Incidence and Determinants of Microalbuminuria in Koreans With Type 2 Diabetes

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OBJECTIVE — The incidence of diabetic nephropathy in type 2 diabetes differs widely by race. Although clinical proteinuria is reportedly more common in East Asian type 2 diabetic patients than in their Caucasian counterparts, data on the incidence of microalbuminuria are not available. This study was undertaken to investigate the incidence and the determinants of microalbuminuria in Korean type 2 diabetic patients.

RESEARCH DESIGN AND METHODS — A cohort of 188 Korean type 2 diabetic patients with initial normoalbuminuria were followed prospectively for 5.5 ± 0.9 years in an outpatient clinic of a university hospital. The incidence of elevated urinary albumin excretion (UAE) (>20 μg/min) and its relationship with baseline characteristics and follow-up data were determined.

RESULTS — Of the 146 patients who finished the study, 37 showed persistently elevated UAE during follow-up, giving an incidence of 52/1,000 person-years. Age, duration of diabetes, and baseline UAE were significantly higher in the progressors than in the nonprogressors. More patients in the progressor group had retinopathy at baseline and at the end of follow-up. The mean values of fasting plasma glucose, HbA_1, and systolic and diastolic blood pressure during the follow-up period were significantly higher in the progressors than in the nonprogressors. Cox proportional hazards analysis revealed that presence of retinopathy, duration of diabetes, mean fasting plasma glucose, and mean systolic blood pressure during follow-up are independent variables that have a statistically significant influence on the development of microalbuminuria.

CONCLUSIONS — The incidence of microalbuminuria in Korean type 2 diabetic patients is lower than that reported in Pima Indians with type 2 diabetes but is as high as that in Caucasians with type 1 diabetes. Presence of diabetic retinopathy, poor glycemic control, and high blood pressure are risk factors for development of microalbuminuria in Koreans with type 2 diabetes.

Elevated urinary albumin excretion (UAE) is an early clinical manifestation of diabetic renal disease. Elevations below the sensitivity of standard dipstick tests for proteinuria (microalbuminuria) predict the development of more advanced renal disease in both type 1 (1,2) and type 2 diabetes (3,4). It is well established that strict metabolic control can prevent the development of microalbuminuria in type 1 diabetes (5,6). However, limited information is available on the determinants of microalbuminuria in type 2 diabetes (7–10).

The incidence of diabetic nephropathy differs widely by race and type of diabetes. Studies in Caucasian populations showed that end-stage renal disease (ESRD) occurs in 30–40% of patients with type 1 diabetes, but less frequently in patients with type 2 diabetes (11,12). Studies in black Americans and Pima Indians showed that the incidence of ESRD due to type 2 diabetes is about four to six times higher in these populations than in Caucasians (12–14). Similarly, we and others reported that clinical proteinuria is more frequently found in East Asian type 2 diabetic patients than in their Caucasian counterparts (15,16). However, the incidence of increased UAE in the range of microalbuminuria in the Far East Asian populations has not been reported. This prospective study was undertaken to examine the incidence and determinants of microalbuminuria in Korean subjects with type 2 diabetes.

RESEARCH DESIGN AND METHODS

The study was performed in type 2 diabetic patients attending a diabetes clinic of a university hospital (the Asan Medical Center) in Seoul, South Korea. Since 1990, all type 2 diabetic patients regularly attending the clinic had been asked to participate in a longitudinal study investigating the development and progression of vascular complications of diabetes. Among 431 subjects who were asked, 248 (58%) gave informed consent to follow-up protocol during 1990–1991, as approved by the institutional ethics committee.

Patients collected a timed overnight urine sample for the determination of UAE by radioimmunoassay (Diagnostic, Los Angeles, CA). This was repeated 4 weeks later. Patients were recalled for a third urine sample if the results of the initial two were inconsistent. Normoalbuminuria was considered to be present if UAE was consistently <20 μg/min. Microalbuminuria was defined as a mean of UAE between 20 and 200 μg/min and overt proteinuria as a mean UAE >200 μg/min (11). Among the 248 patients, 32 had microalbuminuria and 28 had overt proteinuria at baseline. Of the remaining 188 normoalbuminuric patients, 146 patients (78%) were followed for a period of 5.5 ± 0.9 years (4.1–6.8).

Patients were followed every 3 months. Medical care was provided to the patients independent of the study protocol. At every

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Abbreviations: ESRD, end-stage renal disease; FPG, fasting plasma glucose; MAP, mean arterial pressure; UAE, urinary albumin excretion.

Table 1—*Incidence rates (cases/1,000 person-years) of elevated UAE by duration of diabetes*

Duration of diabetes (years)	Person-years at risk	Cases	Incidence rate
0–5	38.5	1	26.0
6–10	259.6	7	27.0
11–15	237.4	11	46.3
>15	181.6	18	99.2
Total	717.1	37	51.6

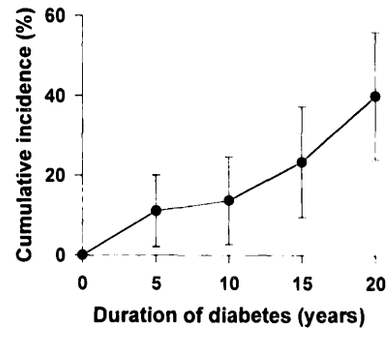

Figure 1—*Cumulative incidence (%) and 95% CIs of microalbuminuria according to duration of diabetes.*

visit, blood pressure was measured and blood samples were collected for determination of plasma glucose, lipids, and HbA_1. Blood pressure was measured with a mercury sphygmomanometer with the patient in a sitting position after a 10-min rest. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, or if antihypertensive treatment was being prescribed.

Mean arterial pressure (MAP) was calculated as the diastolic pressure plus one-third of the systolic pressure. Plasma glucose, triglyceride, and total cholesterol levels were measured using an autoanalyzer with enzymatic techniques. HDL cholesterol was measured after heparin and manganese chloride precipitation (17). HbA_1 was measured by the affinity chromatographic method (Isolab, Akron, OH) (normal range: 4–8%). The initial values and the means of all values during follow-up were used for analysis.

Fundus examination was performed initially and at yearly intervals by an ophthalmologist after mydriasis. Diabetic retinopathy was diagnosed if the patient had microaneurysms, exudates, retinal hemorrhage, intraretinal microvascular abnormalities, venous beading, new vessels, preretinal or vitreous hemorrhage, fibrous tissue proliferation, or macular edema. UAE was measured initially and two times per year in a timed overnight urine collection. If the UAE value exceeded 20 μg/min, this measurement was repeated two more times at 3-month intervals. Persistent microalbuminuria was defined as UAE >20 μg/min on more than two of the three measurements.

The primary end point of the study was the development of persistent microalbuminuria. The period of risk was counted from the month on which the patients received baseline evaluation to the primary end point of the study, or to the last month of follow-up if the subject remained normoalbuminuric. Incidence is expressed as the number of subjects who developed persistent microalbuminuria per 1,000 person-years at risk.

Statistical analysis

Results are expressed as means ± SD. Statistical analysis was performed using SAS computer software. Comparisons between groups were made with the Student's *t* test, the χ^2 test, and the Mann-Whitney *U* test, where appropriate. The duration of diabetes, MAP, HbA_1, and fasting plasma glucose (FPG) were categorized into groups, and the effects of these variables on incidence were evaluated for linear association, controlled for the influence of covariables with the Mantel extension test or for general association (age) with a χ^2 test or stratified Mantel-Haenszel analysis. Cumulative incidence rates were calculated from the incidence rates for each interval of diabetic duration. These rates represent the proportion of subjects who would have had elevated UAE at the end of each period of diabetic duration if the duration-specific rates were constant during the time interval of the study.

Multivariate Cox proportional hazards analysis with proportionality testing by log-log survival plots was used to find independent factors associated with the development of microalbuminuria. A *P* value <0.05 (two-tailed) was considered to be statistically significant.

RESULTS

Incidence rate of microalbuminuria among type 2 diabetic patients

Of the initial cohort of 188 patients, 7 patients died. The majority died from cardiovascular events and malignancies. And of the initial cohort, 35 patients (17 men, 18 women) dropped out of the study after a follow-up period of 6–47 months: 15 moved out of the area, and 20 were unwilling to continue the study. There was no significant difference between the patients who were followed and those who dropped out with regard to age, duration of diabetes, blood pressure, and plasma glucose levels at baseline (data not shown).

Of the 146 patients who finished the study (63 men, 83 women), 37 developed microalbuminuria during follow-up, giving an incidence of 51.6/1,000 person-years. Of those who developed microalbuminuria, 30 (13 men, 17 women) remained within the microalbuminuric range and 7 (3 men, 4 women) developed overt proteinuria at the end of the follow-up.

Incidence rates of microalbuminuria according to known diabetic duration are presented in Table 1. The incidence rose with increasing duration of diabetes (χ^2_{trend} = 13.4, df = 1, $P < 0.001$, controlled for age and sex). The predicted cumulative incidence of increased UAE was 11.1% at 5 years, 13.7% at 10 years, 23.4% at 15 years, and 40.0% at 20 years of diabetic duration (Fig. 1).

Clinical characteristics of patients who developed microalbuminuria

The baseline and follow-up data for the patients who developed microalbuminuria (progressors) and those who did not (nonprogressors) are shown in Table 2. Age (65 ± 11 vs. 59 ± 10 years, $P < 0.01$) and duration of diabetes (17 ± 8 vs. 11 ± 6 years, $P < 0.01$) were higher in the progressors than in the nonprogressors. The baseline UAE was significantly higher in the progressors (8.7 ± 4.3 vs. 6.7 ± 4.0 μg/min, $P < 0.05$). More patients in the progressors had retinopathy at baseline (51 vs. 14%, $P < 0.001$) and at the end of follow-up (76 vs. 28%, $P < 0.001$). The basal FPG and HbA_1 levels were not different between the groups, but the mean FPG (9.6 ± 2.1 vs. 8.7 ± 0.9 mmol/l, $P < 0.05$) and HbA_1 (11.1 ± 2.4 vs. 9.9 ± 2.0%, $P < 0.05$) values during the follow-up

Table 2—*Comparison of clinical characteristics between subjects who did or did not develop microalbuminuria*

	Nonprogressors	Progressors
n (M/F)	109 (51/58)	37 (16/21)
Age (years)	59 ± 10	65 ± 11*
Duration of diabetes (years)	11.1 ± 5.7	16.7 ± 7.9†
BMI (kg/m²)	24.5 ± 3.2	25.2 ± 3.5
FPG (mmol/l)		
Baseline	10.2 ± 2.8	10.5 ± 3.9
Mean	8.7 ± 0.9	9.6 ± 2.1*
HbA_1 (%)		
Baseline	11.2 ± 2.4	11.4 ± 1.8
Mean	9.9 ± 2.0	11.1 ± 2.4*
Systolic blood pressure (mmHg)		
Baseline	133 ± 21	150 ± 21†
Mean	135 ± 16	146 ± 15†
Diastolic blood pressure (mmHg)		
Baseline	84 ± 12	91 ± 9*
Mean	83 ± 8	88 ± 7†
Cholesterol (mmol/l)		
Baseline	5.4 ± 1.3	5.4 ± 1.4
Mean	5.3 ± 0.9	5.4 ± 0.7
Baseline UAE (μg/min)	6.7 ± 4.0	8.7 ± 4.3*
Retinopathy		
Baseline	15 (14)	19 (51)*
At the end of follow-up	31 (28)	28 (76)†
Hypertensive at baseline	31 (28)	19 (51)*
Antihypertensive treatment		
Baseline	24 (22)	15 (41)*
At the end of follow-up	25 (23)	17 (46)*
Insulin treatment (%)	25	35

Data are means ± SD, *n* (%), or %. *$P < 0.05$ vs. nonprogressors; †$P < 0.001$ vs. nonprogressors.

period were significantly higher in the progressors than in the nonprogressors. Baseline and mean values of systolic (150 ± 21 vs. 133 ± 21 mmHg, $P < 0.001$ and 146 ± 15 vs. 135 ± 16 mmHg, $P < 0.001$, respectively) and diastolic (91 ± 9 vs. 84 ± 12 mmHg, $P < 0.05$ and 88 ± 7 vs. 83 ± 8 mmHg, $P < 0.001$, respectively) blood pressures were all significantly higher in the progressors than those in the nonprogressors. More patients among the progressors were hypertensive (51 vs. 28%, $P < 0.05$) and taking antihypertensive treatment at baseline (41 vs. 22%, $P < 0.05$) and at the end of the follow-up (46 vs. 23%, $P < 0.05$) compared with the nonprogressors.

To see the relationship between the development of microalbuminuria and blood pressure and plasma glucose levels independent from the influence of diabetic duration, we divided the patients into three groups according to the tertiles of baseline MAP, mean MAP, FPG, and HbA_1 during follow-up and into three groups according to diabetic duration (at the end of follow-up) of <10, 10–15, and >15 years. Figure 2 shows the cumulative incidence of microalbuminuria according to tertiles of these variables. Cumulative incidence increased with increasing baseline MAP ($P < 0.05$), mean MAP ($P < 0.01$), and HbA_1 ($P < 0.05$) during follow-up (*P* values are determined after adjustment for known diabetic duration by stratified Mantel-Haenszel analysis). The relationship between the development of microalbuminuria and tertiles of mean FPG during follow-up was marginally significant ($P = 0.09$).

Cox proportional hazards analysis was performed with age, duration of diabetes, baseline UAE, presence of retinopathy at baseline, mean HbA_1, and blood pressure as independent variables. This analysis revealed that duration of diabetes (risk ratio = 1.07, 95% CI 1.01–1.12, $P < 0.05$), presence of retinopathy (risk ratio = 2.38, 95% CI 1.04–5.47, $P < 0.05$), mean systolic blood pressure (risk ratio = 1.03, 95% CI 1.01–1.05, $P < 0.05$) and mean HbA_1 (risk ratio = 1.13, 95% CI 1.05–1.21, $P < 0.05$) during the follow-up were independent variables with a statistically significant influence on the development of microalbuminuria.

CONCLUSIONS — Although it is now well known that the frequency of diabetic nephropathy differs widely according to race and type of diabetes, only a few studies have evaluated the incidence of microalbuminuria in diabetic patients (7,9,18,19). The present study reports that the incidence of increased UAE in Korean type 2 diabetic patients (51.6/1,000 person-years) is lower than that reported in Pima Indians with type 2 diabetes (83.5/1,000 person-years) (7) but is as high as that in South Indians with type 2 diabetes (46.9/1,000 person-years) (9) and Caucasians with type 1 diabetes (30–48/1,000 person-years) (18,19). Our data show that longer diabetic duration, the presence of retinopathy and higher UAE rate at baseline, and poor glycemic and blood pressure control during follow-up are associated with the development of microalbuminuria in type 2 diabetes. These results are in line with our previous cross-sectional data showing that Korean type 2 diabetic patients with microalbuminuria are characterized by longer diabetic duration, higher blood pressure, and higher prevalence of retinopathy (15).

The cause of the apparently high incidence of microalbuminuria in Korean type 2 diabetic patients is presently unknown. Genetic factors have been implicated in the pathogenesis of diabetic nephropathy (20). Ethnic differences in these genetic factors, which have not yet been clearly identified, may be responsible. On the other hand, this may be due to the differences in preventable causes such as glycemic and blood pressure control, diet, access to health care, or some other factors. Certainly, future studies are necessary to answer this question.

The association between albuminuria and retinopathy in type 1 diabetes is well established, but several studies in Caucasian populations reported that only 50–60% of type 2 diabetic patients with overt proteinuria have diabetic retinopathy (21–23). In contrast, we previously reported that most Korean type 2 diabetic patients with overt proteinuria have diabetic retinopathy (15). The present study again shows that the presence of retinopathy at baseline and at the end of the follow-up was strongly associated with the development of microalbuminuria. Similar finding was observed

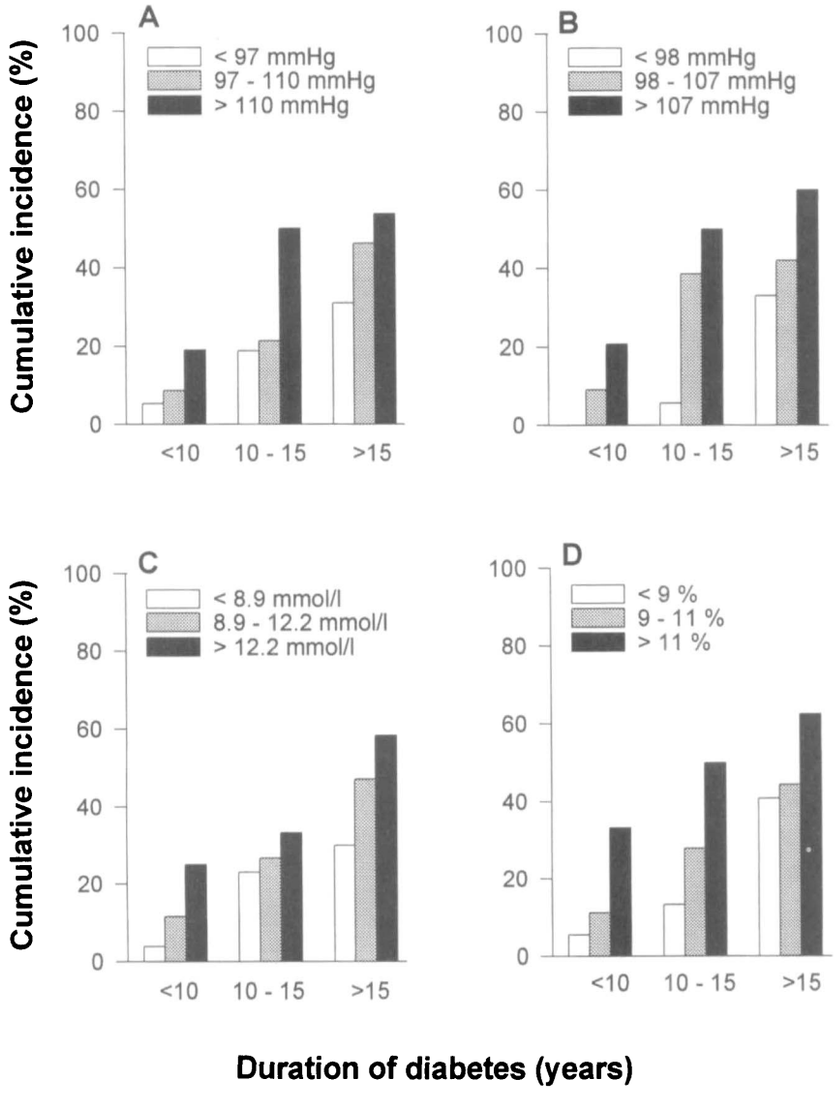

Figure 2—*Cumulative incidence (%) of microalbuminuria according to tertiles of MAP at baseline* (A), *mean MAP* (B), *FPG* (C), *and* HbA_1 (D) *during follow-up. Cumulative incidence increased with increasing baseline MAP* ($P < 0.05$), *mean MAP* ($P < 0.01$), *and* HbA_1 ($P < 0.05$) *during follow-up. (P values are determined after adjustment for known diabetic duration by stratified Mantel-Haenszel analysis.)*

previously in the study performed in Pima Indians (7), but the percentage of patients having diabetic retinopathy was much less than that in our study. It is not yet clear, however, why there is a stronger association between microalbuminuria and retinopathy in Koreans than in other racial groups.

It is now well known that intensified metabolic control can prevent the development of microalbuminuria in type 1 diabetes (5). However, the role of hyperglycemia in the genesis of microalbuminuria in type 2 diabetes is less well established. Although hyperglycemia has been shown to be a risk factor for microalbuminuria and overt proteinuria in patients with type 2 diabetes (7,8,24–28), others have failed to confirm this association (29,30). In the present study, we show that glycemic control was worse in the type 2 diabetic patients who developed microalbuminuria. These results suggest that strict metabolic control would help prevent the development of microalbuminuria.

The role of elevated blood pressure in the pathogenesis of diabetic nephropathy is also controversial. A longitudinal study in type 1 diabetes demonstrated that blood pressure was normal in most of the patients before the appearance of microalbuminuria (31). In that study, blood pressure clearly increased after the development of microalbuminuria. On the other hand, Nelson et al. (10) reported that blood pressure in the prediabetic stage was already higher in type 2 diabetic patients who later developed microalbuminuria and suggested that higher blood pressure may precede and contribute to the development of diabetic nephropathy. Our data showing higher baseline and mean systolic and diastolic blood pressure during follow-up in the progressors are in line with these results and conform to the recent suggestion that control of blood pressure would be necessary in type 2 diabetic patients to prevent the development of diabetic nephropathy (32).

In conclusion, the incidence of microalbuminuria in Korean type 2 diabetic patients is lower than that reported in Pima Indians with type 2 diabetes but is as high as that in Caucasians with type 1 diabetes. Presence of retinopathy, poor glycemic control, and high blood pressure are the major determinants of development of microalbuminuria in Koreans with type 2 diabetes.

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