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ORIGINAL ARTICLE

High-normal albuminuria and incident chronic kidney disease in a male nondiabetic population

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Abstract

Background High-normal albuminuria is an important risk factor for incident chronic kidney disease in diabetic populations, in contrast to an uncertain association in nondiabetic populations. This study aimed to reveal the relationship between high-normal albuminuria and incident chronic kidney disease in a Japanese nondiabetic population.

Methods A 10-year follow-up retrospective cohort study was performed involving 1378 Japanese men (mean age 44 ± 5.3 years) without chronic kidney disease and diabetes mellitus. Chronic kidney disease was diagnosed as either estimated glomerular filtration rate < 60 mL/min/1.73 m^2 or a urine albumin-to-creatinine ratio ≥ 30 mg/g.

Results At baseline, age, estimated glomerular filtration rate, and the presence of hematuria, hypertension, and dyslipidemia were independently associated with the albumin-to-creatinine ratio. Among the 1378 participants, 185 (13.4%) fulfilled diagnostic criteria for chronic kidney disease over the 10-year follow-up period. Median annual estimated glomerular filtration rate decline showed a deterioration with increasing quartiles of baseline albumin-to-creatinine ratio ($P = 0.004$). Participants who had a baseline albumin-to-creatinine ratio in the highest quartile (5.9–28.9 mg/g) were more likely to develop micro- or macroalbuminuria (odds ratio: 16.23, 95% confidence interval 6.56–54.03), chronic kidney disease (odds ratio: 2.48, 95% confidence interval 1.64–3.82), and hypertension (odds ratio 2.06, 95% confidence interval 1.30–3.31), but not diabetes mellitus compared with those who had an albumin-to-creatinine ratio in the lowest quartile (1.3–3.6 mg/g) after adjustment for potential confounders.

Conclusions High-normal albuminuria was associated with incident chronic kidney disease in this Japanese nondiabetic male population.

Keywords High-normal albuminuria · Chronic kidney disease · Nondiabetic populations · Albumin-to-creatinine ratio

Introduction

Chronic kidney disease (CKD) affects more than 10% of the population globally and is a world health concern [1]. The financial impact of CKD is also great, with particularly high costs depending on renal replacement therapy and cardiovascular complications [2, 3]. Recently, the kidney disease: improving global outcomes updated their classifications for determining CKD based on glomerular filtration rate (GFR) and urine albumin-to-creatinine ratio (ACR), with a definition of GFR < 60 mL/min/1.73 m^2 and of ACR ≥ 30 mg/g [4]. Notably, the risks for important outcomes including all-cause mortality, cardiovascular diseases, and kidney failure have been visually captured in a "heat map" [4], providing recommendations on how GFR and ACR should be estimated together. In addition to GFR and primary diseases, the importance of ACR is widely recognized in clinical practice.

ACR from a spot urine sample reflects the daily amount of urinary albumin excretion [4]. The guidelines propose three categories: normal albuminuria (< 30 mg/g); microalbuminuria (30–300 mg/g); and macroalbuminuria (> 300 mg/g) [4]. In the clinical setting, microalbuminuria is widely used as a urinary marker for the early detection of diabetic nephropathy in patients with type 2 diabetes mellitus (DM) [5], and its clinical usefulness has been established [6]. In the general population, microalbuminuria is reported to be

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one predictor of a decline in GFR (< 60 mL/min/1.73 m^2) [7, 8]. These factors suggest that a very small amount of albuminuria may be a precursor or sign of possible renal dysfunction. Although normal albuminuria is classified as low-risk, a previous study reported that high-normal albuminuria is an important risk factor for incident CKD in patients with DM [9]. High-normal albuminuria is reported to predict not only cardiovascular events but also all-cause mortality [10–12]. However, there is currently little information on the association between normal-range albuminuria and future CKD in the nondiabetic population (non-DM).

In this study, we investigated whether increased albuminuria is associated with incident CKD in a non-DM population with an ACR < 30 mg/g. This retrospective cohort study evaluated the correlation between normal albuminuria and the incidence of CKD in 1378 general Japanese men without DM over a 10-year follow-up period.

Materials and methods

Participants

We extracted data of 1709 men from the general health checkup database of the Nippon Telegraph and Telephone West Corp., Chugoku Health Administration Center (Hiroshima, Japan) between April 1999 and March 2004 who had values for serum creatinine and albuminuria that had been measured twice at an interval of 10 years. Four hundred and six people were excluded, because they met exclusion criteria at the first examination. Exclusion criteria were: (1) CKD defined as GFR < 60 mL/min/1.73 m^2 or ACR ≥ 30 mg/g; (2) DM defined as hemoglobin A1c (HbA1c) ≥ 6.5%, 2-h plasma glucose ≥ 200 mg/dL with a 75-g oral glucose tolerance test, fasting plasma glucose ≥ 126 mg/dL, or medical history of DM [13]; and (3) antihypertensive drugs that may affect excretion of albumin. The remaining 1378 people were enrolled in this study.

Anthropometry, blood pressure, and smoking status

Medical information was obtained via a standardized questionnaire, which included demographic background and medical history. Height and weight were measured, and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Blood pressure (BP) was measured in the sitting position using a mercury sphygmomanometer after a 5-min rest. Hypertension was defined as systolic BP ≥ 140 mmHg and diastolic BP ≥ 90 mmHg [14]. Current smoking was defined as having more than one cigarette a day.

Laboratory analysis

Urine albumin was measured using the latex flocculation immunoturbidimetry assay (Eiken Chemical, Tokyo, Japan). Urine creatinine was measured using an enzymatic method. Urine albumin was divided by urine creatinine to obtain the ACR, and the ACR is expressed in milligrams per gram (mg/g). Hematuria was defined as the presence of ≥ five red blood cells/high-powered field or more than 1 + with the dipstick test.

Blood samples were obtained in the morning after an overnight fast. Serum total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, creatinine, uric acid, and urinary creatinine levels were measured using enzymatic methods (Eiken Chemical). Fasting glucose and HbA1c levels were measured using high-performance-liquid chromatography. 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: HbA1c (%) = 1.02 × HbA1c (JDS; %) + 0.25 [15]. We calculated eGFR using the Modification of Diet in Renal Disease equation: $eGFR = 194 \times Cr^{-1.094} \times age^{-0.287}$ [16]. Low-density lipoprotein (LDL) cholesterol levels were calculated using Friedewald's formula [17]. Dyslipidemia was defined as LDL cholesterol ≥ 140 mg/dL, HDL cholesterol < 40 mg/dL, triglycerides ≥ 150 mg/dL, or use of lipid-lowering drugs [18, 19]. Hyperuricemia was defined as urinary acid ≥ 7.0 mg/dL or use of antihyperuricemic drugs [20].

Statistical analysis

Participants were separated by quartiles of ACR (1.3–3.6, 3.7–4.4, 4.5–5.8, and 5.9–28.9 mg/gCr). Variables are expressed as mean ± standard deviation or median and interquartile range (25th–75th percentiles), according to normality of distribution. Kruskal–Wallis and Mantel–Haenszel tests for trend were used to compare the baseline characteristics according to quartiles of ACR. Comparisons between two groups were assessed using Wilcoxon tests, Student's *t* tests, and Chi-squared tests. Stepwise multiple regression analysis was performed to find independent predictors of baseline ACR among potential confounders ($P < 0.05$) in univariate analysis. Final multiple regression analyses were performed. Logistic regression approaches were used to assess determinants of the subsequent incidence of CKD, which are presented as odds ratio (OR) and 95% confidence intervals (95% CI). A P value < 0.05 was considered statistically significant. All analyses were performed using Statistical Package for the Social Sciences software (ver. 21.0; IBM, Armonk, NY, USA).

Results

Median ACR for the 1378 participants was 4.5 mg/g (3.6–5.9 mg/g). Baseline characteristics are shown in Table 1 and are stratified by quartile of ACR. Significant positive trends across ACR quartiles were observed for age ($P = 0.002$), triglycerides ($P = 0.008$), eGFR ($P < 0.001$), BMI ($P = 0.001$), systolic BP ($P < 0.001$), diastolic BP ($P < 0.001$), current smoking ($P = 0.007$), and hematuria ($P < 0.001$).

For cross-sectional analysis, variables were selected by stepwise multiple regression analysis among potential confounders ($P < 0.05$) in univariate analysis. Liner regression analysis revealed that age ($P < 0.001$), eGFR ($P < 0.001$), and the presence of hematuria ($P < 0.001$), hypertension ($P < 0.001$), and dyslipidemia ($P = 0.009$) were independently associated with ACR (Table 2).

Among the 1378 participants, 185 (13.4%) fulfilled diagnostic criteria for CKD over the 10-year follow-up period. When participants who developed incident CKD were compared with participants in whom renal function remained normal, baseline age ($P < 0.001$), ACR ($P < 0.001$), BMI ($P = 0.003$), systolic BP ($P < 0.001$), diastolic BP ($P < 0.001$), and urinary acid ($P = 0.032$) were significantly greater, and HDL cholesterol ($P = 0.016$) and eGFR ($P < 0.001$) were significantly lower (Table 3).

Median subsequent decline in eGFR worsened with increasing quartiles of baseline ACR ($P = 0.004$ for trend) (Fig. 1). There was 22.6% of participants who developed CKD in the highest quartile of baseline ACR and the rate of incident CKD increased with increasing quartiles of ACR ($P = 0.002$ for trend) (Fig. 2). In the highest quartile of baseline ACR, 61.6% of participants remained within the same range of ACR over the 10-year period, while 15.8% developed micro- or macroalbuminuria (Fig. 3). The rates of incident micro- or macroalbuminuria were higher with increasing quartiles of ACR ($P < 0.001$ for trend). In the highest quartile of baseline ACR, 22.6% of participants showed a change to a lower range over the 10-year period (Fig. 3).

Table 2 Multivariate regression model for prediction from baseline ACR

Parameter	β	*P* value
Age	0.13	< 0.001
Hematuria, presence	0.09	< 0.001
Hypertension, presence	0.19	< 0.001
Dyslipidemia, presence	0.07	0.009
eGFR	0.16	< 0.001

The adjusted r^2 of the model was 0.10. *ACR* urine albumin-to-creatinine ratio, *eGFR* estimated glomerular filtration rate. Stepwise multiple regression analysis was performed to find independent predictors of baseline ACR among potential confounders ($P < 0.05$) in univariate analysis. The other initial factor included in this model was body mass index

Table 1 Baseline characteristics according to quartiles of ACR

Variables	Quartile 1 1.3–3.6 mg/g	Quartile 2 3.7–4.4 mg/g	Quartile 3 4.5–5.8 mg/g	Quartile 4 5.9–28.9 mg/g	*P* value
Number	351	329	349	349	
ACR, mg/g	3.3 (2.9–3.5)	4.0 (3.9–4.2)	5.0 (4.6–5.4)	8.0 (6.6–11.1)	< 0.001
Age, years	44.0 ± 5.2	44.0 ± 5.2	44.2 ± 5.7	45.3 ± 5.1	0.002
Total cholesterol, mg/dL	197.2 ± 31.9	198.1 ± 31.7	196.9 ± 31.3	201.8 ± 33.1	0.24
Triglycerides, mg/dL	109.0 (74.0–158.0)	113.0 (83.0–169.5)	107.0 (78.0–164.0)	126.0 (83.5–181.5)	0.008
HDL cholesterol, mg/dL	58.8 ± 16.4	57.3 ± 14.6	59.1 ± 14.2	58.3 ± 16.9	0.24
LDL cholesterol, mg/dL	112.2 ± 29.0	113.0 ± 29.8	111.1 ± 30.5	113.2 ± 32.1	0.83
Urinary acid, mg/dL	6.2 ± 1.2	6.2 ± 1.3	6.1 ± 1.2	6.1 ± 1.3	0.49
eGFR, mL/min/1.73 m^2	78.1 ± 10.0	82.3 ± 11.0	83.3 ± 11.7	85.2 ± 13.5	< 0.001
BMI, kg/m^2	23.5 ± 2.9	23.1 ± 2.7	22.9 ± 2.6	23.8 ± 3.6	0.001
Systolic BP, mmHg	120.0 ± 15.1	121.2 ± 15.1	122.9 ± 16.5	128.4 ± 18.2	< 0.001
Diastolic BP, mmHg	75.0 ± 9.7	76.0 ± 9.8	77.0 ± 10.5	81.5 ± 11.7	< 0.001
Current smoking, *n* (%)	142 (40.9)	142 (44.8)	156 (45.3)	178 (51.6)	0.007
Hematuria, *n* (%)	16 (4.6)	13 (4.0)	26 (7.5)	42 (12.0)	< 0.001
HbA1c, %	5.8 ± 0.4	5.8 ± 0.3	5.7 ± 0.4	5.8 ± 0.4	0.10

Data are expressed as mean ± standard deviation or median (interquartile range) for continuous variables. Kruskal–Wallis and Mantel–Haenszel tests for trend were used to compare the baseline characteristics according to quartiles of ACR

ACR urine albumin-to-creatinine ratio, *BMI* body mass index, *BP* blood pressure, *eGFR* estimated glomerular filtration rate, *HbA1c* hemoglobin A1c, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein

Table 3 Baseline characteristics of participants with or without incident CKD

Variables	Non-incident CKD	Incident CKD	*P* value
Number	1193	185	
Age, years	44.2 ± 5.3	45.8 ± 5.5	< 0.001
ACR, mg/g	4.4 (3.6–5.6)	5.1 (3.9–9.0)	< 0.001
BMI, kg/m^2	23.3 ± 3.0	23.9 ± 2.8	0.003
Hematuria, *n* (%)	81 (6.8)	16 (8.6)	0.36
Systolic BP, mmHg	122.6 ± 16.6	126.9 ± 16.2	< 0.001
Diastolic BP, mmHg	77.0 ± 10.6	80.2 ± 11.1	< 0.001
HbA1c, %	5.8 ± 0.4	5.8 ± 0.3	0.22
Urinary acid, mg/dL	6.1 ± 1.2	6.4 ± 1.3	0.032
Total cholesterol, mg/dL	198.2 ± 31.7	200.4 ± 34.0	0.35
LDL cholesterol, mg/dL	112.0 ± 30.1	115.1 ± 31.6	0.18
Triglycerides, mg/dL	112.0 (80.0–165.0)	117.0 (78.0–181.5)	0.41
HDL cholesterol, mg/dL	58.8 ± 15.8	55.8 ± 13.8	0.016
Current smoking, *n* (%)	533 (45.6)	85 (46.4)	0.82
eGFR, mL/min/1.73 m^2	83.2 ± 11.4	76.1 ± 13.0	< 0.001

Data are expressed as mean ± standard deviation or median (interquartile range) for continuous variables. Wilcoxon and Chi-squared tests were used to compare the baseline characteristics of the two groups

ACR urine albumin-to-creatinine ratio, *BMI* body mass index, *BP* blood pressure, *eGFR* estimated glomerular filtration rate, *HbA1c* hemoglobin A1c, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein

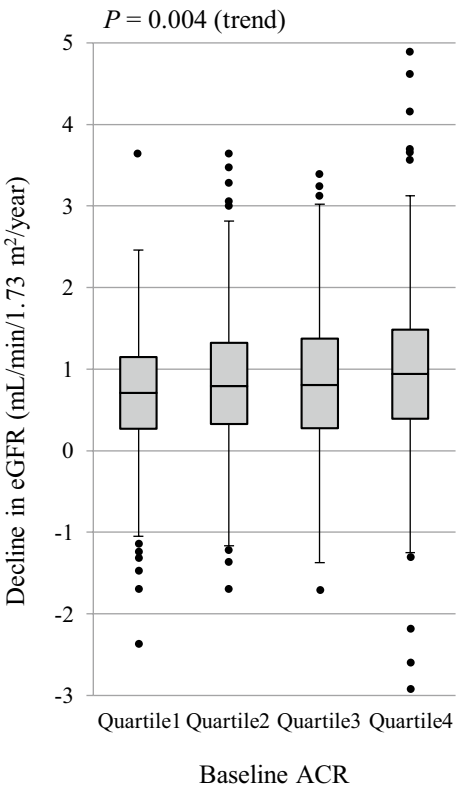

Fig. 1 Decline in eGFR according to quartile of baseline ACR. *ACR* urine albumin-to-creatinine ratio, *eGFR* estimated glomerular filtration rate. Error bars represent standard deviations

With logistic regression analyses, when compared with participants in the lowest ACR quartile, the OR for incident CKD for participants in the highest quartile was 2.48 (95% CI 1.64–3.82; $P < 0.001$) (Table 4). This difference persisted after adjustment for age, baseline eGFR, BMI, smoking status, and the presence of hypertension, hematuria, hyperuricemia, and dyslipidemia (OR 3.57, 95% CI 2.25–5.76; $P < 0.001$). When the highest and lowest quartiles of ACR were compared, the OR for incident micro- or macroalbuminuria was 16.23 (95% CI 6.56–54.03; $P < 0.001$) (Table 4), which also persisted after adjustment for age, baseline eGFR, BMI, smoking status, and the presence of hypertension, hematuria, hyperuricemia, and dyslipidemia (OR 14.03, 95% CI 5.49–47.58; $P < 0.001$).

Because there was the possibility that some patients at the early stage of glomerular nephritis were included in the population with hematuria, we also analyzed those participants without hematuria at baseline. When compared with participants in the lowest quartile of ACR, the OR for incident CKD and incident micro- or macroalbuminuria for participants in the highest quartile were 2.63 (95% CI 1.71–4.11; $P < 0.001$) and 16.87 (95% CI 6.79–56.31; $P < 0.001$), respectively (Table 4). These differences persisted after adjustment for age, baseline eGFR, BMI, smoking status, and the presence of hypertension, hyperuricemia, and dyslipidemia (OR 3.70, 95% CI 2.30–6.06; $P < 0.001$ and OR 13.26, 95% CI 5.17–45.06; $P < 0.001$, respectively) (Table 4).

Over the 10-year follow-up period, 75 participants (5.4%) met the diagnostic criteria for DM. Although the

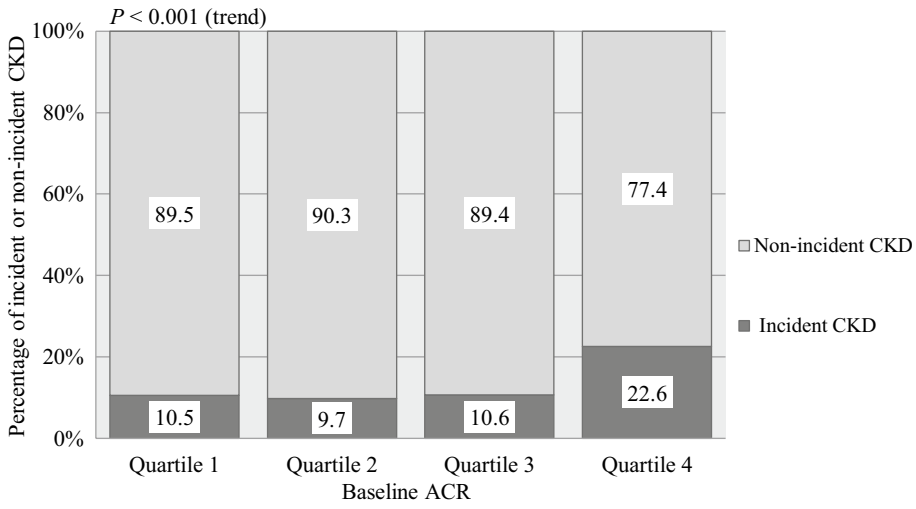

Fig. 2 Rate of incident CKD according to quartile of baseline ACR. *ACR* urine albumin-to-creatinine ratio, *CKD* chronic kidney disease

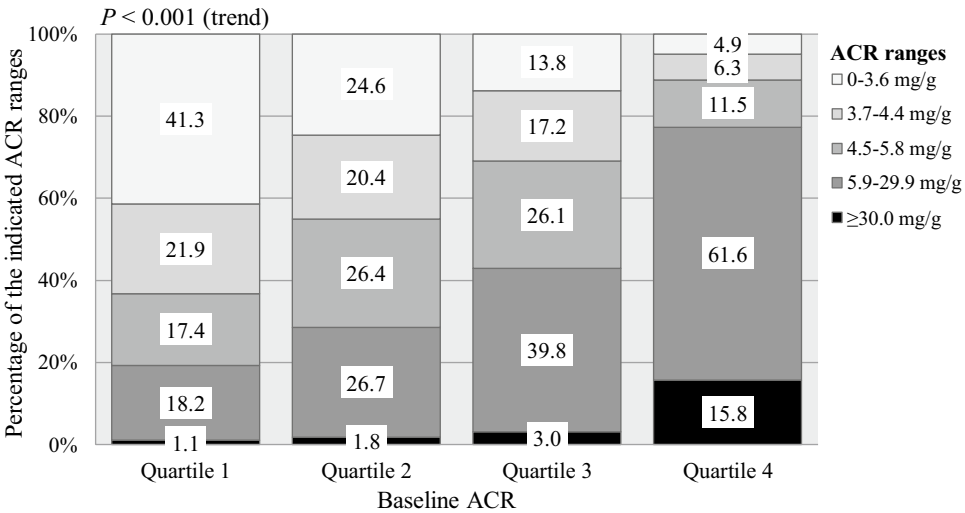

Fig. 3 Transition of ACR ranges over the 10-year period according to quartile of baseline ACR. *ACR* urine albumin-to-creatinine ratio

highest quartile of ACR was associated with an increased risk for incident DM compared with the lowest quartile of ACR (OR 2.10, 95% CI 1.13–4.08; $P = 0.019$), there was no significant association between ACR and incident DM after adjustment for age, baseline GFR, hematuria, BMI, smoking status, hyperuricemia, and dyslipidemia (Table 4). Among the 1124 participants without hypertension at baseline, 194 (17.2%) met the diagnostic criteria for hypertension over the 10-year follow-up period. When compared with participants in the lowest quartile of ACR in this population, the OR for incident hypertension for participants in the highest quartile of ACR was 2.18 (95% CI 1.41–3.39; $P < 0.001$) (Table 5). This difference persisted after adjustment for age, baseline eGFR, hematuria, BMI, smoking status, hyperuricemia, and dyslipidemia (OR 2.06, 95% CI 1.30–3.31; $P = 0.002$).

Discussion

This is a retrospective cohort study of data of medical examinations from 1378 Japanese men without DM. We found that ACR correlated with age, hematuria, hypertension, dyslipidemia, and decline in eGFR. Although ACR is a urinary marker for diabetes nephropathy [9], the results indicate that a high-normal ACR is independently associated with not only the development of micro- or macroalbuminuria but also with the incidence of CKD in this non-DM population. These findings suggest that people with high-normal ACR should be considered as potential future CKD patients.

We found that 13.4% of participants in the study were diagnosed with CKD over the 10-year period from medical

Table 4 Odds ratios for incident CKD and micro- or macroalbuminuria at 10 years after baseline

Parameter	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Incident CKD				
All participants				
No. of cases/no. of participants	37/351	32/329	37/349	79/349
Model 1[a]	1 (reference)	0.91 (0.55–1.50)	1.01 (0.62–1.63)	2.48 (1.64–3.82)[d]
Model 2[b]	1 (reference)	1.18 (0.70–1.98)	1.34 (0.81–2.23)	3.57 (2.25–5.76)[d]
Participants without hematuria at baseline				
No. of cases/no. of participants	35/335	28/316	34/323	72/307
Model 3[a]	1 (reference)	0.83 (0.49–1.40)	1.01 (0.61–1.66)	2.63 (1.71–4.11)[d]
Model 4[c]	1 (reference)	1.05 (0.61–1.81)	1.29 (0.77–2.19)	3.70 (2.30–6.06)[d]
Incident micro- or macroalbuminuria				
All participants				
No. of cases/no. of participants	4/351	6/329	11/349	55/349
Model 5[a]	1 (reference)	1.61 (0.46–6.35)	2.82 (0.96–10.26)	16.23 (6.56–54.03)[d]
Model 6[b]	1 (reference)	1.59 (0.45–6.28)	2.75 (0.92–10.07)	14.03 (5.49–47.58)[d]
Participants without hematuria at baseline				
No. of cases/no. of participants	4/335	6/316	11/323	52/307
Model 7[a]	1 (reference)	1.60 (0.45–6.31)	2.92 (0.99–10.61)	16.87 (6.79–56.31)[d]
Model 8[c]	1 (reference)	1.56 (0.44–6.19)	2.70 (0.90–9.92)	13.26 (5.17–45.06)[d]

Values are expressed as odds ratio (95% confidence interval)

[a]Models 1, 3, 5, and 7 were unadjusted

[b]Models 2 and 6 were adjusted for age, baseline eGFR, hematuria, body mass index, smoking status, hypertension, hyperuricemia, and dyslipidemia. Hyperuricemia was defined as urinary acid ≥ 7.0 mg/dL or use of antihyperuricemic drugs

[c]Models 4 and 8 were adjusted for age, baseline eGFR, body mass index, smoking status, hypertension, hyperuricemia, and dyslipidemia

[d]$P < 0.001$ vs. Quartile 1

Table 5 Odds ratios for incident DM and hypertension at 10 years after baseline

Parameter	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Incident DM				
No. of cases/no. of participants	15/351	17/329	13/349	30/349
Model 1[a]	1 (reference)	1.22 (0.60–2.51)	0.86 (0.40–1.85)	2.10 (1.13–4.08)[d]
Model 2[b]	1 (reference)	1.07 (0.51–2.26)	0.77 (0.35–1.70)	1.57 (0.79–3.22)
Incident hypertension				
No. of cases/no. of participants	41/313	44/283	49/285	60/243
Model 3[a]	1 (reference)	1.22 (0.77–1.94)	1.38 (0.88–2.17)	2.18 (1.41–3.39)[e]
Model 4[c]	1 (reference)	1.23 (0.77–1.98)	1.39 (0.87–2.22)	2.06 (1.30–3.31)[f]

Values are expressed as odds ratio (95% confidence interval)

[a]Models 1 and 3 were unadjusted

[b]Model 2 was adjusted for age, baseline eGFR, hematuria, body mass index, smoking status, hypertension, hyperuricemia, and dyslipidemia

[c]Model 4 was adjusted for age, baseline eGFR, hematuria, body mass index, smoking status, hyperuricemia, and dyslipidemia

[d]$P = 0.019$

[e]$P < 0.001$

[f]$P = 0.002$ vs. Quartile 1

checkups. The previous studies have reported that age, DM, obesity, hypertension, smoking, and low HDL cholesterol levels are risk factors for incident CKD [21, 22]. Although these factors worsen renal function, the findings of the current study suggest that high-normal ACR independently correlated with an increased risk for incident

CKD even after adjustment for these factors (Table 4; Model 2). A possible explanation is that high-normal ACR may reflect the early phase of renal damage. Therefore, evaluation of ACR may be a useful tool to help predict future incident CKD even in patients within the normal range.

In this study, we found that high-normal ACR was a predictive factor for incident hypertension in this population, a finding supported by the previous research [23, 24]. The previous studies report that glomerular endothelial cells act as a barrier against albumin filtration [25], and that endothelial cell dysfunction, such as loss of the glycocalyx, leads to increased albumin excretion [26]. Some studies have also reported an association between urinary albumin excretion and endothelial dysfunction [27–30]. These findings indicate that the relationship between increased albuminuria and the progression of cardiovascular disease as well as kidney disease is suggestive of systemic endothelial dysfunction. In contrast, high-normal ACR was not associated with incident DM in the current study after adjustment for potential confounders, suggesting that normal-range ACR is not a predictor of future impaired glucose tolerance.

In the current study, even though median baseline eGFR increased with increasing quartiles of ACR, the subsequent decline in the eGFR was greatest in the highest quartile. A previous study reported that albuminuria in the range of 15–30 mg/24 h was independently associated with increased glomerular filtration in a non-DM population [31], which eventually leads to renal damage. Baseline albuminuria may increase in response to glomerular hemodynamic changes and, therefore, predict the incidence of CKD. Protein overload may contribute to exacerbate tubulointerstitial injury [32, 33], but the direct influence of low-grade albuminuria on tubulointerstitial damage is poorly understood. Therefore, further studies are needed to help determine the mechanisms.

From baseline data in the current study, multivariate analysis revealed that ACR independently correlated with baseline age, eGFR, and the presence of hematuria, hypertension, and dyslipidemia. In contrast, a past study reported that ACR levels not only increased but also decreased in a non-DM population over time [34, 35]. At the completion of the 10-year follow-up period in the current study, 22.6% of participants were observed to change to a lower ACR range. These findings suggest that the necessity of therapeutic intervention should be evaluated with other risk factors, such as age, baseline eGFR, hematuria, BMI, smoking status, hypertension, hyperuricemia, and dyslipidemia.

In the cross-sectional analysis, the presence of microscopic hematuria was independently associated with albuminuria. We did not exclude extrarenal causes of microscopic hematuria and some patients at the early stage of glomerular nephritis may be included in the group. However, we also found that high-normal ACR was associated with incident CKD, even in participants without hematuria. The previous studies have reported that persistent asymptomatic microscopic hematuria is a predictive risk marker of end-stage renal disease [36, 37]. In the current study, the presence of microscopic hematuria was not associated with the subsequent incidence of CKD and micro- or macroalbuminuria over the 10-year follow-up period (data not shown).

This study has several limitations. First, data were derived from records of medical checkups at a company that we could follow for 10 years retrospectively. As a result, the proportion of female participants was less than 9.1%, and we could not examine the impact of ACR on the incidence of CKD in females. Second, because the study group was people of Japanese ethnicity, the results need to be replicated in other ethnic groups and should not be generalized without caution. Finally, we only used a single urine specimen to assess the ACR, which has day-to-day variability [38].

In summary, we found that high-normal albuminuria was associated with incident CKD in this non-DM population of Japanese men. We also found that baseline ACR correlated with age, hematuria, hypertension, dyslipidemia, and eGFR. These results suggest that evaluation of ACR and ACR-related factors at medical checkups may help to prevent the future incidence of CKD.

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Compliance with ethical standards

Conflict of interest The authors have declared that no conflict 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 no. E-223).

Informed consent Informed consent was obtained from all individual participants included in this study.

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