

# Albuminuria in Recent-Onset Type 2 Diabetes

## The Strong Heart Study

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**OBJECTIVE** — It is not known how frequently abnormal albumin excretion occurs in the initial years after the onset of type 2 diabetes and to what extent its occurrence is related to the severity of diabetes. We have used a prospective cohort study to examine this.

**RESEARCH DESIGN AND METHODS** — A total of 782 participants from the Strong Heart Study who had normal glucose tolerance and normal albumin excretion (albumin-to-creatinine ratio <30 mg albumin/g creatinine) at baseline were assessed for diabetes and abnormal albumin excretion at a follow-up visit (interval  $3.91 \pm 0.95$  years, mean  $\pm$  SD). Logistic regression models were used to examine the associations.

**RESULTS** — Abnormal albumin excretion was detected in 52 (6.6%) and diabetes was determined to be present in 105 (13.4%) of the participants at the follow-up visit. In univariate analyses, abnormal albumin excretion was statistically significantly related to the baseline albumin-to-creatinine ratio, diastolic blood pressure, fasting insulin, and extent of American Indian heritage. Abnormal albumin excretion was much more prevalent in those with recent onset diabetes at the follow-up visit (18 vs. 5%,  $P < 0.001$ ). In a logistic regression analysis, abnormal albumin excretion and diabetes remained strongly related (odds ratio 3.45,  $P < 0.001$ ), and associations of abnormal albumin excretion with baseline albumin-to-creatinine ratio, blood pressure, and American Indian heritage also remained significant in a separate logistic regression analysis, including only those who developed diabetes. There was a strong association between abnormal albumin excretion and fasting glucose levels ( $<0.01$ ) at the follow-up visit.

**CONCLUSIONS** — These data suggest that an appreciable percentage of individuals develop abnormal albumin excretion within the first few years after the onset of type 2 diabetes. Also, the severity of diabetes at onset appears to be a key risk factor for the early development of abnormal albumin excretion.

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It is not known how frequently abnormal urinary albumin excretion occurs in the initial years after the onset of type 2 diabetes. Moreover, there is little information concerning the effect of the severity of type 2 diabetes at onset on the development of abnormal albumin excretion. Some studies have shown that an

appreciable proportion of type 2 diabetic patients have abnormal albumin excretion at diagnosis (1–4); however, the actual onset of diabetes in these patients was in question. Data indicate that the onset of diabetes can precede the diagnosis by a number of years (5). Thus, to obtain more accurate information on the early occur-

rence of abnormal albumin excretion after the onset of diabetes, it is necessary to prospectively follow individuals with normal glucose tolerance who develop diabetes.

To study the frequency of abnormal albumin excretion in the first years of type 2 diabetes and the role of the severity of diabetes in its development, we reassessed Strong Heart Study participants, whose glucose tolerance and albumin excretion were normal at baseline, for the development of diabetes and abnormal albumin excretion. The information presented may be relevant for determining the importance of screening and early treatment intervention of type 2 diabetic patients.

## RESEARCH DESIGN AND METHODS

### Background of the Strong Heart Study

The Strong Heart Study (6) was begun in 1988 to measure risk factors for cardiovascular disease (7,8) among diverse groups of American Indians. Participants were from three geographic sites (Arizona, North and South Dakota, and Oklahoma) and were of varying degrees of American Indian heritage, socioeconomic status, and lifestyles, incorporating both traditional American Indian and Western cultures. Details summarizing the design of this study (6), observed cardiovascular risk factors (9,10), and prevalence of diabetes (11) among the 4,549 original baseline participants are summarized in recent publications.

### Participants

The Strong Heart Study population consisted of 4,549 American Indians aged 45–74 years living in Oklahoma, South and North Dakota, and Arizona. Participants were members of the following tribes: Pima, Maricopa, and Tohono O'odham of central Arizona living in the Gila River, Salt River, and Ak-Chin American Indian communities; seven tribes of

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**Abbreviations:** ADA, American Diabetes Association; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Southwestern Oklahoma (Apache, Caddo, Comanche, Delaware, Fort Sill Apache, Kiowa, and Wichita); the Oglala and Cheyenne River Sioux in South Dakota; and the Spirit Lake Tribe in the Fort Totten area of North Dakota. This study has been approved by an institutional review board.

The baseline examinations occurred between 1 July 1989 and 31 January 1992. Of the surviving cohort, 89% were reexamined in the follow-up examination, which occurred between 1 August 1993 and 31 December 1995. Percent participation rates of the target population at baseline were 71% in Arizona, 53% in North and South Dakota, and 62% in Oklahoma. The participation rates were calculated using the total number of people in the December 1988 tribal lists. Nonrespondents did not differ significantly from respondents in age, BMI, and self-reported incidence of diabetes or hypertension. More respondents were women compared with nonrespondents, and more of the nonrespondents were smokers.

Diabetes was diagnosed at the baseline visit according to the following criteria: receiving treatment with insulin and/or an oral hypoglycemic agent or diagnosed by a glucose tolerance test under World Health Organization (WHO) criteria (12). The subjects included in the present study had normal glucose tolerance and normal albumin excretion (defined as an albumin-to-creatinine ratio  $<30$  mg albumin/g creatinine) at the baseline visit.

### Procedures

Briefly, the standardized clinical examination for both baseline and follow-up took place after a 12-h overnight fast. It consisted of a personal interview, a physical examination including a 12-lead electrocardiogram, a review of current medications, seated blood pressure, fasting blood samples, and a 75-g oral glucose tolerance test (Glutol; Paddock Laboratory, Minneapolis, MN). Additional tests, such as echocardiography and pulmonary function testing, were included in the follow-up examination, but the results are not reported here.

A random urine specimen was obtained on arrival to the clinic (usually between 0800 and 0900) for measurement of creatinine and albumin content. Each laboratory measurement was performed

in a central laboratory using stable methodology standardized to outside reference values. Serum and urine creatinine were measured by the picric acid method (13). Plasma glucose was measured on a Hitachi 704, 705, or 717 autoanalyzer using a hexokinase method (Boehringer Mannheim/HK) standardized to controls provided by the manufacturer (PeciCal, PeciNorm, or PeciAbnorm) and the College of American Pathologists. Urine albumin content was measured by a sensitive nephelometric technique (14).

Triglycerides were measured enzymatically after correction for free glycerol. Glycerol-blanked assays such as this one are preferable in populations with a high prevalence of diabetes. Glucose was measured using a hexokinase method calibrated with aqueous controls derived from the National Institutes of Health. HbA<sub>1c</sub> was measured by high-performance liquid chromatography.

Insulin was measured using antibody 1012, WHO-traceable (1988) insulin standards, and supplies purchased from Linco Research (St. Louis, MO). The inter- and intra-assay coefficients of variation of the insulin assay at midrange were 8.5 and 2.2%, respectively.

Body height was obtained with the participant standing erect in a Frankfort plane using a stadiometer fixed to the wall. Weight was measured using a Detecto model 683-p scale, which was calibrated and adjusted daily. Blood pressures are given as the mean of the final two of three measurements obtained using protocol JNC-V (Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure). Duration of diabetes was defined by the participant's response. Alcohol ingestion, smoking history, and percent American Indian heritage were derived from data obtained during the interview.

### Data analysis

For continuous variables Wilcoxon's rank-sum test was used to compare groups, whereas for categorical variables the  $\chi^2$  test was used. The medians with the values for the 25th and 75th percentiles are displayed for the continuous variables. There were some variables for which data ascertainment was incomplete; in such instances, this information is specifically indicated in the tables.

Logistic regression models were used

to assess associations. For these models, categorical variables were derived from the continuous variables. The models initially included all variables statistically significantly associated with the dependent variable in univariate analyses. However, those variables that did not remain significant were eliminated from the models.

**RESULTS** — The values for the characteristics of subjects at the baseline visit are shown according to sex in Table 1. There were several statistically significant differences between men and women. Men had higher levels of fasting glucose and lower levels of 2-h glucose. More men were current drinkers and smokers. In addition, men had lower baseline fibrinogen levels and lower albumin-to-creatinine ratios.

The mean  $\pm$  SD interval between the baseline and follow-up visits was  $3.91 \pm 0.65$  years. Abnormal albumin excretion (albumin-to-creatinine ratio  $\geq 30$  mg/g) was detected in 52 (6.6%) of the participants at the follow-up visit. Of these, three had albumin-to-creatinine ratios  $>300$  mg/g. A total of 105 (13.4%) of the participants were determined to have diabetes at the follow-up visit.

In Table 2, baseline characteristics of individuals with abnormal albumin excretion at the follow-up visit are compared with those of individuals who maintained normal albumin excretion. Those with abnormal albumin excretion at the follow-up visit had higher baseline albumin-to-creatinine ratios, diastolic blood pressures, and fasting insulin levels. Also, a greater percentage in that group indicated that they were of full American Indian heritage. There was not a statistically significant difference between the groups in the time from the baseline visit to the follow-up visit (median 3.78 years for those with abnormal values vs. 3.89 years for those with normal values).

Abnormal albumin excretion at the follow-up visit was much more prevalent in those with recent onset diabetes (18 vs. 5%,  $P < 0.001$ ) at that visit (Table 3). This is evident in the cumulative frequency distributions shown in Fig. 1 for the albumin-to-creatinine ratios. Those who were determined to have diabetes at the follow-up visit had appreciably higher albumin-to-creatinine ratios at the follow-up visit than those with normal glucose tolerance. The difference in the distributions

Table 1—Characteristics of subjects at baseline according to sex

	Women	Men	P
N	388	394	
Age (years)	52 (48–59)	53 (48–59)	NS
BMI (kg/m <sup>2</sup> )	28.3 (24.5–32.5)	27.8 (25.1–30.7)	NS
Systolic blood pressure (mmHg)	118 (108–129)	122 (113–130)	<0.01
Diastolic blood pressure (mmHg)	73 (68–79)	78 (70–84)	<0.001
Fasting glucose (mg/dl)	98 (92–106)	100 (94–107)	<0.05
2-h glucose (mg/dl)	106 (91–122)	98 (80–116)	<0.001
HbA <sub>1c</sub> (%)	5.0 (4.7–5.3)	5.0 (4.7–5.3)	NS
Insulin (mm/ml)	10.6 (6.4–15.4)	10.0 (6.2–15.5)	NS
Fibrinogen (mg/dl)	280 (244–320)	264 (229–304)	<0.001
Triglycerides (mg/dl)	101 (68–184)	100 (70–144)	NS
Albumin-to-creatinine ratio (mg/g)	6.01 (3.78–9.43)	4.09 (2.29–7.27)	<0.001
Hypertension (%)	20	24	NS
Current drinkers (%)	44	58	<0.001
Current smokers (%)	43	50	<0.05
Full Indian heritage (%)	41	44	NS

Data for continuous variables are median (25th–75th percentile). A total of 52 HbA<sub>1c</sub> values were missing. No more than six values were missing for any of the other variables.

was much smaller at the baseline visit, when those who ultimately developed diabetes had normal glucose tolerance.

The analyses shown in Table 3 were also performed according to the most recent American Diabetes Association (ADA) criteria for diabetes (15). There were essentially no differences in the outcomes when the new ADA criteria were used.

We performed a logistic regression analysis, with albumin-to-creatinine ratios at the follow-up visit (categorized as <30 and ≥30 mg/g) as the dependent variable in the model. The independent variables included diabetes at the follow-up visit, the baseline albumin-to-creatinine ratio, diastolic blood pressure, fasting insulin, and American Indian heritage, which were those variables found to

be significantly different in the univariate analyses (Tables 2 and 3). There continued to be a strong association between abnormal albumin excretion and diabetes (odds ratio 3.45, *P* < 0.001) (Table 4). The association between abnormal albumin excretion and American Indian heritage also remained significant (odds ratio 2.19, *P* < 0.05), as did the associations of abnormal albumin excretion with diastolic blood pressure (*P* < 0.05) and the baseline albumin-to-creatinine ratio (*P* < 0.001). Fasting insulin was excluded from the final model because it was not significantly related in the presence of the above variables.

In an analysis restricted to participants diagnosed with diabetes at the follow-up visit, those with normal and abnormal albumin excretion were compared with regard to several characteristics (Table 5). Individuals with abnormal albumin excretion at the

Table 2—Characteristics of subjects at baseline according to presence or absence of abnormal albumin excretion at the follow-up visit

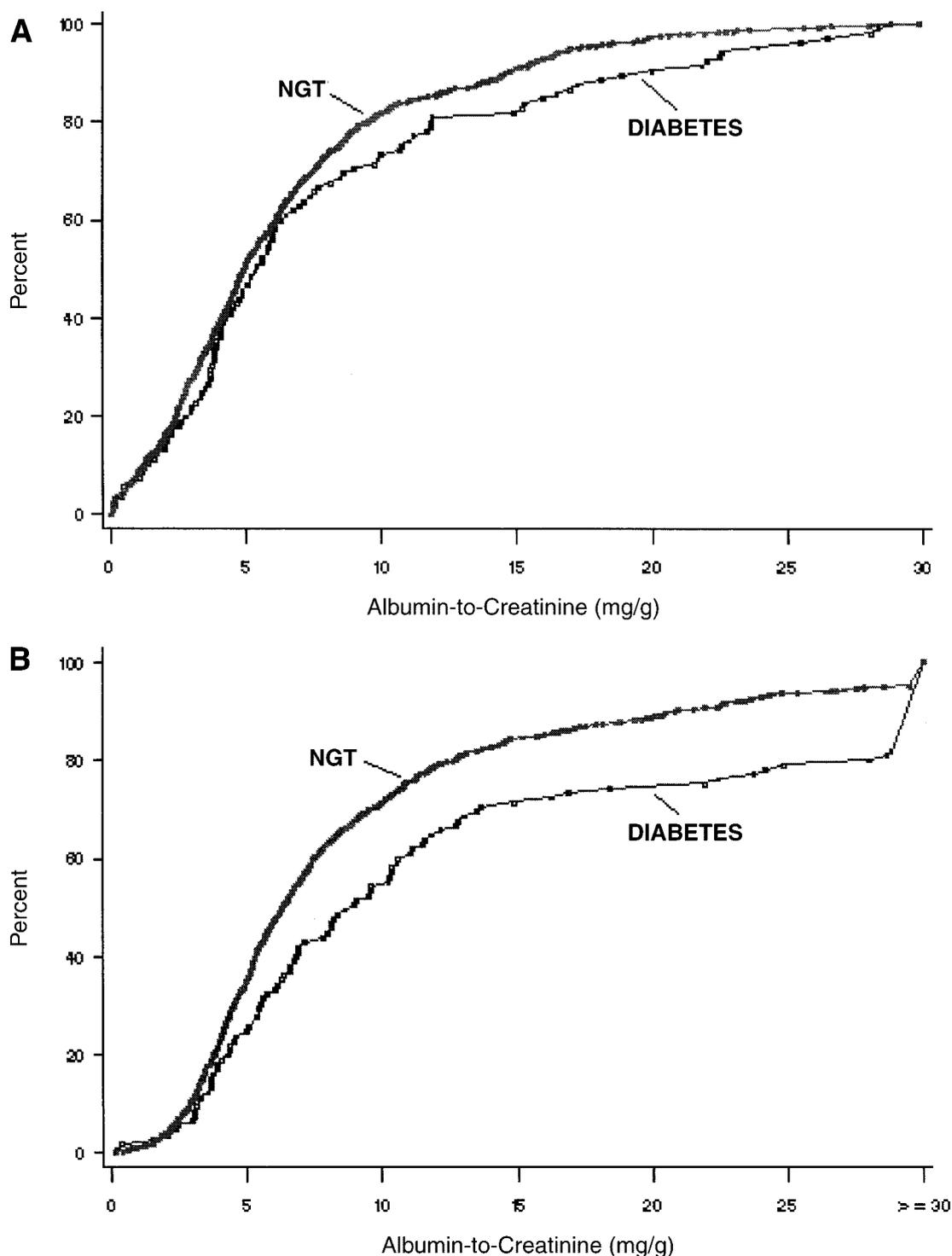
	Albumin-to-creatinine ratio (mg/g)		P
	≥30	<30	
N	52	730	
Age (years)	54 (50–60)	52 (48–59)	NS
BMI (kg/m <sup>2</sup> )	28.2 (24.8–31.5)	28.2 (24.9–31.6)	NS
Systolic blood pressure (mmHg)	121 (111–113)	119 (100–129)	NS
Diastolic blood pressure (mmHg)	78 (72–87)	75 (69–82)	<0.05
Fasting glucose (mg/dl)	100 (94–108)	99 (93–106)	NS
2-h glucose (mg/dl)	110 (89–120)	103 (85–120)	NS
HbA <sub>1c</sub> (%)	5.1 (4.8–5.5)	5.0 (4.7–5.3)	NS
Insulin (mm/ml)	11.8 (8.6–16.5)	10.2 (6.2–15.3)	<0.05
Fibrinogen (mg/dl)	290 (234–336)	270 (234–310)	NS
Triglycerides (mg/dl)	109 (71–154)	100 (69–140)	NS
Albumin-to-creatinine ratio (mg/g)	11.2 (5.1–16.2)	4.9 (2.8–8.1)	<0.001
Sex (%)	52	50	NS
Hypertension (%)	29	22	NS
Current drinkers (%)	48	51	NS
Current smokers (%)	44	46	NS
Full Indian heritage (%)	77	56	<0.01

Data for continuous variables are median (25th–75th percentile). A total of 52 HbA<sub>1c</sub> values were missing. No more than six values were missing for any of the other variables.

Table 3—Presence or absence of abnormal albumin excretion at the follow-up visit according to status of glucose tolerance at the follow-up visit

Albumin-to-creatinine ratio (mg/g)	Normal glucose tolerance	
	Diabetes	
≥30	19	33
<30	86	644

Data are *n*. *P* < 0.001 for association.



**Figure 1**—Cumulative frequency distributions of albumin-to-creatinine ratios are shown at the baseline (A) and follow-up (B) visits according to whether individuals had diabetes at the follow-up visit or whether they continued to have normal glucose tolerance. At the baseline visit, when those with diabetes at the follow-up visit had normal glucose tolerance, there was little difference in the distributions. However, at the follow-up visit, there was a marked shift to the right (higher albumin-to-creatinine ratios) for the group that had developed diabetes.

follow-up visit had significantly higher fasting glucose values at that visit ( $P < 0.05$ ). HbA<sub>1c</sub> values were also higher in those individuals, but the difference

was not significant ( $P = 0.10$ ). There was no significant difference in the time from the baseline visit to the follow-up visit (median of 3.62 years for those

with abnormal ratios vs. 4.00 years for those with normal ratios).

In a logistic regression analysis (Table 6) also restricted to those with recent on-

**Table 4—Logistic model for associations of the albumin-to-creatinine ratio ( $\geq 30$  vs.  $< 30$  mg/g)\* at the follow-up visit, with characteristics of subjects**

Independent variables	Odds ratio	95% CI	P
Baseline diastolic blood pressure (per 10 mmHg increase)	1.38	1.02–1.86	<0.05
Baseline albumin-to-creatinine ratio (per 10 mg/g increase)	2.71	1.81–4.05	<0.001
Follow-up diabetes status (diabetes vs. normal glucose tolerance)	3.45	1.81–6.59	<0.001
Indian Heritage (100 vs. <100%)	2.19	1.10–4.36	<0.05

\* $\geq 30$  mg/g, n = 52;  $< 30$  mg/g, n = 727.

set diabetes at the follow-up visit, the relation between abnormal albumin excretion and fasting glucose persisted ( $P < 0.01$ ), with an allowance for the albumin-to-creatinine ratio at the baseline visit. When HbA<sub>1c</sub> was included in a separate model instead of fasting glucose, its association with abnormal albumin excretion was of borderline significance ( $P = 0.069$ ).

**CONCLUSIONS**— The data presented above suggest that an appreciable percentage of individuals develop abnormal albumin excretion within the first few years after the onset of type 2 diabetes.

The median interval between the baseline and follow-up visits was  $< 4$  years. Moreover, because the interval between the visits represents a maximum possible duration of diabetes, the development of abnormal albumin excretion after diabetes onset probably occurs even earlier in some individuals than we could detect from our data. Although other reports have examined abnormal albumin excretion at the diagnosis of type 2 diabetes (1–4), to our knowledge this report is the first to consider the occurrence of abnormal albumin excretion in relation to the onset of type 2 diabetes.

The data shown in this report suggest

that the severity of diabetes (as indicated by the degree of hyperglycemia) at onset is a key risk factor for the early development of abnormal albumin excretion. Although glucose levels with treatment intervention have been established as a major determinant of diabetic complications (16), it has not been clearly documented that the severity of type 2 diabetes before treatment intervention is in itself a determinant of complications. A relation between abnormal albumin excretion and the extent of hyperglycemia at diagnosis has also been observed in other studies (1,2). However, the duration of diabetes before diagnosis was not indicated in these reports. The short duration before the diagnosis of patients in the present study strongly suggests that fasting glucose levels correlated with the severity of diabetes at onset.

We chose to use WHO criteria (12) for the diagnosis of diabetes for purposes of consistency with prior publications from the Strong Heart Study. The data were similar for Table 3, when the most recent ADA criteria (15) for diabetes were used.

The association between abnormal albumin excretion and degree of American

**Table 5—Characteristics of diabetic participants (determined at the follow-up visit) according to the presence or absence of abnormal albumin excretion at the follow-up visit**

	Albumin-to-creatinine ratio (mg/g)		P
	$\geq 30$	$< 30$	
Baseline			
N	19	86	
Age (years)	51 (47–60)	512 (47–57)	NS
BMI (kg/m <sup>2</sup> )	30.1 (26.4–34.6)	30.6 (27.4–33.5)	NS
Systolic blood pressure (mmHg)	117 (110–130)	121 (113–130)	NS
Diastolic blood pressure (mmHg)	78 (71–86)	75 (70–80)	NS
Fasting glucose (mg/dl)	107 (98–114)	103 (96–110)	NS
2-h glucose (mg/dl)	117 (109–128)	112 (94–126)	NS
HbA <sub>1c</sub> (%)	5.2 (4.9–5.5)	5.1 (4.8–5.5)	NS
Insulin (mm/ml)	13.0 (10.6–17.0)	15.3 (11.0–20.9)	NS
Fibrinogen (mg/dl)	290 (234–326)	284 (248–317)	NS
Triglycerides (mg/dl)	109 (78–153)	112 (80–171)	NS
Albumin-to-creatinine ratio (mg/g)	9.9 (4.5–16)	5.1 (3–9)	<0.05
Sex (%)	42	38	NS
Hypertension (%)	32	22	NS
Current drinkers (%)	53	47	NS
Current smokers (%)	37	42	NS
Full Indian heritage (%)	79	63	NS
Follow-up Visit			
Fasting glucose (mg/dl)	145 (114–263)	121 (106–151)	<0.05
HbA <sub>1c</sub> (%)	6.4 (5.2–8.5)	5.7 (5.2–6.5)	NS

Data for continuous variables are median (25th–75th percentile). A total of 4 HbA<sub>1c</sub> values were missing.

**Table 6—Logistic model for associations in the diabetic patients of albumin-to-creatinine ratio ( $\geq 30$  vs.  $<30$  mg/g)\* at the follow-up visit, with characteristics of subjects**

Independent variables	Odds ratio	95% CI	P
<b>Model 1</b>			
Baseline albumin-to-creatinine ratio (per 10 mg/g increase)	2.6	1.28–5.30	<0.01
Follow-up fasting glucose (per 10 mg/dl increase)	1.13	1.05–1.23	<0.01
<b>Model 2</b>			
Baseline albumin-to-creatinine ratio (per 10-mg/g increase)	2.23	1.14–4.36	<0.05
Follow-up visit HbA <sub>1c</sub> (per 0.5% increase)	1.11	0.99–1.25	0.069

\*Model 1: n = 19 and 86 for  $\geq 30$  and  $<30$  mg/g, respectively; model 2: n = 18 and 83 for  $\geq 30$  and  $<30$  mg/g, respectively.

Indian heritage is similar to other findings, which suggests that American Indians may have genetic propensities and/or environmental pressures for certain conditions (17). It is of interest that the association observed was statistically significant overall, but it was not significant specifically in those who developed diabetes. However, this may be attributable to the relatively small number in that group.

The conclusions drawn from the analyses are based on the assumption that the development of diabetes preceded the onset of abnormal albumin excretion. This may not have always been the case, because data from another study (18) and preliminary data from The Strong Heart Study (19) suggest that abnormal albumin excretion can precede diabetes and be a risk factor for it. However, other data showing that intensive blood glucose control can prevent abnormal albumin excretion (16) further support the view that diabetes preceded the abnormal albumin excretion. The relation between abnormal albumin excretion and the severity of diabetes in the present study also suggests that diabetes occurred before the abnormal albumin excretion.

The implications of abnormal albumin excretion in individuals with the recent onset of type 2 diabetes are not fully clear. There is some evidence that abnormal albumin excretion in such individuals may be transient and be at least partly related to the hyperfiltration associated with hyperglycemia. Studies of newly diagnosed type 1 and type 2 diabetic patients have shown a decrease in albumin excretion with improved glucose levels (2,21,22). However, in another study of

type 2 patients, the frequency of abnormal albumin excretion did not decline, despite a marked lowering of glucose levels after diagnosis (4). Even if abnormal albumin excretion is a function of hyperfiltration, it could still have major consequences. Data suggest that abnormal albumin excretion itself could lead to kidney damage (23). Also, evidence suggests that abnormal albumin excretion is a predictor of cardiovascular mortality (3).

The findings in this report are relevant to policy decisions on screening for type 2 diabetes. Our data provide support for comprehensive diabetes screening, since it appears that abnormal albumin excretion occurs with considerable frequency before diabetes is diagnosed clinically. Perhaps more importantly, the observed relation between the development of abnormal albumin excretion and the degree of hyperglycemia indicates that early intervention might serve to help prevent the development of diabetic nephropathy.

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