The Wisconsin Epidemiologic Study of Diabetic Retinopathy

XIV. Ten-Year Incidence and Progression of Diabetic Retinopathy

Ronald Klein, MD, MPH; Barbara E. K. Klein, MD, MPH; Scot E. Moss, MA; Karen J. Cruickshanks, PhD

Objective: To examine the 10-year incidence and progression of diabetic retinopathy.

Design: Population-based incidence study.

Participants: Seven hundred sixty-five insulin-taking diabetic persons diagnosed before age 30 years, 251 insulin-taking diabetic persons diagnosed at age 30 years or older, and 282 non–insulin-taking diabetic persons diagnosed at age 30 years or older who participated in baseline, 4-year, and 10-year follow-up examinations.

Main Outcome Measures: The 10-year incidence of any retinopathy, progression of retinopathy, and progression to proliferative retinopathy were detected by masked grading of stereoscopic color fundus photographs using the modified Airlie House classification and the Early Treatment Diabetic Retinopathy Study severity scheme.

Results: The 10-year incidence of retinopathy (89%, 79%, and 67%), progression of retinopathy (76%, 69%, and 53%), and progression to proliferative retinopathy (30%, 24%, and 10%) were highest in the group diagnosed before age 30 years, intermediate in the insulin-taking group diagnosed at age 30 years or older, and lowest in the non–insulin-taking group, respectively. Increased risk of proliferative retinopathy was associated with more severe retinopathy at baseline.

Conclusions: These data suggest relatively high 10-year rates of incidence and progression of retinopathy, and despite changes in the treatment of diabetes, there has been little change in the incidence and progression of diabetic retinopathy during the 10-year study period.

(Arch Ophthalmol. 1994;112:1217-1228)

DIABETIC RETINOPATHY remains an important cause of loss of vision in the United States.[1-3] Epidemiologic studies and clinical trials have provided information on the incidence and progression of retinopathy and on the associated risk factors during short intervals, but long-term data are lacking.[4-13] The purposes of this report are to describe the 10-year incidence and progression of diabetic retinopathy and the changes in the incidence and progression of retinopathy in a large population of people with diabetes living in southern Wisconsin.

RESULTS

Characteristics of those who participated in the 10-year follow-up, those who did not participate because they could not be located or they refused, and those who had died in the 6-year interval between the 4-year and 10-year examinations are given in **Table 1** and **Table 2**. With the exception of older age at examination and lower diastolic blood pressure, there were no significant differences in characteristics of those who participated and those who survived but did not participate. The 85 younger-onset persons who had died were older, had a longer duration of diabetes, a higher systolic and diastolic blood pressure, more frequent gross proteinuria, poorer visual acuity, more

See Subjects and Methods on next page

From the Department of Ophthalmology and Visual Sciences, University of Wisconsin Medical School, Madison.

SUBJECTS AND METHODS

STUDY POPULATION

The population, which has been described in previous reports,[4,5,14-16] consisted of a probability sample selected from 10 135 diabetic patients who received primary care in an 11-county area in southern Wisconsin from 1979 to 1980. This sample was composed of a "younger-onset" group (all insulin-taking patients diagnosed before age 30 years [n=1210]) and an "older-onset" group (a sample of people [n=1780] stratified by duration of diabetes of whom 824 were taking insulin and 956 were not).

Of the younger-onset persons, 996 participated in the baseline examination (1980 to 1982),[15] 891 in the 4-year follow-up,[4] and 765 in the 10-year follow-up. Of the 1780 eligible older-onset persons, 1370 participated in the baseline examination,[16] 987 in the 4-year follow-up,[5] and 533 in the 10-year follow-up (**Figure**). The reasons for nonparticipation and comparisons between participants and nonparticipants at baseline and the 4-year follow-up have been presented elsewhere.[4,5,15,16] For the 10-year follow-up, the reasons for nonparticipation are presented in the Figure. Both mean (±SD) and median time between the baseline and 10-year follow-up examinations were 10.1±0.4 years.

PROCEDURES

The baseline and follow-up examinations were performed in a mobile examination van in or near the city where the participants lived. The ocular and physical examinations included taking stereoscopic color fundus photographs of seven standard fields.[17] A structured interview was administered by the examiners.

GRADING PROTOCOL

Grading protocols have been described in detail elsewhere[4,18] and are modifications of the Early Treatment Diabetic Retinopathy Study adaptation of the modified Airlie House classification of diabetic retinopathy.[17,19] Interobserver and intraobserver variations and the validity of the systems have been evaluated, and the results have been presented elsewhere.[4,18-20]

DEFINITIONS

For each eye, the maximum grade in any of the seven standard photographic fields was determined for each of the lesions and used in defining the "retinopathy levels" as follows[21]:

Level 10: No retinopathy.

Level 21: Microaneurysms (MAs) only or retinal hemorrhages (H) or soft exudates in the absence of MAs.

Level 31: Microaneurysms and one or more of the following: venous loops 31 μm or greater; questionable soft exudate, intraretinal microvascular abnormalities (IRMA) or venous beading; and retinal H.

Level 37: Microaneurysms and one or more of the following: hard exudate and soft exudate.

Level 43: Microaneurysms and one or more of the following: H/MAs equaling or exceeding those in Standard Photo (SP) 1 in four or five fields; H/MAs equalling or exceeding those in SP 2A in one field; and IRMA in one to three fields.

Level 47: Microaneurysms and one or more of the following: both IRMA and H/MA characteristics from level 43; IRMA in four or five fields; H/MAs equaling or exceeding those in SP 2A in two or three fields; and venous beading in one field.

Level 53: Microaneurysms and one or more of the following: any two or three characteristics from level 47; H/MAs equaling or exceeding those in SP 2A in four or five fields; IRMA equaling or exceeding those in SP 8A; venous beading in two or more fields.

Level 60: Fibrous proliferations only.

Level 61: No evidence of levels 60 or 65 but scars of photocoagulation either in "scatter" or confluent patches, presumably directed at new vessels.

Level 65: Proliferative diabetic retinopathy (PDR) less than Diabetic Retinopathy Study high-risk characteristics (DRS-HRC). Lesions as follows: new vessels else-

severe retinopathy, and more frequent panretinal photocoagulation at baseline than those who participated ($P<.05$). With few exceptions (higher diastolic blood pressure in the older-onset group taking insulin, greater body mass index, higher glycosylated hemoglobin values, and panretinal photocoagulation in both older-onset groups), relationships between older-onset participants and older-onset people who had died were similar to those found in the younger-onset group (Tables 1 and 2).

The retinopathy severity between eyes at the baseline, 4- and 10-year follow-up examinations were highly correlated. For the younger-onset group, the Spearman correlation coefficient at baseline was .91; at the 4-year follow-up, .91; and at the 10-year follow-up, .90. For the older-onset group taking insulin, the Spearman correlation coefficient at baseline was .85; at the 4-year follow-up, .85; and at the 10-year follow-up, .82. For the older-onset group not taking insulin, the Spearman correlation coefficient at baseline was .68; at the 4-year follow-up, .76; and at the 10-year follow-up, .82. All the correlation coefficients were statistically significant ($P<.0001$). The differences of retinopathy severity of more than two steps between eyes varied from 2.9% to 7.5%.

The 10-year incidence and progression of retinopathy were high in all three diabetic groups (**Table 3**). In the younger-onset group, the percentage of improvement was higher and the percentage of

where (NVE); new vessels on or within 1 disc diameter (NVD) of the disc graded less than SP 10A; or preretinal (PRH) or vitreous hemorrhage (VH) less than 1 disc area (DA).

Level 71: Diabetic Retinopathy Study high-risk characteristics, lesions as follows: VH and/or PRH equaling or exceeding 1 DA; NVE equaling or exceeding one-half DA with VH and/or PRH; NVD less than SP 10A with VH and/or PRH; and NVD equaling or exceeding SP 10A.

Level 75: Advanced PDR, lesions as follows: NVD equalling or exceeding SP 10A with VH and/or PRH.

Level 85: End-stage PDR, lesions as follows: macula obscured by VH and/or PRH; retinal detachment at center of macula; phthisis bulbi; and enucleation secondary to complications of diabetic retinopathy.

The retinopathy level for a participant was derived by concatenating the levels for the two eyes, giving the eye with the higher level greater weight. This scheme provided a 15-step scale (10/10, 21/<21, 21/21, 31/<31, 31/31, 37/<37, 37/37, 43/<43, 43/43, 47/<47, 47/47, 53/<53, 53/53, 60+/<60+, and 60+/60+) when all levels of proliferative retinopathy are grouped as one level. For purposes of classification, if the retinopathy severity could not be graded in an eye, the participant was considered to have a score equivalent to that in the other eye.

The incidence of any retinopathy was estimated from all persons who had no retinopathy at the baseline examination (severity level 10/10) and who participated in the follow-up examination(s). Progression to proliferative retinopathy was estimated from all persons who were free of this complication at the baseline examination. For persons with nonproliferative or no retinopathy, progression was defined as an increase in the retinopathy severity by two steps or more at either of the follow-up examinations. Improvement in retinopathy severity was defined as a two-step or more decrease in the severity of retinopathy at the 4-year follow-up examination, which persisted at the 10-year follow-up examination, or as stable retinopathy at 4 years followed by a two-step decrease at 10 years. Progression and improvement were examined separately in persons who had proliferative retinopathy at the baseline examination because many of these individuals had received panretinal photocoagulation treatment.

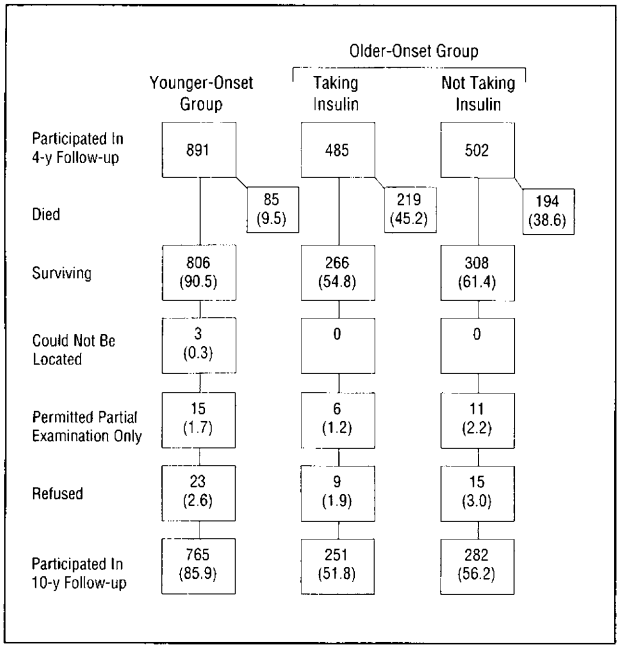
Current age was defined as the age at the time of the baseline examination in 1980 to 1982. Age at diagnosis of diabetes was defined as the age at the time the diagnosis was first recorded by a physician on the patient's chart or on a hospital record. The duration of diabetes was the period between the age at diagnosis and the age at the baseline examination.

STATISTICAL ANALYSES

The rate of an event at 10 years was estimated as the complement of the probability of not developing the event. Furthermore, the probability of not developing the event by the 10-year examination was computed as the product of the probability of not developing the event by the 4-year examination and the probability of not developing the event by the 10-year examination given that the event had not developed by the 4-year examination.[22] The event may be development of any retinopathy, two-step progression of retinopathy, or progression to proliferative retinopathy. This procedure has the advantage of using all the information in each follow-up period even though some persons dropped out between the 4- and 10-year examinations. The most common reason for nonparticipation in this population was death, which cannot be considered to be independent of the incidence or progression of retinopathy. Nevertheless, this technique is a useful tool to summarize and describe the various relationships in the population at the intervals at which we observed them.[22] To test for trends in incidence and progression of retinopathy among subgroups of the population, the test of nonzero correlation of Mantel and Haenszel,[23] stratified on follow-up period, was used. The average annual incidence and progression rates were estimated from the formula: $1 - (1 - p_n)^{1/n}$, where n is equivalent to 4 or 6 and p_n is the 4- or 6-year rate.

progression was lower for females. Progression to proliferative retinopathy was similar for males and females. In the older-onset group not taking insulin, a higher percentage of females improved. By the 10-year follow-up, 29.8% (n=199) of the younger-onset group, 23.6% (n=68) of the older-onset group taking insulin, and 9.7% (n=31) of the older-onset group not taking insulin had developed proliferative retinopathy. In those younger-onset persons with nonproliferative retinopathy (levels 21/21 to 53/53) at the baseline examination, the 10-year rate of improving by two steps or more was 9.8% (n=36); for older-onset persons taking insulin, 21.1% (n=43); and for those not taking insulin, 26.0% (n=28) (Table 3).

The relationships between age and the 10-year incidence of any retinopathy, improvement, progression, or progression to proliferative retinopathy in the younger-onset group are presented in **Table 4**. Younger-onset people who were younger than 10 years at the baseline examination had the lowest 10-year incidence of retinopathy; none progressed to proliferative retinopathy. The relationship of progression of retinopathy to age at baseline was not linear. Younger-onset people who were aged 10 to 29 years at the baseline examination had the highest rates of progression; thereafter, the rates of progression decreased. The 10-year rate of progression to proliferative retinopathy in the younger-onset group increased with



Reasons for nonparticipation in the 10-year follow-up in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (1990-1992). Data are given as number (percentage) of participants.

increasing age from 0% in those who were aged 0 to 9 years to 32.3% in those who were aged 15 to 19 years at the baseline examination; thereafter, the rates varied between 29.0% and 36.6%. The rates of improvement increased with increasing age at baseline.

The relationships between the duration of diabetes and the 10-year incidence of any retinopathy, improvement, progression, or progression to proliferative retinopathy for the younger-onset group are presented in **Table 5**. The 10-year incidence of any retinopathy was consistently high regardless of the duration of diabetes at baseline. The relationships between the 10-year rates of progression of retinopathy or progression to proliferative retinopathy and duration at baseline were not linear. The 10-year incidence of proliferative retinopathy increased with increasing duration in younger-onset persons with fewer than 15 years of diabetes; thereafter, the incidences of proliferative retinopathy varied between 22.9% and 39.1%. The relationships between age or duration of diabetes and the incidence, improvement, progression, or progression to proliferative retinopathy in the older-onset groups are given in **Table 6**. Ten-year incidence and rates of progression declined and improvement of retinopathy increased with increasing age in both older-onset groups.

There were no consistent trends for progression of diabetic retinopathy with increasing retinopathy severity at baseline (**Table 7** and **Table 8**). Progression to proliferative retinopathy was significantly related ($P<.0001$) to greater severity of retinopathy at baseline in the younger- and older-onset groups. In those with retinopathy severity level 43/<43 (moderate nonproliferative retinopathy in at least one eye) or worse at baseline, the 10-year risk of developing proliferative retinopathy was 63.6% in the younger-onset group, 61.8% in the older-onset group taking insulin, and 50.0% in the older-onset group not taking insulin.

Of the 227 younger-onset persons who were found to have proliferative retinopathy at baseline in at least one eye, 40.1% (n=91) had died during the 10-year follow-up. In the 103 persons with DRS-HRC in at least one eye, 54.4% (n=56) had died by 10 years, significantly higher ($P<.0001$) than in the 124 persons without DRS-HRC (28.2%, n=35).

Of 91 younger-onset persons with active proliferative retinopathy in at least one eye (level 65) at baseline who were reexamined, 31.2% (n=26) were found to have proliferative retinopathy with DRS-HRC (levels 71 and 75) in at least one eye, and 6.0% (n=5) were found to have progressed beyond DRS-HRC and to have lost vision in at least one eye (level 85) at the 10-year follow-up. An additional 24.1% (n=20) had a retinopathy level less than DRS-HRC when reexamined but had received new or additional panretinal photocoagulation treatment. Of 38 persons with DRS-HRC in at least one eye who were reexamined, 35.2% (n=13) had progressed to level 85 in at least one eye and 10.5% (n=4) in both eyes.

Of the 115 older-onset persons, taking and not taking insulin, who were found to have proliferative retinopathy at baseline in at least one eye, 73.0% (n=84) had died during the 10-year follow-up. The mortality rate at 10 years was comparable in persons with (74.5%, [35/47]) and without (72.1%, [49/68]) DRS-HRC.

Of the 31 older-onset persons, taking and not taking insulin, with active proliferative retinopathy in at least one eye (level 65) who were reexamined, 19.4% (n=6) were found to have proliferative retinopathy with DRS-HRC (levels 71 and 75) in at least one eye, and 9.7% (n=3) were found to have progressed beyond DRS-HRC and to have lost vision in at least one eye (level 85) at the 10-year follow-up. An additional 32.3% (n=10) had a retinopathy level less than DRS-HRC when reexamined but had received new or additional panretinal photocoagulation treatment. Of 11 persons with DRS-HRC in at least one eye who were reexamined, 36.4% (n=4) had progressed to level 85 in at least one eye and 27.3% (n=2) in both eyes.

The estimates of the annual incidence, progression, and progression to proliferative retinopathy during the first 4 years and next 6 years are presented in **Table 9**. The yearly estimates are similar for incidence and progression among the groups; however, there is an increase in the yearly estimated rates of progression to proliferative retinopathy during the 6-year follow-up. These relationships remained in the older-onset groups after adjusting for duration of diabetes or severity of retinopathy (data not shown).

Table 1. Selected Baseline Characteristics of Younger-Onset Participants and Nonparticipants in the 10-Year Follow-up Examination of the Wisconsin Epidemiologic Study of Diabetic Retinopathy*

Baseline Characteristic	Participants	Nonparticipants	P†	Dead	P†
Age at diagnosis, y	765 (14.2±7.4)	41 (15.6±8.1)	.24	85 (16.6±8.1)	<.005
Duration, y	765 (13.1±9.4)	41 (10.3±6.9)	.07	85 (22.4±9.8)	<.0001
Current age, y	765 (27.2±11.8)	41 (25.9±11.1)	.49	85 (39.0±13.4)	<.0001
Glycosylated hemoglobin, %	726 (12.5±2.6)	40 (11.9±1.8)	.15	79 (13.0±2.9)	.09
Systolic blood pressure, mm Hg	760 (121±17)	41 (123±19)	.40	83 (140±26)	<.0001
Diastolic blood pressure, mm Hg	758 (78±11)	41 (80±12)	.27	83 (85±13)	<.0001
Body mass, kg/m²	764 (23.3±4.1)	41 (24.6±6.6)	.05	84 (23.9±4.5)	.23
Sex					
M	377 (49.3)	22 (53.7)	.63	51 (60.0)	.07
Proteinuria					
Present	123 (16.6)	4 (10.5)	.50	33 (42.9)	<.0001
Visual acuity					
>20/40	732 (96.1)	37 (90.2)		63 (74.1)	
20/40-20/63	20 (2.6)	2 (4.9)	.22	4 (4.7)	<.0001
20/80-20/160	4 (0.5)	1 (2.4)		5 (5.9)	
≤20/200	6 (0.8)	1 (2.4)		13 (15.3)	
Retinopathy severity					
None	241 (31.5)	17 (41.5)		3 (3.5)	
Mild nonproliferative	320 (41.8)	14 (34.1)	.97	21 (24.7)	<.0001
Moderate nonproliferative	81 (10.6)	2 (4.9)		13 (15.3)	
PDR	123 (16.1)	8 (19.5)		48 (56.5)	
Photocoagulation					
Panretinal					
Yes	73 (9.5)	4 (9.8)	1.0	36 (42.4)	<.0001
Focal					
Yes	15 (2.0)	2 (4.9)	.21	3 (3.5)	.41

*Unless otherwise indicated, data are given as number (mean±SD) or number (percentage). PDR indicates proliferative diabetic retinopathy.
†Compared with participants.

COMMENT

The data reported herein provide unique long-term population-based information regarding the incidence and progression of diabetic retinopathy. The cohort was composed of a probability sample of all known patients with diabetes who were receiving treatment in a defined geographic area during a specified period. The cohort was large, there was a broad distribution of retinopathy severity at baseline, the follow-up intervals were defined and uniform for the cohort, there was a very low refusal rate, and unavailability for follow-up was primarily owing to death. The standardized protocols of measurement, including objective recording of diabetic retinopathy using stereoscopic fundus photographs of seven standard fields, were consistent over time.[17] The grading of fundus photographs was done in masked fashion using a standard classification system.[19]

The overall 10-year incidence of any retinopathy (74%), rates of progression of retinopathy (64%), and progression to proliferative retinopathy (17%) were high. Based on the Wisconsin Epidemiologic Study of Diabetic Retinopathy data, it is estimated that during the 10-year study period, of the 5.8 million Americans with known diabetes, 915 000 (15.8%) will develop proliferative retinopathy and 320 000 (5.5%) will develop proliferative retinopathy with DRS-HRC. In addition, there appears to be little change in the estimated annual incidence and progression of retinopathy in the younger-onset group and an increase in the estimated annual incidence of proliferative retinopathy within the older-onset groups between the first and second follow-up periods.

This information is important in planning for counseling and rehabilitative services, projecting costs, measuring temporal trends, developing causal inferences, and providing sample size estimates for conducting clinical trials. For example, if there is a "true" annual increase in the incidence of proliferative retinopathy, there may be a need for additional health care resources to detect and treat these individuals with panretinal photocoagulation.

Despite marked changes in the treatment of insulin-dependent diabetes,[24,25] the incidence and progression of diabetic retinopathy during the 10-year study period were high. Of participants without retinopathy at baseline, 89% of the younger-onset group, 79% of the older-onset group

Table 2. Selected Baseline Characteristics of Older-Onset Participants and Nonparticipants in the 10-Year Follow-up Examination

Baseline Characteristic	Taking Insulin				
	Participants	Nonparticipants	P†	Dead	P†
Age at diagnosis, y	251 (46.1±10.7)	15 (49.1±14.0)	.31	219 (51.6±11.5)	<.0001
Duration, y	251 (13.3±7.8)	15 (9.7±7.4)	.08	219 (16.1±8.6)	<.0005
Current age, y	251 (59.5±10.5)	15 (58.8±14.1)	.81	219 (67.7±9.7)	<.0001
Glycosylated hemoglobin, %	225 (11.7±2.2)	14 (11.5±2.0)	.78	204 (12.1±2.3)	.05
Systolic blood pressure, mm Hg	251 (141±21)	15 (138±15)	.62	219 (151±26)	<.0001
Diastolic blood pressure, mm Hg	251 (79±11)	15 (79±8)	.87	219 (79±12)	.65
Body mass, kg/m²	251 (29.1±6.5)	15 (29.7±4.5)	.74	218 (28.0±5.2)	<.05
Sex					
M	107 (42.6)	4 (26.7)	.29	108 (49.3)	.16
Proteinuria					
Present	19 (7.8)	0 (0)	.61	46 (22.5)	<.0001
Visual acuity					
>20/40	243 (96.8)	15 (100.0)	.63	170 (77.6)	<.0001
20/40-20/63	6 (2.4)	0 (0)		28 (12.8)	
20/80-20/160	0 (0.0)	0 (0)		15 (6.8)	
≤20/200	2 (0.8)	0 (0)		6 (2.7)	
Retinopathy					
None	88 (35.1)	8 (53.3)	.08	53 (24.2)	<.01
Mild nonproliferative	100 (39.8)	6 (40.0)		89 (40.6)	
Moderate nonproliferative	39 (15.5)	1 (6.7)		42 (19.2)	
PDR	24 (9.6)	0 (0)		35 (16.0)	
Photocoagulation					
Panretinal					
Yes	16 (6.4)	0 (0)	.61	15 (6.8)	.85
Focal					
Yes	8 (3.2)	0 (0)	1.0	14 (6.4)	.13

*Unless otherwise indicated, data are given as number (mean± SD) or number (percentage). PDR indicates proliferative diabetic retinopathy.
†Compared with participants.

taking insulin, and 67% of the older-onset group not taking insulin developed it. Of participants without proliferative retinopathy at baseline, 76% of the younger-onset group, 69% of the older-onset group taking insulin, and 53% of the older-onset group not taking insulin progressed two or more steps. In addition, after 10 years of follow-up of the cohort, 30% of the younger-onset group, 24% of the older-onset group taking insulin, and 10% of the older-onset group not taking insulin had developed proliferative retinopathy. These findings are consistent with the few clinic[9-11,13,20] and population-based[8-12] cohorts with longer follow-up to which these data can be compared. The data suggest that despite the different periods and populations studied, retinopathy incidence and progression remain largely unchanged.

Duration of diabetes is one of the most important risk variables for prevalence and, in some studies, for the incidence of diabetic retinopathy.[13,15,16] While this characteristic was an important predictor during the observation period, it did not always exert a consistent linear effect on the rate of development or progression of retinopathy. For the younger-onset group, for those with 20 or more years of diabetes, the 10-year risk of progression declined, while the rates of improvement increased. The 10-year incidence of proliferative retinopathy also decreased after 15 years of diabetes in the younger-onset group. The relationships of incidence and progression of retinopathy were also not consistent in the older-onset groups. In those using insulin at baseline, longer duration of diabetes at baseline was associated with a decreased risk of incidence and progression of retinopathy, while in those not using insulin, there appeared to be no relationship with duration of diabetes. These findings are consistent with earlier reports and our findings after 4 years of follow-up.[4,5,10]

Different relationships within and among the different diabetic groups between duration of diabetes and the incidence of any retinopathy, improvement, progression, and progression to proliferative retinopathy may be explained by a number of factors. Possible reasons for

of the Wisconsin Epidemiologic Study of Diabetic Retinopathy*

Not Taking Insulin				
Participants	Nonparticipants	P*	Dead	P*
282 (55.1±10.2)	26 (57.6±11.4)	.23	194 (62.0±11.4)	<.0001
282 (7.0±5.3)	26 (9.1±6.7)	.07	194 (9.5±7.2)	<.0001
282 (62.1±10.1)	26 (66.6±9.7)	<.05	194 (71.6±9.4)	<.0001
267 (10.0±2.4)	23 (9.8±1.6)	.71	176 (10.6±2.2)	<.05
282 (142±19)	26 (146±24)	.29	193 (153±25)	<.0001
281 (82±10)	26 (78±13)	.05	191 (79±12)	<.005
282 (30.0±5.6)	26 (30.2±5.9)	.88	194 (29.0±5.6)	.05
118 (41.8)	11 (42.3)	1.0	97 (50.0)	.09
13 (4.7)	2 (7.7)	.37	29 (16.0)	<.0001
273 (97.2)	24 (92.3)	.96	160 (82.9)	<.0001
5 (1.8)	2 (7.7)		24 (12.4)	
1 (0.4)	0 (0)		7 (3.6)	
2 (0.7)	0 (0)		2 (1.0)	
189 (67.0)	18 (69.2)	.08	96 (49.5)	<.0001
82 (29.1)	5 (19.2)		77 (39.7)	
6 (2.1)	1 (3.8)		18 (9.3)	
5 (1.8)	2 (7.7)		3 (1.5)	
1 (0.4)	1 (3.8)	.16	0 (0)	1.0
1 (0.4)	1 (3.8)	.16	4 (2.1)	.16

Table 3. Ten-Year Incidence of Any Retinopathy, Improvement or Progression of Retinopathy, or Progression to PDR by Sex*

	Younger-Onset Group			Older-Onset Group					
				Taking Insulin			Not Taking Insulin		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
No. at risk	142	119	**261**	58	88	**146**	144	157	**301**
Incidence of any retinopathy, %	93.0	84.9	89.3	76.9	80.4	79.2	69.1	65.3	66.9
95% CI	88.6-97.4	78.2-91.6	85.4-93.2	62.1-91.7	69.4-91.3	70.4-88.0	59.6-78.5	56.6-73.9	60.5-73.3
No. at risk	184	200	**384**	114	109	**223**	40	73	**113**
Improvement, %	6.9	12.4	9.8	18.6	23.7	21.1	17.5	30.0	26.0
95% CI	3.1-10.6	7.8-17.1	6.7-12.9	10.6-26.6	15.1-32.4	15.2-27.0	5.7-29.3	18.9-41.0	17.3-34.6
No. at risk	354	358	**712**	194	223	**417**	217	270	**487**
Progression, %	80.2	71.6	75.8	66.2	70.8	68.7	54.8	51.5	52.9
95% CI	75.8-84.5	66.7-76.4	72.5-79.1	57.6-74.9	63.2-78.4	63.0-74.5	46.3-63.2	44.1-58.8	47.4-58.5
Progression to PDR, %	29.0	30.5	29.8	24.8	22.6	23.6	6.7	11.8	9.7
95% CI	24.1-33.9	25.6-35.4	26.3-33.3	16.8-32.7	15.8-29.4	18.4-28.8	2.5-10.9	7.0-16.7	6.4-13.1

*PDR indicates proliferative diabetic retinopathy; CI, confidence interval. See "Subjects and Methods" section for definition of at-risk groups.

Table 4. Ten-Year Incidence of Any Retinopathy, Improvement or Progression of Retinopathy, or Progression to PDR* by Age at Baseline Examination in the Younger-Onset Group

Age at Baseline Examination, y	No. at Risk	Incidence of Any Retinopathy, %†	No. at Risk	Improvement, %‡	No. at Risk	Progression, %§	Progression to PDR, %‖
0-9	26	73.3	0	...	27	62.3	0.0
10-14	66	90.6	5	...	80	80.5	14.8
15-19	62	94.2	57	3.5	140	85.2	32.3
20-24	40	89.2	83	6.0	130	80.4	34.0
25-29	24	100.0	68	9.2	101	78.0	36.6
30-34	32	85.0	58	7.2	102	74.8	29.0
35+	11	81.8	113	17.5	132	59.0	33.2

*PDR indicates proliferative diabetic retinopathy. See "Subjects and Methods" section for definition of at-risk groups.
†$P<.05$, for test of trend.
‡$P<.01$, for test of trend.
§$P=.09$, for test of trend.
‖$P<.005$, for test of trend.

Table 5. Ten-Year Incidence of Any Retinopathy, Improvement or Progression of Retinopathy, or Progression to PDR* by Duration of Diabetes at Baseline Examination in the Younger-Onset Group

Duration of Diabetes at Baseline Examination, y	No. at Risk	Incidence of Any Retinopathy, %†	No. at Risk	Improvement, %‡	No. at Risk	Progression, %§	Progression to PDR, %‖
0-2	69	82.8	5	...	75	62.9	10.1
3-4	67	92.9	5	...	84	82.5	9.1
5-9	99	92.0	94	6.4	229	82.7	28.0
10-14	26¶	88.5¶	112	4.5	140	85.0	49.8
15-19	...	...	68	6.6	79	73.4	38.4
20-24	...	...	41	12.9	42	59.4	28.2
25-29	...	...	32	23.6	34	53.8	39.1
30+	...	...	27	27.1	29	42.1	22.9

*PDR indicates proliferative diabetic retinopathy. See "Subjects and Methods" section for definition of at-risk groups.
†$P<.001$, for test of trend.
‡$P<.005$, for test of trend.
§$P=.06$, for test of trend.
‖$P<.0001$, for test of trend.
¶Number and rate for duration ≥ 10 years.

these findings include a lower frequency of factors necessary for the progression of nonproliferative retinopathy after 20 years of diabetes. People with such long duration of insulin-dependent diabetes are less likely to develop diabetic nephropathy and associated changes in blood pressure, lipoproteins, renin, prorenin, angiotensin, platelet adhesiveness, and blood viscosity, factors hypothesized to be related to progression of retinopathy.[26-29] A second explanation for declining progression of retinopathy, especially in those with longer duration of diabetes at baseline, may be that the force of mortality competes with the "force of complications." In our study, younger-onset persons who progressed to PDR were at greater risk of death during the 6-year follow-up (R.K. and S.E.M., unpublished data, July 18, 1993). This might cause an apparent decrease in the rates of progression of retinopathy in persons with long duration of diabetes, if progression were undetected before death (or nonparticipation).

In some comparisons of differences between the sexes, women faired somewhat better than men. Whether this is related to the biologic characteristics of the disease or is more related to mortality cannot be assessed in these data.

In all groups studied, those who did not participate in the follow-up examination because of death were older at diagnosis, had longer duration of diabetes, were older, were more likely to have proteinuria, had poorer visual acuity, and had more severe retinopathy at baseline than participants. Therefore, systematic differences between participants and nonparticipants may well be influencing the incidence. The influence of nonparticipation is of concern if one were attempting to document cumulative incidence. This is not the case in the present study. Incidence is always difficult to estimate in chronic diseases when the influence of mortality cannot be considered to be independent of the incident disease event. For example, in older-onset people taking insulin at base-

Table 6. Ten-Year Incidence of Any Retinopathy, Improvement or Progression of Retinopathy, or Progression to PDR* by Age and Duration of Diabetes at Baseline Examination in the Older-Onset Group

	Age or Duration of Diabetes at Baseline Examination, y	No. at Risk	Incidence of Any Retinopathy, %†	No. at Risk	Improvement, %†	No. at Risk	Progression, %†	Progression to PDR, %†
				By Age				
Using insulin	30-44	17	93.1	6	0	26	82.2	14.5
	45-59	44	83.6	76	8.5	136	78.9	26.3
	60-74	57	79.1	121	27.8	200	61.8	27.4
	75+	28	43.8	20	40.0	55	39.0	0
Not using insulin	30-44	12	70.0	3	. . .	19	55.8	17.1
	45-59	80	66.4	23	8.7	114	59.8	13.1
	60-74	160	68.4	53	22.6	257	51.8	7.1
	75+	49	49.3	34	53.7	97	37.6	12.5
				By Duration of Diabetes				
Using insulin	0-4	48	88.5	21	22.9	77	72.8	14.8
	5-9	44	90.9	22	9.1	78	83.3	18.7
	10-14	22	69.7	40	20.0	73	74.3	31.3
	15+	32	50.0	140	23.4	189	56.8	25.5
Not using insulin	0-4	143	65.6	25	21.6	202	50.0	8.4
	5-9	97	67.4	36	30.6	152	50.0	9.0
	10-14	25	76.7	17	17.6	52	63.3	3.8
	15+	36	61.1	35	25.7	81	60.0	20.3

*PDR indicates proliferative diabetic retinopathy. See "Subjects and Methods" section for definition of at-risk groups.

†The relationship between age and incidence of any retinopathy, improvement, progression, and progression to PDR for those using insulin ($P<.005$, $P<.0001$, $P<.0001$, and $P=.28$, for test of trend) and for those not using insulin ($P=.98$, $P<.005$, $P<.05$, and $P=.06$, for test of trend), respectively. The relationship between duration of diabetes and these same four variables for those using insulin ($P=.20$, $P=.44$, $P=.48$, and $P<.05$, for test of trend) and those not using insulin ($P=.23$, $P=.84$, $P<.05$, and $P=.08$, for test of trend), respectively.

Table 7. Changes in the Severity of Diabetic Retinopathy Between the Baseline and Follow-up Examinations in the Younger-Onset Group*

Severity of Retinopathy at Baseline	No. at Risk	Improvement, %†	Progression, %‡	Progression to	
				PDR, %§	DRS-HRC, %§
10/10	261	. . .	78.5	8.7	2.1
21/<21, 21/21	156	2.2	75.6	25.4	7.1
31/<31, 31/31	74	3.1	81.4	46.8	16.4
37/<37, 37/37	125	11.7	69.0	44.4	9.9
43/<43, 43/43	52	21.5	63.9	50.2	20.0
47/<47, 47/47	32	16.5	86.4	82.0	38.3
53/<53, 53/53	12	19.8	75.0	75.0	53.3

*PDR indicates proliferative diabetic retinopathy; DRS-HRC indicates proliferative retinopathy with Diabetic Retinopathy Study high-risk characteristics for severe visual loss of 5/200 or worse.[6] See "Subjects and Methods" section for definition of at-risk groups and retinopathy levels.

†$P<.005$, for test of trend.

‡$P=.34$, for test of trend.

§$P<.0001$, for test of trend.

line, there were 577 people free of PDR at the prevalence examination. Sixty-eight of these people had developed proliferative disease by the 10-year follow-up. However, 219 people were reexamined who had gradable retinopathy. Thus, the incidence would be 11.8% if the denominator were considered to be 577 but would be 31.1% if the denominator were taken to be 219. If one includes death (130 people died between the baseline and 4-year follow-up and 170 died between the 4- and 10-year follow-up) or proliferative retinopathy (32 developed proliferative retinopathy by the 4-year follow-up, of whom 22 died before the 10-year follow-up, and 36 developed proliferative retinopathy by the 10-year follow-up) as the "event" of interest, then using 577 as the denominator, the rate of a "severe event" would be 63.8% (368/577). Depending on the use of the data, either

Table 8. Changes in the Severity of Diabetic Retinopathy Between the Baseline and Follow-up Examinations in the Older-Onset Group*

Severity of Retinopathy at Baseline	Using Insulin					Not Using Insulin	
	No. at Risk	Improvement, %†	Progression, %‡	Progression to PDR, %§	Progression to DRS-HRC, %‖	No. at Risk	Improvement, %¶
10/10	146	. . .	70.2	7.8	1.2	301	. . .
21/<21, 21/21	72	0.0	71.2	12.2	8.2	102	31.0
31/<31, 31/31	53	11.3	86.5	26.6	5.7	33	17.4
37/<37, 37/37	65	26.4	53.8	27.5	11.4	27	25.9
43/<43, 43/43	48	35.7	60.7	51.0	11.5	11	18.2
47/<47, 47/47	20	25.0	80.0	80.5	21.5	8	25.0
53/<53, 53/53	13	23.1	61.5	61.5	20.9	5	80.0

*PDR indicates proliferative diabetic retinopathy; DRS-HRC indicates proliferative retinopathy with Diabetic Retinopathy Study high-risk characteristics for severe visual loss of 5/200 or worse.[6] See "Subjects and Methods" section for definition of at-risk groups and retinopathy levels.

†P=.05, for test of trend.

‡P=.99, for test of trend.

§P<.0001, for test of trend.

‖P<.0005, for test of trend.

¶P=.31, for test of trend.

Table 9. Estimates of Average Annual Incidence, Progression, and Progression to PDR in the Three Study Groups*

	Period	No. at Risk	Younger-Onset, %	No. at Risk	Older-Onset Taking Insulin, %	No. at Risk	Older-Onset Not Taking Insulin, %
Incidence per year	First 4 y	261	20.0	146	14.8	301	10.2
	Next 6 y	103	19.0	47	14.8	146	10.1
Progression per year	First 4 y	712	13.6	417	11.6	487	7.1
	Next 6 y	579	13.4	210	11.8	269	9.0
Progression to PDR per year	First 4 y	712	2.7	417	2.0	487	0.6
	Next 6 y	579	4.0	210	3.2	269	1.3

*PDR indicates proliferative diabetic retinopathy. See "Subjects and Methods" section for definition of at-risk groups.

method of determining the impact of diabetes during the 10-year follow-up would be appropriate. For estimating health care provision needs for retinopathy after 10 years of follow-up, it is probably only the 219 who survived who are of interest.

In the younger-onset group, incidence (73%) was lowest in those who were younger than age 10 years at baseline. No one younger than 10 years at baseline progressed to proliferative retinopathy during the 10-year follow-up. These data are consistent with observations from a number of other studies,[9,30-34] suggesting that there was a relative "protective" effect of developing diabetes before puberty that remained even though almost all children had passed through puberty after 10 years of the study. The higher incidence and progression of retinopathy after puberty have been hypothesized to be a result of increased hyperglycemia associated with poorer compliance in maintaining glycemic control and increased insulin resistance,[35-37] hormonal changes,[38] and increased growth factors associated with adolescence.[39]

Progression to proliferative retinopathy was associated with severity of baseline retinopathy. In the entire Wisconsin Epidemiologic Study of Diabetic Retinopathy population, the 10-year rate of progression to proliferative retinopathy varied from 7% in those with no retinopathy at baseline to 81% in those with moderately severe nonproliferative retinopathy (level 47 in either eye) at baseline. Higher average annual incidence of proliferative retinopathy has been reported in eyes with moderately severe nonproliferative retinopathy in the Diabetic Retinopathy Study[6] and the Early Treatment Diabetic Retinopathy Study.[21] However, the severity of diabetic retinopathy in persons in both studies in whom that rate is based was probably more severe than in the present study; the fellow eyes in the Diabetic Retinopathy Study and some in the Early Treatment Diabetic Retinopathy Study had active proliferative retinopathy. Our data suggest that even people with no retinopathy at baseline are in need of ophthalmologic observation because of the significant number at risk of progressing to proliferative retinopathy during the 10 years of follow-up.

Not Using Insulin		
	Progression to	
Progression, %†	PDR, %§	DRS-HRC, %§
49.1	4.9	2.5
59.0	10.3	3.4
78.8	22.4	3.0
45.7	38.7	27.3
18.2	54.5	0.0
50.0	50.0	25.0
20.0	20.0	20.0

Table 10. Projected New Cases of Proliferative Retinopathy Over 10 Years (Weighted) in Wisconsin Health Service Area 1*

Severity Scores of Proliferative Retinopathy	Total New Cases of Proliferative Retinopathy	No. (%)	
		Younger Age at Onset	Older Age at Onset
60-65	387	156 (40.3)	231 (59.7)
71-75	175	59 (33.7)	116 (66.3)
85	51	11 (21.6)	40 (78.4)
Total	**613**	**226** (36.9)	**387** (63.1)

**Population 839 324. Estimate based on fractions at the baseline examination when participants were sampled (1979-1980), according to the duration of diabetes.*

There was an inverse effect of age on the incidence and progression of retinopathy in the older-onset groups. Those who were aged 30 to 44 years were between 1.5 to 2.0 times as likely to develop or have their retinopathy progress as those older than 75 years. In addition, the oldest older-onset people were more likely to show an improvement in their retinopathy during the 10-year follow-up. These findings may be a result of selective survival (the oldest persons at risk of progression were least likely to survive to have their progression detected at the 4- or 10-year follow-up).

The 10-year incidence of proliferative retinopathy was higher in the younger-onset group than in the older-onset groups. However, the estimates of the number of incident cases in the 10-year period are higher in the group with older-onset age than in the younger-onset age group (387 vs 226; **Table 10**). It is possible that the burden of health care due to older-onset diabetes may be underestimated by these data, as some of these people may have required treatment for retinopathy (before death) and would not have been included in our data.

Extrapolating from our data, the majority of eyes that develop proliferative retinopathy with DRS-HRC for severe visual loss or worse during the 10-year period would occur in the group with older age at onset (Table 10). The high frequency of severe retinopathy associated with older age at onset of diabetes underscores the need for timely referral and appropriate ophthalmologic care for people with older-onset diabetes.

In summary, our data confirm current guidelines for ophthalmologic care for people with diabetes.[40,41] Ophthalmologic care for detection of vision-threatening retinopathy is not indicated in persons who are younger than 12 years because proliferative disease is rare in that age group. Thereafter, diabetic persons should be under ophthalmologic observation depending on the duration of diabetes, severity of retinopathy found, and methods used to detect retinopathy. Diabetic persons should be informed about their risk of developing severe retinopathy and the need for ophthalmologic observation and care. In addition, our data suggest the need for further study of risk factors and development of interventions to reduce the high incidence and rates of progression of retinopathy in the population.

Accepted for publication November 24, 1993.

This work was supported by grant EY03083 from the National Eye Institute, Bethesda, Md (Dr R. Klein). Dr R. Klein is a Research To Prevent Blindness senior scientific investigator.

Presented in part at the Annual Meeting of the Association for Research in Vision and Ophthalmology, Sarasota, Fla, May 2, 1993.

We are grateful to the 452 Wisconsin physicians and their staffs who participated in and supported this study. We thank Richard Chappell, PhD; Matthew D. Davis, MD; Polly Newcomb, PhD; and Mari Palta, PhD, for their assistance; the local hospitals that provided supportive services for the mobile examination van; and the State of Wisconsin Division of Health, for donating the van.

Reprint requests to Department of Ophthalmology and Visual Sciences, Clinical Science Center, 600 Highland Ave—F4/336, Madison, WI 53792-3220 (Dr R. Klein).

REFERENCES

1. National Society To Prevent Blindness. *Vision Problems in the US: Data Analysis, Definitions, Data Sources, Detailed Data Tables, Analysis, Interpretation.* New York, NY: National Society To Prevent Blindness; 1980.
2. Klein R, Klein BEK, Moss SE. Visual impairment in diabetes. *Ophthalmology.* 1984;91:1-9.
3. Moss SE, Klein R, Klein BEK. The incidence of vision loss in a diabetic population. *Ophthalmology.* 1988;95:1340-1348.
4. Klein R, Klein BEK, Moss SE, Davis MD, DeMets DL. The Wisconsin Epidemiologic Study of Diabetic Retinopathy, IX: four-year incidence and progression of diabetic retinopathy when age at diagnosis is less than 30 years. *Arch*

Ophthalmol. 1989;107:237-243.
5. Klein R, Klein BEK, Moss SE, Davis MD, DeMets DL. The Wisconsin Epidemiologic Study of Diabetic Retinopathy, X: four-year incidence and progression of diabetic retinopathy when age at diagnosis is 30 years or more. *Arch Ophthalmol.* 1989;107:244-249.
6. Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy: clinical application of Diabetic Retinopathy Study (DRS) findings: DRS Report No. 8. *Ophthalmology.* 1981;88:583-600.
7. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema: Early Treatment Diabetic Retinopathy Study Report Number 1. *Arch Ophthalmol.* 1985;103:1796-1806.
8. Yanko L, Goldbourt U, Michaelson IC, Shapiro A, Yaari S. Prevalence and 15-year incidence of retinopathy and associated characteristics in middle-aged and elderly diabetic men. *Br J Ophthalmol.* 1983;67:759-765.
9. Goldstein DE, Blinder KJ, Ide CH, et al. Glycemic control and development of retinopathy in youth-onset insulin-dependent diabetes mellitus: results of a 12-year longitudinal study. *Ophthalmology.* 1993;100:1125-1132.
10. Krolewski AS, Warram JH, Rand LI, Christlieb AR, Busick EJ, Kahn CR. Risk of proliferative diabetic retinopathy in juvenile-onset type I diabetes: a 40-year follow-up study. *Diabetes Care.* 1986;9:443-452.
11. Burditt AF, Caird FI, Draper GJ. The natural history of diabetic retinopathy. *Q J Med.* 1967;37:303-317.
12. Dwyer MS, Melton LJ III, Ballard DJ, Palumbo PJ, Trautman JC, Chu C-P. Incidence of diabetic retinopathy and blindness: a population-based study in Rochester, Minnesota. *Diabetes Care.* 1985;8:316-322.
13. Pirart J. Diabetes mellitus and its degenerative complications: a prospective study of 4400 patients observed between 1947 and 1973. *Diabetes Care.* 1978; 1:168-188, 252-263.
14. Klein R, Klein BEK, Moss SE, DeMets DL, Kaufman I, Voss PS. Prevalence of diabetes mellitus in southern Wisconsin. *Am J Epidemiol.* 1984;119:54-61.
15. Klein R, Klein BEK, Moss SE, Davis MD, DeMets DL. The Wisconsin Epidemiologic Study of Diabetic Retinopathy, II: prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. *Arch Ophthalmol.* 1984; 102:520-526.
16. Klein R, Klein BEK, Moss SE, Davis MD, DeMets DL. The Wisconsin Epidemiologic Study of Diabetic Retinopathy, III: prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. *Arch Ophthalmol.* 1984; 102:527-532.
17. Diabetic Retinopathy Study Research Group. Report VII: a modification of the Airlie House classification of diabetic retinopathy. *Invest Ophthalmol Vis Sci.* 1981;21:210-226.
18. Klein R, Klein BEK, Magli YL, et al. An alternative method of grading diabetic retinopathy. *Ophthalmology.* 1986;93:1183-1187.
19. Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie House classification: ETDRS Report No. 10. *Ophthalmology.* 1991;98:786-806.
20. Klein BEK, Davis MD, Segal P, et al. Diabetic retinopathy: assessment of severity and progression. *Ophthalmology.* 1984;91:10-17.
21. Early Treatment Diabetic Retinopathy Study Research Group. Fundus photographic risk factors for progression of diabetic retinopathy: ETDRS Report No. 12. *Ophthalmology.* 1991;98:823-833.
22. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 1958;53:457-481.
23. Mantel N. Chi-square tests with one degree of freedom: extensions of the Mantel-Haenszel procedure. *J Am Stat Assoc.* 1963;58:690-700.
24. Klein R, Moss SE, Klein BEK. Change in glycemia in a four-year interval in insulin-dependent diabetes. *Ann Epidemiol.* 1992;2:283-294.
25. Hiss RG, Lengyel MC, Hess GE, Bowbeer LA. *Diabetes in Communities.* Ann Arbor: Michigan Diabetes Research and Training Center and Department of Postgraduate Medicine and Health Professions Education, The University of Michigan Medical School; 1986:1-100.
26. Anderson AR, Christiansen JS, Anderson JK, Kreiner S, Deckert T. Diabetic nephropathy in type I (insulin-dependent) diabetes: an epidemiological study. *Diabetologia.* 1983;25:496-501.
27. Borch-Johnsen K, Kreiner S. Proteinuria: value as predictor of cardiovascular mortality in insulin-dependent diabetes mellitus. *BMJ.* 1987;294:1651-1654.
28. Winocour PH, Durrington PN, Ishola M, Anderson DC, Cohen H. Influence of proteinuria on vascular disease, blood pressure, and lipoprotein in insulin-dependent diabetes mellitus. *BMJ.* 1987;294:1648-1651.
29. Klein R, Klein BEK, Moss SE. The incidence of gross proteinuria in people with insulin-dependent diabetes mellitus. *Arch Intern Med.* 1991;151:1344-1348.
30. Kostraba JN, Dorman JS, Orchard TJ, et al. Contribution of diabetes duration before puberty to development of microvascular complications in IDDM subjects. *Diabetes Care.* 1989;12:686-693.
31. Murphy RP, Nanda M, Plotnick L, Enger C, Vitale S, Patz A. The relationship of puberty to diabetic retinopathy. *Arch Ophthalmol.* 1990;108:215-218.
32. Frank RN, Hoffman WH, Podgor MJ, et al. Retinopathy in juvenile-onset type I diabetes of short duration. *Diabetes.* 1982;31:874-882.
33. Palmberg P, Smith M, Waltman S, et al. The natural history of retinopathy in insulin-dependent juvenile-onset diabetes. *Ophthalmology.* 1981;88:613-618.
34. Klein BEK, Moss SE, Klein R. Is menarche associated with diabetic retinopathy? *Diabetes Care.* 1990;13:1034-1038.
35. Allen C, Zaccaro DJ, Palta M, Klein R, Duck SC, Dalessio DJ. Glycemic control in early IDDM. *Diabetes Care.* 1992;15:980-987.
36. Daneman D, Wolfson DH, Becker DJ, Drash AL. Factors affecting glycosylated hemoglobin values in children with insulin-dependent diabetes. *J Pediatr.* 1981; 99:847-853.
37. Blethen SL, Sargeant DL, Whitlow MG, Santiago JV. Effect of pubertal stage and recent blood glucose control on plasma somatomedin C in children with insulin-dependent diabetes mellitus. *Diabetes.* 1981;30:868-872.
38. Haffner SM, Klein R, Dunn JF, Moss SE, Klein BEK. Increased testosterone in type I diabetic subjects with severe retinopathy. *Ophthalmology.* 1990;97:1270-1274.
39. Merimee TJ, Zapf J, Froesch ER. Insulin-like growth factors. *N Engl J Med.* 1983;309:527-530.
40. Division of Diabetes Translation. *The Prevention and Treatment of Five Complications of Diabetes: A Guide for Primary Care Practitioners.* Atlanta, Ga: Centers for Disease Control; 1991:41-49.
41. Klein R, Moss SE, Klein BEK. New management concepts for timely diagnosis of diabetic retinopathy treatable by photocoagulation. *Diabetes Care.* 1987;10: 633-638.