Urinary Albumin to Creatinine Ratio and Incidence of Metabolic Syndrome in Korean population

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Urinary Albumin to Creatinine Ratio and Incidence of Metabolic Syndrome in Korean population

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ABSTRACT

Urinary albumin to creatinine ratio and incidence of metabolic syndrome in Korean population

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Background

Urinary albumin excretion even in non-pathologic range (<30mg/g) is associated with an increasing risk of CVD and blood pressure progression. Recently, several studies have suggested that urinary albumin excretion is positively associated with prevalence of MetS and its components in various participants. Moreover, there were some studies that have shown the association between change of urinary albumin excretion and arterial stiffness or carotid intima-media thickness. However, there are currently a small number of studies published that have been evaluated the association between MetS, which is also intermediate risk factor of CVD, and low-grade albuminuria. And to our knowledge, there were no studies that investigated the association between change of urinary albumin excretion and MetS.

Purpose

The purpose of this study was to examine the prospective association of UACR with the risk of MetS incidence and its components and to evaluate the association of UACR change from baseline over follow-up period with the change in risk of MetS incidence in Korean general population.

Methods

To investigate the association between UACR levels and MetS, baseline survey was included 6,489 participants (2,653 men and 3,836 women) aged 40 to 70 years. We prospectively examined incident risk for MetS and its components among 1,686 participants (740 men and 946 women) without metabolic syndrome at baseline. The subjects were 40 to 70 years of age and from the Korean Genome and Epidemiology Study on Atherosclerosis Risk of Rural Areas in the Korean General Population cohort. All subjects received medical examination according to standard procedures.

Results

In baseline survey, mean waist circumference, systolic and diastolic blood pressure, fasting plasma glucose and median triglyceride increased in a linear fashion in both genders according to UACR quartile. High-density lipoprotein cholesterol was shown decreased in a linear fashion according to UACR quartile. Compared to the lowest quartile of UACR, the odds ratios (ORs) for prevalence of MetS in participants who were categorized in the highest quartile of UACR were 1.87 (95% confidence interval (CI), 1.43–2.45) and 1.90 (1.54–2.35) in men and women, respectively, when adjusted for age, baseline BMI and other covariates. During a mean of 2.6 years of follow-up, 129 men (17.4%) and 183 women (19.3%) developed MetS. In prospective study, the ORs for incident MetS comparing the highest with the lowest tertiles of UACR levels were not significant as 0.93 (0.56-1.52) and 1.25 (0.82-1.89) in men and women, respectively. Compared to the group of less than 10% UACR increase from baseline and less than 5mg/g increase from baseline, the ORs for incident MetS in the group of more than 20% UACR increase and the group of more than 10mg/g increase from baseline were 1.44 (1.05-1.97) and 2.00 (1.22-3.28), respectively. UACR change was associated with incident risk of MetS (highest versus lowest tertile : 0.62, 95% CI 0.47-0.92). After stratification of cutoff points of UACR (10.6mg/g), compared to the group of less than 10% UACR increase from baseline and less than 5mg/g increase from baseline, the ORs for incident MetS in the group of more than 20% UACR increase and more than 10mg/g increase were 1.66 (1.12-2.46) and 4.16 (1.91-9.08) at levels below the cut-off, respectively. Similarly, an UACR change was associated with decreased incidence of MetS (highest versus 2^{nd} , lowest tertile : 2^{nd}, 0.54, 95% CI 0.36-0.81; lowest, 0.31 95% CI 0.09-1.12). . In contrast, UCAR change was not associated with incident MetS at levels above the cutoff points.

Conclusion

Our findings demonstrate that UACR change was positively associated with incident MetS. Especially this association was maintained in the group of below cutoff points of baseline UACR, within the very low-grade albuminuria (<10.6 mg/g). These findings suggest increasing UACR change in the range of less than current microalbuminuria threshold may be a predictor for new-onset MetS.

Key Words : Urinary albumin creatinine ratio, Metabolic syndrome, UACR change, low-grade albuminuria

I. INTRODUCTION

The metabolic syndrome (MetS) refers to a characterized clustering of risk factors including abdominal obesity, elevated blood pressure, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, elevated fasting glucose, and insulin resistance. The prevalence of MetS is approximately 20 to 60% in American and European adults and about 20 to 30% in Asian population (Ford, 2002; Eckel, 2005; Thomas, 2005; Lim, 2011). Persons with MetS have been associated with increased risk for type 2 diabetes mellitus, cardiovascular disease (CVD), and all-cause mortality (Sattar, 2008; Schmieder, 2007). Given the high prevalence of the MetS and its poor outcomes, there is substantial interest in understanding its causes and mechanisms in population-based studies.

Urinary albumin excretion is regarded as a renal expression of general vascular endothelial dysfunction, and early indicator of atherosclerosis (Deckert, 1989). Recent studies suggest that microalbuminuria, defined as urine albumin to urine creatinine ratio (UACR) of 30 to 300 mg/g (National Kidney Foundation, 2002), is related to the cardiovascular risk factors including hypertension (Wang, 2005; Palaniappan, 2003; Pascual, 2005), abdominal obesity (Bonnet, 2006), and other components of the MetS (Shankar, 2004; Lin, 2007). In addition, there have been several studies investigating the relationship between microalbuminuria and MetS (Palaniappan, 2003; Sung, 2008; Rowley 2003). World Health Organization (WHO) thus proposed microalbuminuria to be included as one of the 6 diagnostic criteria for the definition of MetS (Alberti, 1998). Microalbuminuria is also a strong predictor for all-cause mortality including cardiovascular disease and end-stage renal disease in individuals with hypertension or diabetes (Sarnak, 2003; Bigazzi, 1998; Deckert, 1996; Dinneen, 1997; Gerstein, 2001).

Recent evidences suggest that urinary albumin excretion even in non-pathologic range (<30mg/g) is associated with an increasing risk of CVD and blood pressure progression (Hillege, 2002; Arnlov 2005; Wang, 2005). In addition, several studies have recently suggested that urinary albumin excretion is positively associated with prevalence of MetS and its components in non-diabetic hypertensive participants (Vyssoulis, 2010), in individuals with type 2 diabetes (Ritz 2010), and in middle-aged and elderly population (Zhang, 2013). Moreover, a study showed a reduction of urinary albumin excretion was associated with arterial stiffness reduction (Matsui, 2010), and in MESA study, higher carotid intima-media thickness was associated with progression of urinary albumin excretion (Yu, 2011). However, there have been a small number of studies that evaluated the association between urinary albumin excretion and MetS, which is also intermediate risk factor of CVD, and low-grade albuminuria. And to our knowledge, there is no studies that investigated the association between change of urinary

albumin excretion and MetS.

Thus, this study aimed to examine the association of UACR with MetS and its components in a general Korean population. Next, we studied the prospective association of UACR with the risk of incident MetS and its components. Finally, we evaluated the association of UACR from baseline to the change in follow-up period with the risk of incident MetS as well as the predictive value of UACR change in individuals who are susceptible in developing MetS.

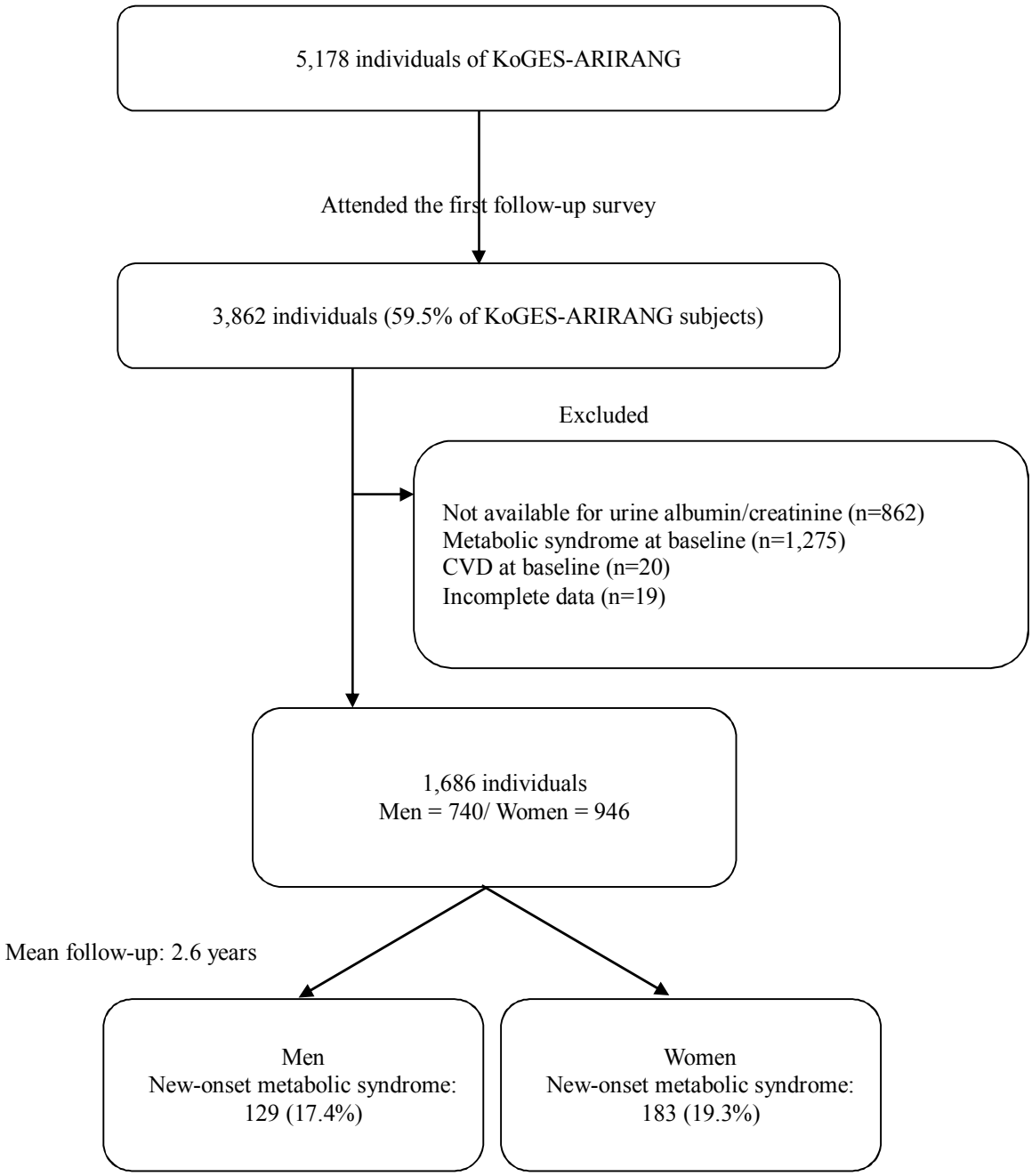
II. MATERIALS AND METHODS

1. STUDY POPULATION

A comprehensive demographic and health survey was completed by 10,114 healthy adults from the Korean Genome and Epidemiology Study on Atherosclerosis Risk of Rural Areas in the Korean General Population (KoGES-ARIRANG), a population-based prospective cohort study to assess the prevalence, incidence and risk factors for chronic degenerative disorders such as hypertension, diabetes, osteoporosis, and cardiovascular disease. KoGES-ARIRANG invited all adults aged 40 to 70 years in rural areas of Wonju, Pyengchang, Keumsan, Naju, and Kangreung in South Korea where demographic shifts are infrequent and long-term follow up is frequent.

The baseline survey was completed from November 2005 to January 2008. Participants with a known diagnosis of myocardial infarction, a history of cerebrovascular disease, without baseline UACR measurements or with incomplete data were excluded. The baseline survey included 6,489 participants (2,653 men and 3,836 women) aged 40 to 70 years. Among them, we chose 5,178 participants in 2 areas (2,127 men and 3,051 women in Wonju and Pyengchang) for follow-up survey. All study participants were invited to the follow-up survey between April 2008 to January 2011, and of whom 3,862 (74.6%) attended. We then excluded 1,275 subjects with metabolic syndrome at baseline, 20 subjects with the history of cardiovascular disease, 862 subjects without baseline UACR measurements, and 19 subjects with incomplete data. The final sample size for the prospective analysis was 1,686 participants (740 men and 946 women) (Figure 1). All participants completed an informed consent form prior to participation. This study protocol was approved by the Institutional Review Board of Wonju Christian Hospital, Yonsei University College of Medicine, Wonju, South Korea.

Figure 1. Study population for prospective studey



2. Data collection

Study participants completed a standardized medical history and lifestyle questionnaire and underwent a comprehensive health examination according to standard procedures at baseline and the follow-up examination. Body weight and height were measured to the nearest 0.1kg and 0.1cm, respectively, while participants wore light indoor clothing without shoes. Waist circumference was measured at the narrowest point between the lower border of the rib cage and the iliac crest. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Blood pressure was measured twice in the right arm after the participant had rested for at least 5 minutes in a quiet room using a standard mercury sphygmomanometer (Baumanometer, Copiague, NY). The mean of the two blood pressure readings was used for data analyses. Smoking status was determined based on self-report. Non-smokers were defined as participants who had smoked less than 100 cigarettes (<5 packs of cigarettes) in their lifetime. Former smokers were defined as participants who had smoked more than 100 cigarettes in their lifetime but who reported “abstained from smoking” in the questionnaire. Current smokers were defined as participants who had smoked more than 100 cigarettes in their lifetime and who reported “currently smoking” in the questionnaire. Details on daily alcohol consumption were requested and converted into grams per day. Subjects who answered yes to the question: ‘Do you perform physical exercise regularly enough to make you sweat?’ were assigned to the regular exercise group.

Blood samples were collected from the antecubital vein after a 12-hour overnight fast. Fasting glucose was determined by a glucose oxidase-based assay. Fasting insulin was determined by a double-antibody RIA assay (Biosource, Belgium). Serum concentrations of low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol and triglycerides (TG) were determined by enzymatic methods (Advia 1650, Siemens, Tarrytown, NY). High sensitivity C-reactive protein (hs-CRP) was measured by the Denka Seiken (Tokyo, Japan) assay, which has been validated against the Dade Behring method. Insulin resistance was calculated using the homeostasis model assessment of insulin resistance (HOMA-IR) model using the following formula: fasting plasma glucose (mg/dL) × fasting insulin (μIU/mL) / 405. We defined UACR as the amount of albumin (mg/dL) divided by creatinine (mg/dL) in randomly voided urine. Intra-assay and inter-assay coefficient of variations (CV) of urinary albumin were 1.1 % and 1.2%, respectively. In case of urinary creatinine, intra and inter-assay CVs were 0.5% and 1.4%, respectively.

3. Endpoint definition

The study endpoint was the development of metabolic syndrome at the follow-up visit, defined following the harmonized definition for metabolic syndrome (Alberti, 2009) as the presence of at least 3 of the following criteria: 1) Abdominal obesity, defined as a waist circumference ≥ 90 cm for men or ≥ 85 cm for women as suggested by Korean-specific cutoffs for abdominal obesity defined by the Korean Society of Obesity (Lee, 2007); 2) Hypertriglyceridemia, defined as a serum triglyceride concentration ≥ 150 mg/dL (1.69 mmol/L); 3) Low HDL cholesterol, defined as a serum HDL cholesterol concentration < 40 mg/dL (1.04 mmol/L) for men or < 50 mg/dL (1.29 mmol/L) for women; 4) High blood pressure, defined as a systolic blood pressure ≥ 130 mmHg or a diastolic blood pressure ≥ 85mmHg, or treatment with antihypertensive agents; and 5) High fasting glucose, defined as a fasting serum glucose ≥100 mg/dL or taking anti-diabetic medication.

4. Statistical analysis

Since women have higher levels of UACR compared to men, we performed all analyses separately for men and women. We divided the study population into sex-specific quartiles of UACR levels. First, we evaluated the association of baseline UACR levels with prevalence of metabolic syndrome and each components of metabolic syndrome. To evaluate the incidence of new-onset metabolic syndrome and its components, we excluded subjects with metabolic syndrome at baseline. Then, we excluded subjects with the presence of each component of metabolic syndrome at baseline in order to evaluate the association of baseline UACR levels with the components of metabolic syndrome at the follow-up. Multivariable logistic regression was used to assess the independent association of baseline UACR levels with a prevalence of metabolic syndrome and its components. We used three models with progressive degrees of adjustment. First, we performed an age-adjusted analysis. Second, we adjusted for age (continuous variable), body mass index (continuous variable), smoking (current/former/non) and regular exercise (yes/no). Third, we further adjusted for baseline levels of hs-CPR (log-transformed continuous variable), LDL-cholesterol and HOMA-IR (log-transformed continuous variable) included as covariates.

To evaluate the association of UACR increase from baseline to follow-up with incidence of metabolic syndrome, we divided the study population into 6 subgroups according to UACR increase in different definitions: 1) less than 10% increase from baseline, 2) 10 to 20% increase from baseline, 3) more than 20% increase from baseline, 4) less than 5mg/g increase from baseline, 5) 5 to 10mg/g increase from baseline, 6) more than 10mg/g increase from baseline. To identify the association between UACR change (ΔUACR) and incidence of metabolic syndrome, UACR was stratified into three tertile groups. The three tertile groups of UACR change (ΔUACR) were categorized as follow; T1: less than -6.58mg/g, T2: -6.58mg/g to -0.46mg/g, T3: at least -0.46mg/g. In

addition, we defined ΔUACR as 2 different categories. First, ΔUACR was divided into less than 10% increase from baseline, 10 to 20% increase from baseline, and more than 20% increase from baseline. Second, ΔUACR was divided into less than 5mg/g increase from baseline, 5 to 10 mg/g increase from baseline, and more than 10mg/g increase from baseline. We used multivariable logistic regression to assess the independent association of UACR change (ΔUACR) with incident metabolic syndrome. UACR cutoff point predicting metabolic syndrome was determined using receiver-operating characteristic (ROC) curve. Additionally, we examined the association of UACR increase and change with incident metabolic syndrome in individuals with below the cutoff levels of UACR and above the cutoff levels of UACR at baseline. Results were expressed as odds ratios (ORs) with 95% confidence intervals (CI). We also used multivariable logistic regression to assess the independent association of UACR Ratio (UACR at follow-up / UACR at baseline) with incident metabolic syndrome.

To evaluate the added discrimination provided by UACR change to predict incident cases of metabolic syndrome beyond the information provided by the components of the metabolic syndrome, we compared the areas under the receiver operator curve (ROC) in models that included waist circumference, HDL cholesterol, systolic blood pressure, triglycerides, and glucose levels with and without UACR change. In addition, we calculated reclassification tables for models with and without UACR change into three categories of predicted risk (cutoffs at 10 and 20%), as well as the continuous (or category-free) net reclassification improvement (NRI) and the integrated discrimination improvement (IDI). The NRI compared classifications from the model with and without UACR change for changes by incident metabolic syndrome for a net calculation of changes in the right direction. It represents the sum of the percentage of participants with an improvement in specificity after considering the new marker among those who developed the event plus the increase in specificity after considering the new marker among those who do not develop the event. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA). P values of less than 0.05 were considered to be statistically significant.

III. RESULTS

1. GENERAL CHARACTERISTICS OF THE STUDY SUBJECTS

The mean or median values of age, waist circumference, SBP, DBP, fasting plasma glucose, TG, hs-CRP, alcohol intake, and eGFR were significantly higher in men than those in women, while BMI, serum total cholesterol, LDL-C, HDL-C, insulin, and HOMA-IR were higher in women than those in men. The percentage of current smokers was higher in men, while the percentage of subjects engaging in regular exercise, subjects with hypertension was higher in women (Table 1). Table 1 shows the characteristics of the 6,489 participants (2,653 men and 3,836 women). The median UACRs were significantly lower in men when compared to women (8.9 mg/g in men VS. 11.3 mg/g in women, $p<0.001$).

Table 2 and 3 represent the subject characteristics according to the baseline UACR quartile. The mean or median value of BMI, waist circumference, SBP, DBP, fasting plasma glucose, total cholesterol, TG, HDL cholesterol, fasting insulin, HOMA-IR, and hs-CRP increased as UACR quartile increased in both men and women. Alcohol intake increased with increasing UACR quartile in men. On the other hand, the mean HDL-C level and percentage of subjects engaged in regular exercise were inversely associated with UACR quartile in women.

Table 1 General characteristics of the study subjects.

	Men (n=2653)	Women (n=3836)	p-value
Age (yr)	57.0 ± 8.1	55.6 ± 8.3	<0.001
BMI (m/kg^2)	24.0 ± 3.0	24.8 ± 3.3	<0.001
WC (cm)	85.8 ± 8.1	82.3 ± 8.7	<0.001
SBP (mmHg)	131.0 ± 17.3	128.5 ± 18.2	<0.001
DBP (mmHg)	84.7 ± 11.3	82.1 ± 11.9	<0.001
FPG (mg/dL)	99.7 ± 24.9	94.6 ± 21.6	<0.001
TC (mg/dL)	195.2 ± 37.1	204.1 ± 38.2	<0.001
TG (mg/dL)	135.0 (92.0, 203.0)	116.0 (82.0, 170.0)	<0.001
HDL (mg/dL)	45.1 ± 11.9	47.2 ± 10.8	<0.001
LDL (mg/dL)	111.6 ± 31.8	122.3 ± 32.8	<0.001
Insulin (μU/mL)	7.7 ± 5.1	8.6 ± 4,7	<0.001
HOMA-IR	1.54 (1.16, 2.12)	1.69 (1.31, 2.27)	<0.001
hs-CRP	0.99 (0.52, 2.16)	0.75 (0.39, 1.61)	<0.001
Smoking status (n, %)			<0.001
Never smoker	800 (30.2)	3738 (98.0)	
Former smoker	842 (31.8)	19 (0.5)	
Current smoker	1005 (38.0)	58 (1.5)	
Regular exercise (n, %)	610 (22.9)	999 (26.1)	0.005
Alcohol intake (g/day)	30.0 ± 64,1	2.7 ± 12.9	<0.001
eGFR ($mL/min/1.73m^2$)	77.6 ± 11.4	75.0 ± 10.4	<0.001
UACR (mg/g)	8.9 (5.0, 18.1)	11.3 (6.5, 20.3)	<0.001
Hypertension (n, %)	409 (15.4)	820 (21.4)	<0.001
Diabetes (n, %)	201 (7.6)	271 (7.1)	0.46

$eGFR = 186.3 \times (\text{serum creatinine}^{-1.154}) \times (\text{age}^{-0.203}) \times 0.742$ (if women)

All data except smoking status, drinking status, exercise, TG, HOMA-IR, hs-CRP, and UACR are represented as mean ± standard deviation (SD).

TG, HOMA-IR, hs-CRP, and UACR are represented as median (lower, higher quartile)

[a] *p* – value as determined by Mann-Whitney *U* test.

[b] *p* – value as determined by chi square test.

Abbreviations: BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high sensitivity C-reactive protein eGFR, estimated glomerular filtration rate; UACR, urinary albumin to creatinine ratio.

Table 2. Subject characteristics according to quartile of UACR in men

Men	UACR-Q1 (n=655)	UACR -Q2 (n=672)	UACR -Q3 (n=662)	UACR -Q4 (n=664)	P-value
Age (yr)	56.4 ± 8.3	56.4 ± 8.2	56.9 ± 8.0	58.2 ± 7.8	<0.001
BMI (m/kg^2)	23.9 ± 2.9	23.9 ± 3.1	23.7 ± 3.1	24.7 ± 3.0	<0.001
WC (cm)	85.1 ± 7.6	85.2 ± 8.0	84.8 ± 8.3	88.0 ± 7.9	<0.001
SBP (mmHg)	127.4 ± 16.4	127.7 ± 15.3	132.1 ± 17.5	136.7 ± 18.2	<0.001
DBP (mmHg)	83.0 ± 10.7	83.3 ± 10.5	85.0 ± 11.5	87.5 ± 7.9	<0.001
FPG (mg/dL)	94.0 ± 14.9	96.1 ± 19.7	100.0 ± 22.9	108.5 ± 35.1	<0.001
TC (mg/dL)	188.9 ± 33.8	193.3 ± 36.2	197.0 ± 36.3	201.6 ± 40.6	<0.001
TG (mg/dL)	122.0 (85.0, 177.0)	133.0 (90.5, 191.0)	136.0 (92.0, 203.0)	164.0 (104.0, 236.5)	<0.001
HDL (mg/dL)	45.0 ± 11.1	45.0 ± 12.4	45.4 ± 11.8	45.0 ± 12.4	0.89
LDL (mg/dL)	111.2 ± 30.1	111.3 ± 33.0	112.0 ± 31.5	112.1 ± 32.5	0.92
Insulin (μU/mL)	7.3 ± 3.6	7.3 ± 4.9	7.7 ± 6.2	8.6 ± 5.4	<0.001
HOMA-IR	1.4 (1.1, 1.9)	1.5 (1.1, 2.0)	1.5 (1.2, 2.1)	1.8 (1.3, 2.6)	<0.001
hs-CRP	0.9 (0.5, 1.8)	0.9 (0.5, 2.1)	1.0 (0.5, 2.3)	1.2 (0.7, 2.6)	<0.001
Smoking status (n, %)					0.43
Never smoker	207 (31.6)	214 (31.9)	181 (27.5)	198 (29.8)	
Former smoker	192 (29.3)	213 (32.0)	225 (34.2)	212 (31.9)	
Current smoker	256 (39.1)	243 (36.3)	252 (38.3)	254 (38.3)	
Regular exercise (n, %)	164 (25.1)	166 (24.7)	138 (20.8)	142 (21.4)	0.15
Alcohol intake (g/day)	27.6 ± 69.9	26.3 ± 65.9	30.4 ± 51.2	35.8 ± 67.3	0.038
eGFR ($mL/min/1.73m^2$)	77.7 ± 10.3	77.9 ± 10.6	79.1 ± 11.2	75.7 ± 13.4	<0.001
UACR (mg/g)	2.9 (2.2, 3.9)	6.9 (6.0, 7.9)	11.9 (10.3, 14.4)	38.8 (24.8, 78.1)	<0.001

eGFR = 186.3 x (serum creatinine$^{-1.154}$) x (age$^{-0.203}$) x 0.742 (if women)

All data except smoking status, drinking status, exercise, TG, HOMA-IR, hs-CRP, and UACR are represented as mean ± standard deviation (SD).

TG, HOMA-IR, hs-CRP, and UACR are represented as median (lower, higher quartile)

[a] *p* – value as determined by Mann-Whitney *U* test.

[b] *p* – value as determined by chi square test.

Abbreviations: BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high sensitivity C-reactive protein eGFR, estimated glomerular filtration rate; UACR, urinary albumin to creatinine ratio.

Table 3. Subject characteristics according to quartile of UACR in women

Women	UACR-Q1 (n=959)	UACR -Q2 (n=957)	UACR -Q3 (n=961)	UACR -Q4 (n=959)	P-value
Age (yr)	54.4 ± 8.4	55.1 ± 8.4	56.1 ± 8.1	57.1 ± 8.0	<0.001
BMI (m/kg^2)	24.3 ± 3.1	24.6 ± 3.2	24.7 ± 3.3	25.5 ± 3.5	<0.001
WC (cm)	80.8 ± 8.4	81.3 ± 8.4	82.4 ± 8.5	84.5 ± 8.8	<0.001
SBP (mmHg)	123.4 ± 16.7	126.3 ± 17.2	129.6 ± 18.0	134.8 ± 18.9	<0.001
DBP (mmHg)	79.4 ± 11.6	81.1 ± 8.4	82.4 ± 8.5	85.7 ± 12.1	<0.001
FPG (mg/dL)	90.6 ± 15.2	92.1 ± 13.9	94.3 ± 19.6	101.2 ± 31.6	<0.001
TC (mg/dL)	196.2 ± 35.7	203.1 ± 37.4	205.9 ± 38.3	211.2 ± 39.8	<0.001
TG (mg/dL)	103.0 (75.0, 144.0)	112.0 (79.0, 161.0)	119.0 (84.0, 177.0)	134.0 (96.0, 193.0)	<0.001
HDL (mg/dL)	48.8 ± 10.8	47.3 ± 10.4	46.4 ± 10.6	46.4 ± 11.1	<0.001
LDL (mg/dL)	118.0 ± 32.2	121.4 ± 32.5	123.1 ± 32.4	126.8 ± 33.5	<0.001
Insulin (μU/mL)	7.9 ± 3.3	8.3 ± 4.2	8.6 ± 4.0	9.6 ± 6.6	<0.001
HOMA-IR	1.6 (1.2, 2.1)	1.6 (1.3, 2.2)	1.7 (1.3, 2.4)	1.9 (1.4, 2.7)	<0.001
hs-CRP	0.7 (0.4, 1.4)	0.7 (0.4, 1.4)	0.7 (0.4, 1.5)	0.9 (0.5, 1.9)	<0.001
Smoking status (n, %)					0.119
Never smoker	930 (97.2)	940 (98.8)	932 (97.8)	936 (98.1)	
Former smoker	5 (0.5)	2 (0.2)	8 (0.8)	4 (0.4)	
Current smoker	22 (2.3)	9 (1.0))	13 (1.4)	14 (1.5)	
Regular exercise (n, %)	278 (29.0)	275 (28.7)	217 (22.6)	229 (23.9)	0.001
Alcohol intake (g/day)	3.4 ± 14.4	2.5 ± 13.3	2.7 ± 14.7	1.9 ± 7.8	0.095
eGFR (mL/min/1.73m^2)	75.0 ± 9.4	75.0 ± 10.0	75.2 ± 10.3	74.3 ± 12.0	0.263
UACR (mg/g)	4.1 (3.1, 5.3)	8.8 (7.7, 10.8)	14.7 (12.9, 17.1)	34.7 (25.2, 69.1)	<0.001

eGFR = 186.3 x (serum creatinine$^{-1.154}$) x (age$^{-0.203}$) x 0.742 (if women)

All data except smoking status, drinking status, exercise, TG, HOMA-IR, hs-CRP, and UACR are represented as mean ± standard deviation (SD).

TG, HOMA-IR, hs-CRP, and UACR are represented as median (lower, higher quartile)

[a] *p* – value as determined by Mann-Whitney *U* test.

[b] *p* – value as determined by chi square test.

Abbreviations: BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high sensitivity C-reactive protein eGFR, estimated glomerular filtration rate; UACR, urinary albumin to creatinine ratio.

2. ASSOCIATION BETWEEN UACR AND PREVALENCE OF MEATBOLIC SYNDROME AND ITS COMPONENTS

The proportions of MetS from lowest to highest quartile were 8.04 %, 9.77 %, 11.19 %, and 14.16%, respectively. The corresponding ORs (95% CI) were 1.32 (1.21- 1.56) in second quartile, 1.58 (1.34-1.86) in third quartile, and 1.88 (1.59- 2.22) in the highest quartile in multivariable adjusted models (Table 4). In subgroup analysis according to the gender, the ORs (95% CI) for proportions of MetS when compared the highest to the lowest quartiles of UACR levels were 1.87 (1.43-2.45) in men and 1.90 (1.54-2.35) in women. However, the ORs (95% CI) for prevalence of MetS comparing the highest to the lowest quartiles of UACR levels were different between the presence and absence of diabetes [1.81 (1.53-2.15) with diabetes vs. 0.91 (0.38-2.18)] and hypertension [1.87 (1.55-2.26) with hypertension vs. 1.38 (0.93-2.06) without hypertension].

Among men, the proportions of participants who had MetS, high waist circumference, low HDL cholesterol, high triglycerides, high blood pressure and high blood glucose were 37.77 % ,32.94 %, 35.62 %, 43.35 %, 67.81% , and 32.45 %, respectively.

In multivariable adjusted models (Table 5), the ORs for MetS comparing men in the highest to those in the lowest quartile of UACR was 1.87 (95% CI 1.43 – 2.45; P for trend <0.001). The corresponding ORs (95% CI) for new-onset high waist circumference, low HDL cholesterol, high triglycerides, high blood pressure, and high blood glucose were 1.15 (0.83– 1.60), 0.77 (0.61–0.99), 2.05 (1.62–2.59), 2.34 (1.81–3.03), and 2.12 (1.61–2.79), respectively.

Among women, the proportions of participants who had MetS, high waist circumference, low HDL cholesterol, high triglycerides, high blood pressure and high blood glucose were 46.90 %,61.57 %, 63.66 %, 32.51 %, 61.29 %, and 21.43 %, respectively.

In multivariable adjusted models (Table 5), the ORs for MetS comparing women in the highest to those in the lowest quartile of UACR was 1.90 (95% CI 1.54 – 2.35; P for trend < 0.001). The corresponding ORs (95% CI) for new-onset high waist circumference, low HDL cholesterol, high triglycerides, high blood pressure, and high blood glucose were 1.18 (0.90– 1.53), 1.16 (0.96–1.41), 1.86 (1.51–2.30), 2.11 (1.72–2.59), and 1.57 (1.22–2.02), respectively.

Table 4. Odds ratios for baseline metabolic syndrome by baseline UACR quartile.

	OR (95% CI)				P for trend
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Men (n=2653)					
UACR at baseline	<5.00	5.00-8.98	8.99-18.11	≥18.12	
Metabolic syndrome	1.00	1.19 (0.91-1.56)	1.29 (0.99-1.69)	1.87 (1.43-2.45)	< 0.001
High WC	1.00	1.07 (0.77-1.49)	0.92 (0.66-1.29)	1.15 (0.83-1.60)	0.48
Low HDL cholesterol	1.00	1.14 (0.90-1.44)	0.99 (0.78-1.26)	0.77 (0.61-0.99)	0.002
High TG	1.00	1.39 (1.10-1.75)	1.48 (1.17-1.86)	2.05 (1.62-2.59)	< 0.001
High blood pressure	1.00	1.17 (0.93-1.47)	1.48 (1.17-1.88)	2.34 (1.81-3.03)	< 0.001
High fasting glucose	1.00	1.33 (1.01-1.76)	1.75 (1.33-2.29)	2.12 (1.61-2.79)	< 0.001
Women (n=3836)					
UACR at baseline	<6.52	6.52-11.29	11.30-20.25	≥20.26	
Metabolic syndrome	1.00	1.41 (1.14-1.74)	1.79 (1.45-2.21)	1.90 (1.54-2.35)	< 0.001
High WC	1.00	1.17 (0.91-1.51)	1.14 (0.88-1.47)	1.18 (0.90-1.53)	0.75
Low HDL cholesterol	1.00	1.22 (1.01-1.47)	1.32 (1.10-1.60)	1.16 (0.96-1.41)	0.93
High TG	1.00	1.40 (1.13-1.73)	1.56 (1.27-1.92)	1.86 (1.51-2.30)	< 0.001
High blood pressure	1.00	1.23 (1.02-1.49)	1.60 (1.31-1.94)	2.11 (1.72-2.59)	< 0.001
High fasting glucose	1.00	1.07 (0.82-1.40)	1.09 (0.84-1.42)	1.57 (1.22-2.02)	0.01

adjusted for age, baseline BMI, smoking, regular exercise, hs-CRP, HOMA-IR

Abbreviations: UACR, urine albumin to creatinine ratio; BMI, body mass index; TG, triglyceride; HDL, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; hs-CRP, high sensitivity C-reactive protein.

Table 5. Odds ratios for baseline metabolic syndrome and its components by baseline UACR quartile.

	OR (95% CI)			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Men (n=2653)				
UACR at baseline	<5.00	5.00-8.98	8.99-18.11	≥18.12
Metabolic syndrome	1.00	1.19 (0.91-1.56)	1.29 (0.99-1.69)	1.87 (1.43-2.45)
High WC	1.00	1.07 (0.77-1.49)	0.92 (0.66-1.29)	1.15 (0.83-1.60)
Low HDL cholesterol	1.00	1.14 (0.90-1.44)	0.99 (0.78-1.26)	0.77 (0.61-0.99)
High TG	1.00	1.39 (1.10-1.75)	1.48 (1.17-1.86)	2.05 (1.62-2.59)
High blood pressure	1.00	1.17 (0.93-1.47)	1.48 (1.17-1.88)	2.34 (1.81-3.03)
High fasting glucose	1.00	1.33 (1.01-1.76)	1.75 (1.33-2.29)	2.12 (1.61-2.79)
Women (n=3836)				
UACR at baseline	<6.52	6.52-11.29	11.30-20.25	≥20.26
Metabolic syndrome	1.00	1.41 (1.14-1.74)	1.79 (1.45-2.21)	1.90 (1.54-2.35)
High WC	1.00	1.17 (0.91-1.51)	1.14 (0.88-1.47)	1.18 (0.90-1.53)
Low HDL cholesterol	1.00	1.22 (1.01-1.47)	1.32 (1.10-1.60)	1.16 (0.96-1.41)
High TG	1.00	1.40 (1.13-1.73)	1.56 (1.27-1.92)	1.86 (1.51-2.30)
High blood pressure	1.00	1.23 (1.02-1.49)	1.60 (1.31-1.94)	2.11 (1.72-2.59)
High fasting glucose	1.00	1.07 (0.82-1.40)	1.09 (0.84-1.42)	1.57 (1.22-2.02)

adjusted for age, baseline BMI, smoking, regular exercise, hs-CRP, HOMA-IR

Abbreviations: UACR, urine albumin to creatinine ratio; BMI, body mass index; WC, waist circumference; TG, triglyceride; HDL, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; hs-CRP, high sensitivity C-reactive protein.

3. BASELINE CHARACTERISTICS OF THE SUBJECTS WITH LONGITUDINAL STUDY

Table 6 lists the characteristics of the 1,686 participants (740 men and 946 women) according to baseline UACR tertile for prospective analysis. The mean or median value of age, waist circumference, SBP, DBP, total cholesterol, fasting insulin, HOMA-IR, and eGFR elevated in accordance with UACR quartile increase. The percentages of current smokers and subjects engaged in regular exercise were higher in the lowest UACR tertile.

Table 6. Subject characteristics according to tertile of UACR at baseline

	UACR-T1 (n=563)	UACR -T2 (n=561)	UACR -T3 (n=562)	P-value
Age (yr)	53.2 ± 8.0	54.5 ± 8.6	55.4 ± 8.2	<0.001
BMI (m/kg^2)	23.6 ± 2.6	23.4 ± 2.8	23.6 ± 2.9	0.30
Male (%)	286 (50.8)	246 (43.9)	208 (37.0)	<0.001
WC (cm)	80.1 ± 7.7	79.8 ± 7.9	81.1 ± 8.4	0.03
SBP (mmHg)	121.3 ± 14.5	122.2 ± 16.6	126.7 ± 17.7	<0.001
DBP (mmHg)	78.7 ± 10.6	79.2 ± 11.2	82.0 ± 11.8	<0.001
FPG (mg/dL)	89.6 ± 10.2	90.4 ± 12.8	91.4 ± 15.5	0.07
TC (mg/dL)	193.1 ± 35.1	198.7 ± 36.0	201.1 ± 37.2	<0.001
TG (mg/dL)	95.0 (70.0, 127.0)	100.0 (74.0, 129.0)	101.0 (76.0, 130.0)	0.06
HDL (mg/dL)	49.6 ± 10.7	50.5 ± 11.7	50.5 ± 10.5	0.23
LDL (mg/dL)	115.7 ± 31.0	114.8 ± 31.2	117.2 ± 31.2	0.41
Insulin (μU/mL)	7.2 ± 3.3	7.3 ± 3.1	7.7 ± 4.1	0.04
HOMA-IR	1.4 (1.1, 1.8)	1.4 (1.2, .9)	1.5 (1.2, 1.9)	0.001
hs-CRP	0.6 (0.4, 1.4)	0.6 (0.3, 1.5)	0.7 (0.4, 1.5)	0.25
Smoking status (n, %)				0.02
Never smoker	366 (65.1)	383 (68.8)	411 (73.4)	
Former smoker	78 (13.9)	76 (13.6)	53 (9.5)	
Current smoker	119 (21.1)	98 (17.5)	96 (17.1)	
Regular exercise (n, %)	179 (31.8)	150 (26.7)	125 (22.2)	0.002
Alcohol intake (g/day)	11.3 ± 29.3	12.6 ± 29.5	11.3 ± 29.1	0.71
eGFR ($mL/min/1.73m^2$)	76.5 ± 9.5	78.5 ± 10.3	78.4 ± 12.3	0.002
UACR (mg/g)	4.0 (2.8, 5.3)	9.0 (7.6, 11.0)	22.4 (16.0, 43.9)	<0.001

eGFR = 186.3 x (serum creatinine$^{-1.154}$) x (age$^{-0.203}$) x 0.742 (if women)

All data except smoking status, drinking status, exercise, TG, HOMA-IR, hs-CRP, and UACR are represented as mean ± standard deviation (SD).

TG, HOMA-IR, hs-CRP, and UACR are represented as median (lower, higher quartile)

[a] *p* – value as determined by Mann-Whitney *U* test.

[b] *p* – value as determined by chi square test.

Abbreviations: BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high sensitivity C-reactive protein eGFR, estimated glomerular filtration rate; UACR, urinary albumin to creatinine ratio.

4. RISK FOR INCIDENT METABOILIC SYNDROME AND METABOLIC SYNDROME COMPONETS BY BASELINE UACR TERTILE

In comparison with participants categorized in the lowest UACR tertile, the ORs for developing MetS in the highest UACR tertile were 1.16 (95% CI, 0.86-1.57), 1.00 (95% CI, 0.63-1.60) and 1.31 (95% CI, 0.88-1.96) in total population, men and women, respectively, when adjusted for age (Model 1). In multivariate adjusted model, the ORs for total population, men and women between developing MetS in the highest with those in the lowest tertile of UACR was insignificant statistically (Table 7). Table 8 shows that the corresponding ORs (95% CI) for developing high waist circumference, low HDL cholesterol, high TG, high blood pressure, and high fasting glucose were 0.59 (0.40-0.87), 0.49 (0.35-0.69), 0.80 (0.55-1.17), 1.47 (0.90-2.38), and 0.85 (0.57-1.28), respectively, when adjusted for age, sex, baseline BMI, smoking, regular exercise, hs-CRP, HOMA-IR and other components of MetS.

Table 7. Odds ratios for incident metabolic syndrome by baseline UACR tertile.

	OR (95% CI)		
	Tertile 1	Tertile 2	Tertile 3
Total (n=1686)			
UACR at baseline	<6.30	6.30-12.99	≥12.99
No. of incident MetS	96 (17.1%)	96 (17.1%)	120 (21.4%)
Model 1	1.00	1.03 (0.76-1.40)	1.16 (0.86-1.57)
Model 2	1.00	1.04 (0.76-1.43)	1.12 (0.82-1.54)
Model 3	1.00	1.02 (0.74-1.40)	1.07 (0.78-1.48)
Men (n=740)			
UACR at baseline	<5.77	5.77-11.38	≥11.38
No. of incident MetS	44 (19.9%)	42 (17.1%)	43 (17.3%)
Model 1	1.00	0.96 (0.60-1.54)	1.00 (0.63-1.60)
Model 2	1.00	0.99 (0.61-1.61)	1.01 (0.62-1.64)
Model 3	1.00	0.96 (0.59-1.58)	0.93 (0.56-1.52)
Women (n=946)			
UACR at baseline	<7.07	7.07-14.17	≥14.17
No. of incident MetS	53 (16.8%)	59 (18.7%)	71 (22.5%)
Model 1	1.00	1.09 (0.72-1.64)	1.31 (0.88-1.96)
Model 2	1.00	1.10 (0.72-1.68)	1.26 (0.83-1.91)
Model 3	1.00	1.09 (0.71-1.67)	1.25 (0.83-1.90)

Model 1: adjusted for age; in case of total population, adjusted for age, sex
Model 2: Model 1 + additionally adjusted for baseline BMI, smoking, regular exercise
Model 3: Model 2 + additionally adjusted for baseline LDL cholesterol, hs-CRP, HOMA-IR
Abbreviations: UACR, urine albumin to creatinine ratio; BMI, body mass index; HOMA-IR, homeostatic model assessment of insulin resistance; hs-CRP, high sensitivity C-reactive protein.

Table 8. Odds ratios for incident metabolic syndrome components by baseline UACR tertile.

	OR (95% CI)		
	Tertile 1	Tertile 2	Tertile 3
High waist circumference			
Model 1	1.00	0.83 (0.58-1.20)	0.62 (0.42-0.91)
Model 2	1.00	0.82 (0.57-1.18)	0.59 (0.40-0.87)
Δ Waist circumference	3.20 ± 5.21	1.90 ± 5.53	0.91 ± 6.40
Low HDL cholesterol			
Model 1	1.00	0.62 (0.45-0.86)	0.52 (0.38-0.73)
Model 2	1.00	0.61 (0.43-0.85)	0.49 (0.35-0.69)
Δ HDL cholesterol	-2.64 ± 9.22	-1.36 ± 9.53	-1.67 ± 10.23
High TG			
Model 1	1.00	1.09 (0.77-1.55)	0.83 (0.57-1.20)
Model 2	1.00	1.09 (0.77-1.55)	0.80 (0.55-1.17)
Δ TG	13.57 ± 65.29	7.11 ± 67.09	3.00 ± 66.58
High blood pressure			
Model 1	1.00	1.43 (0.91-2.24)	1.59 (0.99-2.55)
Model 2	1.00	1.39 (0.88-2.18)	1.47 (0.90-2.38)
Δ SBP	-4.26 ± 16.64	-2.55 ± 16.23	-4.32 ± 17.95
High fasting glucose			
Model 1	1.00	0.78 (0.52-1.17)	1.05 (0.71-1.55)
Model 2	1.00	0.74 (0.49-1.12)	0.85 (0.57-1.28)
Δ fasting glucose	2.58 ± 9.95	1.13 ± 10.84	1.41 ± 14.67

Model 1 adjusted for age, sex, baseline BMI, smoking, regular exercise, hs-CRP, HOMA-IR

Model 2 adjusted for all confounders in Model 1 plus high waist circumference (except for high waist circumference), low HDL cholesterol (except for low HDL cholesterol), high TG (except for high TG), high blood pressure (except for high blood pressure), high blood glucose (except for high blood glucose)

Abbreviations: UACR, urine albumin to creatinine ratio; BMI, body mass index; TG, triglyceride; HDL, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; hs-CRP, high sensitivity C-reactive protein.

5. RISK FOR INCIDENT METABOILIC SYNDROME BY UACR CHANGE (⊿ UACR)

Table 9 shows the results of the logistic regression analyses designed to investigate the relationship between UACR change and developing of MetS. In comparison with participants who were categorized in the group of less than 10% increase from baseline, the ORs for developing MetS in whom participants were categorized in the group of more than 20% increase from baseline was 1.44 (95% CI, 1.05–1.98). In comparison with participants who were categorized in the group of less than 5mg/g increase from baseline, the ORs for developing MetS in whom participants were categorized in the group of more than 10mg/g increase from baseline was 1.94 (95% CI, 1.18–3.98). Furthermore, compared to the highest tertile of Δ UACR, the lowest tertile of Δ UACR showed a lower rate in developing MetS (OR=0.63, 95% CI=0.44-0.89). In multivariate adjusted models (Table 10), when compared between men in the groups of less than 10% increase from baseline and more than 10mg/g increase from baseline and between men in the groups of more than 20% increase from baseline and less than 5mg/g increase from baseline, the ORs for developing MetS were 2.00 (95% CI, 1.24-3.24) and 2.69 (95% CI, 1.30-5.54), respectively. Moreover, when compared to the highest tertile of ΔUACR, the lowest tertile of ΔUACR showed a lower rate of developing MetS (OR=0.32, 95% CI=0.17-0.59). However, as it is shown in table 11, the ORs for developing MetS when compared between women in the groups of less than 10% increase from baseline and more than 10mg/g increase from baseline and between women in the groups of more than 20% increase from baseline and less than 5mg/g increase from baseline were not significantly associated. Compared to the highest tertile of ΔUACR, the lowest tertile of Δ UACR did not also show a significant OR for developing MetS (OR=0.94, 95% CI=0.60-1.47).

Table 9. Odds ratios for incident metabolic syndrome by UACR change (Δ UACR)

	OR (95% CI)		
	Δ UACR (N, %)		
	less than10% increase from baseline (1323, 78.50)	10~20% increase from baseline (59, 3.50)	more than 20% increase from baseline (304, 18.03)
Metabolic syndrome			
Model 1	1.00	1.10 (0.56-2.16)	1.37 (1.01-1.85)
Model 2	1.00	1.02 (0.51-2.06)	1.42 (1.03-1.94)
Model 3	1.00	1.06 (0.53-2.14)	1.44 (1.05-1.98)
	Δ UACR (N, %)		
	Less than 5mg/g increase from baseline (1534, 90.98)	5~10 mg/g increase from baseline (63, 3.74)	More than 10mg/g increase from baseline (89, 5.28)
Metabolic syndrome			
Model 1	1.00	1.57 (0.88-2.82)	2.02 (1.26-3.23)
Model 2	1.00	1.56 (0.85-2.87)	2.03 (1.24-3.31)
Model 3	1.00	1.60 (0.87-2.95)	1.94 (1.18-3.18)
	Δ UACR		
	Tertile 1 < -6.58mg/g	Tertile 2 --6.58mg/g ~ -0.46mg/g	Tertile 3 ≥-0.46mg/g
Metabolic syndrome			
Model 1	0.66 (0.47-0.92)	0.65 (0.47-0.91)	1.00
Model 2	0.65 (0.46-0.92)	0.64 (0.45-0.91)	1.00
Model 3	0.63 (0.44-0.89)	0.63 (0.44-0.89)	1.00

Model 1 adjusted for age, sex
Model 2 adjusted for age, baseline BMI, smoking, regular exercise
Model 3 adjusted for all confounders in Model 2 plus , hs-CRP, HOMA-IR
Abbreviations: UACR, urine albumin to creatinine ratio; BMI, body mass index; HOMA-IR, homeostatic model assessment of insulin resistance; hs-CRP, high sensitivity C-reactive protein.

Table 10. Odds ratios for incident metabolic syndrome by UACR change (Δ UACR) in men

	OR (95% CI)		
	Δ UACR (N, %)		
	less than10% increase from baseline (589, 79.59)	10~20% increase from baseline (25, 3.38)	more than 20% increase from baseline (126, 17.03)
Metabolic syndrome			
Model 1	1.00	1.00 (0.34-2.99)	1.91 (1.21-3.02)
Model 2	1.00	0.87 (0.28-2.74)	1.91 (1.19-3.06)
Model 3	1.00	0.93 (0.29-2.96)	2.00 (1.24-3.24)
	Δ UACR (N, %)		
	Less than 5mg/g increase from baseline (673, 90.95)	5~10 mg/g increase from baseline (26, 3.51)	More than 10mg/g increase from baseline (41, 5.54)
Metabolic syndrome			
Model 1	1.00	1.24 (0.46-3.38)	2.75 (1.39-5.42)
Model 2	1.00	1.35 (0.48-3.79)	2.70 (1.33-5.51)
Model 3	1.00	1.32 (0.46-3.80)	2.69 (1.30-5.54)
	Δ UACR		
	Tertile 1 < -6.58mg/g	Tertile 2 --6.58mg/g ~ -0.46mg/g	Tertile 3 ≥-0.46mg/g
Metabolic syndrome			
Model 1	0.38 (0.21-0.67)	0.46 (0.28-0.75)	1.00
Model 2	0.36 (0.20-0.65)	0.44 (0.26-0.74)	1.00
Model 3	0.32 (0.17-0.59)	0.40 (0.24-0.68)	1.00

Model 1 adjusted for age
Model 2 adjusted for age, baseline BMI, smoking, regular exercise
Model 3 adjusted for all confounders in Model 2 plus , hs-CRP, HOMA-IR
Abbreviations: UACR, urine albumin to creatinine ratio; BMI, body mass index; HOMA-IR, homeostatic model assessment of insulin resistance; hs-CRP, high sensitivity C-reactive protein.

Table 11. Odds ratio for incident metabolic syndrome by UACR change (Δ UACR) in women

	OR (95% CI)		
	Δ UACR (N, %)		
	less than10% increase from baseline (734, 77.60)	10~20% increase from baseline (34, 3.59)	more than 20% increase from baseline (178, 18.82)
Metabolic syndrome			
Model 1	1.00	1.15 (0.49-2.72)	1.04 (0.69-1.57)
Model 2	1.00	1.10 (0.45-2.68)	1.09 (0.71-1.67)
Model 3	1.00	1.10 (0.45-2.68)	1.09 (0.72-1.68)
	Δ UACR (N, %)		
	Less than 5mg/g increase from baseline (861, 91.01)	5~10 mg/g increase from baseline (37, 3.91)	More than 10mg/g increase from baseline (48, 5.07)
Metabolic syndrome			
Model 1	1.00	1.83 (0.88-3.81)	1.60 (0.82-3.12)
Model 2	1.00	1.80 (0.83-3.90)	1.64 (0.82-3.28)
Model 3	1.00	1.81 (0.84-3.92)	1.63 (0.81-3.27)
	Δ UACR		
	Tertile 1 < -6.58mg/g	Tertile 2 --6.58mg/g ~ -0.46mg/g	Tertile 3 ≥-0.46mg/g
Metabolic syndrome			
Model 1	0.96 (0.62-1.48)	0.92 (0.58-1.44)	1.00
Model 2	0.94 (0.60-1.47)	0.91 (0.57-1.46)	1.00
Model 3	0.94 (0.60-1.47)	0.91 (0.57-1.46)	1.00

Model 1 adjusted for age
Model 2 adjusted for age, baseline BMI, smoking, regular exercise
Model 3 adjusted for all confounders in Model 2 plus , hs-CRP, HOMA-IR
Abbreviations: UACR, urine albumin to creatinine ratio; BMI, body mass index; HOMA-IR, homeostatic model assessment of insulin resistance; hs-CRP, high sensitivity C-reactive protein.

6. RISK FOR INCIDENT METABOILIC SYNDROME BY UACR RATIO

Table 12 presents the relationship between UACR ratio, defined as UACR at follow-up / UACR at baseline, and developing MetS by the logistic regression analyses model. After adjusting for age, sex, baseline BMI, smoking, exercise stats, HOMA-IR, and hs-CRP, the ORs for incident MetS were 1.68 (95% CI, 1.15-2.45) in the middle tertile and 2.06 (95% CI, 1.43-2.97) in the highest tertile. After stratification by sex, this trend was evident and significant in men, but not in women.

Table 12. Odds ratios for incident metabolic syndrome by UACR Ratio (UACR at follow-up / UACR at baseline)

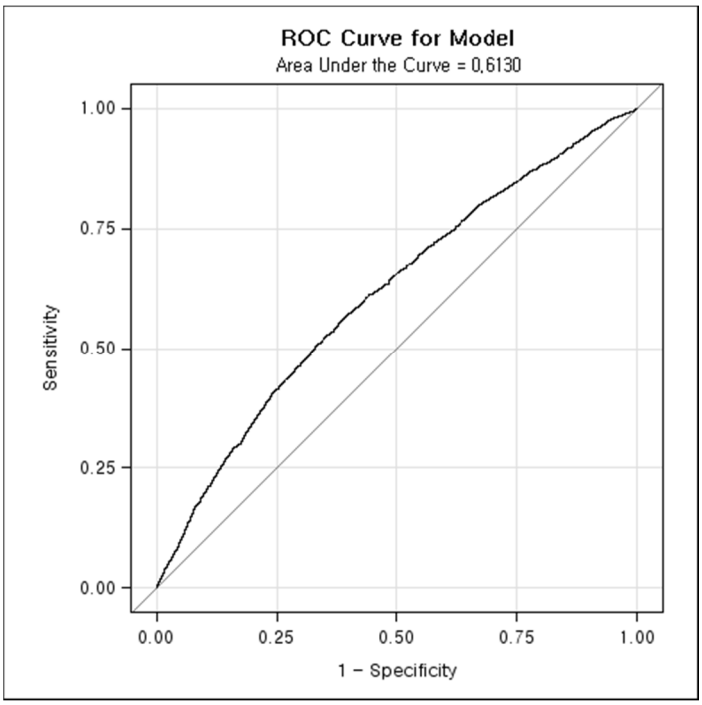
	OR (95% CI)		
	UACR Ratio		
	Tertile 1 < 0.3943	Tertile 2 < 0.8960	Tertile 3 ≥0.8960
Metabolic syndrome			
Model 1	1.00	1.57 (1.10-2.26)	1.92 (1.35-2.72)
Model 2	1.00	1.65 (1.13-2.40)	1.99 (1.38-2.87)
Model 3	1.00	1.68 (1.15-2.45)	2.06 (1.43-2.97)
	UACR Ratio		
Men	Tertile 1 < 0.4064	Tertile 2 < 0.9060	Tertile 3 ≥0.9060
Metabolic syndrome			
Model 1	1.00	2.20 (1.64-4.17)	3.76 (2.07-6.85)
Model 2	1.00	2.19 (1.12-4.26)	4.01 (2.14-7.48)
Model 3	1.00	2.20 (1.12-4.32)	4.35 (2.30-8.23)
	UACR Ratio		
Women	Tertile 1 < 0.3909	Tertile 2 < 0.8862	Tertile 3 ≥0.8862
Metabolic syndrome			
Model 1	1.00	1.35 (0.86-2.11)	1.20 (0.76-1.89)
Model 2	1.00	1.42 (0.89-2.26)	1.23 (0.77-1.97)
Model 3	1.00	1.43 (0.90-2.27)	1.24 (0.78-1.99)

Model 1 adjusted for age
Model 2 adjusted for age, baseline BMI, smoking, regular exercise
Model 3 adjusted for all confounders in Model 2 plus , hs-CRP, HOMA-IR
Abbreviations: UACR, urine albumin to creatinine ratio; BMI, body mass index; HOMA-IR, homeostatic model assessment of insulin resistance; hs-CRP, high sensitivity C-reactive protein.

7. RISK FOR INCIDENT METABOILIC SYNDROME BY UACR CHANGE (⊿ UACR) AFTER STRATIFIED BY UACR LEVELS AT BASELINE

From the ROC curve analysis, the optimal cutoff point of baseline UACR to predict the MetS was 10.6mg/g (Figure 2). Table 13 shows the results of the logistic regression analyses designed to investigate the relationship between ΔUACR and developing of MetS according to below the cutoff points and above the cutoff points of UACR at baseline. In comparison with participants who were categorized in the subgroups of less than 10% increase from baseline and less than 5mg/g increase from baseline, the ORs for developing MetS in participants who were categorized in the subgroups of more than 20% increase from baseline and more than 10mg/g increase from baseline were 1.67 (95% CI, 1.13-2.47) and 4.10 (95% CI, 1.89-8.92), respectively, in the group of below the cutoff points of baseline UACR. However, this association between ΔUACR and incident MetS was not shown in the group of above the cutoff points of baseline UACR. Compared to the highest tertile of ΔUACR, the lowest tertile of ΔUACR did not show significantly lower rate of developing MetS in the groups of both below and above the cutoff points of baseline UACR.

Figure 2. ROC curves for metabolic syndrome by UACR at baseline



Total (Optimal cut-off of UACR =10.6145)

Table 13. Odds ratios for incident metabolic syndrome by UACR change (Δ UACR) after stratification of UACR levels at baseline

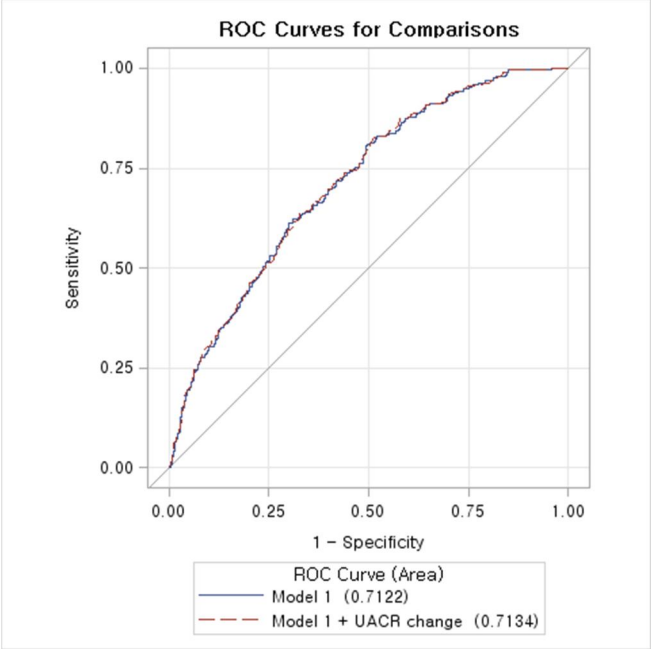
	OR (95% CI)		
	Δ UACR		
	less than10% increase from baseline	10~20% increase from baseline	more than 20% increase from baseline
Metabolic syndrome			
<10.6mg/g UACR at baseline	1.00	1.22 (0.57-2.59)	1.67 (1.13-2.47)
≥10.6mg/g UACR at baseline	1.00	0.55 (0.06-5.10)	1.10 (0.56-2.16) 1.08 (0.66-2.11) 1.37 (1.01-1.85)
	Δ UACR		
	Less than 5mg/g increase from Baseline	5~10 mg/g increase from baseline	More than 10mg/g increase from baseline
Metabolic syndrome			
<10.6mg/g UACR at baseline	1.00	1.59 (0.77-3.30)	4.10 (1.89-8.92)
≥10.6mg/g UACR at baseline	1.00	1.83 (0.57-5.84)	1.10 (0.57-2.16) 1.27 (0.66-2.45) 1.37 (
	Δ UACR		
	Tertile 1 < -6.58mg/g	Tertile 2 -6.58mg/g ~ -0.46mg/g	Tertile 3 ≥-0.46mg/g
Metabolic syndrome			
<10.6mg/g UACR at baseline	0.32 (0.09-1.13)	0.54 (0.36-0.81)	1.00
≥10.6mg/g UACR at baseline	0.63 (0.37-1.09)	1.00 1.01 (0.49-2.09)	1.10 (0.56-2.16) 1.37 (

adjusted for all confounders in Model 2 plus , hs-CRP, HOMA-IR
Abbreviations: UACR, urine albumin to creatinine ratio; BMI, body mass index; HOMA-IR, homeostatic model assessment of insulin resistance; hs-CRP, high sensitivity C-reactive protein.

8. PREDICTED RISK FOR AN INCIDENT METABOLIC SYNDROME EVENT BEFORE AND AFTER RECLASSIFICATION WITH A CHANGE OF UACR

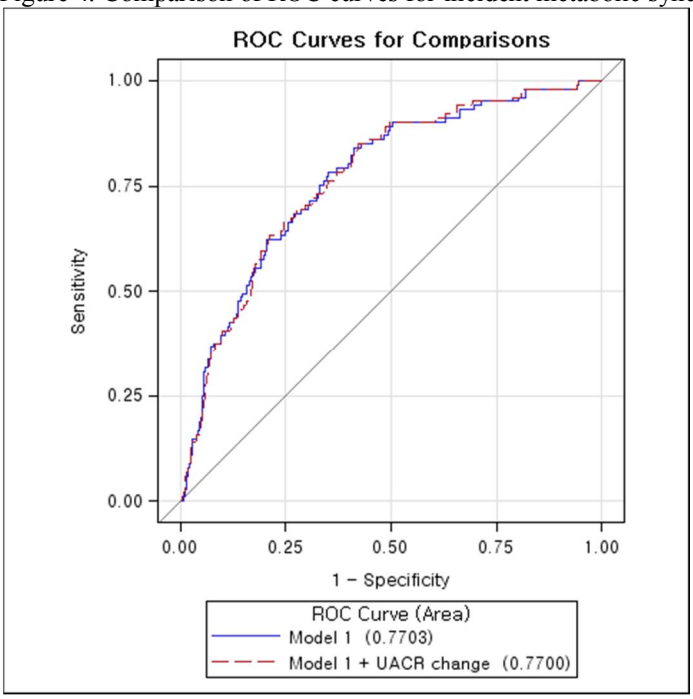
We evaluated how well UACR change predict incident MetS beyond the information provided by baseline levels of components of MetS. The area under the ROC curve to predict incident MetS using waist circumference, blood pressure, blood glucose, HDL cholesterol, and triglyceride levels were 0.7122 in total population. After ΔUACR levels were added to the model, the corresponding area under the ROC curve was 0.7134. The *P* value for comparison in areas under the ROC curves for the models with and without UACR change was 0.5275. The areas under the ROC curve to predict incident MetS using waist circumference, blood pressure, blood glucose, HDL cholesterol, and triglyceride levels were 0.7703 and 0.7405 in men and women, respectively. After ΔUACR levels were added to the model, the corresponding areas under the ROC curve were 0.7700 and 0.7417, respectively. The *P* value for comparison in areas under the ROC curves for the models with and without UACR change was 0.9105 and 0.4302 in men and women, respectively (Fig. 3,4, and 5). Tables 14, 15 and 16 showed the reclassification tables for improved prediction after adding change of UACR to a model including the components of MetS, separated for participants with and without new-onset MetS. For men, the category free NRI was 0.33 (95% CI 0.15-0.52; $P = 0.002$), and IDI was 0.0015 ($P = 0.56$).There were 43% more cases that were reclassified in the correct direction using change of UACR. However, the increase in IDI was not significant in men. For women and total population, the NRI were -0.12 (-0.23 - -0.01; $P = 0.20$) and 0.02 (-0.05 -0.08; $P = 0.83$), respectively, and IDI were 0.0017 ($P = 0.56$) and 0.0032 ($P = 0.32$), respectively.

Figure 3. Comparison of ROC curves for incident metabolic syndrome in men and women



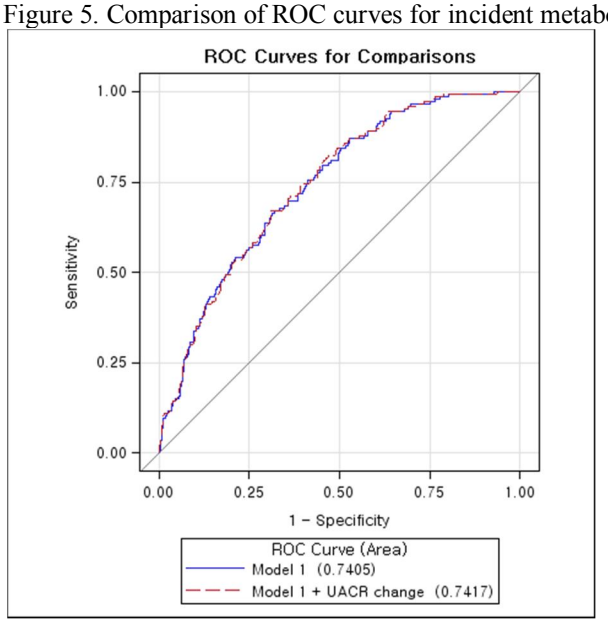
Model 1: Baseline waist circumference, HDL cholesterol, TG, Systolic blood pressure, fasting serum glucose
P value for comparison in areas under the ROC curves for the models with and without UACR change = 0.5275

Figure 4. Comparison of ROC curves for incident metabolic syndrome in men



Model 1: Baseline waist circumference, HDL cholesterol, TG, Systolic blood pressure, fasting serum glucose
P value for comparison in areas under the ROC curves for the models with and without UACR change = 0.9105

Figure 5. Comparison of ROC curves for incident metabolic syndrome in women



Model 1: Baseline waist circumference, HDL cholesterol, TG, Systolic blood pressure, fasting serum glucose
P value for comparison in areas under the ROC curves for the models with and without UACR change = 0.4302

Table 14. Predicted risk for an incident metabolic syndrome event before and after reclassification with a change of UACR in men and women who did (A) or did not (B) experience an event

	Model 2 (with a change of UACR)			
A	0-<10%	10-<20%	≥20%	Total
Model 1 (without a change of UACR)				
0-<10%	18	0	0	18
10-<20%	4	76	1	81
≥20%	0	10	138	148
Total	22	86	139	247
B				
Model 1 (without a change of UACR)				
0-<10%	342	0	0	342
10-<20%	33	432	1	466
≥20%	0	30	324	354
Total	375	462	325	1162

Model 1: Baseline waist circumference, HDL cholesterol, TG, Systolic blood pressure, fasting serum glucose
Model 2: Model 1 + a change of UACR

Table 15. Predicted risk for an incident metabolic syndrome event before and after reclassification with a change of UACR in men who did (A) or did not (B) experience an event

	Model 2 (with a change of UACR)			
A	0-<10%	10-<20%	≥20%	Total
Model 1 (without a change of UACR)				
0-<10%	10	0	0	10
10-<20%	0	21	0	21
≥20%	0	3	67	70
Total	10	24	67	101
B				
Model 1 (without a change of UACR)				
0-<10%	207	1	0	231
10-<20%	34	121	1	169
≥20%	0	16	126	142
Total	241	138	127	506

Model 1: Baseline waist circumference, HDL cholesterol, TG, Systolic blood pressure, fasting serum glucose
Model 2: Model 1 + a change of UACR

Table 16. Predicted risk for an incident metabolic syndrome event before and after reclassification with a change of UACR in women who did (A) or did not (B) experience an event

	Model 2 (with a change of UACR)			
A	0-<10%	10-<20%	≥20%	Total
Model 1 (without a change of UACR)				
0-<10%	8	0	0	8
10-<20%	1	44	0	45
≥20%	0	5	88	93
Total	9	49	88	146
B				
Model 1 (without a change of UACR)				
0-<10%	226	1	0	227
10-<20%	13	217	1	231
≥20%	0	14	184	198
Total	239	232	185	656

Model 1: Baseline waist circumference, HDL cholesterol, TG, Systolic blood pressure, fasting serum glucose
Model 2: Model 1 + a change of UACR

IV. DISCUSSION

In the present prospective cohort study, although we found that elevated UACR at baseline was not significantly associated with the increased incident MetS and its components in middle-aged and elderly Korean population, the change was positively associated with incident MetS in men. The same significance was not found in women. The magnitude of this association persisted in the group of below cutoff points of baseline UACR, especially, not in the group of above cutoff points of baseline UACR. These findings indicate that an increase of UACR change within the very low-grade albuminuria (<10.6 mg/g) may be a predictor of incident MetS. Moreover, our analyses show that UACR change may increase the predictive ability for identification of subjects at risk for developing MetS beyond that of the information provided by the components of the MetS in men.

Microalbuminuria is a well- known prognostic marker of cardiovascular and renal disease, and included in the WHO′s definition of MetS. Recently several studies have demonstrated that the risk of cardiovascular disease and mortality was associated with urinary albumin excretion that is less than microalbumin threshold (Gersten, 2001; Wang, 2005; Arnlov, 2005; Klausen, 2004; Ingelsson, 2007). Data from the PREVEND study showed urinary albumin excretion is a predictor of all-cause mortality and cardiovascular mortality in the general population, and the relationship between urinary albumin excretion and mortality was apparent at lower levels of microalbuminuria currently considered to be normal (Hillege, 2002). In the Framingham Heart Study, it was shown that low-grade albuminuria less than normal range of microalbuminuria threshold predicted blood pressure progression and an increased incidence of cardiovascular disease events (Wang, 2005; Arnlov, 2005). A previous Korean study indicated that low-grade albuminuria in Korean men was associated with a variety of cardiovascular risk factors. However, an association of low-grade albuminuria with MetS was not shown in multivariable-adjusted model (Sung, 2006). Another data of Chinese population indicated that low-grade albuminuria was associated with the increasing risk of MetS and metabolic components (Zhang, 2013). In our cross-sectional analysis, we also confirmed the association between lower level of urinary albumin excretion and MetS and its components in both genders. On the basis of these results, we conducted a prospective study of the relationship between urinary albumin excretion and incident MetS. Our findings showed there was no significant relationship between UACR and incidence of MetS and its components. We have considered some possible explanations for this lack of significant relationship between UACR and incidence of MetS. One possibility is that the study lacked sufficient study population. Another possibility is because of short duration of follow-up period, the cases of

incident MetS is not too sufficient to find the relationship between urinary albumin excretion and incident MetS. The developing high waist circumference and low HDL cholesterol with baseline UACR showed negative association. However, these findings was presented on the account that an increase of waist circumference from baseline to follow-up period in the lowest UACR tertile is greater than in the highest UACR tertile and a decrease of HDL cholesterol from baseline to follow-up period in the lowest UACR tertile is greater than in the highest UACR tertile.

Interestingly, our findings have demonstrated that the increase of urinary albumin excretion is a predictor of incident MetS. These results were shown consistently in the relationship between UACR change (ΔUACR) and incident MetS. In other words, compared to the highest tertile of ΔUACR, the risk of incident MetS was significantly decreased in the lowest tertile of ΔUACR, the group with the greatest decrease of urinary albumin excretion. Furthermore, this association was maintained in the group of below cutoff points of baseline UACR but not in the group of above cutoff points of baseline UACR. The prospective design and the graded dose-response relationships suggest that ΔUACR may play a role in the development of new-onset MetS.

The potential mechanism linking low urinary albumin excretion to MetS is not fully understood and is inconsistent. Nevertheless, several mechanisms may explain the relationships between low-grade albuminuria and incidence of MetS. Microalbuminuria may be an indicator, such as glomerular endothelial dysfunction. The leakage of albumin may reflect the renal manifestation of generalized abnormality of endothelial dysfunction (Deckert, 1989). Increased urinary albumin excretion was associated with impaired arterial dilatation and diffuse vascular disease (Deckert, 1989; Clausen, 2001). Insulin resistance is the most accepted underlying hypothesis to explain the pathophysiology of the MetS. Insulin resistance is closely associated with impairments in production of nitric oxide (NO) in endothelium and reduced PI3K/Akt signaling pathway in vascular endothelium (Kim, 2006, Eckel, 2010, Tesauro, 2011). Thus, impairment in insulin signaling to endothelial dysfunction causes decreased blood flow that can contribute to insulin resistance in skeletal muscle by reducing delivery of glucose and insulin (Kim, 2006, Muniyappa, 2007). Therefore, slightly elevated urinary albumin excretion could be an early marker of insulin resistance. Recent studies have shown that elevated urinary albumin excretion independently predicted the risk of type 2 diabetes (Brantsma, 2005; Halimi, 2008).

We found no improvement in the area under the ROC curve in models that added ΔUACR to metabolic components. On the other hand, the NRI but not IDI was significantly improved in men. The NRI and IDI may be considered more sensitive than the area under the ROC curve for identifying improvements in predicting value (Pencina, 2008). Our findings show that ΔUACR may have a practical value in screening the prevalent risk of

MetS in men. However, because IDI was not significantly improved in men and the improvements of NRI and IDI were not shown in women, further studies with large sample size and validation samples are needed to describe risk scoring tools and clinical cutoff points to predict developing MetS in addition to measuring ΔUACR.

To the best of our knowledge, this current study is the first research which has dealt with the association of UACR with incident risk of MetS in a prospective design. Most previous studies examining the association between urinary albumin excretion and MetS and its components were cross-sectional studies. Therefore, those were not able to conclude a causal relationship between urinary albumin excretion and MetS.

There are some limitations which should be considered when the findings of present work are interpreted. First, the present study was conducted in middle-aged and elderly Koreans living in a rural area with a relatively high prevalence and high incidence of MetS. The prevalence of MetS in our cohort is similar to that of the Korean National Health and Nutrition Examination Survey, a representative study of the Korean population (Lim, 2011). Our results may not be considered for generalization to other populations, in particular, to those with different races, nations or younger age. Second, because the mean follow-up period was only 2.6 years, this relatively short follow up period may not allow us to evaluate whether the association between UACR and incident MetS will continue in a longer follow-up trail. Third, UACR was assessed on a single urine specimen. However, the use of spot specimens for UACR is more convenient for a large cohort sample and the results correlate well with those of 24 hour urine collections (Bakker, 1999; Eknoyan, 2003).

In conclusion, this study presents a significant relationship between baseline UACR and MetS and its components in the general Korean population. In this prospective study, UACR change was positively associated with incident MetS. This association was particularly evident in the group of below cutoff points of baseline UACR, within the very low-grade albuminuria (<10.6 mg/g). These findings suggest increased UACR change in the range of less than current microalbuminuria threshold may be a predictor for new-onset MetS.

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국문요약

한국인 인구집단에서 요알부민크레아티닌비와 대사증후군 발생과의 관련성

연구배경

정상범위의 요알부민배설은 심혈관질환 및 혈압의 진행과 관련이 있다는 보고가 있으며, 최근에는 다양한 연구집단에서 요알부민배설이 대사증후군 및 대사증후군의 여러인자들의 유병률과 관련이 있다는 연구들이 있었다. 또한, 요말부민배설의 변화와 동맥경직도, 경동맥내중막두께가 양의 관련성을 보인다는 몇몇 보고가 있으나 정상범위의 알부민뇨와 대사증훈구에 대한 연구는 많지 않으며, 요알부민배설의 변화와 대사증후군에 대한 연구는 거의 보고되지 않았다.

연구목적

저자들은 한국인 일반 인구집단에서 요알부민크레아티닌비와 대사증후군의 발생 및 대사증후군의 인자들의 발생위험과의 관련성을 알아보고, 추적 기간 동안 요알부민크레아티닌비의 변화와 대사증후군 발생위험과의 연관성을 알아보고자 한다.

연구방법

한국인 일반 인구집단에서 시골 지역의 동맥경화 위험을 알아보기 위한 한국 유전체역학연구의 40세에서 70세 사이의 연구대상자를 대상으로 기반조사에서 요알부민크레아티닌비와 대사증후군의 관련성을 알아보기 위해 6,489명(남자 2,653명, 여자 3,836명)을 분석하였다. 기반조사에서 대사증후군이 없는 1,686명(남자 740명, 여자 946명)을 대상으로 요알부민크레아티닌비에 따른 대사증후군과 대사증후군 인자들의 발생 위험을 분석하였다.

연구결과

기반조사에서 요알부민크레아티닌비의 사분위수에 따라 평균 허리둘레, 수축기 및 이완기 혈압, 공복혈당과 중성지방의 중위수는 증가하였다. 고밀도 리포단백콜리스테롤은 요알부민크레아티닌비의 사분위수에 따라 감소하였다. 요알부민크레아티닌비의 가장 낮은 사분위수와 비교할 때, 가장 높은 사분위수의 요알부민크레아티닌비의 대사증후군의 유병률에 대한 비치비는 남자에서 1.87(95% 신뢰구간 1.43-2.45), 여성에서 1.90 (.54-2.35) 였다. 평균 2.6년의 추적 기간 동안 남자에서는 129명(17.4%), 여자에서는 183명(19.3%)의 대사증후군이 발생하였다. 전향적 연구에서, 요알부민크레아티닌비의 가장 낮은 삼분위수와 비교할 때, 가장 높은 삼분위수의 요알부민크레아티닌비의 대사증후군의 발생에 대한 비치비는 남자에서 0.93(0.56-1.52), 여성에서 1.25 (0.82-1.89) 였다. 기준치로부터 요알부민크레아티닌비가 10% 미만 증가 또는 5mg/g 미만으로 증가한 군과 비교할 때, 요알부민크레아티닌비가 20% 이상 증가하거나 10mg/g 이상으로 증가한 군의 대사증후군의 발생에 대한 비치비는 1.44 (1.05-1.97), 2.00 (1.22-3.28) 였다. 기준치로부터 추적기간의 요알부민크레아티닌비의 변화를 삼분위수로 나누어 대사증후군의 발생에 대한 비차비를 분석하였을 때, 가장 낮은 삼분위수에 비해 가장 높은 삼분위수의 비차비는 0.62(0.47-0.92) 였다. 요알부민크레아티닌비의 절단점(10.6mm/g)으로 층화하여 분석한 경우, 절단점 미만에서는 요알부민크레아티닌비가 10% 미만 증가 또는 5mg/g 미만으로 증가한 군과 비교할 때, 요알부민크레아티닌비가 20% 이상 증가하거나 10mg/g 이상으로 증가한 군의 대사증후군의 발생에 대한 비치비는 1.66 (1.12-2.46), 4.16 (1.91-9.08) 였다. 하지만, 절단점 이상의 군에서는 요알부민크레아티닌비의 변화와 대사증후군의 발생과는 의미 있는 관련성을 보이지 않았다.

결론

기준치로부터 요알부민크레아티닌비가 증가할수록 대사증후군의 발생의 위험이 높아진다. 특히 절단점 미만의 매우 낮은 알부민뇨를 보이는 군에서 연관성은 더 뚜렷하였다. 미세단백뇨 이하의 범위에서 요알부민크레아티닌비의 증가는 새로운 대사증후군 발생의 예측인자가 될 수 있다.

핵심어 : 요알부민크레아티닌비, 대사증후군, 요알부민크레아티닌비의 변화, 저등급알부민뇨