



Published in final edited form as:

Pediatrics. 2010 April ; 125(4): e844–e851. doi:10.1542/peds.2009-1230.

Predictive value of albuminuria in American Indian youth with or without type 2 diabetes

Nan Hee Kim, MD, PhD^{1,2}, Meda E. Pavkov, MD, PhD^{1,3}, William C. Knowler, MD, DrPH¹, Robert L. Hanson, MD MPH¹, E. Jennifer Weil, MD¹, Jeffrey M. Curtis, MD, MPH¹, Peter H. Bennett, MB, FRCP¹, and Robert G. Nelson, MD, PhD¹

¹Diabetes Epidemiology and Clinical Research Section, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Phoenix, Arizona

²Department of Endocrinology and Metabolism, Korea University Medical School, Seoul, Korea

³Centers for Disease Control and Prevention, Atlanta, GA

Abstract

Objective—We examined the prognostic significance of elevated albuminuria in youth with type 2 diabetes.

Patients and Methods—Cross-sectional and prospective studies were conducted in Pima Indian youth aged 5-19 years at baseline who were examined between July 1, 1982 and December 31, 2007. Prevalence and sequential changes in the level of microalbuminuria (30–300 mg/g albumin-to-creatinine ratio) and macroalbuminuria (albumin-to-creatinine ratio \geq 300 mg/g) and incidence of macroalbuminuria were computed according to the presence or absence of type 2 diabetes.

Results—The prevalence of micro- and macroalbuminuria was 6.5% and 0.6% in the 3,856 nondiabetic youth and 18.5% and 2.9% in the 103 youth with diabetes. One-hundred-forty-one (75.4%) of 187 nondiabetic youth, but only one (7.1%) of 14 diabetic youth with elevated albumin-to-creatinine ratio (\geq 30 mg/g) regressed to undetectable or normal albumin-to-creatinine ratio ($<$ 30 mg/g) on subsequent examination. In a subset of 2,666 youth with a median follow-up of 8.1 years, 36 nondiabetic and 30 diabetic youth with baseline albumin-to-creatinine ratio $<$ 300 mg/g developed macroalbuminuria. For a given albumin-to-creatinine ratio level, the incidence of macroalbuminuria was 15.9-fold (95% CI = 11.1 to 22.6) higher in the diabetic than in the nondiabetic youth.

Conclusions—Elevated albuminuria is infrequent and largely transient in nondiabetic youth, but is relatively frequent and largely persistent in those with diabetes. Microalbuminuria in youth with type 2 diabetes strongly predicts progression to macroalbuminuria, supporting annual screening for albuminuria.

Keywords

diabetic nephropathy; epidemiology; incidence; longitudinal; prevalence; risk factors

Corresponding author: Dr. Robert G. Nelson, National Institutes of Health, 1550 East Indian School Road, Phoenix, AZ 85014-4972 USA. rgnelson@niddk.nih.gov Telephone: (602) 200-5205 Facsimile: (602) 200-5225.

Financial Disclosures: none

Conflicts of Interest: none

Introduction

Type 2 diabetes is emerging among youth and accounts for up to 45% of new cases of diabetes in persons less than 20 years old [1, 2]. Elevated urinary albumin excretion is an early marker of kidney disease in youth and adults with type 1 diabetes [3-7], but the prognostic significance of elevated albuminuria in youth with type 2 diabetes or in nondiabetic youth is not clear. Most studies of the prevalence and risk factors for elevated albuminuria in youth with type 2 diabetes are clinic-based [8-11] and may therefore suffer from referral bias and not accurately reflect the long-term implications of elevated albuminuria in a diabetic population.

Among Pima Indian youth from the Gila River Indian Community, the prevalence of type 2 diabetes has increased two-fold since 1967 [12]. Diabetes is entirely type 2 [13, 14], and kidney disease is a major complication of diabetes in this population [15]. We describe sequential changes in urinary albumin-to-creatinine ratio (ACR) and estimate prevalence of micro- and macroalbuminuria in Pima Indians aged 5-19 years with or without type 2 diabetes. In a prospective analysis, we compute incidence of macroalbuminuria according to ACR level.

Patients and Methods

Since 1965, members of the Gila River Indian Community who were 5 years old were invited to have a research examination approximately every 2 years. This study was approved by the National Institute of Diabetes and Digestive and Kidney Diseases. Each participant gave informed consent.

Examinations were conducted after an overnight fast and included measurement of venous plasma glucose, obtained 2h after a 75g oral glucose load, and assessment for complications of diabetes. Diabetes was diagnosed by 1985 World Health Organization criteria [16] when the 2h post-load plasma glucose (2hPG) was ≥ 11.1 mmol/l (200 mg/dl), impaired glucose tolerance (IGT) when the 2hPG was ≥ 7.8 mmol/l (140 mg/dl) and <11.1 mmol/l (200 mg/dl), and normal glucose tolerance (NGT) when the 2hPG was <7.8 mmol/l (140 mg/dl). Fasting glucose was not measured routinely, so for consistency only the 2hPG was used for diagnosis. The date of diagnosis of diabetes was determined from these examinations or from review of clinical records if diabetes was diagnosed during routine care.

Albumin and creatinine concentrations were measured in urine specimens collected at the end of the glucose tolerance test. Urinary albumin was measured at all examinations on or after July 1, 1982 by nephelometric immunoassay [17] and urinary creatinine by a modification of the Jaffe reaction [18]. Microalbuminuria was defined by an ACR ≥ 30 and <300 mg albumin/g creatinine and macroalbuminuria by an ACR ≥ 300 mg/g. Urinary albumin concentrations below the threshold detected by the assay (6.8 mg/l or lower) were shown as undetectable in the frequency distribution, but were combined with normal ACR for other analyses. ACR ≥ 30 mg/g, i.e., microalbuminuria or macroalbuminuria, was considered "elevated".

Glomerular filtration rate (eGFR) was estimated using the Schwartz equation [19] in subjects <18 years old and by the 4-variable Modification of Diet in Renal Disease (MDRD) study equation [20] in those ≥ 18 years old and the level of eGFR was staged according to National Kidney Foundation guidelines [21]. Mean arterial pressure (MAP) was calculated as $(\text{systolic blood pressure} + 2 \times \text{diastolic blood pressure})/3$. Body mass index (BMI) was defined as weight divided by the square of height (kg/m^2). BMI standard deviation scores (SDS) were derived from the Centers for Disease Control and Prevention standards [22]. HbA1c was measured by electrophoresis [23] through December 1989, and HbA1c by high-

performance liquid chromatography [24] thereafter. The correlation between the two measures was 0.92, and a linear regression formula $HbA1c = 0.99 \times HbA1 - 1.535$ was used to estimate HbA1c in the 710 subjects in whom HbA1 was measured [25].

The study population included persons of at least half Pima or Tohono O'odham heritage who were ≥ 5 years of age and had one or more research examinations between July 1, 1982 and December 31, 2007 that included ACR measurements. Subjects 5-19 years old were classified as youth and those ≥ 20 years old as adults.

Statistical Analysis

Cross-sectional analysis used data from the first research examination during the study period. Clinical features at baseline were compared between groups by analysis of covariance adjusted for age and sex. Differences in ACR between groups were analyzed with the Kruskal–Wallis test. Mean glycemia levels in the newly-diagnosed and known diabetic youth and mean BMI SDS between diabetic and nondiabetic youth were compared by t-tests. Relative frequency distributions of ACR in youth were examined on a logarithmic scale according to the presence or absence of diabetes, and compared with those in adults. All other cross-sectional and longitudinal analyses included only those who were youth at the first research examination; follow-up for the sequential assessment of albuminuria or for the incidence of macroalbuminuria could extend into adulthood. The associations of micro- and macroalbuminuria with glucose tolerance were analyzed by the Mantel-Haenszel Chi-square test adjusted for age and sex [26]. The 50th, 75th, and 95th percentiles of ACR were computed by age. Sequential changes in ACR category were assessed in those who remained in the same nondiabetic or diabetic category at a second research examination.

Incidence of macroalbuminuria was computed as the number of new cases per 1,000 person-years at risk. New cases were identified at the first appearance of macroalbuminuria in subjects who had at least one previous examination before 20 years of age with an ACR < 300 mg/g. In nondiabetic subjects, the period at risk extended from the date of the first nondiabetic research examination to the date of the first nondiabetic examination at which macroalbuminuria was diagnosed or, in those who did not develop macroalbuminuria, to the date of the last nondiabetic examination within the study period. In diabetic subjects, the period at risk extended from the date of the first diabetic examination to the date of the first examination at which macroalbuminuria was diagnosed or, in those who did not develop macroalbuminuria, to the date of the last examination within the study period. Subjects could be counted as both nondiabetic and diabetic if they developed diabetes during follow-up and had at least two nondiabetic and two diabetic examinations with ACR measurements. Time-dependent Cox regression models were used to estimate the risk of macroalbuminuria associated with ACR level adjusted for age, sex, BMI, blood pressure and duration of diabetes (in the diabetic subjects). The final model in the diabetic subjects was stratified by blood pressure because this variable violated proportionality assumptions and by sex because of its significant interaction with ACR.

Tests for linear association, controlled for age and sex, were computed by the Mantel extension test [27] modified for person-time denominators. Poisson regression was used to examine the incidence of macroalbuminuria in diabetic youth relative to nondiabetic youth adjusted for ACR [28]. Analyses were performed using SAS software version 8 (SAS Institute, Cary, NC).

Results

The cross-sectional study included 3,959 Pima Indian youth (3,597 with NGT, 259 with IGT, and 103 with diabetes). The prevalence of elevated albuminuria was virtually identical

in youth with NGT (7.2%) and IGT (6.6%), but was significantly higher in those with type 2 diabetes (21.4%; $p < 0.0001$). Accordingly, NGT and IGT were combined in subsequent analyses. Characteristics of the youth are presented in Table 1. Youth with diabetes had higher BMI, BMI SDS, blood pressure, eGFR, and median ACR, and lower serum creatinine concentration than those without diabetes ($p < 0.001$). By definition, measures of glycemia were also higher in the youth with diabetes. Among the diabetic youth, those known to have diabetes at the baseline examination had, on average, higher HbA1c ($9.5\% \pm 3.3$ vs. $7.1\% \pm 2.4$; $p < 0.001$) and slightly higher 2hPG (18.3 ± 7.8 mmol/L vs. 16.3 ± 5.0 mmol/L; $p = 0.23$) than those with newly-diagnosed diabetes. Median ACR level was undetectable in the nondiabetic youth, and the youngest subjects had the highest 75th and 95th percentiles of ACR. By contrast, the proportion of diabetic youth with detectable ACR was far higher. At baseline, one nondiabetic youth with chronic glomerulonephritis had an eGFR < 60 ml/min/1.73m² and 15 had eGFR of 60-89 ml/min/1.73m²; no diabetic youth had eGFR < 90 ml/min/1.73m². Only four nondiabetic youth and three diabetic youth reported taking antihypertensive medicines at baseline.

Relative frequency distributions of ACR in youth and adults are compared in Figure 1. In nondiabetic subjects, 56.0% of the youth and 44.0% of the adults had undetectable albuminuria. The prevalence of micro- and macroalbuminuria in nondiabetic subjects was 6.5% and 0.6% in the youth and 8.1% and 1.5% in the adults, respectively (Figure 1A). In diabetic subjects, 45.6% of the youth and 27.6% of the adults had undetectable albuminuria. The prevalence of micro- and macroalbuminuria in diabetic subjects was 18.5% and 2.9% in the youth and 27.5% and 18.2% in the adults, respectively (Figure 1B).

Sequential changes in ACR category were examined in the 2,549 nondiabetic and 76 diabetic youth who remained in the nondiabetic or diabetic category for two successive examinations (Table 2). The median time between the two ACR measurements was 2.8 years (range = 1.1-24.0 years) in nondiabetic subjects and 3.0 years (range = 1.1-17.8 years) in diabetic subjects. Among those with normal ACR at the first measurement, 94.1% of the nondiabetic subjects and 53.2% of the diabetic subjects remained in this category at the second measurement. Among those with micro- or macroalbuminuria at the first measurement, 75.4% of the nondiabetic subjects regressed to normal or undetectable ACR, whereas only one (7.1%) of the diabetic subjects regressed. Among those with microalbuminuria at the first measurement, two (1.2%) nondiabetic subjects progressed to macroalbuminuria, whereas three (27.3%) diabetic subjects progressed at the subsequent examination.

Incidence of macroalbuminuria was computed in 2,666 youth who had follow-up ACR measurements. Thirty-six of the 2,534 nondiabetic and 30 of the 132 diabetic subjects developed macroalbuminuria during a follow-up of up to 25.2 years. Unadjusted incidence of macroalbuminuria in nondiabetic and diabetic subjects according to the presence or absence of microalbuminuria at baseline is shown in Table 3. The incidence of macroalbuminuria was positively associated with baseline ACR in the nondiabetic ($p_{\text{trend}} = 0.001$) and more modestly in the diabetic ($p_{\text{trend}} = 0.083$) youth. The incidence of macroalbuminuria was 15.9-fold (95% CI = 11.1 to 22.6) higher in the diabetic youth when adjusted for ACR (Figure 2). The incidence of macroalbuminuria in subjects with undetectable ACR and in those with ACR < 10 mg/g was similar in both the diabetic and nondiabetic groups. In nondiabetic subjects, the age-sex-adjusted incidence of macroalbuminuria in those with microalbuminuria was 8.2 (95% CI, 2.1-32.4) times as high as in those with normoalbuminuria; in diabetic subjects the incidence was 7.6 (95% CI, 1.8-32.8) times as high (Table 3). After further adjustment for age, sex, BMI, MAP and duration of diabetes (in those with diabetes), the incidence rate ratios were 4.3 (95% CI, 1.9-9.8) and 4.2 (95% CI, 1.6-11.3) in the nondiabetic and diabetic subjects, respectively.

These results were unchanged if systolic blood pressure was substituted for MAP in the proportional-hazards models.

Follow-up data after the first appearance of macroalbuminuria were available for 21 of 36 nondiabetic subjects (58.3%) and for 22 of 30 diabetic subjects (73.3%). The 21 nondiabetic subjects had a median follow-up of 6.7 years (range=1.4-13.2 years) after the first onset of macroalbuminuria; the 22 diabetic subjects had a median follow-up of 5.0 years (range=1.0-17.5 years). Only 42.9% of the nondiabetic subjects, whereas 90.9% of the diabetic subjects, remained macroalbuminuric after its first appearance.

Discussion

The prevalence of elevated albuminuria is significantly higher in Pima Indian youth with type 2 diabetes than in those without. In those with diabetes, elevated albuminuria is more likely to persist and is highly predictive of progression to persistent macroalbuminuria, whereas in those without diabetes it is largely transient. The persistence of elevated ACR in diabetic youth is consistent with previous findings in diabetic Pima adults [29]. The frequency of persistent albuminuria is higher than in youth with type 1 in the Steno Diabetes Study [6] or the Oxford Regional Prospective Study [7].

The prevalence of micro- and macroalbuminuria in diabetic Pima youth was lower than in diabetic adults, perhaps because of the youths' shorter average duration of diabetes—more than half of the ACR measurements in the youth were made at the diagnosis of diabetes. Nevertheless, the prevalence of elevated albuminuria was similar to that reported among youth with type 2 diabetes in the SEARCH for Diabetes in Youth Study (SEARCH), but much higher than the 9% reported among those with type 1 diabetes in the same study [30]. Youth with type 2 diabetes from other populations are also reported to have a significantly higher prevalence of elevated albuminuria than those with type 1 diabetes, despite shorter duration of diabetes and lower HbA1c; however long-term follow-up was not available in these previous studies [8].

At baseline, only one nondiabetic subject had eGFR <60 ml/min/1.73m² and 15 had eGFR of 60-89 ml/min/1.73m²; no diabetic youth had eGFR <90 ml/min/1.73m². Because only one diabetic subject developed eGFR <60 ml/min/1.73m² and four developed eGFR of 60-89 ml/min/1.73m² during follow-up, progression of diabetic kidney disease was assessed only by the incidence of macroalbuminuria. The present study indicates that microalbuminuria strongly predicts progression to macroalbuminuria in diabetic youth. A similar probability of progression to macroalbuminuria was reported in the Oxford Regional Prospective Study [7] in youth and adults with type 1 diabetes. Moreover, previous findings indicate that an equivalent duration of type 2 diabetes in a young person is as damaging to the kidneys as it is in an older person [31, 32], reflecting the importance of diabetes duration, regardless of age, in the development of kidney disease in both types of diabetes.

Although the relationship between ACR and kidney disease progression is continuous, for clinical purposes a cut point is useful for identifying those at substantially increased risk. In adults, we previously arbitrarily selected an ACR cut point of 30 mg/g as abnormal, since this level was approximately the 95th percentile of ACR in a "healthy" subset of Pima Indians aged 15 years who had NGT, took no medicines, had no known renal or cardiovascular diseases, normal blood pressure, and normal serum creatinine [15]. This cut point is equivalent to 20 μg/min or 30 mg/24 hr from timed urine collections [21]. In diabetic youth with microalbuminuria by this ACR definition, the age-sex-adjusted incidence of macroalbuminuria was 7.6 times (95% CI, 1.8-32.8) as high as in those with normal ACR, suggesting that the adult cut points are useful for identifying increased risk of

more advanced kidney disease in diabetic youth. In nondiabetic youth, the incidence of macroalbuminuria was also much higher in those with ACR ≥ 30 mg/g, but the risk of developing macroalbuminuria was much lower than in those with diabetes and macroalbuminuria was more often transient. Furthermore, most nondiabetic individuals with ACR ≥ 30 mg/g regressed to normoalbuminuria. Thus, the clinical utility of measuring albuminuria is less certain in nondiabetic youth.

The prevalence of microalbuminuria in nondiabetic Pima youth was 6.5%; lower than 9.5% prevalence in nondiabetic youth in NHANES III [33]. The higher prevalence in NHANES may be due, in part, to the higher probability of undiagnosed diabetes, since subjects in that study were not tested for diabetes with an oral glucose tolerance test, as in the present study. Urinary albumin excretion in youth may also be influenced by a number of other factors, as in adults. Lower creatinine excretion for a given level of albumin excretion will increase the prevalence of microalbuminuria, particularly in younger children, due to their lower muscle mass. This effect is illustrated in Table 1 by the higher 75th and 95th percentiles of ACR in the younger nondiabetic children. Likewise, in adults, low muscle mass is an important confounder of ACR as a marker of microalbuminuria [34].

Precision of albuminuria estimates is enhanced by obtaining multiple specimens, so guidelines from the American Diabetes Association [35] and the National Kidney Foundation [21] recommend repeated measurements when screening diabetic patients. Nevertheless, single measures of albuminuria, as used in the present study, are highly predictive of progressive kidney disease in both children and adults with type 2 diabetes [36]. Moreover, a recent study in the Pima Indians [29] finds that preceding ACR measures add minimal predictive value beyond the latest measurement. Accordingly, we do not believe a single measurement of albuminuria represents a serious limitation. Furthermore, we propose that in screening situations in which multiple measurements are not feasible, a single screening test is useful for identifying persons with diabetic kidney disease.

Observations in the Pima Indians are relevant to other populations. The bimodality of plasma glucose, first described in this population [37], combined with the presence of retinopathy and nephropathy among those in the upper component of the distribution [38] led to standardized criteria for the diagnosis of diabetes adopted by the National Diabetes Data Group [39], the World Health Organization [16, 40], and the American Diabetes Association [41]. In the Diabetes Prevention Program [42], a clinical trial of diabetes prevention, Southwestern American Indians (many of whom were Pima), had the same risk of type 2 diabetes and the same reductions in risk from the interventions as members of other race/ethnic groups. Each of the major determinants of diabetic kidney disease found in the Pima Indians has been reported in other populations. Of note, type 2 diabetes in children was first reported in the Pima Indians [43]. Decades of follow-up of this population-based cohort permits us to examine the impact of elevated albuminuria in children with type 2 diabetes before it can be adequately assessed in other populations. Findings from the Pima Indians may therefore provide clinicians with potentially useful information as they encounter children with type 2 diabetes and elevated albuminuria in their practice.

Conclusion

Elevated ACR is infrequent and largely transient in youth without diabetes. On the other hand, elevated albuminuria is relatively frequent, largely persistent, and highly predictive of progression to more severe kidney disease in those with type 2 diabetes, supporting annual ACR screening in diabetic youth.

Acknowledgments

This research was supported by the Intramural Research Program of the National Institute of Diabetes and Digestive and Kidney Diseases. We are indebted to the members of the Gila River Indian Community for participating in this investigation and to the staff of the Diabetes Epidemiology and Clinical Research Section for conducting the examinations.

There are no financial arrangements between any author and any company whose product or competing product may have been mentioned in this manuscript.

Abbreviations

2hPG	two-hour post-load plasma glucose concentration
ACR	urinary albumin-to-creatinine ratio
BMI	body mass index
CI	confidence interval
eGFR	estimated glomerular filtration rate
HbA1	glycosylated hemoglobin A1
HbA1c	glycosylated hemoglobin A1c
IGT	impaired glucose tolerance
MAP	mean arterial pressure
MDRD	Modification of Diet in Renal Disease
NGT	normal glucose tolerance

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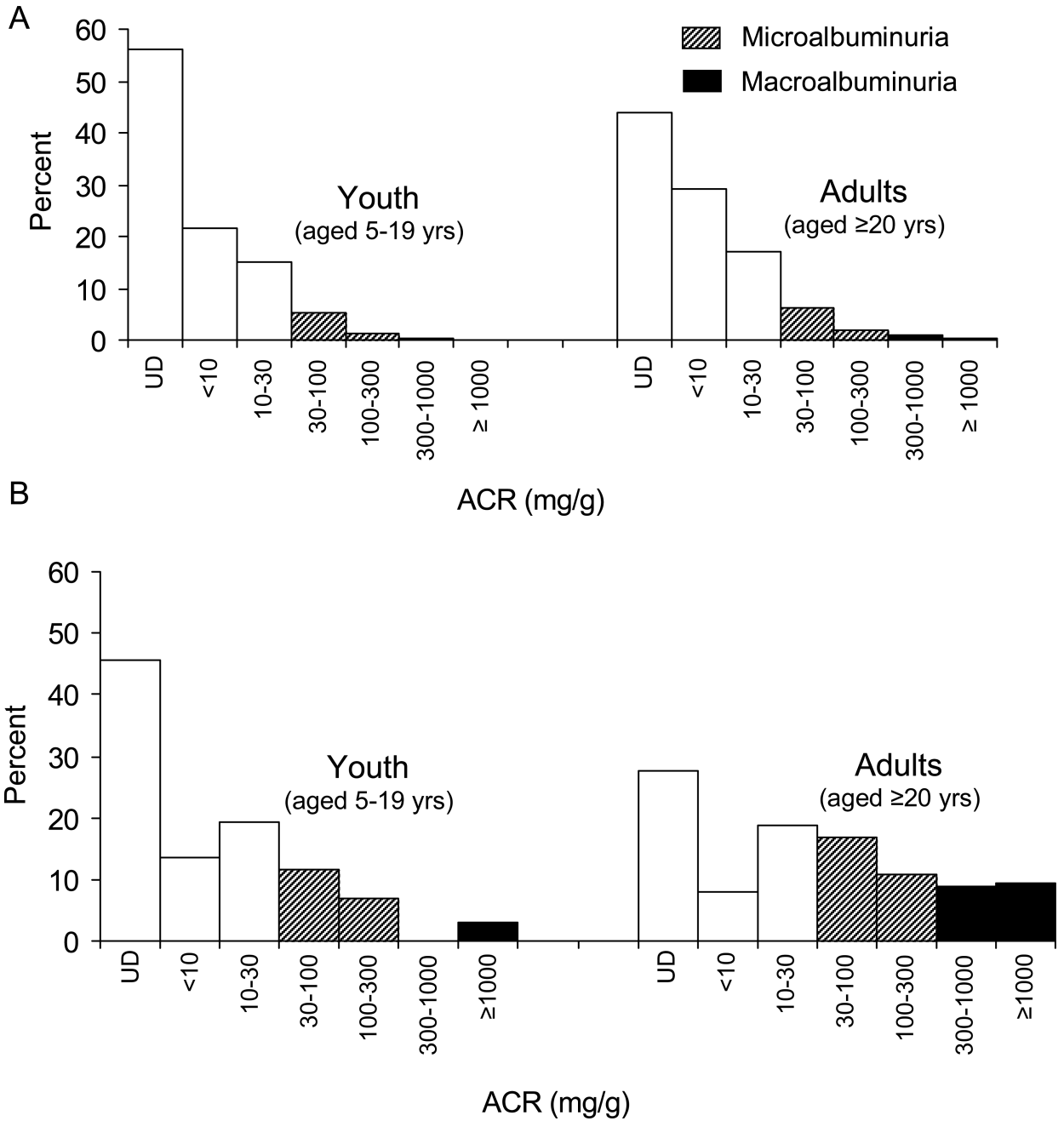


Figure 1. Frequency distribution of several ACR categories in youth and adults without (A) or with type 2 diabetes (B). The hatched and black bars represent micro- and macroalbuminuria, respectively. UD represents undetectable albuminuria, in which case ACR cannot be calculated.

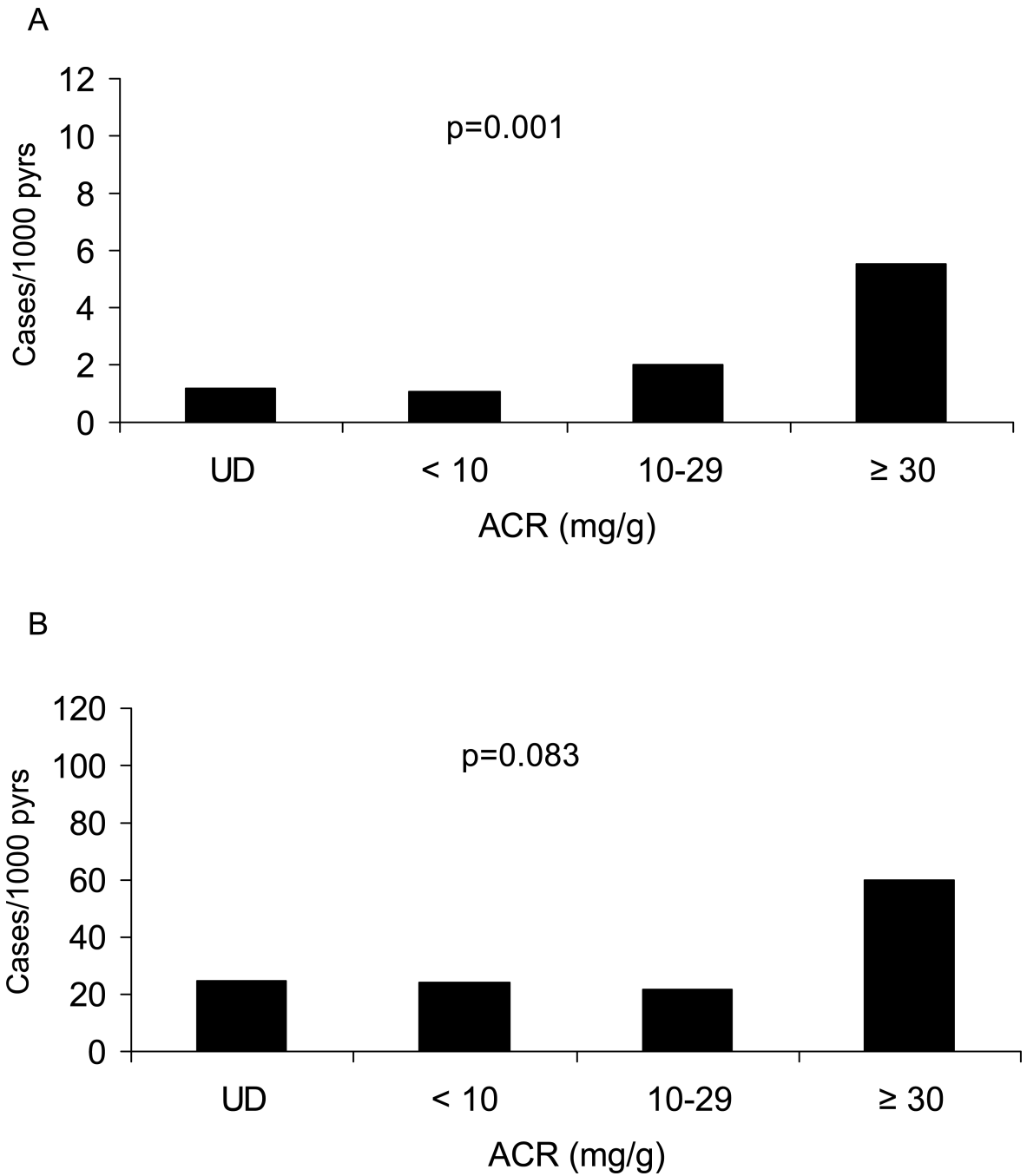


Figure 2. Unadjusted incidence rates of macroalbuminuria according to ACR categories in youth aged 5-19 years without diabetes (A) or with type 2 diabetes (B). UD represents undetectable albuminuria. Note the 10-fold difference in the y-axis scales between panels.

Table 1

Demographic and clinical characteristics of Pima Indian youth according to diabetes.

	No Diabetes	Diabetes
N	3,856	103
Male	1,876	40
Female	1,980	63
Age (years)	13.0 ± 3.8	14.5 ± 3.0
Duration of diabetes (years) [*]	-	1.3(0-2.1)
BMI (kg/m ²)	25.7 ± 7.3	34.9 ± 7.4
BMI SDS	1.34±1.01	2.25±0.50
HbA1c (%)	5.0 ± 0.5	8.1 ± 3.0
2-hour plasma glucose (mmol/L)	5.7 ± 1.3	16.9 ± 6.0
MAP (mmHg)	75.9 ± 10.1	83.6 ± 9.9
Serum creatinine (μmol/L)	56 ± 15	55 ± 11
Estimated GFR [†]	141±21	154±27
ACR (mg/g) [‡]	UD (UD-8.9)	6.6 (UD-21.9)
Percentiles of ACR (mg/g) by age group		
Age 5-9 years	N=982	N=4 [§]
50 th	UD	
75 th	11.4	
95 th	51.3	
Age 10-14 years	N=1,469	N=48
50 th	UD	8.5
75 th	9.1	23.6
95 th	48.3	190.2
Age 15-19 years	N=1,405	N=51
50 th	UD	5.2
75 th	7.4	20.9
95 th	27.7	210.0

Abbreviations: ACR, urinary albumin-to-creatinine ratio; BMI, body mass index; BMI SDS, body mass index standard deviation score; GFR, glomerular filtration rate; MAP, mean arterial pressure; UD, undetectable albuminuria.

^{*} Statistics are mean and standard deviation

[‡] %median (25th-75th percentile).

[†] Glomerular filtration rate was estimated using the Schwartz equation [19] in subjects less than 18 years of age and by the 4-variable Modification of Diet in Renal Disease (MDRD) study equation [20] in those 18 years and older.

[§] Percentiles not reported due to the small number of subjects.

Table 2

Changes in ACR categories between two ACR measurements in Pima Indian youth with and without type 2 diabetes. Cells represent the number of subjects in each category (percent of row). Bolded numbers represent subjects with stable ACR.

		No Diabetes				Diabetes				
		ACR2				ACR2				
		Normo	Micro	Macro	N	Normo	Micro	Macro	N	
Normo		2,223 (94.1%)	132 (5.6%)	7 (0.3%)	2,362	Normo	33 (53.2%)	25 (40.3%)	4 (6.5%)	62
ACR1	Micro	133 (76.9%)	38 (22.0%)	2 (1.2%)	173	ACR1	Micro	1 (9.1%)	7 (63.6%)	11
	Macro	8 (57.1%)	3 (21.4%)	3 (21.4%)	14	Macro	0	0	3 (100%)	3
	N	2363	173	12	2,549	N	34	32	10	76

Abbreviations: ACR, urinary albumin-to-creatinine ratio; Normo, normoalbuminuria; Micro, microalbuminuria; Macro, macroalbuminuria.

ACR1: ACR category at the first examination. ACR2: ACR category at the second examination

Table 3

Unadjusted incidence (cases/1,000 person-years) of macroalbuminuria in nondiabetic and diabetic Pima Indians aged 5-19 years at baseline according to the presence or absence of microalbuminuria and age-sex-adjusted incidence rate ratios (IRR; microalbuminuria/normoalbuminuria and 95% confidence intervals (CI).

	Pearson-Years	Cases	Incidence
No Diabetes			
Normoalbuminuria	21,830.0	28	1.3
Microalbuminuria	1,450.0	8	5.5
IRR=8.2 (95% CI, 2.1- 32.4)			
Diabetes			
Normoalbuminuria	800.5	19	23.7
Microalbuminuria	183.4	11	60.0
IRR=7.6 (95% CI, 1.8- 32.8)			