

Development, Progression, and Regression of Microalbuminuria in Japanese Patients With Type 2 Diabetes Under Tight Glycemic and Blood Pressure Control

The Kashiwa Study

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OBJECTIVE — The goal of this study was to know the fate of albuminuria in Japanese patients with type 2 diabetes under tight blood pressure and glycemic control.

RESEARCH DESIGN AND METHODS — Patients having normoalbuminuria (urinary albumin excretion <30 mg/g creatinine, $n = 179$) or microalbuminuria (albumin excretion 30–299 mg/g creatinine, $n = 94$) at baseline have been followed up for 8 years: ratio of men to women was 160/113, the mean age was 58 years, pretreatment HbA_{1c} (A1C) was 8.8%, and blood pressure was 136/76 mmHg. A1C <6.5% and blood pressure <130/80 mmHg were targeted, and the A1C of $6.5 \pm 0.7\%$ (mean \pm SD) and blood pressure of $127 \pm 11/72 \pm 6$ mmHg have been maintained during the 8 years. Development of microalbuminuria or macroalbuminuria (albumin excretion ≥ 300 mg/g creatinine) in initially normoalbuminuric patients and progression to macroalbuminuria or regression to normoalbuminuria in initially microalbuminuric patients were assessed at year 8.

RESULTS — Development occurred in 27 (15%) of the normoalbuminuric patients and progression and regression in 16 (17%) and 20 (21%), respectively, of the microalbuminuric patients. Significant independent relationships existed between development and higher achieved mean systolic blood pressure (SBP) and regression and lower achieved mean SBP. In the patients with achieved mean SBP <120 mmHg, development was 3%, progression was 11%, and regression was 44% during 8 years. Prediction for nephropathy by blood pressure and glycemia alone was limited. Nevertheless, albumin excretion at year 8 was positively correlated with achieved mean SBP and baseline albuminuria.

CONCLUSIONS — Development and progression were low and regression was high with SBP of 120 mmHg, provided A1C was maintained at 6.5%.

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Abbreviations: DBP, diastolic blood pressure; JDS, Japan Diabetes Society; NGSP, National Glycohemoglobin Standardization Program; SBP, systolic blood pressure; UAE, urinary albumin excretion.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Diabetic nephropathy is now the leading cause of end-stage renal failure in Europe, the U.S., and Japan (1), and the establishment of an effective treatment strategy for diabetic nephropathy is of paramount importance. In particular, early intervention is hoped to bring about 1) the prevention of new development of nephropathy, 2) the prevention of progression of early-phase nephropathy, and 3) the regression of existing nephropathy (1–3). Urinary albumin excretion (UAE) is a marker of early-phase diabetic nephropathy (1–3), and the amount of UAE correlates with renal pathologic changes in both type 1 and type 2 diabetes (4). Accordingly, many studies have been performed with UAE as a marker of diabetic nephropathy (5–7). The development and progression of nephropathy were improved by glycemic and blood pressure controls as expected (5–8). Antihypertensive therapy and improved glycemic control were independent predictors of the regression from micro- to normoalbuminuria (8). In this study, we analyzed the fate of early-phase diabetic nephropathy as indexed by the change in UAE in Japanese patients with type 2 diabetes over an 8-year period. In particular, the relationship between blood pressure and the state of albuminuria was meticulously analyzed in comparison with the previously accumulated evidence (6–12).

RESEARCH DESIGN AND METHODS

— In this study, 273 patients with normoalbuminuria or microalbuminuria (see below for definition) who were not taking any medication at the initial visit were analyzed. The study was conducted at Kashiwa Hospital, a referral center in a city with ~330,000 residents. The data used were obtained from patients followed up for at least 8 years during 1994–2004. We made a diagnosis of type 2 diabetes according to the 1985 World Health Organization criteria (13).

Table 1—Baseline characteristics of the patients

Characteristic	All	Normoalbuminuric	Microalbuminuric	P*
n	273	179	94	
Men/women	160/113	104/75	56/38	0.92
Age (years)	58 ± 10	58 ± 10	59 ± 11	0.24
BMI (kg/m ²)	23.7 ± 3.3	23.5 ± 3.4	24.4 ± 3.6	0.03
FPG (mg/dl)†	169 ± 56	164 ± 53	178 ± 60	0.17
FIRI (μU/ml)†	7.7 ± 3.8	7.3 ± 3.5	8.3 ± 4.4	0.21
A1C (%)	8.8 ± 1.7	8.6 ± 1.5	9.2 ± 1.8	0.01
SCr (mg/dl)	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.17
Blood pressure (mmHg)				
SBP	136 ± 24	130 ± 21	147 ± 26	<0.001
DBP	76 ± 12	74 ± 12	79 ± 12	0.01
UAE (mg/g creatinine)	41 ± 54	13 ± 8	92 ± 65	<0.001
Use of antihypertensive drugs	50 (18%)	18 (10%)‡	32 (34%)§	<0.001

Data are means ± SD unless otherwise indicated. Conversion factors are 0.055 for fasting plasma glucose (FPG) (mg/dl to mmol/l), 6 for fasting serum immunoreactive insulin (FIRI) (μU/ml to pmol/l), and 88.4 for serum creatinine (SCr) (mg/dl to μmol/l). Conversion factor for the JDS A1C (the values shown here) to NGSP A1C is +0.4 up to 7.4% and +0.3 for 7.5–9.0% (17). *Comparison between normo- and microalbuminuric patients by Mann-Whitney *U* test (for numerical variables) and χ^2 test (for categorical variables). †FPG and FIRI were determined in 165 patients: the 55 and 110 in the normo- and microalbuminuric groups, respectively. ‡At year 8, 14 patients were taking Ca²⁺ channel blockers, 4 were taking ACE inhibitors, and 8 were taking angiotensin receptor blockers. §At year 8, 25 patients were taking Ca²⁺ channel blockers, 12 were taking ACE inhibitors, and 6 were taking angiotensin receptor blockers.

Many patients visited the medical facility several years after receiving a diagnosis of diabetes (14).

Normo-, micro-, and macroalbuminuria were defined as, respectively, UAE <30 mg/g creatinine, 30–299 mg/g creatinine, and ≥300 mg/g creatinine (2–4,15). Establishment of micro- or macroalbuminuria in the initially normoalbuminuric patients by year 8 was defined as development of albuminuria. Transition from microalbuminuria to macroalbuminuria and reversal from microalbuminuria to normoalbuminuria by year 8 were defined as progression and regression of microalbuminuria, respectively.

All patients were seen at the outpatient clinic once every 4–8 weeks. UAE was determined by random samples: samples were obtained twice 2 months apart at the initial visit, and the mean value of the two samples was used for the baseline classification of each patient. Thereafter, UAE was determined at least 3 times a year. Patients were asked to avoid intensive exercise shortly before urine sampling. Treatment was targeted to HbA_{1c} (A1C) <6.5% and blood pressure <130/80 mmHg. If A1C <6.5% was not achieved with recommendations of diet and exercise, oral hypoglycemic agents such as sulfonylureas, biguanides, α -glucosidase inhibitors, and/or thiazolidinediones were administered alone or in combination. The number of patients

receiving oral hypoglycemic agents at year 8 was 264 (97%). As antihypertensive agents, Ca²⁺ channel blockers, ACE inhibitors, angiotensin receptor blockers, α_1 -blockers, β -blockers, and/or diuretics were used alone or in combination. The number of patients taking antihypertensive agents at year 8 was 54 (20%). Nevertheless, blood pressure control was excellent as a group (see below), implying that the majority of the cohort consisted of patients without hypertension.

Plasma glucose, A1C, and blood pressure were determined at each visit. Yearly mean values for UAE, A1C, and blood pressure, calculated by using individual data obtained at each visit, were used as “the value of the respective year.” The mean value for the entire treatment period (years 1–8) was calculated by taking the mean of the value of the respective year. Plasma glucose was determined by the glucose oxidase method, A1C by high-performance liquid chromatography (with the standard provided by the Japan Diabetes Society [JDS], normal range 4.3–5.8%), urinary albumin by the immunoturbidimetric method, and serum immunoreactive insulin by enzyme-linked immunoassay. There is a significant difference between the JDS A1C and the National Glycohemoglobin Standardization Program (NGSP) A1C values (16): JDS A1C 6.5, 7.0, 7.5, 8.0, 8.5, and 9.0% in this study are equivalent

to NGSP A1C 6.9, 7.4, 7.8, 8.3, 8.8, and 9.3%, respectively.

Statistical analysis

The Mann-Whitney *U* test, Spearman's rank correlation, logistic regression analysis, multiple regression analysis, Wilcoxon's rank correlation, and the χ^2 test were used for statistical analysis as needed. *P* < 0.05 was considered significant.

RESULTS

The patients were middle-aged ethnic Japanese, with a male-to-female ratio of 160/113 (Table 1). Mean A1C was 8.8%, blood pressure was 136/76 mmHg, and BMI was 23.7 kg/m², which is a common value for Japanese patients with type 2 diabetes (5). Low BMI in this cohort at least partially accounts for the low rate of nephropathy. Waist-to-hip ratio was not determined. Of the patients, 179 (66%) were normoalbuminuric and 94 (34%) were microalbuminuric at the initial examination, and the data for the two groups are shown separately. Prediction for nephropathy by blood pressure and glycemia alone without information on the duration of diabetes, serum lipids, and history of smoking was limited; nevertheless, we obtained the following significant findings.

The baseline correlation between UAE and other clinical variables was examined by using Spearman's rank correlation. Baseline UAE (UAE₀) was significantly correlated with age (*P* = 0.04, ρ = 0.124), baseline A1C (A1C₀) (*P* < 0.001, ρ = 0.206), baseline systolic blood pressure (SBP₀) (*P* < 0.001, ρ = 0.361), and baseline diastolic blood pressure (DBP₀) (*P* = 0.003, ρ = 0.178). By using multiple regression analysis taking UAE₀ (log transformed) as a dependent variable and age, A1C₀, and SBP₀ as independent variables, A1C₀ (*P* = 0.001, standardized correlation coefficient = 0.181) and SBP₀ (*P* < 0.001, standardized correlation coefficient = 0.349) were independently correlated with UAE₀. Correlation was stronger and more significant for UAE₀ and SBP₀ than for UAE₀ and A1C₀.

Prevalence of development, progression, and regression

Low A1C (Fig. 1A) and blood pressure (Fig. 1B and C) were maintained as a group for 8 years: the achieved A1C was 6.5 ± 0.7% (mean ± SD) and blood pressure was 127 ± 11/72 ± 6 mmHg. Nevertheless, microalbuminuria (*n* = 26) and macroalbuminuria (*n* = 1) developed

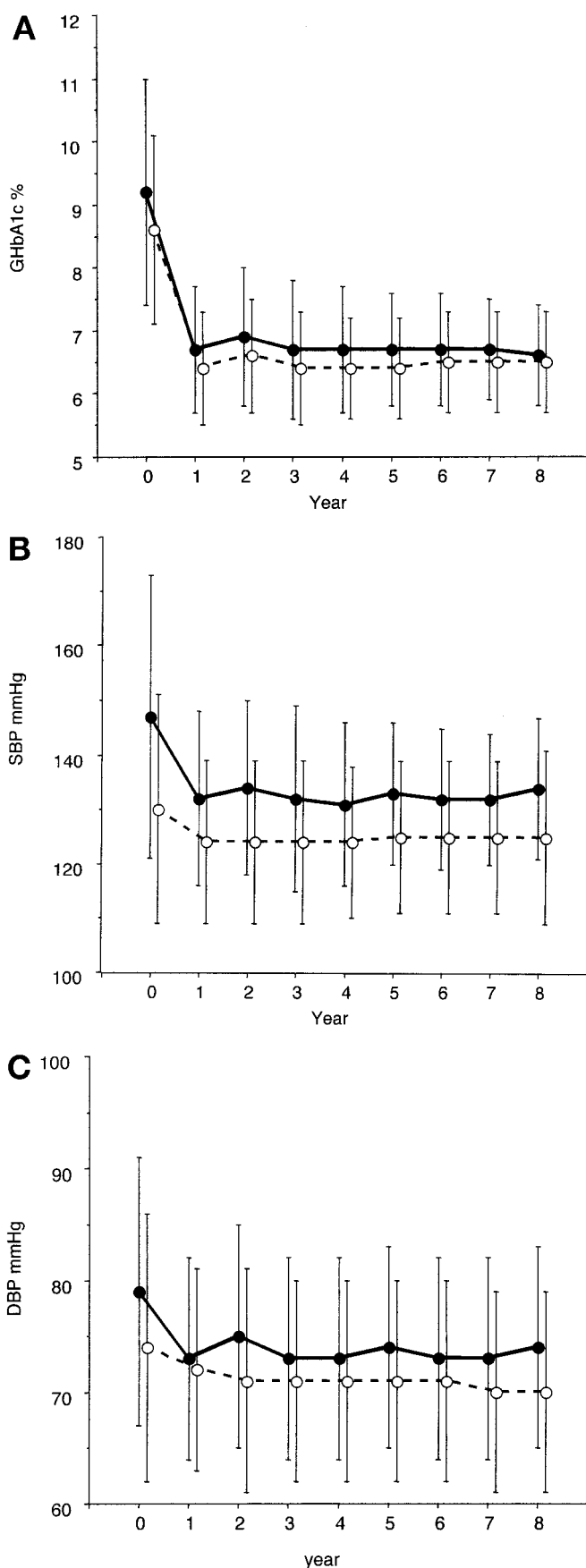


Figure 1—A1c (A), SBP (B), and DBP (C) before and during the treatment. ●, initially microalbuminuric patients; ○, initially normoalbuminuric patients. Data are means \pm SD.

newly in 179 initially normoalbuminuric patients (27 of 179 [15%]), and the incidence was clearly increasing at year 8 (Fig. 2A). UAE in the rest of the initially normoalbuminuric patients (152 of 179 [85%]) did not significantly increase during the observation period ($P = 0.36$, Wilcoxon's rank correlation).

The progression and regression took place in 16 (17%) and 20 (21%), respectively, of the 94 initially microalbuminuric patients. The incidence of the progression increased during the observation period. The incidence of the regression was greatest at years 3–5 and tended to decline thereafter (Fig. 2B). UAE in the rest of the initially microalbuminuric patients (58 of 94 [61%]) did not significantly increase during the observation period ($P = 0.52$, Wilcoxon's rank correlation).

Factors significantly related to development, progression, and regression

Univariate logistic regression analysis showed that higher UAE_0 , SBP_0 , DBP_0 , achieved mean SBP (SBP_{1-8}), achieved mean DBP (DBP_{1-8}), and the use of antihypertensive drugs were significantly related to development (Table 2). Other variables including $A1C_0$ and achieved mean A1C ($A1C_{1-8}$) were not significantly related to development. Multiple logistic regression analysis showed that only higher SBP_{1-8} was significantly related to development (Table 2). In the patients who experienced development, higher blood pressure than that in other patients had been present for 2 years before establishment of microalbuminuria.

Univariate logistic regression analysis showed that higher UAE_0 , baseline serum creatinine, and the use of antihypertensive drugs were significantly related to progression. However, UAE_0 was the only significant variable related to the progression by multivariate analysis (Table 2).

Univariate logistic regression showed that lower UAE_0 , SBP_{1-8} , and higher $A1C_0$ were significantly related to regression (Table 2). Multiple logistic regression analysis showed that lower UAE_0 , lower SBP_{1-8} , and higher $A1C_0$ were independently related to regression (Table 2). In the patients who experienced regression, lower blood pressure than that in others had been present for 1 year before restoration of normoalbuminuria. A significant relationship of higher, not lower, $A1C_0$ to regression may be due simply to the overall excellent glycemic control of this co-

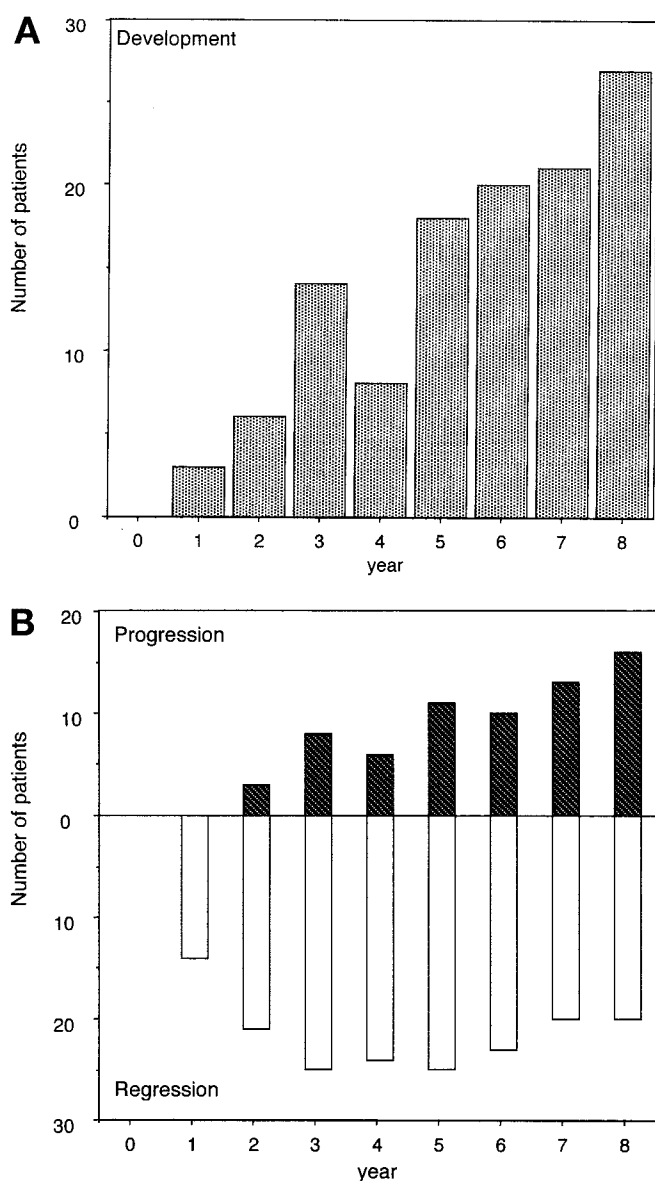


Figure 2—Cumulative number of patients who experienced development (A), progression (B, upper panel), and regression (B, lower panel) of nephropathy during treatment. Among 27 patients who developed nephropathy, development was confirmed by microalbuminuria in 26 and by macroalbuminuria in 1.

hort. A glycemic threshold for the development of microalbuminuria was reportedly A1C 8.1% (17).

By taking albuminuria as a continuous variable, rather than a categorical one, UAE_8 was positively correlated with SBP_{1-8} and UAE_0 (both $P < 0.001$ in the initially normoalbuminuric patients, and $P = 0.034$ and $P < 0.001$, respectively, in the initially microalbuminuric patients, by Spearman's rank correlation). However, UAE_8 and $A1C_0$ were significantly correlated in neither population.

The use of ACE inhibitors and/or angiotensin receptor blockers was not significantly related to outcome. There was a

slight but significant increase of BMI by year 8 in the initially normoalbuminuric patients ($23.5 \pm 3.4 \text{ kg/m}^2$ at baseline and $23.8 \pm 3.5 \text{ kg/m}^2$ at year 8, $P = 0.04$ by Wilcoxon's rank correlation) but not in the initially microalbuminuric patients ($24.4 \pm 3.6 \text{ kg/m}^2$ at baseline and $24.4 \pm 3.3 \text{ kg/m}^2$ at year 8, $P = 0.95$).

Threshold blood pressure and UAE values for development, progression, and regression

To identify the possible threshold SBP, the patients were divided into four groups based on decades of SBP_{1-8} : those with $SBP_{1-8} < 120$, 121–130, 131–140, and

$\geq 141 \text{ mmHg}$. Analysis based on UAE_0 quartiles was also performed in the initially microalbuminuric patients: UAE_0 in the first, second, third, and fourth quartiles was 30–41, 42–65, 66–130, and $\geq 131 \text{ mg/g}$ creatinine, respectively.

The development was more frequent with higher SBP_{1-8} : 2 of 61 (3%), 7 of 64 (11%), 14 of 43 (33%), and 4 of 10 (40%) in the first, second, third, and fourth groups, respectively. The incidences in the third ($SBP_{1-8} 131\text{--}140 \text{ mmHg}$) and fourth ($SBP_{1-8} \geq 141 \text{ mmHg}$) groups was significantly higher than that in the first group ($SBP_{1-8} < 120 \text{ mmHg}$) ($P < 0.001$ and $P = 0.002$, respectively). The development was zero in patients with $SBP_{1-8} < 110 \text{ mmHg}$ ($n = 20$); however, incidence was not significantly different from the value in those with $110 \text{ mmHg} \leq SBP < 120 \text{ mmHg}$.

The progression was least frequent in those in the lowest SBP_{1-8} decade ($SBP_{1-8} < 120 \text{ mmHg}$, 1 of 9 [11%]). It was more frequent in those with higher SBP_{1-8} : 5 of 23 (22%), 6 of 47 (13%), and 4 of 15 (27%) in patients in the second, third, and fourth SBP_{1-8} decades. The incidence did not become progressively higher with higher SBP nor was there any significant difference among groups. The incidence of the progression was 1 of 24 (4%), 2 of 23 (9%), 3 of 24 (13%), and 10 of 23 (43%) in the first, second, third, and fourth UAE_0 quartiles, respectively. The incidence in the fourth group was clearly higher than that in the other groups (fourth quartile vs. first quartile $P = 0.002$, vs. second quartile $P = 0.02$, and vs. third quartile $P = 0.02$).

The incidence of the regression was most frequent in patients with the lowest SBP_{1-8} : 4 of 9 (44%), 5 of 23 (22%), 8 of 47 (17%), and 3 of 15 (20%) in the first, second, third, and fourth SBP_{1-8} decades. However, the incidence was not significantly different among any groups. The regression occurred in two of the four patients (50%) with $SBP_{1-8} < 110 \text{ mmHg}$. The incidences of regression were 11 of 24 (46%), 5 of 23 (22%), 2 of 24 (8%), and 2 of 23 (9%) in the first, second, third, and fourth UAE_0 quartiles, respectively, and the values were significantly lower in the third and fourth quartiles than in the first quartile ($P = 0.008$ for the two comparisons).

CONCLUSIONS— In this study, the achieved mean blood pressure for the entire group was 127/72 mmHg: the value

Table 2—Variables related to the development, progression, and regression of nephropathy

Variables	Univariate analysis			Multivariate analysis		
	P	β	OR (95%CI)	P	β	OR (95%CI)
Significantly related to the development of nephropathy						
UAE ₀	0.02	2.431	1.083 (1.016–1.155)	0.07	1.825	1.069 (0.995–1.148)
SBP ₀	<0.001	3.631	1.038 (1.017–1.059)	0.87	0.168	1.004 (0.962–1.047)
SBP _{1–8}	<0.001	3.884	1.104 (1.050–1.161)	0.03	2.141	1.076 (1.006–1.150)
DBP ₀	0.01	2.670	1.059 (1.017–1.103)	0.38	0.885	1.026 (0.969–1.086)
DBP _{1–8}	0.01	2.553	1.119 (1.027–1.220)	0.99	–0.014	0.999 (0.890–1.121)
Use of antihypertensive drugs	<0.001	3.338	5.937 (2.086–16.897)	0.78	0.279	1.292 (0.213–7.838)
Significantly related to the progression of nephropathy						
UAE ₀	<0.001	3.503	1.015 (1.006–1.023)	0.001	3.275	1.015 (1.006–1.024)
SCr ₀	0.03	2.139	39.799 (1.360–1164.373)	0.27	1.103	7.888 (0.201–310.228)
Use of antihypertensive drugs	0.046	1.999	3.075 (1.022–9.248)	0.27	1.093	2.046 (0.567–7.389)
Age	0.048	1.975	1.057 (1.000–1.118)	0.15	1.456	1.050 (0.983–1.122)
Significantly related to the regression of nephropathy						
UAE ₀	0.02	–2.414	0.982 (0.968–0.997)	0.01	–2.445	0.980 (0.965–0.996)
SBP _{1–8}	0.02	–2.299	0.942 (0.896–0.991)	0.046	–1.993	0.944 (0.892–0.999)
A1C ₀	0.01	2.532	1.422 (1.083–1.867)	0.01	2.816	1.565 (1.146–2.137)

Results of logistic regression analysis. Development of nephropathy was confirmed by microalbuminuria in 26 patients and by macroalbuminuria in 1 patient. *P* values, odds ratio (OR), and 95% CI for the variables that are not significantly related to the development, progression, or regression of nephropathy according to univariate analysis are not shown. β , standardized logit coefficient; A1C₀, baseline A1C; DBP₀, baseline DBP; DBP_{1–8}, achieved mean DBP during years 1–8; SBP₀, baseline SBP; SBP_{1–8}, achieved mean SBP during years 1–8; SCr₀, baseline serum creatinine; UAE₀, baseline UAE.

was lower than mean blood pressure values in intensively treated patients with type 2 diabetes in previous studies, which were 144/82 mmHg (6), 146/85 mmHg (7,8), 132–137/72–73 mmHg (9), 132–135/80–82 mmHg (10), 141/83 mmHg (11), and 136/79 or 137/79 mmHg (12). The rates of development and progression in the current study are lower than those for intensively treated groups in previous studies (6–12) and similar to those in Japanese normotensive patients with type 2 diabetes under intensive glycemic control (5). Low BMI in this cohort at least partially accounts for the low rate of nephropathy. The regression of microalbuminuria in the current study (21%) was comparable to previously reported values: 30%/7.8 years (8) or 15.4 and 23.8%/5.5 years (9). We ascertained that UAE did not significantly increase in 210 of the 273 patients (77%) who remained in the same categories. Such analysis was not performed in previous studies (5–12). Thus, the treatment outcome in this study was fair but not ideal. In particular, the progression of microalbuminuria to macroalbuminuria appears to be increasing at year 8, strongly suggesting that both glycemic and blood pressure control was suboptimal as a group.

The level of blood pressure attained was significantly related to development and regression but not progression of nephropathy. In particular, among those with achieved mean SBP <120 mmHg, the rate of development was 3%/8 years and the rate of regression was as high as 44%/8 years. The development of nephropathy was a phenomenon observed solely in patients with normal baseline UAE by definition, i.e., without nephropathy. Of the regression, 80% (16 of 20) occurred in patients with lower baseline microalbuminuria (UAE ≤65 mg/g creatinine). Thus, in our study population, lower blood pressure was particularly beneficial for patients without nephropathy or with relatively mild nephropathy, such as a level of UAE ≤65 mg/g creatinine. In contrast, most of the patients who experienced progression of nephropathy (13 of 16, 81%) had a higher level of microalbuminuria at baseline (UAE ≥66 mg/g creatinine). UAE of 45 mg/24 h was a value to distinguish which patients have advanced glomerular lesions (18), which roughly approximates to 65 mg/g creatinine (15). Although the cause and result relationship cannot be decisively determined in an observation study, the blood pressure change preceding the change in UAE (Table 2) strongly suggests that ele-

vation and lowering of blood pressure are the causes of increases and decreases in UAE, respectively.

The achieved A1C was not significantly related to any of the three albuminuric outcomes in this study. This is a striking difference from previous intervention studies in type 2 diabetes in which higher glycemia was independently related to development and progression (5–7), and lower glycemia was independently related to regression (8). The achieved mean A1C in this study was 6.5%, and this level was well sustained for the entire period: this A1C value was lower than that in the intensively treated groups of previous intervention studies (5–8,16). The attained level of glycemia may be low enough for nephroprotection in the majority of the patients so that glycemia was no longer significantly related to nephropathic fate. The rate of development of microalbuminuria in this study was even lower than that seen in nondiabetic patients with essential hypertension (19).

The major drawback of the current study was that information such as the duration of diabetes (20), serum lipid levels (1), history of smoking (21), degree of insulin resistance (1), and genetic factors was not obtained. By inclusion of such

information, we may be able to more reliably predict the fate of nephropathy.

We considered SBP 120 mmHg to be low enough for optimal nephroprotection for the following reasons. First, the incidence of alterations in the albuminuric state was not significantly different in those with the achieved mean SBP <110 and 110–120 mmHg. Second, regression of nephropathy from a considerably advanced state did occur with the attainment of normoglycemia for 10 years in patients with a pancreas transplant (22). In this study, the mean blood pressure was 95 mmHg (22), which is clearly higher than the mean blood pressure of patients with SBP of 120 mmHg in the current study, which was 90 mmHg. Therefore, normalization of glycemia, not further lowering of blood pressure, may be required for further improvement of nephropathic outcome. We therefore confirmed a previous suggestion that a target level of blood pressure should be \leq 120/80 mmHg for optimal nephroprotection (2).

In summary, development and progression were low and regression was high with SBP of 120 mmHg in Japanese middle-aged patients with type 2 diabetes in whom mean A1C of 6.5% was attained.

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