6.314]). After further adjustments for hypertension history, intermediate normal levels were no longer significantly associated with the highest tertiles of the FRS (OR, 1.351; 95% CI, 0.981 to 1.859), but this association remained significant in subjects with high normal levels (OR, 1.642; 95% CI, 1.124 to 2.400) and microalbuminuria (OR, 3.385; 95% CI, 2.088 to 5.488).

Relationship between CVD risk and UACR

There were few subjects with a ≥20% 10-year risk of CVD (Table 2). Thus, we evaluated the relationship between a ≥10% 10-year risk of CVD and UACR with multivariate logistic re-

gression analyses (Table 4). After adjustments for lifestyle behaviors and sociodemographic factors, intermediate normal, high normal levels, and microalbuminuria were significantly associated with a ≥10% 10-year risk of CVD ([OR, 1.829; 95% CI, 1.123 to 2.980], [OR, 2.281; 95% CI, 1.398 to 3.724], and [OR, 4.224; 95% CI, 2.288 to 7.800], respectively) compared with the optimal subgroup. After further adjustments for known CVD risk factors, the ORs were attenuated but remained significant ([intermediate normal: OR, 1.768; 95% CI, 1.075 to 2.908], [high normal: OR, 2.103; 95% CI, 1.285 to 3.443], and [microalbuminuria: OR, 3.825; 95% CI, 1.987 to 7.366]). These independent associations remained after adjusting for reproductive factors, in addition to the above factors ([intermediate normal: OR, 1.669; 95% CI, 1.027 to 2.713], [high normal: OR, 2.050; 95% CI, 1.270 to 3.309], and [microalbuminuria: OR, 3.449; 95% CI, 1.682 to 7.075]). After further adjustments for eGFR levels, intermediate normal levels were no longer significantly associated with a ≥10% 10-year risk of CVD (OR, 1.654; 95% CI, 0.997 to 2.743), but this association remained significant in subjects with high normal levels (OR, 2.134; 95% CI, 1.323 to 3.444]) and microalbuminuria (OR, 3.389; 95% CI, 1.642 to 6.994). After adjustments for the previous factors and hypertension history, the association remained significant ([high normal: OR, 1.853; 95% CI, 1.122 to 3.060] and [microalbuminuria: OR, 2.831; 95% CI, 1.327 to 6.037]).

DISCUSSION

In this study, microalbuminuria was independently associated with a higher risk of increased FRS and a ≥10% 10-year risk of CVD in postmenopausal women without diabetes, after adjusting for multiple potential confounding variables. Interestingly, this association even extends into the normal range of albuminuria. Subjects with high normal albuminuria levels (10.0≤ UACR≤29.9 mg/g) had a significantly higher risk of increased FRS and a ≥10% 10-year risk of CVD compared with those in the optimal ranges (UACR ≤5.0 mg/g). To our knowledge, this large population-based study is the first to focus on the association between albuminuria levels and CVD risk in postmenopausal women without diabetes. Our results indicate that microalbuminuria and albuminuria levels in the high range of normal reflect CVD risk in postmenopausal women without diabetes.

Microalbuminuria is known as a marker of early stage renal damage, which is an independent risk factor of CVD and has been associated with an increased risk of CVD mortality in diabetes patients [1-3]. Moreover, the relationship between microalbuminuria and CVD risk has been reported in nondiabetic patients [4,5,8]. The UACR was positively related to carotid atherosclerotic plaque-initiation and plaque-growth in nondiabetic patients [6]. The Heart Outcomes Prevention Evaluation (HOPE) study [7] reported that UACR was an independent and continuous risk factor of future CVD risk in nondiabetic individuals and suggested that any degree of albuminuria is a risk factor of CVD.

Recently, although there has been debate, several studies have suggested that patients with high-normal albuminuria levels that are still within the normal range also have an increased risk of CVD. These studies have questioned the concept that albumin excretion levels less than 30 mg/g are normal [9-16]. In data from the Framingham Heart Study [13], urinary albumin excretion below the conventional threshold for microalbuminuria predicted the development of CVD and mortality in middle-aged nonhypertensive, nondiabetic individuals. The Strong Heart Study [14] also showed that albuminuria levels lower than the traditional cutoff value predicted CVD and CVD mortality independent of other CVD risk factors. Hong et al. [15] reported that albuminuria levels within normal ranges were significantly associated with estimated cardiovascular (CV) risk based on the FRS and metabolic syndrome in the general Korean population. A meta-analysis has reported that a UACR of 10 mg/g or more was an independent predictor of mortality risk in the general population [16].

In the current study, we evaluated the association between urinary albumin excretion and CVD risk by estimating the FRS in postmenopausal women without diabetes. The FRS is a widely used tool for assessing the 10-year risk of CVD events in asymptomatic individuals [25]. The results of our study are consistent with previous reports showing an association between albuminuria and CVD risk in the general population. We found a significant positive association between albuminuria and FRS, even for levels that were below the traditional cutoff value for microalbuminuria, and this association remained after adjusting for conditions potentially affecting the results, including traditional and nontraditional CVD risk factors. Hypertension has a known positive correlation with albuminuria [26]. After adjusting for hypertension history, the association was attenuated, but it remained significant. This finding suggests that urinary albumin excretion may itself play an independent role in CVD risk in postmenopausal women without diabetes, in addition to other CVD risk factors. Additional studies are needed to explore these potential causal relationships in more detail.

Some studies have reported that postmenopause might be re-

lated to albuminuria [19-21]; estrogen reportedly modulates the renin-angiotensin-aldosterone system [27]. In rats, estrogen reduces the angiotensin converting enzyme mRNA and downregulates angiotensin-converting enzyme (ACE) transcription and the conversion of angiotensin I to angiotensin II, which could decrease the efferent arteriolar pressure. This would therefore decrease intraglomerular pressure and albuminuria levels [19,20]. Based on this evidence, postmenopause, which is an estrogen-deficient state, could affect and mediate the increase in albuminuria. When considering albuminuria as a potential predictor of future CVD risk in the general population, it is important to identify the association between the degree of urinary albumin excretion and CVD risk in postmenopausal women. Moreover, postmenopause is related to metabolically deleterious changes in insulin, glucose, BP, and lipids, and it is associated with CVD risk [17,18]. Roest et al. [28] have demonstrated an independent predictive role of urinary albumin excretion in the risk of future CV mortality in postmenopausal women in the general population. However, they did not exclude women with diabetes. With appropriate adjustments for diabetes, it is possible that there are residual and unmeasured confounding effects related to diabetes. We evaluated postmenopausal women without diabetes, and our results provide evidence that urinary albumin excretion may play a role as an indicator of CVD risk and may be useful in stratifying the individual risk in postmenopausal women.

This study has a cross-sectional design; therefore, it was not possible to establish pathophysiological mechanisms. One of the potential mechanisms is generalized endothelial dysfunction, which could represent systemic hemodynamic instability, which initiates atherosclerosis. The leakage of albumin into the vessel wall through endothelial dysfunction culminates in an inflammatory response and a perturbation of the vascular matrix, which mediates atherosclerosis. These vascular disturbances progress to loss of vessel dilatation and vascular impairment, thereby increasing glomerular pressure and leading to increased urinary albumin excretion [29,30]. Endothelial dysfunction can also affect remodeling of the arterial wall and the target vessel, leading to increased arterial stiffness, which affects the glomerular barrier permeability and leads to urinary albumin excretion [31,32]. Albuminuria could be an index of subclinical vascular abnormalities.

The strength of this study is that it was a large population-based national representative study that considered a comprehensive range of possible confounding and mediating factors, including sociodemographic, lifestyle, anthropometric, and reproductive factors. Nevertheless, there are several limitations. The measurements were performed at a certain time with a cross-sectional design; thus, a causal relationship could not be clearly determined. For the identification and exclusion of diabetes, the lack of oral glucose tolerance tests data is also a limitation of this study, as is the fact that we had only a single measurement of FPG. Another limitation is that the UACR was measured from a single-spot urine sample; therefore, we could not exclude the possibility that UACR variations influenced the results. In addition, the FRS for CVD and specific outcomes could not be assessed; thus, we cannot provide insight into whether increased FRS actually led to CVD events. We also did not have information regarding preexisting renal diseases or asymptomatic urinary tract infections, which can affect albuminuria. Finally, we did not have information regarding specific types of anti-hypertensive medication that may influence albuminuria.

In conclusion, urinary albumin excretion reflects CVD risk in postmenopausal women without diabetes, and high normal levels and microalbuminuria were independently associated with a higher risk of CVD. We propose that urinary albumin excretion may reflect the CVD risk in postmenopausal women without diabetes, and that it should be considered a risk factor of CVD. Therefore, to effectively prevent CVD in postmenopausal women without diabetes, more attention should be focused on women with microalbuminuria, even those with higher albuminuria levels that are within the normal range. A prospective study is needed to explore the possible causal relationship between higher urinary albumin excretion and subsequent CVD risk.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

This study was supported by research fund of the Honam Branch of the Korean Endocrine Society.

ORCID

Sang Yong Kim *http://orcid.org/0000-0002-3902-622X*

REFERENCES

1. Basi S, Fesler P, Mimran A, Lewis JB. Microalbuminuria in

type 2 diabetes and hypertension: a marker, treatment target, or innocent bystander? Diabetes Care 2008;31 Suppl 2:S194-201.
2. Rachmani R, Levi Z, Lidar M, Slavachevski I, Half-Onn E, Ravid M. Considerations about the threshold value of microalbuminuria in patients with diabetes mellitus: lessons from an 8-year follow-up study of 599 patients. Diabetes Res Clin Pract 2000;49:187-94.
3. de Zeeuw D, Parving HH, Henning RH. Microalbuminuria as an early marker for cardiovascular disease. J Am Soc Nephrol 2006;17:2100-5.
4. Hillege HL, Janssen WM, Bak AA, Diercks GF, Grobbee DE, Crijns HJ, et al. Microalbuminuria is common, also in a nondiabetic, nonhypertensive population, and an independent indicator of cardiovascular risk factors and cardiovascular morbidity. J Intern Med 2001;249:519-26.
5. Kweon SS, Shin MH, Choi JS, Nam HS, Lee YH, Park KS, et al. Prevalence of albuminuria and associated cardiovascular risk factors: a community cohort in Namwon City, Korea. Diabetes Res Clin Pract 2012;97:492-8.
6. Ma H, Lin H, Hofman A, Hu Y, Li X, He W, et al. Low-grade albuminuria is associated with carotid atherosclerosis in normotensive and euglycemic Chinese middle-aged and elderly adults: the Shanghai Changfeng Study. Atherosclerosis 2013;228:237-42.
7. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA 2001;286:421-6.
8. Hillege HL, Fidler V, Diercks GF, van Gilst WH, de Zeeuw D, van Veldhuisen DJ, et al. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. Circulation 2002;106:1777-82.
9. Lieb W, Mayer B, Stritzke J, Doering A, Hense HW, Loewel H, et al. Association of low-grade urinary albumin excretion with left ventricular hypertrophy in the general population: the MONICA/KORA Augsburg Echocardiographic Substudy. Nephrol Dial Transplant 2006;21:2780-7.
10. Solbu MD, Kronborg J, Jenssen TG, Njolstad I, Lochen ML, Mathiesen EB, et al. Albuminuria, metabolic syndrome and the risk of mortality and cardiovascular events. Atherosclerosis 2009;204:503-8.
11. Jorgensen L, Jenssen T, Heuch I, Jacobsen BK. The combined effect of albuminuria and inflammation on all-cause and cardiovascular mortality in nondiabetic persons. J Intern Med 2008;264:493-501.
12. Schmieder RE, Schrader J, Zidek W, Tebbe U, Paar WD, Bramlage P, et al. Low-grade albuminuria and cardiovascular risk: what is the evidence? Clin Res Cardiol 2007;96:247-57.
13. Arnlov J, Evans JC, Meigs JB, Wang TJ, Fox CS, Levy D, et al. Low-grade albuminuria and incidence of cardiovascular disease events in nonhypertensive and nondiabetic individuals: the Framingham Heart Study. Circulation 2005;112:969-75.
14. Xu J, Knowler WC, Devereux RB, Yeh J, Umans JG, Begum M, et al. Albuminuria within the "normal" range and risk of cardiovascular disease and death in American Indians: the Strong Heart Study. Am J Kidney Dis 2007;49:208-16.
15. Hong JW, Ku CR, Noh JH, Ko KS, Rhee BD, Kim DJ. Association between low-grade albuminuria and cardiovascular risk in Korean adults: the 2011-2012 Korea National Health and Nutrition Examination Survey. PLoS One 2015;10:e0118866.
16. Chronic Kidney Disease Prognosis Consortium, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet 2010;375:2073-81.
17. Kim HM, Park J, Ryu SY, Kim J. The effect of menopause on the metabolic syndrome among Korean women: the Korean National Health and Nutrition Examination Survey, 2001. Diabetes Care 2007;30:701-6.
18. Stefanska A, Bergmann K, Sypniewska G. Metabolic syndrome and menopause: pathophysiology, clinical and diagnostic significance. Adv Clin Chem 2015;72:1-75.
19. Gallagher PE, Li P, Lenhart JR, Chappell MC, Brosnihan KB. Estrogen regulation of angiotensin-converting enzyme mRNA. Hypertension 1999;33(1 Pt 2):323-8.
20. Elving LD, Wetzels JF, de Nobel E, Hoitsma AJ, Berden JH. Captopril acutely lowers albuminuria in normotensive patients with diabetic nephropathy. Am J Kidney Dis 1992;20:559-63.
21. Schunkert H, Danser AH, Hense HW, Derkx FH, Kurzinger S, Riegger GA. Effects of estrogen replacement therapy on the renin-angiotensin system in postmenopausal women. Circulation 1997;95:39-45.
22. Lamb EJ, Tomson CR, Roderick PJ; Clinical Sciences Reviews Committee of the Association for Clinical Biochemistry. Estimating kidney function in adults using formulae. Ann Clin Biochem 2005;42(Pt 5):321-45.

23. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143-421.
24. Blecker S, Matsushita K, Kottgen A, Loehr LR, Bertoni AG, Boulware LE, et al. High-normal albuminuria and risk of heart failure in the community. Am J Kidney Dis 2011;58:47-55.
25. Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. Am Heart J 1991;121(1 Pt 2): 293-8.
26. Won JC, Lee YJ, Kim JM, Han SY, Noh JH, Ko KS, et al. Prevalence of and factors associated with albuminuria in the Korean adult population: the 2011 Korea National Health and Nutrition Examination Survey. PLoS One 2013;8:e83273.
27. Xue B, Johnson AK, Hay M. Sex differences in angiotensin II- and aldosterone-induced hypertension: the central protective effects of estrogen. Am J Physiol Regul Integr Comp Physiol 2013;305:R459-63.
28. Roest M, Banga JD, Janssen WM, Grobbee DE, Sixma JJ, de Jong PE, et al. Excessive urinary albumin levels are associated with future cardiovascular mortality in postmenopausal women. Circulation 2001;103:3057-61.
29. Deckert T, Feldt-Rasmussen B, Borch-Johnsen K, Jensen T, Kofoed-Enevoldsen A. Albuminuria reflects widespread vascular damage. The Steno hypothesis. Diabetologia 1989; 32:219-26.
30. Clausen P, Jensen JS, Jensen G, Borch-Johnsen K, Feldt-Rasmussen B. Elevated urinary albumin excretion is associated with impaired arterial dilatory capacity in clinically healthy subjects. Circulation 2001;103:1869-74.
31. Jensen JS. Renal and systemic transvascular albumin leakage in severe atherosclerosis. Arterioscler Thromb Vasc Biol 1995;15:1324-9.
32. Stehouwer CD, Smulders YM. Microalbuminuria and risk for cardiovascular disease: analysis of potential mechanisms. J Am Soc Nephrol 2006;17:2106-11.