Association Between Remission of Macroalbuminuria and Preservation of Renal Function in Patients With Type 2 Diabetes With Overt Proteinuria

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OBJECTIVE—Studies on the rate of remission of macroalbuminuria in patients with type 2 diabetes mellitus (T2DM) and the effects of reduction in albuminuria on renal prognosis in a primary care setting are absolutely lacking.

RESEARCH DESIGN AND METHODS—A total of 211 T2DM patients with albuminuria ≥300 mg/g were enrolled in a prospective observational study (mean of 4.5 years). The incidence of patients with remission of macroalbuminuria at every 1-year study time point after starting intensified diabetes treatment and the factors associated with remission were evaluated. The association of reduction in albuminuria with renal events (doubling of serum creatinine and end-stage renal disease) was also investigated.

RESULTS—During the 5-year study period, remission to microalbuminuria occurred in 116 patients and the 5-year cumulative incidence was 58.3%. Notably, most cases (82.8%) obtained remission at the 1-year study time point. The remission rate increased with achieving therapeutic targets for blood pressure and blood glucose. Remission and reduction in albuminuria of ≥50% were associated with preservation of renal function. In particular, patients who obtained both remission and 50% reduction at the 1-year study time point exhibited a significantly reduced risk for renal events as compared with those with no remission and no reduction (adjusted hazard ratio 0.30 [95% CI 0.12–0.76]).

CONCLUSIONS—Remission of macroalbuminuria occurs frequently and is associated with the preservation of renal function in T2DM patients. The initial adequate diabetes treatment aimed at reducing albuminuria may lead to improved renal prognosis in the primary care setting.

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Diabetic nephropathy in patients with type 2 diabetes mellitus (T2DM) is a leading cause of end-stage renal disease (ESRD) all over the world (1). The typical progressive course of diabetic nephropathy is initially developing an increase in albuminuria (known as microalbuminuria), progressing to macroalbuminuria, and, thereafter, a rapid decline in renal function (1). A few decades ago, diabetic nephropathy was considered to be a progressive and irreversible chronic complication. Moreover, the progression of macroalbuminuria was considered the "point of no return." Thus, the main therapeutic target for T2DM patients with macroalbuminuria was the prevention of the progression to ESRD. Recently, growing evidence has contradicted this point of no return concept. Several clinical studies have reported that intensive intervention including inhibition of the renin-angiotensin system could induce a reduction in macroalbuminuria and improve renal prognosis (2–7). Thus, reduction of macroalbuminuria could be considered an important therapeutic target to improve renal outcomes in diabetic patients. However, how often remission from macroalbuminuria to microalbuminuria or normoalbuminuria occurs and its effect on the deterioration of renal function of T2DM patients remain unclear. In particular, there is almost no evidence from a primary care setting. Actually, in the clinical practice, we often encounter patients with T2DM that has already been complicated by macroalbuminuria at the time when they first consulted the hospital because they were unaware that they were suffering from diabetes. Moreover, a considerable number of T2DM patients progress to advanced nephropathy because of long-standing poor diabetes control. These patients must be at high risk for the progression to ESRD. However, it remains unclear whether their renal prognosis can be improved by later intensified diabetes treatment in primary care practice.

Thus, the aim of this study was to clarify the clinical characteristics of T2DM patients who showed a reduction in macroalbuminuria in the primary care practice and to estimate the rate of reduction in macroalbuminuria and its effect on renal function. In particular, we focused on T2DM patients with macroalbuminuria who had not been treated for diabetes or had not received adequate intensified diabetes treatment according to clinical recommendations before they first consulted the clinic.

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RESEARCH DESIGN AND METHODS

Study population

This 5-year prospective observational cohort study was performed in a primary care setting to investigate the potential probability of reduction in albuminuria, i.e., remission from macroalbuminuria to microalbuminuria and a decrease in albuminuria ≥50%, to explore the factors associated with the reduction and to assess the effect of reduction on renal prognosis. Subjects were recruited consecutively from Japanese patients with T2DM who were new patients at an outpatient clinic of Jiyugaoka Internal Medicine from 2002 to 2008 (n = 2,500) and met the following criteria at the first visit: macroalbuminuria (urinary albumin-to-creatinine ratio [ACR] >300 mg/g creatinine (Cr) in a random spot urine) and estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2. Those included had not been treated for diabetes or had not received adequate intensive diabetes treatment. Namely, patients visited the clinic with or without referral letters and with or without prior treatment histories. Patients with known nondiabetic kidney disease were excluded. At the first visit, the medical team, composed of medical doctors, nurses, and dietitians in the clinic, assessed patients' diabetic condition and immediately started adequate diabetes care for them according to the clinical practice recommendations for diabetes treatment. Thereafter, patients attended the clinic every month and received appropriate diabetes care and education, which was intended to maintain glycosylated hemoglobin A_{1c} (HbA_{1c}) values <7.0% (53 mmol/mol), blood pressure (BP) <130/80 mmHg, serum concentrations of total cholesterol <5.2 mmol/L (200 mg/dL), triglycerides <1.7 mmol/L (150 mg/dL), HDL cholesterol >1.0 mmol/L (40 mg/dL), and BMI 20–24 kg/m^2, as recommended by the Japan Diabetes Society (JDS) guidelines. In this study, patients who continuously received diabetes care at the clinic for >1 year were included. The study was approved by the local ethics committee and was carried out in accordance with the Declaration of Helsinki II.

Measurements and definition

T2DM was defined according to the JDS criteria (8). BP was measured in the sitting position after taking a rest of >5 min. Nonfasting blood samples and random urine samples were obtained from each patient. HbA_{1c} was measured by high-performance liquid chromatography, which was certified by the American National Glycohemoglobin Standardization Program. Serum and urinary concentrations of Cr were measured by an enzymatic method with an isotope-dilution mass spectrometry traceable calibrator (N-assay L Creatinine Kit; Nittoubo Medical Co., Tokyo, Japan). The measurement of serum Cr was performed every 4 months to obtain the eGFR. The eGFR was calculated using the following equation proposed by the Japanese Society of Nephrology: eGFR (mL/min/1.73 m^2) = $194 \times (\text{age [years]})^{-0.287} \times (\text{serum Cr [mg/dL]})^{-1.094} \times 0.739$ (if female) (9). The new Japanese equation is reasonably accurate in estimating GFR for Japanese populations and is more accurate than the modified Modification of Diet in Renal Disease equation refitted for Japanese by overcoming the underestimation of GFR at high values up to 110 mL/min/1.73 m^2 (9). Diabetic retinopathy was diagnosed after pupillary dilation by ophthalmologists. Neuropathy was diagnosed in patients with two or more of three components: the presence of symptoms, the absence of ankle tendon reflexes, and abnormal scores of the vibration perception threshold using a C128 tuning fork, where bilateral spontaneous pain, hypoesthesia, or paresthesia of the legs was considered a neuropathic symptom. The history of cardiovascular disease (CVD) included ischemic heart disease, ischemic cerebrovascular stroke, and peripheral artery disease.

The urinary albumin excretion was assessed by using ACR in random spot urine samples when the subject did not have any urinary tract infections and menstruation. Urinary albumin was measured by a turbidimetric immunoassay. To determine the baseline ACR, a single measurement before starting diabetes treatment was used. Three collections of ACR prior to the intensive treatment were theoretically ideal. However, this was difficult to achieve, since treatments for blood glucose and BP were started immediately based on the patient's intentions, and the inconvenience to patients of repeatedly bringing urine samples should

Table 1—*Baseline characteristics of T2DM subjects with ACR ≥300 mg/g Cr and eGFR ≥30 mL/min/1.73 m^2*

Characteristic	Total group (N = 211)
Male/female	149/62
Age (years)	60 ± 12
Known duration of diabetes (years)	11 ± 11
BMI (kg/m^2)	26.7 ± 5.1
Smoking (%)	46
Blood glucose control	
Diet/oral agents/insulin (%)	36/42/22
HbA_{1c} (%)	9.17 ± 2.11
HbA_{1c} (mmol/mol)	77 ± 18
BP control	
Taking antihypertensive drugs (%)	47
Taking RASI (%)	27
Systolic BP (mmHg)	147 ± 21
Diastolic BP (mmHg)	80 ± 14
Lipid control	
Taking lipid-lowering drugs (%)	23
Total cholesterol (mg/dL)	214 ± 48
HDL cholesterol (mg/dL)	53 ± 14
Triglycerides (mg/dL)	165 (111–250)
ACR (mg/g Cr)	815.8 (462.9–1,529.7)
eGFR (mL/min/1.73 m^2)	71.9 ± 24.9
≥60/30–59 (%)	66/34
Diabetic retinopathy (%)	62
Diabetic neuropathy (%)	65
CVD (%)	21

Data are mean ± SD or median (IQR). RASI, renin-angiotensin system inhibitor.

be avoided to enhance the adherence to treatments.

Follow-up and evaluations

After 1 year of treatment, ACR was measured three times a year. At each year based on the three samples, the stage of nephropathy was defined as normoalbuminuria, microalbuminuria, or macroalbuminuria, corresponding to ACR <30 mg/g Cr, 30≤ ACR <300 mg/g Cr, or ACR ≥300 mg/g Cr, respectively, in at least two of three samples. The geometric mean from three samples was used as a continuous variable. Changes in stages of nephropathy were defined as follows.

Remission. Remission was defined as stage of albuminuria, determined each year, improved from macroalbuminuria to micro/normoalbuminuria at least once.

Relapse. Relapse was defined as the worsening of the albuminuria stage from microalbuminuria to macroalbuminuria.

Subjects were followed until the end of observation or onset of ESRD. The main evaluation of this study was to estimate the rate of remission of macroalbuminuria to ACR <300 mg/g Cr and the reduction in ACR of ≥50% from the baseline. The second evaluation was to investigate the association between reduction in albuminuria and development of renal events, i.e., doubling of serum Cr or onset of ESRD. The decline in renal function estimated by the GFR slope was also compared between those with and without remission and reduction in albuminuria. This study was also designed to explore the effect of intensive diabetes treatment on the subsequent reduction in ACR. The levels of blood glucose control, BP control, and lipid profiles at the 1-year time point after starting intensified diabetes treatment were used because these variables almost persisted throughout the whole follow-up period.

Statistical analysis

Data are expressed as mean ± SD or median (interquartile range [IQR]). For comparisons between two groups, the unpaired Student *t* test was used for normally distributed variables and the Mann-Whitney *U* test for variables with skewed distribution. Statistical significance of the differences for categorical variables between the groups was determined by χ^2 test. For each subject, a linear regression model of time on GFR (least-squares method) was created, and the slope of the regression line was used to estimate the subject's change in GFR over time. Then, the GFR slope was expressed as percent per year by dividing the slope by the baseline GFR value. Cumulative incidence of remission to ACR <300 mg/g Cr and to ACR <30 mg/g Cr was calculated using life-table analysis. Logistic regression analysis was used to compute odds ratio (OR) and 95% CI to assess the effect of blood glucose and BP controls on remission of macroalbuminuria. Since remission of macroalbuminuria is a categorical analysis, we concomitantly used changes in ACR from the baseline to follow-up as a continuous analysis to compensate for the inherent problem associated with the categorical analysis. Cox proportional hazards analysis was used to compute the hazard ratio and 95% CI to assess the effect of obtaining remission and/or the reduction in ACR of ≥50% at the 1-year study time point on the renal events of doubling serum Cr or onset of ESRD after adjustment for baseline considerable variables. Age, sex, smoking, BMI, systolic BP, HbA_{1c}, HDL cholesterol, triglycerides, albuminuria, eGFR, retinopathy, and prevalent CVD were included in the multivariate model as baseline clinical variables. A *P* value <5% (two tailed) was considered significant. All analyses were performed with the statistical software package SPSS (SPSS Japan, Tokyo, Japan).

RESULTS—Baseline characteristics of the subjects are shown in Table 1. About half of the subjects had previously been treated with antidiabetic and/or antihypertensive drugs, but their blood glucose and BP control were insufficient. Diabetic retinopathy and/or neuropathy were present in 165 (78%) patients. During a mean of 4.5 years follow-up (median 4.2 years [IQR 2.4–5.8]) after the initiation of intensive diabetes treatment, 116 patients (55%) obtained remission to ACR <300 mg/g Cr, including 28 patients (13%) with ACR <30 mg/g Cr (Table 2). Most of the cases obtained the remission to ACR <300 mg/g Cr at the 1-year study time point after starting the intensive treatment. The 5-year cumulative incidences of remission to ACR <300 mg/g Cr and <30 mg/g Cr were 58.3 and 18.5%, respectively.

The clinical characteristics of the study groups stratified by remission of macroalbuminuria (categorical analysis) or of those stratified by a reduction in ACR of ≥50% (continuous analysis) are shown in Table 3. Both comparisons indicated significantly higher proportions of female sex and nonsmoking in the albuminuria reduction groups. Baseline values of ACR were not different between the two study groups in continuous analysis, whereas these were significantly lower in the albuminuria reduction groups in categorical analysis. Otherwise, no major differences were found with respect to baseline characteristics among the groups. At 1 year, patients with remission or albuminuria reduction of ≥50% had lower

Table 2—*Number of patients who obtained remission to ACR <300 mg/g Cr or <30 mg/g Cr and the cumulative incidence at each 1-year study time point*

	1-year period	2-year period	3-year period	4-year period	5-year period
Number being followed, *n*	211	191	156	127	95
Remission to ACR <300 mg/g Cr					
Number of new cases, *n*	96	13	5	1	1
Total number of patients, *n* (%)	96 (45.5)	88 (46.1)	60 (38.5)	55 (43.1)	46 (48.4)
Cumulative incidence, % (SE)	44.1 (3.4)	51.8 (3.5)	55.1 (3.6)	56.0 (3.6)	58.3 (3.8)
Remission to ACR <30 mg/g Cr					
Number of new cases, *n*	7	7	0	9	5
Total number of patients, *n* (%)	7 (3.3)	11 (5.8)	1 (0.6)	15 (11.8)	12 (12.6)
Cumulative incidence, % (SE)	3.3 (1.2)	7.0 (1.8)	7.0 (1.8)	14.1 (2.8)	18.5 (3.4)

Table 3—*Clinical data at baseline, at 1 year, and in the whole period of follow-up, which were compared among groups with or without remission to microalbuminuria and normoalbuminuria (categorical analysis) and between those with albuminuria reduction of ≥50% from the baseline and those without (continuous analysis)*

	Albuminuria remission (categorical analysis)			Albuminuria reduction, % (continuous analysis)	
	Persistent Mac, *n* = 95	With remission to Mic, *n* = 88	With remission to Nor, *n* = 28	<50%, *n* = 106	≥50%, *n* = 105
At baseline					
Age (years)	59 ± 13	61 ± 12	59 ± 13	60 ± 13	60 ± 12
Duration (years)	12 ± 13	10 ± 10	9 ± 8	12 ± 13	10 ± 10
Male (%)	81	66	50[b]	83	58[c]
BMI (kg/m^2)	26.6 ± 4.9	26.4 ± 4.6	28.3 ± 6.9	26.5 ± 4.5	26.9 ± 5.7
Current smoking (%)	53	34	42[a]	54	37[a]
Blood glucose control					
Diet/tablet/insulin (%)	32/42/26	42/40/18	39/46/15	35/41/24	39/43/18
HbA_{1c} (%)	9.15 ± 2.26	9.12 ± 2.01	9.42 ± 1.94	9.14 ± 2.20	9.20 ± 2.02
HbA_{1c} (mmol/mol)	76 ± 19	76 ± 17	79 ± 16	76 ± 19	77 ± 17
BP control					
Taking antihypertensive drugs (%)	56	39	50	47	49
Taking RASI (%)	37	20	23[a]	32	24
Systolic BP (mmHg)	150 ± 23	143 ± 19	151 ± 23[a]	146 ± 20	148 ± 23
Diastolic BP (mmHg)	80 ± 15	79 ± 12	85 ± 14	79 ± 13	81 ± 14
Lipid control					
Taking lipid-lowering drugs (%)	20	23	31	18	28
Total cholesterol (mg/dL)	213 ± 55	213 ± 41	220 ± 49	212 ± 52	216 ± 44
HDL cholesterol (mg/dL)	50 ± 12	55 ± 16	55 ± 16	51 ± 13	55 ± 15
Triglycerides (mg/dL)[e]	167 (123–253)	161 (105–248)	168 (93–237)	164 (120–253)	169 (95–244)
eGFR (mL/min/1.73 m^2)	66.4 ± 23.4	76.8 ± 26.2	74.9 ± 22.5[a]	70.2 ± 25.1	73.6 ± 24.8
ACR (mg/g Cr)[e]	1,445.0 (757.9–2,561.5)	580.1 (411.0–1,005.7)	467.2 (342.1–666.5)[d]	968.2 (507.4–1,944.1)	649.6 (449.9–1,272.8)
Diabetic retinopathy (%)	54	33	42[a]	45	42
CVD (%)	21	23	8	24	17
At 1 year					
Blood glucose control					
Diet/tablet/insulin (%)	6/52/42	7/62/31	12/50/38	5/57/38	10/55/35
HbA_{1c} (%)	7.70 ± 1.43	7.41 ± 1.14	7.25 ± 1.22	7.74 ± 1.45	7.30 ± 1.07[a]
HbA_{1c} (mmol/mol)	61 ± 11	57 ± 9	56 ± 9	61 ± 11	56 ± 8
BP control					
Taking antihypertensive drugs (%)	93	82	92	91	86
Taking RASI (%)	79	69	81	75	75
Systolic BP (mmHg)	138 ± 14	130 ± 11	131 ± 12[c]	136 ± 13	132 ± 13
Diastolic BP (mmHg)	71 ± 11	68 ± 9	69 ± 7	71 ± 10	69 ± 9
Lipid control					
Taking lipid-lowering drugs (%)	27	26	50[a]	22	35[a]
Total cholesterol (mg/dL)	210 ± 48	201 ± 42	205 ± 49	206 ± 45	205 ± 47
HDL cholesterol (mg/dL)	50 ± 11	52 ± 15	54 ± 16	50 ± 11	53 ± 15

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Table 3—*Continued*

	Albuminuria remission (categorical analysis)			Albuminuria reduction, % (continuous analysis)	
	Persistent Mac, $n = 95$	With remission to Mic, $n = 88$	With remission to Nor, $n = 28$	<50%, $n = 106$	≥50%, $n = 105$
Triglycerides (mg/dL)[e]	165 (117–255)	155 (116–239)	133 (94–192)	165 (116–282)	150 (108–202)
eGFR (mL/min/1.73 m^2)	59.2 ± 23.8	68.3 ± 23.3	63.6 ± 22.8[a]	62.5 ± 24.6	64.8 ± 22.9
In the whole period of follow-up					
Total follow-up period (year)	4.1 ± 2.4	4.5 ± 2.1	6.3 ± 4.0[c]	4.3 ± 2.5	4.7 ± 2.8
GFR slope (%/year)	−10.3 ± 12.2	−4.8 ± 6.8	−3.4 ± 5.8[c]	−9.7 ± 11.4	−4.4 ± 7.3[d]
Doubling of serum Cr (%)	33	16	12[b]	33	12[c]
Progression to ESRD (%)	15	2	0[b]	15	0[c]
Final ACR (mg/g Cr)[e]	1,419.0 (754.8–3,276.0)	177.3 (100.5–285.1)	26.3 (17.1–67.8)[d]	1,287.5 (610.1–3,239.0)	122.2 (55.5–241.1)[d]
Mac/Mic/Nor (%)	100/0/0	24/76/0	11/31/58[d]	92/8/0	22/64/14[d]

The statistical analysis to compare the clinical data on the left (categorical analysis) was performed by one-way ANOVA and on the right (continuous analysis) was performed by Student *t* test or χ^2 test. Mac, macroalbuminuria; Mic, microalbuminuria; Nor, normoalbuminuria; RASI, renin-angiotensin system inhibitor. [a]$P < 0.05$. [b]$P < 0.01$. [c]$P < 0.001$. [d]$P < 0.0001$. [e]Median and IQR are given.

HbA_{1c} and systolic BP levels and a higher proportion taking lipid-lowering drugs. Both categorical and continuous analyses in the whole period of follow-up indicated a clearly beneficial effect of albuminuria reduction on GFR decline and the onset of doubling serum Cr or ESRD. The overall incidence of ESRD (per 1,000 person-years) was 13.6 (95% CI 7.3–23.2), and it was high in subjects with persistent macroalbuminuria (25.1 [13.4–42.5]) and in subjects with albuminuria reduction of <50% (35.4 [20.3–56.7]).

Among 116 subjects with remission to ACR <300 mg/g Cr, 67 (57.8%) patients remained in remission until the end of follow-up, with a follow-up time of 4.1 ± 2.2 years and a duration of remission of 3.5 ± 2.0 years, and 49 (42.2%) patients relapsed from remission, with a follow-up time of 5.8 ± 2.1 years and duration of remission of 3.4 ± 2.0 years. No differences were found with respect to clinical characteristics, including renal events between patients without and with relapse, except for the final ACR, with the median being significantly higher in patients with relapse (323.9 [IQR 111.3–574.6]) than in those without (102.0 [49.8–174.5], $P < 0.0001$).

The combined effects of systolic BP and HbA_{1c} on remission to ACR <300 mg/g Cr are presented in Table 4. Patients were stratified according to predefined target levels of systolic BP and HbA_{1c} at 1 year. The achievement of the systolic BP therapeutic target significantly increased the remission rate whether the HbA_{1c} target was achieved or not, and BP and blood glucose control increased the remission rate significantly. There was no interaction between BP and blood glucose control. Of interest, similar significant ORs were obtained when the analysis was confined to subjects with higher ACR or lower ACR divided by the median ACR (data not shown), and rates of remission were apparently lower in subjects with higher ACR than those with lower ACR (34.9 vs. 75.2%, $P < 0.0001$). Furthermore, the rates of patients obtaining remission to ACR <300 mg/g Cr according to quartiles of systolic BP at 1 year (≥142, 141–132, 131–124, and <124 mmHg) were 36, 46, 68, and 74%, respectively. According to quartiles of HbA_{1c} at 1 year (≥8.0, 7.9–7.3, 7.2–6.7, and <6.7%), the rates were 44, 50, 70, and 56%, respectively. If continuous data were used, the OR (95% CI) for remission to ACR <300 mg/g Cr associated with a 10-mmHg decline in systolic BP at 1 year

Table 4—*Rates and adjusted ORs for remission to ACR <300 mg/g Cr in subjects stratified by achievement of target levels of systolic BP and HbA_{1c} at 1 year after starting intensive diabetes treatment*

Systolic BP <130 at 1 year	No	No	Yes	Yes
HbA_{1c} <7.0% (53 mmol/mol) at 1 year	No	Yes	No	Yes
Rates of remission to ACR <300 mg/g	40.0%	48.9%	69.1%	77.4%
Adjusted OR				
Model 1	1.0	1.59 (0.75–3.38)	3.59 (1.69–7.63)	4.98 (1.88–13.18)
Model 2	1.0	1.27 (0.49–3.29)	3.46 (1.27–9.45)	8.29 (2.15–31.97)

ORs were analyzed by logistic regression analyses. Adjusted variables included age and sex for model 1 and age, sex, smoking, BMI, baseline values of systolic BP, HbA_{1c}, HDL cholesterol, triglycerides, albuminuria, eGFR, retinopathy, and prevalent CVD for model 2.

was 2.23 (1.48–3.36) ($P < 0.0001$) and with a reduction of 1% in HbA_{1c} was 1.41 (1.04–1.92) ($P = 0.03$) after adjustment for the baseline clinical covariates.

Finally, the association of the combined effect of remission of macroalbuminuria and reduction of ≥50% in albuminuria at the 1-year study time point with renal events (onset of doubling serum Cr and ESRD) was investigated. Percentages of the events (number of events/total number of patients) were 9.2 (8/87), 22.2 (2/9), 27.3 (6/22), and 29.0 (27/93) in groups with remission+/reduction+, remission+/reduction−, remission−/reduction+, and remission−/reduction−, respectively. As compared with those with no remission and no reduction, hazard ratios (95% CI) adjusted for baseline clinical covariates (Table 4, model 2) were 0.30 (0.12–0.76) with obtaining both remission and reduction and 0.79 (0.34–1.82) with obtaining either remission or reduction.

CONCLUSIONS—We found in this study that *1*) more than half of patients with macroalbuminuria obtained remission to microalbuminuria after the intensive diabetes treatment in a primary care setting, *2*) the rate of remission increased according to the achievement of therapeutic targets for BP and blood glucose, and *3*) the reduction in macroalbuminuria at the 1-year study time point after starting the intensive diabetes treatment was associated with the preservation of renal function. These results suggest that the progressive decline in renal function of T2DM with macroalbuminuria can be prevented by adequate diabetes treatment in a primary care setting. In particular, whether or not the reduction in macroalbuminuria can be achieved soon after starting the intensive diabetes treatment is quite important with respect to renal prognosis. Given that the risk for ESRD is directly and strongly related to the level of albuminuria (6), and that reductions in albuminuria are associated with reductions in the risk for ESRD (7), the beneficial effects of the results on such outcomes obtained in the primary care setting can be anticipated in the longer term.

This study showed that the 5-year cumulative incidence rates of remission from macroalbuminuria to microalbuminuria or normoalbuminuria were 58.3 or 18.5%. To date, a few clinical studies have reported the rate of remission from macroalbuminuria to microalbuminuria or normoalbuminuria in T2DM. The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study reported that 229 (57.1%) of 401 T2DM subjects with macroalbuminuria obtained remission to microalbuminuria ($n = 131$) or normoalbuminuria ($n = 98$) in 4.3 years (2). The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study also indicated that 101 (42.6%) of 237 patients with macroalbuminuria obtained remission over 4.7 years of observation (3). The JDDM study also reported that 39 (22.3%) of 136 patients obtained remission over 3.8 years of observation (10). Overall, these results clearly indicate that remission of macroalbuminuria in patients with T2DM is not rare and can be frequently achieved by the adequate diabetes treatment.

Notably, remission occurred at the 1-year study time point after starting the intensive treatment in 96 (82.8%) of 116 patients who obtained remission, and the reduction in albuminuria in response to the initial intensive treatment was valuable in terms of predicting renal prognosis. The high remission rate seen in the early course of treatment may be attributable to insufficient prior controls, or may reflect the preserved renal function at that time. On the other hand, a considerable number of patients did not show a reduction in macroalbuminuria. Male sex and smoking were also associated with unresponsiveness, which is consistent with previous studies indicating that these were risk factors for albuminuria progression and renal function loss in subjects with nephropathy (4,5,11). The unresponsiveness to the intensive treatment may be explained by the existence of irreversible structural alterations in the kidneys or genetic differences, which may be responsible for the variability in responses to treatment.

In terms of the effect on remission, lowering BP appeared to be stronger than lowering blood glucose in this study. This finding was in accordance with other studies (4,5). It was interesting that the OR for obtaining remission was similar between those with higher and lower albuminuria. This may indicate that there is no threshold of albuminuria that discriminates the response to the intensive diabetes treatment. The remission rate of 34.9% seen in subjects with higher albuminuria (>815.8 mg/g Cr), together with a report indicating that 26% (32/122) of patients showed a reduction in nephrotic range albuminuria after aggressive lowering of BP in type 1 diabetes (4), may support the commencing of intensive treatment, although the remission rate itself is low due to the severity of existing glomerular damage as reflected by high albuminuria. In addition, the higher proportion of lipid modification treatment observed in subjects with a reduction in albuminuria may indicate the pleiotropic effect of lipid-lowering drugs on albuminuria reduction (12), although differences in lipid profiles were not prominent between the groups.

We found that 42% of subjects who experienced remission experienced relapse. Only the final ACR was higher in subjects with relapse than those without relapse. Otherwise, no differences were found between the two. As reported in type 1 diabetes, 46% of subjects who obtained remission of macroalbuminuria experienced relapse (5), so this phenomenon of relapse is common. However, few studies have discussed it in detail until now. The implications of relapse should be considered carefully, and longer follow-up is required on this issue.

There are some limitations and strengths in this study. We should acknowledge that the single measurement of ACR at the baseline may have included patients with microalbuminuria because of the physiological variation in albuminuria, leading to an overestimation of remission rate from macroalbuminuria. However, data on albuminuria in each year after starting the intensive treatment were collected from multiple urine samples, and changes in albuminuria from the baseline level were analyzed in two ways: improvement in stage of diabetic nephropathy and percent albuminuria change from the baseline. A serious problem inherent in an observational cohort study is the reason for censoring. Some censored cases were due to the end of the observation period, but in ~30% of the subjects in our study, they were due to loss of follow-up. Loss of follow-up was likely due to moving to other cities/hospitals or discontinuation of treatment. Those due to nonattendance are likely to develop events, since medication noncompliance and clinic nonattendance are closely associated with development of complications (13). This "survival effect" may have yielded an overestimation of remission in this study. We believe that the present prospective observational cohort simply reflected real-world practice and is valuable and important.

In conclusion, this study showed that a reduction in macroalbuminuria of T2DM subjects frequently occurred and was associated with the preservation of renal function. This result expands the concept regarding the effect of remission of microalbuminuria to normoalbuminuria on the improvement of renal prognosis in patients with T2DM (14,15). Taken together, these results strongly suggest the importance of adequate initial intervention aimed at reducing albuminuria to improve renal prognosis in T2DM patients in primary care practice.

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H.Y. reviewed and edited the manuscript, participated in recruitment and clinical work, conducted the research study, and was primarily responsible for data collection, integrity, and analysis. S.-i.A., T.M., and M.H. reviewed and edited the manuscript and were primarily responsible for data collection, integrity, and analysis. J.H., S.O., D.Y., R.S., and H.Sh. participated in recruitment and clinical work, conducted the research study, contributed to the discussion of the data, and performed critical review of the manuscript. H.So. reviewed and edited the manuscript, participated in recruitment and clinical work, conducted the research study, contributed to the discussion of the data, and performed critical review of the manuscript. All authors contributed to writing the manuscript. H.Y. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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