Incidence of Retinopathy and Nephropathy in Youth-Onset Compared With Adult-Onset Type 2 Diabetes

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OBJECTIVE — To examine the risk of retinopathy and nephropathy in participants in whom type 2 diabetes was diagnosed in youth (before 20 years of age) compared with those in whom type 2 diabetes was diagnosed at older ages.

RESEARCH DESIGN AND METHODS — Subjects in whom youth-onset or adult-onset diabetes was diagnosed in the longitudinal study of health in the Pima Indians of Arizona were followed for microvascular complications. Diabetes was diagnosed in 178 subjects before 20 years of age (youth), in 1,359 subjects at 20–39 years of age (younger adults), and in 971 subjects at 40–59 years of age (older adults). Incidence rates of diabetic retinopathy diagnosed by direct ophthalmoscopy through dilated pupils and nephropathy (protein-to-creatinine ratio ≥0.5 g/g) were calculated by age at diagnosis.

RESULTS — Over 25 years, nephropathy developed in 35 of the participants with youth-onset type 2 diabetes; this incidence rate was not significantly different from that in patients with adult-onset diabetes ($P = 0.77$). Incidence rates of retinopathy, however, were significantly lower for the youth-onset group ($P = 0.007$). Adjusted for sex, glycemia, and blood pressure, risk of retinopathy was lower in patients with youth-onset diabetes than in those with adult-onset diabetes (hazard rate ratio [HRR] 0.42, 95% CI 0.24–0.74, $P = 0.003$), but risk of nephropathy was not different (HRR 1.2, 95% CI 0.77–1.3, $P = 0.38$).

CONCLUSIONS — In Pima Indians, the risk of nephropathy as a function of duration of diabetes is similar in all age groups. By contrast, the risk of retinopathy is lower in patients with youth-onset type 2 diabetes.

T he prevalence of obesity in children and adolescents in the U.S. has doubled in the last 20 years (1). Accompanying this increase in obesity is an increase in the frequency of type 2 diabetes in those aged <20 years (often identified as youth-onset type 2 diabetes) in a variety of racial and ethnic groups (2–5). In the Pima Indians of Arizona, the prevalence of type 2 diabetes in youth has increased twofold since 1967 (6). Diabetes in the Pima Indians is entirely type 2 diabetes, even when diagnosed in youth (7–9).

The impact of youth-onset type 2 diabetes on the development of later complications is a largely unknown but clinically important issue. The assumption that young patients with type 2 diabetes might follow the same course as adult-onset patients may not be justified. Retinopathy and nephropathy occur with increased frequency and progress more rapidly in young Japanese patients with type 2 diabetes than in those with type 1 diabetes (10,11), and severe microvascular complications develop rapidly in those with poor glycemic control (12). However, whether these complications occur earlier in the course of the disease in youth than in adults with type 2 diabetes has not been examined.

RESEARCH DESIGN AND METHODS

Study subjects
Members of the Gila River Indian Community participate in a longitudinal study of health. Every 2 years since 1965, regardless of health status, residents aged ≥5 years are invited for an examination, which includes measurement of blood pressure, height, and weight; direct ophthalmoscopy; a 75-g oral glucose tolerance test; and a spot urine collection for measurement of creatinine and protein. Direct ophthalmoscopy is performed after pupillary dilatation in those aged ≥15 years and without knowledge of the diabetes status of the participants. In this study, retinopathy is defined as the presence, in either eye, of at least one microaneurysm, hemorrhage, or evidence of proliferative retinopathy or its treatment as detected by direct ophthalmoscopy. Blood pressure was measured in the supine position in the right arm using an appropriate-sized cuff for arm circumference. Systolic and diastolic blood pressures were recorded to the nearest 2 mmHg at the first and fourth Korotkoff sounds. Plasma glucose concentrations were measured by the potassium ferricyanide method (Technicon, Tarrytown, NY) or, after October 1991, by the hexokinase method (Ciba-Corning, Palo Alto, CA). Subjects were asked to void at the beginning of the oral glucose tolerance test, and a urine specimen was collected 2 h later. Proteinuria was assessed by dipstick. If the dipstick protein was trace or greater, the total urine protein concentration was

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measured by the method of Shevky and Stafford (13). Urine creatinine concentrations were measured by the alkaline-picrate method. Nephropathy was defined by protein-to-creatinine ratio ≥0.5 (g protein/g creatinine). Diabetes was diagnosed by World Health Organization criteria (14). When diabetes was not diagnosed at a study visit, the date of diagnosis was confirmed by chart review.

Statistical analyses

The population was a dynamic cohort. The baseline examination was defined as the first research examination at or after the diagnosis of diabetes. Each analysis was restricted to subjects who did not have the relevant complication at the baseline examination. Person-time at risk was calculated until the first occurrence of retinopathy or nephropathy at a research examination or until the last examination, whichever came first. Incidence rates were calculated as events per 1,000 person-years, and 95% CIs were calculated as described previously (15). The incidence rates and cumulative incidence of retinopathy and nephropathy were calculated for successive 5-year periods of diabetes duration. Incidence rates were compared between three groups using the Mantel Haenzel test based on age at diagnosis of diabetes: <20 years (youth), 20–39 years (younger adults), or 40–59 years (older adults). Incidence rates were also calculated for successive 5-year intervals of attained age and stratified by age at diagnosis of diabetes.

To limit the potential influence of imprecision in the date of onset of diabetes, incidence rates of retinopathy and nephropathy were also determined in a subset of participants who had a nondiabetic glucose tolerance test within 6 years of diagnosis of diabetes.

The hazard rate ratio (HRR) for development of microvascular complications in those with youth-onset diabetes compared with those with adult-onset diabetes was assessed with proportional hazards regression, which allows for the inclusion of covariates to control for potentially confounding variables. Because the incidence of nephropathy and retinopathy was similar in both adult groups, the HRR for the youth group compared with both adult groups combined was evaluated in these analyses. The assumption that the HRR remains proportional over the duration of follow-up was as-

sessed with a time-dependent interaction term. For retinopathy, the proportionality assumption was valid up to 15 years of follow-up. For this reason, follow-up time was limited to 15 years for all models. Duration of diabetes at first examination (to account for duration in subjects in whom diabetes was diagnosed outside the research examinations), sex, fasting glucose, and mean arterial pressure (calculated as 1/3 [systolic blood pressure − diastolic blood pressure] + diastolic blood pressure) were included in the model. Glucose concentrations and arterial pressure were treated as continuous, time-dependent variables.

To examine potential differences in glycemic and blood pressure control between the groups, glucose concentrations and blood pressure were analyzed before, at, and after the diagnosis of diabetes. Mean values for fasting and 2-h glucose and systolic and diastolic blood pressures were calculated for each group at these various time points. For examinations before the diagnosis of diabetes, the analysis was restricted to participants who had a nondiabetic examination within 6 years of the diagnosis of diabetes. For the analysis at the diagnosis of diabetes, partic-

ipants were included if diabetes was diagnosed at a study examination. Analysis of glucose concentrations and blood pressure from the diagnosis of diabetes onward was performed for successive 5-year intervals by duration of diabetes. The mean value of all examinations during a particular period was used for individuals who had multiple examinations within that period (so that each individual contributed only one value to the calculation of the mean for the entire group for that duration period). Differences between the groups were analyzed using ANOVA.

RESULTS — Subjects available for inclusion in the analysis were as follows: 178 subjects in the youth-onset group (117 women, 61 men), 1,359 subjects in the younger adult group (803 women, 556 men), and 971 subjects in the older adult group (375 men, 596 women). Incident cases of nephropathy and retinopathy, respectively, were 36 and 31 in the youth-onset group, 281 and 324 in the younger adult group, and 197 and 226 in the older adult group. The number of cases of nephropathy and retinopathy by

Table 1—*Cases and person-years by duration of diabetes for retinopathy and nephropathy*

Duration (years)	Nephropathy			Retinopathy		
	Youth	Younger adults	Older adults	Youth	Younger adults	Older adults
<5						
Cases	5	23	13	0	13	18
Person-years	375	2,712	1,996	406	2,837	1,998
5–10						
Cases	4	29	34	3	68	60
Person-years	287	2,266	1,804	310	2,358	1,709
10–15						
Cases	10	76	55	9	120	86
Person-years	193	1,618	1,272	213	1,414	1,005
15–20						
Cases	10	86	64	9	73	44
Person-years	111	837	678	131	588	444
20–25						
Cases	6	45	20	5	41	15
Person-years	47	353	241	52	217	123
>25						
Cases	1	22	11	5	9	3
Person-years	16	156	74	17	76	26

Data are *n*. Youth, onset age of diabetes <20 years; younger adults, onset age of diabetes 20–39 years; older adults, onset age of diabetes 40–59 years. Nephropathy is defined as protein-to-creatinine ratio in spot urine test ≥0.5 g/g. Duration is defined as time from diagnosis of diabetes. Retinopathy is defined as presence of at least one microaneurysm or hemorrhage or evidence of proliferative retinopathy or its treatment.

duration of diabetes for each group are shown in Table 1.

Incidence rates of nephropathy increased with duration of diabetes and were similar in each age group ($P = 0.77$) (Fig. 1A). By contrast, incidence rates of retinopathy were significantly lower in the youth-onset group than in either adult group in all duration categories ($P = 0.007$) (Fig. 1B). To test whether the lower incidence rates for retinopathy were due to differences in the accuracy of the date of diagnosis by age of onset, for instance leading to adults having undiagnosed diabetes for a longer period of time than those in the youth-onset group, the incidence rates were examined in a subset of subjects who underwent a nondiabetic examination within 6 years of diagnosis of diabetes. The youth-onset group still had significantly lower incidence of retinopathy in this analysis ($P = 0.02$). Incidence rates for nephropathy using the same restrictions showed similar rates between the groups ($P = 0.30$). Because pupils were dilated for fundus examination only in persons aged ≥15 years and to exclude the influence of prepubertal duration of diabetes, the retinopathy incidence analysis was also repeated comparing only subjects diagnosed with diabetes at age 15–19 years. The incidence of retinopathy was still lower than in the adult groups ($P = 0.02$).

Incidence rates of retinopathy and nephropathy plotted by attained age, but stratified by age of onset of diabetes (Fig. 2), demonstrated different patterns for nephropathy and retinopathy. In the youth-onset group, nephropathy was detected in participants <20 years of age, whereas retinopathy occurred only in those aged ≥20 years. To illustrate the public health impact of diabetes in youth, cumulative incidence of retinopathy or nephropathy was plotted by duration of diabetes (Fig. 3). The groups were separated according to age at onset of diabetes, defining the midpoint of the age range for each group as the zero duration time for each group. In those with youth-onset diabetes, the cumulative incidence of retinopathy was lower than the incidence of nephropathy. The patterns were different than in the adult groups, in which cumulative incidence of retinopathy was consistently higher than the incidence of nephropathy. Nevertheless, despite lower rates of retinopathy, by an average age of 30 years, nephropathy had developed in
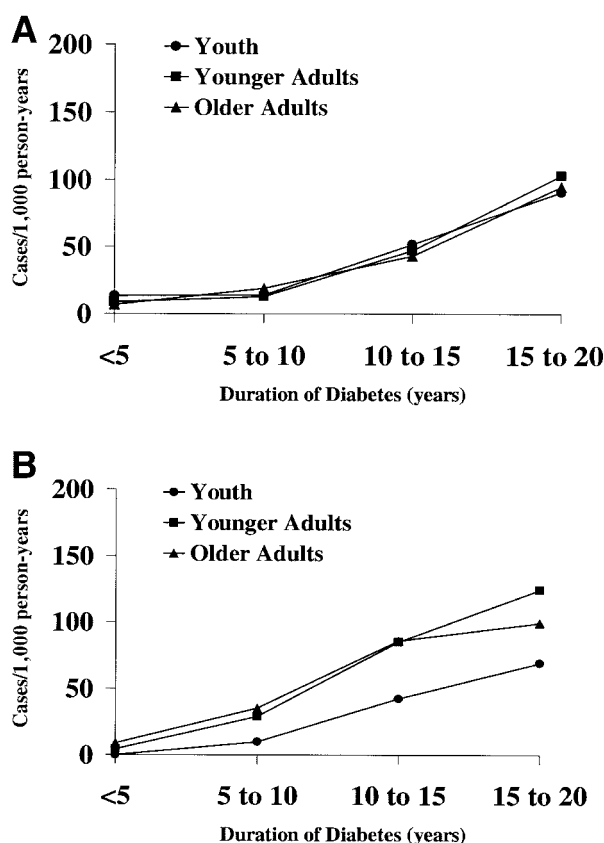

Figure 1—A: *Incidence of nephropathy by age at onset of diabetes. Youth, onset age of diabetes <20 years; younger adults, onset age of diabetes 20–39 years; older adults, onset age of diabetes 40–59 years. Test for trend,* P = 0.77, *calculated using Mantel-Haenzel test to compare incidence rates between age groups, controlling for duration.* B: *Incidence of retinopathy by age at onset of diabetes. Youth, onset age of diabetes <20 years; younger adults, onset age of diabetes 20–39 years; older adults, onset age of diabetes 40–59 years. Test for trend,* P = 0.007, *calculated using Mantel-Haenzel test to compare incidence rates between age groups, controlling for duration.*

an estimated 57% of participants with youth-onset diabetes and retinopathy had developed in 45% of these subjects.

Glucose and blood pressure before, at the time of, and after diagnosis of diabetes are shown in Table 2. The mean time from examination before diagnosis of diabetes was similar in all three groups (3.1 ± 1.1, 3.0 ± 1.1, and 2.9 ± 1.1 years for the youth-onset, younger adult, and older adult groups, respectively; $P = 0.3$). Fasting and 2-h glucose levels before the diagnosis of diabetes were higher in the adult groups. However, youth had higher fasting and 2-h glucose levels at diagnosis. Glycemia worsened in all groups over time. Fasting but not 2-h glucose was higher in youth after 5 years' duration of diabetes. Systolic and diastolic blood pressures were consistently lower in subjects with youth-onset diabetes, even after 10 years' duration (at which point most of

the youth-onset participants were ≥20 years of age).

The risk of nephropathy was similar between the youth-onset subjects and the adults when controlled for fasting glucose level, mean arterial pressure, sex, and duration to first examination after diagnosis of diabetes in a proportional hazards analysis (HRR 1.2, 95% CI 0.77–1.3, $P = 0.38$). On the other hand, adjusted for the same covariates, the risk of retinopathy was significantly lower in youth (HRR 0.42, 95% CI 0.24–0.74, $P = 0.003$) than in those in whom diabetes developed during adulthood. The HRR did not change if 2-h glucose rather than fasting glucose was used in the model (data not shown).

CONCLUSIONS — Type 2 diabetes in youth is an emerging epidemic (16), and these patients are at risk for microvas-
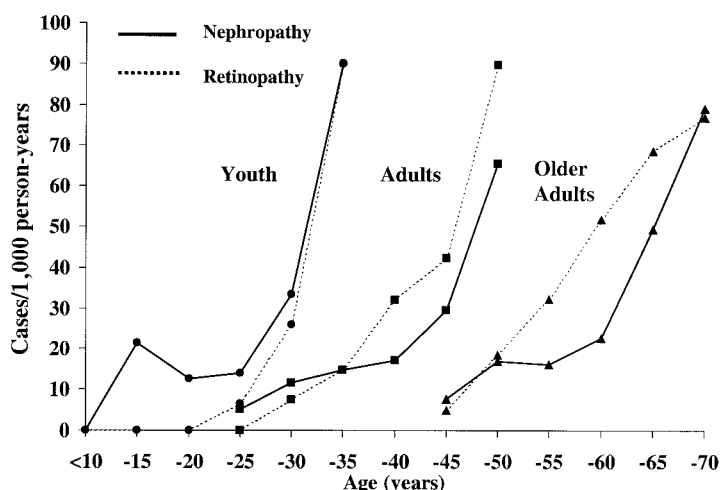
Figure 2—*Incidence rate of nephropathy or retinopathy by attained age. Youth, onset age of diabetes <20 years; younger adults, onset age of diabetes 20–39 years; older adults, onset age of diabetes 40–59 years. Attained age is defined as age at the particular research examination.*

cular complications while still relatively young. Indeed, in the present study, despite lower blood pressures at diagnosis, the risk of nephropathy over the same duration of diabetes was equal in those in whom diabetes was diagnosed in youth compared with those in whom diabetes was diagnosed in adulthood. The risk of retinopathy, however, differed by age at diagnosis; rates were lower in those in whom diabetes was diagnosed in youth (Fig. 1B). In fact, retinopathy did not occur in any subject before 20 years of age (Fig. 2), whereas nephropathy was present even in subjects aged 10–15 years. Whereas retinopathy occurred more frequently than nephropathy in adults with the same disease duration, the opposite was true in the youth-onset group (Fig. 3).

It is important to consider whether our findings may be due to an artifactual failure to identify retinopathy in younger participants (e.g., due to the examiner being less likely to entertain the diagnosis of retinopathy in a young participant). However, we were able to compare our results with graded retinal photographs, which were available for a subgroup of participants. Readings from retinal photographs for participants aged <20 years supported our findings. Retinopathy was rare in this group. Of 36 sets of photographs in 31 subjects with youth-onset diabetes, only one case of retinopathy was identified based on the presence of microaneurysms in one eye. In the Pima Indian study, diagnosis of retinopathy by direct

ophthalmoscopy resulted in fewer cases of retinopathy compared with examination of retinal photographs. These "missed" cases are most often microaneurysms without other lesions. However, there is no correlation between the age of the participant and underdiagnosis of retinopathy (unpublished data, H.C.L.). Therefore, missed cases would be expected in all age groups and would not change the results of this analysis.

Accuracy of the date at diagnosis of

diabetes could also have affected the incidence rates of retinopathy and nephropathy if participants with youth-onset diabetes had been diagnosed earlier in their disease course. The youth-onset group had lower prediagnostic but higher diagnostic glucose concentrations, implying that the change in glycemia during the transition to diabetes was more marked in the youth-onset group than for either adult group. Therefore, development of symptoms of hyperglycemia might be more likely in young subjects, causing them to seek treatment relatively earlier in their disease, whereas adults, with more subtle glucose elevations, may have remained undiagnosed for a longer period. The present results were unchanged, however, when the analysis included only subjects with more precisely determined dates of diabetes diagnosis, suggesting that variation in the accuracy of diabetes diagnosis was not responsible for these findings.

An important consideration for this study was whether nephropathy, as defined herein, represents true diabetic nephropathy, implying eventual decline in renal function. Lesser degrees of albuminuria in Pima Indians with diabetes have been shown to predict overt nephropathy (17). In addition, macroalbuminuria (defined as >300 mg albumin/g of creatinine on spot urine test) is clearly associated
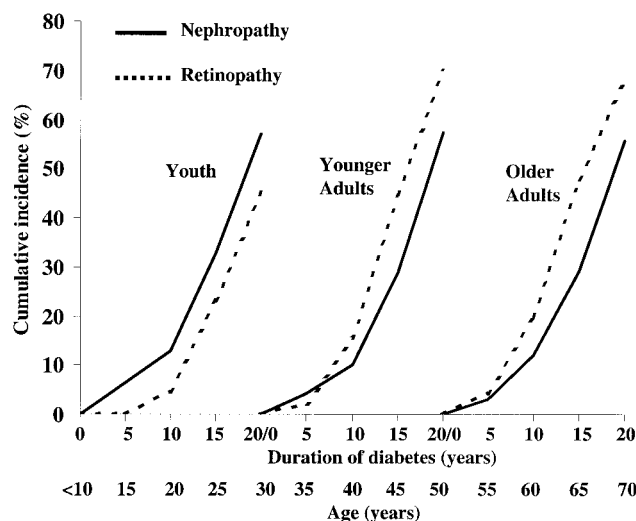

Figure 3—*Cumulative incidence of nephropathy and retinopathy by age at onset of diabetes. Duration of diabetes from 0 to 20 years is plotted separately for each age group. Age of subjects also plotted on the X axis (bottom number line). For each group, duration of diabetes was plotted from the midpoint for each age group (e.g., the youth group is defined as age of onset of diabetes <20 years, duration plot begun at 10 years; the younger adult group is defined as age of onset of diabetes 20–39 years, duration plot begun at 30 years; the older adult group is defined as age of onset of diabetes 40–59 years, duration plot begun at 50 years).*

Table 2—*Glucose concentrations and blood pressure before, at, and after onset of diabetes in youth, younger adults, and older adults*

Duration of diabetes (years)	Youth	Younger adult	Older adult	*P**
Fasting plasma glucose (mmol/l)				
Prediagnosis†	5.4 ± 0.5 (57)	5.7 ± 0.7 (242)	5.9 ± 0.7 (138)	<0.0001
At diagnosis†	9.7 ± 4.3 (63)	9.1 ± 3.7 (280)	8.1 ± 3.2 (168)	0.002
0–5	10.3 ± 4.6 (140)	10.1 ± 3.9 (894)	10.0 ± 4.0 (555)	0.7
5–10	13.0 ± 4.6 (65)	11.9 ± 3.9 (464)	11.6 ± 3.9 (350)	0.04
10–15	13.6 ± 4.9 (48)	13.1 ± 3.8 (356)	11.9 ± 4.2 (321)	0.0002
2-h plasma glucose (mmol/l)				
Prediagnosis†	7.2 ± 1.6 (73)	7.8 ± 1.7 (350)	8.0 ± 1.7 (226)	0.008
At diagnosis†	16.8 ± 5.2 (79)	16.3 ± 5.6 (355)	15.5 ± 4.6 (230)	0.07
0–5	16.7 ± 6.1 (144)	17.4 ± 6.1 (1,119)	17.9 ± 6.2 (794)	0.04
5–10	18.8 ± 6.5 (56)	19.4 ± 6.0 (512)	19.4 ± 6.2 (436)	0.74
10–15	21.6 ± 5.7 (42)	21.6 ± 5.6 (376)	20.6 ± 6.3 (365)	0.08
Systolic blood pressure (mmHg)				
Prediagnosis†	115 ± 16 (79)	121 ± 16 (347)	128 ± 19 (227)	<0.0001
At diagnosis†	120 ± 14 (79)	122 ± 17 (353)	130 ± 20 (229)	<0.0001
0–5	121 ± 14 (150)	124 ± 16 (1,135)	133 ± 22 (797)	<0.0001
5–10	115 ± 14 (72)	124 ± 18 (587)	135 ± 22 (491)	<0.0001
10–15	116 ± 14 (53)	128 ± 21 (428)	139 ± 23 (410)	<0.0001
Diastolic blood pressure (mmHg)				
Prediagnosis†	62 ± 11 (79)	72 ± 12 (347)	79 ± 12 (226)	<0.0001
At diagnosis†	67 ± 13 (79)	74 ± 12 (353)	81 ± 12 (229)	<0.0001
0–5	68 ± 11 (150)	76 ± 11 (1,135)	81 ± 11 (797)	<0.0001
5–10	69 ± 11 (72)	77 ± 12 (587)	80 ± 10 (490)	<0.0001
10–15	72 ± 10 (53)	79 ± 12 (427)	80 ± 11 (409)	<0.0001

Data are means ± SD (*n*). Values for participants with more than one examination during the same duration period are averaged before calculating the overall average for that duration period for each group. *Calculated by ANOVA; †Mean times between prediagnosis examination and examination at diagnosis for youth, younger adults, and older adults were 3.1 ± 1.1, 3.0 ± 1.1, and 2.9 ± 1.1 years, respectively, *P* = 0.3 by ANOVA. Youth, onset age of diabetes <20 years; younger adults, onset age of diabetes 20–39 years; older adults, onset age of diabetes 40–59 years.

with a decrease in glomerular filtration rate (18). Furthermore, kidney tissue from Pima Indians with diabetes and various stages of proteinuria has consistently demonstrated features of diabetic glomerular injury (19,20). Presence of proteinuria also increases mortality in Pima Indians aged >45 years (21). Orthostatic proteinuria is another potential cause of proteinuria in youth, but in this condition proteinuria generally does not exceed 1.0 g protein/24 h (22,23). Because protein-to-creatinine ratios correlate well with 24-h urine collections in both children and adults (24–27), this is equivalent to a protein-to-creatinine ratio of 1.0 g/g. When we analyzed the data using a different threshold to define nephropathy (e.g., protein-to-creatinine ratio of ≥1.0 or ≥3.0 g/g), rates of nephropathy remained similar in the three age groups. Furthermore, of the 36 cases of nephropathy in those with youth-onset diabetes, 29 subjects (80.5%) had protein-to-creatinine ratios of ≥1.0 or prolonged follow-up, demonstrating persistent and/or progressive proteinuria. This percentage was similar to that for the adult patients. In addition, four participants with youth-onset type 2 diabetes required renal replacement therapy at ages ranging from 36 to 53 years. Three of these subjects had nephropathy as defined in this study; the fourth subject had microalbuminuria at an earlier visit but did not return for follow-up until renal replacement therapy had begun. Therefore, the definition of nephropathy used in this study did identify subjects with glomerular pathology due to diabetes.

In the older adult group, death may have limited the ascertainment of subjects in whom retinopathy or nephropathy developed. This may be particularly true because proteinuria confers excess mortality in Pima Indians with diabetes (21). If a subject developed microvascular disease but died before being seen at a research examination, that complication would be undetected and, therefore, the rates would be underestimated. However, this problem is inherent in longitudinal studies unless very frequent (or nearly continuous) measurements of these complications are performed.

Because both glucose concentrations and blood pressure have been implicated as modifiable risks in the development of retinopathy and nephropathy (28–33), a differential effect of these variables in different age groups could explain the differences in rates of retinopathy and nephropathy. Compared with the adult groups, the youth-onset group had lower glucose concentrations before diagnosis (Table 2). Because differences in the precision of the date of diagnosis of diabetes did not account for our findings, it is possible that this mild prediabetic hyperglycemia in adults induced physiologic changes that predisposed individuals to development of retinopathy after diagnosis of diabetes. In addition, although the youth-onset group was more hyperglycemic at diagnosis, these subjects were slightly less hyperglycemic than the adults during the first 5 years after diagnosis and had uniformly lower blood pressures, also possibly accounting for the lower rates of retinopathy (Table 2). However, the youth-onset subjects remained at lower risk for retinopathy even after adjustment for glucose concentrations and blood pressure in the proportional hazards model. Nephropathy rates were nearly identical between the groups, despite differences in blood pressure and glucose concentrations, and risk was similar in the proportional hazards model after adjustment for these covariates.

The most important finding of our study is that patients with youth-onset diabetes are at considerable risk for nephropathy and eventual renal failure as young adults, in keeping with reports from Japan (11). Although retinopathy rates were relatively lower in youth, a substantial percentage nevertheless devel-

oped retinopathy as young adults, which also indicates that patients with youth-onset type 2 diabetes develop significant microvascular disease in young adulthood (Fig. 3). The presence of microvascular disease in young adults may also increase the risk of cardiovascular disease (34). In summary, although youth are somewhat protected from retinopathy compared with adults, the epidemic of type 2 diabetes in youth is likely to lead to an epidemic of microvascular disease while these patients are still young adults. This emphasizes the need to delay the onset of diabetes as long as possible and for early aggressive treatment once diabetes is diagnosed.

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