Original Article

Factors Associated With Frequent Remission of Microalbuminuria in Patients With Type 2 Diabetes

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To estimate the frequency of remission/regression of microalbuminuria and to identify factors affecting such outcomes in Japanese patients with type 2 diabetes, we observed 216 patients with type 2 diabetes and microalbuminuria enrolled during an initial 2-year evaluation period for the next 6 years. Remission was defined as shift to normoalbuminuria and regression as a 50% reduction in urinary albumin excretion rate (AER) from one 2-year period to the next. Reduction of urinary AER was frequent, with a 6-year cumulative incidence of 51% (95% CI 42–60) for remission and 54% (45–63) for regression, whereas the frequency of progression to overt proteinuria was 28% (19–37). Microalbuminuria of short duration, the use of renin-angiotensin system-blocking drugs, and lower tertiles for HbA_{1c} (<6.95%) and systolic blood pressure (<129 mmHg) were independently associated with remission or regression in the pooled logistic regression analysis. The results indicate that reduction in urinary AER occurs frequently in Japanese patients with type 2 diabetes. Early detection of microalbuminuria and a multifactorial control may result in improved outcomes for diabetic nephropathy and cardiovascular events. *Diabetes* 54: 2983–2987, 2005

Diabetic nephropathy is a serious complication of diabetes and a leading cause of end-stage renal disease (ESRD). The earliest clinical sign of diabetic nephropathy is an elevated urinary albumin excretion, referred to as microalbuminuria. Microalbuminuria is defined as an albumin excretion rate (AER) of 20–199 μg/min in a timed or a 24-h urine collection (equivalent to 30–299 mg/g creatinine in a random spot sample) (1). Microalbuminuria in diabetic patients has been recognized not only as a predictor of progression of diabetic nephropathy but also as a powerful independent risk factor for cardiovascular disease (2–7). Thus, the prevention of elevated urinary albumin excretion is an important therapeutic target for the prevention of renal and cardiovascular events, and it continues to be important to explore modifiable factors that affect microalbuminuria.

Recently, the concept of remission or regression of microalbuminuria has been proposed as an outcome. Intervention studies with ACE inhibitors or angiotensin II type 1 receptor blockers (ARBs) in subjects with type 2 diabetes have shown that reduction of microalbuminuria can be induced (8–10). Also, Perkins et al. (11) from the Joslin Diabetes Center have reported that regression of microalbuminuria in type 1 diabetes occurred more frequently than progression to persistent proteinuria.

In the present study, we estimated the frequencies of remission and regression of microalbuminuria in Japanese patients with type 2 diabetes and identified the factors affecting these outcomes. In addition, we evaluated whether clinical practice guidelines were adequate to induce remission and regression of microalbuminuria.

RESEARCH DESIGN AND METHODS

The subjects were recruited from among the participants in the Shiga Prospective Observational Follow-Up Study for Diabetic Complications, which has been conducted since 1996 to elucidate the course of diabetic complications in Japanese patients with type 2 diabetes, at the outpatient clinic of the Department of Medicine, Shiga University of Medical Science (12). During 1996 to 1998, patients clinically diagnosed as having type 2 diabetes in accordance with World Health Organization criteria (13) were examined with at least two measurements of AER in 24-h urine collections, and their diabetic nephropathy status for the first 2 years was determined. Those classified as having microalbuminuria or normoalbuminuria in the first 2-year period were observed for the next 6 years. No patient with only one measurement of AER in the initial evaluation period was enrolled in this study. Patients who had complicating cancer, liver disease, or nondiabetic kidney disease confirmed by the renal biopsy were excluded from this study. For the analysis, observations were classified into four 2-year periods, consisting of an initial evaluation period (the first 2-year period during which microalbuminuria was present) and first, second, and third follow-up periods (total of 8 years). Microalbuminuria was present initially in 179 patients (the prevalence cohort) and developed newly in 37 patients during the first or second follow-up period (the incidence cohort). The patients in the incidence cohort thus have a shorter duration after the development of microalbuminuria. The initial evaluation was made after 2 and 4 years in 24 and 13 subjects in the incidence cohort, respectively. During the follow-up periods, each subject underwent standardized physical examination, biochemical measurements under fasting condition, and measurement of AER and estimation of sodium and protein intake in a 24-h urine collection at least once a year. All participants received treatment based on the standard strategies for diabetes, hypertension, and hyperlipidemia during these periods. The study protocol and informed consent procedure were approved by the Ethics Committee of Shiga University of Medical Science.

Assessment of urinary AER. Urinary AER was measured by immunoturbidimetry assay (HITACHI 7070E; Hitachi High-Technologies, Tokyo, Japan) in 24-h urine samples after the absence of pyuria in the last voided urine of a 24-h collection was confirmed by a dipstick test for leukocyte esterase and the traditional method of counting the number of white blood cells. The levels of

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AER, albumin excretion rate; ARB, angiotensin II type 1 receptor blocker; ESRD, end-stage renal disease; RAS, renin-angiotensin system; SBP, systolic blood pressure.

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TABLE 1
The levels of urinary albumin excretion rate for each 2-year study period

Status	Evaluation period	Follow-up period		
		First	Second	Third
Overt proteinuria		20 (9)	22 (13)	21 (19)
Microalbuminuria	216 (100)	147 (69)	92 (54)	66 (58)
Normoalbuminuria		48 (22)	55 (33)	26 (23)
Total	216 (100)	215 (100)	169 (100)	113 (100)

Data are *n* (%). Evaluation period was the first 2-year period during which microalbuminuria was present. Microalbuminuria was present initially in 179 patients (the prevalence cohort) and developed later in another 37 patients during the first or second follow-up period (the incidence cohort). In the incidence cohort, the initial evaluation period took place after 2 years in 24 subjects and after 4 years in 13 subjects.

albumin excretion in each measurement of AER were classified as normoalbuminuria if AER was <20 μg/min, microalbuminuria if AER was ≥20 and <200 μg/min, and overt proteinuria if AER was ≥200 μg/min. In the initial evaluation period, the subjects (regardless of duration of diabetes) were enrolled as having microalbuminuria if they showed the last two or more consecutive microalbuminuria and the geometric mean for all of their AER values also indicated microalbuminuria. In follow-up periods, the status of diabetic nephropathy was determined by the geometric mean of AER in each follow-up period. The mean measurements of AER in each study period were 2.7 times (range 2–9 times) in the initial evaluation period, 2.2 (2–7) in the first follow-up period, 2.1 (2–7) in the second follow-up period, and 2.1 (2–4) in the third follow-up period. AER was measured only twice in 58% of the patients in the initial evaluation period and in 91% in the follow-up periods. Of the patients who underwent AER only twice, 100% showed concordance of the two measurements in the initial evaluation period and 87% in the follow-up periods. Among patients with discordance, three patients were classified into spontaneous remission and one into regression.

Definitions of outcome used. No generally accepted definition for remission or regression of microalbuminuria has yet been established. We applied the definitions given below as well as those used in the Joslin Diabetes Center study of subjects with type 1 diabetes (11). According to diabetic nephropathy status based on the geometric mean of AER in each 2-year follow-up period, remission of microalbuminuria was defined as shift of AER from microalbuminuria to normoalbuminuria. When the diabetic nephropathy status described above was used, the patients with AER close to the lower boundary for microalbuminuria might frequently revert to normoalbuminuria because of random measurement error. To minimize this inherent problem, we defined regression of microalbuminuria as a 50% reduction in the geometric mean of AER from one 2-year period to the next 2-year period. Progression of microalbuminuria was defined as shift of AER into overt proteinuria according to the geometric mean of AER in each 2-year follow-up period.

Statistical analysis. Cumulative incidence rates of subjects in whom remission, regression, or progression had occurred during the 6-year follow-up period were estimated by the life-table method. Follow-up time was censored if each outcome of microalbuminuria occurred or if the patient was unavailable for observation in the next follow-up period. Descriptive statistics were calculated. A comparison between groups was performed by using χ^2 tests for categorical variables and Student's *t* test for continuous variables. The estimated sodium and protein intake were assessed on the basis of urinary excretion of sodium and urea nitrogen using 24-h urine samples (14).

To identify factors associated with the outcome of microalbuminuria, the analyses of univariate and multivariate regression models using the pooled logistic regression analysis were performed with SPSS software (version 11; SPSS, Chicago, IL). The pooled logistic regression analysis is equivalent to a Cox time-dependent regression analysis and allows the covariates in the multivariate models to change over time, with the clinical variables redefined at each follow-up period (15). All time-dependent variables (modifiable factors) within each 2-year period were averaged, and the mean per 2-year period was used for the analysis. Each modifiable factor was trisected according to the number of patients and was applied as three categories in the analysis. The use of antihypertensive drugs was recorded if subjects had taken these drugs for at least 1 year in a given 2-year period. Among antihypertensive drugs, the renin-angiotensin system (RAS) blockade drugs including ACE inhibitors or ARBs and other antihypertensive drugs were separately recorded and analyzed. To analyze the importance of each clinical practice recommendation, the levels of HbA_{1c} (A1C), blood pressure, and lipid profile were dichotomized as salutary or nonsalutary according to the clinical practice recommendations of the Japanese Diabetes Society (16) as follows: A1C <6.5%; blood pressure <130/80 mmHg; and lipid profile <200 mg/dl for total cholesterol, <150 mg/dl for triglyceride, and >40 mg/dl for HDL were regarded as salutary levels. These values are similar to the recommendations given in several guidelines (17–20). Then, we coded each follow-up period of observation on a scale of 0–3 according to the number(s) of the three factors at the salutary level and applied this number in the pooled logistic regression model.

RESULTS

The distribution of the patients according to the levels of urinary AER for each 2-year study period is shown in Table 1. The prevalence of normoalbuminuria was 22, 33, and 23% at each 2-year follow-up period. During the follow-up period, 81 subjects achieved remission of microalbuminuria, 61 in the prevalence cohort and 20 in the incidence cohort. The 6-year cumulative incidence of remission of microalbuminuria was 51% (95% CI 42–60). To minimize the boundary effect between normoalbuminuria and mi-

TABLE 2
Clinical characteristics according to the presence of regression of microalbuminuria at the evaluation period

	Regression (n = 85)	No regression (n = 131)	*P*
Sex (men:women)	52:33	89:42	0.31
Age (years)	62 ± 8	61 ± 9	0.49
Duration of diabetes (years)	15 ± 8	13 ± 8	0.08
A1C (%)	7.5 ± 1.0	7.5 ± 1.0	0.96
SBP (mmHg)	138 ± 16	136 ± 17	0.50
Diastolic blood pressure (mmHg)	78 ± 9	77 ± 10	0.48
Total cholesterol (mg/dl)	210 ± 32	206 ± 29	0.33
Triglycerides (mg/dl)	119 ± 52	129 ± 71	0.28
HDL cholesterol (mg/dl)	55 ± 13	53 ± 13	0.21
BMI (kg/cm^2)	23.8 ± 3.7	24.2 ± 2.9	0.32
Serum creatinine (mg/dl)	0.70 ± 0.17	0.73 ± 0.18	0.25
AER (μg/min)	68 ± 48	62 ± 48	0.41
Estimated sodium intake (g/day)	14.0 ± 5.6	14.8 ± 5.0	0.30
Estimated protein intake ($g \cdot kg^{-1} \cdot day^{-1}$)	1.2 ± 0.3	1.3 ± 0.4	0.51
Retinopathy (%)	85	83	0.68
Use of ACE inhibitor or ARB (%)	28	24	0.51
Incidence cohort (%)	20	15	0.35

Data are means ± SD unless otherwise indicated.

TABLE 3
The ORs of factors associated with the regression and remission of microalbuminuria with the pooled logistic regression model

	Adjusted OR (95% CI)*	
	Regression	Remission
Nonmodifiable factors		
Incidence cohort (vs. prevalence)	2.0 (1.03–3.9)	2.0 (1.1–3.9)
Modifiable factors		
Use of ACE inhibitors or ARBs (vs. none)	2.3 (1.4–4.0)	1.9 (1.1–3.3)
A1C (%)		
A1C < 6.95	2.2 (1.2–4.2)	3.0 (1.5–6.0)
6.95 ≤ A1C < 7.75	1.2 (0.6–2.3)	2.1 (1.01–4.2)
7.75 ≤ A1C	1.0 (ref.)	1.0 (ref.)
SBP (mmHg)		
SBP < 129	2.0 (1.04–3.9)	2.7 (1.4–5.2)
129 ≤ SBP < 143	1.6 (0.8–3.0)	1.8 (0.9–3.5)
143 ≤ SBP	1.0 (ref.)	1.0 (ref.)

*The multivariate model was adjusted for sex, mean urinary albumin excretion in the initial evaluation period, total cholesterol, estimated sodium intake, and estimated protein intake. ref., reference category.

croalbuminuria, we also investigated the estimated frequency of regression of microalbuminuria defined as a reduction of 50% or more in AER from one 2-year period to the next 2-year period. A total of 85 subjects with microalbuminuria achieved regression of microalbuminuria, 68 in the prevalence cohort and 17 in the incidence cohort. The 6-year cumulative incidence of regression was 54% (45–63). The prevalence of proteinuria was 9, 13, and 19% at each 2-year follow-up period. During the study period, 36 subjects progressed to overt proteinuria, 34 in the prevalence cohort and 2 in the incidence cohort. Among them, five subjects had reverted to the stage of microalbuminuria by the end of study and three had required hemodialysis therapy. The 6-year cumulative incidence for progression of microalbuminuria was 28% (19–37), indicating that remission/regression of microalbuminuria occurred more frequently than progression from microalbuminuria to overt proteinuria. The clinical characteristics at the initial evaluation period for subgroups classified according to whether microalbuminuria regressed are shown in Table 2. There were no differences in any factors between the two groups.

Next, the factors associated with regression of microalbuminuria in the follow-up period were examined with the pooled logistic regression model. In preliminary univariate analysis, A1C, systolic blood pressure (SBP), total cholesterol, the use of ACE inhibitors or ARBs, estimated sodium intake, and estimated protein intake, among modifiable factors, and the incidence cohort among nonmodifiable factors, were associated with regression. In the multivariate model mutually adjusted for sex, mean urinary AER in the initial evaluation period, and the presence of these risk factors, we found that the incidence cohort, the use of ACE inhibitors or ARBs, and lower tertiles of A1C (<6.95%) and SBP (<129 mmHg) were independently associated with regression of microalbuminuria (Table 3), whereas lower tertiles of total cholesterol (odds ratio [OR] 1.5 [95% CI 0.8–2.8]), estimated sodium intake (1.5 [0.8–3.0]), and estimated protein intake (1.7 [0.8–3.3]) were not associated with regression. Similar results were observed in the multivariate analysis regarding remission of microalbuminuria (Table 3). In the analysis for remission, even the middle tertile for A1C (6.95% ≤ A1C < 7.75%) showed high OR in comparison with the upper tertile for A1C (≤7.75%). Even though the analysis was limited in the prevalence cohort, the importance of the use of ACE inhibitors or ARBs, A1C, and SBP in remission/regression did not change (data not shown). Also, the use of any antihypertensive drugs except RAS blockade drugs was not associated with remission/regression.

Finally, the importance of the levels of glycemic exposure, blood pressure, and lipid profile maintained at or below levels recommended in the clinical practice guidelines was investigated in the multivariate model adjusted for sex, mean urinary AER in the initial evaluation period, use of ACE inhibitors or ARBs, and incidence cohort. The OR for remission/regression of microalbuminuria increased with each increment in the number of factors at the salutary level (Table 4); when two and three factors were at the salutary level, the OR for regression was 2.4 (95% CI 1.2–4.6) and 5.9 (1.3–25.8).

DISCUSSION

This study showed that remission/regression of microalbuminuria in subjects with type 2 diabetes (~50%) occurred more frequently than progression to overt proteinuria (only 28%). This study also provides evidence that rigorous control of glycemic exposure and SBP, use of RAS blockade drugs, and microalbuminuria of short duration were independently associated with the remission/regression. This result underscores the importance of aggressive multifactorial control to prevent progression of diabetic nephropathy and cardiovascular events in subjects with type 2 diabetes (20,21).

The phenomenon of remission/regression of microalbuminuria has recently been reported in subjects with type 1 and type 2 diabetes. Perkins et al. (11) found that regression was more frequent than progression, with a 6-year cumulative incidence of 58% (95% CI 52–64). Also, microalbuminuria reverted to normoalbuminuria in 50.6% of the type 1 diabetic patients over 7.3 years in the EURODIAB Prospective Complication Study, whereas 13.9% showed progression (22). Very recently, Gæde et al. (23) have reported that 46 of 151 type 2 diabetic patients with

TABLE 4
Additive effects of factors controlled at the recommended levels on the regression and remission on microalbuminuria

	Number of factors at salutary levels			
	0	1	2	3
Regression of microalbuminuria*	1.0 (ref.)†	1.4 (0.8–2.5)	2.4 (1.2–4.6)	5.9 (1.3–25.8)
Remission of microalbuminuria*	1.0 (ref.)†	1.2 (0.7–2.2)	2.0 (1.01–3.9)	6.2 (1.6–24.2)

Data are OR (95% CI). *The ORs were adjusted for sex, mean urinary albumin excretion in the initial evaluation period, the use of ACE inhibitors or ARBs, and the incidence cohort. †Absence of any of the three factors at a salutary level was considered the reference category (ref.).

microalbuminuria attained remission to normoalbuminuria after a mean follow-up period of 7.8 years. In our study, we found frequent remission/regression, with ~50% incidence at the 6-year follow-up period in subjects with type 2 diabetes. These observations strongly indicate that microalbuminuria frequently regresses contrary to our expectation.

What is the clinical significance of reduction of elevated AER? Numerous studies in diabetic individuals with microalbuminuria demonstrate higher morbidity and mortality from cardiovascular disease (2–6). Microalbuminuria in diabetic subjects strongly predicts cardiovascular mortality even in the setting of acute myocardial infarction (24). This evidence suggests that remission/regression of microalbuminuria results in reduction of risk from cardiovascular disease. Also, the intensified intervention involving multiple risk factors was reported to reduce the risk of cardiovascular events among patients with type 2 diabetes and microalbuminuria (20). Thus, detection of microalbuminuria is a powerful way to identify patients at risk for subsequent multiple cardiovascular events. Moreover, reduction of microalbuminuria may indicate the adequacy of that intervention.

The present study also identified the factors associated with the reduction of microalbuminuria in type 2 diabetes. In our study, the low tertile for A1C (<6.95%) was independently associated with remission/regression. This cutoff value is compatible with the recommended therapeutic target (<7.0%) for A1C (17,18). In a study at the Joslin Diabetes Center, A1C level <8.0%, which is higher than the cutoff we used, was considered salutary (11). This difference suggests that a different salutary level of A1C should be considered in those with type 2 diabetes. In fact, both the Kumamoto (25) and the Steno type 2 randomized (21) studies showed that the target A1C level to prevent progression of diabetic nephropathy was <6.5%. In our study, the OR for regression in subjects with A1C <6.5% was slightly increased, to 3.4 (95% CI 1.6–7.2). Thus, we suggest that the A1C level should be kept at least at <7.0% to delay progression of diabetic nephropathy and to reduce the risk of cardiovascular diseases in subjects with type 2 diabetes. If tolerated, further and more aggressive lowering of A1C, to <6.5%, is the therapeutic optimum.

Control of blood pressure has widely been accepted to prevent progression of diabetic nephropathy and cardiovascular events. Recent target guidelines in diabetic patients have emphasized the importance of aggressive blood pressure reduction (26). Maintaining blood pressure at <130/80 mmHg is recommended in diabetic patients for preservation of renal function and reduction of cardiovascular events (16–18). Our subjects with the lower tertile for SBP (<129 mmHg) frequently attained regression of microalbuminuria, whereas diastolic blood pressure had no effect. Thus, to delay or prevent progression of diabetic nephropathy, SBP should be maintained at ≤130 mmHg.

Our study confirmed the importance of RAS blockade drugs in regression of microalbuminuria, although uncontrolled. This is compatible with the results from some clinical intervention studies of RAS blockade in subjects with type 2 diabetic and microalbuminuria (8–10,27). Treatment with ACE inhibitors in subjects with type 2 diabetes and microalbuminuria who were followed up for a 5-year mean duration was associated with a 13% reduction in urinary AER compared with baseline (8). In the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA-II) study, irbesartan (an ARB) reduced the urinary AER by 24–38% over a 2-year period (9). Similarly, in the Microalbuminuria Reduction with Valsartan (MARVAL) study, which was designed to evaluate the blood pressure–independent effect of valsartan (another ARB) on urinary AER in type 2 diabetic patients with microalbuminuria over a 24-week period, subjects treated with valsartan showed a 44% reduction in the urinary AER, and 29.9% of patients allocated valsartan reverted to normoalbuminuria (10). Furthermore, combination therapy with ACE inhibitor and ARB was reported to result in a 50% reduction in urinary albumin excretion in the Candesartan and Lisinopril Microalbuminuria (CALM) study (27). In contrast, the Joslin Diabetes Center study and the EURODIAB Prospective Complication Study focusing on regression in type 1 diabetic patients did not show any effect of RAS blockade on reduction of urinary albumin excretion (11,22). The precise reason for the discrepancy among these studies and ours remains unclear. One explanation may be the difference of the indication for RAS blockade drugs, because patients with type 2 diabetes tend to be older and have higher frequency of hypertension than those with type 1 diabetes.

Microalbuminuria of short duration (the incidence cohort) was an independent factor for regression of elevated AER, suggesting the importance of frequent screening for microalbuminuria in diabetic patients. Detection of microalbuminuria at the early stage may result in prompt adequate intervention and, as a result, prevent progression of diabetic nephropathy and cardiovascular disease.

On the other hand, the levels of total cholesterol, estimated sodium intake, and estimated protein intake were not identified as independent factors associated with regression of microalbuminuria in the multivariate model, although an association was indicated in the univariate model. Several clinical trials and clinical guidelines have suggested that the restriction of sodium or protein intake might prevent progression of diabetic nephropathy (7,18–20). However, it remains inconclusive whether the renoprotective effects of modifying these factors are equal or superior to those of controlling hyperglycemic exposure or blood pressure. The renoprotective effects related to these factors may be weaker than those related to hyperglycemic exposure or blood pressure in subjects with type 2 diabetes. Thus, in the multivariate model including A1C and blood pressure, these factors were not shown to be independently associated with regression of microalbuminuria.

Recently, numerous guidelines for patients with diabetes have been published and are offered for patient care. The Japanese Diabetes Society has also published clinical practice recommendations for treatment of diabetic patients; they recommend therapeutic targets of A1C at <6.5%; blood pressure at <130/80 mmHg; and lipid profile at <200 mg/dl for total cholesterol, <150 mg/dl for triglyceride, and >40 mg/dl for HDL (16). Our study, consistent with that of the Joslin Diabetes Center study (11), revealed the combined beneficial effect of these three factors on regression/remission of microalbuminuria. Thus, recommended therapeutic goals for glycemic exposure, blood pressure, and lipid profile are clinically reasonable and effective in reduction of elevated urinary AER in diabetic patients.

There are several limitations of the present study. At present, there is no generally accepted definition of remission or regression of microalbuminuria. We defined regression as a 50% reduction in urinary AER between two

successive 2-year periods, as in the Joslin Diabetes Center study (11). Although this definition served to estimate the frequency of reduction, it does not always reflect the change of renal function. Also, it remains unclear whether the 50% reduction reflects improvement of morphological abnormalities because we obtained no confirmation by histological documentation. Thus, the combination of reduction of microalbuminuria with another measurement, such as the annual change of glomerular filtration rate, might have been more effective. Second, the present study did not make it clear whether regression of microalbuminuria finally results in reduction of the incidence of ESRD or cardiovascular mortality. Hovind et al. (28) reported that remission of nephrotic-range albuminuria by aggressive antihypertensive treatment improved the rate of survival free of ESRD. Further study is required to determine the beneficial effect of regression of microalbuminuria on these final outcomes.

In conclusion, the present study indicates that microalbuminuria frequently regresses in subjects with type 2 diabetes. This observation should not be construed as indicating that microalbuminuria is an unreliable indicator. Rather, it should be taken to emphasize the importance of aggressive multifactorial control including glycemic exposure, blood pressure, and the use of drugs blocking the RAS system as early as possible to prevent progression of diabetic nephropathy and cardiovascular events. Also, it suggests that the reduction of elevated urinary AER may serve as a surrogate parameter helpful in predicting the beneficial effects of therapeutic intervention.

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