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Relationship between Kidney Function and Subclinical Atherosclerosis Progression Evaluated by Coronary Artery Calcification

Namuun Ganbaatar[1], Aya Kadota[1], Takashi Hisamatsu[1, 2], Shin-Ichi Araki[3], Shinji Kume[3], Akira Fujiyoshi[1, 4], Sayaka Kadowaki[1], Sayuki Torii[1], Keiko Kondo[1], Hiroyoshi Segawa[1], Ebtehal Salman[1], Itsuko Miyazawa[3, 5], Takashi Yamamoto[3], Yoshihisa Nakagawa[3], Hiroshi Maegawa[3], Katsuyuki Miura[1] and Hirotsugu Ueshima[1] for the SESSA Research Group

[1]NCD Epidemiology Research Center, Shiga University of Medical Science, Shiga, Japan
[2]Department of Public Health, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan
[3]Department of Medicine, Shiga University of Medical Science, Shiga, Japan
[4]Department of Hygiene, Wakayama Medical University, Wakayama, Japan
[5]Education Center for Medicine and Nursing, Shiga University of Medical Science, Shiga, Japan

Aims: The roles of urinary albumin, eGFRcystatin (eGFRcys), and eGFRcreatinine (eGFRcre) in the progression of coronary artery calcification (CAC) remain unclear. Therefore, the present study investigated the relationship between kidney function and CAC progression.

Methods: A total of 760 Japanese men aged 40-79 years were enrolled in this population-based study. Kidney function was measured using eGFRcre, eGFRcys, and the urine albumin-to-creatinine ratio. CAC scores were calculated using the Agatston method. CAC progression was defined as an annual increase of >10 Agatston units (AU) among men with 0<CAC<100 AU at baseline, that of >10% among those with CAC ≥ 100 AU, and any progression for those with CAC=0 at baseline. The relative risk (RR) of CAC progression based on kidney function was assessed using a robust Poisson regression model.

Results: The mean follow-up period was 4.9 years. CAC progression was detected in 45.8% of participants. Positive associations between CAC progression and albuminuria (>30mg/g) (RR: 1.29; 1.09 to 1.53; $p=0.004$) and low eGFRcys (<60ml/min/1.73m^2) (RR: 1.27; 1.05 to 1.53; $p=0.012$) remained significant after adjustments for age, the follow-up time, and computerized tomography type. Following further adjustments for hypertension, diabetes mellitus, dyslipidemia, C-reactive protein, and lifestyle factors, CAC progression was associated with albuminuria (RR: 1.20; 1.01 to 1.43; $p=0.04$) and low eGFRcys (RR: 1.19; 0.99 to 1.43; $p=0.066$), but not with eGFRcre.

Conclusion: CAC progression was associated with albuminuria; however, its relationship with eGFRcys was weakened by adjustments for risk factors.

Key words: Estimated glomerular filtration rate, Urinary albumin, Coronary artery calcification progression

Introduction

Chronic kidney disease (CKD) is a global public health issue[1)], and affects 10-15% of the global population due to its many causes[2)]. It is strongly associated with cardiovascular disease (CVD) events and mortality[3)]. CKD is diagnosed by increases in urinary albumin or decreases in the estimated glomerular filtration rate (eGFR). Therefore, urinary albumin and eGFR may predict the progression of

Address for correspondence: Aya Kadota, NCD Epidemiology Research Center, Shiga University of Medical Science, 520-2192, Seta Tsukinowa-cho, Otsu, Shiga, Japan E-mail: ayakd@belle.shiga-med.ac.jp

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subclinical atherosclerosis, such as coronary artery calcification (CAC), which is strongly predictive of CVD events[4].

However, an increase in urinary albumin and decrease in eGFR do not always coexist because they occur through common and different pathophysiological pathways[5]. eGFR and urinary albumin may perform different roles in the progression of atherosclerosis. Urinary albumin is not only a marker for renal impairment, it has also been implicated in vascular endothelial dysfunction; however, the relationship between CAC progression and urinary albumin remains unclear[6, 7]. Lower eGFR by creatinine (eGFRcre) is independently associated with vascular calcification and contributes to CVD events and mortality[5, 8]. eGFRcre is also inversely associated with CAC scores[9, 10]. However, discrepancies have been reported in this relationship[7, 11]. eGFR by cystatin C (eGFRcys) is reportedly a superior marker to eGFRcre for predicting CVD mortality[12, 13]. CAC may be more strongly associated with eGFRcys than with eGFRcre. However, limited information is currently available on the relationship between eGFRcys and CAC progression.

Based on these findings, we hypothesized that urinary albumin and eGFR may predict CAC progression independently from each other, and also that predictability of eGFRcre and eGFRcys for CAC progression may differ.

Aim

We investigated whether urinary albumin, eGFRcys and eGFRcre were associated with CAC progression in general Japanese men.

Methods

Study Participants

The present study was an observational population-based longitudinal study of the Shiga Epidemiological Study of Subclinical Atherosclerosis (SESSA). The detailed design of this study is described elsewhere[14, 15]. In brief, 2,381 male residents from Kusatsu city, Shiga, Japan aged 40 - 79 years were randomly selected based on age strata. The number of 40 to 79-year-old men in Kusatsu city was 25,394 in 2005. The extraction rate was 9.4% (2,381/25,394)[14]. Of these men, 1,094 voluntarily enrolled in the present study at baseline (May 2006–March 2008) by SESSA. They were asked to complete a follow-up survey between 2010 to 2014, and 853 (78%) participants complied.

After excluding participants with a history of myocardial infarction (n=18), and stroke (n=22); because medication treatment for stroke may affect both kidney function and CAC progression, and missing variables on urinary albumin (n=21), cystatin C (n=2), creatinine (n=1), LDL-C (n=16), and step counts (n=13), 760 men who participated in the follow-up survey were included in the present study.

All participants provided written informed consent. The Institutional Ethics Committee of the Shiga University of Medical Science (Otsu city, Shiga, Japan) approved the present study (G2008-61).

Study Examination

Self-administered questionnaires were completed to obtain information on demographical characteristics, previous medical histories, medication use, smoking and drinking habits, and other risk factors. The smoking status was initially categorized as "current", "ex", or "never", and the "ex" and "never" categories were then combined as "non-smokers". The drinking status was categorized in the same manner.

A physical examination was performed to obtain information on height, weight, and blood pressure. Body mass index (BMI, kg/m^2) was calculated as weight (kg) divided by height (m) squared. Blood pressure was measured twice in a sitting position after 5 min of rest using an automated sphygmomanometer with an appropriately sized cuff. The mean of two measurements was used for the analysis. Hypertension was defined as the use of antihypertensive medication, systolic blood pressure (SBP) ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg. A pedometer (DIGI-Walker, DW-200) was used in the baseline examination to record step count data for seven consecutive days. Daily step counts greater than 30,000 or less than 500 steps were considered to be outliers and removed[16]. The average step count per day in the first five days was calculated to minimize missing data.

Laboratory Measurements

Spot urine was collected to measure urinary albumin. Laboratory-based blood samples were obtained by venipuncture after fasting for 12 hours. We separated serum by centrifugation (3,000 rpm for 15 min) at 4℃ within 90 min. Samples were sent for routine laboratory tests. Triglycerides (TG) were measured using enzymatic assays. HDL-C was assessed using a direct method. LDL-C was estimated in participants with TG <400 mg/dl using the Friedewald formula as follows: LDL-C (mg/dl) = total cholesterol (mg/dl) − HDL-C (mg/dl) − TG (mg/dl)/5 [17]. Dyslipidemia was defined as TG ≥ 150 mg/dl, HDL-C <40 mg/dl, LDL-C ≥ 140 mg/dl, or the use

of dyslipidemia medication. Glycated hemoglobin A1c (HbA1c) was measured using latex agglutination immunoassays according to the protocol by the Japanese Diabetes Society and converted to the National Glycohemoglobin Standardization Program (NGSP) value. Diabetes mellitus (DM) was defined as either fasting glucose ≥ 126 mg/dl, HbA1c ≥ 6.5%, or the use of medication[18]. C-reactive protein (CRP) levels were measured by nephelometry using a BN II Analyzer[19].

Kidney Function Measurements

Urinary albumin was measured using immunonephelometry and pyrogallol red methods[20]. Albuminuria was defined as an albumin-to-creatinine ratio of more than 30 mg/g. Cystatin C was measured using a colloidal gold-enhanced immune turbidimetry method (Alfresa Pharma, Osaka, Japan) with intra- and inter-assay coefficients of variation $<1.7\%$[21]. Based on the GFR estimating equation using cystatin C for Japanese men, eGFRcys was calculated as follows[22]: eGFRcys (ml/min/1.73m^2) = (104 × cystatin C$^{-1.019}$ × 0.996^{age}) − 8.

Serum creatinine levels were measured using an enzymatic method (Espa CRE-liquid II; NIPRO, Osaka, Japan)[23]. eGFRcre was calculated using the Japanese Society of Nephrology equation as follows[24]: eGFRcre (ml/min/1.73m^2) = 194 × sCr (mg/dl)$^{(-1.094)}$ × age (year)$^{(-0.287)}$. Participants with eGFR $<$60ml/min/1.73m^2 were categorized as low eGFR.

CAC Measurements

CAC measurements have been described in detail elsewhere[15]. In brief, CAC at baseline was measured using electron-beam computed tomography (EBCT) with the C-150 scanner (Imatron, South San Francisco, CA, US) or 16-channel multi-detector-row computed tomography (MDCT) with the Aquilon scanner (Toshiba, Tokyo, Japan). CAC at the follow-up was measured using MDCT. Images from the level of the root aorta through to the heart with a slice thickness of 3 mm were considered with a scan time of 100 ms (EBCT) or 320 ms (MDCT). Images were acquired at 70% of the cardiac cycle using electrocardiography triggered during a single breath-hold. AccuImage software (AccuImage Diagnostic, South San Francisco, CA, USA) was used to quantify CAC scores. CAC was considered to be present with three contiguous pixels (area = 1 mm^2) ≥ 130 Hounsfield Units. CAC scores were evaluated according to the Agatston method[25]. All CT images were evaluated by one physician who was trained and blinded to the information of participants. The protocol was adapted from a different cohort study, in which the reproducibility of scans showed an intraclass correlation of 0.98 [26]. The definitions of CAC by EBCT and MDCT were considered to be equivalent[15].

CAC progression was categorized as present and absent. Similar to previous studies, CAC progression was diagnosed in the present study as follows: CAC = 0 at baseline, progression was defined as CAC score >0 in the follow-up, $0<$CAC<100 at baseline, defined as an annualized change ((CAC$_{follow}$ − CAC$_{baseline}$)/follow-up years) of ≥ 10 Agatston units in the follow-up, and CAC ≥ 100 at baseline, defined as an annualized percent change ≥ 10% in the follow-up[27].

Statistical Analysis

In the characteristics table, continuous variables were described as means ± standard deviations (SD) and skewed continuous variables as medians and interquartile ranges (IQR). Categorical variables were described as numbers and percentages.

We used log-transformed values for skewed variables, such as urinary albumin, TG, and CRP. A robust Poisson regression analysis was performed to estimate the relative risk (RR) and 95% confidence interval (CI) of CAC progression per one SD elevation for continuous variables as log-transformed urinary albumin, eGFRcys, eGFRcre, albuminuria, low eGFRcys (less than 60 ml/min/1.73m^2), and low eGFRcre[28]. We also examined the RRs of the combination models, which included both albuminuria and low eGFR (eGFRcre or eGFRcys) together. A multivariable logistic regression analysis was also performed to estimate the odds ratio (OR) and 95% CI of CAC progression by log-transformed urinary albumin, eGFR, albuminuria, low eGFRcys (less than 60 ml/min/1.73m^2), and low eGFRcre. Adjusted variables are shown below:

Model 1: Age, CT type, and follow-up time; Model 2: Model 1 + BMI, current smoker, current drinker, and step counts; Model 3: Model 2 + SBP, HDL-C, LDL-C, log TG, HbA1c, log CRP, and the use of DM medication, hypertension medication, and lipid medication; Model 4: Model 2 + hypertension, DM, dyslipidemia, and log CRP. In the subgroup analysis, we repeated the Poisson robust error analysis excluding CAC = 0 and CAC $>$ 100 at baseline.

Analyses were conducted using SAS software (version 9.4, SAS Institute Inc.). Two-tailed p values of ≤ 0.05 were considered to be significant.

Results

The overall baseline characteristics of participants are shown in **Table 1**. Mean age was 64.0 ± 9.4 years. The mean values of eGFRcys and eGFRcre were

Table 1. Characteristics in 760 male participants aged 40-79 years in the SESSA Study, 2006-2008

Variables	Overall
Age, years	64.0 (9.4)
Systolic blood pressure, mmHg	135.6 (18.1)
Body mass index, kg/m^2	23.6 (2.9)
Daily step counts	8497.7 (3640.2)
HDL-cholesterol, mg/dl	59.4 (17.0)
LDL-cholesterol, mg/dl	126.2 (30.5)
Triglycerides, mg/dl	102.0 (76.0 - 146.5)
HbA1c, (%)	5.6 (0.7)
High sensitive C-reactive protein, μg/ml	0.4 (0.2 - 0.9)
Urinary albumin per creatinine, mg/g[†]	7.4 (4.4 - 17.8)
eGFR cystatin, ml/min/1.73m^2	75.4 (15.0)
eGFR creatinine, ml/min/1.73m^2	72.9 (13.7)
Albuminuria, *n* (%)	133 (17.5)
eGFR cystatin <60 ml, *n* (%)	109 (14.4)
eGFR creatinine <60 ml, *n* (%)	118 (15.5)
CAC = 0 at baseline, *n* (%)	281 (37.0)
CAC 0 – 100 at baseline, *n* (%)	314 (41.3)
CAC >100 at baseline, *n* (%)	165 (21.7)
CAC progression, *n* (%)	348 (45.8)
Current smoker, *n* (%)	234 (30.8)
Current drinker, *n* (%)	599 (78.8)
Medication for hypertension, *n* (%)	227 (29.9)
Medication for diabetes mellitus, *n* (%)	75 (9.9)
Medication for dyslipidemia, *n* (%)	99 (13.0)
Hypertension, *n* (%)	402 (52.9)
Diabetes mellitus, *n* (%)	164 (21.6)
Dyslipidemia, *n* (%)	413 (54.3)

Continuous variables expressed as mean (SD), median (IQR). Categorical variables expressed as a number (percentage). CAC, coronary artery calcification. eGFR, estimated glomerular filtration rate; TG, triglyceride; Albuminuria described as >30mg/g; Diabetes mellitus defined as either fasting glucose ≥ 126 mg/dL, or HbA1c ≥ 6.5%, or medication use. Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or medication use; Dyslipidemia defined as TG ≥ 150 mg/dl, HDL-C < 40 mg/dl, LDL-C ≥ 140 mg/dl or medication use. [†]Spot urine.

75.4±15.0 ml/min/1.73m^2 and 72.9±13.7 ml/min/1.73m^2, respectively. The median and IQR of urinary albumin was 7.4 (4.4 - 17.8) mg/g. Albuminuria was noted in 133 participants (17.5%); the mean values of eGFRcre and eGFRcre were 71.3±17.4 ml/min/1.73m^2 and 69.4±16.1 ml/min/1.73m^2, respectively. Low eGFRcys of less than 60 ml/min/1.73m^2 was observed in 109 participants (14.4%). Moreover, 118 participants (15.5%) had low eGFRcre of less than 60 ml/min/1.73m^2. The mean follow-up period was 4.9 years. In the follow up survey, CAC progression was observed in 25% of participants with CAC=0 at baseline, 54% of those with 0<CAC<100 at baseline, and 15% of those with CAC ≥ 100 at baseline. In total, 348 participants (45.8%) showed CAC progression.

The relationships between CAC progression and kidney function according to 1SD increased urinary albumin, eGFRcys, and eGFRcre are shown in **Table 2**. In unadjusted models, CAC progression was associated with an increase in urinary albumin (p=0.001) and inversely associated with eGFRcys (p=0.001). The association between CAC progression and the increase in urinary albumin remained significant after adjustments for age, the follow-up time, CT type, and lifestyle factors. However, after adjustments for CVD risk factors, its relationships with urinary albumin and eGFRcys were no longer significant. Furthermore, no relationship was observed between eGFRcre and CAC progression.

Table 3 shows the results of the RR and 95% CI of CAC progression according to albuminuria, low eGFRcys, and low eGFRcre. In the unadjusted model, albuminuria positively associated with CAC

Table 2. Unadjusted and multivariable adjusted relative risks of CAC progression according to a 1SD increase in urinary albumin and eGFR at baseline in 760 men aged 40-79 years with a mean follow-up of 4.9 years in the SESSA Study

	Unadjusted RR (95% CI)	Model 1 RR (95% CI)	Model 2 RR (95% CI)	Model 3 RR (95% CI)	Model 4 RR (95% CI)
Urinary albumin	1.11 (1.04 - 1.19)	1.09 (1.02 - 1.17)	1.08 (1.01 - 1.16)	1.01 (0.94 - 1.08)	1.04 (0.97 - 1.12)
eGFRcys	0.88 (0.81 - 0.95)	0.94 (0.85 - 1.03)	0.96 (0.87 - 1.06)	0.99 (0.90 - 1.09)	0.98 (0.89 - 1.08)
eGFRcre	0.98 (0.91 - 1.06)	1.03 (0.95 - 1.12)	1.03 (0.96 - 1.12)	1.04 (0.97 - 1.12)	1.04 (0.96 - 1.12)

eGFRcys, eGFR by cystatin C (ml/min/1.73 m^2); eGFRcre, eGFR by creatinine (ml/min/1.73 m^2); RR, relative risk; 95% CI, 95% confidence interval; A robust Poisson regression model was used to estimate RR and 95% CI; Urinary albumin, eGFRcys, eGFRcre are per 1 SD increase; Model 1 was adjusted for age, follow up period, CT type; Model 2 further adjusted by BMI, step counts, current-smoker, current-drinker; Model 3 was further adjusted for SBP, HDL-C, LDL-C, logTG, HbA1c, hypertension medication, diabetes medication, lipid medication, log-CRP; Model 4 was adjusted for Model 2 plus hypertension, diabetes, dyslipidemia, log-CRP.

Table 3. Unadjusted and multivariable adjusted relative risks of CAC progression according to albuminuria and low eGFR in 760 men aged 40-79 years with a mean follow-up of 4.9 years in the SESSA Study

	Unadjusted RR (95% CI)	Model 1 RR (95% CI)	Model 2 RR (95% CI)	Model 3 RR (95% CI)	Model 4 RR (95% CI)
Albuminuria	1.32 (1.11 - 1.56)	1.29 (1.09 - 1.53)	1.27 (1.07 - 1.51)	1.12 (0.94 - 1.34)	1.20 (1.01 - 1.43)
Low eGFRcys	1.42 (1.20 - 1.69)	1.27 (1.05 - 1.53)	1.21 (1.01 - 1.46)	1.17 (0.97 - 1.41)	1.19 (0.99 - 1.43)
Low eGFRcre	1.13 (0.93 - 1.38)	1.03 (0.85 - 1.25)	1.02 (0.83 - 1.23)	0.98 (0.81 - 1.19)	0.99 (0.82 - 1.21)

RR, relative risk; 95% CI, 95% confidence interval; Albuminuria described as >30mg/g. Low eGFR by cystatin C described as <60 ml/min/1.73m^2. Low eGFR by creatinine described as <60 ml/min/1.73m^2. A robust Poisson regression model was used to estimate RR and 95% CI; Model 1 was adjusted for age, follow up period, CT type; Model 2 further adjusted by BMI, step counts, current-smoker, current-drinker; Model 3 was further adjusted for SBP, HDL-C, LDL-C, logTG, HbA1c, hypertension medication, diabetes medication, lipid medication, log-CRP; Model 4 was adjusted for Model 2 plus hypertension, diabetes, dyslipidemia, log-CRP.

progression (1.32; 95% CI: 1.11 - 1.56). This relationship remained significant after adjustments for age, the follow-up time, CT type, and lifestyle factors (Model 1: 1.29; 95% CI: 1.09 - 1.53; Model 2: 1.27; 95% CI: 1.07 - 1.51), but was not observed after multivariable adjustments in Model 3 (1.12; 95% CI: 0.94 - 1.34). In Model 4, the relationship remained significant after adjustments for traditional CVD factors (1.20; 95% CI: 1.01 - 1.43). CAC progression was positively associated with low eGFRcys after similar adjustments to those for albuminuria (Unadjusted: 1.42; 95% CI: 1.20 - 1.69; Model 1: 1.27; 95% CI: 1.05 - 1.53; Model 2: 1.21; 95% CI: 1.01 - 1.46). The relationship between CAC progression and low eGFRcys was weakened by multivariable adjustments for traditional CVD factors (Model 4: (1.19; 95% CI: 0.99 - 1.43)). Furthermore, no relationship was observed between CAC progression and low eGFRcre in any model.

In mutually adjusted models (albuminuria and low eGFRcys), CAC progression was positively associated with albuminuria in the model with adjustments for hypertension, DM, dyslipidemia, smoking, drinking, and CRP. However, it was not associated with low eGFRcys, except for in Model 1 **(Table 4a)**. Moreover, in mutually adjusted models, including albuminuria and low eGFRcre, CAC progression was positively associated with albuminuria after adjustments for other risk factors (**Table 4b**, Model 4). The results of the multivariable logistic regression analysis are shown in **Supplemental Table 1 and 2**. An increased risk of CAC progression was associated with albuminuria after adjustments for lifestyle and CVD factors. Its relationship with low eGFRcys was weakened by adjustments for traditional CVD factors, while no relationship was observed with low eGFRcre. These results were similar to those obtained from the Poisson regression analysis.

According to mutually adjusted models in **Supplemental Table 2a, b**, CAC progression was positively associated with albuminuria after adjustments for low eGFRcys and low eGFRcre. It was also marginally associated with low eGFRcys **(Supplemental Table 2a)**, but not with low eGFRcre **(Supplemental Table 2b)**.

Supplemental Tables 3, and 4 show results of the sub analysis, excluding those with CAC=0 at baseline. CAC progression was not associated with albuminuria, low eGFRcre, or low eGFRcys in Models 2 to 4. RR results for low eGFRcys and low eGFRcre were similar to those from the analysis of all participants in **Table 3**. However, the RR of

Table 4. Multivariable adjusted relative risk of CAC progression and kidney function according to mutually adjusted albuminuria with low eGFRcys and that with low eGFRcre in 760 men aged 40-79 years with a mean follow-up of 4.9 years in the SESSA Study

	Albuminuria RR (95% CI)	Low eGFRcys RR (95% CI)	Low eGFRcre RR (95% CI)
a) Albuminuria and low eGFRcys			
Model 1	1.26 (1.06 - 1.50)	1.23 (1.02 - 1.49)	-
Model 2	1.25 (1.06 - 1.49)	1.18 (0.98 - 1.43)	-
Model 3	1.11 (0.92 - 1.32)	1.16 (0.96 - 1.40)	-
Model 4	1.18 (0.99 - 1.41)	1.17 (0.97 - 1.41)	-
b) Albuminuria and low eGFRcre			
Model 1	1.29 (1.09 - 1.53)	-	1.01 (0.83 - 1.23)
Model 2	1.27 (1.07 - 1.51)	-	0.99 (0.81 - 1.21)
Model 3	1.12 (0.94 - 1.34)	-	0.97 (0.80 - 1.18)
Model 4	1.20 (1.01 - 1.43)	-	0.98 (0.81 - 1.19)

RR, relative risk; 95% CI, 95% confidence interval;
a) Both albuminuria and low eGFRcys included in the model; b) Both albuminuria and low eGFRcre included in the model; Albuminuria described as >30mg/g; Low eGFR by cystatin C described as <60 ml/min/1.73m^2. Low eGFR by creatinine described as <60 ml/min/1.73m^2. A robust Poisson regression model was used to estimate RR and 95% CI; Model 1 was adjusted for age, follow up period, CT type; Model 2 further adjusted by BMI, step counts, current-smoker, current-drinker; Model 3 was further adjusted for SBP, HDL-C, LDL-C, logTG, HbA1c, hypertension medication, diabetes medication, lipid medication, log-CRP; Model 4 was adjusted for Model 2 plus hypertension, diabetes, dyslipidemia, log-CRP.

albuminuria was slightly lower than that of the analysis of all participants **(Supplemental Tables 3, and 4)**. **Supplemental Tables 5 and 6** show the results obtained after the exclusion of participants with CAC>100 at baseline. A significant association was observed between albuminuria and CAC progression, and RR of albuminuria was slightly higher than that of the entire population **(Tables 3 and 4)**. Low eGFRcys was positively associated with an increased risk of CAC progression in the unadjusted model, while no relationship was noted between low eGFRcre and CAC progression.

Discussion

In this longitudinal study, we examined whether urinary albumin, eGFRcys, and eGFRcre were associated with CAC progression. The results obtained showed that albuminuria was associated with CAC progression with adjustments for other risk factors, and the relationship between low eGFRcys and CAC progression was weakened by adjustments for other CVD risk factors. No relationship was observed between eGFRcre and CAC progression. To the best of our knowledge, this is the first study to investigate whether urinary albumin and eGFRcys are associated with CAC progression in a general population in Asia. The results obtained indicated that reduced kidney function influenced CAC progression in a healthy population.

A relationship was observed between albuminuria and CAC progression after adjustments for lifestyle and CVD risk factors, such as age, hypertension, DM, dyslipidemia, smoking, drinking, step counts, and CRP. These results are consistent with previous findings from general population studies, showing that albuminuria was independently associated with CAC[11]. Therefore, albuminuria may be a measure of systemic vascular damage[6]. However, in the present study, the significance of the relationship between urinary albumin and CAC progression decreased after multivariable adjustments. These results were also consistent with previous findings showing that urinary albumin was not associated with CAC progression after adjustments for CVD risk factors[7, 29]. A possible explanation for this discrepancy is whether urinary albumin is used as a binary or continuous variable. Moreover, most of the participants in the present study were relatively healthy. Accordingly, a stronger relationship may be observed between more progressive impairments in kidney function and CAC progression[30].

The pathophysiological mechanisms underlying the relationship between albuminuria and atherosclerosis have not yet been elucidated in detail[11]. Albuminuria has been implicated in vascular endothelial dysfunction[31], leading to damage to the glomerular filtration barrier. As a result, the passage of inflammatory cells and deposits of lipoproteins is permitted, which triggers systemic vascular inflammation and increases atherosclerotic plaque formation[32]. Moreover, endothelial impairments

under clinical conditions, such as hypertension, renal failure, and atherosclerosis, may be responsible for the development of accelerated atherosclerosis in CKD patients[33].

The present study revealed that decreased eGFRcys was associated with an increase in CAC progression after adjustments for lifestyle factors. However, the significance of this relationship was weakened by adjustments for traditional CVD risk factors. Similarly, the Rotterdam Study reported that the relationship between eGFRcys and CAC was attenuated after adjustments for CVD factors[30]. The MESA study also found no relationship between cystatin C and the CAC progression in a multivariable model. The findings suggest that in the general population, the relationship between eGFR and CAC is explained by the influence of CVD risk factors[29, 30]. The present results demonstrated that the significance of the relationship between eGFRcys as a continuous variable and CAC progression was weakened by adjustments for CVD risk factors, indicating that advanced kidney dysfunction may be strongly associated with atherosclerotic CVD.

We did not observe a relationship between eGFRcre and CAC progression. Similarly, Jassal *et al.* reported that eGFRcre was not associated with CAC progression[7]. The exposure and outcome characteristics of their study were similar to those of the present study. Furthermore, another study did not find a relationship between low eGFRcre and CAC[11]. In contrast, the Rotterdam Study, revealed a relationship between eGFRcre and CAC progression in elderly participants older than 70 years[10]. Therefore, the relationship between eGFRcre and CAC progression may be affected by age and CVD risk factors. Furthermore, prognosis of CKD in association with intima media thickness was influenced by age[34].

The molecular mechanisms underlying endothelial dysfunction in the early stage of calcification and CKD have not yet been elucidated[35], and may be associated with conventional risk factors that are related to CKD, as well as stroke, MI, and CVD[36, 37]. Furthermore, CAC progression may be more strongly related to advanced CKD stages explained by alternative risk factors, such as parathyroid hormone, hyperphosphatemia, fibroblast growth factor-23, and other factors[38]. However, the present study, only examined traditional risk factors and did not establish whether lower eGFR was related to these factors in CAC progression in the general population.

The present results suggest that low eGFRcys is more useful than low eGFRcre for predicting CAC progression. Recent studies reported that lower categories of eGFRcys were more strongly associated with CAC than the category of eGFRcys >90 ml/min/1.73m^2 [39]. Cystatin C may improve the classification of kidney function assessed by eGFR more than creatinine. Cystatin C has been shown to strengthen the relationship between eGFR and CVD risk factors in the elderly[40] and reduce all-cause mortality across diverse populations[41]. Furthermore, non-GFR factors affecting serum creatinine, including muscle mass, and physical activity, may confound the relationship between filtration markers and outcomes[41]. A previous study reported that creatinine-based eGFR had a U-curve association with CAC[30]. Since the analysis in the present study involved the general population, severe cases of kidney disease were not examined, which may have contributed to the lack of a relationship between eGFRcre and CAC progression.

Low eGFR and albuminuria are quantitative measurements for assessing CKD and predictors of CVD as well as the risk of mortality[42], thereby providing a more detailed disease prognosis. In the multivariable adjustment analysis with low eGFR and albuminuria, albuminuria was associated with CAC progression after adjustments for lifestyle factors. Furthermore, the relationship between low eGFRcys and CAC was weaker than that for albuminuria after adjustments for conventional risk factors. Low eGFRcys was marginally associated with CAC progression, while no relationship was observed for low eGFRcre. These results may be attributed to urinary albumin and eGFR differences in the pathophysiological mechanisms underlying the mild to moderately impaired kidney function categories for subclinical atherosclerosis. Accordingly, albuminuria may be more strongly related to endothelial dysfunction in the early phase of atherosclerosis and may predict subclinical atherosclerosis in patients with mild CKD.

The strength of the present study is that it was a longitudinal cohort population-based study. However, there were some limitations. Firstly, we only examined general Japanese men, and, thus, the results obtained cannot be generalized to other populations, such as women and those with advanced kidney dysfunction. Furthermore, we were unable to establish the exact time of CAC progression. Moreover, kidney function marker assessments were only conducted once at the baseline examination. Further, medication during the follow-up period might modify the relationship between CAC progression and urinary albumin, eGFRcys, and eGFRcre. However, we could not assess the effect due to the small sample size. In addition, because the follow-up period was relatively short in the present study, the longitudinal effects of kidney

function remain unclear. Therefore, further studies with longer follow-up periods may provide more important results.

Conclusion

The present results demonstrated that CAC progression was associated with albuminuria. Regarding eGFR, a relationship was also observed between low eGFRcys and CAC progression only, the significance of which decreased after adjustments for traditional CVD risk factors. These results indicate that predictions of atherosclerotic CVD may differ based on the kidney function markers used.

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Conflict of Interest

The authors declare that there are no conflicts of interest.

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Supplemental Table 1. Odds ratios of the presence of CAC progression by kidney function according to albuminuria or low eGFR in 760 men aged 40-79 years with a mean follow-up of 4.9 years in the SESSA Study

	Unadjusted OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)
Albuminuria	1.74 (1.19 - 2.54)	1.69 (1.15 - 2.50)	1.70 (1.14 - 2.52)	1.32 (0.86 - 2.02)	1.52 (1.01 - 2.30)
Low eGFRcys	2.10 (1.39 - 3.18)	1.73 (1.11 - 2.69)	1.60 (1.02 - 2.51)	1.55 (0.97 - 2.47)	1.56 (0.98 - 2.47)
Low eGFRcre	1.27 (0.86 - 1.88)	1.07 (0.71 - 1.61)	1.03 (0.68 - 1.55)	0.97 (0.63 - 1.49)	0.99(0.65 - 1.52)

OR, odds ratio; 95% CI, 95% confidence interval;
Albuminuria described as >30mg/g; Low eGFR by cystatin C described as <60 ml/min/1.73m^2; Low eGFR by creatinine described as <60 ml/min/1.73m^2; A multivariable logistic regression analysis was used to estimate odds ratio with 95% CI; Model 1 was adjusted for age, follow up period, CT type; Model 2 further adjusted by BMI, step counts, current-smoker, current-drinker; Model 3 was further adjusted for SBP, HDL-C, LDL-C, logTG, HbA1c, hypertension medication, diabetes medication, lipid medication, log-CRP; Model 4 was adjusted for Model 2 plus hypertension, diabetes, dyslipidemia, log-CRP.

Supplemental Table 2. Multivariable adjusted odds ratios of CAC progression by kidney function according to mutually adjusted albuminuria with low eGFRcys and that with low eGFRcre in 760 men aged 40-79 years with a mean follow-up of 4.9 years in the SESSA Study

	Albuminuria OR (95% CI)	Low eGFRcys OR (95% CI)	Low eGFRcre OR (95% CI)
a) Albuminuria and low eGFRcys			
Model 1	1.62 (1.09 - 2.40)	1.63 (1.05 - 2.55)	-
Model 2	1.64 (1.10 - 2.45)	1.52 (0.97 - 2.40)	-
Model 3	1.29 (0.84 - 1.98)	1.52 (0.96 - 2.43)	-
Model 4	1.48 (0.98 - 2.25)	1.52 (0.96 - 2.40)	-
b) Albuminuria and low eGFRcre			
Model 1	1.69 (1.14 - 2.50)	-	1.02 (0.68 - 1.55)
Model 2	1.70 (1.14 - 2.52)	-	0.99 (0.65 - 1.50)
Model 3	1.32 (0.86 - 2.03)	-	0.96 (0.62 - 1.48)
Model 4	1.52 (1.01 - 2.31)	-	0.97 (0.64 - 1.49)

OR, odds ratio; 95% CI, 95% confidence interval;
a) Both albuminuria and low eGFRcys included in the model; b) Both albuminuria and low eGFRcre included in the model; Albuminuria described as >30mg/g; Low eGFR by cystatin C described as <60 ml/min/1.73m^2. Low eGFR by creatinine described as <60 ml/min/1.73m^2. A multivariable logistic regression analysis was used to estimate the odds ratio with 95% CI; Model 1 was adjusted for age, follow up period, CT type; Model 2 further adjusted by BMI, step counts, current-smoker, current-drinker; Model 3 was further adjusted for SBP, HDL-C, LDL-C, logTG, HbA1c, hypertension medication, diabetes medication, lipid medication, log-CRP; Model 4 was adjusted for Model 2 plus hypertension, diabetes, dyslipidemia, log-CRP.

Supplemental Table 3. Relative risk of CAC progression in 479 men, excluding those with CAC=0 at baseline, according to albuminuria or low eGFR (age 40-79 years with a mean follow-up of 4.9 years) in the SESSA Study

	Unadjusted RR (95% CI)	Model 1 RR (95% CI)	Model 2 RR (95% CI)	Model 3 RR (95% CI)	Model 4 RR (95% CI)
Albuminuria	1.12 (0.94 - 1.34)	1.12 (0.94 - 1.33)	1.14 (0.96 - 1.36)	1.07 (0.89 - 1.28)	1.12 (0.94 - 1.34)
Low eGFRcys	1.32 (1.10 - 1.57)	1.21 (1.01 - 1.46)	1.19 (0.99 - 1.44)	1.17 (0.97 - 1.41)	1.19 (0.98 - 1.43)
Low eGFRcre	1.06 (0.86 - 1.30)	1.01 (0.83 - 1.23)	1.02 (0.84 - 1.23)	1.01 (0.83 - 1.23)	1.00 (0.82 - 1.21)

RR, relative risk; 95% CI, 95% confidence interval; Albuminuria described as >30mg/g. Low eGFR by cystatin C described as <60 ml/min/1.73m^2. Low eGFR by creatinine described as <60 ml/min/1.73m^2. A robust Poisson regression model was used to estimate RR and 95% CI; Model 1 adjusted for age, CT type; Model 2 further adjusted for BMI, step counts, current-smoker, current-drinker; Model 3 further adjusted for SBP, HDL-C, LDL-C, log TG, HbA1c, hypertension medication, diabetes medication, lipid medication, log-CRP; Model 4 adjusted for Model 2 plus hypertension, diabetes, dyslipidemia, log-CRP.

Supplemental Table 4. Relative risk of CAC progression in 479 men, excluding those with CAC=0 at baseline, according to mutually adjusted low eGFRcys with albuminuria and low eGFRcre with albuminuria (age 40-79 years with a mean follow-up of 4.9 years) in the SESSA Study

	Albuminuria RR (95% CI)	Low eGFRcys RR (95% CI)	Low eGFRcre RR (95% CI)
a) Albuminuria and low eGFRcys			
Model 1	1.10 (0.92 - 1.31)	1.20 (0.99 - 1.44)	-
Model 2	1.12 (0.94 - 1.34)	1.17 (0.97 - 1.42)	-
Model 3	1.05 (0.88 - 1.27)	1.16 (0.96 - 1.40)	-
Model 4	1.11 (0.92 - 1.32)	1.18 (0.97 - 1.42)	-
b) Albuminuria and low eGFRcre			
Model 1	1.12 (0.94 - 1.34)	-	1.00 (0.82 - 1.22)
Model 2	1.14 (0.96 - 1.36)	-	1.00 (0.82 - 1.22)
Model 3	1.07 (0.89 - 1.29)	-	1.00 (0.82 - 1.22)
Model 4	1.13 (0.94 - 1.35)	-	0.99 (0.81 - 1.20)

RR, relative risk; 95% CI, 95% confidence interval; a) Both albuminuria and low eGFRcys included in the model; b) Both albuminuria and low eGFRcre included in the model; Albuminuria described as >30mg/g; Low eGFR by cystatin C described as <60 ml/min/1.73m^2. Low eGFR by creatinine described as <60 ml/min/1.73m^2. A robust Poisson regression model was used to estimate RR and 95% CI; Model 1 adjusted for age, CT type; Model 2 further adjusted for BMI, step counts, current-smoker, current-drinker; Model 3 further adjusted for SBP, HDL-C, LDL-C, log TG, HbA1c, hypertension medication, diabetes medication, lipid medication, log-CRP; Model 4 adjusted for Model 2 plus hypertension, diabetes, dyslipidemia, log-CRP.

Supplemental Table 5. Relative risk of CAC progression in 595 men, excluding those with CAC >100 at baseline, according to albuminuria or low eGFR (age 40-79 years with a mean follow-up of 4.9 years) in the SESSA Study

	Unadjusted RR (95% CI)	Model 1 RR (95% CI)	Model 2 RR (95% CI)	Model 3 RR (95% CI)	Model 4 RR (95% CI)
Albuminuria	1.39 (1.09 - 1.76)	1.38 (1.09 - 1.75)	1.38 (1.09 - 1.75)	1.19 (0.93 - 1.52)	1.29 (1.02 - 1.64)
Low eGFRcys	1.32 (1.01 - 1.73)	1.19 (0.90 - 1.58)	1.18 (0.89 - 1.56)	1.10 (0.84 - 1.45)	1.13 (0.86 - 1.49)
Low eGFRcre	1.11 (0.84 - 1.47)	1.04 (0.78 - 1.37)	1.04 (0.78 - 1.38)	0.95 (0.72 - 1.26)	1.01 (0.77 - 1.34)

RR, relative risk; 95% CI, 95% confidence interval; Albuminuria described as >30mg/g. Low eGFR by cystatin C described as <60 ml/min/1.73m^2. Low eGFR by creatinine described as <60 ml/min/1.73m^2. A robust Poisson regression model was used to estimate RR and 95% CI; Model 1 adjusted for age, follow up period, CT type; Model 2 further adjusted for BMI, step counts, current-smoker, current-drinker; Model 3 further adjusted for SBP, HDL-C, LDL-C, log TG, HbA1c, hypertension medication, diabetes medication, lipid medication, log-CRP; Model 4 adjusted for Model 2 plus hypertension, diabetes, dyslipidemia, log-CRP.

Supplemental Table 6. Relative risk of CAC progression in 595 men, excluding those with CAC >100 at baseline, with mutually adjusted low eGFRcys and albuminuria and low eGFRcre and albuminuria (age 40-79 years with a mean follow-up of 4.9 years) in the SESSA Study

	Albuminuria RR (95% CI)	Low eGFRcys RR (95% CI)	Low eGFRcre RR (95% CI)
a) Albuminuria and low eGFRcys			
Model 1	1.37 (1.08 - 1.74)	1.17 (0.88 - 1.55)	-
Model 2	1.37 (1.08 - 1.74)	1.16 (0.87 - 1.53)	-
Model 3	1.19 (0.93 - 1.52)	1.09 (0.83 - 1.44)	-
Model 4	1.29 (1.01 - 1.64)	1.12 (0.85 - 1.48)	-
b) Albuminuria and low eGFRcre			
Model 1	1.38 (1.09 - 1.75)	-	1.02 (0.77 - 1.35)
Model 2	1.38 (1.09 - 1.75)	-	1.02 (0.77 - 1.35)
Model 3	1.19 (0.93 - 1.52)	-	0.95 (0.72 - 1.26)
Model 4	1.29 (1.02 - 1.64)	-	1.01 (0.76 - 1.33)

RR, relative risk; 95% CI, 95% confidence interval; a) Both albuminuria and low eGFRcys included in the model; b) Both albuminuria and low eGFRcre included in the model; Albuminuria described as >30mg/g; Low eGFR by cystatin C described as <60 ml/min/1.73m^2. Low eGFR by creatinine described as <60 ml/min/1.73m^2. A robust Poisson regression model was used to estimate RR and 95% CI; Model 1 adjusted for age, follow up period, CT type; Model 2 further adjusted for BMI, step counts, current-smoker, current-drinker; Model 3 further adjusted for SBP, HDL-C, LDL-C, log TG, HbA1c, hypertension medication, diabetes medication, lipid medication, log-CRP; Model 4 adjusted for Model 2 plus hypertension, diabetes, dyslipidemia, log-CRP.