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ORIGINAL ARTICLE

Very low-grade albuminuria reflects susceptibility to chronic kidney disease in combination with cardiovascular risk factors

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Low-grade albuminuria has been proposed as a cardiovascular risk factor that is below the conventional cut-off point for microalbuminuria, which has been previously identified as a marker for cardiovascular disease and chronic kidney disease (CKD). Metabolic syndrome has also been shown to be related with microalbuminuria and CKD. We assessed the relationship among low-grade albuminuria, CKD and metabolic syndrome among 5998 non-diabetic subjects. The subjects were divided into six groups: subjects with urine albumin-to-creatinine ratio (UACR) $<30\,mg\,g^{-1}$ were divided into five groups in accordance with their UACR values, and subjects with $30 \leqslant UACR < 300\,mg\,g^{-1}$ were allocated to the microalbuminuria group. The prevalence of CKD increased in parallel with increasing UACR values and greater numbers of metabolic syndrome characteristics, which were in turn associated with a reduced UACR cut-off point for an increased prevalence of CKD. Among the subjects with metabolic syndrome, UACR values above $10.2\,mg\,g^{-1}$ were related to increased CKD prevalence (odds ratio (OR): 2.63, 95% confidence interval (CI) 1.11–6.24), as were values of $30\,mg\,g^{-1}$ among those with 1 or 2 components of metabolic syndrome (OR: 2.98, 95% CI 1.83–4.83); elevated UACR was not observed to increase the risk of CKD in subjects who had no components of metabolic syndrome. The cut-off point varied in subjects with various cardiovascular risk profiles such as serum uric acid level, gender or hypertension. Very low levels of albuminuria were associated with increased CKD prevalence. The UACR cut-off point for increased CKD risk varied according to the risk profile, including the number of metabolic syndrome components.
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Keywords: chronic kidney disease; metabolic syndrome; microalbuminuria

INTRODUCTION

Levels of microalbuminuria, which is defined by a urine albumin-to-creatinine ratio (UACR) of 30–300 $mg\,g^{-1}$, were originally determined in patients with diabetes mellitus to predict diabetic nephropathy.[1] It was also demonstrated that microalbuminuria is a risk factor for cardiovascular and kidney diseases in patients with hypertension, as well as in the general population.[2–4]

Recently, the original definition of microalbuminuria has been challenged. Several studies have provided evidence of increased cardiovascular morbidity and mortality when urinary albumin excretion rates are below the currently conventional cut-off point for microalbuminuria, among the general population as well as those with diabetes or hypertension.[5–10] Although the threshold level at which microalbuminuria is predictive of cardiovascular outcomes is getting lower, there is a paucity of data showing the relationship between low-grade albuminuria and renal risk.

Microalbuminuria has also been considered as a marker of chronic kidney disease (CKD). CKD is a worldwide public health problem. It is a major risk factor for end-stage renal disease and cardiovascular disease, and has been shown to cause premature death.[11] Nevertheless, little is currently known about the association between low-grade albuminuria and CKD.

Metabolic syndrome is known to be related to microalbuminuria and CKD.[12–14] The incidence of metabolic syndrome is increasing worldwide and has been associated with an increased risk of mortality from cardiovascular disease.

In this study, we assessed the relationship among low-grade albuminuria, CKD and metabolic syndrome in non-diabetic subjects.

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METHODS

Study population

This study included a population of Korean adults who had visited the Seoul National University Bundang Hospital for routine health status checkups. This established service program included a medical questionnaire, a physical examination and a series of laboratory tests for a variety of adult diseases. All participants visited the hospital voluntarily, and paid for the service.

A total of 6915 subjects completed a standardized checkup in 2006. Among these, we excluded the following: 523 subjects with diabetes (defined as a history of diabetes mellitus or a fasting blood glucose level of 126 mg per 100 ml or more), 22 subjects with macroalbuminuria (UACR $\geqslant 300\,mg\,g^{-1}$) and 372 subjects with hematuria (dipstick $\geqslant 1+$). A total of 5998 subjects were ultimately included in this study.

Measurements and definitions

Assessments of medical history, smoking status and medications were based on replies to a standardized questionnaire. Current smokers were defined as those who were habitual smokers at the time of the interview. Blood pressure (BP) was measured using a standardized sphygmomanometer with patients in a sitting position after a 5-min rest, and the average of three measurements was recorded. The height and weight of the subjects were measured with the individuals dressed in only an examination gown and wearing no shoes. Body mass index was expressed as weight in kilograms divided by height in meters ($kg\,m^{-2}$). Waist circumference was measured in the standing position at the level of the umbilicus, by a single examiner. Hypertension was defined as systolic BP $\geqslant 140$ mm Hg or diastolic BP $\geqslant 90$ mm Hg. Participants taking antihypertensive medication were included in this category. Blood samples collected after at least 12 h of fasting were used for the determination of triglyceride, high-density lipoprotein cholesterol, glucose, creatinine and C-reactive protein (CRP) levels. Serum creatinine concentration was measured using the Jaffe rate reaction. Plasma CRP was measured via particle-enhanced light-scattering immunoassays using a TBA-200FR system (Toshiba, Tokyo, Japan) in accordance with the manufacturer's instructions, and the normal range was set to less than $5\,mg\,l^{-1}$.

A random single-void urine sample was obtained at the baseline examination to measure the UACR ($mg\,g^{-1}$) using the clean-catch technique. The urine sample was obtained after at least 12 h of fasting. Urinary albumin was measured by an immunoturbidimetric assay, and urinary creatinine was measured using the Jaffe rate reaction. The glomerular filtration rate (GFR) was estimated using the abbreviated equation described in the Modification of Diet in Renal Disease (MDRD) study.[11] We defined the cut-off points for high serum uric acid as 7 mg per 100 ml in men and 6 mg per 100 ml in women.

Metabolic syndrome was defined in accordance with the criteria of the revised Adult Treatment Panel III[15] when a subject exhibited three or more of the known risk factors. Hypertriglyceridemia was defined as $\geqslant 150$ mg per 100 ml, low high-density lipoprotein cholesterol as $\leqslant 40$ mg per 100 ml in men and $\leqslant 50$ mg per 100 ml in women; high BP as a systolic BP of $\geqslant 130$ mm Hg or a diastolic BP of $\geqslant 85$ mm Hg, and high fasting glucose was defined as $\geqslant 100$ mg per 100 ml. Abdominal obesity was defined as a waist circumference of $\geqslant 90$ cm in men and $\geqslant 80$ cm in women, in accordance with the 1998 World Health Organization Asian Pacific Guideline. CKD was defined as a reduced estimated GFR ($<60\,ml\,min^{-1}$ per $1.73\,m^2$).

Statistical analysis

The participants were divided into six groups: subjects with low-grade albuminuria (UACR $<30\,mg\,g^{-1}$) were categorized in quintiles of UACR, and subjects with microalbuminuria ($30 \leqslant$ UACR $<300\,mg\,g^{-1}$) were defined as the microalbuminuria group. The odds ratios (ORs) for CKD prevalence were calculated for quintiles of UACR and microalbuminuria by logistic regression analysis. All statistical analyses of the data were conducted with SPSS version 12.0 software (SPSS, Chicago, IL, USA). All reported *P*-values were two-tailed, and the threshold of statistical significance was set at $P<0.05$.

RESULTS

Clinical characteristics of albuminuria groups

The clinical characteristics of the study population in relationship to albuminuria levels are reported in Table 1. The distribution of estimated GFR is shown in Figure 1. Overall, 678 subjects (11.3%) had CKD and 629 subjects (10.5%) had metabolic syndrome. The prevalence of CKD increased with UACR across groups (9.1% in Q1, 10.7% in Q3, 12.3% in Q5 and 18.4% in the microalbuminuria group).

Table 1 Clinical characteristics of albuminuria groups

	UACR quintile groups (below microalbuminuria)						
Charateristic	*Q1 (<4.1)*	*Q2 (4.1–5.3)*	*Q3 (5.4–6.9)*	*Q4 (7.0–10.1)*	*Q5 (10.2–29.9)*	*Microalbuminuria*	P-*value by one-way ANOVA*
Number	1172	1166	1125	1152	1138	245	
UACR (IQR) ($mg\,g^{-1}$)	3.30 (2.80–4.80)	4.70 (4.40–5.00)	6.00 (5.60–6.40)	8.20 (7.45–8.95)	14.10 (10.80–17.40)	48.30 (29.35–67.25)	<0.001
Age (year)	47.54 ± 9.6	49.06 ± 9.78	50.14 ± 9.99	50.91 ± 10.43	52.45 ± 10.46	54.95 ± 11.57	<0.001
CRP ($mg\,l^{-1}$)	1.08 ± 2.53	1.01 ± 2.73	1.01 ± 2.39	1.27 ± 4.12	1.85 ± 8.07	2.51 ± 5.22	<0.001
BMI ($kg\,m^{-2}$)	23.78 ± 2.62	23.58 ± 2.65	23.44 ± 2.89	23.67 ± 3.08	23.91 ± 3.13	24.95 ± 3.55	<0.001
SBP (mm Hg)	112.33 ± 12.49	113.67 ± 13.36	113.69 ± 14.07	115.21 ± 14.47	118.49 ± 15.54	124.08 ± 17.61	<0.001
DBP (mm Hg)	71.75 ± 10.57	72.75 ± 11.13	72.2 ± 11.52	73.11 ± 11.71	74.99 ± 12.44	78.86 ± 12.44	<0.001
Estimated GFR	71.31 ± 9.29	71.2 ± 9.94	70.84 ± 9.26	70.98 ± 10.06	71.23 ± 11.13	68.73 ± 10.72	0.010
FBS (mg per 100 ml)	89.29 ± 10.9	90.05 ± 10.96	90.19 ± 11.07	90.81 ± 11.61	91.94 ± 12.07	95.09 ± 11.83	<0.001
Uric acid (mg per 100 ml)	5.92 ± 1.37	5.56 ± 1.38	5.37 ± 1.43	5.38 ± 1.51	5.52 ± 1.54	6.1 ± 1.68	<0.001
Total cholesterol ($mmol\,l^{-1}$)	199.64 ± 32.62	200.19 ± 32.81	203.96 ± 35.23	205.84 ± 36.14	208.07 ± 35.42	208.22 ± 36.37	<0.001
LDL (mg per 100 ml)	103.37 ± 24.03	102.7 ± 24.33	105.08 ± 25.57	106.56 ± 26.3	108.14 ± 26.19	106.82 ± 26.51	<0.001
HDL (mg per 100 ml)	56.83 ± 13.56	59.26 ± 15.09	60.07 ± 14.97	59.13 ± 14.19	58.84 ± 14.76	57.09 ± 14.95	<0.001
Triglyceride (mg per 100 ml)	124.31 ± 72.91	118.09 ± 71.02	118.57 ± 76.78	125.18 ± 79.37	129.44 ± 89.23	150.3 ± 126.64	<0.001
Men (%)	75.0	60.8	47.2	46.0	50.8	62.4	
Smoking (%)	67.9	56.9	48.7	48.1	50.5	60.9	
HT drug (%)	8.2	10.4	12.9	14.9	19.4	39.6	
Chronic kidney disease (%)	9.1	11.2	10.7	11.5	12.3	18.4	

Abbreviations: ANOVA, analysis of variance; BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; FBS, fasting blood sugar; GFR, glomerular filtration rate; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; SBP, systolic blood pressure; UACR, urine albumin-to-creatinine ratio; HT drug, percent of the individuals taking antihypertensive drugs.

Association of UACR with the prevalence of CKD

Among all subjects, UACR levels of over 10.5 mg g^{-1} were associated with increased CKD prevalence. In the multivariate model, the OR for CKD increased with UACR value. Low-grade albuminuria (UACR, 10.1–29.9 mg g^{-1}; OR, 1.37; 95% confidence interval (CI) 1.05–1.78) was associated with increased CKD prevalence as well as microalbuminuria (30.0–290.69 mg g^{-1}; OR, 2.19; 95% CI 1.50–3.20) (Table 2).

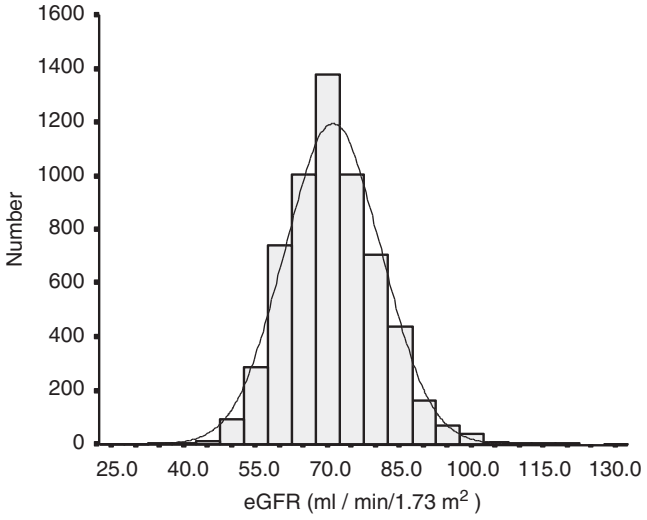

Figure 1 The distribution of estimated glomerular filtration rate (eGFR).

Table 2 Odds ratios for chronic kidney disease according to UACR levels

	Number	*Multivariate-adjusted OR[a] (95% CI)*	P-*value*
UACR quintile groups (below microalbuminuria)			
Q1 (UACR < 4.1 mg g^{-1})	1172	Ref.	
Q2 (4.1–5.3)	1166	1.23 (0.94–1.61)	0.129
Q3 (5.4–6.9)	1125	1.16 (0.88–1.53)	0.281
Q4 (7.0–10.1)	1152	1.27 (0.97–1.66)	0.078
Q5 (10.2–29.9)	1138	1.37 (1.05–1.78)	0.021
Microalbuminuria	245	2.19 (1.50–3.20)	<0.001

Abbreviations: BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; LDL, low-density lipoprotein; OR, odds ratio; UACR, urine albumin-to-creatinine ratio.
[a]Adjusted for age, gender, hypertension, smoking, BMI, serum LDL level, serum uric acid level and serum CRP level (log transformed).

Association of UACR with the prevalence of CKD is dependent on the number of metabolic syndrome components present

The prevalence of CKD increased with the number of metabolic syndrome components (10.5% in subjects with no or one metabolic syndrome component, 13.1% in patients with two components and 13.7% in those with metabolic syndrome). In the multivariate model, higher metabolic component numbers were associated with increased CKD prevalence. Relative to subjects with 0 or 1 component(s) of metabolic syndrome, those with 2 components of metabolic syndrome (still not sufficient for a diagnosis of metabolic syndrome) had ORs for CKD of 1.28 (95% CI 1.04–1.56), and participants with metabolic syndrome had ORs of 1.33 (95% CI 1.03–1.71); these results were independent of age, sex, hypertension, smoking status, body mass index, serum low-density lipoprotein, uric acid and CRP levels.

The UACR cut-off point for an increased prevalence for CKD decreased progressively with a higher number of metabolic syndrome components (Table 3). Among individuals without components of metabolic syndrome, elevated UACR levels did not increase the ORs for CKD even with regard to the level of microalbuminuria. Among those with 1 or 2 metabolic syndrome components, only microalbuminuria was associated with an increased OR for CKD (30.0–290.69 mg g^{-1}; OR: 2.98, 95% CI 1.83–4.83). CKD prevalence was elevated in the highest quintile (10.2–29.9 mg g^{-1}; OR: 2.63; 95% CI 1.11–6.24) of subjects with metabolic syndrome.

Association of UACR with the prevalence of CKD is dependent on serum uric acid level, gender and hypertension

When classified according to serum uric acid levels, the UACR cut-off value for increased prevalence of CKD risk was 7.0 mg g^{-1} in subjects with high uric acid levels. In the multivariate model, CKD prevalence was elevated in the fourth quintile (7.0–10.1 mg g^{-1}; OR: 1.60, 95% CI 1.05–2.45) among those with high uric acid levels, whereas there was no significant increase in OR with UACR among those with low uric acid levels (Table 4). The OR for CKD increased in parallel with UACR group: the OR for CKD was 1.86 in the highest quintile (10.2–29.9 mg g^{-1}; 95% CI 1.25–2.77) and the OR was 2.42 in the microalbuminuria group (30.0–290.69 mg g^{-1}; 95% CI 1.39–4.19). Likewise, in the analysis classified by gender, the multivariate-adjusted OR for CKD was elevated in the highest quintile (10.2–29.9 mg g;$^{-1}$ OR: 1.42, 95% CI 0.99–1.98) among men, although this difference was statistically insignificant. Among women, the OR was elevated only in the microalbuminuria group (30.0–290.69 mg g^{-1}; OR: 1.94; 95% CI 1.04–3.65) (Table 5). Among individuals with hypertension,

Table 3 Odds ratios for chronic kidney disease according to the number of metabolic syndrome components and UACR levels

	Component=0			*Components=1 or 2*			*Components=3, 4 or 5*		
	Number	*Multivariate-adjusted OR[a] (95% CI)*	P-*value*	*Number*	*Multivariate-adjusted OR[a] (95% CI)*	P-*value*	*Number*	*Multivariate-adjusted OR[a] (95% CI)*	P-*value*
UACR quintile groups (below microalbuminuria)									
Q1 (UACR < 4.1 mg g^{-1})	527	Ref.		565	Ref.		78	Ref.	
Q2 (4.1–5.3)	490	0.94 (0.62–1.43)	0.788	589	1.45 (0.99–2.13)	0.053	86	1.34 (0.48–3.70)	0.579
Q3 (5.4–6.9)	457	0.95 (0.62–1.46)	0.826	577	1.19 (0.80–1.77)	0.381	90	1.56 (0.58–4.18)	0.376
Q4 (7.0–10.1)	440	1.24 (0.82–1.87)	0.313	557	1.29 (0.87–1.91)	0.207	152	1.03 (0.40–2.66)	0.953
Q5 (10.2–29.9)	349	0.92 (0.58–1.46)	0.719	622	1.32 (0.90–1.94)	0.148	165	2.63 (1.11–6.24)	0.028
Microalbuminuria	40	0.66 (0.19–2.22)	0.497	147	2.98 (1.83–4.83)	<001	58	1.86 (0.65–5.34)	0.247

Abbreviations: BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; LDL, low-density lipoprotein; OR, odds ratio; UACR, urine albumin-to-creatinine ratio.
[a]Adjusted for age, gender, smoking, BMI, serum LDL level, serum uric acid level and serum CRP level (log transformed).

Table 4 Odds ratios for chronic kidney disease according to uric acid and UACR levels

	Low			*High*		
	Number	*Multivariate-adjusted OR[a] (95% CI)*	P-*value*	*Number*	*Multivariate-adjusted OR[a] (95% CI)*	P-*value*
UACR quintile groups (below microalbuminuria)						
Q1 (UACR $<4.1\,mg\,g^{-1}$)	593	Ref.		579	Ref.	
Q2 (4.1–5.3)	701	1.11 (0.78–1.58)	0.550	465	1.26 (0.83–1.92)	0.277
Q3 (5.4–6.9)	763	0.98 (0.69–1.40)	0.927	362	1.16 (0.74–1.84)	0.517
Q4 (7.0–10.1)	778	0.94 (0.66–1.35)	0.756	374	1.60 (1.05–2.45)	0.029
Q5 (10.2–29.9)	707	0.91 (0.63–1.32)	0.616	431	1.86 (1.25–2.77)	0.002
Microalbuminuria	125	1.66 (0.97–2.86)	0.077	120	2.42 (1.39–4.19)	0.002

Abbreviations: BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; LDL, low-density lipoprotein; OR, odds ratio; UACR, urine albumin-to-creatinine ratio.
[a]Adjusted for age, gender, hypertension, smoking, BMI, serum LDL level and serum CRP level (log transformed).

Table 5 Odds ratios (ORs) for chronic kidney disease according to gender and UACR levels

	Female			*Male*		
	Number	*Multivariate-adjusted OR[a] (95% CI)*	P-*value*	*Number*	*Multivariate-adjusted OR[a] (95% CI)*	P-*value*
UACR quintile groups (below microalbuminuria)						
Q1 (UACR $<4.1\,mg\,g^{-1}$)	293	Ref.		876	Ref.	
Q2 (4.1–5.3)	457	1.12 (0.71–1.77)	0.616	709	1.22 (0.87–1.72)	0.240
Q3 (5.4–6.9)	594	0.99 (0.64–1.54)	0.966	530	1.13 (0.78–1.64)	0.523
Q4 (7.0–10.1)	622	1.11 (0.72–1.72)	0.631	528	1.15 (0.79–1.67)	0.466
Q5 (10.2–29.9)	559	1.03 (0.65–1.61)	0.914	577	1.40 (0.99–1.98)	0.060
Microalbuminuria	92	1.94 (1.04–3.65)	0.039	153	1.76 (1.06–2.94)	0.029

Abbreviations: BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; LDL, low-density lipoprotein; OR, odds ratio; UACR, urine albumin-to-creatinine ratio.
[a]Adjusted for age, hypertension, smoking, BMI, serum uric acid level, serum LDL level and serum CRP level (log transformed).

Table 6 Odds ratios for chronic kidney disease according to the presence or absence of hypertension and UACR levels

	Non-hypertension			*Hypertension*		
	Number	*Multivariate-adjusted OR[a] (95% CI)*	P-*value*	*Number*	*Multivariate-adjusted OR[a] (95% CI)*	P-*value*
UACR quintile groups (below microalbuminuria)						
Q1 (UACR $<4.1\,mg\,g^{-1}$)	1019	Ref.		152	Ref.	
Q2 (4.1–5.3)	986	1.15 (0.86–1.54)	0.343	180	1.64 (0.76–3.54)	0.211
Q3 (5.4–6.9)	910	1.00 (0.74–1.36)	0.982	214	1.76 (0.84–3.69)	0.137
Q4 (7.0–10.1)	889	1.15 (0.85–1.55)	0.372	263	1.56 (0.75–3.24)	0.235
Q5 (10.2–29.9)	793	1.12 (0.82–1.53)	0.479	344	1.98 (0.99–3.97)	0.053
Microalbuminuria	113	1.44 (0.81–2.56)	0.210	0.196	3.02 (1.42–6.43)	0.004

Abbreviations: BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; LDL, low-density lipoprotein; OR, odds ratio; UACR, urine albumin-to-creatinine ratio.
[a]Adjusted for age, gender, smoking, BMI, serum uric acid level, serum LDL level and serum CRP level (log transformed).

the OR for CKD was elevated in the microalbuminuria group ($30.0–290.69\,mg\,g^{-1}$; OR: 3.02; 95% CI 1.42–6.43), whereas no significant increase in OR according to UACR was noted in subjects who did not have hypertension (Table 6). A slightly stronger tendency was noted according to gender in the hypertensive subjects. Among hypertensive men, the OR of CKD increased by 3.37-fold in the microalbuminuria group ($30.0–290.69\,mg\,g^{-1}$; 95% CI 1.34–8.28), whereas no significant increase was observed in women.

DISCUSSION

The principal objective of this study was to investigate the relationship among low-grade albuminuria, metabolic syndrome and CKD in non-diabetic subjects. The results of this study show that even low levels of albuminuria are associated with increased CKD prevalence, particularly, in populations with high cardiovascular risk profiles, including metabolic syndrome. Moreover, our large cross-sectional analysis shows that a large number of metabolic syndrome components are

associated with increased CKD prevalence, as well as a reduced UACR cut-off point for increased CKD prevalence. Thus, low-grade albuminuria might have clinical implications for the prediction of CKD, particularly, in the populations with more metabolic syndrome components, independent of diabetes.

These data are in line with recent studies suggesting that the relationship between albuminuria and cardiovascular risk is not restricted to the microalbuminuria range, and extends to very low-grade albuminuria. Several studies provide evidence of increased cardiovascular morbidity and mortality at urinary albumin excretion rates below the conventional cut-off point for microalbuminuria in the general population, in addition to patients with diabetes or hypertension.[5–10] Klausen *et al.*[5] found that a UACR value above the upper quartile, that is, 4.8 mcg min^{-1}, is associated with an increased risk of coronary heart disease (relative risk 2.0; 95% CI 1.4–3.0) and death (relative risk 1.9; 95% CI 1.5–2.4), independent of age, sex, renal creatinine clearance, diabetes mellitus, hypertension, and plasma lipids in non-diabetic and non-hypertensive adults. In the MONICA/KORA substudy,[10] it was noted that UACR levels of 4–10 mg g^{-1} may be associated with increased cardiovascular risk, considering the results of several studies, including the Framingham Heart Study, even though this level is far below the currently used threshold of 30 mg g^{-1} UACR. In our study, we demonstrated that low albuminuria levels were associated with increased CKD prevalence, particularly, in the populations with high-risk cardiovascular profiles, such as metabolic syndrome. The UACR cut-off point in our study (10.2 mg g^{-1}) for increased CKD prevalence was similar to those suggested in a previous study for cardiovascular risk.[10] These results support the notion that low-grade albuminuria may be associated with both cardiovascular and renal risks such as microalbuminuria.

In this study, it was found that the presence of more metabolic syndrome components is associated with increased CKD prevalence and a decreased UACR cut-off point for CKD. In subjects exhibiting no components of metabolic syndrome, elevated UACR did not increase CKD risk, even in the microalbuminuria group. The UACR cut-off point for CKD was 30 mg g^{-1} in those with 1 or 2 components of metabolic syndrome, and the cut-off point was 10.2 mg g^{-1} in the subjects with metabolic syndrome. This means that microalbuminuria may be clinically significant in subjects with only 1 or 2 components of metabolic syndrome, and a UACR value of even 10.2 mg g^{-1} may be worth noting in those subjects with metabolic syndrome. We also analyzed the combined effect of low-grade albuminuria and the accumulation of eight cardiovascular risk profiles including low-density lipoprotein, uric acid and CRP on the prevalence of CKD. The results were similar to those shown in the analyses that investigated five components of metabolic syndrome, although the UACR cut-off point for CKD was 30 mg g^{-1} in those with two or three risk factors.

The mechanisms that underlie the observed link between low-grade albuminuria and CKD may involve insulin resistance, as suggested by our findings that metabolic syndrome components influence the UACR cut-off point for CKD. Recently, microalbuminuria has been identified as an indicator of insulin resistance and of increased renal and cardiovascular risks (also known as cardio-renal syndrome) associated with metabolic syndrome.[16,17] Insulin resistance has been reported to increase the risk of CKD.[18,19] Chen *et al.*[18,19] determined that metabolic syndrome[19] and insulin resistance estimated by a homeostasis model assessment[18] were associated with an increased CKD risk in participants in the NHANES III study.

Among subjects with high serum uric acid, a UACR above 7.0 mg g^{-1} was related to an increased CKD prevalence in our study, whereas we noted no significant increase in ORs for CKD according to UACR in those subjects with low uric acid levels. This is lower than the level that has been detected among subjects with metabolic syndrome or hypertension. Uric acid has been related to cardiovascular morbidity and mortality in a number of previous studies.[20,21] In the MONICA cohort, hyperuricemia was associated significantly with cardiovascular mortality, independent of body mass index, hypertension, diuretic or alcohol use and smoking.[22] Uric acid has also been identified as an independent predictor of microalbuminuria in healthy subjects.[23] Consistent with these studies, elevated serum uric acid levels affected the prevalence of CKD and the cut-off point for CKD in our study. Further studies will be required to determine the relevant mechanisms involved in this process.

Similar results were observed in this study, supporting the notion that the CKD cut-off point varies in subjects with various cardiovascular risk profiles. Consistent with the results of previous studies, the risk for CKD according to UACR differs between men and women. Data from the Framingham Heat Study[8] shows that the cut-off for an elevated rate of cardiovascular events was a UACR of 3.9 mg g^{-1} for men and a UACR of 7.5 mg g^{-1} for women. The gender-specific differences in cut-off points may be due to different urinary creatinine excretion levels. A second explanation for this difference might be found in the fact that women are generally considered to have lower-risk cardiovascular profiles than men. Likewise, the cut-off for elevated CKD prevalence varies according to the presence or absence of hypertension, and the accumulation of eight cardiovascular risk profiles including low-density lipoprotein, uric acid and CRP not only the components of metabolic syndrome (Supplementary Tables 1, 2). Thus, low-grade albuminuria may have a variable clinical significance according to the risk profiles of the subjects, independent of diabetes.

As metabolic syndrome is associated with increased CKD risk, the number of components affects the risk of CKD.[19,24] In one study, the risk for CKD was reported to increase progressively with higher numbers of metabolic syndrome components.[19] Compared with participants with 0 or 1 components of metabolic syndrome, participants with 2, 3, 4 and 5 metabolic syndrome components had multivariate-adjusted ORs of 2.21 (CI 1.16–4.24), 3.38 (CI 1.48–7.69), 4.23 (CI 2.06–8.63) and 5.85 (CI 3.11–11.0), respectively. Consistent with these results, higher numbers of metabolic syndrome components were found to be associated with increased CKD prevalence in our study. Although a similar tendency was noted, the ORs observed in our study were lower. This difference may be caused by the exclusion of subjects with diabetes or macroalbuminuria; non-diabetic subjects with lower UACR values are expected to exhibit CKD prevalence that is lower than that of the general population. Moreover, metabolic syndrome is known to be less prevalent in Asian populations than in Western populations. In a study conducted with Asian, non-diabetic and non-hypertensive subjects,[24] the ORs for CKD as related to the number of metabolic syndrome components were lower than those observed in a previous study that analyzed a Western population.

Among subjects with metabolic syndrome, the prevalence of CKD was not significantly elevated in accordance with microalbuminuria levels, whereas the prevalence of CKD was elevated in the highest quintile. This unexpected result may be the consequence of the inclusion of a relatively small number of subjects with metabolic syndrome and microalbuminuria. As we excluded those subjects with diabetes or macroalbuminuria, the number of patients with metabolic syndrome, CKD and microalbuminuria was only nine. Further studies with a larger sample size will be required.

Several limitations of our study should be noted. First, our study was a cross-sectional study and the cohort was voluntary. The study design may have induced some bias, and may also have made it difficult to infer causality between low-grade albuminuria and CKD risk. A prospective study will be necessary to elucidate the mechanism underlying the relationship between low-grade albuminuria and CKD. Second, urinary albumin excretion was assessed in only one morning urine sample. Although timed (for example, 24-h or overnight) urine collections were originally used to measure albumin excretion, good correlations were reported between the UACR and albuminuria levels measured in the overnight and 24-h urine collections. However, it has been recommended that several samples should be obtained, because of the variability and false-positive results that plague microalbuminuria measurements.[25] To prevent the possibility that contamination may result in false-positive data, we excluded subjects with hematuria from our analysis. Another limitation is that GFR was not measured in the 24-h urine collection, but was estimated with the MDRD formula. Although the MDRD formula has been used extensively in large epidemiological studies, as well as in clinical practice, it is yet to be validated for the Korean population. The median GFR in our subjects was $71\,ml\,min^{-1}$ per $1.73\,m^2$, which was similar to that reported in a study of Japanese subjects,[26] but lower than that reported in other studies of general US and Chinese populations.[14,19,27] One possible explanation may be that the equation underestimates GFR in Koreans; alternatively, Koreans may be prone to renal damage. Validation of the MDRD formula for the Korean population is another necessary step that will require additional research.

In conclusion, we determined that very low levels of albuminuria were associated with increased CKD prevalence, and that the UACR cut-off point for increased CKD risk varied according to a subject's risk profile, most notably the number of metabolic syndrome components. Thus, in populations with high cardiovascular risk, therapeutic interventions targeted at modifying renal and cardiovascular risk factors that may be of greatest benefit to those who have UACR values below the current conventional cut-off point for microalbuminuria.

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Supplementary Information accompanies the paper on Hypertension Research website (http://www.nature.com/hr)