



High-normal albuminuria is strongly associated with incident chronic kidney disease in a nondiabetic population with normal range of albuminuria and normal kidney function

Aiko Okubo¹ · Ayumu Nakashima^{1,2} · Shigehiro Doi¹ · Toshiki Doi¹ · Toshinori Ueno¹ · Kazuya Maeda¹ · Ryo Tamura¹ · Kiminori Yamane³ · Takao Masaki¹

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Abstract

Background Albuminuria and estimated glomerular filtration rate (eGFR) are clinically measured to evaluate the severity of chronic kidney disease (CKD). The aim of our study was to clarify the association between clinical parameters, including albuminuria and eGFR, and the risk of incident CKD in a nondiabetic population with normal range of albuminuria and eGFR.

Methods A 10-year follow-up, retrospective cohort study involving 317 Japanese men (mean age, 42 years) with eGFR ≥ 90 mL/min/1.73 m² and urine albumin-to-creatinine ratio (UACR) < 30 mg/gCr was performed. Participants were free of diabetes mellitus. Multivariate logistic regression approaches were used to assess independent predictors of the incidence of CKD.

Results Twenty-nine (9%) participants developed CKD (eGFR < 60 mL/min/1.73 m² and/or UACR ≥ 30 mg/gCr) through 10 years of follow-up. At the baseline examination, age, blood pressure, UACR, and eGFR were higher in participants who developed CKD than in those without CKD. After adjustment for confounders, high-normal albuminuria ($P < 0.001$) and hypertension ($P = 0.045$) were associated with an increased incidence of CKD. From receiver-operating characteristic curves, UACR ≥ 7.0 mg/gCr was defined as high-normal albuminuria. Logistic regression analysis also showed that, in addition to presence of hypertension, UACR ≥ 7.0 mg/gCr was identified as an independent risk of incident CKD within 10 years after adjustment for age, body mass index, smoking status, and dyslipidemia [UACR: odds ratio (OR) 17.36 (95% CI 6.16–48.93, $P < 0.001$)].

Conclusion High-normal albuminuria and hypertension are associated with incident CKD in a nondiabetic population with normal-range UACR and eGFR.

Keywords High-normal albuminuria · Normal kidney function · Chronic kidney disease

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- ✉ Ayumu Nakashima
ayumu@hiroshima-u.ac.jp
- ✉ Takao Masaki
masakit@hiroshima-u.ac.jp

¹ Department of Nephrology, Hiroshima University Hospital, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan

² Department of Stem Cell Biology and Medicine, Graduate School of Biomedical and Health Sciences, Hiroshima

University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8553, Japan

³ Nippon Telegraph and Telephone West Corporation Chugoku Health Administration Center, 11-40, Hiji Yamahonmachi, Minami-ku, Hiroshima 732-0816, Japan

Introduction

Chronic kidney disease (CKD) affects 753 million people globally and is therefore recognized as a world health concern, with evidence of increased risk for not only end-stage renal disease [1, 2] but also cardiovascular disease (CVD) [3, 4]. The definition of CKD includes individuals with evidence of kidney damage, such as albuminuria and decline of estimated glomerular filtration rate (eGFR), for longer than 3 months. Moreover, the Kidney Disease: Improving Global Outcomes 2012 Clinical Practice Guideline proposes a risk map using urine albumin-to-creatinine ratio (UACR) and eGFR categories [2]. Thus, to calculate UACR and eGFR, urine tests and blood tests are widely performed for the diagnosis of CKD as well as to evaluate severity in the clinical setting. However, the association of normal-range UACR and eGFR with incidence of CKD in the general population remain unknown.

Although $\text{UACR} < 30 \text{ mg/gCr}$ is defined as normal-range, we have recently demonstrated that $\text{UACR} \geq 5.9 \text{ mg/gCr}$ predicts incidence of CKD in participants with $\text{eGFR} \geq 60 \text{ mL/min/1.73 m}^2$ [5]. Importantly, $\text{eGFR} \geq 60 \text{ mL/min/1.73 m}^2$ includes the “mildly decreased” category; therefore, the effect of high-normal albuminuria on the incidence of CKD should be determined in a population with $\text{eGFR} \geq 90 \text{ mL/min/1.73 m}^2$ that is classified in the “normal or high” category. In addition to albuminuria, early decline of eGFR may be associated with incidence of CKD. However, its impact on the incidence of CKD in the population with normal kidney function remains unclear.

In this study, we investigated the association of normal-range UACR and eGFR with the incidence of CKD in the nondiabetic population. We also investigated the clinical factors that are reportedly associated with incident CKD. Furthermore, we examined the cut-off value of clinical parameters to predict the incidence of CKD. The data presented here provide evidence that data from a medical checkup can predict the incidence of CKD in a nondiabetic population with UACR and eGFR within the normal range.

Materials and methods

Study population

From the database of the Nippon Telegraph and Telephone West Corporation Chugoku Health Administration Center (Hiroshima, Japan) for general health checkups between April 1999 and March 2004, we selected 1,709 male subjects who had two values of serum creatinine and

albuminuria measured at an interval of 10 years. A total of 1,392 subjects were excluded because they met the following exclusion criteria at the first examination: (1) subjects with $\text{eGFR} < 90 \text{ mL/min/1.73 m}^2$ or $\text{UACR} \geq 30 \text{ mg/gCr}$; (2) subjects with diabetes mellitus (DM) defined by a hemoglobin A1c (HbA1c) level $\geq 6.5\%$, 2-h plasma glucose $\geq 200 \text{ mg/dL}$ with a 75-g oral glucose tolerance test, fasting plasma glucose $\geq 126 \text{ mg/dL}$, or medical history of DM [6]; (3) subjects using antihypertensive drugs including angiotensin II receptor blockers or angiotensin-converting enzyme inhibitors. However, we did not exclude the hypertensive population not undergoing treatment. The remaining 317 participants were evaluated. In this study, CKD was defined as $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$ and/or $\text{UACR} \geq 30 \text{ mg/gCr}$ [7]. This study was performed following the Declaration of Helsinki, and the protocol was licensed by the hospital ethics committees of the Hiroshima University Hospital (approval number E-1411, registered October 30, 2018).

Measurements and description of variables

Identical methods for all laboratory data were applied at baseline (1999–2004) and follow-up (2009–2014). Serum total cholesterol, triglycerides (TG), high-density lipoprotein (HDL) cholesterol, creatinine (Cr), urinary acid (UA), and urinary creatinine levels were measured by enzymatic methods (Eiken Chemical, Tokyo, Japan). Fasting glucose and HbA1c levels were measured by high-performance liquid chromatography and corrected to the value consistent with the Japan Diabetes Society. After correcting to the value suggested by the Japan Diabetes Society, we estimated the HbA1c level as the National Glycohemoglobin Standardization Program equivalent value using the formula: $\text{HbA1c} (\%) = 1.02 \times \text{HbA1c (JDS; \%)} + 0.25$ [8]. Urinary albuminuria was measured by the latex flocculation immunoturbidimetry assay (Eiken Chemical). UACR was calculated for each urine specimen. eGFR was estimated using the recalibrated version of the modification of diet in renal disease (MDRS) equation: $\text{eGFR} = 194 \times \text{Cr} - 1.094 \times \text{Age} - 0.287$ [9]. Low-density lipoprotein (LDL) cholesterol levels were calculated by Friedewald’s formula. Blood pressure (BP) was measured while in the sitting position by a mercury sphygmomanometer after 5 min of rest. Hypertension was defined as systolic BP $\geq 130 \text{ mmHg}$ or diastolic BP $\geq 80 \text{ mmHg}$ [10]. Hematuria was defined as the presence of ≥ 5 red blood cells per high-power field or more than 1+ in the dipstick test. Dyslipidemia was defined as LDL cholesterol $\geq 140 \text{ mg/dL}$, HDL cholesterol $< 40 \text{ mg/dL}$, triglycerides $\geq 150 \text{ mg/dL}$, or use of lipid-lowering drugs. We obtained information about current smoking and medication use by using questionnaires. Current smoking was defined as having more than one cigarette every day.

Statistical analysis

Data are presented as mean values \pm standard deviation (SD) or median and interquartile range (25–75th percentiles) for skewed distributions. Differences between the groups were analyzed using the chi-squared test or Mann–Whitney *U* test. We constructed receiver-operating characteristic (ROC) curves for the baseline UACR and incident CKD over the 10-year observation period, and determined the area under the curve (AUC). The optimal cut-off value for balancing the sensitivity and specificity of each factor was identified as the point on the ROC curve closest to the upper left-hand corner. Logistic regression approaches were used to assess independent predictors of incident CKD, which were presented as odds ratio (OR) and 95% confidence interval (CI). These parameters were included as explanatory variables in the models based on a recent meta-analysis [11–15]. All analyses were performed using Statistical Package for the Social Sciences software (ver. 21.0; IBM, Armonk, NY, USA). *P* value < 0.05 was considered statistically significant.

Results

Table 1 shows the clinical characteristics of the 317 study participants divided into groups with and without incident CKD. Among these participants, 29 (9%) fulfilled the diagnostic criterion of CKD through 10 years of follow-up, among whom 3 participants had decreased eGFR < 60 mL/min/1.73 m² and 26 increased UACR \geq 30 mg/gCr. At the baseline examination, age, blood pressure, UACR, and eGFR were higher in participants who developed CKD (eGFR \geq 60 mL/min/1.73 m² and UACR \geq 30 mg/gCr) than in those without CKD. In particular, UACR was remarkably high in cases with incidence of CKD (Fig. 1). After adjustment for confounding factors, UACR, but not eGFR, was significantly associated with an increased risk of incident CKD 10 years later (UACR: OR 1.24, 95% CI 1.14–1.35, *P* < 0.001; eGFR: OR 1.00, 95% CI 0.96–1.06, *P* = 0.84) (Table 2). Multivariate analysis was also performed for only the cases with UACR > 30 mg/gCr after

Table 1 Clinical characteristics of study subjects

Variables	Non-incident CKD <i>N</i> = 288	Incident CKD eGFR < 60 ^a , UACR < 30 ^b <i>N</i> = 3	Incident CKD eGFR \geq 60 ^a , UACR \geq 30 ^b <i>N</i> = 26
Age, years	41.8 \pm 0.3	45.0 \pm 3.2	43.2 \pm 1.1*
BMI, kg/m ²	22.8 \pm 3.7	22.8 \pm 4.2	25.6 \pm 3.8
Current smoking, <i>n</i> (%)	144 (51.4)	2 (66.7)	16 (61.5)
Systolic BP, mmHg	122.7 \pm 16.0	126.0 \pm 22.6	137.7 \pm 16.7*
Diastolic BP, mmHg	77.2 \pm 10.2	83.3 \pm 15.3	86.7 \pm 11.8*
Hematuria, <i>n</i> (%)	12 (4.2)	0 (0)	1 (3.9)
Urinary acid, mg/dL	5.9 \pm 1.3	6.4 \pm 0.9	6.2 \pm 1.0
UACR, mg/gCr	5.7 \pm 0.2	5.6 \pm 2.0	12.8 \pm 0.7* [†]
Hemoglobin, g/dL	14.9 \pm 0.8	14.2 \pm 0.2	15.3 \pm 0.9 [†]
Albumin, g/dL	4.6 \pm 0.2	4.5 \pm 0.3	4.6 \pm 0.2
Total cholesterol, mg/dL	192.5 \pm 30.2	199.7 \pm 5.1	195.6 \pm 30.6
LDL cholesterol, mg/dL	105.5 \pm 30.3	103.3 \pm 15.5	104.5 \pm 30.1
HDL cholesterol, mg/dL	59.5 \pm 15.5	53.0 \pm 19.0	61.2 \pm 14.7
Triglycerides, mg/dL	137.4 \pm 119.1	216.7 \pm 126.2	149.1 \pm 89.2
BUN, mg/dL	12.8 \pm 2.8	12.9 \pm 1.2	12.7 \pm 2.8
Creatinine, mg/dL	0.70 \pm 0.003	0.73 \pm 0.03	0.68 \pm 0.01*
eGFR, mL/min/1.73 m ²	99.0 \pm 0.5	92.6 \pm 4.7	101.8 \pm 1.6* [†]
High-sensitivity CRP, mg/dL	0.28 \pm 1.22	0.04 \pm 0.17	0.10 \pm 0.10
HbA1c, %	5.8 \pm 0.8	5.9 \pm 0.5	5.8 \pm 0.7

Data are mean \pm SD or median (interquartile range) for continuous variables. Differences between the groups were analyzed using the Mann–Whitney *U* test or chi-square test

UACR urine albumin to urine creatinine ratio, BMI body mass index, BP blood pressure, eGFR estimated glomerular filtration rate

**P* < 0.05 versus non-incident CKD, [†]*P* < 0.05 versus incident CKD eGFR < 60^a, UACR < 30^b

^aeGFR (mL/min/1.73 m²)

^bUACR (mg/gCr)

Fig. 1 Comparison of UACR in the group with and without the onset of CKD after 10 years. UACR urine albumin to urine creatinine ratio. The error bars represent the interquartile range. $P < 0.001$ versus incident CKD group

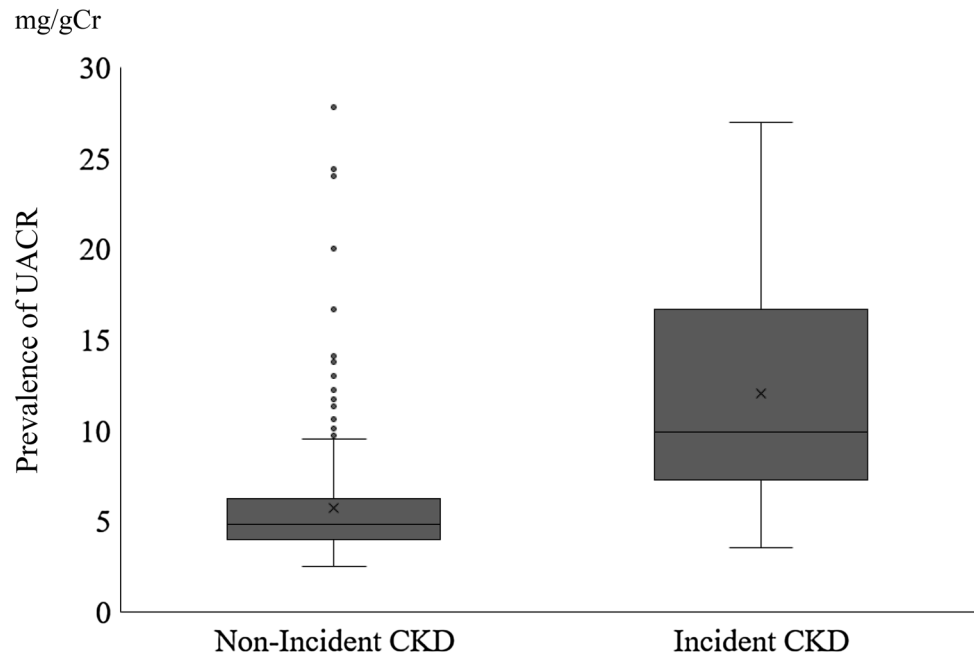


Table 2 Multivariate logistic regression analysis of parameters related to incident CKD

Parameters	Odds ratio	95% CI	P value
Age, 1 year	1.01	0.93–1.10	0.80
BMI, 1 kg/m ²	1.00	0.92–1.11	0.91
Current smoker, presence	1.18	0.46–2.98	0.73
Hypertension, presence	2.52	0.97–6.53	0.045
UACR, 1 mg/gCr	1.24	1.14–1.35	<0.001
Dyslipidemia, presence	1.16	0.47–2.84	0.74
eGFR, 1 mL/min/1.73 m ²	1.00	0.96–1.06	0.84

The adjusted r^2 of the model was 0.25. Hypertension was defined as systolic blood pressure (BP) ≥ 130 mmHg or diastolic BP ≥ 80 mmHg. Dyslipidemia was defined as LDL cholesterol ≥ 140 mg/dL, HDL cholesterol < 40 mg/dL, triglycerides ≥ 150 mg/dL, or use of lipid-lowering drugs

CI confidence interval, BMI body mass index, UACR urine albumin to urine creatinine ratio, eGFR estimated glomerular filtration rate

10 years, whereby the results were similar (Supplemental Table 1). Next, we performed multivariate analysis in which hematuria was added in place of UACR and eGFR. The results showed that hematuria was not an independent risk factor for the onset of CKD (Supplemental Table 2).

Figure 2 shows the ROC curve of baseline UACR for incidence of CKD. The AUC of the ROC curve was 0.83 and the optimal cut-off value of baseline UACR was 7.0 mg/gCr (sensitivity, 0.79; specificity, 0.81). We divided the participants into two groups with UACR ≥ 7.0 mg/gCr and < 7.0 mg/gCr, and the baseline clinical characteristics of each group are shown in Table 3. Age, number of current smokers, and systolic and diastolic BP were significantly

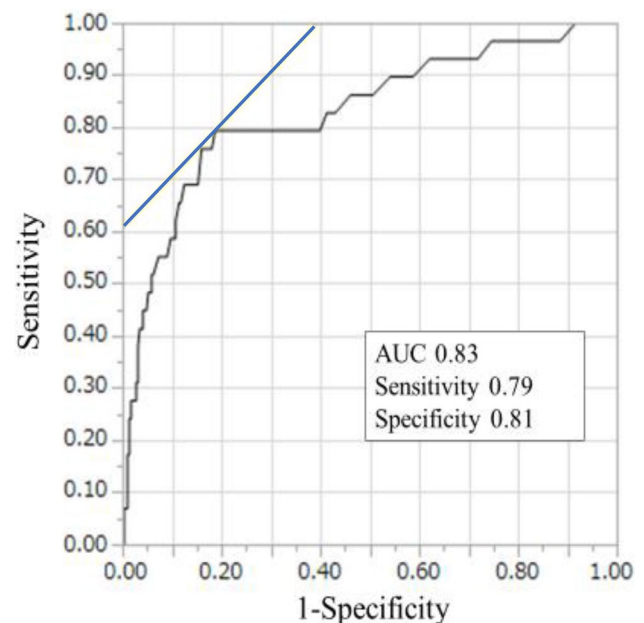


Fig. 2 Receiver-operating characteristic (ROC) curve of baseline UACR and incident CKD 10 years later. The area under the curve (95% confidence interval) was 0.83, and optimal cut-off points (sensitivity, specificity) of incident CKD 10 years later were 7.0 mg/gCr (0.79, 0.81)

higher, but serum levels of LDL cholesterol and Cr were lower in the subjects with UACR ≥ 7.0 mg/gCr than in those with UACR < 7.0 mg/gCr. Among the participants who had baseline UACR < 7.0 mg/gCr, 6 participants had developed CKD by 10 years later (2 participants with eGFR < 60 mL/min/1.73 m² and 4 with UACR ≥ 30 mg/gCr), one of whom

Table 3 Comparison of clinical characteristics according to albuminuria levels

Variables	UACR < 7.0 mg/gCr N = 240	UACR ≥ 7.0 mg/gCr N = 77	P value
Age, years	41.2 ± 5.7	44.0 ± 4.8	< 0.001
BMI, kg/m ²	22.6 ± 2.8	24.2 ± 5.7	0.053
Current smoker, n (%)	113 (48.1)	50 (66.7)	0.005
Systolic BP, mmHg	122.1 ± 15.5	129.9 ± 18.5	0.002
Diastolic BP, mmHg	76.6 ± 9.9	82.5 ± 11.9	< 0.001
Hematuria, n (%)	8 (3.3)	5 (6.5)	0.22
Urinary acid, mg/dL	5.9 ± 1.2	6.0 ± 1.3	0.37
UACR, mg/gCr	4.6 ± 1.0	11.5 ± 5.3	< 0.001
Hemoglobin, g/dL	14.9 ± 0.8	15.0 ± 0.8	0.76
Albumin, g/dL	4.6 ± 0.2	4.6 ± 0.3	0.60
Total cholesterol, mg/dL	193.4 ± 30.0	191.2 ± 30.5	0.73
LDL cholesterol, mg/dL	107.6 ± 29.5	98.7 ± 31.3	0.02
HDL cholesterol, mg/dL	59.4 ± 15.6	60.2 ± 15.1	0.33
Triglycerides, mg/dL	132.0 ± 100.6	161.5 ± 156.1	0.09
BUN, mg/dL	12.9 ± 2.6	12.5 ± 3.0	0.50
Creatinine, mg/dL	0.71 ± 0.05	0.68 ± 0.06	< 0.001
eGFR, mL/min/1.73 m ²	98.6 ± 7.4	101.0 ± 9.7	0.08
High-sensitivity CRP, mg/dL	0.3 ± 1.3	0.1 ± 0.1	0.44
HbA1c, %	5.7 ± 0.7	5.7 ± 0.8	0.49

Data are mean ± SD or median (interquartile range) for continuous variables. Differences between the groups were analyzed using the Mann–Whitney U test or Chi-squared test

BMI body mass index, BP blood pressure, UACR urine albumin to urine creatinine ratio, eGFR estimated glomerular filtration rate, BUN blood urea nitrogen, HbA1c hemoglobin A1c, CRP C-reactive protein

Table 4 Multivariable odds ratios for incident CKD according to the value of UACR

Parameters	Odds ratio	95% CI	P value
UACR ≥ 7.0 mg/gCr	17.36	6.16–48.93	< 0.001
Age, 1 year	1.00	0.91–1.09	0.95
BMI, 1 kg/m ²	0.99	0.90–1.08	0.78
Current smoker, presence	1.01	0.41–2.52	0.97
Hypertension, presence	2.71	1.05–6.98	0.04
Dyslipidemia, presence	1.41	0.59–3.39	0.45
eGFR, 1 mL/min/1.73 m ²	1.00	0.95–1.05	0.91

The adjusted *r*² of the model was 0.26. Hypertension was defined as systolic BP ≥ 130 mmHg or diastolic BP ≥ 80 mmHg. Dyslipidemia was defined as LDL cholesterol ≥ 140 mg/dL, HDL cholesterol < 40 mg/dL, triglycerides ≥ 150 mg/dL, or use of lipid-lowering drugs

UACR urine albumin to urine creatinine ratio, BMI body mass index, eGFR estimated glomerular filtration rate

(eGFR < 60 mL/min/1.73 m²) has hypertension and suspected nephrosclerosis; for the other 5 participants, the diagnosis is unspecific because they do not have hematuria, hypertension, diabetes, and/or obesity. In Table 4, the results of multivariate logistic regression analysis show clinical parameters related to incident CKD. We defined individuals with a UACR < 7.0 mg/gCr as the reference

group. Logistic regression revealed that UACR ≥ 7.0 mg/gCr and presence of hypertension were independent risks for incidence of CKD after adjustment for age, BMI, smoking status, dyslipidemia, and eGFR (UACR: OR 17.36, 95% CI 6.16–48.93, *P* < 0.001; hypertension: OR 2.71, 95% CI 1.05–6.98, *P* = 0.04). We also performed multivariate analysis using systolic BP (continuous variable) instead of hypertension. Similarly, high systolic BP was an independent risk factor for the incidence of CKD 10 years later (Supplemental Tables 3 and 4).

To confirm the importance of measuring UACR in subjects with eGFR ≥ 90 mL/min/1.73 m², we included 1061 participants with 60 ≤ eGFR < 90 mL/min/1.73 m², whereby a total of 1378 participants were investigated. The remaining participants were categorized into the following groups: G1 (60 ≤ eGFR < 90 mL/min/1.73 m² and UACR < 7.0 mg/gCr), G2 (eGFR ≥ 90 mL/min/1.73 m² and UACR ≥ 7.0 mg/gCr), G3 (60 ≤ eGFR < 90 mL/min/1.73 m² and UACR < 7.0 mg/gCr), and G4 (60 ≤ eGFR < 90 mL/min/1.73 m² and UACR ≥ 7.0 mg/gCr). The characteristics of the study participants according to combined eGFR and UACR are shown in Supplemental Table 5. In group G2, age, body mass index (BMI), the presence of current smoker, and systolic and diastolic BP were higher, and LDL cholesterol lower than in G1. Similarly, in group G3, age, BMI, total cholesterol, LDL cholesterol, BUN, Cr, and UA were higher while UACR

value, the presence of current smoker, and eGFR lower than in G1. In group G4, UACR, age, BMI, systolic and diastolic BP, the presence of hematuria, hemoglobin, total cholesterol, LDL cholesterol, TG, BUN, Cr, and UA were higher, and the presence of smoker, HDL cholesterol, and eGFR lower than in G1. Ten years later, 6 participants (2.5%) in G1, 22 participants (29.3%) in G2, 109 participants (12.1%) in G3, and 48 participants (29.1%) in G4 had developed CKD. In addition, we compared the risk of incident CKD in each group (Supplemental Table 6). In multivariate logistic analysis, the risk of incident CKD was significantly higher in G2, G3, and G4 than in G1 (reference group) in the non-adjusted model. Based on the analysis of model 3 (adjusted for age, BMI, the presence of current smoker, hypertension, and dyslipidemia), the onset of CKD in G2 was equivalent to that in G4. Furthermore, in the analysis of model 4 with adjustment by adding eGFR, the odds ratio of G2 is 20.93 (95% CI 7.84–55.86), unchanged compared with that before adjustment; however, the odds ratio of G4 decreases to 1.65 (95% CI 0.60–4.58). These results revealed that both UACR and eGFR contributed to the onset of CKD in G4 ($60 \leq \text{eGFR} < 90 \text{ mL/min/1.73 m}^2$ and $\text{UACR} \geq 7.0 \text{ mg/gCr}$), and that UACR, not eGFR, was strongly associated with the onset of CKD in G2 ($\text{eGFR} \geq 90 \text{ mL/min/1.73 m}^2$ and $\text{UACR} \geq 7.0 \text{ mg/gCr}$). Therefore, it is considered that the importance of measuring UACR is higher in the group with eGFR higher than $90 \text{ mL/min/1.73 m}^2$ rather than the group with eGFR 60 to $90 \text{ mL/min/1.73 m}^2$.

Figure 3 shows the transition of UACR ranges 10 years later. During the 10 years of observation, 1.7% of the population with baseline UACR $< 7.0 \text{ mg/gCr}$ developed

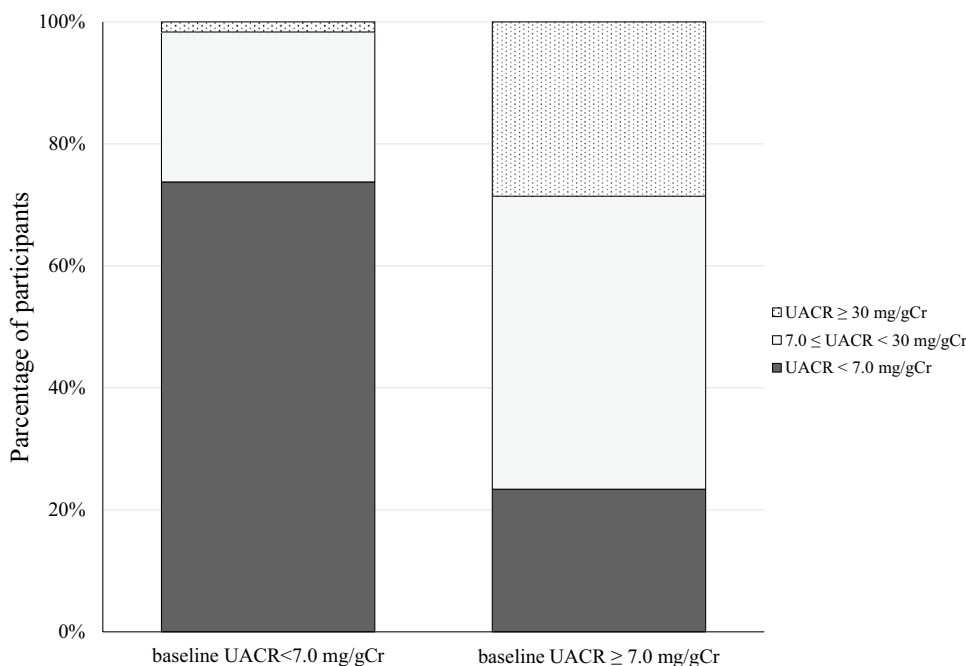
$\text{UACR} \geq 30 \text{ mg/gCr}$, whereas 28.6% of participants with baseline $\text{UACR} \geq 7.0 \text{ mg/gCr}$ developed $\text{UACR} \geq 30 \text{ mg/gCr}$ ($P < 0.001$). Additionally, we observed 18 individuals (23.4%) with baseline $\text{UACR} \geq 7.0 \text{ mg/gCr}$ in whom albuminuria decreased to less than 7.0 mg/gCr 10 years later. To confirm the reproducibility of UACR to the same extent, we investigated UACR in 128 participants who received a health checkup and albuminuria assessment the following year. Among these participants, the baseline UACR was $6.3 \pm 3.9 \text{ mg/gCr}$ and after 1 year $6.7 \pm 5.2 \text{ mg/gCr}$, a 1-year rate of change of $15.6\% \pm 76.3\%$. UACR after 10 years was $13.0 \pm 25.7 \text{ mg/gCr}$, with a rate of change of $84.6\% \pm 253.5\%$.

Discussion

The present study was conducted to identify the impact of normal-range UACR and eGFR on the incidence of CKD in a nondiabetic population with normal kidney function and normal range of albuminuria. Increased UACR and presence of hypertension, but not eGFR, are associated with incidence of CKD. $\text{UACR} \geq 7.0 \text{ mg/gCr}$ is calculated as a cut-off value and is independently associated with the incidence of CKD. During the 10 years of observation, incidence of CKD was higher in the subjects with $\text{UACR} \geq 7.0 \text{ mg/gCr}$ than in those with $\text{UACR} < 7.0 \text{ mg/gCr}$. These findings suggest that high-normal albuminuria independently predicts incident CKD in the population with $\text{eGFR} \geq 90 \text{ mL/min/1.73 m}^2$.

Currently, UACR is widely measured to detect diabetic nephropathy in the clinical setting. In a nondiabetic

Fig. 3 Transition of UACR ranges after 10 years. UACR urine albumin to urine creatinine ratio. Participants who developed $\text{UACR} \geq 30 \text{ mg/gCr}$ after 10 years are shown as light-gray polka-dot bar, and cases $7.0 \leq \text{UACR} < 30 \text{ mg/gCr}$ after 10 years are shown as light-gray bar. Cases with UACR of $< 7.0 \text{ mg/gCr}$ even after 10 years are shown as dark-gray bar



population, a previous study reported that UACR of 10.5–29.9 mg/gCr was associated with increased CKD prevalence [16]. We have also reported UACR ≥ 5.9 mg/gCr as a risk factor for incidence of CKD in a nondiabetic population with eGFR ≥ 60 mL/min/1.73 m² [5]. In the present study, we have demonstrated that increased UACR is associated with future incidence of CKD in a nondiabetic population with eGFR ≥ 90 mL/min/1.73 m², and that UACR ≥ 7.0 mg/gCr is the optimal cut-off value for incidence of CKD within 10 years. These results suggest that, even though UACR < 30 mg/gCr is classified as the normal range, high-normal albuminuria is a risk factor for the incidence of CKD in a nondiabetic population with normal kidney function.

As a possible mechanism by which increased UACR predicts the incidence of CKD, we assume that glomerular hyperfiltration may contribute to increased UACR. Glomerular hyperfiltration occurs not only in a state of decreasing glomerular function [17] but also in various conditions such as pre-DM [18], obesity [19], and activation of the renin–angiotensin–aldosterone system [20]. These conditions are well known to eventually lead to kidney damage, suggesting that UACR may reflect a state under stimuli that cause CKD. Moreover, increased UACR is reported to be a marker of early vascular endothelial dysfunction [21, 22]. In fact, previous studies have reported that endothelial damage plays an important role in the development of vascular disease, including CKD, and that increased UACR is associated with the incidence of CVD [23, 24]. Taken together, increased UACR reflects the early phase of renal damage, thereby predicting the incidence of CKD.

Our present results show that the presence of hypertension is associated with the incidence of CKD. Because hypertension is well recognized to cause nephrosclerosis, management of BP plays an important role in preventing the progression of kidney damage [25]. Another study has described that, in addition to elevation of BP, the population undergoing antihypertensive treatment still carries an increased risk of developing CKD [26]. Furthermore, according to a past study, essential hypertension infrequently leads to end-stage kidney disease, whereas salt-sensitive hypertension induces progression of renal dysfunction [27]. Therefore, among the population with hypertension, individuals with increased salt sensitivity are more likely to develop CKD. In contrast, although CKD is also responsible for the development of hypertension [28], subjects in this study exhibited a normal range of albuminuria and normal kidney function. These findings suggest that the presence of hypertension per se increases the risk for incident CKD.

Clinically, eGFR is generally used in place of renal function, and is measured to diagnose CKD as well as evaluate the risk for progression to end-stage kidney disease [29, 30]. These facts suggest that early decline of eGFR predicts the incidence of CKD [31]. However, differently from UACR,

we did not observe a significant association between eGFR and incidence of CKD. As already mentioned, although glomerular hyperfiltration causes an increase in eGFR, it eventually contributes to the decline of renal function [32]. Another explanation is that some individuals congenitally exhibit low eGFR even without a condition that causes renal damage [33]. Collectively, in a population with eGFR ≥ 90 mL/min/1.73 m², a change in eGFR does not always show a linear decline during the development of CKD [34]. Therefore, early decline of eGFR is not associated with incidence of CKD.

To confirm the clinical importance of measuring UACR in subjects with eGFR ≥ 90 mL/min/1.73 m², we included 1061 participants with $60 \leq \text{eGFR} < 90$ mL/min/1.73 m², whereby a total of 1378 participants were investigated. As shown in Supplemental Table 6, we consider that the importance of measuring UACR is higher in the group with eGFR ≥ 90 mL/min/1.73 m² compared with the group with $60 \leq \text{eGFR} < 90$ mL/min/1.73 m². At present, there is no unified view as to whether treatment and intervention aimed at reducing UACR is related to suppression of future onset of CKD and improvement in mortality rate, and for this reason further prospective studies are needed. However, even in such apparently general populations, physicians should carefully evaluate the risk of CKD in patients whose albuminuria is within the normal range.

This study has several limitations. First, the data were derived from a population we followed over 10 years retrospectively at general health checkups, raising the possibility of selection bias. Second, because subjects were exclusively men, we were unable to assess sex-related factors. Third, we used only a single urine specimen to assess UACR values, which are known to have day-to-day variability. However, we investigated the rate of change of UACR in 128 participants after 1 year and 10 years, and considered that the reproducibility of UACR was acceptable. Lastly, our cohort comprises only Japanese people, so the resulting data cannot be generalized to other populations. Despite these limitations, this study has strength in that it is the first to show that high-normal albuminuria is associated with incident CKD in a nondiabetic population with albuminuria and kidney function within the normal range through 10 years of follow-up.

In summary, we conducted a retrospective study to discover the risk factors for the incidence of CKD in a nondiabetic population with normal-range albuminuria and eGFR. Although CKD is diagnosed using the data from albuminuria and eGFR, we identified increased UACR and the presence of hypertension, but not a decline in eGFR, as independent risk factors. We also show that UACR ≥ 7.0 mg/gCr is the optimal cut-off value, with 28.6% of the population developing UACR ≥ 30 mg/gCr 10 years later. The data presented here suggest that high-normal albuminuria should be recognized as a risk factor for the incidence of CKD.

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Compliance with ethical standards

Conflict of interest All of the authors have declared that no conflicts of interest exist.

Ethical approval This study was performed in accordance with the guidelines contained within the Declaration of Helsinki and the protocol was licensed by the hospital ethics committee of Hiroshima University Hospital (approval number: E-1411, registered on October 30, 2018).

Informed consent Written informed consent was not required because of the non-intervention and retrospective design. However, this study was approved by the hospital ethics committees of the Hiroshima University Hospital (approval number E-1411, registered October 30, 2018).

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