Incidence and Determinants of Elevated Urinary Albumin Excretion in Pima Indians With NIDDM

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OBJECTIVE — To examine the incidence and determinants of elevated urinary albumin excretion in Pima Indians with non-insulin-dependent diabetes mellitus (NIDDM).

RESEARCH DESIGN AND METHODS — The incidence of elevated urinary albumin excretion (≥30 mg albumin/g creatinine) and its relationship with baseline characteristics was determined in 456 Pima Indians ≥15 years old with NIDDM who were followed for up to 11.6 years (median 4.7 years).

RESULTS — Of these 456 subjects, 192 (42%; 58 men, 134 women) developed elevated urinary albumin excretion, 172 of whom (90%) were within the microalbuminuric range (30–299 mg/g). The incidence of elevated urinary albumin excretion was related to retinopathy, type of diabetes treatment, longer duration of diabetes, lower body mass index, and higher values of mean arterial pressure, HbA_1, and fasting and 2-h postload plasma glucose concentration at the baseline examination, but not to sex. A relationship with cholesterol was found in durations of diabetes of ≥10 years. The cumulative incidence of elevated albumin excretion was 17% after 5 years of NIDDM.

CONCLUSIONS — The incidence of elevated urinary albumin excretion in Pima Indians with NIDDM is at least as high as that reported previously in insulin-dependent diabetes mellitus, and its major determinants are the same as those shown previously to predict the development of more advanced renal disease in this population.

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IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; BMI, body mass index; MAP, mean arterial pressure; CI, confidence interval.

Elevated urinary albumin excretion is an early clinical manifestation of diabetic renal disease, and elevations below the sensitivity of standard dipstick tests for proteinuria—often referred to as microalbuminuria—predict the development of more advanced renal disease in both insulin-dependent diabetes mellitus (IDDM) (1–4) and non-insulin-dependent diabetes mellitus (NIDDM) (5–8). However, data on the incidence and determinants of elevated urinary albumin excretion within the microalbuminuric range among people with diabetes are limited (9–11), and no data are available for NIDDM.

Pima Indians from the Gila River Indian Community in Arizona have high prevalence and incidence rates of NIDDM (12). Nearly half of those with NIDDM have elevated urinary albumin excretion (13), and the incidence of end-stage renal disease, of which over 90% is attributable to diabetes, is more than 20 times that reported in the general U.S. population (14). This study examines the incidence and determinants of elevated urinary albumin excretion in Pima Indians with NIDDM.

RESEARCH DESIGN AND METHODS

The National Institute of Diabetes and Digestive and Kidney Diseases has been conducting a study of diabetes and its complications in the Gila River Indian Community. As part of this study, each member of the Community ≥5 years of age is invited, regardless of health, to participate in research examinations every 2 years (15). These biennial examinations include an oral glucose tolerance test with determination of the glucose concentration in venous plasma drawn while the patient is fasting and 2 h after the ingestion of a 75-g carbohydrate load. World Health Organization criteria are used for the diagnosis of diabetes (16). Height and weight are measured, and body mass index (BMI) is computed as the weight divided by the square of height (kg/m^2). After pupillary dilation, the reti-

nae are examined by a physician or nurse practitioner using an ophthalmoscope. Diabetic retinopathy is diagnosed by the presence of microaneurysms, hemorrhages, exudates, or neovascularization. Blood pressure is measured to the nearest 2 mmHg with a mercury sphygmomanometer while the subject is resting in the supine position. Diastolic blood pressure is measured at the fourth Korotkoff sound. Mean arterial pressure (MAP) is calculated as the diastolic pressure plus one-third of the pulse pressure. Subjects void at the beginning of the glucose tolerance test and again approximately 2 h later. A urine specimen is collected from the second voiding and stored at −20°C until assay within 30 days.

After 1 July 1982, the starting date for this analysis, all urine specimens from subjects ≥15 years of age were assayed for albumin with a nephelometric immunoassay (17). Creatinine concentration was measured in the same urine specimen using a modification of the picrate method of Jaffe (18) and Chasson et al. (19), and an albumin:creatinine ratio (mg albumin:g creatinine) was used as a measure of urinary albumin excretion (13,20). Elevated urinary albumin excretion was defined as an albumin:creatinine ratio of ≥30 mg/g (8,13). Plasma glucose concentration was measured with an autoanalyzer. HbA_1 was measured by agar gel electrophoresis (21). Serum cholesterol concentration was measured by an enzymatic method (22).

The study population included 456 subjects ≥15 years old with NIDDM and normal urinary albumin excretion (albumin:creatinine ratio <30 mg/g) (13) at the first examination on or after 1 July 1982. The heritage of each subject was at least 50% Pima, Tohono O'odham, or a mixture of these two closely related tribes.

Table 1—*Baseline characteristics of the subjects according to whether or not they developed elevated urinary albumin excretion during follow-up*

	Remained normoalbuminuric	Developed elevated urinary albumin excretion
n (% women)	264 (67)	192 (70)
Age, years (range)	41 (16–79)	44 (15–78)
Duration of diabetes, years (range)	4.5 (0–25.1)	7.9 (0–25.6)
Prevalence of retinopathy (%)	10.3	21.5
Median albumin:creatinine ratio (mg/g)	7.4	12.2
BMI (kg/m^2)	34.3 ± 1.9	32.7 ± 1.1
MAP (mmHg)	89 ± 1	91 ± 1
Fasting plasma glucose (mmol/l)	10.2 ± 0.2	12.6 ± 0.3
2-h post-load plasma glucose (mmol/l)	15.2 ± 0.4	19.0 ± 0.4
HbA_1 (%)	8.6 ± 0.2	10.1 ± 0.2
Serum cholesterol (mmol/l)	4.52 ± 0.05	4.45 ± 0.06
Prevalence of antihypertensive treatment (%)	13.0	13.6
Prevalence of diabetes treatment (% oral hypoglycemic drugs, % insulin)	30.3, 17.0	50.0, 31.2

Data are means ± SE unless otherwise indicated. Retinopathy data were missing in 2 subjects. Fasting plasma glucose data were missing in 2 subjects. HbA_1 data were missing in 27 subjects. Antihypertensive treatment data were missing in 3 subjects.

Statistical analysis

Incidence is expressed as the number of subjects who developed elevated urinary albumin excretion at a subsequent examination per 1,000 person-years at risk. The period of risk extended from the date of the first examination to the date on which elevated urinary albumin excretion was first detected or, if the subject had not developed elevated albumin excretion, to the date of the last examination up to 31 December 1993. Incidence was calculated as the number of cases divided by the person-years of follow-up in each age and duration category. When the values for age and duration of diabetes changed during follow-up, person-years for each subject were apportioned to the appropriate strata.

Potential risk factors for elevated urinary albumin excretion (BMI, MAP, HbA_1, fasting and 2-h postload plasma glucose concentration, serum cholesterol concentration, retinopathy, and type of diabetes treatment) were analyzed and stratified by age, sex, and duration of diabetes. To evaluate the relationship between the type of diabetes treatment and elevated urinary albumin excretion, subjects were classified at their first examination according to whether they had ever received insulin or oral hypoglycemic drugs (but no insulin) or had received neither type of drug. Likewise, values for all variables other than age and duration of diabetes were measured (and fixed) at the first examination.

Incidence-rate ratios were used to express the effect of the dichotomous variables (sex, retinopathy, and drug treatment) on the incidence of elevated urinary albumin excretion. These ratios and their confidence intervals (CIs) were computed by a modification of the Mantel and Haenszel procedure for follow-up data (23,24). Continuous variables (duration of diabetes, BMI, MAP, HbA_1, fasting and 2-h postload plasma glucose concentrations, and serum cholesterol concentration) were categorized into groups, and their effects were evaluated for linear association, controlled for the influence of covariables, with the Mantel extension test (25) or for general association (age) with a χ^2 test (26) modified for person-time denominators (24). For these analyses, comparisons were made using only strata in which person-years of follow-up were present in each category of the variables.

Cumulative incidence rates were

Table 2—*Incidence rates (cases/1,000 person-years) of elevated urinary albumin excretion in diabetic Pima Indians ≥15 years of age by sex*

Age (years)	Men			Women		
	Person-years at risk	Cases	Incidence rate	Person-years at risk	Cases	Incidence rate
15–24	56.2	5	89.0	65.7	4	60.9
25–34	73.7	4	54.3	285.3	13	44.6
35–44	199.8	12	60.1	386.4	25	64.7
45–54	219.9	20	91.0	434.2	43	99.0
55–64	105.8	11	104.0	306.2	34	111.0
≥65	42.6	6	140.8	123.5	15	121.5
Total	698.0	58	83.1	1,601.3	134	83.7

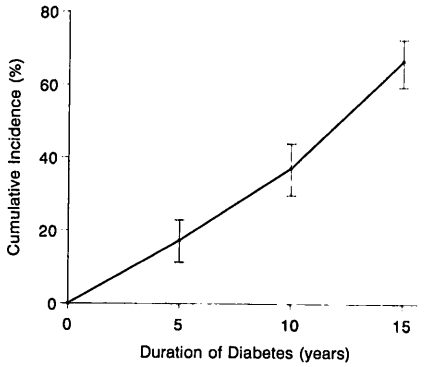

Figure 1—*Cumulative incidence (%) and 95% CIs of elevated urinary albumin excretion according to the duration of diabetes in Pima Indians ≥15 years old.*

calculated from the incidence rates for each interval of diabetes duration. These rates represent the proportion of subjects who would have had elevated urinary albumin excretion at the end of each period of diabetes duration if the duration-specific incidence rates were constant during the time interval of the study. CIs for the cumulative incidence rates were computed as described previously (27).

RESULTS— Of 456 subjects (146 men, 310 women) ≥15 years of age with NIDDM and normal urinary albumin excretion at the baseline examination, 192 (42%; 58 [40%] men and 134 [43%] women) developed elevated urinary albumin excretion during follow-up. Of those developing elevated urinary albumin excretion, 172 (90%) were within the microalbuminuric range (30–299 mg/g) when elevated urinary albumin excretion was detected. Median follow-up of the 456 subjects was 4.7 years, with a maximum of 11.6 years. Of the 192 subjects who developed elevated urinary albumin excretion, 102 (53%) had at least one subsequent examination and in 77 (75%) elevated urinary albumin excretion persisted. Baseline characteristics of the subjects are presented in Table 1.

Incidence rates of elevated urinary albumin excretion are presented in Table 2 according to age and sex. The overall incidence was similar in men and women (incidence rate ratio [men:women] 1.0; 95% CI, 0.7–1.4, controlled for age) and was higher at older ages in women (χ^2 = 13.1, df = 5, P = 0.023) but not in men (χ^2 = 4.5, df = 5, P = 0.49). The relationship with age, however, was not significant in either sex after controlling for the duration of diabetes (χ^2 = 1.1, df = 5, P = 0.96 in men; χ^2 = 3.3, df = 5, P = 0.66 in women). The incidence rose with increasing duration of diabetes (χ^2_{trend} = 46.7, df = 1, P < 0.001, controlled for age and sex) as shown in Table 3. The predicted cumulative incidence of elevated urinary albumin excretion was 17% at 5 years, 37% at 10 years, and 67% at 15 years of diabetes duration (Fig. 1).

The incidence of elevated urinary albumin excretion was examined in relation to variables measured at the first examination. In the 68 subjects who had retinopathy at the first examination, the incidence of elevated urinary albumin excretion was 1.6 times as high as in those who did not (95% CI, 1.1 to 2.2, controlled for age, sex, and duration of diabetes). Elevated urinary albumin excretion was also associated with higher MAP (χ^2_{trend} = 16.8, df = 1, P < 0.001), 2-h plasma glucose concentration (χ^2_{trend} = 37.7, df = 1, P < 0.001), and lower BMI (χ^2_{trend} = 5.7, df = 1, P < 0.02), controlled for age, sex, and duration of diabetes. The relationship with cholesterol was significant only at durations of diabetes of ≥10 years (χ^2_{trend} = 4.8, df = 1, P = 0.029). Fig. 2 shows the cumulative incidence of elevated urinary albumin excretion according to tertiles of these variables. Higher fasting plasma glucose concentration (available for all but 1 subject; χ^2_{trend} = 35.6, df = 1, P < 0.001) and HbA_1 (available for all but 27 subjects; χ^2_{trend} = 10.1, df = 1, P = 0.002) also predicted elevated urinary albumin excretion.

Of the 456 subjects in this study, 105 (23%; 28 men and 77 women) had received treatment with insulin by their first examination and 113 (25%; 43 men and 70 women) had received only oral hypoglycemic agents. The incidence of el-

Table 3—*Incidence rates (cases/1,000 person-years) of elevated urinary albumin excretion in diabetic Pima Indians ≥15 years of age by duration of diabetes*

Duration of diabetes (years)	Person-years at risk	Cases	Incidence rate
0–4	739.7	28	37.9
5–9	670.3	37	55.2
10–14	482.3	61	126.5
≥15	406.9	66	162.2
Total	2,299.2	192	83.5

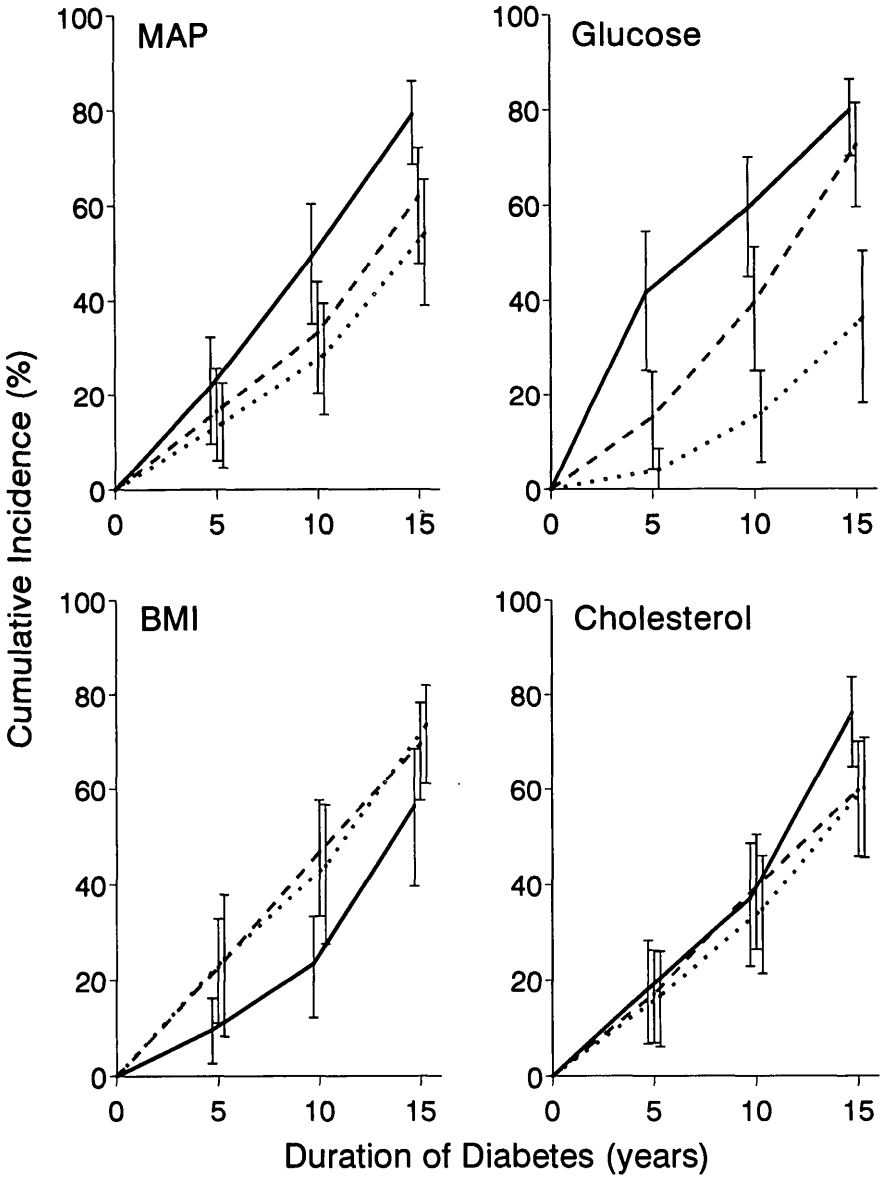

Figure 2—*Cumulative incidence (%) and 95% CIs of elevated urinary albumin excretion in diabetic Pima Indians ≥15 years old according to tertiles of MAP, 2-h postload plasma glucose concentration, BMI, and serum cholesterol concentration at the baseline examination.* ——, *highest tertile;* – – – –, *middle tertile;* • • • • •, *lowest tertile.*

evated urinary albumin excretion in insulin-treated subjects was somewhat higher than that in the subjects treated only with oral agents (incidence rate ratio [insulin: oral drug] 1.4; 95% CI, 1.0–1.9; controlled for age, sex, and duration of diabetes). The incidence in subjects treated with either insulin or oral drugs, however, was 2.8 times that in those who had not received either drug at the time of the initial examination (95% CI, 1.9–4.2).

CONCLUSIONS— Pima Indians with NIDDM are at substantial risk of developing elevated urinary albumin excretion, with an incidence rate twice that reported in IDDM (9–11). Coonrod et al. (9) reported an incidence of urinary albumin excretion >20 μg/min of 4.8 cases/100 person-years among 256 subjects with IDDM who were followed for 2 years, and Rudberg et al. (11) reported an incidence of 3.0 cases/100 person-years among 156 subjects followed for 15 years. The incidence based on a median follow-up of 4.7 years in Pima Indians (sexes combined) with NIDDM was 8.4 cases/100 person-years. The 10-year cumulative incidence of urinary albumin excretion ≥30 mg/24 h was 18% in 200 subjects with IDDM followed for 10 years by Mathiesen et al. (10), and the 15-year cumulative incidence reported by Rudberg et al. (11) was 24%. The cumulative incidence based on incidence rates in duration-specific strata in Pima Indians was 37% at 10 years and 67% at 15 years. These cumulative incidence rates are compatible with the duration-specific prevalence rates of elevated urinary albumin excretion reported previously in this population (13). To our knowledge, the incidence of elevated urinary albumin excretion has not been reported previously in NIDDM.

Because urinary albumin excretion was measured at intervals of 2 years or more in this study and the onset of elevated albumin excretion could precede its detection by several months, the incidence of elevated excretion in Pima Indians may be underestimated. On the other hand, only a single measurement of urinary albumin excretion was required for the detection of elevated urinary albumin excretion, whereas at least two measurements were required to determine its presence in previous studies (9–11). Given the fluctuating nature of urinary albumin excretion (6), a single measurement may overestimate the incidence of persistent albuminuria. Nevertheless, urinary albumin excretion remained elevated at subsequent research examinations in three-fourths of Pima Indians in whom it was detected by a single measurement. Even if one-fourth of the incident cases had only transient elevations of urinary albumin excretion, the incidence is still at least as high as reported previ-

ously in IDDM. The number of subjects whose urinary albumin excretion returned to normal after the diagnosis of elevated excretion in the previous studies (9–11) is not known.

In Pima Indians, the level of albuminuria was determined by albumin:creatinine ratios, whereas timed excretion rates were used in the previous studies (9–11). Nonetheless, the albumin:creatinine ratio provides an excellent estimate of timed excretion rates in Pima Indians, because an albumin:creatinine ratio of 30 mg/g is approximately equivalent to an excretion rate of 33 μg/min in men or 21 μg/min in women (unpublished data derived from a comparison of urinary albumin:creatinine ratios with 2-h timed excretion rates in 143 subjects). Consequently, excretion ratios and timed excretion rates should give comparable results for incidence of elevated urinary albumin excretion.

Many of the changes in plasma lipoproteins associated with renal disease are believed to be sequelae of the renal dysfunction, but recent studies have suggested that hyperlipidemia is associated with the development of glomerular injury (28,29). Coonrod et al. (9) have reported that higher low-density lipoprotein cholesterol and triglyceride levels predicted the development of elevated urinary albumin excretion in IDDM. Similar findings for total serum cholesterol were seen in this study, but only in those with diabetes of long duration.

Obesity is common among the Pima Indians (30), and the most obese subjects were at the lowest risk of developing elevated urinary albumin excretion. This finding is compatible with previous studies that found lower risks of retinopathy (31,32) and death from coronary heart disease (33) among Pima Indians with higher degrees of obesity and suggests that slenderness in these diabetic patients reflects a greater severity of diabetes, which in turn leads to a greater risk of diabetic complications. Other factors, such as the presence of retinopathy, type of diabetes treatment, longer duration of diabetes, higher blood pressure, and plasma glucose concentration were also found to predict the development of elevated urinary albumin excretion within the microalbuminuric range.

Renal disease is a major source of morbidity and mortality in NIDDM and is the leading cause of death in Pima Indians with NIDDM (34). In this population, the principal marker of progressive renal disease is elevated urinary albumin excretion (8,14), and its incidence was at least as high as that reported previously in IDDM. The major determinants of elevated urinary albumin excretion are the same as those shown previously to predict the development of more advanced renal disease in this population (14,27,35,36).

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