Brief Report

Reduction in Microalbuminuria as an Integrated Indicator for Renal and Cardiovascular Risk Reduction in Patients With Type 2 Diabetes

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OBJECTIVE—Microalbuminuria in diabetic patients is a predictor for diabetic nephropathy and cardiovascular disease. The aim of this study is to investigate the clinical impact of reducing microalbuminuria in type 2 diabetic patients in an observational follow-up study.

RESEARCH DESIGN AND METHODS—We enrolled 216 type 2 diabetic patients with microalbuminuria during an initial 2-year evaluation period and observed them for the next 8 years. Remission and a 50% reduction of microalbuminuria were defined as a shift to normoalbuminuria and a reduction <50% from the initial level of microalbuminuria. The association between reducing microalbuminuria and first occurrence of a renal or cardiovascular event and annual decline rate of estimated glomerular filtration rate (eGFR) was evaluated.

RESULTS—Twelve events occurred in 93 patients who attained a 50% reduction of microalbuminuria during the follow-up versus 35 events in 123 patients without a 50% reduction. The cumulative incidence rate of events was significantly lower in patients with a 50% reduction. A pooled logistic regression analysis revealed that the adjusted risk for events in subjects after a 50% reduction was 0.41 (95% CI 0.15–0.96). In addition, the annual decline rate of eGFR in patients with a 50% reduction was significantly slower than in those without such a reduction. The same results were also found in the analysis regarding whether remission occurred.

CONCLUSIONS—The present study provides clinical evidence implying that a reduction of microalbuminuria in type 2 diabetic patients is an integrated indicator for renal and cardiovascular risk reduction. ***Diabetes*** **56:1727–1730, 2007**

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AER, albumin excretion rate; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate.

Microalbuminuria in patients with type 2 diabetes is an important predictor of progression for diabetic nephropathy, and a worsening of albuminuria has been reported as associated with a rapid decline in renal function (1,2). Moreover, microalbuminuria in diabetic patients is also a powerful risk factor for cardiovascular disease (3–8). Microalbuminuria is therefore considered to be an important therapeutic target for the protection against renal and cardiovascular complications.

Recently, we and others reported that remission/regression of microalbuminuria in diabetic patients occurs frequently and is associated with the control of multiple risk factors (9,10). However, the findings of these previous studies were not analyzed concerning subsequent clinical impact and outcomes from the achieved reduction of microalbuminuria. We therefore extended our pervious study (10) and investigated whether changes in microalbuminuria translate into changes in renal and cardiovascular risk in type 2 diabetic patients with microalbuminuria. For this purpose, we assessed two outcomes: *1*) the first occurrence of a renal or cardiovascular event and *2*) the kidney function as indicated by estimated glomerular filtration rate (eGFR).

The clinical characteristics at the initial evaluation period in the subgroups, classified according to whether a 50% reduction of microalbuminuria occurred at least once, are shown in Table 1. No differences were observed between the two groups in any factors at the initial evaluation period.

In a total of 47 patients, evaluated renal and cardiovascular events occurred during the 8-year follow-up period. There were 12 events (1 dialysis, 3 myocardial infarctions, 5 cases of angina, 1 worsening of congestive heart failure, and 2 strokes) in the 50% reduction group, in comparison with 35 events (3 dialyses, 5 myocardial infarctions, 7 cases angina, 2 worsening of congestive heart failure, and 18 strokes) in the nonreduction group. The 8-year cumulative incidence of evaluated events was significantly lower in the 50% reduction group than in the nonreduction group ($P = 0.0019$) (Fig. 1). When all patients were stratified according to whether remission had occurred, the cumulative incidence in the remission group was similarly lower than in the nonremission group ($P = 0.010$).

We next evaluated the influence of the changes in conventional risk factors, medical treatment, and the

TABLE 1
Clinical characteristics at the initial evaluation period in the subgroups according to the status of a 50% reduction of UAE

	50% reduction	Nonreduction
n	93	123
Sex (male/female)	56/37	85/38
Age (years)	62 ± 8	61 ± 10
Duration of diabetes (years)	14 ± 8	13 ± 9
A1C (%)	7.5 ± 0.9	7.5 ± 1.0
Blood pressure (mmHg)		
Systolic	138 ± 17	136 ± 17
Diastolic	77 ± 9	77 ± 10
Cholesterol (mg/dl)		
Total	210 ± 31	207 ± 30
Triglycerides	109 (83–144)	112 (85–149)
HDL	54 ± 12	53 ± 14
BMI (kg/m^2)	23.7 ± 3.4	24.2 ± 3.1
eGFR (ml/min per 1.73 m^2)	103 ± 24	101 ± 25
AER (μg/min)	49 (34–97)	42 (29–74)
Retinopathy (%)	83	84
Antihypertensive treatment (%)		
No/ACE-I or ARB/others	57/28/15	56/24/20
Lipid-lowering treatment (%)	22	21
Current smoker (%)	32	42
History of cardiovascular diseases (%)	15	20

Data are means ± SD for normally distributed continuous variables or median (25th–75th interquartiles) for skewed continuous variables unless otherwise indicated. ACE-I, ACE inhibitor; ARB, angiotensin receptor blocker.

status of albuminuria over the follow-up period regarding this association. In the 50% reduction group, the mean levels of systolic blood pressure and BMI at the period when a 50% reduction was achieved were lower than those at the period when it was not achieved (Table 2). In addition, in the 50% reduction group, five events (one dialysis, two myocardial infarctions, and two cases of angina) occurred in patients whose levels of albuminuria were aggravated again after a 50% reduction was achieved. Therefore, to assess these points, we applied the pooled logistic regression method. This analysis allows the variables redefined at each follow-up period in the multivariate model to change over the follow-up period (11). As a result, the adjusted risk for events in subjects after a 50% reduction was 0.41 (95% CI 0.15–0.96) in comparison with those without a 50% reduction (Table 3). Similarly, the adjusted risk for events in subjects after remission was 0.25 (0.07–0.87) in comparison with those whose status of microalbuminuria did not change, while that after progression was 2.55 (1.04–6.30) (Table 3).

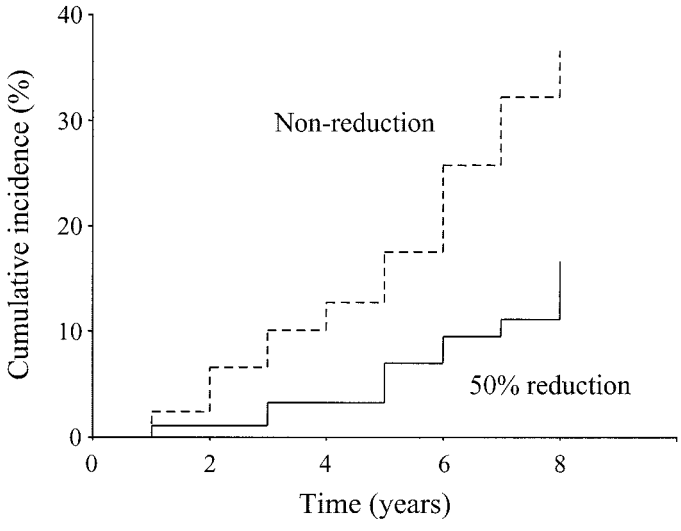

FIG. 1. The cumulative incidence of death from and hospitalization for renal and cardiovascular events for the groups stratified by a 50% reduction of microalbuminuria. For 50% reduction, $n = 93$; nonreduction, $n = 123$. $P = 0.0019$ by the log-rank test; $\chi^2 = 9.61$ with 1 d.f.

Finally, we assessed the influence of changes in the degree of microalbuminuria on kidney function. The annual decline rate of eGFR in the 50% reduction group was significantly slower than in the nonreduction group (−1.8 ml/min per 1.73 m^2/year [interquartile range −0.001 to −4.4] vs. −3.1 [−1.0 to −5.3]; $P = 0.038$). This association was seen even when all patients were stratified according to whether remission had occurred.

This study showed that either remission or a 50% reduction of microalbuminuria in type 2 diabetic patients was related to risk reduction of future renal and cardiovascular events. Furthermore, reducing the degree of albuminuria also led to a preservation of kidney function. These results therefore provide clinical evidence implying that a reduction of microalbuminuria in type 2 diabetic patients is an integrated indicator for renal and cardiovascular risk reduction.

A few decades ago, the main therapeutic objective for diabetic patients with microalbuminuria was to prevent a progression to overt proteinuria. In addition, albuminuria has been reported to be an independent risk factor for cardiovascular morbidity and mortality (12–14). The present study showed that a reduction of microalbuminuria is associated with a lower risk for cardiovascular and renal events. Moreover, even patients whose status of microalbuminuria did not change had a higher risk for these events than those with remission. These results indicate that preventing a progression of microalbuminuria may not be sufficient to improve outcomes. We therefore should consider shifting the therapeutic focus from the prevention of progression to a reduction of albuminuria and, if a reduction of albuminuria cannot be achieved, encouraging more aggressive treatment.

The relationship between a reduction in microalbuminuria and a reduction in cardiovascular events has also been observed in patients with hypertension (15). The LIFE (Losartan Intervention For End Point Reduction) in Hypertension Study showed that the levels of albuminuria during antihypertensive treatment are closely related to the cardiovascular events (15). Therefore, microalbuminuria may be an integrated marker of generalized vascular abnormalities regardless of the specific disease.

Decreased glomular filtration rate (GFR) has consistently been found a risk factor for cardiovascular disease, independent of albuminuria (16–18). The present study revealed regression to a slower decline rate of eGFR in patients with a 50% reduction of microalbuminuria. Similarly, the Steno-2 Study reported that remission to normoalbuminuria was associated with a decreased GFR decline in type 2 diabetic patients with microalbuminuria (2). These results indicate that reducing albuminuria and the preservation of the kidney function are mutually related, which may result in cardiovascular risk reduction.

The limitations of the present study should be noted. In the present study, reducing microalbuminuria is associated with a risk reduction of renal and cardiovascular events even after adjusting for modifiable factors at each

TABLE 2
Clinical characteristics in the subgroups according to the status of a 50% reduction of UAE at each follow-up period

	50% reduction group		
	Achieved period	Absent period	Nonreduction group
A1C (%)	7.3 ± 1.1*	7.4 ± 0.8	7.5 ± 1.0
Blood pressure (mmHg)			
Systolic	133 ± 16*†	139 ± 16	139 ± 18
Diastolic	74 ± 9	76 ± 9	76 ± 10
Cholesterol (mg/dl)			
Total	201 ± 29	204 ± 23	205 ± 30
Triglycerides	97 (75–146)	104 (75–138)	110 (80–149)
HDL	53 ± 14	56 ± 13	53 ± 15
BMI (kg/m^2)	23.7 ± 3.7*†	24.7 ± 3.3	24.3 ± 3.3
RAS blockade treatment (%)	48	46	43
Lipid-lowering treatment (%)	34	32	27
Current smoker (%)	23	28	30

Data are means ± SD for normally distributed continuous variables or median (25th–75th interquartiles) for skewed continuous variables unless otherwise indicated. In the 50% reduction group, the mean levels of systolic blood pressure and BMI at the period when a 50% reduction was achieved (achieved period) were lower than those at the period when it was not achieved (absent period). Renin-angiotensin system (RAS) blockade treatment includes ACE inhibitors and angiotensin II receptor blockers. *$P < 0.05$ vs. the nonreduction group; †$P < 0.05$ vs. absent period.

follow-up period. However, because reducing microalbuminuria may result from an accumulation of improved conventional risk factors, it is difficult to conclude whether reducing microalbuminuria independently influences these events. In addition, the influence of the dosage of renin-angiotensin system blockade drugs or the combination with diuretics in the follow-up period was not investigated in this study. Therefore, these issues need to be confirmed in a prospective interventional controlled study. In addition, we used the MDRD (Modification of Diet in Renal Disease) study equation to estimate GFR. It remains debatable whether the MDRD equation can be accurately applied to Japanese patients. However, in serial measurements of eGFR, the difference between the estimation of GFR and actual GFR is unlikely to change the main conclusions (19).

In conclusion, the present study indicates that a reduction of microalbuminuria in patients with type 2 diabetes is a powerful indicator for cardiovascular and renal risk reduction. As a result, the reduction of microalbuminuria, as induced by aggressive multifactorial control, is considered to be an integrated marker for evaluating the beneficial efficacy of therapeutic intervention to improve outcomes.

RESEARCH DESIGN AND METHODS

The subjects were recruited from among participants in the Shiga Prospective Observational Follow-up Study for Diabetic Complications, as described previously (10). A total of 216 patients with type 2 diabetes and microalbuminuria were enrolled during 1996–1998. In the present study, the follow-up period was extended by a 2-year period beyond our previous study (10). The participants were observed for a total of 8 years after the initial 2-year evaluation period. For the analysis, observations were classified into five 2-year periods, consisting of an initial evaluation period (the first 2-year period during which microalbuminuria was present) and four 2-year follow-up periods. During the follow-up periods, each subject underwent standardized physical examination, biochemical measurements under fasting conditions, and the measurement of albumin excretion rate (AER) based on 24-h urine collection at least once per year. The study protocol and informed consent procedure were approved by the ethics committee of Shiga University of Medical Science.

Assessment of urinary AER. Microalbuminuria was classified as ≤20 AER <200 μg/min (1). In the initial evaluation period, the subjects (regardless of duration of diabetes) were enrolled as having microalbuminuria if they showed microalbuminuria for the last two or more consecutive measurements and the geometric mean for all of their AER values also indicated microalbuminuria. In the follow-up period, the status of diabetic nephropathy was determined by the geometric mean of AER as measured during each follow-up period. The mean measurements of AER in each study period were 2.7 times (range 2–9) in the initial evaluation period and 2.2 (2–7) in the first, 2.1 (2–7) in the second, 2.1 (2–4) in the third, and 2.0 (2–4) in the forth follow-up period.

TABLE 3
The risk of death from and hospitalization for renal and cardiovascular events, evaluated using the pooled logistic regression analysis

	Crude risk (95% CI)	Adjusted risk (95% CI)	
		Model 1	Model 2
Reduction of albuminuria			
50% reduction	0.38 (0.16–0.91)	0.47 (0.17–0.98)	0.41 (0.15–0.96)
Nonreduction	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Stage of diabetic nephropathy			
Remission	0.30 (0.09–0.98)	0.27 (0.08–0.91)	0.25 (0.07–0.87)
No change	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Progression	2.31 (1.06–5.07)	2.45 (1.06–5.65)	2.55 (1.04–6.30)

Model 1 adjusted for sex and age, initial AER levels, and a history of cardiovascular disease. Model 2 adjusted for sex, age, initial AER levels, a history of cardiovascular disease, current smoking, A1C, total and HDL cholesterol, triglyceride, systolic and diastolic blood pressure, BMI, and the use of ACE inhibitors, angiotensin receptor blockers, or lipid lowering-drugs. ref., referent.

Definition of remission and a 50% reduction of microalbuminuria. According to diabetic nephropathy status in each 2-year follow-up period, remission was defined as shift from microalbuminuria to normoalbuminuria, and progression was defined as shift into overt proteinuria. We also evaluated the effect of a 50% reduction on the geometric mean of AER from the initial evaluation period.

Definition of renal and cardiovascular event. The primary study evaluation was death from and hospitalization for renal and cardiovascular events. Nonfatal renal, cardiovascular, and cerebrovascular events were defined as hospitalization for the first occurrence of required dialysis, myocardial infarction, angina, a worsening of congestive heart failure, and stroke in the follow-up period. Myocardial infarction was defined as a clinical presentation characterized by typical symptoms, electrocardiographic changes associated with an elevation of cardiac biomarkers, and angiographic evidence of coronary thrombosis. Angina was defined as a history of typical chest pain and electrocardiographic changes compatible with ischemic heart disease or the detection of myocardial perfusion defects with exercise stress tests. A worsening of congestive heart failure was defined as events requiring hospitalization for worsening typical symptoms of heart failure (validated by echocardiography). Stroke was defined as a persistent focal neurological symptom in which onset was sudden and not due to trauma or a tumor and where the responsible lesion was detected by imaging studies. These assessments were evaluated by an observer who did not know the patient's status of albuminuria.

Annual decline rate of eGFR. The eGFR was estimated by using equation 6 in the MDRD study (20). In this study, we used the adjusted values of creatinine, which were measured by the enzymatic method, to adapt to this equation. The annual decline rate in eGFR was determined from the slope of the plot of all measurements of eGFR for each individual (median 8 times [range 4–13]) and then was calculated using a linear regression analysis. In this analysis, 199 subjects (88 in the 50% reduction group and 111 in the nonreduction group) with three or more measurements of eGFR in the follow-up period were included.

Statistical analysis. A comparison between the groups was performed by using χ^2 tests for categorical variables, an unpaired Student's t test, ANOVA followed by Tukey test for normally distributed variables, and the Mann-Whitney U test and Kruskal-Wallis for non–normally distributed variables. For a time-to-first-event analysis, the association between the reduction of microalbuminuria and the first occurrence of an evaluated event in the follow-up period was estimated using the Kaplan-Meier procedure, and it was compared by the log-rank test. In this analysis, all the subjects who attained remission or a 50% reduction of microalbuminuria in at least one period before the occurrence of any evaluated events were considered as in the remission or the 50% reduction groups. The follow-up time was censored if the evaluated event first occurred or if the patient was unavailable for follow-up. Furthermore, to adjust the influence of conventional risk factors modified during the study period, we applied the pooled logistic regression method. This method is equivalent to a Cox time-dependent regression analysis, and it allows the covariates in the multivariate models to change over time (11). All time-dependent variables at each 2-year period were averaged. All data were analyzed using the SPSS software package (version 11; SPSS, Chicago, IL).

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