

## Research Article

# Predictors of Microalbuminuria among Hyperuricemia with Hypertension Patients

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Submitted: 30 December 2014

Accepted: 14 January 2015

Published: 17 January 2015

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## Keywords

- Albuminuria
- Hypertension
- Hyperuricemia
- Diabetes mellitus

## Abstract

Recently, the link between urinary albumin excretion and increased incidence of cardiovascular mortality has been demonstrated. Besides, clinical trials demonstrated the reduction of urinary albumin excretion during treatment translated into a reduction on cardiovascular event. On the other hand, hyperuricemia has been focused as one of cardiovascular events. However, the reported prevalence of microalbuminuria (MAU) in patients with hyperuricemia with hypertension is unknown.

**Aims and methods:** We conducted a cross-sectional single center study investigating the prevalence of urinary albumin excretion in patients with hyperuricemia and essential hypertension as a sub-study of the Jonan Irbesartan Microalbuminuria Study (JIMS). A total of 266 outpatients with hyperuricemia with essential hypertension were enrolled into this study.

**Results:** Mean systolic and diastolic blood pressure was  $129.5 \pm 13.3$  mmHg and  $74.0 \pm 9.3$  mmHg respectively. The prevalence of MAU was 45.5% in this cohort. Predictive factors of the presence of MAU were age and diabetes mellitus, (OR; 1.023 and 1.917, respectively).

**Conclusions:** The present study showed that the prevalence of MAU was >45% in hyperuricemia with hypertensive patients, even though blood pressure was relatively well controlled. Additionally, age and presence of diabetes mellitus were predictive factors of the presence of MAU. These findings may suggest that there is a substantial number of essential hypertension and hyperuricemia patients with MAU, and the importance of strict control of these factors for the improvement of the prognosis.

## ABBREVIATIONS

CKD: Chronic Kidney Disease; ESRD: End Stage Renal Disease (MAU): Microalbuminuria; JIMS: Jonan Irbesartan Microalbuminuria Study; BMI: Body Mass Index MDRD: Modification Of Diet In Renal Disease; GFR: Glomerular Filtration Rate JDS: Japan Diabetes Society; ARB: Angiotensin Receptor Blocker; ACEI: Angiotensin-Converting-Enzyme Inhibitor; Hb: Hemoglobin; BUN: Blood Urea Nitrogen; Cr: Creatinine

## INTRODUCTION

Recent epidemiological studies have shown that chronic kidney disease (CKD) is an independent risk factor for cardiovascular mortality and morbidity, and shown that the population of CKD has growing recently [1-3]. Because ischemic heart disease remains main cause of mortality, much attentions have to be paid for the awareness and understanding of CKD. One of the important points of the concept of CKD is the fact that the risk of cardiovascular disease increases not only at the

end stage renal disease (ESRD) but at the early stage of CKD [2,4,5]. Therefore, early detection and appropriate treatment for CKD could be clinically meaningful. It seems to be reasonable to consider that treatment should start at an earlier stage, leading to a better outcome. However early stage of CKD is unlikely to be diagnosed timely, and easily overlooked. Numerous studies demonstrated that microalbuminuria (MAU), a powerful predictor of glomerular injury, is also a predictor for the development of renal and cardiovascular complications [6-10]. This association is independent of the widely accepted cardiovascular risk factors. Furthermore, the LIFE study demonstrated that the reduction of urinary albumin excretion during treatment translated into a reduction in cardiovascular event [11]. However, reported prevalence of MAU in studied population is highly variable among studies ranging 7 to 58.4% [12-14]. These differences may be explained by prescribed drugs, and researched population. Especially, recent progress in pharmacological therapy showing beneficial effects of blood pressure control may affect the favorite effects on the secretion of MAU.

On the other hand, some data suggest that hyperuricemia is associated with cardiovascular disease risk factors and cardiovascular disease, often being a predictor of incident events [15].

Therefore, we tried to investigate the prevalence and risk factors for the presence of MAU in Japanese hyperuricemia with hypertension patients under the current medical treatment.

## METHODS AND SUBJECTS

Jonan (Irbesartan (Microalbuminur (Study (JIMS) investigators conducted a cross-sectional multicenter cohort study looking at the prevalence of urinary albumin excretion in patients with treated essential hypertension under current practice [16]. This study is sub analysis of the JIMS and we conducted a cross-sectional single center study investigating the prevalence of urinary albumin excretion in patients with hyperuricemia and essential hypertension. Consecutive patients with hypertension who had already been pointed out hyperuricemia, visited our hospital were enrolled. This study was started in July 2009. By the end of August 2010, a total of 266 hyperuricemia with essential hypertension patients had been enrolled into this study. Exclusion criteria were secondary hypertension, renal insufficiency with plasma creatinine concentration > 2.0 mg/dl, and persistent macroproteinuria by conventional dipstick test of spot urine sample (positive  $\geq 2$ ). Patients with acute fever, concomitant urinary tract infection, having undertaken strenuous physical activity within preceding 24 hours as well as female participants who were pregnant or menstruation were also excluded due to the likely presence of false-positive results. Systolic and diastolic blood pressure were measured by using a mercury manometer, placed on the right arm of seated subjects who had rested in a sitting position for at least 5 min before measurement. Hypertension was defined as an average blood pressure >140/90 mmHg on at least two different occasions during routine examination. Diabetes was defined as follows; subjects who were receiving oral hypoglycemic or insulin treatment were defined as treated diabetes. Subjects with fasting blood sugar >126mg/dl, random blood sugar >200mg/dl or HbA1c value >6.1% were also defined as diabetic. Hypercholesterolemia was defined as total cholesterol >240 mg/dl. Obesity was defined as a body mass index (BMI) >25kg/m<sup>2</sup>, calculated as body weight in kilograms divided by the square of the height in meters. Hyperuricemia was defined as follows; serum uric acid > 7.0 mg/dl or past history of gout or under medical treatment was defined as hyperuricemia. This study was approved by the medical ethics committee (number 21-5) and all the patients gave informed consent.

### Laboratory findings

Serum creatinine levels were measured by enzymatic method. Glomerular filtration rate (GFR) was estimated from adjusted serum creatinine using the simplified equation developed from the Modification of Diet in Renal Disease (MDRD) study as follows.  $GFR (ml/min/1.78M^2) = 186.3 \times (\text{serum creatinine})^{-1.154} \times \text{age}^{0.203} \times 0.742$  for female subjects [17]. Freshly voided urine was obtained and dip stick test of urine was done by CLINTEK<sup>®</sup> Microalbumin 2 (Siemens Healthcare Diagnostics Inc., Erlangen, Germany). Proteinuria was evaluated semi quantitatively (-,  $\pm$

**Table 1:** Baseline Patient Demographics.

(n=226)	
Age (years)	71.010.9
Male (%)	171(64.3)
Height (cm)	161.0 $\pm$ 8.8
Body weight (kg)	3.1 $\pm$ 12.2
BMI (kg/m <sup>2</sup> )	24.2 $\pm$ 3.8
Systolic BP (mmHg)	129.5 $\pm$ 13.3
Diastolic BP (mmHg)	74.0 $\pm$ 9.3
Laboratory findings	
WBC ( $\mu$ l)	6406 $\pm$ 1621
Hb (g/dL)	13.0 $\pm$ 1.9
Hct (%)	39.5 $\pm$ 4.9
PLT( $\times 10^4/\mu$ l)	20.7 $\pm$ 6.0
eGFR (mL/min/1.73m <sup>2</sup> )	54.0 $\pm$ 18.7
TP (g/dl)	7.6 $\pm$ 0.6
AST (IU/L)	23.6 $\pm$ 10.2
ALT (IU/L)	21.0 $\pm$ 12.6
LDH (IU/L)	433.2 $\pm$ 86.3
$\gamma$ GTP (IU/L)	27.2 $\pm$ 34.9
BUN (mg/dl)	19.3 $\pm$ 9.3
Cr (mg/dl)	1.10 $\pm$ 0.55
UA (mg/dl)	6.4 $\pm$ 1.3
T-CHO (mg/dl)	178.7 $\pm$ 31.7
TG (mg/dl)	144.2 $\pm$ 77.6
HDL-CHO (mg/dl)	55.3 $\pm$ 14.3
LDL-CHO (mg/dl)	97.3 $\pm$ 27.3
GLU (mg/dl)	120.2 $\pm$ 35.9
HbA1c (%; JDS)	5.7 $\pm$ 0.6
CKD staging	
CKD stage1 (eGFR $\geq$ 90)	7(2.6%)
CKD stage2 (60 $\leq$ eGFR 90)	100(37.6)
CKD stage3 (30 $\leq$ eGFR 60)	132(49.6)
CKD stage4 (15 $\leq$ eGFR 30)	24(9.0%)
CKD stage5 (eGFR 15)	3(1.1%)
Medical treatments	
CB	161(60.5)
ARB	164(61.6)
ACEI	69(25.9)
Diuretics	75(28.2)
Beta blocker	101(38.0)
Alfa blocker	29(10.9)
Allopurinol	124(46.6)
Sulfonylurea	24(9.0)
Metformin	13(4.9)
Statin	147(55.3)

BMI: Body Mass Index; BP: Blood Pressure; WBC: White Blood Cell; Hb: Hemoglobin; Hct: Hematocrit; PLT: Platelet; Egfr : Estimated Glomerular Filtration Rate; TP: Total Protein; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; LDH: Lactate Dehydrogenase;  $\gamma$ gtp: Gamma-Glutamyltranspeptidase; BUN: Blood Urea Nitrogen; Cr: Creatinine; UA: Uric Acid; T-CHO: Total Cholesterol; TG: Triglyceride; HDL-CHO: High Density Lipoprotein Cholesterol; LDL-CHO: Low Density Lipoprotein Cholesterol; GLU: Glucose; Hba1c: Hemoglobin A1c; JDS: Japan Diabetes Society; CKD: Chronic Kidney Disease; CB: Calcium Channel Blocker; ARB: Angiotensin Receptor Blocker; ACEI: Angiotensin Converting Enzyme Inhibitor

and +). The CLINTEK urinary chemistry analyzer is a portable reflectance photometer which is highly sensitive, purely chemical albumin test strip method based on dye binding by albumin. This urinary dip reagents strip provides the detection of albumin concentration from 10 to 150 mg/l, and also allows simultaneous urinary creatinine concentration [18].

**Statistical analysis**

Continuous variables were expressed as mean±standard deviation and categorical data were presented as frequencies. For comparisons between groups, we used Student’s t-test to evaluate difference in means and  $\chi^2$  tests to evaluate the differences in proportions. To test the independent relationship between MAU and variables, potential factors was selected by univariate regression analysis, and selected variables were assessed in a multiple logistic regression analysis model. All statistical analysis was performed using the software of SPSS12.0 (SPSS Inc, Chicago, IL, US). A significant difference was defined as  $p < 0.05$ .

**RESULTS**

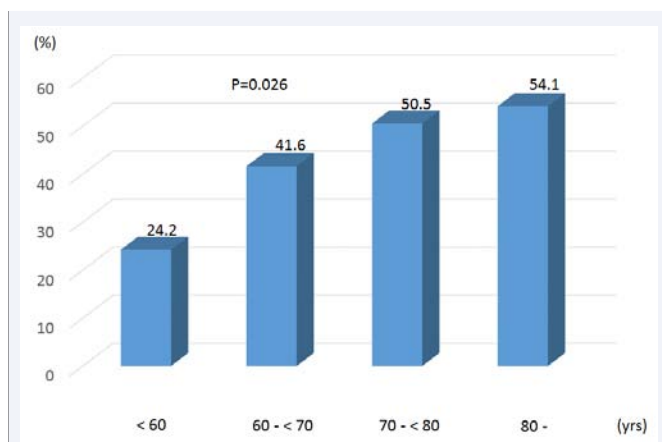
**Patients’ demographics**

A total of 226 patients were enrolled in the present study. Registered patients demographics are shown in (Table1). Mean age was 71.0±10.9 years, and male was 64.3%. Mean systemic blood pressure was 129.5±13.3/74.0±9.3 mm Hg, and obesity with BMI>25kg/m<sup>2</sup> was 33.6 %. Mean HbA1c (JDS value: Japan Diabetes Society) was 5.7±0.6 and mean uric acid was 6.4±1.3 mg/dl. The majority of patients were prescribed with angiotensin receptor blocker (ARB; 61.7%) or calcium channel blocker (60.5%). About half of patients (46.6%) were prescribed allopurinol for hyperuricemia.

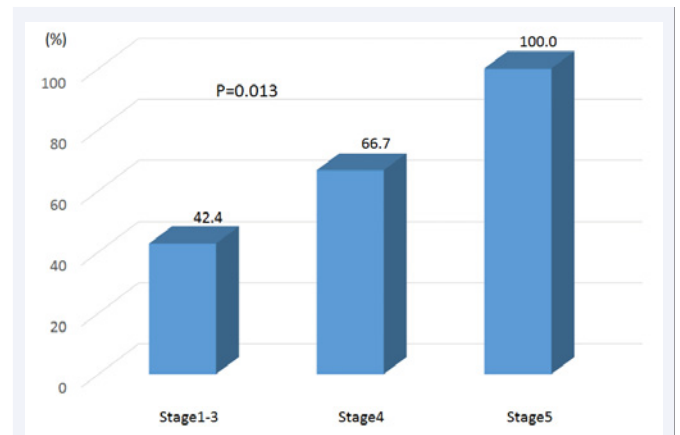
MAU was prevalent across all age group and the proportion of subjects with MAU increased with each increase in age and CKD staging (Figure 1, 2).

**Predictors for MAU**

Table 2 demonstrated patient’s profile of subjects with



**Figure 1** Prevalence of microalbuminuria by age  
 Microalbuminuria was prevalent across all age group and increasing according to the age.



**Figure 2** CKD staging and the prevalence of microalbuminuria  
 Microalbuminuria was prevalent across all CKD groups and increasing according to the staging.  
 CKD: Chronic Kidney Disease

**Table 2:** Predictors for MAU.

	MAU (-)	MAU (+)	p value
Total number (%)	145(54.5)	121(45.5)	
Age (years)	69.2±11.7	73.1±9.4	0.0031
male gender(%)	96(66.2)	75(62.0)	0.4741
Body Mass Index	24.4±3.4	24.0±4.3	0.4153
systolic BP(mmHg)	127.7±13.9	131.6±12.2	0.0163
diastolic BP	74.6±9.9	73.2±8.6	0.2171
<i>laboratory findings</i>			
eGFR (ml/min/1.78m <sup>2</sup> )	57.2±17.8	50.1±19.1	0.0021
AST (IU/L)	23.8±11.0	23.4±9.1	0.7803
ALT (IU/L)	20.9±12.9	21.0±12.3	0.9813
BUN (mg/dl)	18.1±9.0	20.4±9.6	0.0338
Cr (mg/dl)	1.02±0.37	1.20±0.60	0.0035
Uric acid (mg/dl)	6.6±1.4	6.3±1.2	0.0659
Glucose (mg/dl)	117±32	124±40	0.1199
HbA1c (JDS)	5.6±0.6	5.8±0.7	0.0276
<i>medication</i>			
CB	55.9%	66.1%	0.0884
ARB	59.3%	64.5%	0.3894
ACEI	22.1%	30.6%	0.1149
Diuretics	28.3%	28.1%	0.9746
Beta blocker	38.6%	37.2%	0.8108
<i>vascular events</i>			
IHD	44.8%	55.4%	0.0868
CVD	18.6%	17.4%	0.7893
PAD	6.2%	14.1%	0.0320
<i>comorbidities</i>			
DM	31.0%	46.3%	0.0107
DL	80.0%	69.4%	0.0467

BP: Blood Pressure; GFR: Glomerular Filtration Rate; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; BUN: Blood Urea Nitrogen; Cr: Creatinine; JDS: Japan Diabetes Society; CB: Calcium Channel Blocker; ARB: Angiotensin Receptor Blocker; ACEI: Angiotensin Converting Enzyme Inhibitor; IHD: Ischemic Heart Disease; CVD: Cerebrovascular Disease; PAD: Peripheral Artery Disease; DM: Diabetes Mellitus; DL: Dyslipidemia

prevalent MAU. There was a statistical significant difference between MAU + and - group regarding age, systolic blood pressure, eGFR and level of HbA1c. However, there was no significant difference on the prevalence of MAU among patients with ARB, angiotensin-converting-enzyme inhibitor (ACEI), or other anti-hypertensive agent usage. Regarding the relationship between the prevalence of MAU and vascular events, the existence of ischemic heart disease were prone to have positive MAU. Moreover, peripheral artery disease which is in the advanced arteriosclerotic stage reveals more positive MAU, and significant difference. Using a univariate logistic regression analysis, following factors were revealed to be associated with the excretion of MAU; age, systolic blood pressure, eGFR, BUN, Cr, HbA1c, and presence of diabetes mellitus, dyslipidemia and peripheral artery disease (Table 3). Multiple logistic regression analysis identified that systolic blood pressure and presence of diabetes was independent factors. The risk of MAU was increased 1.023 times with each 1mmHg increase of systolic blood pressure.

## DISCUSSIONS

The present study was observational study of patients with treated hypertension with hyperuricemia in the real world practice in Japan. The main findings of the present study include 1) the prevalence of albuminuria was >45%. 2) Independent predictive factors of the excretion of MAU were systolic blood pressure and diabetes mellitus. Because it has been shown that albuminuria is more sensitive than proteinuria in detecting CKD, screening program to identify the disease before clinical phase could be meaningful, though there have been no studies on the direct comparison between proteinuria and MAU in terms of utilities.

### The prevalence of MAU

The detection of MAU was as high as 46% in the present study. This finding may suggest that the early stage of CKD was actually overlooked and under- diagnosed clinically. Reported prevalence of MAU in hypertensive population absolutely exceeds those in general population [12-14,19-21]. However, the prevalence rate in hypertensive population was highly variable among studies within range of 26.6% - 58.4% [14,20,21].

Several factors could affect the results of investigations. Aging is recognized as independent risk factor for renal disease due to glomerular ischemia secondary to the change in renal blood flow that occurs with aging. In addition, it has been demonstrated that the prevalence of MAU increases with age [13,14]. Mean

Table 3:

Variable	OR	95%CI	P-value
Age	1.010	0.979-1.043	0.5268
Systolic BP	1.023	1.002-1.045	0.0298
eGFR	0.991	0.972-1.011	0.3755
DM	1.917	1.089-3.376	0.0242
DL	0.575	0.309-1.070	0.0809
PAD	2.319	0.904-5.951	0.0801

OR: Odds Ratio; CI: Confidence Interval; BP: Blood Pressure; GFR: Glomerular Filtration Rate; DM: Diabetes Mellitus; DL: Dyslipidemia; PAD: Peripheral Artery Disease

age of the present cohort was around 70 years old, and the studied population was older than those of previous studies. A 38.0% of enrolled population was diabetic, whereas in other studies diabetic patients were excluded [22,23]. Furthermore, hypertensive patients with known atherosclerotic disease were included in the present study. Thus, the current cohort is likely to represent hyperuricemic hypertensive population in real world practice. On the other hand, mean blood pressure was 129.5/74.0 mmHg in our cohort. In i-SERACH study reporting 58.4% of albuminuria, mean blood pressure was 149.2±20.2mmHg, and 76.8 % of uncontrolled hypertensive patients were included [14]. Therefore, 45.5% of albuminuria in our relatively well controlled hypertensive population suggests remarkably high prevalence of MAU in current practice because presumably hyperuricemia may be influential. Another possible explanation is the differences in the method including collection of urine sample, and diagnosis criteria might affect the outcomes in our series. Besides, Weir et al reported 40% prevalence of MAU in Asian hypertensive diabetic patient [24]. Konta et al also demonstrated the higher prevalence of MAU in Japanese general population [13]. Therefore, there is a possibility that Asian population might be susceptible to MAU.

### Predictors of MAU

The results of the present study also demonstrated that within the hyperuricemia and hypertensive patients, the risk of developing MAU was significantly greater if patients had higher blood pressure as well as the presence of diabetes. These data suggest strong and independent influences of systemic arterial pressure on urinary albumin extraction, and are well consistent with a recent report showing development of MAU linked to insufficient blood pressure control in essential hypertension [25,26].

Furthermore, recent investigations demonstrated strict blood pressure control reduces proteinuria and prevent progression of ESRD [11,27-29]. In this analysis, mean systolic blood pressure of patients with positive and negative MAU are 131.6±12.2/73.2±8.6 mmHg and 127.7±13.9/74.6±9.9 mmHg respectively. Thus, the difference of mean systolic blood pressure between 2 groups was only limited to 3.9 mmHg. These findings confirm the importance of strict control of blood pressure to prevent the glomerular injury, and also are likely to strongly suggest that blood pressure and glucose control should be managed more strictly at early phase of hypertension.

It has been reported that certain class of antihypertensive medications such as angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists reduce proteinuria [22,27-29]. However, the difference of renal preservation effect among drugs was unclear in this study. Because the information about doses and the duration of prescribed medication and duration of hypertensive status were not available in this study.

Other important contributions to increased risk of MAU were the comorbidity of diabetes. Diabetes is well-known predictor for developing proteinuria, and it has been shown that strict control of glucose level can reduce and prevent proteinuria [30,31]. These findings are consistent with the present study. MAU was more frequently observed in polyvascular disease. It has been shown that the lower ankle-brachial index is the risk



of cardiovascular complication is greater. Moreover, in REACH registry, the incidence of future cardiovascular event was higher in patients with peripheral artery disease compared to those with other arteriosclerotic disease [32]. Taken together, the proposed hypothesis that MAU is a marker of more generalized and wide spread endothelial dysfunction and atherosclerosis is likely to be consistent with the present study. Moreover, the view that MAU is an independent factor for atherosclerotic disease, and carries prognostic information beyond that of other risk factors may be supported.

## LIMITATIONS

There are several limitations we should mention. First of all, this is an observational study. There may be selection bias in our study population. Thus, generalization of present study outcomes may be somewhat limited. Besides, we believe that enrollment of consecutive out-patients represents the actual accurate findings. Second, the urine check was limited to the once, which did not completely confirm to the requirement of multiple urine collections for MAU [33]. However, Brantsma et al revealed that single measurement has enough power to predict the future prognosis [34]. Third, the GFR estimates using the simplified prediction equation derived from the MDRD study might not be sufficiently correct, because it is based on the single blood sample. However, this equation is considered to be the most precise one [35]. Finally, no information regarding the severity or duration of hypertension was obtained in present study.

## CONCLUSIONS

The present study showed that the prevalence of MAU was >45% in hyperuricemia among hypertensive patients, even though blood pressure was relatively well controlled. In addition, predictive factors of the presence of MAU were systolic blood pressure, and presence of diabetes. These findings may suggest that early detection and awareness of this sensitive marker is quite important for the management of hyperuricemic and hypertensive patients in real world practice.

## ACKNOWLEDGMENTS

We appreciate the Associations for Establishment of Evidence in Interventions for financial supports.

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Cite this article

Hara H, Nakamura M (2015) Predictors of Microalbuminuria among Hyperuricemia with Hypertension Patients. *Ann Clin Exp Hypertension* 3(1): 1018.