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Prevalence of diabetic nephropathy in primary care type 2 diabetic patients with hypertension: data from the Korean Epidemiology Study on Hypertension III (KEY III study)

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Abstract

Background. The prevalence of albuminuria is known to be higher in hypertensive compared to normotensive non-diabetic patients. In addition, systolic blood pressure (BP) is found to be an independent risk factor for albuminuria in type 2 diabetes mellitus (T2DM). Based on these findings, the prevalence of albuminuria is expected to be higher in T2DM with hypertension relative

to T2DM without hypertension, but it has been largely unexplored.

Methods. Prevalence rates of microalbuminuria, macroalbuminuria and renal insufficiency (RI) were investigated among 3738 hypertensive T2DM patients from 350 nationwide primary care clinics. Independent factors associated with albuminuria and RI were also characterized.

Results. Clinical and laboratory data of 3712 patients were included in the analysis. BP was controlled in only 1164 patients (31.4%). There were 2595 normoalbuminuric patients (70.6%), and microalbuminuria and macroalbuminuria were present in 850 (23.1%) and 230 (6.3%), respectively. The prevalence of RI was 32.1% based on estimated glomerular filtration rate (eGFR) by Modification of Diet in Renal Disease formula. Systolic BP correlated significantly with the natural logarithmic values of urinary albumin-to-creatinine ratio (ACR) ($R = 0.16$, $P < 0.0001$). Multivariate logistic regression analysis revealed that male sex, the duration of diabetes, systolic BP, glycated hemoglobin and eGFR were significant independent factors associated with the presence of albuminuria, while advanced age, female sex, the duration of diabetes and urinary ACR were significant independent risk factors for RI.

Conclusions. A significant proportion of T2DM patients with hypertension had albuminuria and RI, and the duration of diabetes mellitus rather than the duration of hypertension was a significant independent factor associated with albuminuria and RI.

Keywords: albuminuria; diabetic nephropathy; hypertension; renal insufficiency; type 2 diabetes

Introduction

Recently, the number of patients with diabetes and/or hypertension has strikingly increased in most countries. Moreover, since diabetes and hypertension are well-known risk factors for cardiovascular mortality in not only the general population but also specific groups of patients [1, 2], they have become common serious problems throughout the world. Accumulating evidence has also shown that there is a close relationship between diabetes and hypertension. The prevalence of hypertension in patients with type 2 diabetes (T2DM) is known to be 1.5–3 times higher than in the age-matched nondiabetic population [3, 4]. In the other direction, patients with hypertension are at a two to three times higher risk for developing diabetes than those with normal blood pressure (BP) [5].

Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD) worldwide [6]. Since early detection of renal involvement in diabetic patients is a critical issue in terms of delaying the progression of renal disease, several markers have been used for screening. Proteinuria has been known for a long time as an independent significant risk factor for ESRD and cardiovascular disease in diabetic patients [7, 8]. However, the focus has moved recently to much earlier stages in renal disease as established by the presence of microalbuminuria. Microalbuminuria is not only established as a significant predictor for the development of overt diabetic nephropathy but is also associated with increased cardiovascular morbidity and mortality risk in both type 1 and type 2 diabetes [9, 10]. The prevalence rate of microalbuminuria is also known to be ~2-fold higher in nondiabetic patients with hypertension [11]. In addition, systolic BP is found to be an independent risk factor for microalbuminuria in patients with T2DM [12]. Based on these findings, the prevalence of microalbuminuria is expected to be higher in T2DM patients with hypertension compared to those with T2DM or hypertension alone, but it has been largely unexplored.

Numerous studies have clearly demonstrated that strict BP control is more beneficial in diabetic than in nondiabetic hypertensive patients [13]. As a result, recently released guidelines set the target level of BP <130/80 mmHg in diabetic patients with hypertension [14]. This indicates that a more aggressive antihypertensive treatment is needed in diabetic hypertensive patients. Nevertheless, previous studies have found that BP control rates in these patients are lower compared to nondiabetic patients with hypertension [15, 16], and little is known on the difference in BP control rates according to the stages of diabetic nephropathy and/or the stages of chronic kidney disease (CKD). In addition, the relationship between BP control and albuminuria or renal insufficiency (RI) has not been extensively investigated in primary care diabetic patients with hypertension.

Therefore, we performed a nationwide cross-sectional primary care clinic-based study on T2DM patients with hypertension to investigate (i) the prevalence of microalbuminuria and macroalbuminuria, (ii) the frequency of RI, (iii) the relationship between BP control and albuminuria and (iv) the relationship between BP control and RI.

Materials and methods

Study design and population

The Korean Epidemiology Study on Hypertension III (KEY III study) was a nationwide, cross-sectional primary care unit-based study. Random selection of nationwide primary care physicians based on the number of residents of each city or province was performed, and survey letters were sent to the selected 350 primary care clinics. Of the invited physicians, 300 physicians in 292 clinics agreed to participate in this study (85.7%).

The eligibility criteria were patients aged >18 years with T2DM and hypertension. Subjects were considered to have diabetes if they were receiving insulin or oral hypoglycemic agents or if fasting blood glucose levels >126 mg/dL. Hypertension was defined based on the patient medical record or if the patient was taking antihypertensive medications. Patients with type 1 diabetes, pregnancy, acute fever, significant bacteriuria or hematuria, or previously diagnosed nondiabetic glomerular disease, or patients who performed excessive exercise within 24 h were excluded. Informed consent was obtained from all subjects.

Measurements

All subjects were asked to complete a questionnaire to collect information on demography, lifestyle data and family history of hypertension and cardiovascular disease. Anthropometrical data, medical history and antihypertensive medication were also recorded by the primary physician.

BP was measured by the physician using a standard electronic sphygmomanometer (MX3; Omron Co. Ltd, Dalian, China). Measurement was performed on the arm of the subject supported at the heart level with an appropriate cuff after ~10 min of rest in the sitting position. The average of two consecutive measurements with a 5-min interval was used for analysis.

Morning spot urine and blood samples were sent to the core laboratory (Green Cross Reference Laboratory, Seoul, Korea) for urinary albumin-to-creatinine ratio (ACR), serum creatinine and glycated hemoglobin (HbA1C) level measurements. Urinary albumin concentrations were

determined by a turbidimetric immunoassay, and plasma and urine creatinine levels by kinetic colorimetric assay using the Jaffe method. HbA1C was measured by high-performance liquid chromatography.

Microalbuminuria was defined as ACR of 30–299 mg/g and macroalbuminuria as ACR >300 mg/g [17]. We used the Modification of Diet in Renal Disease (MDRD) formula [18] to calculate the estimated glomerular filtration rate (eGFR) (mL/min/1.73m^2). The stages of CKD were defined according to the American National Kidney Foundation [19]: Stage 1, eGFR ≥90; Stage 2, eGFR 60–89; Stage 3, eGFR 30–59; Stage 4, 15–29 and Stage 5, eGFR <15 or dialysis. CKD of Stage 3 or higher was defined as RI.

Statistical analysis

All values are expressed as means ± SDs or percentages. Statistical analyses were performed using SAS (version 9.1; SAS Institute, Cary, NC). Results were analyzed using analysis of variance (ANOVA), Student's *t*-test or chi-square test for comparisons. Significant differences found by ANOVA were further confirmed by the Student's *t*-test with the Bonferroni correction. The correlations between the natural logarithmic values of urinary ACR or eGFR and clinical and laboratory parameters were determined by Pearson's correlation analysis and independent factors associated with the presence of albuminuria or RI were identified by multivariate logistic regression analysis. P-values <0.05 were considered to be statistically significant.

Results

Demographic characteristics

Among the 3738 recruited cases, 26 patients were excluded: 12 patients did not meet the inclusion criteria and 14 patients with missing data. Therefore, a total of 3712 patients were included in the analysis.

The mean age of the patients was 62.0 ± 10.7 years, and 1677 (45.2%) were male. The mean durations of diabetes and hypertension were 7.0 ± 5.9 and 7.7 ± 6.0 years, respectively, and the mean BP was 130.5 ± 13.5/78.3 ± 9.1 mmHg. BP was controlled (<130/80 mmHg) at the time of visit in only 1164 patients (31.4%), although the primary care physicians considered 93.4% of the subjects had a well-controlled BP (Table 1).

Among the 3675 patients with available urinary ACR results, 2595 patients (70.6%) were normoalbuminuric, and microalbuminuria and macroalbuminuria were present in 850 patients (23.1%) and 230 patients (6.3%), respectively. The prevalence of RI was 32.1% (Table 2).

Relationship between BP control and albuminuria

Urinary ACR was significantly lower in patients with controlled hypertension compared to those with uncontrolled hypertension (59.6 ± 178.7 versus 81.4 ± 210.7 mg/g, P = 0.0013).

Relationship between BP control and RI

There was a significant difference in eGFR between patients with and without controlled hypertension (68.6 ± 17.9 versus 66.8 ± 16.2 mL/min/1.73m^2, P = 0.0026).

Factors associated with albuminuria

Pearson's correlation analysis revealed that the duration of diabetes (R = 0.20, P < 0.0001), systolic BP (R = 0.16, P < 0.0001), HbA1C levels (R = 0.24, P < 0.0001) and eGFR (R = −0.22, P < 0.0001) correlated significantly with the natural logarithmic values of urinary ACR.

On the other hand, when the patients were divided into the normo-, micro- and macroalbuminuric groups there were significant differences in the duration of diabetes and hypertension, the presence of diabetic complications, systolic and diastolic BP, the proportion of patients with controlled hypertension, patients receiving renin-angiotensin system blockades or calcium channel blockers, HbA1C levels, urinary ACR, serum creatinine concentrations, eGFR and the proportion of patients with RI among the three groups (Table 3).

Multivariate logistic regression analysis revealed that the duration of diabetes [odds ratio (OR) = 1.04, 95% confidence interval (CI) = 1.02–1.05, P < 0.0001], the presence of diabetic complications (OR = 1.54, 95% CI = 1.29–1.85, P < 0.0001), systolic BP (OR = 1.02, 95% CI = 1.01–1.03, P < 0.0001), HbA1C (OR = 1.34, 95% CI = 1.26–1.41, P < 0.0001) and eGFR (OR = 0.98, 95% CI = 0.97–0.98, P < 0.0001) were significant independent factors associated with the presence of microalbuminuria or macroalbuminuria (Table 4).

Further multivariate logistic regression analysis was performed with albuminuric patients to identify independent differentiating factors of macroalbuminuria from microalbuminuria. As a result, age (OR = 0.96, 95% CI =

Table 1. Demographic characteristics of patients (N = 3712)[a]

	Mean ± SD or N (%)
Age (years)	62.0 ± 10.7
Male:female	1677:2035
Body mass index (kg/m^2)	24.8 ± 3.2
Duration of diabetes (years)	7.0 ± 5.9
Duration of hypertension (years)	7.7 ± 6.0
Family history	
Diabetes	1724 (46.4)
Hypertension	1447 (39.2)
Smoking	
Smoker	724 (19.6)
Ex-smoker	703 (19.1)
Nonsmoker	2260 (61.3)
Drinker	1394 (37.8)
Diabetic complications (yes)	894 (24.1)
Systolic BP (mmHg)	130.5 ± 13.5
Diastolic BP (mmHg)	78.3 ± 9.1
Antihypertensive drugs	
ARB or ACEi	2841 (76.5)
CCB	1728 (46.6)
Beta-blocker	417 (11.2)
Diuretics	1600 (43.1)
Others	204 (5.5)
BP control	
Controlled	1164 (31.4)
Uncontrolled	2548 (68.6)

[a]ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

Table 2. Laboratory findings of patients

	Mean ± SD or n (%)
Glucose (mg/dL)	175.3 ± 48.3
HbA1C (%)	7.09 ± 1.36
Urinary ACR (mg/g)	74.6 ± 201.4
Serum creatinine (mg/dL)	1.10 ± 0.58
eGFR (mL/min/1.73m^2)	68.0 ± 17.4
Albuminuria	
Normoalbuminuria	2595 (70.6)
Microalbuminuria	850 (23.1)
Macroalbuminuria	230 (6.3)
RI	1188 (32.1)

Table 3. Comparison between patients with normo-, micro- and macroalbuminuria[a]

	Normo- ($N = 2595$)	Micro- ($N = 850$)	Macro- ($N = 230$)	P-value
Age (years)	61.8 ± 10.5	62.7 ± 11.3	61.1 ± 10.4	0.0468
Sex				0.4743
Male	1156 (44.5)	384 (45.2)	112 (48.7)	
Female	1439 (55.5)	466 (54.8)	118 (51.3)	
Body mass index (kg/m^2)	24.8 ± 3.2	24.7 ± 3.2	24.6 ± 2.9	0.4429
Duration of diabetes (years)	6.4 ± 5.4	8.1 ± 6.6	10.1 ± 7.5	<0.0001
Duration of hypertension (years)	7.4 ± 5.8	8.2 ± 6.3	9.3 ± 7.0	<0.0001
Diabetic complications	524 (20.2)	244 (28.7)	113 (49.3)	<0.0001
Systolic BP (mmHg)	129.3 ± 12.8	132.3 ± 14.1	136.6 ± 15.4	<0.0001
Diastolic BP (mmHg)	77.8 ± 8.7	78.9 ± 9.7	80.8 ± 10.3	<0.0001
Antihypertensive drugs				
ARB or ACEi	1964 (75.7)	645 (75.9)	216 (93.9)	0.0256
CCB	1171 (45.1)	435 (51.2)	107 (46.5)	0.0090
Beta-blocker	291 (11.2)	90 (10.6)	34 (14.8)	0.1985
Diuretics	1138 (43.9)	337 (39.6)	104 (45.2)	0.1408
Others	137 (5.3)	45 (5.3)	20 (8.7)	0.0892
BP control				<0.0001
Controlled	880 (33.9)	223 (26.2)	50 (21.7)	
Uncontrolled	1715 (66.1)	627 (73.8)	180 (78.3)	
HbA1C (%)	6.91 ± 1.22	7.47 ± 1.48	7.74 ± 1.71	<0.0001
Urinary ACR (mg/g)	12.6 ± 6.60	87.5 ± 61.4	725.4 ± 408.5	<0.0001
Serum creatinine (mg/dL)	1.05 ± 0.50	1.09 ± 0.33	1.65 ± 1.25	<0.0001
eGFR (mL/min/1.73m^2)	69.8 ± 15.9	67.0 ± 17.9	53.2 ± 23.2	<0.0001
CKD stage				<0.0001
Stage 1 or 2	1863 (71.8)	538 (63.3)	86 (37.4)	
Stages 3–5	732 (28.2)	312 (36.7)	144 (62.6)	

[a]ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

Table 4. Factors associated with the presence of micro-/macroalbuminuria[a]

Factor	OR (95% CI)	P-value
Age (years)	0.99 (0.98–1.00)	0.0309
Sex (male versus female)	1.31 (1.11–1.54)	0.0024
Duration of diabetes (years)	1.04 (1.02–1.05)	<0.0001
Duration of hypertension (years)	1.00 (0.98–1.01)	0.5407
Diabetic complications (yes versus no)	1.54 (1.29–1.85)	<0.0001
Systolic BP (mmHg)	1.02 (1.01–1.03)	<0.0001
Diastolic BP (mmHg)	1.01 (1.00–1.02)	0.7344
Usage of ARB or ACEi (yes versus no)	0.99 (0.82–1.19)	0.2634
Usage of CCB (yes versus no)	1.27 (1.08–1.50)	0.0039
HbA1C (%)	1.34 (1.26–1.41)	<0.0001
eGFR (mL/min/1.73m^2)	0.98 (0.97–0.98)	<0.0001

[a]ARB, angiotensin receptor blocker; ACEi, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker.

0.94–0.98, P < 0.0001), male sex (OR = 0.61, 95% CI = 0.43–0.84, P = 0.0033), systolic BP (OR = 1.02, 95% CI = 1.01–1.04, P < 0.0001), HbA1C (OR = 1.13, 95% CI = 1.02–1.25, P = 0.0191) and eGFR (OR = 0.96, 95% CI = 0.95–0.97, P < 0.0001) were significantly associated with the presence of macroalbuminuria.

Factors associated with RI

Pearson's correlation analysis revealed that age ($R = -0.32$, P < 0.0001), the duration of diabetes ($R = -0.20$, P < 0.0001), the duration of hypertension ($R = -0.17$, P < 0.0001) and the natural logarithmic values of urinary ACR ($R = -0.25$, P < 0.0001) correlated significantly with the values of eGFR.

On the other hand, when the patients were divided into two groups based on eGFR by the MDRD formula: Group 1 consisted of patients with CKD of Stage 1 or 2, Group 2 was patients with RI, the mean age and the proportion of female were significantly higher in patients with RI. The duration of diabetes and hypertension was significantly longer, diastolic BP was significantly lower and patients with controlled hypertension were significantly more prevalent in the RI group. HbA1C levels and urinary ACR were significantly higher, and the proportion of patients with micro- or macroalbuminuria was significantly higher in Group 2 patients (Table 5).

Multivariate logistic regression analysis revealed that age (OR = 1.07, 95% CI = 1.06–1.08, P < 0.0001), female sex (OR = 0.34, 95% CI = 0.27–0.43, P < 0.0001), the duration of diabetes (OR = 1.03, 95% CI = 1.01–1.04, P = 0.0012), the presence of diabetic complications (OR = 1.37, 95% CI = 1.13–1.66, P = 0.0116) and urinary ACR (OR = 1.00, 95% CI = 1.00–1.00, P < 0.0001) were significant independent risk factors for RI (Table 6).

Discussion

The Korean Epidemiology Study on Hypertension III (KEY III study), which included the largest number of only hypertensive T2DM patients managed by primary care physicians in a single nation, was designed to explore the prevalence of diabetic nephropathy and to identify the independent factors associated with diabetic nephropathy in these patients. The results of this study reveal that a significant proportion of T2DM patients with hypertension

Table 5. Comparison between patients without and with RI based on eGFR[a]

	RI (−) ($N = 2510$)	RI (+) ($N = 1188$)	P-value
Age	59.7 ± 10.5	66.8 ± 9.6	<0.0001
Sex			<0.0001
Male	1321 (52.6)	347 (29.2)	
Female	1189 (47.4)	841 (70.8)	
Body mass index (kg/m^2)	24.8 ± 3.2	24.7 ± 3.2	0.3900
Duration of diabetes (years)	6.3 ± 5.3	8.6 ± 6.8	<0.0001
Duration of hypertension (years)	7.1 ± 5.6	9.0 ± 6.6	<0.0001
Diabetic complications	508 (20.3)	384 (32.4)	<0.0001
Systolic BP (mmHg)	130.5 ± 13.1	130.5 ± 14.4	0.9185
Diastolic BP (mmHg)	79.0 ± 8.9	76.9 ± 9.4	<0.0001
Antihypertensive drugs			
ARB or ACEi	1904 (75.9)	918 (77.3)	0.4845
CCB	1167 (46.5)	554 (46.6)	0.9369
Beta blocker	245 (9.8)	170 (14.3)	<0.0001
Diuretics	1070 (42.6)	524 (44.1)	0.0280
Others	126 (5.0)	77 (6.5)	0.0684
BP control			0.0456
Controlled	761 (30.3)	399 (33.6)	
Uncontrolled	1749 (69.7)	789 (66.4)	
HbA1C (%)	7.04 ± 1.31	7.21 ± 1.45	0.0007
Urinary ACR (mg/g)	50.5 ± 142.5	126.2 ± 283.0	<0.0001
Serum creatinine (mg/dL)	0.95 ± 0.15	1.41 ± 0.92	<0.0001
Albuminuria			<0.0001
Normoalbuminuria	1863 (74.9)	721 (61.4)	
Microalbuminuria	538 (21.6)	309 (26.3)	
Macroalbuminuria	86 (3.5)	144 (12.3)	

[a]ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

Table 6. Factors associated with the presence of RI

Factors	OR (95% CI)	P-value
Age (years)	1.07 (1.06–1.08)	<0.0001
Sex (male versus female)	0.34 (0.27–0.43)	<0.0001
Duration of diabetes (years)	1.03 (1.01–1.04)	0.0012
Duration of hypertension (years)	1.00 (0.98–1.01)	0.3838
Diabetic complications (yes versus no)	1.37 (1.13–1.66)	0.0116
Diastolic BP (mmHg)	0.99 (0.99–1.01)	0.2763
Usage of beta blocker (yes versus no)	1.50 (1.17–1.92)	0.0047
Usage of diuretics (yes versus no)	1.06 (0.90–1.24)	0.2646
HbA1C (%)	1.04 (0.97–1.10)	0.4197
Urinary ACR (mg/g)	1.00 (1.00–1.00)	<0.0001

(~30%) had albuminuria (micro or macro) and/or RI. In addition, the duration of diabetes, systolic BP, HbA1C and the presence of RI were significant independent factors associated with the presence of albuminuria, while age, the duration of diabetes and urinary ACR were significant independent risk factors for RI.

Microalbuminuria is not only the earliest manifestation of diabetic nephropathy but is also a significant risk factor for the progression of nephropathy in diabetic patients [20]. Accumulating evidence has also shown that microalbuminuria is closely associated with cardiovascular morbidity or mortality in patients with diabetes [9, 10]. In addition, reduction of urinary albumin excretion by using inhibitors of the renin-angiotensin system improves the course of diabetic nephropathy as well as cardiovascular risks in diabetic patients [21, 22]. Therefore, early detection and aggressive management of microalbuminuria is vitally important in diabetic patients. In the same context, the American Diabetes Association recommends annual screening for microalbuminuria in patients with diabetes [17]. However, since microalbuminuria is asymptomatic and determination of urinary ACR is not invariably performed in primary care clinics in many countries, including Korea, the prevalence of nephropathy in diabetic patients cared by primary care physicians may be actually higher than recognized by patients or doctors. In the present study, diabetic nephropathy as diagnosed by physician or known by patient was only 6.1%, but micro- or macroalbuminuria were actually present in 850 patients (23.1%) and 230 patients (6.3%), respectively. Bramlage *et al.* [23] also observed a great discordance between the proportion of patients with nephropathy diagnosed by physician and by laboratory results. Even though only 7.3% of 39025 primary care attendees had nephropathy as diagnosed by the physician, dipstick test revealed microalbuminuria in 7416 patients (19.0%). Moreover, among diabetic patients, the proportion of patients with microalbuminuria increased to 33.6%. Based on these findings, a significantly large number of diabetic patients seem to be underdiagnosed and undertreated by primary care physicians in many countries and therefore, an intensive education of patients as well as general practitioners on microalbuminuria is mandatory to detect patients at higher cardiovascular risk early and to aggressively treat microalbuminuria, one of the modifiable risk factors in diabetic patients. On the other hand, most of the previous studies including a large number of patients used semiquantitative dipstick such as Micral-Test II® (Boehringer Mannheim, Mannheim, Germany), Clinitek 50® (Bayer Diagnostic Manufacturing Ltd, Bridgend, UK) or Multistix® 10SG (Bayer Diagnostic Manufacturing Ltd) for screening of microalbuminuria [23–26]. Even

though the sensitivity and specificity of these strips have been reported to be relatively high [27], they are less accurate compared to direct measurement of urinary albumin and creatinine concentrations. In this study, therefore, we directly determined urinary albumin and creatinine concentrations to precisely classify >3600 patients into normo-, micro- or macroalbuminuric patients based on the results of urinary ACR. Nevertheless, there is a possibility that a few patients may be classified into an incorrect group. According to the guidelines, the diagnosis of micro- and macroalbuminuria should be made based on the results of three urine specimens collected within a 6-month period. However, since collection of three random urine samples from the same patients in nationwide primary care clinics was not easy to perform, a single morning urine sample was used to determine urinary ACR in the present study. Instead, we tried to exclude patients with a potential to have elevated urinary ACR, such as pregnant patients, patients with febrile illness or urinary tract infection or patients who performed excessive exercise within 24 h.

Surprisingly, the proportion of patients with RI was significantly higher than that observed by physicians or patients. Among 3712 patients, 1193 (32.1%) were patients with CKD of more than Stage 3. Two recent studies also revealed high incidence of RI in Asian T2DM patients attending primary care clinics [28, 29]. Pan *et al.* [28] found that 23% of 2841 primary care patients with T2DM had RI and Yokoyama *et al.* [29] observed that the proportion of primary care T2DM with RI was 15.3%. Compared to these two studies, the incidence of renal failure in this study was somewhat higher, which may be attributed to the presence of concomitant hypertension. Hypertension was accompanied in 52.0 and 48.4% in the studies by Pan *et al.* [28] and Yokoyama *et al.* [29], respectively, while all subjects of our study were hypertensive T2DM patients. Taken together, a significant proportion of T2DM patients in primary care settings, regardless of the presence of hypertension, have RI without patients' or doctors' recognition, necessitating close monitoring of the patients' serum creatinine by their primary care physicians.

Hypertension *per se* is associated with higher risk of cardiovascular and renal diseases [2, 30]. The incidence of microalbuminuria is also found to be higher in hypertensive patients, even in nondiabetic patients [11]. The results of the study by Bramlage *et al.* [23] demonstrated that even though the frequency rates of microalbuminuria were comparable among nondiabetic patients with a BP <120/70, 120/70–130/80 and 130/80–140/90 mmHg, the rates were increased in cases with BP >140/90 mmHg. In contrast, the increase in BP was closely related to an increase in the incidence of microalbuminuria in T2DM patients over the whole range of BP categories. A recent Hong Kong study on 492 hypertensive T2DM patients also showed that the magnitude of systolic BP was one of the predictive factors for the presence of microalbuminuria [31]. On the other hand, MicroAlbuminuria Prevalence Study (MAPS), the first large multicenter epidemiological study in Asia to determine the prevalence of microalbuminuria and macroalbuminuria in 6801 patients with hypertension and T2DM, revealed that the duration of hypertension was associated with the degree of albuminuria on univariate analysis [25]. In the present study, we also found that systolic BP correlated significantly with urinary ACR and was a significant independent factor associated with the presence of albuminuria, which was in concordance with most of the previous reports.

Based upon the concept that BP is an important risk factor for microalbuminuria and macroalbuminuria, especially in diabetic patients, treatment of hypertension is imperative in terms of reducing renal and cardiovascular risks and should be executed as early as possible. Nevertheless, BP control is largely unsatisfactory in the general population and is even lower in patients with diabetes and CKD. The Hypertension and Diabetes Risk Screening and Awareness study, which assessed the prevalence as well as characteristics, comorbidities and management issues of hypertension in 45125 primary care attendees in Germany, demonstrated that BP control rates were only 18.7% [32]. The data from the US National Health and Nutrition Examination Survey revealed that the rate of BP control in hypertensive patients was also low, 29.2% in 1999–2000 and 36.8% in 2003–2004 [15]. In contrast, a recent Korean Epidemiology Study on Hypertension (KEY study) showed that BP was controlled in 51.0% of hypertensive patients treated in primary care clinics [16]. The reason for the divergence of the rates of BP control may be due to the difference in the characteristics of patients, such as the presence of diabetes and obesity, and the ethnicity included in each study. On the other hand, the BP control rates in diabetic patients are reported considerably low in many studies. The Developing Education on Microalbuminuria for Awareness of Renal and Cardiovascular risk in Diabetes (DEMAND) study, a cross-sectional clinic/medical center-based study on T2DM patients in 33 countries, demonstrated that 81.0% had systolic BP ≥130 mmHg and/or diastolic BP ≥80 mmHg [26]. In addition, the results of the MAPS and KEY study also revealed that BP was controlled only in 11.6% of Asian and 21.6% of Korean hypertensive T2DM patients, respectively [16, 25]. These low control rates of BP in diabetic patients is not surprising because the target BP is lower and the response to antihypertensive medications is worse in diabetic versus nondiabetic patients [33]. In this study, however, the proportion of patients with controlled BP (31.4%) was relatively higher compared to those of the previous studies, which could be attributed to the possibility that since the majority of primary care physicians, who participated in the KEY study, was invited to this KEY III study, they might treat hypertension in diabetic patients more aggressively after the knowledge of the results of KEY study.

Numerous studies have tried to identify the independent risk factors for RI as well as micro- and/or macroalbuminuria in primary care T2DM attendees with or without hypertension. In summary advanced age [12, 25, 31], male sex [25, 29, 31], high body mass index [25, 29], long duration of diabetes [25, 26], the presence of diabetic complications [12, 25, 26, 29], high systolic and diastolic BP [12, 25, 26, 31], poor diabetes control [12, 26, 29], presence of RI [26, 29] and current smoking status [26] have been reported as independent risk factors for micro- and/or macroalbuminuria. In addition, one recent Japanese study

found that age, the duration of diabetes, HbA1C, hyperlipidemia, smoking and the presence of microalbuminuria were independently associated with RI in these patients [29]. In agreement with a number of previous studies, we also demonstrated that male sex, the duration of diabetes, the presence of diabetic complications, systolic BP, HbA1C and the presence of RI were independent risk factors for micro-/macroalbuminuria, while advanced age, female sex, the duration of diabetes, the presence of diabetic complications and urinary ACR were independently associated with RI. These findings support the well-known fact that strict BP and glucose control are mandatory to prevent the development of albuminuria even in hypertensive T2DM patients.

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