ORIGINAL ARTICLE

Slight increase in urinary albumin excretion within the normal range predicts incident hypertension in a community-based Japanese population: the Takahata study

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Recent studies have suggested that urine albumin excretion in the high normal range predicts hypertension. However, the relationship between urinary albumin excretion in spot urine and incident hypertension remains unclear in the general Japanese population. To clarify this relationship, we conducted a cohort study in a community-based population of 412 normotensive individuals without diabetes and renal insufficiency and examined the incidence of hypertension using the urinary albumin-to-creatinine ratio (UACR) at baseline. Incident hypertension was defined as new-onset systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg and/or the use of anti-hypertensive drugs. During the follow-up period (median, 6.7 years), 133 subjects (32.3%) newly developed hypertension. The incidence of hypertension increased with an increase in baseline UACR (20.4% for UACR < 5 mg g⁻¹, 34.0% for 5–9.9 mg g⁻¹ UACR and 40.4% for 10–29.9 mg g⁻¹, $P = 0.002$). Multivariate logistic regression analysis, after adjustment for possible confounders, showed that UACR 5–9.9 mg g⁻¹ and 10–29.9 mg g⁻¹ were independent risks for incident hypertension compared with UACR < 5 mg g⁻¹ (odds ratio (OR) 2.15, 95% confidence interval (CI) 1.16–4.10 and OR 2.67, 95% CI 1.36–5.38, respectively). Subgroup analysis revealed that subjects with increased UACR (≥ 5 mg g⁻¹) had a higher risk of incident hypertension than did those with low UACR (< 5 mg g⁻¹), irrespective of their backgrounds (age, sex, smoking, alcohol consumption, obesity and urinary sodium excretion). In conclusion, this study showed that a slight increase in urinary albumin excretion might predict incident hypertension in a community-based Japanese population.

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INTRODUCTION

Hypertension is a major health problem, contributing to increased mortality in both developed and developing countries. It remains a main cause of cardiovascular and cerebrovascular disease.¹ Excess body weight, alcohol consumption, and sodium intake and low physical activity are important modifiable risk factors in the development of hypertension.² However, the pathophysiology and mechanism underlying the development of hypertension are still unclear.

Chronic kidney disease is recognized as a risk factor for increased mortality,³ and albuminuria is an early clinical manifestation of chronic kidney disease. Albuminuria is defined as increased urinary excretion of albumin (urine albumin-to-creatinine ratio (UACR)

≥ 30 mg g⁻¹ in spot urine). Albuminuria is an independent risk factor for all-cause and cardiovascular mortality in the general population in Japan.⁴

Hypertension is generally thought to induce albuminuria. However, several studies have shown that albuminuria precedes the development of hypertension.^{5–9} Furthermore, studies have shown that a slight increase in urinary albumin excretion, even within the normal range, is associated with a high risk of incident hypertension, mainly in Western populations.^{6,8} However, to our knowledge no study has investigated the association between urine albumin excretion and development of hypertension in East Asian populations, whose genetic background and dietary habits differ from those of Western populations. Therefore, our aim was to clarify

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whether a higher level of UACR within the normal range predicts incident hypertension in a community-based population in Japan.

METHODS

Study population

The Takahata study recruited adult subjects from a community-based, annual health check-up, to which all inhabitants aged ≥ 40 years in the town of Takahata (Yamagata prefecture, Japan) were invited. The institutional ethics committees of the Yamagata University School of Medicine and the town of Takahata approved this study (24 May 2004, No. 3), and all subjects provided written informed consent. The procedures were performed in accordance with the Helsinki Declaration. Details of the study design, recruitment procedure and profile of the population have been published elsewhere.⁴

We conducted a baseline survey from 2004 to 2006 and a follow-up survey in 2011. Among 1546 subjects who agreed to join the survey at baseline, 99 subjects had missing critical information (that is, blood pressure (BP), blood glucose, estimated glomerular filtration rate and UACR), and 881 subjects were excluded because they had hypertension, diabetes, estimated glomerular filtration rate ≤ 60 ml min⁻¹ per 1.73 m², UACR ≥ 30 mg g⁻¹ (albuminuria) or a history of cardiovascular and/or kidney disease at baseline. Therefore, in this analysis, the eligible number of subjects at baseline was 566, and 412 subjects attended the follow-up survey (follow-up rate, 72.8%; median follow-up period, 6.7 years; Figure 1).

Baseline survey

At baseline, participants used a self-reported questionnaire to document medical history, current medication, family history, smoking habits (current, past or never) and alcohol consumption. Systolic and diastolic BPs were determined using a mercury monometer with the subject seated for at least 5 min before the measurement. The measurement was performed twice, and the mean value was used for statistical analyses. Hypertension was defined as systolic BP ≥ 140 mm Hg and/or diastolic BP ≥ 90 mm Hg and/or the use of anti-hypertensive medication. Normal BP was defined as systolic BP < 120 mm Hg and diastolic BP < 80 mm Hg. Prehypertension was defined as $120 \leq$ systolic BP < 140 mm Hg and/or $80 \leq$ diastolic BP < 90 mm Hg.² Body mass index (BMI) was calculated using measurements of weight and height. Obesity was defined as BMI ≥ 25 kg m⁻² in both men and women. Plasma glucose was measured using the hexokinase enzymatic method. The presence of diabetes was ascertained by the use of hypoglycemic medication and/or fasting plasma glucose ≥ 126 mg dl⁻¹ and/or glycosylated hemoglobin (HbA1c) $\geq 6.5\%$ (cut-off values as recommended by the Japan Diabetes Society). Urinary albumin concentration was determined by immunoturbidimetry. UACR was measured in single-spot urine specimens collected before breakfast. Serum creatinine was measured using an enzymatic method, and estimated glomerular filtration rate was obtained using the Japanese equation for estimated glomerular filtration rate.¹⁰ Twenty-four-hour urinary sodium excretion was estimated in spot urine specimens using Kawasaki's equation.¹¹

Follow-up survey

We conducted the follow-up survey in 2011. BP values were measured in the same manner as at baseline, and information on medication was collected. Incident hypertension was defined as new-onset systolic BP ≥ 140 mm Hg and/or diastolic BP ≥ 90 mm Hg and/or the use of anti-hypertensive medication at follow-up.

Statistical analyses

We categorized subjects into three groups according to UACR values (< 5 , 5–9.9 and 10–29.9 mg g⁻¹). χ^2 -Tests, analysis of variance and Kruskal–Wallis tests were used to compare baseline characteristics. We performed multivariate logistic regression analyses to estimate the odds ratio and 95% confidence interval of UACR for incident hypertension, using age, sex, alcohol consumption, smoking status, BMI, 24-h urinary excretion of sodium and HbA1c as confounding factors in Model 1. We then further adjusted for BP categories at baseline (normal BP and prehypertension) in Model 2. Subgroup analyses were performed in subjects divided by age, sex, smoking, obesity, alcohol intake, estimated urinary sodium excretion and BP categories. A significant difference was defined as $P < 0.05$. All statistical analyses were performed using JMP version 10.0 software (SAS Institute, Cary, NC, USA).

RESULTS

Baseline characteristics

A comparison between 412 attendants and 154 non-attendants at the follow-up survey showed that attendants were older with higher urinary sodium excretion; however, the other characteristics were not significantly different between the two groups (Table 1). During the follow-up period, 133 subjects (32.3%) developed hypertension. The baseline characteristics of subjects with incident hypertension and those of normotensive subjects at the follow-up survey are shown in Table 2. Compared to normotensive subjects, those with incident hypertension were older, had higher systolic and diastolic BP, BMI and UACR; a higher proportion were males.

Association between UACR and incident hypertension

The numbers of subjects with UACR < 5 , 5–9.9 and 10–29.9 mg gCr⁻¹ were 98 (23.8%), 199 (48.3%) and 115 (27.9%), respectively. The crude incidence rate of hypertension increased with an increase in UACR levels from baseline (20.4, 34.0 and 40.4% for UACR < 5 , 5–9.9 and 10–29.9 mg g⁻¹, respectively; $P = 0.002$). Simple logistic regression analysis showed that the increased UACR

Table 1 Comparison of baseline characteristics between attendants and non-attendants at the follow-up survey

	Attendants	Non-attendants	P-value
Number	412	154	
Age (years)	56.9 $\pm$ 8.6	55.4 $\pm$ 11.3	0.03
Men (%)	39.3	36.3	0.52
Systolic BP (mm Hg)	122.0 $\pm$ 11.3	120.3 $\pm$ 12.3	0.15
Diastolic BP (mm Hg)	73.7 $\pm$ 8.4	73.7 $\pm$ 8.6	0.90
Smoker (%)	29.1	36.4	0.09
Alcohol consumption (%)	42.0	40.3	0.71
Body mass index (kg m ⁻²)	22.6 $\pm$ 2.8	22.5 $\pm$ 3.3	0.33
Estimated GFR (ml min ⁻¹ per 1.73 m ²)	86.0 $\pm$ 14.2	84.2 $\pm$ 14.6	0.19
HbA1c (%)	5.1 $\pm$ 0.4	5.1 $\pm$ 0.4	0.71
Estimated Na excretion (mEq per day)	220.0 $\pm$ 59.0	202.4 $\pm$ 51.0	< 0.01
UACR (mg g ⁻¹)	8.5 $\pm$ 5.3	7.9 $\pm$ 4.8	0.24

Abbreviations: BP, blood pressure; GFR, glomerular filtration ratio; HbA1c, hemoglobin A1c; UACR, urine albumin-to-creatinine ratio. Values are mean $\pm$ s.d.

Figure 1 Derivation of the study population.

levels were significantly associated with incident hypertension (odds ratio 2.35, 95% confidence interval 1.28–4.46 for UACR 5–9.9 mg g⁻¹ and odds ratio 2.78, 95% confidence interval 1.44–5.52 for UACR

10–29.9 vs. UACR <5 mg g⁻¹, respectively). The multivariate model showed that the associations between the UACR level and incident hypertension remained significant after adjusting for possible confounders, including age, sex, smoking status, alcohol consumption, BMI, HbA1c and 24-h urinary excretion of sodium (Model 1; Table 3). The difference in baseline UACR levels between the subjects with and without prehypertension had marginal significance (8.8 ± 5.6 vs. 7.8 ± 4.6 mg gCr⁻¹, $P=0.09$). Therefore, in Model 2 we further adjusted for BP categories at baseline in addition to covariates in Model 1, and the significance between UACR and incident hypertension association was preserved.

Subgroup analyses

We performed multiple logistic regression analyses (Model 1) in subgroups divided by the following categories: age (<60 and ≥60 years old), sex (men and women), smoking status (smoker and never-smoker), alcohol consumption (habitual drinker and non-habitual drinker), obesity (obesity and non-obesity), estimated urinary sodium excretion (<220 and ≥220 mEq per day) and BP categories (normal BP and prehypertension). This analysis showed that subjects with increased UACR (≥5 mg g⁻¹) had a higher risk for incident hypertension than those with low UACR (<5 mg g⁻¹) in any subgroup, and there were no significant interactions among these groups (Table 4).

Table 2 Comparison of baseline characteristics between subjects with incident hypertension and normotensive subjects at follow-up survey

	Incident		
	hypertension	Normotensive	P-value
Number of participants	133	279	
Age (years)	59.4 ± 8.8	55.6 ± 8.3	<0.01
Men (%)	46.6	35.9	0.04
Systolic BP (mm Hg)	127.1 ± 9.4	119.5 ± 11.4	<0.01
Diastolic BP (mm Hg)	76.7 ± 6.9	72.2 ± 8.7	<0.01
Smoker (%)	30.8	27.9	0.54
Alcohol consumption (%)	48.1	39.1	0.08
Body mass index (kg m ⁻²)	23.0 ± 2.8	22.4 ± 2.7	0.03
Estimated GFR (ml min ⁻¹ per 1.73 m ²)	86.8 ± 14.0	85.6 ± 14.4	0.22
HbA1c (%)	5.1 ± 0.4	5.1 ± 0.4	0.99
Estimated Na excretion (mEq per day)	226.4 ± 62.1	217.6 ± 57.4	0.17
UACR (mg g ⁻¹)	10.1 ± 6.5	7.8 ± 4.4	<0.01

Abbreviations: BP, blood pressure; GFR, glomerular filtration ratio; HbA1c, hemoglobin A1c; UACR, urine albumin-to-creatinine ratio. Values are mean ± s.d.

Table 3 Risk factors for incident hypertension

Baseline factors		Model 1; OR (95% CI)	P-value	Model 2; OR (95% CI)	P-value
Age	per 1 year increase	1.05 (1.03–1.08)	<0.01	1.05 (1.02–1.08)	<0.01
Men	vs. Women	1.40 (0.74–2.67)	0.30	1.24 (0.64–2.39)	0.52
Smoker	vs. Non-smoker	0.90 (0.50–1.63)	0.74	1.12 (0.61–2.07)	0.72
Alcohol consumption	vs. No alcohol consumption	1.38 (0.79–2.42)	0.26	1.39 (0.78–2.47)	0.26
Body mass index	per 1 kg m ⁻² increase	1.10 (1.02–1.20)	0.02	1.08 (0.99–1.18)	0.06
HbA1c	per 0.1% increase	0.71 (0.39–1.30)	0.27	0.62 (0.33–1.14)	0.12
Estimated Na excretion	>220 mEq per day	0.89 (0.56–1.40)	0.62	0.88 (0.55–1.40)	0.58
UACR 5.0–9.9 mg g ⁻¹	vs. <5 mg g ⁻¹	2.35 (1.28–4.46)	<0.01	2.15 (1.16–4.10)	0.01
UACR 10.0–29.9 mg g ⁻¹	vs. <5 mg g ⁻¹	2.78 (1.44–5.52)	<0.01	2.67 (1.36–5.38)	<0.01
Prehypertension	vs. Normal BP			3.54 (2.00–6.55)	<0.01

Abbreviations: BP, blood pressure; 95% CI, 95% confidence interval; HbA1c, hemoglobin A1c; OR, odds ratio; UACR, urine albumin-to-creatinine ratio.

Table 4 Odds ratio of UACR ≥5 mg g⁻¹ (vs. UACR <5 mg g⁻¹) for incident hypertension in subgroups

Subgroup	n	OR (95% CI)	P-value	P for interaction
Age <60 years	255	2.49 (1.20–5.51)	0.01	0.93
Age ≥60 years	157	2.46 (1.02–6.37)	0.04	
Women	250	1.64 (0.68–4.42)	0.28	0.63
Men	162	2.64 (1.29–5.61)	<0.01	
Non-smoker	292	2.03 (0.98–4.46)	0.06	0.76
Smoker	120	2.91 (1.20–7.54)	0.02	
No alcohol consumption	239	3.01 (1.18–8.70)	0.02	0.22
Alcohol consumption	173	1.78 (0.85–3.84)	0.13	
BMI <25 kg m ⁻²	334	2.19 (1.14–4.40)	0.02	0.69
BMI ≥25 kg m ⁻²	78	1.93 (0.61–6.64)	0.27	
Estimated Na excretion <220 mEq per day	225	1.41 (0.64–3.24)	0.40	0.13
Estimated Na excretion ≥220 mEq per day	187	3.18 (1.40–7.85)	<0.01	
Normal BP	123	0.91 (0.23–3.96)	0.90	0.28
Prehypertension	289	2.59 (1.37–5.12)	<0.01	

Abbreviations: BMI, body mass index; BP, blood pressure; 95% CI, 95% confidence interval; OR, odds ratio; UACR, urine albumin-to-creatinine ratio.

DISCUSSION

In this cohort study, we showed that a slight increase in urinary albumin excretion ($5\text{--}29.9\text{ mg g}^{-1}$), even within the normal range, is an independent risk of incident hypertension in a community-based Japanese population. This association was preserved in subgroups divided by the subjects' backgrounds. This finding suggests that UACR measurements are useful for predicting the future development of hypertension in the general population.

Hypertension is generally recognized as a cause of albuminuria. However, our results showed that increased urinary albumin excretion within the normal range precedes hypertension. Albuminuria is a biomarker of microvascular endothelial injury and an early clinical manifestation of chronic kidney disease.^{12,13} Recent studies have reported a link between endothelial dysfunction, arterial stiffness and BP.^{14–17} Vascular endothelial dysfunction may induce an increase in BP, and this process may be reflected as a slight increase in urinary albumin excretion. The mechanisms underlying this relationship need to be further examined.

Previous studies have reported relationships between low-grade UACR, even within the normal range ($5.6\text{--}15\text{ mg g}^{-1}$), and all-cause and cardiovascular mortality,^{3,4,18} cardiovascular disease^{19–21} and atherosclerotic indicators.^{22–24} Although we adopted a cut-off value of UACR 5 mg g^{-1} in this analysis, this value might differ depending on the characteristics of the examined population. Further studies are required for determining the optimal cut-off value for targeting several outcomes.

Urinary albumin excretion is reported to be associated with salt intake, alcohol consumption, BMI and smoking.^{25–27} We analyzed these interactions in this study; however, there were no significant interactions. This result may be because of the relatively small sample size and the healthy, non-obese population of this study, in which a small but significant association could not be determined.

The rate of incident hypertension in other studies is $8.9\text{--}26.5\%$ over 2–8 years of follow-up.^{5–9} Compared with these studies, the current study showed a higher rate of incident hypertension (33.1%). This discrepancy may be partially explained by the characteristics of the examined population, which included older subjects, and the relatively longer follow-up period. However, our result was in line with the results in Western populations. Accordingly, the current study conducted in Japanese subjects confirmed the usefulness of UACR as a predictive factor for incident hypertension in a population with different background characteristics.

In the normal BP subgroup, high UACR ($>5\text{ mg gCr}^{-1}$) did not show a significant increase in odds ratio for incident hypertension, unlike other groups. We speculate that this is partly due to the small number of events in this subgroup (17 incident hypertension among 123 subjects with normal BP at baseline). This point should be examined in a longer follow-up period.

The strengths of this study include the large, community-based population, standardized ascertainment of BP and credible clinical information adjusted for multiple conventional risk factors associated with hypertension. However, this study also has several potential limitations. First, we had limited statistical power to determine the presence of a linear correlation between UACR and incident hypertension. Second, we obtained only a single urine sample to measure UACR. Although UACR shows day-to-day variation, a single-void urine sample correlates well with 24-h urinary albumin excretion.²⁸ Third, the subjects in this study constituted a self-selected population; therefore, caution is required when generalizing our findings to other populations.

In conclusion, slight increases in urine albumin excretion, even within the normal range, were associated with an increased risk of incident hypertension in this community-based Japanese population. The measurement of urinary albumin excretion might be useful as a simple and non-invasive tool for predicting incident hypertension in the general population.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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