Chapter 14

Vision Disorders in Diabetes

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SUMMARY

Diabetes, particularly diabetic retinopathy, is the leading cause of new cases of blindness in people age 20-74 years in the United States. Approximately 8% of those who are legally blind are reported to have diabetes as the etiology, and it is estimated that more than 12% of new cases of blindness are attributable to diabetes. Twelve percent of insulin-dependent persons with diabetes for 30 or more years are blind. Persons who have diabetic retinopathy are 29 times more likely to be blind than nondiabetic persons. Blindness due to diabetes is estimated to involve lost income and public welfare expense of $500 million annually.

Three complications of diabetes may lead to blindness. They are retinopathy, cataracts, and glaucoma. Diabetic retinopathy is characterized by alterations in the small blood vessels in the retina. An estimated 97% of insulin-taking and 80% of noninsulin-taking persons who have had diabetes for ≥15 years have retinopathy; approximately 40% of insulin-taking and 5% of noninsulin-taking persons have the most severe stage, proliferative diabetic retinopathy.

The Diabetes Control and Complications Trial (DCCT), completed in 1993, has demonstrated that those persons with insulin-dependent diabetes mellitus (IDDM) with no retinopathy at baseline with intensive insulin treatment had a 60% risk reduction in progression of retinopathy compared with persons with conventional insulin treatment. For those with retinopathy at baseline, intensive insulin treatment was associated with a 54% reduction in progression, a 47% reduction in the incidence of preproliferative or proliferative retinopathy, and a 54% reduction in laser treatment compared with conventional insulin treatment.

Clinical trials have shown the efficacy of panretinal photocoagulation in reducing the incidence of serious loss of vision (worse than 5/200) in persons with severe proliferative retinopathy by about 50% and focal photocoagulation in reducing the incidence of doubling of the visual angle (i.e., going from 20/20 to 20/40 visual acuity) also by about 50%. Regular ophthalmologic consultation and examination are indicated in the care of these patients because timely panretinal photocoagulation treatment may prevent loss of vision. This is especially important for diabetic individuals, who may be unaware of the potential for loss of vision because early diabetic retinopathy is usually asymptomatic and does not cause impaired vision. Even patients with new blood vessel growth may be unaware of the threat to sight until a serious hemorrhage into the vitreous occurs.

Other causes of decreased vision that occur more frequently in patients with diabetes are cataract (clouding of the lens), glaucoma (damage to the optic nerve, with subsequent loss of visual field due to relatively increased intraocular pressure), and corneal disease.

Data from the DCCT and other epidemiological studies suggest that hyperglycemia is associated with increased risk of incidence and progression of diabetic retinopathy and incidence of impaired vision. High blood pressure, early age at onset of diabetes, and longer duration of diabetes are also associated with increased risk of progression of retinopathy. A number of preventive trials for intervention on risk factors have been completed or are under way to determine whether medical therapy other than glycemic control can prevent disease progression and loss of vision.

There is a need for national population-based data on the prevalence and incidence of loss of vision. Accurate data concerning the needs of the visually impaired for occupational, vocational, psychosocial, and medical services are also necessary to describe the current situation and to plan for future health care delivery.

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IMPAIRMENT OF VISION AND BLINDNESS

DEFINITIONS

The following classifications of impairment of vision have been widely used. They are described in terms of a Snellen fraction in the better eye (Council on Clinical Classifications 1978):

- No impairment — better than 20/40 in the better eye
- Minimal impairment — 20/40 to 20/60
- Moderate impairment — 20/70 to 20/160
- Severe impairment (legal blindness) — 20/200 or worse

PREVALENCE

Estimates of rates of legal blindness in the United States have been reported by the National Society to Prevent Blindness from data of the Model Reporting Area (MRA) registry[1-3]. It was estimated that 7.9% of people who were legally blind reported diabetes as the cause of their blindness (Table 14.1).

Prevalence rates for diabetes-related legal blindness increased with increasing age to a maximum in persons age 65-74 years; thereafter, the rates declined. This decline may have been due to excess deaths in the elderly diabetic population, in which the disease had already progressed to the stage of blindness. The relative proportion of cases of blindness attributed to diabetic retinopathy declined with increasing age. Rates for females were higher than for males. Higher rates of legal blindness were found in white females and in nonwhite males and females, compared with white males (Table 14.2). Since the MRA registry data were based on self-reports and required registration at specific agencies in 16 states, the rates are thought to underestimate the actual prevalence of legal blindness by as much as 50%[4].

Table 14.2
Age-Adjusted Relative Risk of Blindness Due to Diabetes, by Race and Sex, Model Reporting Area Registry, 1978

Race and sex	Relative risk compared with diabetic white males
White males	1.00
White females	1.25
Nonwhite males	1.27
Nonwhite females	3.83

Age-adjusted by direct method to total 1970 census population of 14 participating Model Reporting Area states.

Source: Reference 4

Blindness from all causes in the United States is shown in Table 14.3 for comparison to blindness attributable to diabetic retinopathy.

Another source of information concerning the rate of visual impairment in persons with diabetes is the 1989 National Health Interview Survey (NHIS)[5]. These survey data were obtained by questioning a probability sample of adults in the United States. Self-

Table 14.1
Prevalence of Legal Blindness Due to Diabetes and Diabetic Retinopathy, by Age and Sex, U.S., 1978

Age and sex	No. of cases of legal blindness due to diabetes	% of total cases of legal blindness due to diabetes	No. of cases of legal blindness due to diabetic retinopathy	% of total cases of legal blindness due to diabetic retinopathy
Age (years)				
<5	0	0	0	0
5-19	<50	<0.1	<50	<0.1
20-44	4,000	4.8	3,500	4.2
45-64	12,250	11.3	10,600	9.8
65-74	13,700	14.4	11,150	11.7
75-84	7,850	7.5	6,200	6.0
≥85	1,700	2.6	1,200	1.8
Sex				
Males	14,750	6.1	12,800	5.3
Females	24,750	9.7	19,850	7.7
Total	39,500	7.9	32,650	6.6

Source: Reference 1; data are estimated from 1970 Model Reporting Area data

Table 14.3

Leading Causes of Legal Blindness, by Age and Sex, U.S., 1978

Age, sex, and cause	No.	Percent	Rate*
Total, all ages			
1. Glaucoma, except congenital	62,100	12.5	28.1
2. Macular degeneration	58,250	11.7	26.3
3. Senile cataract	41,500	8.3	18.7
4. Optic nerve atrophy	34,500	7.0	15.6
5. Diabetic retinopathy	32,650	6.6	4.8
6. Retinitis pigmentosa	23,250	4.7	10.5
7. Myopia	19,850	4.0	8.9
All other	225,900	45.2	102.1
Total, all ages	498,000	100.0	225.1
Age <5 years			
1. Prenatal cataract	1,050	16.3	6.8
2. Optic nerve atrophy	800	12.4	5.2
3. Retrolental fibroplasia	600	9.3	3.9
4. Anophthalmos, microphthalmos	400	6.2	2.6
Glaucoma, congenital	400	6.2	2.6
5. Retinoblastoma	250	3.9	1.6
All other	2,700	45.7	17.6
Total in age group	6,450	100.0	42.0
Age 5-19 years			
1. Prenatal cataract	4,500	12.9	8.0
2. Optic nerve atrophy	4,250	12.2	7.5
3. Retrolental fibroplasia	2,950	8.5	5.2
4. Albinism	2,500	7.1	4.4
5. Myopia	2,250	6.5	4.0
6. Nystagmus	1,900	5.5	3.4
All other	16,400	47.3	29.0
Total in age group	34,750	100.0	61.6
Age 20-44 years			
1. Retrolental fibroplasia	8,950	10.8	11.4
2. Optic nerve atrophy	8,550	10.3	10.9
3. Retinitis pigmentosa	6,200	7.5	7.9
4. Prenatal cataract	4,450	5.4	5.7
5. Myopia	4,050	4.9	5.2
6. Macular degeneration	3,650	4.4	4.7
7. Diabetic retinopathy	3,500	4.2	4.5
All other	43,450	52.5	55.5
Total in age group	82,800	100.0	105.7
Age 45-64 years			
1. Glaucoma, except congenital	12,150	11.2	27.7
2. Diabetic retinopathy	10,600	9.8	24.2
3. Retinitis pigmentosa	9,550	8.8	21.8
4. Optic nerve atrophy	9,300	8.6	21.2
5. Senile cataract	5,850	5.4	13.3
6. Macular degeneration	5,400	5.0	12.3
7. Myopia	5,300	4.9	12.1
All other	49,900	36.3	113.8
Total in age group	108,050	100.0	246.4
Age 65-74 years			
1. Glaucoma, except congenital	17,250	18.1	115.5
2. Diabetic retinopathy	11,150	11.7	74.7
3. Senile cataract	8,600	9.0	57.6
4. Macular degeneration	8,300	8.7	55.6
5. Optic nerve atrophy	6,200	6.5	41.5
6. Retinitis pigmentosa	4,200	4.4	28.1
7. Myopia	4,150	4.4	27.8
All other	35,250	37.2	236.0
Total in age group	95,100	100.0	636.8
Age 75-84 years			
1. Macular degeneration	21,800	20.8	315.3
2. Glaucoma, except congenital	20,050	19.2	290.0
3. Senile cataract	12,950	12.4	187.3
4. Diabetic retinopathy	6,200	6.0	89.7
5. Optic nerve atrophy	3,900	3.8	56.4
All other	39,700	37.8	574.2
Total in age group	104,600	100.0	1,512.9
Age ≥85 years			
1. Macular degeneration	17,900	27.8	811.4
2. Senile cataract	13,650	20.6	618.8
3. Glaucoma, except congenital	10,850	16.4	491.8
All other	22,050	35.2	999.5
Total in age group	66,250	100.0	3,003.2
Age ≥65 years			
1. Glaucoma, except congenital	48,150	18.1	200.2
2. Macular degeneration	48,000	18.0	199.6
3. Senile cataract	35,200	13.2	146.3
4. Diabetic retinopathy	18,500	7.0	76.9
5. Optic nerve atrophy	11,600	4.4	48.2
All other	104,500	39.3	434.4
Total in age group	265,950	100.0	1,105.6
Males			
1. Glaucoma, except congenital	27,600	11.4	26.0
2. Macular degeneration	21,900	9.1	20.6
3. Optic nerve atrophy	21,500	8.9	20.3
4. Retinitis pigmentosa	15,000	6.2	14.1
5. Senile cataract	14,500	6.0	13.7
All other	141,050	58.4	133.0
Total males	241,550	100.0	227.8
Females			
1. Macular degeneration	36,350	14.2	32.5
2. Glaucoma, except congenital	34,500	13.5	30.8
3. Senile cataract	27,000	10.5	24.1
4. Diabetic retinopathy	19,850	7.7	17.7
5. Optic nerve atrophy	13,000	5.1	11.6
All other	125,750	49.0	112.3
Total females	256,450	100.0	228.9

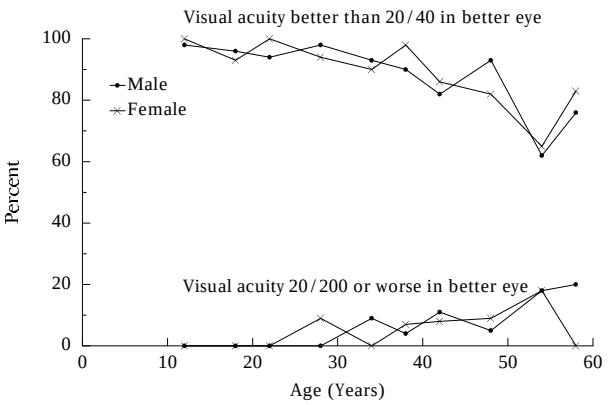
* Number per 100,000 population in each age group and sex. The rates are based on the following population estimates (in thousands) as of July 1, 1978: <5 years, 15,361; 5-19 years, 56,458; 20-44 years, 78,340; 45-64 years, 43,845; 65-74 years, 14,934; 75-84 years, 6,914; ≥85 years, 2,206; males, 106,043; females, 112,016. Data are estimated from 1970 Model Reporting Area Data.

Source: Reference 1

reported rates of "trouble seeing" (in response to the question, "Do you have any other trouble seeing with one or both eyes even when wearing glasses?") and of "blindness" (in response to the question, "Do you have blindness in one or both eyes?") are presented in Table 14.4. Age-specific rates of "trouble seeing" and "blindness" are consistently higher in people with a self-reported history of diabetes. In people age <45 years, those with IDDM had higher self-reported frequencies of "blindness" and "trouble seeing" than those with non-insulin-dependent diabetes mellitus (NIDDM). These data probably underestimate visual impairment, because the sensitivity of responses to questions about vision is low (~32%-45%)[6].

Population-based estimates of frequencies of impaired vision in diabetic persons were reported in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR)[7], in which a standardized protocol for determination of visual acuity was used[8]. The objectives of the study were to describe the prevalence and severity of diabetic retinopathy, decreased vision, and other ocular and systemic conditions. The associations of these conditions with other personal and demographic characteristics in a geographically defined population in an 11-county area in southern Wisconsin were examined[9-11]. The participants and their diabetic management were typical of medical practice in Wisconsin. Four hundred fifty-two physicians (98.9% of all physicians who offered primary care to diabetic patients in the 11-county area) participated. Of the 10,135 diabetic patients identified in this survey, all insulin-taking persons diagnosed at age <30 years (1,210 persons, the "younger-onset" group) and a probability sample of patients diagnosed as having diabetes at age ≥30 years (1,780 persons, the "older-onset" group) were invited to participate in the examination phase of the study, conducted from September 1980 to July 1982. Ninety-two percent of the younger-onset group had no impairment (best corrected visual acuity in the better eye of better than 20/40)[7]. The frequency of visual impairment increased with increasing age (Figure 14.1). No cases of legal blindness were found in persons age <25 years. The rate of legal blindness increased in both males and females, reaching peaks of 14% and 20%, respectively. In the older-onset group, rates of blindness increased with increasing age and accounted for 2.2% in persons not taking insulin and 1.6% in those taking insulin (Figure 14.2). The age-specific rates of legal blindness in both younger- and older-onset diabetic patients in the WESDR were higher than those estimated for the general U.S. population in the First National Health and Nutrition Examination Survey (NHANES I)[12] or for all participants in the Framingham Eye Study (FES)[13] (Figure 14.3).

Figure 14.1
Prevalence of No Visual Impairment and of Legal Blindness in Insulin-Taking Persons Diagnosed with Diabetes at Age <30 Years, by Age



Source: Klein R. Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), 1980-82; unpublished data

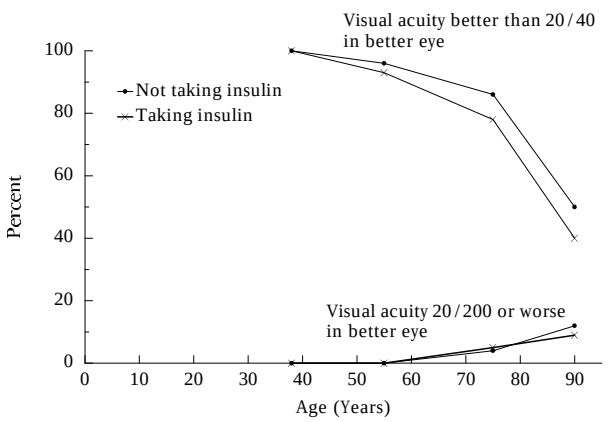
Legal blindness was related to duration of diabetes in both younger- and older-onset participants in the

Table 14.4
Self-Reported Vision Problems in Adults by Diabetes Status and Age, U.S., 1989

		All people without diabetes		All people with diabetes		People with IDDM		People with NIDDM	
Age (years)	Condition	No.	%	No.	%	No.	%	No.	%
18-44	Trouble seeing	1,888	2.60	52	11.32	17	14.47	35	9.64
	Blindness	1,888	0.03	52	2.18	17	6.26	35	0.00
45-64	Trouble seeing	836	3.78	134	11.56			133	11.65
	Blindness	836	0.00	134	1.23			133	1.24
≥65	Trouble seeing	640	6.88	188	15.92			188	15.92
	Blindness	640	0.60	188	2.49			188	2.49
Total ≥18	Trouble seeing	3,364	3.58	374	13.72			356	13.71
	Blindness	3,364	0.11	374	2.01			356	1.78

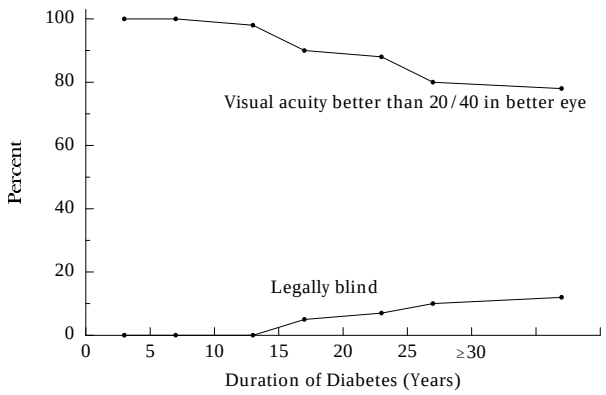
Source: Harris MI: National Diabetes Data Group. Unpublished data from the National Health Interview Survey, 1989

Figure 14.2
Prevalence of No Visual Impairment and of Legal Blindness in Persons Diagnosed with Diabetes at Age ≥30 Years, by Age



Source: Klein R. Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), 1980-82; unpublished data

Figure 14.4
Percent with Visual Acuity Better Than 20/40 and with Legal Blindness Among Insulin-Taking Persons Diagnosed with Diabetes at Age <30 Years, by Duration of Diabetes



Data are from the 1980-82 Wisconsin Epidemiologic Study of Diabetic Retinopathy.

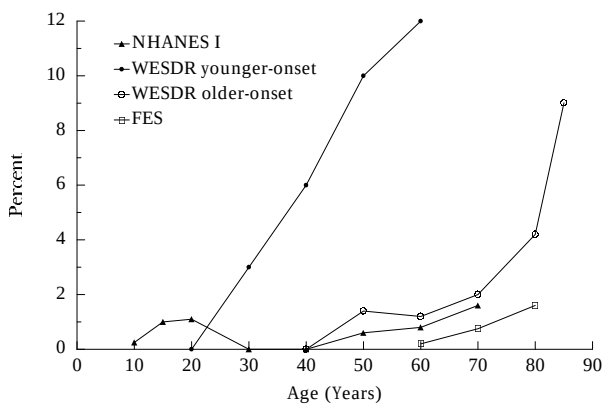
Source: Reference 7

WESDR (Figures 14.4 and 14.5)[7]. In the younger-onset group, legal blindness first occurred in persons having diabetes for ~15 years or more and increased from 3% in those with 15-19 years duration to 12% in persons with diabetes for ≥30 years. In the older-onset group, rates of legal blindness were lower, only reaching 7% in persons having diabetes for 20-24 years.

Diabetic retinopathy was partially or totally responsible for legal blindness (acuity of 20/200 or worse) in 86% of eyes of younger-onset persons with such severe impairment (Figure 14.6)[7]. Diabetic retinopathy was less often a cause of legal blindness in the older-onset patients; other causes of visual impairment, such as macular degeneration or cataracts, were more frequently responsible in this group.

In a study in Poole, England, 2% of 449 noninsulin-taking persons, and 1% of 212 insulin-taking diabetic persons, were legally blind[14]. In another population-based study in Oxford, England, in 1982, 28% of 188 people age ≥60 years with known NIDDM were visually impaired[15].

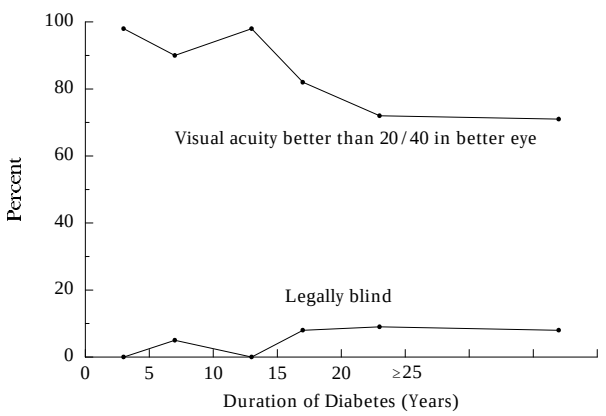
Figure 14.3
Percent of Diabetic Persons with Visual Acuity of ≥20/200 in Better Eye, by Age



WESDR, patients in the Wisconsin Epidemiologic Study of Diabetic Retinopathy, 1980-82; NHANES I, general population examined in the 1970-75 First National Health and Nutrition Examination Survey; FES, community-based patients examined in the Framingham Eye Study.

Source: References 7, 12, and 13

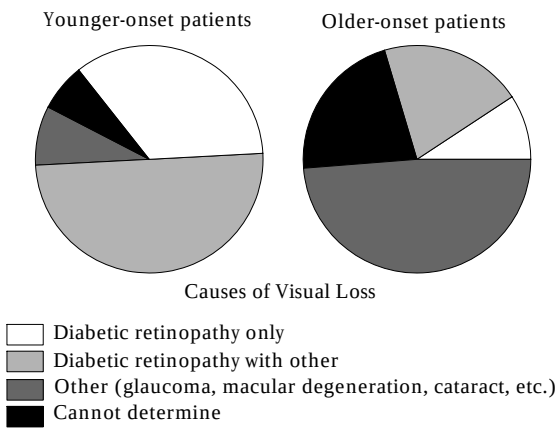
Figure 14.5
Percent with Visual Acuity Better Than 20/40 and with Legal Blindness Among Persons Diagnosed with Diabetes at Age ≥30 Years, by Duration of Diabetes



Data are from the 1980-82 Wisconsin Epidemiologic Study of Diabetic Retinopathy.

Source: Reference 7

Figure 14.6
Causes of Visual Loss (Visual Acuity 20/200 or Worse) in Diabetic Patients



Data are from the 1980-82 Wisconsin Epidemiologic Study of Diabetic Retinopathy. Younger-onset, diabetes diagnosed at age <30 years, n=113; older-onset, diabetes diagnosed at age ≥30 years, n=113.

Source: Reference 7

In a Danish study, 3.4% of males and 2.6% of females in a cohort of 727 people with IDDM diagnosed at age <30 years were legally blind[16]. Legal blindness was estimated to be 50-80 times higher in people with diabetes. Proliferative retinopathy was the primary cause of legal blindness in this study.

INCIDENCE

In data from the MRA registries, the highest incidence of new cases of legal blindness due to diabetes occurred in persons age 45-64 years (Table 14.5)[1]. As with the prevalence data, the relative proportion of cases due to diabetic retinopathy decreased with age. Rates for females were higher than for males. Of new cases of legal blindness, 12.4% were attributed to diabetes, the majority due to diabetic retinopathy. Diabetic retinopathy was the third most common diagnosis responsible for legal blindness in persons of all ages and was the leading cause of new cases of blindness in persons age 20-74 years (Table 14.6). There are no recent national population-based registry data available in the United States.

In persons age 20-79 years with NIDDM who participated in the University Group Diabetes Program (UGDP), the 5-year incidence of legal blindness was 3.8% or less in each treatment group (Table 14.7)[17]. The incidence of 20/200 or worse visual acuity in either eye was 9.4% or less in each treatment group at the 5-year followup and rose to about 12% at the 12-year followup.

Data from the Radcliffe Infirmary Diabetes Clinic in England indicate that for insulin-taking diabetic patients diagnosed at age ≤20 years, the incidence of blindness was 0.1% after 10 years, 1.6% after 20 years, and 3.5% after 30 years of diabetes[18]. For persons diagnosed at age ≥60 years, the incidence of blindness was 1.8% after 10 years and 5.5% after 20 years of diabetes. An 8-year incidence of 7.6 per 1,000 patient-years in males and 10.2 per 1,000 patient-years in females with IDDM was reported from Denmark[16]. In a later study in Oxford, England, 4.8% of those with NIDDM and age ≥60 years at baseline became legally blind over a median period of 6 years[15].

The frequency of change in rates of impaired vision in

Table 14.5
Incidence of Legal Blindness Due to Diabetes and Diabetic Retinopathy, by Age and Sex, U.S., 1978

Age and sex	No. of new cases of legal blindness due to diabetes per year	% of total new cases of legal blindness due to diabetes	No. of new cases of legal blindness due to diabetic retinopathy	% of total new cases of legal blindness due to diabetic retinopathy
Age (years)				
<5	0	0	0	0
5-19	<50	<0.1	<50	<0.1
20-44	700	13.4	600	11.5
45-64	2,450	22.6	2,050	18.9
65-74	1,750	21.5	1,350	16.6
75-84	800	7.0	600	5.3
≥85	100	1.7	100	1.7
Sex				
Males	2,350	11.0	2,100	9.8
Females	3,450	13.7	2,600	10.3
Total	5,800	12.4	4,700	10.1

Data are estimated from 1970 Model Reporting Area Data.

Source: Reference 1

the WESDR is presented in Table 14.8[21]. Among those persons not impaired at baseline, the older-onset group taking insulin had the highest incidences of impaired vision (16.1%) or legal blindness (1.2%). The estimated annual incidence of blindness reported in the WESDR was 3.3 per 100,000 population. This is higher than the estimated annual incidence rates of legal blindness due, in part, to diabetes of 1.6 to 2.1 per 100,000 persons in the general population derived from the MRA data[1]. Rates in the WESDR are comparable to those reported in the Rochester, MN study[22]. Interpolating back from 20 years in the Rochester population produces an estimated 4-year rate of legal blindness of 1.6% in all diabetic persons, compared with 2.2% in the WESDR study.

There are few population-based data available to determine trends in the frequency of decreased vision. Two studies, one in the county of Avon and the other in the county of Leicestershire, England, compared

Table 14.6
Leading Causes of New Cases of Legal Blindness, by Age and Sex, U.S., 1978

Age, sex, and cause	No.	Percent	Rate*
Total, all ages			
1. Macular degeneration	7,850	16.8	3.5
2. Glaucoma, except congenital	5,350	11.5	2.4
3. Diabetic retinopathy	4,700	10.1	2.1
4. Senile cataract	4,550	9.8	2.0
5. Optic nerve atrophy	2,000	4.3	0.9
All other	22,150	47.5	10.0
Total, all ages	46,600	100.0	21.0
Age <5 years			
1. Prenatal cataract	250	16.7	1.6
2. Optic nerve atrophy	200	13.4	1.3
3. Retrolental fibroplasia	150	10.0	0.9
All other	900	59.9	5.9
Total in age group	1,500	100.0	9.8
Age 5-19 years			
1. Optic nerve atrophy	450	12.3	0.8
Prenatal cataract	450	12.3	0.8
2. Albinism	300	8.2	0.5
Myopia	300	8.2	0.5
Macular degeneration	300	8.2	0.5
3. Nystagmus	250	6.8	0.4
4. Retinitis pigmentosa	200	5.5	0.3
All other	1,400	38.4	2.5
Total in age group	3,650	100.0	6.5
Age 20-44 years			
1. Diabetic retinopathy	600	11.5	0.8
2. Optic nerve atrophy	450	8.6	0.6
Retinitis pigmentosa	450	8.6	0.6
3. Optic neuritis	300	5.8	0.4
Macular degeneration	300	5.8	0.4
All other	3,100	59.7	4.0
Total in age group	5,200	100.0	6.6
Age 45-64 years			
1. Diabetic retinopathy	2,050	18.9	4.7
2. Glaucoma, except congenital	1,500	13.8	3.4
3. Senile cataract	1,250	11.6	2.8
4. Macular degeneration	700	6.4	1.6
5. Retinitis pigmentosa	550	5.1	1.2
6. Optic nerve atrophy	450	4.1	1.0
All other	4,350	40.1	9.9
Total in age group	10,850	100.0	24.7
Age 65-74 years			
1. Diabetic retinopathy	1,350	16.6	9.0
2. Glaucoma, except congenital	1,300	16.0	8.7
Macular degeneration	1,300	16.0	8.7
3. Senile cataract	800	9.8	5.4
All other	3,400	41.6	22.8
Total in age group	8,150	100.0	54.6
Age 75-84 years			
1. Macular degeneration	3,450	30.5	49.9
2. Glaucoma, except congenital	1,700	15.0	24.6
3. Senile cataract	1,300	11.4	18.8
4. Diabetic retinopathy	600	5.3	8.7
All other	4,300	37.8	62.2
Total in age group	11,350	100.0	164.2
Age ≥85 years			
1. Macular degeneration	1,800	30.5	81.6
2. Senile cataract	1,200	20.3	54.4
3. Glaucoma, except congenital	650	11.0	29.5
All other	2,250	38.2	102.0
Total in age group	5,900	100.0	267.5
Age ≥65 years			
1. Macular degeneration	6,550	25.8	27.2
2. Glaucoma, except congenital	3,650	14.3	15.2
3. Senile cataract	3,300	13.0	13.7
4. Diabetic retinopathy	2,050	8.1	8.5
All other	9,850	38.8	40.9
Total in age group	25,400	100.0	105.6
Males			
1. Macular degeneration	2,900	13.5	2.7
2. Glaucoma, except congenital	2,600	12.1	2.5
3. Diabetic retinopathy	2,100	9.8	2.0
4. Senile cataract	1,550	7.2	1.5
5. Optic nerve atrophy	1,250	5.8	1.2
All other	11,000	51.6	10.4
Total males	21,400	100.0	20.2
Females			
1. Macular degeneration	4,950	19.6	4.4
2. Senile cataract	3,000	11.9	2.7
3. Glaucoma, except congenital	2,750	10.9	2.5
4. Diabetic retinopathy	2,600	10.3	2.3
5. Optic nerve atrophy	750	3.0	0.7
All other	11,150	44.3	10.0
Total females	25,200	100.0	22.5

* Number per 100,000 population in each age group and sex. Data are estimated from 1970 Model Reporting Area Data.

Source: Reference 1

Table 14.7
Incidence of Ocular Complications in Diabetic Patients in the University Group Diabetes Program

	Follow-up time (years)	Placebo		Tolbutamide		Insulin standard		Insulin variable	
		No.	%	No.	%	No.	%	No.	%
Legal blindness	5	186	2.7	188	3.7	188	1.6	184	3.8
Visual acuity worse than	5	179	6.7	181	9.4	179	5.6	175	5.7
20/200 in either eye	12	180	11.7			180	12.2	174	12.1
Glaucoma*		167	12.0			175	8.0	169	7.7
NPDR									
(mild retinal abnormalities)	12	144	32.6			155	29.0	138	31.9
Severe NPDR or proliferative									
retinopathy	12	147	2.0			155	4.5	138	2.9
Photocoagulation	12	188	1.1			195	1.0	182	1.1

* Glaucoma obtained by history at the 1967 follow-up examination; NPDR, nonproliferative diabetic retinopathy.

Source: Reference 17

rates of registration for blindness benefits attributed to diabetic retinopathy in 1985 with those recorded in England in 1965[23-25]. In Avon in 1985, blindness due to diabetes (1.8 registrations per 100,000) was similar to that in England in 1965 (1.6 registrations per 100,000)[23]. This was attributed, in part, to the increase in the number of people diagnosed as having diabetes since 1965. In Leicestershire, a significant decrease in the frequency of those registered as being blind between 1975 and 1985 was attributed to better local care and the increased use of laser photocoagulation[24].

The WESDR cohort was re-examined 10 years after the baseline examination[26]. The 10-year incidences of impaired vision, doubling of the visual angle, and legal blindness by diabetes group are presented in Table 14.9[27].

There appeared to be a decrease in the estimated annual incidence of blindness in the three WESDR diabetic groups in the last 6 years compared with the first 4 years of the study (Table 14.10)[27]. Possible reasons for the decrease in the estimated annual incidence of blindness are not explained by changes in the incidence of proliferative retinopathy or an increased frequency of panretinal photocoagulation in the second 6-year period[26]. Higher frequencies of focal photocoagulation for macular edema and lens extraction for cataract in the second 6-year period of the study compared with the first 4 years may explain only part of the decrease in frequency of blindness over time. It

Table 14.8
Four-Year Incidence of Visual Impairment in Diabetic Persons, WESDR, 1980-86

		Visual impairment at followup			
Visual impairment at baseline	No. of participants	None (%)	Mild (%)	Moderate (%)	Blind (%)
Younger-onset					
None	832	95.3	2.8	1.4	0.5
Mild	26	26.9	42.3	15.4	15.4
Moderate	10	10.0	10.0	30.0	50.0
Blind	20	0	0	0	100.0
Older-onset, taking insulin					
None	423	83.9	10.6	4.3	1.2
Mild	27	29.6	22.2	40.7	7.4
Moderate	15	6.7	13.3	26.7	53.3
Blind	8	0	0	0	100.0
Older-onset, not taking insulin					
None	454	91.0	5.5	2.9	0.7
Mild	29	20.7	31.0	31.0	17.2
Moderate	7	0	0	28.6	71.4
Blind	4	0	0	0	100.0

Younger-onset, diabetes diagnosed at age <30 years; older-onset, diabetes diagnosed at age ≥30 years; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

Source: Reference 21

Table 14.9
Ten-Year Incidence of Blindness, Visual Impairment, and Doubling of the Visual Angle in Diabetic Persons, WESDR, 1980-92

Diabetic group	Blindness No.	Blindness %	Visual impairment No.	Visual impairment %	Doubling of the visual angle No.	Doubling of the visual angle %
Younger-onset	868	1.8	832	9.4	880	9.2
Older-onset taking insulin	465	4.0	423	37.2	472	32.8
Older-onset not taking insulin	490	4.8	454	23.9	494	21.4

Younger-onset, diabetes diagnosed at age <30 years; older-onset, diabetes diagnosed at age ≥30 years; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

Source: Reference 27

is possible that early detection and treatment of proliferative retinopathy may have resulted in the decline in rates of legal blindness over the last 6 years of the study.

RISK FACTORS FOR DEVELOPMENT OF VISION LOSS AND LEGAL BLINDNESS

Sex and Race

In the WESDR, sex was not associated with the 10-year incidence of legal blindness except for a slightly higher incidence in older-onset women not taking insulin than in older-onset men not taking insulin (5.8% versus 3.6%) and in older-onset women taking insulin than in older-onset men taking insulin (5.4% versus 2.3%)[27]. Analyses of MRA registry data indicate that the highest rates of legal blindness due to diabetes occurred in nonwhite females; nonwhite males and white females were intermediate, and white males had the lowest rates[4]. In the Baltimore Eye Survey, legal blindness due to diabetic retinopathy was equally prevalent in whites (6%) and in blacks (5%) age ≥40 years[28]. This comparison must be made cautiously, as there were only seven eyes in which legal blindness was present.

Table 14.10
Annual Incidence of Blindness in Diabetic Persons, WESDR, 1980-92

	1980-82 to 1984-86 (%)	1984-86 to 1990-92 (%)
Younger-onset	0.38	0.05
Older-onset taking insulin	0.82	0.14
Older-onset not taking insulin	0.67	0.37

Younger-onset, diabetes diagnosed at age <30 years; older-onset, diabetes diagnosed at age ≥30 years; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

Source: Reference 27

Table 14.11
Four-Year Incidence of Blindness in Diabetic Persons, by Age at Baseline Examination, WESDR, 1980-86

Baseline age (years)	Younger-onset No.	Younger-onset %	Older-onset taking insulin No.	Older-onset taking insulin %	Older-onset not taking insulin No.	Older-onset not taking insulin %
0-9	25	0				
10-19	222	0				
20-29	282	1.8				
30-44	242	2.1	26	0	19	0
45-54	97*	3.1*	86	1.2	52	1.9
55-64			137	1.5	148	2.7
65-74			160	3.1	177	0
≥75			56	12.5	94	8.5
p†	<0.025		<0.001		0.051	

* Sample size and rate for age ≥45 years. † Based on a test for trend. Younger-onset, diabetes diagnosed at age <30 years; older-onset, diabetes diagnosed at age ≥30 years; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

Source: Reference 21

Age and Duration of Diabetes

The 4-year incidence of blindness and doubling of the visual angle increased with increasing age in all of the WESDR diabetic groups and increased with increasing

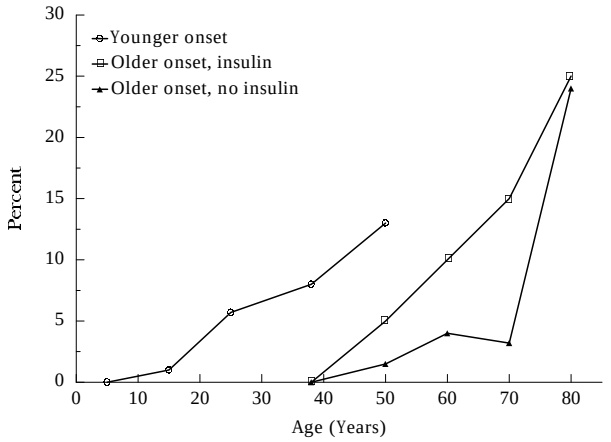
Table 14.12
Four-Year Incidence of Blindness in Diabetic Persons by Duration of Diabetes at Baseline Examination, WESDR, 1980-86

Baseline duration (years)	Younger-onset No.	Younger-onset %	Older-onset taking insulin No.	Older-onset taking insulin %	Older-onset not taking insulin No.	Older-onset not taking insulin %
0-4	157	0	78	0	204	2.9
5-9	232	0	83	3.6	151	2.0
10-14	162	1.2	78	2.6	54	1.9
15-19	117	5.1	106	3.8	54	5.6
20-24	73	2.7	75	2.7	27*	0*
25-29	61	4.9	28	10.7		
≥30	66	0	17	5.9		
p†	<0.005		0.056		0.93	

* Sample size and rate for duration of diabetes ≥20 years. † Based on a test for trend. Younger-onset, diabetes diagnosed at age <30 years; older-onset, diabetes diagnosed at age ≥30 years; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

Source: Reference 21

Figure 14.7
Four-Year Incidence of Doubling of the Visual Angle in Patients with Diabetes, by Age

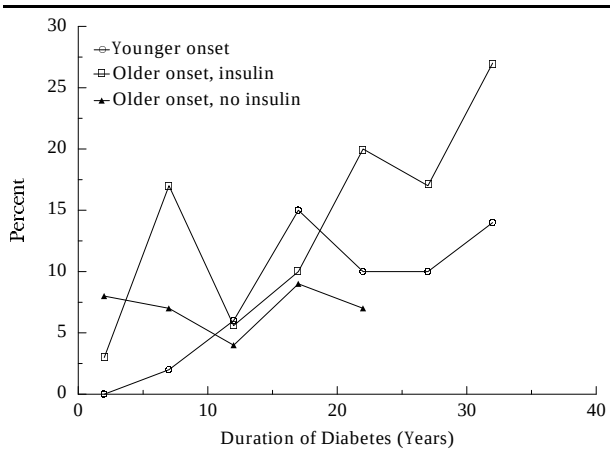


Data are from the 1980-86 Wisconsin Epidemiologic Study of Diabetic Retinopathy. Younger-onset, diabetes diagnosed at age <30 years; older-onset, diabetes diagnosed at age ≥30 years.

Source: Reference 21

duration only in the younger- and older-onset groups taking insulin (Tables 14.11 and 14.12, Figures 14.7 and 14.8)[21]. The relationship of the 10-year incidence of blindness and doubling of visual angle to age and duration of diabetes at baseline was similar to the 4-year incidence rates (data not shown)[27]. Others have also reported similar relationships between longer duration of diabetes and impaired vision[15,16,18,22].

Figure 14.8
Four-Year Incidence of Doubling of the Visual Angle in Patients with Diabetes, by Duration of Diabetes



Data are from the 1980-86 Wisconsin Epidemiologic Study of Diabetic Retinopathy. Younger-onset, diabetes diagnosed at age <30 years; older-onset, diabetes diagnosed at age ≥30 years.

Source: Reference 21

Severity of Retinopathy and Macular Edema

In the WESDR, the 4-year incidence of legal blindness increased with increasing severity of retinopathy (Table 14.13)[21]. The 4-year relative risk of legal blindness in diabetic patients with retinopathy compared with the general population was estimated to be 29.

Prior to the widespread use of panretinal photocoagulation, the risk of legal blindness associated with severe retinopathy was higher. Among 51 IDDM patients with proliferative retinopathy followed in the Steno Hospital in Denmark, 50% had become legally blind after 5 years[29].

Untreated eyes with high-risk characteristics in the Diabetic Retinopathy Study (DRS) had a cumulative incidence of severe loss of vision (acuity poorer than 5/200) of 14% at 2 years, 27% at 4 years, and 37% at 6 years (Figure 14.9)[30]. Panretinal photocoagulation was found to reduce the rate of such severe loss by 50% or more.

In the Early Treatment Diabetic Retinopathy Study (ETDRS), untreated eyes with clinically significant macular edema had a cumulative incidence of doubling of the visual angle (i.e., going from 20/20 to 20/40 or worse, or from 20/30 to 20/60 or worse) of 24% at 3 years[31]. Photocoagulation of the macular area was found to reduce the rate by 50% (Figure 14.10)[31].

In the WESDR, the 4-year incidence of doubling of the visual angle was increased in the presence of macular edema at baseline (relative risk 3.5, 95% Confidence Interval (CI) 1.8,6.9 in the younger-onset; relative

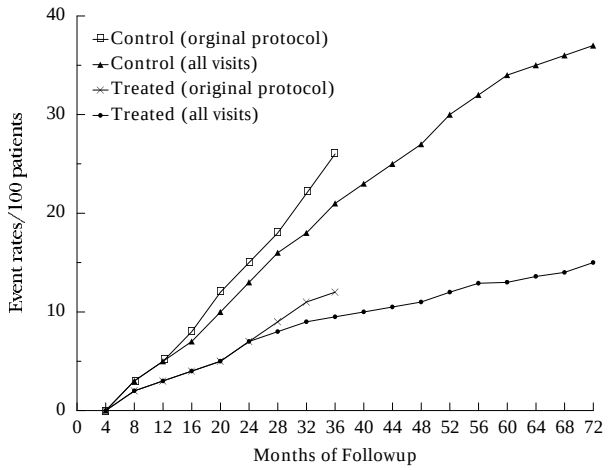
Table 14.13
Four-Year Incidence of Blindness in the Right Eye by Retinopathy Level at Baseline Examination, WESDR, 1980-86

Baseline retinopathy level in the right eye	Younger-onset		Older-onset taking insulin		Older-onset not taking insulin	
	No.	%	No.	%	No.	%
1	307	0.3	178	4.5	343	3.2
1.5-2	166	0.6	65	3.1	65	4.6
3	119	2.5	67	10.4	33	6.1
4-5	136	4.4	106	12.3	33	24.2
6	96	6.2	31	6.5	2	
7	21	23.8	4	0	1	
p*	<0.0001		<0.05		<0.001	

* Based on a test for trend. Younger-onset, diabetes diagnosed at age <30 years; older-onset, diabetes diagnosed at age ≥30 years; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

Source: Reference 21

Figure 14.9
Cumulative Rates of Severe Visual Loss in Eyes of Patients in the Diabetic Retinopathy Study



Data include and exclude observations made after the 1976 protocol change, argon and xenon groups combined (treated) and control (untreated).

Source: Reference 30

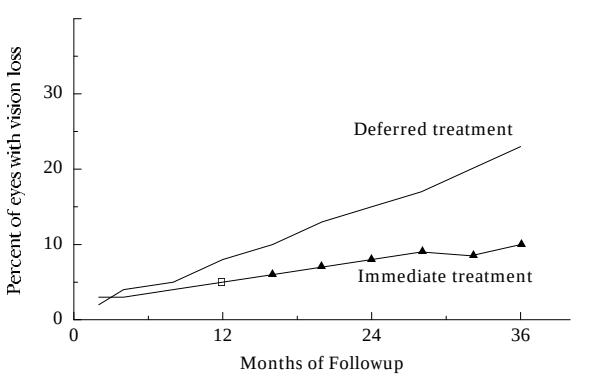
risk 2.8, 95% CI 1.8,4.3 in the older-onset group taking insulin; and relative risk 5.6, 95% CI 3.2,9.6 in the older-onset group not taking insulin)[21].

Other Risk Factors

In addition to age, duration of diabetes, and severity of retinopathy, glycosylated hemoglobin (younger-onset group taking insulin, relative risk for the fourth versus the first quartile 2.9, 95% CI 1.2,6.7; older-onset group taking insulin, relative risk 2.2, 95% CI 1.1,4.4) and gross proteinuria (younger-onset group taking insulin, relative risk 5.3, 95% CI 3.1,9.3; older-onset group taking insulin, relative risk 2.2, 95% CI 1.3,4.0) were associated with a significant increased 4-year risk of doubling of the visual angle in both WESDR groups taking insulin[21].

In the WESDR, at the 4-year followup, diabetic retinopathy was found to be the sole or contributing cause of impaired vision in 69% of eyes of younger-onset persons, 42% of eyes of older-onset persons taking insulin, and 26% of eyes of older-onset persons not taking insulin[21].

Figure 14.10
Visual Loss in Diabetic Patients Treated with Immediate and Deferred Photocoagulation



□ 2.58 ≤Z <3.29. ▲ Z ≥3.29. Visual loss defined as loss of ≥15 letters (equivalent to at least doubling of the initial visual angle or loss of ≥3 lines) in eyes with macular edema and mild to moderate diabetic retinopathy. Bottom line, patients assigned to immediate focal photocoagulation (n=754); upper line, patients assigned to deferred photocoagulation (n=1,490). Data are from the Early Treatment of Diabetic Retinopathy Study.

Source: Reference 31

REHABILITATION AND ECONOMIC COSTS OF BLINDNESS

A number of sources for aids, appliances, and other information for diabetic people who are visually impaired are listed in Appendix 14.1.

There are few data describing the socioeconomic and psychosocial characteristics of diabetic persons who have impaired vision and who need rehabilitative services. In the WESDR, younger-onset men age ≥25 years who had proliferative retinopathy and who were employed at baseline were more likely to become unemployed 4 years later[32]. Younger-onset women who were married and had impaired vision at baseline had an increased 4-year incidence of divorce.

Data from two English studies suggest that diabetic persons have a greater disadvantage than people with other diseases when seeking work[33,34].

Psychological distress in diabetic persons with either stable or fluctuating decreases in vision, even when mild, has been thought to be a result of physical inactivity and inability to manage their diabetes[35,36]. Rehabilitation programs consisting of education concerning diabetes self-management skills, nutrition counseling, and exercise programs have been shown to lead to significant improvements in psychological profiles in diabetic patients with fluctuating vision or loss of vision[37].

Recent studies have provided estimates of costs associated with blindness due to diabetes. A minimum cost to the federal government of $12,769 was estimated for a "person-year" of blindness for a working-age American who becomes blind in adulthood; for those age ≥65 years, it was $823[38]. These estimates did not include reduced productivity, output loss, societal burdens of rehabilitation, and other local expenses.

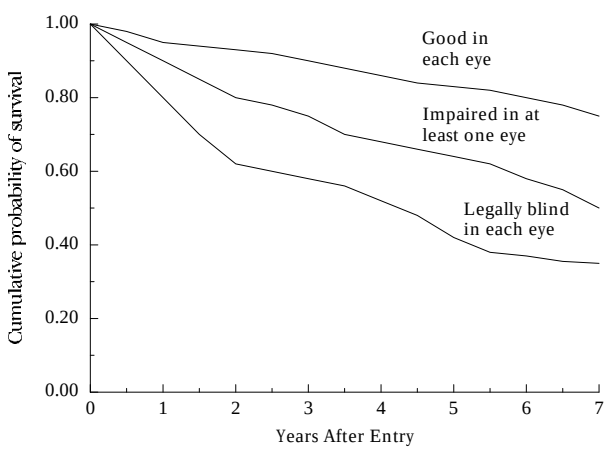
Based on the WESDR estimates of prevalence of blindness among people with diagnosed diabetes in the United States in 1980-82, we estimate an annual cost of ~$500 million per year[7].

Three studies[39-41] have estimated the cost-effectiveness of strategies for detecting diabetic retinopathy. Data from these analyses suggest that screening for diabetic retinopathy and obtaining ophthalmologic care result in significant savings in people with younger-onset diabetes. One analysis[41] predicted an annual savings of an estimated $240.5 million and 138,390 person-years of sight for 60% screening and treatment rate implementation level; if all patients were to receive appropriate eye care, the predicted savings would exceed $400 million and savings of 230,000 person-years of sight in younger-onset people. Another analysis[39] also found that targeting the younger-onset cohort and the older-onset cohort taking insulin could achieve cost savings. Conversely, the incremental number of sight-years to be gained in the older-onset population not taking insulin, even by annual ophthalmologic examination with fundus photography, was reported to be small. However, macular edema, an important cause of vision loss, was not included in the analyses.

VISUAL ACUITY AS A PREDICTOR OF DEATH

The relationship between visual acuity and the probability of survival in insulin-taking diabetic patients seen in an eye clinic in Wisconsin is presented in Figure 14.11[42]. The probability of survival declined with decreasing levels of visual acuity. The observed 5-year survival was ~40% in persons who were legally blind.

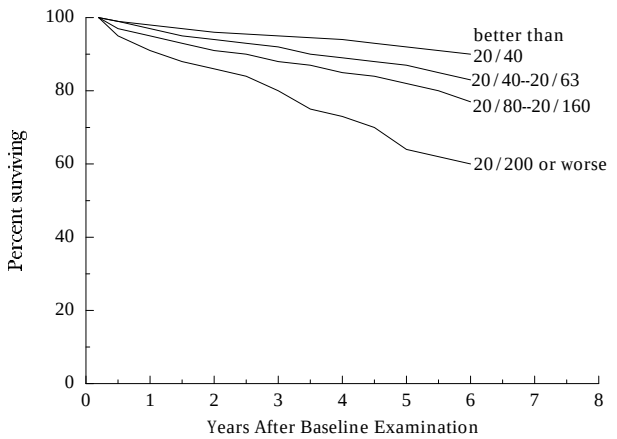
Figure 14.11
Survival for Insulin-Taking Patients with Diabetes Diagnosed at Age <50 Years, According to Visual Acuity



Patients were from a Wisconsin clinic. Visual acuity was determined at entry to the study.

Source: Reference 42

Figure 14.12
Survival in Patients Diagnosed with Diabetes at Age <30 Years, According to Visual Acuity

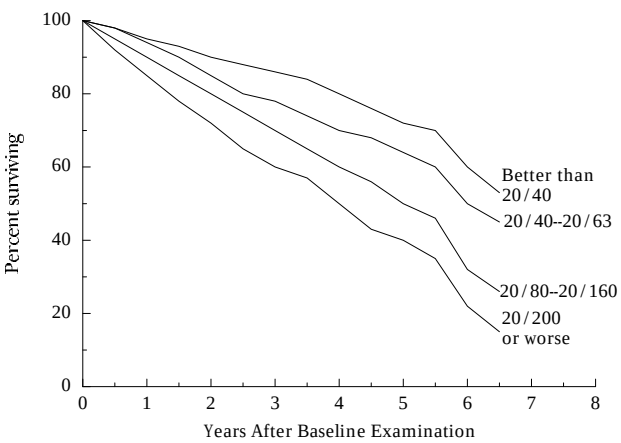


Visual acuity status was determined at baseline examination (1980-82) in the Wisconsin Epidemiologic Study of Diabetic Retinopathy. Data are age- and sex-adjusted.

Source: Reference 43

In the WESDR, after adjusting for age and sex, younger-onset persons with visual acuity of 20/200 or poorer in their better eye at baseline had a 6-year survival rate of 57.9%, compared with 89.9% in per-

Figure 14.13
Survival in Patients Diagnosed with Diabetes at Age ≥30 Years, According to Visual Acuity



Visual acuity status was determined at baseline examination (1980-82) in the Wisconsin Epidemiologic Study of Diabetic Retinopathy. Data are age- and sex-adjusted.

Source: Reference 43

sons whose visual acuity was better than 20/40 in the better eye (Figure 14.12)[43]. Poor 6-year survival was also seen in the older-onset group with poorer visual acuity at baseline (Figure 14.13). Those with a visual acuity of 20/200 or worse in the better eye at baseline had a 6-year survival rate of 18.4%, compared with 56.2% for those whose visual acuity was better than 20/40 in the better eye. The relationship between survival and visual acuity remained after controlling for other factors associated with mortality such as increased age, longer duration of diabetes, higher blood pressure, higher glycosylated hemoglobin, history of cardiovascular disease, and being male. These data suggest that people with diabetes and poor visual acuity should be examined frequently by their primary care physicians to detect and possibly treat early renal disease, elevated blood pressure, and cardiovascular disease to minimize their effects.

NEEDS

National population-based estimates of prevalence and incidence of visual impairment are needed to assess the effects of changes in management of diabetes and its ocular complications over time. Population-based incidence data to define risk variables and estimates of the relative importance of these factors in determining visual impairment in different ethnic and racial groups are needed. Data about the problems of the visually impaired with respect to occupational, vocational, psychosocial, and medical care are necessary to describe adequately the current status and to project future health care delivery needs.

DIABETIC RETINOPATHY

Diabetic retinopathy is characterized by specific alterations in the appearance of the retina. The earliest change that can be seen with the aid of the ophthalmoscope is the retinal microaneurysm. Retinal blot hemorrhages, hard exudates, cotton-wool spots, intraretinal microvascular abnormalities, venous beading, and venous reduplication are other lesions that may be found in the nonproliferative phase of diabetic retinopathy. Proliferative retinopathy is characterized by the growth of abnormal blood vessels and fibrous tissue from the optic nerve head or from the inner retinal surface elsewhere. Swelling of the macular region of the retina, called macular edema, may occur in the presence of either nonproliferative or proliferative retinopathy.

PREVALENCE AND ASSOCIATED RISK FACTORS IN WESDR

In the WESDR, stereoscopic fundus photographs of seven standard photographic fields were taken of each eye[10]. Objective grading of retinopathy by standard protocols was used to assure reproducible assessment and classification of the severity of retinopathy[19,44,45]. In the WESDR, 71% of younger-onset persons (onset age <30 years) had retinopathy, 23% had proliferative retinopathy, and 6% had clinically significant macular edema[10,46].

In older-onset persons in the WESDR, 39% of those who did not take insulin, and 70% of those who did, had retinopathy; 3% of the former and 14% of the latter had proliferative retinopathy, 4% of the former and 11% of the latter had clinically significant macular edema[11,46].

Using WESDR estimates of prevalence of retinopathy, 1990 U.S. Census estimates, and 1989 National Health Interview Survey estimates of diabetes, the National Society to Prevent Blindness has developed estimates of 4-6 million diabetic people with retinopathy in the United States. They also provide state-specific estimates of retinopathy. Based on the WESDR data and an estimate in 1980-82 of 5.8 million Americans known to have diabetes, 700,000 had proliferative retinopathy and 325,000 had clinically significant macular edema.

PREVALENCE DATA FROM OTHER STUDIES

Prevalence data have been reported in other population-based studies (Table 14.14)[14,22,26,47-70]. Comparisons among studies must be made cautiously. There are a number of possible reasons for differences among them. First, there are differences in the definitions of diabetes and its component complications. Second, methods used to detect and classify retinopathy may vary from study to study. Third, there are often age, sociodemographic, and genetic differences among groups under study. The use of standardized protocols for detecting and classifying diabetic retinopathy have been developed. Use of photographic documentation of diabetic retinopathy and photographic standards for grading severity of retinal lesions have facilitated comparisons among some studies[10,45,60,62].

The frequencies of retinopathy in the WESDR are higher than those previously reported from other large, population-based studies using ophthalmoscopy to detect retinopathy[10,11,47-50,70]. Without ad-

Table 14.14

Selected List of Population-Based Studies Describing the Prevalence and Incidence of Diabetic Retinopathy

Ref.	Site	Type of diabetes	No. studied	Duration of diabetes (years)	Retinopathy detection*	Crude prevalence (%)	Crude incidence
47	Pima Indians, AZ	NIDDM	399	0-10+	O	18	
48, 70	Pima Indians, AZ	NIDDM	279		O		4 years = 2.6%
49	Framingham, MA	NIDDM	229		O	18	
50, 68, 69	Oklahoma Indians	NIDDM	973	0-20+	O, P	24	10-16 years = 72.3%
14	Poole, England	IDDM	714	0-30+	O, P		
		NIDDM				Severe Ret. 8.3	
51	Nauru, Central Pacific	NIDDM	343	0-10+	O	24	
22	Rochester, MN	IDDM	75				45.8/1000 person-years
52	Rochester, MN	NIDDM	1,060		O		15.6/1000 person-years
53	Iceland	IDDM	212	0-20+	P	34	
54	Perth, Australia	IDDM	179	0-20+	O, P	33	
55		NIDDM	904	0-20+	O, P	27	
56	County of Fynn, Denmark	IDDM	718	0-30+	O	48	
57, 58	Falster, Denmark	IDDM	215	0-58	P	66	1 year = 3.7%
		NIDDM	333	0-42	P	41	1 year = 3.7%
59	Switzerland	IDDM	105	0-30+	O	51	8 years = 39%
		NIDDM	94			9	8 years = 15%
60	San Antonio, TX	NIDDM	257	0-10+	O, P	45	
61	Gotland, Sweden	IDDM	160	0-20+	P	56-65	
		NIDDM	140	0-20+		17	
62	San Luis Valley, CO (Hispanics)	NIDDM	166	0-5+	P	19	
				15+		88	
63	Leicester, England	IDDM	350	0-30+	O, P	41	
10, 11, 19, 20	South-Central WI	IDDM	996	0-30+	O, P	71	4 years = 59%
		NIDDM	1,370	0-30+	O, P	39	4 years = 34%
64, 65	Allegheny County, PA	IDDM	657	6-38	O, P	86	2 years = 33%
66	Seattle, WA (2nd generation Japanese-American men)	IDDM NIDDM	78	0-10+	O, P	11.5	
67, †	Alberta, Canada	IDDM	2,300	0-60+	O, P	59.9	
		NIDDM	1,346	0-35+	O, P	29.9	

* O, ophthalmoscopy; P, photography; † unpublished data.

Source: Reference 160

Table 14.15

Four-Year Incidence of Any Retinopathy, Improvement or Progression of Retinopathy, and Progression to PDR in Younger-Onset Diabetic Persons, WESDR, 1980-86

	Male			Female			Total		
	No. at risk	%	95% CI	No. at risk	%	95% CI	No. at risk	%	95% CI
Incidence of any retinopathy	143	55.9	47.8, 64.0	128	62.5	54.1, 70.9	271	59.0	53.1, 64.9
Improvement	181	4.4	1.4, 7.4	195	9.2	5.1, 13.3	376	6.9	4.3, 9.5
No change	354	54.5	49.3, 59.7	359	55.7	50.6, 60.8	713	55.1	51.4, 58.8
Progression	354	43.2	38.0, 48.4	359	39.3	34.2, 44.4	713	41.2	37.6, 44.8
Progression to PDR	354	11.3	8.0, 14.6	359	9.8	6.7, 12.9	713	10.5	8.2, 12.8

PDR, proliferative diabetic retinopathy; CI, confidence interval; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy; younger-onset, diabetes diagnosed at age <30 years. Number at risk for incidence of any retinopathy refers to group that had no retinopathy (level 10/10) at the baseline examination and were at risk of developing retinopathy at the follow-up examination. Number at risk for improvement in retinopathy refers to those with retinopathy levels of 21/21 to 5I/51 at baseline who could have a decrease in their retinopathy severity by at least two steps or more at the follow-up examination. Number at risk for no change, progression, or progression to PDR refers to those with retinopathy levels of 10/10 to 51/51 who either did not change by two or more steps or progressed by two or more steps.

Source: Reference 19

Table 14.16
Four-Year Incidence of Any Retinopathy, Improvement or Progression of Retinopathy, and Progression to PDR in Older-Onset Diabetic Persons, WESDR, 1980-86

	Male			Female			Total		
	No. at risk	%	95% CI	No. at risk	%	95% CI	No. at risk	%	95% CI
Using insulin									
Incidence of any retinopathy	62	46.8	34.4, 59.2	92	47.8	37.6, 58.0	154	47.4	39.5, 55.3
Improvement	107	10.3	4.5, 16.1	108	20.4	12.8, 28.0	215	15.3	10.5, 20.1
No change	193	62.2	55.4, 69.0	225	54.7	48.2, 61.2	418	58.1	53.4, 62.8
Progression	193	32.1	25.5, 38.7	225	35.6	29.3, 41.9	418	34.0	29.5, 38.5
Progression to PDR	193	7.3	3.6, 11.0	225	7.6	4.1, 11.1	418	7.4	4.9, 9.9
Not using insulin									
Incidence of any retinopathy	151	32.5	25.0, 40.0	169	36.1	28.9, 43.3	320	34.4	29.2, 39.6
Improvement	35	11.4	0.9, 21.9	66	24.2	13.9, 34.5	101	19.8	12.0, 27.6
No change	216	72.7	66.8, 78.6	270	69.6	64.1, 75.1	486	71.0	67.0, 75.0
Progression	216	25.5	19.7, 31.3	270	24.4	19.3, 29.5	486	24.9	21.1, 28.7
Progression to PDR	216	2.8	0.6, 5.0	270	1.9	0.3, 3.5	486	2.3	1.0, 3.6

PDR, proliferative diabetic retinopathy; CI, confidence interval; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy; older-onset, diabetes diagnosed at age ≥30 years. Number at risk for incidence of any retinopathy refers to group that had no retinopathy (level 10/10) at the baseline examination and were at risk of developing retinopathy at the follow-up examination. Number at risk for improvement in retinopathy refers to those with retinopathy levels 21/21 to 51/51 at baseline who could have a decrease in their retinopathy severity by at least two steps or more at the follow-up. Number at risk for no change, progression, or progression to PDR refers to those with retinopathy levels 10/10 to 51/51 who either did not change by two or more steps or progressed by two or more steps.

Source: Reference 20

justing for duration of diabetes, age, level of glycemia, and other factors associated with the prevalence of retinopathy, comparisons among populations are of limited usefulness, even when fundus photography and grading have been used to detect retinopathy.

INCIDENCE AND PROGRESSION OF DIABETIC RETINOPATHY

The incidence of retinopathy in a 4-year interval in the entire WESDR population was 40.3%[19,20]. The 4-year incidence and progression of diabetic retinopathy in the WESDR are presented in Tables 14.15 and 14.16. The younger-onset group using insulin had the highest 4-year incidence, rate of progression, and progression to proliferative retinopathy, while the older-onset group not using insulin had the lowest rates. The older-onset group taking insulin had the highest 4-year incidence of macular edema (Table 14.17)[71]. There were no differences in the 4-year incidence or progression of retinopathy in men compared with women. While the incidence of proliferative retinopathy was higher in people with younger onset, the estimates of the number of incident cases in the 4-year period were higher in the group with older-onset age than in the group with younger-onset age (120 versus 83, Table 14.18) due to the higher frequency of people with older-onset diabetes.

Based on WESDR data, it is estimated that, of the ~7.8 million Americans with known diabetes in 1993, 84,000 will develop proliferative retinopathy each year and 40,000 will develop proliferative retinopathy

Table 14.17
Four-Year Incidence of Macular Edema and Clinically Significant Macular Edema by Type of Diabetes, WESDR, 1980-86

Group	No. of persons	No. with macular edema	Incidence %	No. with CSME	Incidence %
Younger-onset	610	50	8.2	26	4.3
Older-onset	652	34	5.2	19	2.9
Taking insulin	273	23	8.4	14	5.1
Not taking insulin	379	11	2.9	5	1.3
Oral	243	9	3.7	4	1.6
Diet only	102	1	1.0	1	1.0
None	34	1	2.9	0	0

CSME, clinically significant macular edema as defined by the Early Treatment Diabetic Retinopathy Study. Younger onset, diabetes diagnosed at age <30 years; older onset, diabetes diagnosed at age ≥30 years; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

Source: Reference 71

Table 14.18
Estimated Number of New Cases of Proliferative Retinopathy in 4 Years in Wisconsin Health Service Area 1

Proliferative retinopathy severity grade	Total no. of cases	Diabetes diagnosis at age <30 years		Diabetes diagnosis at age ≥30 years	
		No.	%	No.	%
60-65	105	54	51.4	51	48.6
70	85	28	32.9	57	67.1
80	13	1	7.7	12	92.3
Total	203	83	40.9	120	59.1

Estimates are based on rates in the Wisconsin Epidemiologic Study of Diabetic Retinopathy sampled in 1979-80 according to type and duration of diabetes, weighted to the Wisconsin HSA1 population of 839, 324.

Source: Reference 20

with DRS high-risk characteristics for severe loss of vision. Each year, 95,000 people with diabetes are estimated to develop macular edema.

In the WESDR, the estimated annual incidence and rates of progression of retinopathy were compared for the first 4 years of the study with the next 6 years of the study[26]. There were few differences in the estimated annual incidence or rates of progression between these two periods. However, the estimated annual incidence of proliferative diabetic retinopathy was higher in the last 6 years compared with the first 4 years of the study (Table 14.19). After adjusting for the severity of retinopathy or duration of diabetes at baseline and the 4-year followup, the estimated annual incidence of proliferative retinopathy remained higher over the last 6 years of the study only in the older-onset groups (data not shown). These data suggest that incidence and progression of retinopathy remained unchanged or worsened despite improvements in glycemic control in people taking insulin over the first 4 years of the study.

RISK FACTORS FOR DIABETIC RETINOPATHY

Sex

In the WESDR, higher frequencies of proliferative retinopathy were present in younger-onset males compared with females[10]. However, there were no significant differences in the 4- or 10-year incidence or progression of diabetic retinopathy between the sexes[19,26]. There were no significant differences in the prevalence, incidence, or rates of progression to proliferative retinopathy between the sexes in people with older-onset diabetes in the WESDR[11,20,26].

Race

Pima and Oklahoma Indians with NIDDM appear to be at increased risk of developing proliferative retinopathy compared with whites with NIDDM[69,70]. The reason for this difference is not clear. American Indians may have been exposed to longer periods of more severe hyperglycemia at a younger age than whites with NIDDM. However, the prevalence and severity of retinopathy appears to vary among different Indian groups[47,50,67-70]. This may reflect different levels of the same risk factors, different relative importance of those risk factors, or genetic differences.

Using similar protocols to measure risk factors and to detect diabetic retinopathy, after controlling for all measured risk factors, the frequency of retinopathy in Mexican Americans in San Antonio, TX was 2.4 times as high as the frequency of retinopathy in non-Hispanic whites studied in the WESDR[60]. Similarly, in the NHANES III, retinopathy was more prevalent in Mexican Americans compared with non-Hispanic whites age ≥40 years (Figure 14.14). However, there was no difference in the frequency of retinopathy between Hispanics and non-Hispanic whites examined in the San Luis Valley Study[62]. The crude prevalence of pro-

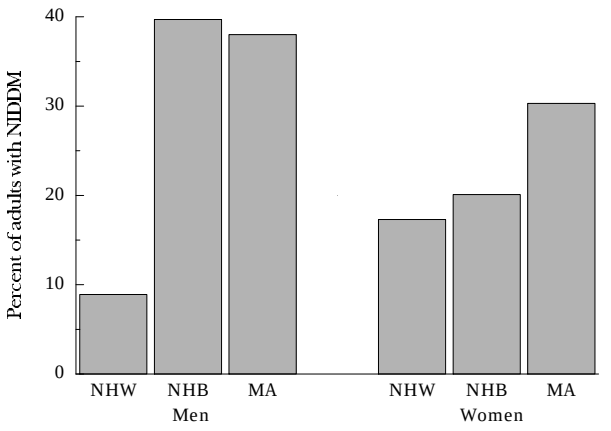
Table 14.19
Average Annual Incidence, Progression, and Progression to PDR in Diabetic Persons, WESDR, 1980-92

		Younger-onset		Older-onset taking insulin		Older-onset not taking insulin	
	Period	No. at risk	%	No. at risk	%	No. at risk	%
Incidence/year	First 4 years	261	20.0	146	14.8	301	10.2
	Next 6 years	103	19.0	47	14.8	146	10.1
Progression/year	First 4 years	712	13.6	417	11.6	487	7.1
	Next 6 years	579	13.4	210	11.8	269	9.0
Progression to PDR/year	First 4 years	712	2.7	417	2.0	487	0.6
	Next 6 years	579	4.0	210	3.2	269	1.3

PDR, proliferative diabetic retinopathy; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy. Younger-onset, diabetes diagnosed at age <30 years; older-onset, diabetes diagnosed at age ≥30 years.

Source: Reference 26

Figure 14.14
Prevalence of Diabetic Retinopathy in Persons with NIDDM Age ≥40 Years, by Sex and Race/Ethnic Group



NHW, non-Hispanic white; NHB, non-Hispanic black; MA, Mexican American. Data are from the 1988-91 cycle of the National Health and Nutrition Examination Survey III.

Source: Reference 158

liferative diabetic retinopathy in Hispanic groups in Colorado (7%) was slightly but not significantly higher than the frequency of proliferative retinopathy in non-Hispanic whites with known NIDDM in Colorado (5%)[62].

At present, published data are not available on the prevalence of retinopathy and macular edema in black populations living in the United States. Based on observations of diabetic patients attending retina clinics, it has been suggested that blacks with NIDDM may have more severe diabetic retinopathy and loss of vision than whites with this disease[72]. In the NHANES III, retinopathy was more prevalent in non-Hispanic black men than in non-Hispanic white men age ≥40 years; there was no difference in non-Hispanic black women and non-Hispanic white women age ≥40 years (Figure 14.14). However, after correction for glycemia and other risk factors, no difference was reported in the frequency of nonproliferative retinopathy (as detected by direct ophthalmoscopy) in black Jamaicans with NIDDM, compared with whites with NIDDM[73]. In a clinic-based cohort in St. Louis, MO after controlling for other risk factors, African Americans with IDDM, despite higher frequencies of hyperglycemia and hypertension, had a lower rate of progression of retinopathy than a group of non-Hispanic whites[74]. The reasons for these findings were not apparent.

The prevalence of retinopathy in second-generation Japanese-American males (Nisei), 12%, was significantly lower than that reported in the diabetes clinic at Tokyo University Hospital (49% among patients with an onset of diabetes from 20-59 years of age and 47% among those with an onset age >59 years) and in whites reported in the WESDR (36%)[11,66].

Genetic Factors

The relationships between genetic factors and the prevalence and incidence of retinopathy have been inconsistent[75-79]. Clinical studies have reported a positive association between retinopathy severity and the presence of HLA-B8, HLA-B15, or HLA-DR4 antigens in people with IDDM. In a case-control study of Joslin Clinic patients with IDDM, the patients with DR 3/0, 4/0, and X/X were more likely to have proliferative diabetic retinopathy than patients with 3/X, 4/X, or 3/4.[77] However, antigens of the BF locus, located on chromosome 6, have not been found by others to be related to proliferative retinopathy[78].

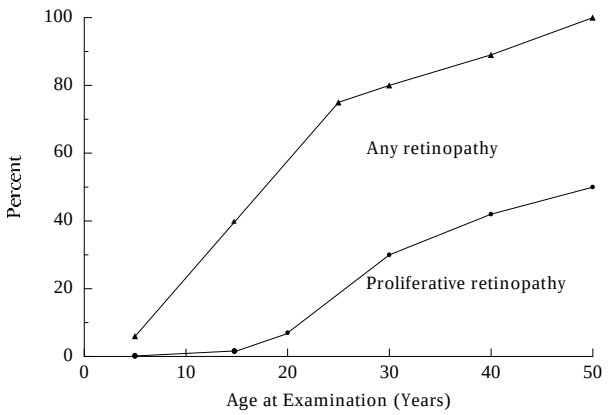
In a subset of the WESDR younger-onset group, after adjusting for factors associated with proliferative retinopathy, the presence of DR4 and the absence of DR3 was associated with a 5.4 times increase in the odds of having proliferative retinopathy compared with the absence of both DR4 and DR3[79]. No other genetic factors were statistically significantly associated with the presence of proliferative retinopathy. However, based on analyses of the 10-year follow-up data from this study, DR4 appeared to have a statistically significant protective effect for the incidence of proliferative diabetic retinopathy[80]. This might be explained, in part, by the higher mortality experienced by DR4+ individuals (7.6%) compared with DR4- individuals (4.7%). However, the protective effect was found even in people with shorter durations of diabetes, where mortality was low, suggesting that selective mortality did not completely explain this relationship.

The reasons why specific HLA-DR antigens would change the risk of developing more severe retinopathy are not apparent. Study of specific genetic factors associated with the hypothesized pathogenetic factors for retinopathy, such as glycosylation, aldose reductase activity, collagen formation, and platelet adhesiveness and aggregation may yield a better understanding of the possible causal relationships between genetic factors and diabetic retinopathy.

Age

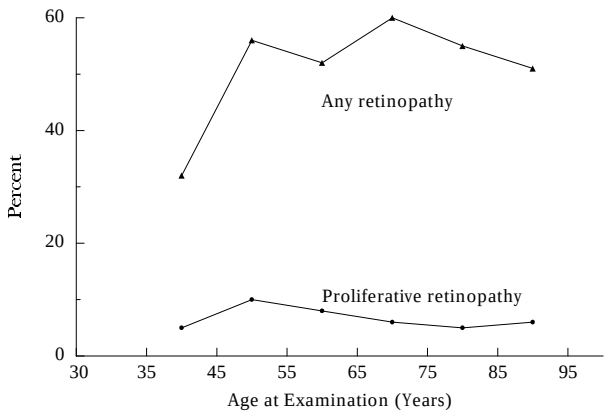
The prevalence and severity of diabetic retinopathy increased with increasing age in younger-onset persons (Figure 14.15)[10]. Prior to 13 years of age, diabetic retinopathy was infrequent, irrespective of the duration of the disease. In older-onset persons, the prevalence rates of retinopathy did not increase consistently with age (Figure 14.16)[11].

Figure 14.15
Prevalence of Any and of Proliferative Retinopathy in Insulin-Taking Persons with Diabetes Diagnosed at Age <30 Years, by Age



Source: Klein R. Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), 1980-82; unpublished data

Figure 14.16
Prevalence of Any and of Proliferative Retinopathy in Persons with Diabetes Diagnosed at Age ≥30 Years, by Age



Source: Klein R. Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), 1980-82; unpublished data

Tables 14.20 and 14.21 describe the relationships between the 4-year incidence and progression of diabetic retinopathy and age in the WESDR younger- and older-onset groups[19,20]. For younger-onset people taking insulin, the 4-year incidence of retinopathy increased with increasing age, with the sharpest increase in incidence occurring in persons 10-12 years old at baseline. Four-year rates of progression of retinopathy in younger-onset persons rose steadily with increasing age until 15-19 years of age, after which there was a gradual decline. No person age <13 years at baseline was found to have proliferative retinopathy at the 4-year followup. In older-onset persons, for those taking insulin, the 4-year incidence of retinopathy and progression of retinopathy had a tendency to decrease with increasing age (Table 14.21). The 4-year frequency of improvement tended to increase with increasing age. For those not taking insulin, the 4-year rate of progression to proliferative retinopathy decreased with increasing age.

These findings are consistent with data from other population-based studies[22,59,65,69]. In one such study of people with NIDDM in Rochester, MN, a lower incidence of retinopathy with increasing age was reported for diabetic people age >60 years[52].

Table 14.20
Four-Year Incidence of Any Retinopathy, Improvement or Progression of Retinopathy, and Progression to PDR in Younger-Onset Persons, by Age at Baseline Examination, WESDR, 1980-86

Age at baseline examination (years)	Incidence of any retinopathy		Improvement		No. at risk	No change %	Progression %	Progression to PDR %
	No. at risk	%	No. at risk	%				
0-9	26	15.4	0		27	96.3	3.7	0
10-12	42	54.8	2		48	70.8	27.1	0
13-14	25	48.0	2		32	62.5	37.5	3.1
15-19	66	72.7	56	7.1	140	47.9	49.3	10.0
20-24	42	64.3	81	3.7	130	48.5	49.2	11.5
25-29	25	72.0	67	6.0	101	49.5	46.5	15.8
30-34	34	61.8	57	8.8	102	52.0	43.1	11.8
≥35	11	63.6	111	8.1	133	60.2	33.1	12.8
35-39	7		40	5.0	51	56.9	39.2	9.8
40-44	3		21	4.8	25	56.0	40.0	16.0
≥45	1		50	12.0	57	64.9	24.6	14.0

PDR, proliferative diabetic retinopathy; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy; younger-onset, diabetes diagnosed at age <30 years.

Source: Reference 19

Table 14.21

Four-Year Incidence of Any Retinopathy, Improvement or Progression of Retinopathy, and Progression to PDR in Older-Onset Persons, by Age at Baseline Examination, WESDR, 1980-86

Insulin use and age at baseline examination (years)	Incidence of any retinopathy		Improvement		No. at risk	No change %	Progression %	Progression to PDR %
	No. at risk	%	No. at risk	%				
Using insulin								
30-44	18	50.0	6	16.7	26	57.7	38.5	3.8
45-59	47	59.6	70	5.7	135	54.1	43.0	8.9
60-74	61	45.9	119	17.6	202	58.4	31.2	8.9
≥75	28	28.6	20	35.0	55	67.3	20.0	0
p	<0.05		<0.01			0.16	<0.01	0.29
Not using insulin								
30-44	14	50.0	4	25.0	19	63.2	31.6	5.3
45-59	83	30.1	21	4.8	114	68.4	30.7	4.4
60-74	168	32.7	48	20.8	257	73.2	23.0	1.9
≥75	55	41.8	28	28.6	96	69.8	21.9	0
p	0.47		0.08			0.58	0.09	<0.05

PDR, proliferative diabetic retinopathy; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy; older-onset, diabetes diagnosed at age ≥30 years; p-values are by test for trend.

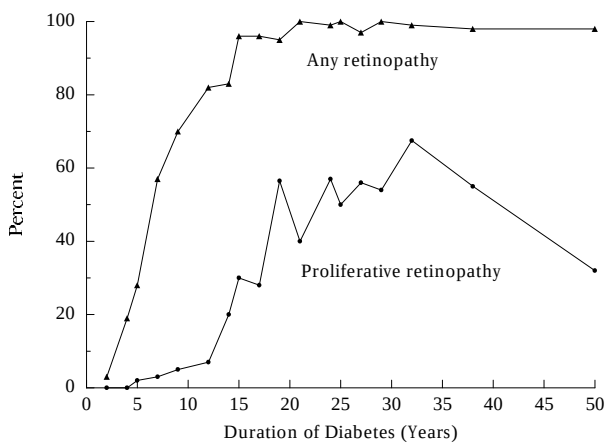
Source: Reference 20

Duration of Diabetes

For younger-onset persons, both the frequency and severity of retinopathy increased with increasing duration of diabetes (Figure 14.17)[10,11]. The prevalence of retinopathy 3-4 years after the diagnosis of diabetes was 14.5% in males and 24.3% in females, and in all cases it was mild. On the other hand, in persons with diabetes for 19-20 years, 50% of males and 33% of females had proliferative retinopathy. After diagnosis of diabetes, retinopathy was more frequent in the older-onset groups compared with the younger-onset group. In the first 3 years after diagnosis of diabetes, 23% of the older-onset group not taking insulin had retinopathy, and 2% had proliferative retinopathy (Figure 14.18). However, after 20 years or more of diabetes, fewer older-onset people not taking insulin had retinopathy (60% versus 99%) or proliferative retinopathy (5% versus 53%) than younger-onset people.

Figure 14.17

Prevalence of Any and of Proliferative Retinopathy in Persons Diagnosed with Diabetes at Age <30 Years, by Diabetes Duration

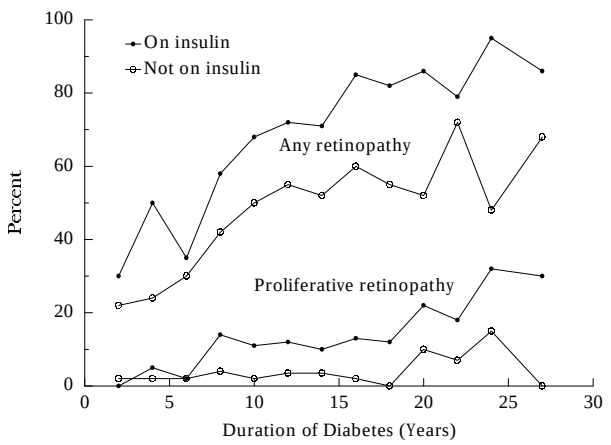


Data are from the Wisconsin Epidemiologic Study of Diabetic Retinopathy baseline examination, 1980-82.

Source: Reference 159

Figure 14.18

Prevalence of Any and of Proliferative Retinopathy in Persons Diagnosed with Diabetes at Age ≥30 Years, by Diabetes Duration



Data are from the Wisconsin Epidemiologic Study of Diabetic Retinopathy, 1980-82.

Source: Reference 159

Table 14.22

Four-Year Incidence of Any Retinopathy, Improvement or Progression of Retinopathy, and Progression to PDR in Younger-Onset Persons, by Duration of Diabetes, WESDR, 1980-86

Duration of diabetes at baseline examination (years)	Incidence of any retinopathy		Improvement		No. at risk	No change	Progression	Progression to PDR
	No. at risk	%	No. at risk	%		%	%	%
0-2	69	37.7	4		75	80.0	18.7	0
3-4	68	61.8	5		84	64.3	34.5	1.2
5-6	60	65.0	30	3.3	103	54.4	44.7	3.9
7-8	32	68.8	37	5.4	85	40.0	57.6	8.2
9-10	23	73.9	53	5.7	84	54.8	41.7	11.9
≥11	19	73.7						
11-12			43	0	54	44.4	55.6	22.2
13-14			38	7.9	43	30.2	62.8	27.9
15-19			68	2.9	79	55.7	41.8	16.5
20-24			39	15.4	42	57.1	28.6	14.3
25-29			32	9.4	34	61.8	29.4	14.7
≥30			27	14.8	30	56.7	30.0	16.7

PDR, proliferative diabetic retinopathy; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy; younger-onset, diabetes diagnosed at age <30 years.

Source: Reference 19

To examine the relationship between retinopathy and clinical diagnosis of NIDDM, data regarding retinopathy prevalence at different durations of diabetes from older-onset persons in the WESDR and a study in Australia were extrapolated to the time when retinopathy prevalence was estimated to be zero[81]. It was calculated that the onset of detectable retinopathy occurred about 4-7 years before diagnosis of NIDDM in these populations.

The 4-year incidence of diabetic retinopathy increased with increasing duration of diabetes at baseline (Tables 14.22 and 14.23)[19,20]. The risk of developing retinopathy in the younger-onset group was high even after 10 years of diabetes (73.7%).

The 4-year incidence of proliferative retinopathy increased from 0% during the first 3 years after diagnosis of diabetes to 27.9% in younger-onset people with 13-14 years of diabetes. Thereafter, the incidence of proliferative retinopathy remained stable. There are a number of reasons for these findings. First, different risk factors, e.g., diabetic nephropathy, may be operative during the first 15 years of diabetes compared

Table 14.23

Four-Year Incidence of Any Retinopathy, Improvement or Progression of Retinopathy, and Progression to PDR in Older-Onset Persons, by Duration of Diabetes, WESDR, 1980-86

Insulin use and duration of diabetes at baseline examination (years)	Incidence of any retinopathy		Improvement		No. at risk	No change	Progression	Progression to PDR
	No. at risk	%	No. at risk	%		%	%	%
Using insulin								
0-4	48	27.1	19	15.8	77	77.9	18.2	0
5-9	48	70.8	19	10.5	78	47.4	50.0	5.1
10-14	24	54.2	38	21.1	73	50.7	38.4	5.5
≥15	34	38.2	139	14.4	190	57.4	32.1	12.1
p	0.22		0.73			0.10	0.68	<0.001
Not using insulin								
0-4	155	31.0	24	16.7	201	79.1	18.9	2.0
5-9	99	32.3	29	27.6	152	69.1	25.7	2.0
10-14	29	37.9	15	6.7	52	63.5	34.6	0
≥15	37	51.4	33	21.2	81	59.3	32.1	4.9
p	0.06		0.99			<0.001	<0.01	0.43

PDR, proliferative diabetic retinopathy; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy; older-onset, diabetes diagnosed at age ≥30 years; p-values are by test for trend.

Source: Reference 20

with the years that follow. Second, it is possible that younger-onset people who have diabetes for >15 years and who develop proliferative retinopathy are more likely to die before being examined in the WESDR. In the older-onset groups, 2.0% of those with <5 years duration who were not taking insulin at baseline developed signs of proliferative retinopathy at the 4-year followup (Table 14.23).

There are few other population-based data concerning the incidence or progression of retinopathy. Data from some of these studies are presented in Table 14.14.

Age at Diagnosis

In the WESDR, after controlling for duration of diabetes, age at diagnosis was not related to the 4-year incidence or progression of diabetic retinopathy in any of the diabetic groups studied[19,20]. In contrast, after controlling for other risk factors in a cohort with NIDDM in Rochester, MN, the development of retinopathy was significantly associated with younger age at diagnosis[52].

Puberty

After controlling for other factors, such as diastolic blood pressure and duration of diabetes, younger-onset subjects who were postmenarchal in the WESDR were 3.2 times as likely to have diabetic retinopathy as those who were premenarchal[82]. Duration of diabetes after menarche conferred an increased risk of having any retinopathy compared with duration before menarche. The incidences of any retinopathy or proliferative retinopathy over the following 4-year period were higher in those who were postmenarchal at baseline compared with those who were premenarchal. This has been reported by others[83,84]. A number of changes occurring at puberty, such as increases in insulin-like growth factor I, growth hormone, sex hormones, blood pressure, and poorer glycemic control (secondary to increased insulin resistance, poorer compliance, and inadequate insulin dosage) have been suggested as resulting in an increased risk in progression of retinopathy[85-91].

Hyperglycemia

There is a growing body of epidemiologic studies that

Table 14.24
Characteristics Associated with Incidence, Prevalence, and Progression of Diabetic Retinopathy in Population-Based Studies

Ref.	Type of diabetes	Hyperglycemia	High blood pressure	History of smoking	History of renal disease	High lipids
Incidence						
52	NIDDM	Yes	No	No	No	
59	IDDM	No	Yes			
	NIDDM	Yes	Yes			
10, 11, 93, 94, 114,	IDDM	Yes	Yes	No	Yes	Yes
120-122, 126, 127	NIDDM	Yes	Yes/no‡	No	No	
Prevalence						
47	NIDDM	Yes	Yes			
48, 70	NIDDM	Yes	Yes			
50, 68, 69	NIDDM	Yes	No/yes†	No	Yes/no†	No/yes†
14	IDDM		Yes			
	NIDDM		Yes			
51	NIDDM	Yes	Yes			
53	IDDM	No				
55	IDDM	Yes	Yes		Yes	No
	NIDDM	Yes	Yes		Yes	No
56	IDDM	Yes	No	Yes	No	
60	NIDDM	Yes	Yes	No	Yes	
61	IDDM	Yes			Yes	
	NIDDM	Yes				
62	NIDDM	Yes	Yes	Yes		No
63	IDDM	No	Yes			
64, 65	IDDM	Yes	Yes	No	Yes	Yes
66	NIDDM	Yes				

† No relationship of high blood pressure or high cholesterol with prevalence, significant relationship with incidence; relationship of gross proteinuria is significant with prevalence but not incidence of retinopathy. ‡ Relationship of high blood pressure with prevalence but not 4-year incidence of retinopathy is significant.

Source: Reference 160

demonstrate a strong relationship between hyperglycemia and the development or progression of diabetic retinopathy (Table 14.24)[10,11,47-52,55,56,59-62,64,65,67,68,92-94]. In the WESDR, the glycosylated hemoglobin level at baseline was found to be a significant predictor of the 4- and 10-year incidence of retinopathy, progression, progression to proliferative retinopathy (Table 14.25), and incidence of macular edema in all three diabetic groups studied[71,93,94]. These relationships remained after controlling for duration of diabetes, severity of retinopathy, and other risk factors measured at baseline. In addition, a decrease in glycosylated hemoglobin between baseline and the 4-year follow-up examination was associated with a significant decrease in the progression of retinopathy and the incidence of proliferative retinopathy in most of the WESDR diabetic groups (Tables 14.26-14.28)[94]. The WESDR data also suggest that, at any duration of diabetes prior to the development of severe nonproliferative or proliferative retinopathy, there was no "point of no return" with regard to the glycosylated hemoglobin-retinopathy relationship. Rather, the relationship between level of glycemia and risk of retinopathy extended across the whole range of levels of glycemia,

Table 14.25

Four- and 10-Year Incidence and Progression Rates by Quartile of Glycosylated Hemoglobin for Persons with Nonproliferative Retinopathy at the Baseline Examination, WESDR, 1980-92

	Incidence of any retinopathy				Progression of retinopathy				Progression to proliferative retinopathy		
Glycosylated hemoglobin	No. at risk	%	RR	(95% CI)	No. at risk	%	RR	(95% CI)	%	RR	(95% CI)
Four-Year											
Younger-onset											
1st quartile	80	45.0	1.0		177	17.0	1.0		1.1	1.0	
2nd quartile	68	50.0	1.1	(0.8, 1.6)	164	32.9	1.9	(1.3, 2.9)	3.0	2.7	(0.5, 14.1)
3rd quartile	50	66.0	1.5	(1.1, 2.0)	172	49.4	2.9	(2.0, 4.2)	16.3	14.8	(3.5, 62.4)
4th quartile	59	84.8	1.9	(1.4, 2.5)	167	68.3	4.0	(2.9, 5.7)	24.0	21.8	(5.3, 90.5)
Older-onset taking insulin											
1st quartile	49	38.8	1.0		106	24.5	1.0		3.8	1.0	
2nd quartile	39	43.6	1.1	(0.7, 1.9)	89	25.8	1.1	(0.6, 1.7)	3.4	0.9	(0.2, 3.9)
3rd quartile	28	46.4	1.2	(0.7, 2.0)	93	32.3	1.3	(0.8, 2.1)	6.4	1.7	(0.5, 5.8)
4th quartile	27	74.1	1.9	(1.3, 2.9)	92	52.2	2.1	(1.4, 3.1)	15.2	4.0	(1.4, 11.7)
Older-onset not taking insulin											
1st quartile	85	12.9	1.0		114	7.9	1.0		1.8	1.0	
2nd quartile	80	28.8	2.2	(1.2, 4.3)	116	15.5	2.0	(0.9, 4.2)	0.9	0.5	(0, 5.2)
3rd quartile	75	49.3	3.8	(2.1, 7.0)	116	31.0	3.9	(2.0, 7.8)	0.9	0.5	(0, 5.2)
4th quartile	56	51.8	4.0	(2.2, 7.4)	104	49.0	6.2	(3.2, 12.0)	6.7	3.7	(0.8, 17.3)
Ten-Year											
Younger-onset											
1st quartile	85	80.0	1.0		187	58.0	1.0		8.7	1.0	
2nd quartile	53	95.3	1.5	(1.2, 1.9)	153	73.6	1.5	(1.2, 1.9)	22.7	2.6	(1.5, 4.6)
3rd quartile	54	92.2	1.5	(1.2, 1.9)	174	85.6	2.1	(1.7, 2.5)	41.3	5.5	(3.5, 8.8)
4th quartile	56	98.2	1.9	(1.5, 2.4)	168	92.0	2.9	(2.3, 3.5)	49.8	7.1	(4.6, 11.1)
Older-onset taking insulin											
1st quartile	44	70.4	1.0		101	54.9	1.0		12.3	1.0	
2nd quartile	43	80.6	1.1	(0.7, 1.7)	92	59.3	1.1	(0.8, 1.6)	18.5	1.2	(0.5, 2.9)
3rd quartile	25	79.6	1.1	(0.7, 1.8)	99	72.7	1.4	(1.0, 1.9)	24.2	2.0	(1.0, 4.3)
4th quartile	23	100.0	1.9	(1.3, 2.9)	87	86.6	2.1	(1.6, 2.8)	37.9	3.1	(1.5, 6.1)
Older-onset not taking insulin											
1st quartile	91	47.0	1.0		125	30.7	1.0		2.0	1.0	
2nd quartile	71	57.2	1.4	(0.9, 2.2)	114	45.7	1.8	(1.2, 2.7)	2.4	1.2	(0.2, 8.3)
3rd quartile	69	83.9	2.5	(1.7, 3.5)	110	66.8	2.8	(1.9, 4.2)	9.6	4.0	(1.0, 16.6)
4th quartile	50	89.7	2.7	(1.9, 4.0)	106	80.5	4.3	(3.0, 6.2)	30.0	13.8	(4.8, 39.5)

RR, relative risk; CI, confidence interval. Values of glycosylated hemoglobin (%) for the younger-onset group are 5.6-9.4, 9.5-10.5,10.6-12.0 and 12.1-19.5; for the older-onset group taking insulin, 5.9-8.8, 8.9-10.2, 10.3-11.5 and 11.6-17.0; and for the older-onset group not taking insulin 5.4-7.6, 7.7-8.6, 8.7-10.0 and 10.1-20.8.

Source: References 93 and 94

Table 14.26
Multivariate Analysis for 10-Year Incidence of Any Retinopathy, WESDR

Characteristics	p	Retinopathy more likely if	Odds ratio (95% CI)
Younger-onset			
Duration, 10 years	<0.01	Longer	3.4 (1.4-8.6)
Age, 10 years	<0.05	Older	1.4 (1.0-2.0)
Sex (0= female, 1= male)	0.17		
Glycosylated hemoglobin, %*	<0.0001	Higher	1.6 (1.4-1.9)
Glycosylated hemoglobin change, %†	0.10	Increase	1.1 (1.0-1.3)
Older-onset taking insulin			
Duration, 10 years	0.97		
Age, 10 years	<0.001	Younger	0.6 (0.5-0.8)
Sex (0= female, 1= male)	0.32		
Glycosylated hemoglobin, %*	<0.05	Higher	1.3 (1.0-1.6)
Glycosylated hemoglobin change, %†	0.35		
Older-onset not taking insulin			
Duration, 10 years	0.41		
Age, 10 years	0.37		
Sex (0= female, 1= male)	0.47		
Glycosylated hemoglobin, %*	<0.0001	Higher	1.6 (1.4-1.8)
Glycosylated hemoglobin change, %†	<0.005	Increase	1.2 (1.1-1.4)

* Per one percentage point increase. † Defined as glycosylated hemoglobin measured at 4-year followup minus glycosylated hemoglobin at baseline, per one percentage point increase. CI, confidence interval.

Source: Reference 94

with no evidence of a threshold. Appendix 14.2 shows the 10-year rates for incidence and progression of retinopathy according to glycohemoglobin level measured at baseline for younger-onset, older-onset taking insulin, and older-onset not taking insulin participants in the WESDR[161].

Most of the earlier small clinical trials failed to demonstrate a beneficial effect of glycemic control in preventing the development or progression of diabetic retinopathy in people with IDDM[95-101]. They were limited by their small size, relatively short follow-up times, and inclusion of people with diabetes who had

Table 14.27
Multivariate Analysis for 10-Year Progression of Retinopathy, WESDR

Characteristics	p	Progression more likely if	Odds ratio (95% CI)
Younger-onset			
Duration, 10 years	0.15		
Age, 10 years	0.88		
Sex (0= female, 1= male)	<0.05	Male	1.4 (1.1-1.9)
Retinopathy severity (10/10-53/53)	0.70		
Glycosylated hemoglobin, %*	<0.0001	Higher	1.7 (1.6-1.9)
Glycosylated hemoglobin change, %†	<0.0001	Increase	1.2 (1.1-1.3)
Older-onset taking insulin			
Duration, 10 years	0.78		
Age, 10 years	<0.0001	Younger	0.7 (0.6-0.8)
Sex (0= female, 1= male)	0.87		
Retinopathy severity (10/10-53/53)	0.18		
Glycosylated hemoglobin, %*	<0.0001	Higher	1.4 (1.2-1.6)
Glycosylated hemoglobin change, %†	0.31		
Older-onset not taking insulin			
Duration, 10 years	<0.05	Longer	1.4 (1.0-2.0)
Age, 10 years	<0.001	Younger	0.7 (0.6-0.9)
Sex (0= female, 1= male)	0.56		
Retinopathy severity (10/10-53/53)	0.87		
Glycosylated hemoglobin, %*	<0.0001	Higher	1.8 (1.5-2.0)
Glycosylated hemoglobin change, %†	<0.0001	Increase	1.4 (1.2-1.5)

* Per one percentage point increase. † Defined as glycosylated hemoglobin measured at 4-year followup minus glycosylated hemoglobin at baseline, per one percentage point increase. CI, confidence interval.

Source: Reference 94

Table 14.28
Multivariate Analysis for 10-Year Progression to Proliferative Retinopathy, WESDR

Characteristics	p	Proliferative retinopathy more likely if	Odds ratio (95% CI)
Younger-onset			
Duration, 10 years	0.73		
Age, 10 years	0.25		
Sex (0 = female, 1 = male)	0.96		
Retinopathy severity, per step (10/10-53/53)	<0.0001	More severe	1.5 (1.4-1.6)
Glycosylated hemoglobin, %*	<0.0001	Higher	1.9 (1.7-2.2)
Glycosylated hemoglobin change, %†	<0.0001	Increase	1.3 (1.2-1.4)
Older-onset taking insulin			
Duration, 10 years	0.59		
Age, 10 years	0.13	Younger	0.8 (0.5-1.1)
Sex (0 = female, 1 = male)	0.80		
Retinopathy severity, per step (10/10-53/53)	<0.0001	More severe	1.4 (1.3-1.6)
Glycosylated hemoglobin, %*	<0.001	Higher	1.5 (1.2-1.9)
Glycosylated hemoglobin change, %†	0.07	Increase	1.2 (1.0-1.5)
Older-onset not taking insulin			
Duration, 10 years	0.92		
Age, 10 years	0.06	Younger	0.7 (0.4-1.0)
Sex (0 = female, 1 = male)	0.66		
Retinopathy severity, per step (10/10-53/53)	<0.0001	More severe	1.5 (1.3-1.8)
Glycosylated hemoglobin, %*	<0.0001	Higher	1.9 (1.5-2.5)
Glycosylated hemoglobin change, %†	<0.005	Increase	1.4 (1.1-1.8)

WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy; CI, confidence interval. * Per one percentage point increase. † Defined as glycosylated hemoglobin measured at 4-year followup minus glycosylated hemoglobin at baseline, per one percentage point increase.

Source: Reference 94

moderately severe nonproliferative retinopathy at study entry. Initial worsening of retinopathy, manifest by the appearance of soft exudates and intraretinal microvascular abnormalities, were consistently found in the experimental tightly controlled groups in persons who had minimal or no retinopathy at baseline in these clinical trials. However, a meta-analysis[102] of 16 published randomized clinical trials showed that the risk of retinopathy progression was insignificantly higher at 6-12 months of intensive glycemic control (odds ratio 2.11, 95% CI 0.54,8.31). Furthermore, after ≥2 years of intensive glycemic control, the risk of retinopathy progression was significantly lower (odds ratio 0.49, 95% CI 0.28,0.85). In addition, the incidence of severe hypoglycemia increased by 9.1 episodes per 100 person-years of followup in the intensively controlled patients. In the UGDP trial, metabolic control was not related to the incidence or progression of retinopathy in people with NIDDM[17].

The DCCT, a large randomized controlled clinical trial of 1,441 patients with IDDM, provided information on the relationships of intensive glycemic control to the development and progression of diabetic reti-

Table 14.29
Risk Reduction in Incidence and Progression of Retinopathy, DCCT Primary Prevention Group

Retinopathy	Risk reduction, intensive vs. conventional treatment group %	95% CI
≥1 microaneurysm	27	11-40
≥3-step progression	60	47-70
≥Sustained 3-step progression	76	62-85

Only 6 subjects developed proliferative diabetic retinopathy, 5 developed macular edema, 4 needed laser treatment; DCCT, Diabetic Control and Complications Trial; CI, confidence interval.

Source: Reference 104

Table 14.30
Risk Reduction in Incidence and Progression of Retinopathy, DCCT Secondary Intervention Group

Retinopathy	Risk reduction, intensive vs. conventional treatment group %	95% CI
≥3-step progression	34	18-46
≥Sustained 3-step progression	54	38-65
Incidence of preproliferative or PDR	47	13-67
Incidence of macular edema	22	15-47
Laser treatment	54	23-74

PDR, proliferative diabetic retinopathy; DCCT, Diabetic Control and Complications Trial; CI, confidence interval.

Source: Reference 104

nopathy[103,104]. The DCCT demonstrated that intensive glycemic control was associated with a reduced risk of incidence and progression of retinopathy, progression to preproliferative and proliferative retinopathy, and incidence of macular edema as well as a reduced need for panretinal photocoagulation compared with conventional insulin treatment (Tables 14.29 and 14.30). However, the group under intensive glycemic control experienced a 60% increased risk of weight gain and a 330% increased risk of severe hypoglycemic reactions compared with the conventional treatment group. While these data suggest a favorable risk-benefit ratio for intensive glycemic control for most people with IDDM with no or early nonproliferative retinopathy, caution must be exercised in translating these results for the treatment of people with NIDDM. Results of the United Kingdom Prospective Diabetes Study may provide such information[105].

C-Peptide Status

The relationship of endogenous insulin secretion to diabetic retinopathy, independent of glycemic control, is not certain[106-109]. Some studies suggest a protective effect of remaining endogenous insulin secretion whereas others do not. In the WESDR, the highest frequencies and most severe retinopathy were found in insulin-using individuals with undetectable or low plasma C-peptide (<0.3 nM), whereas the lowest frequencies of retinopathy were found in older-onset overweight individuals not using insulin (Tables 14.31-14.33)[110]. Older- and younger-onset individuals who were using insulin and who had no detectable C-peptide had similar frequencies of proliferative retinopathy. After controlling for characteristics associated with retinopathy in older-onset people with NIDDM, there was no relationship between higher levels of C-peptide and lower frequency of less severe retinopathy. These findings suggest that the level of glycemia, not the level of endogenous C-peptide, is more important in determining the presence and severity of retinopathy in individuals with NIDDM.

Table 14.31
Frequency and Severity of Diabetic Retinopathy, Macular Edema, and CSME in Younger-Onset Diabetic Persons by C-Peptide Level, WESDR

	C-peptide level					
	Undetectable		<0.3 nM		≥0.3 nM	
	No.	%	No.	%	No.	%
Retinopathy level						
10	90	12.6	18	18.8	3	12.5
21-31	266	37.2	31	32.3	9	37.5
41-51	164	22.9	23	24.0	3	12.5
60-65	124	17.3	16	16.7	5	20.8
≥70	71	9.9	8	8.3	4	16.7
Macular edema						
Absent	546	90.0	78	92.9	14	93.3
Present	61	10.0	6	7.1	1	6.7
CSME						
Absent	575	94.7	81	96.4	15	100.0
Present	32	5.3	3	3.6	0	0

CSME, clinically significant macular edema; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy; younger-onset, diabetes diagnosed at age <30 years.

Source: Reference 110

Table 14.32
Frequency and Severity of Diabetic Retinopathy, Macular Edema, and CSME in Older-Onset Diabetic Persons Using Insulin by C-Peptide Level, WESDR

	C-peptide level					
	Undetectable		<0.3 nM		≥0.3 nM	
	No.	%	No.	%	No.	%
Retinopathy level						
10	12	11.7	25	18.8	67	23.3
21-31	29	28.2	54	40.6	116	40.4
41-51	31	30.1	34	25.6	69	24.0
60-65	19	18.4	9	6.8	25	8.7
≥70	12	11.7	11	8.3	10	3.5
Macular edema						
Absent	61	79.2	89	86.4	199	87.7
Present	16	20.8	14	13.6	28	12.3
CSME						
Absent	66	85.7	95	92.2	209	92.1
Present	11	14.3	8	7.8	18	7.9

CSME, clinically significant macular edema; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy; older-onset, diabetes diagnosed at age ≥30 years.

Source: Reference 110

Table 14.33
Frequency and Severity of Diabetic Retinopathy, Macular Edema, and CSME in Older-Onset Diabetic Persons Not Using Insulin with C-Peptide ≥0.3 nM by Weight Status, WESDR

	Not overweight		Overweight		Total	
	No.	%	No.	%	No.	%
Retinopathy level						
10	64	46.4	116	52.5	203	51.5
21-31	48	34.8	79	35.7	137	34.8
41-51	17	12.3	25	11.3	43	10.9
60-65	5	3.6	1	0.5	6	1.5
≥70	4	2.9	0	0	5	1.3
Macular edema						
Absent	104	95.4	203	97.1	327	96.7
Present	5	2.9	6	2.9	11	3.3
CSME						
Absent	107	99.1	205	98.1	332	98.5
Present	1	0.9	4	1.9	5	1.5

CSME, clinically significant macular edema; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy; older-onset, diabetes diagnosed at age ≥30 years.

Source: Reference 110

Exogenous Insulin

Exogenous insulin has been suggested as a possible cause of atherosclerosis and retinopathy in people with NIDDM[111]. In the WESDR, there was no association between the amount or type of exogenous insulin used and the presence and severity of retinopathy in the older-onset group using insulin whose C-peptide was ≥0.3nM[110]. These data suggest that exogenous insulin itself is probably not causally related to retinopathy in diabetic people with normal C-peptide.

Blood Pressure

Anecdotal observations from clinical studies suggest a relationship between hypertension and the severity of diabetic retinopathy[112]. Increased blood pressure, through an effect on blood flow, has been hypothesized to damage the retinal capillary endothelial cells, resulting in development and progression of retinopathy[113]. Epidemiologic data from cross-sectional studies suggest a positive relation of prevalence of retinopathy and hypertension, but data from cohort studies regarding the relationship between high blood pressure or hypertension and development and progression of retinopathy have not yielded consistent findings (Table 14.24)[10,11,14,47,48,50-52,55,56,59,60,62-65,67-69,114]. Some of the earlier studies were limited by small sample size, selection of patients, failure to control for possible confounders, selective drop-out of patients, and by insensitive measures of detecting retinopathy.

In the WESDR, systolic blood pressure was a significant predictor of the 4-year incidence of diabetic retinopathy and diastolic blood pressure was a predictor of the 4-year progression of retinopathy only in people with younger-onset diabetes (Tables 14.34 and 14.35)[114]. After controlling for other risk factors, such as retinopathy severity, glycosylated hemoglobin, and duration of diabetes at baseline, the relationships between blood pressure and the incidence or progression of retinopathy remained in the younger-onset group. However, in the WESDR, neither the systolic nor the diastolic blood pressure was found to be related to the 4-year incidence or progression of retinopathy in either of the older-onset groups. The failure to find a relationship in the older-onset groups persisted after controlling for the use of antihypertensive medications.

These data suggest there may be a differential effect of blood pressure, depending on the age at onset and type of diabetes present. The lack of a consistent relationship of high blood pressure with the incidence or progression of retinopathy suggests that blood pressure itself may be more of a risk indicator than a causal factor in the development of retinopathy. It is possible that elevated blood pressure in the younger-onset group reflects early diabetic nephropathy or an alteration in the angiotensin-renin levels, while in the older-onset group it reflects nonrenal vascular disease. This is consistent with a finding that nephropathic normotensive patients with IDDM had more severe retinal changes than hypertensive IDDM patients without albuminuria but had less severe retinal changes than IDDM patients with both diabetic nephropathy and hypertension[115].

Table 14.34
Four-Year Incidence and Progression of Retinopathy for Younger-Onset Persons with No or Nonproliferative Retinopathy at the Baseline Examination, by Blood Pressure Quartile, WESDR, 1980-86

		Incidence of any retinopathy				Progression of retinopathy				Progression to PDR		
	Range, mmHg	No. at risk	%	RR	95% CI	No. at risk	%	RR	95% CI	%	RR	95%CI
Systolic blood pressure quartile												
1st	78-110	108	49.1	1.0		200	38.5	1.0		5.0	1.0	
2nd	111-120	81	61.7	1.3	1.0, 1.6	216	42.1	1.1	0.9, 1.4	11.1	2.2	1.1, 4.5
3rd	121-134	61	63.9	1.3	1.0, 1.7	192	42.7	1.1	0.9, 1.4	10.9	2.2	1.1, 4.5
4th	135-221	19	89.5	1.8	1.4, 2.3	100	41.0	1.1	0.8, 1.4	18.0	3.6	1.7, 7.5
Test of trend			p<0.005				p=0.45			p<0.001		
Diastolic blood pressure quartile												
1st	42-71	105	58.1	1.0		207	35.3	1.0		2.9	1.0	
2nd	72-78	70	50.0	0.9	0.6, 1.1	189	38.1	1.1	0.8, 1.4	11.6	4.0	1.7, 9.7
3rd	79-85	57	66.7	1.1	0.9, 1.5	170	47.6	1.3	1.1, 1.7	10.0	3.4	1.4, 8.6
4th	86-117	35	71.4	1.2	0.9, 1.6	140	46.4	1.3	1.0, 1.7	20.0	6.9	2.9, 16.2
Test of trend			p=0.36				p<0.05			p<0.0001		

RR, relative risk; CI, confidence interval; PDR, proliferative diabetic retinopathy; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy; younger-onset, diabetes diagnosed at age <30 years.

Source: Reference 114

Table 14.35

Four-Year Incidence and Progression of Retinopathy for Older-Onset Persons with No or Nonproliferative Retinopathy at the Baseline Examination by Blood Pressure Quartile, WESDR, 1980-86

		Incidence of any retinopathy				Progression of retinopathy				Progression to PDR		
	Range, mmHg	No. at risk	%	RR	95% CI	No. at risk	%	RR	95% CI	%	RR	95% CI
Using insulin												
Systolic blood pressure quartile												
1st	80-128	52	50.0	1.0		109	32.1	1.0		5.5	1.0	
2nd	129-144	40	57.5	1.2	0.8, 1.7	114	37.7	1.2	0.8, 1.7	3.5	0.6	0.2, 2.2
3rd	145-160	43	41.9	0.8	0.5, 1.3	114	37.7	1.2	0.8, 1.7	9.6	1.7	0.7, 4.6
4th	161-263	19	31.6	0.6	0.3, 1.3	80	25.0	0.8	0.5, 1.2	11.2	2.0	0.8, 5.5
Diastolic blood pressure quartile												
1st	45-69	35	54.3	1.0		88	31.8	1.0		4.5	1.0	
2nd	70-77	45	42.2	0.8	0.5, 1.2	111	29.7	0.9	0.6, 1.4	7.2	1.6	0.5, 5.2
3rd	78-86	41	48.8	0.9	0.6, 1.4	112	35.7	1.1	0.8, 1.7	8.0	1.8	0.6, 5.6
4th	87-129	33	45.5	0.8	0.5, 1.4	106	37.7	1.2	0.8, 1.8	8.5	1.9	0.6, 6.0
Not using insulin												
Systolic blood pressure quartile												
1st	94-132	97	33.0	1.0		132	21.2	1.0		1.5	1.0	
2nd	133-145	97	35.1	1.1	0.7, 1.6	137	26.3	1.2	0.8, 1.9	3.6	2.4	0.5, 12.3
3rd	146-161	75	36.0	1.1	0.7, 1.7	111	27.9	1.3	0.8, 2.1	0.9	0.6	0.1, 6.6
4th	162-236	51	33.3	1.0	0.6, 1.6	105	24.8	1.2	0.7, 1.9	2.9	1.9	0.3, 11.4
Diastolic blood pressure quartile												
1st	47-72	73	37.0	1.0		116	22.4	1.0		2.6	1.0	
2nd	73-79	88	29.5	0.8	0.5, 1.2	124	17.7	0.8	0.5, 1.3	0.8	0.3	0.0, 2.9
3rd	80-87	80	40.0	1.1	0.7, 1.6	119	31.9	1.4	0.9, 2.2	2.5	1.0	0.2, 4.7
4th	88-121	77	31.2	0.8	0.5, 1.3	123	27.6	1.2	0.8, 1.9	3.3	1.3	0.3, 5.5

RR, relative risk; CI, confidence interval; PDR, proliferative diabetic retinopathy; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy; older-onset, diabetes diagnosed at age ≥30 years.

Source: Reference 114

Epidemiologic data suggest that the type of antihypertensive drug chosen to control blood pressure may also be important[116,117]. If the relationship between blood pressure and retinopathy is, in part, a result of alterations in angiotensin-renin levels, then the use of ACE inhibitors may be beneficial in reducing rates of progression of retinopathy. This remains to be evaluated by a controlled clinical trial. In addition, data from the WESDR and the Joslin Clinic suggest that the use of diuretics may be associated with poorer long-term survival, even while controlling for other risk factors[43,118,119].

Proteinuria and Diabetic Nephropathy

Data from most studies suggest a strong association between the prevalence of diabetic nephropathy, as manifest by microalbuminuria or gross proteinuria, and retinopathy[10,11,50,55,60,61,63,120,121]. Rheological, lipid, and platelet abnormalities associated with nephropathy may be involved in the pathogenesis of retinopathy. In the WESDR, in the younger-onset group taking insulin, the relative risk of proliferative retinopathy developing over 4 years in those with gross proteinuria at baseline was 2.32 (95% CI 1.40,3.83) compared with those without gross proteinuria[121]. For the older-onset group taking insulin, the relative risk was 2.02 (95% CI 0.91,4.44) and for those not taking insulin it was 1.13 (95% CI 0.15,8.50). After controlling for other risk variables, the relationship was of borderline statistical significance (p=0.052) in the younger-onset group with no or early nonproliferative retinopathy at baseline. A greater proportion of those with IDDM participating in a cohort study in Pittsburgh, PA who had microalbuminuria or overt nephropathy at entry in the study progressed to proliferative disease over a 2-year followup[65]. However, in the same study, nephropathy at baseline was not associated with overall progression of retinopathy. Data from these studies suggest that in those with IDDM, gross proteinuria is a risk indicator for proliferative retinopathy and that these patients might benefit from having regular ophthalmologic evaluation.

In a study of Oklahoma Indians, while gross proteinuria was associated with retinopathy at baseline, it

was not found to be a risk factor for the development of retinopathy[50,69]. In Pima Indians with NIDDM, after controlling for other risk factors, the presence of proteinuria or renal insufficiency predicted the development of proliferative retinopathy[70]. The incidence-rate ratio was 4.8. However, in people with NIDDM in Rochester, MN, persistent proteinuria was not an independent predictor of subsequent incidence of retinopathy[52].

Serum Lipids

The relationship between serum lipids and the presence, development, or progression of diabetic retinopathy remains uncertain[50,55,62,64,65,69,122] (Table 14.24). In the WESDR, higher total serum cholesterol was associated with higher prevalence of retinal hard exudates in both the younger- and older-onset groups using insulin[122]. In the ETDRS, higher levels of serum lipids (triglycerides, LDL cholesterol, and VLDL cholesterol) were associated with increased risk of developing hard exudates in the macula[123].

Cigarette Smoking

Smoking is known to cause tissue hypoxia by increasing blood carbon monoxide levels[124]. Additionally, smoking may lead to increased platelet aggregation and adhesiveness[125,126]. Both of these mechanisms are postulated to explain, in part, the association of cigarette smoking with development of myocardial infarction and peripheral vascular disease. However, most epidemiologic data show no relationship between cigarette smoking and diabetic retinopathy (Table 14.24)[19,20,50,52,61,64,68,69,126,127]. In the WESDR, cigarette smoking was not associated with the 4-year incidence or progression of diabetic retinopathy[127]. Despite the lack of an association, diabetic patients should be advised not to smoke because of an increased risk of cardiovascular and respiratory disease as well as cancer. In the WESDR, after controlling for other risk factors, younger-onset people who smoked were 2.4 times and older-onset people were 1.6 times as likely to die as those who did not smoke[43].

Alcohol

There are few epidemiologic studies on the relationship of alcohol consumption to diabetic retinopathy[128-130]. One might anticipate a possible protective effect of alcohol as a result of decreased platelet aggregation and adhesiveness[131]. Data from one study suggested a beneficial effect of alcohol while another study suggested an increased risk of proliferative retinopathy in people with diabetes[128,129]. In the WESDR, alcohol consumption was associated with a lower frequency of proliferative retinopathy in the younger-onset group[130]. However, there was no relationship between alcohol consumption at the 4-year examination and the incidence and progression of retinopathy in either the younger- or older-onset groups at the 10-year followup.

Body Mass Index

There has been no consistency in the relationship between diabetic retinopathy and body mass index among various studies investigating this[10,50,52,70,132,133]. In the WESDR, body mass was inversely related to the presence or severity of diabetic retinopathy only in the older-onset people not using insulin. However, it was not predictive of the 4-year incidence or progression of retinopathy.

Physical Activity

Few epidemiologic data are available describing the relationship between diabetic retinopathy and physical activity[133,134]. An earlier study suggested no relationship between participation in team sports in high school and college and a history of laser treatment or blindness in people with IDDM[133]. In the WESDR, in women diagnosed to have diabetes at age <14 years, those who participated in team sports were less likely to have proliferative diabetic retinopathy than those who did not. There was no association between physical activity or leisure time energy expenditure and the presence and severity of diabetic retinopathy in men[134].

Socioeconomic Status

Inconsistent relationships between socioeconomic status and retinopathy severity have been reported[50,135,136]. A significant correlation was found between proliferative retinopathy and occupational status (working class) or a lower income in a case-control study of 49 people with IDDM[135]. However, there was no relationship between lower socioeconomic status, measured using a combination of the Duncan Socioeconomic Index, educational attainment, and income, to more severe retinopathy in 343 Mexican Americans and 79 non-Hispanic whites with NIDDM in San Antonio[136]. Neither was a relationship observed between retinopathy severity and education level in a population of Oklahoma Indians with NIDDM[50].

In the WESDR, with the exception of a positive association of lower incidence of proliferative retinopathy with more education in younger-onset women age ≥25 years, socioeconomic status (education level and Duncan Socioeconomic Index score) was not associated with increased risk of developing proliferative

retinopathy[32]. The reason for not finding a relationship of socioeconomic status with retinopathy severity in these studies may be because hyperglycemia, which may be causally related to retinopathy, was not related to socioeconomic status in the WESDR.

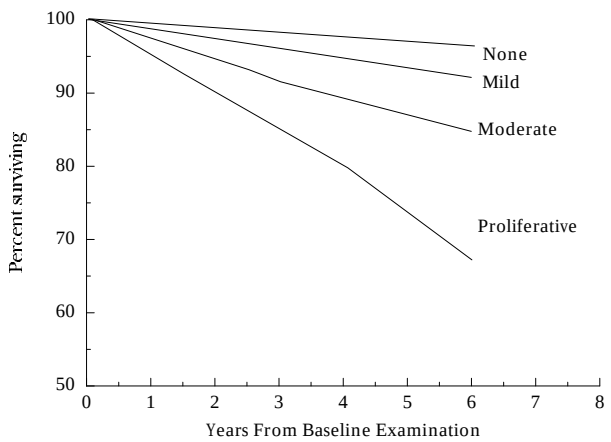
Pregnancy

Data from epidemiologic studies suggest that pregnancy is a significant predictor of progression of diabetic retinopathy[137]. In a case-control study of women with IDDM, the frequency of progression to proliferative retinopathy was higher in those who were pregnant compared with those who were not (7.3% versus 3.7%)[138]. Women in this study were similar in age, duration of diabetes, and retinopathy status at baseline. Pregnancy remained a significant predictor of the progression of diabetic retinopathy after controlling for glycosylated hemoglobin and diastolic blood pressure. Severe retinopathy is also a risk indicator for higher risk of congenital abnormalities in children born of mothers with IDDM[139].

CO-MORBIDITY AND MORTALITY

In the WESDR, the risk of developing a heart attack, stroke, diabetic nephropathy, and amputation was higher in those with proliferative diabetic retinopathy compared with those with no or minimal nonproliferative retinopathy at baseline[140]. This is consistent with the association of severe retinopathy with cardiovascular disease risk factors such as increased fibrinogen, increased platelet aggregation, hyperglycemia, and hypertension.

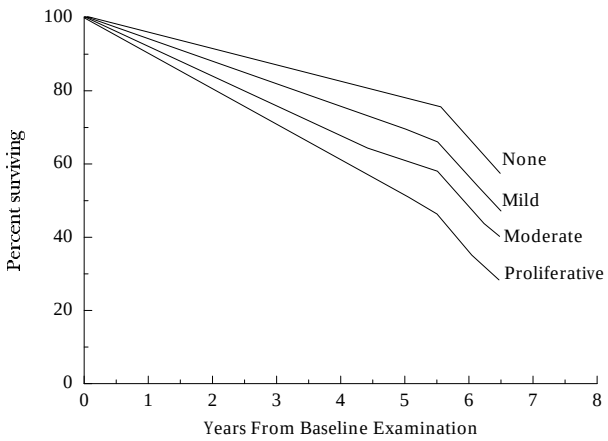
Figure 14.19
Survival Among Patients with Diabetes Diagnosed at Age <30 Years by Retinopathy Status at Baseline Examination



Survival is adjusted for age and sex. Data are from the Wisconsin Epidemiologic Study of Diabetic Retinopathy, 1980-86.

Source: Reference 43

Figure 14.20
Survival Among Patients with Diabetes Diagnosed at Age ≥30 Years by Retinopathy Status at Baseline Examination



Survival is adjusted for age and sex. Data are from the Wisconsin Epidemiologic Study of Diabetic Retinopathy, 1980-86.

Source: Reference 43

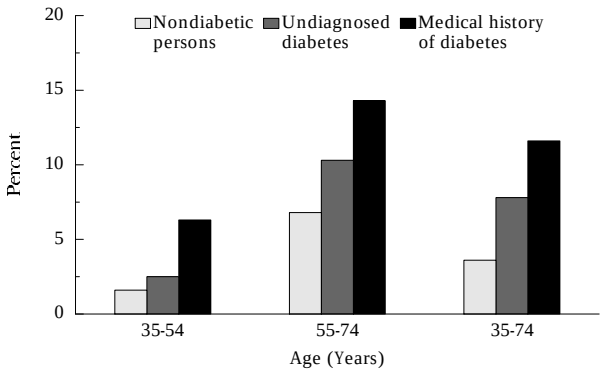
The ETDRS demonstrated that aspirin, when needed for the prevention of myocardial infarction or stroke, does not increase the risk of vitreous hemorrhage or loss of vision in people with proliferative retinopathy[141]. Aspirin was not found to prevent the progression of retinopathy in the ETDRS and in the WESDR[141,142].

In the WESDR, increasing severity of retinopathy at baseline was associated with decreased survival over a 6-year period in both younger- and older-onset groups (Figures 14.19 and 14.20)[43]. This had been reported by others[42] and is consistent with the association of severe retinopathy with the incidence of cardiovascular disease and diabetic nephropathy described above.

CATARACT

Cataracts are frequent in older Americans and were one of the most common causes of decreased visual acuity in older-onset subjects in the WESDR[7]. They were responsible for more decrease in vision than diabetic retinopathy in older-onset persons. Cataracts are common in both diabetic and nondiabetic subjects and increase with increasing age in all persons[7]. Interview data collected during the NHANES II and the 1989 NHIS indicate the frequency of cataracts and the

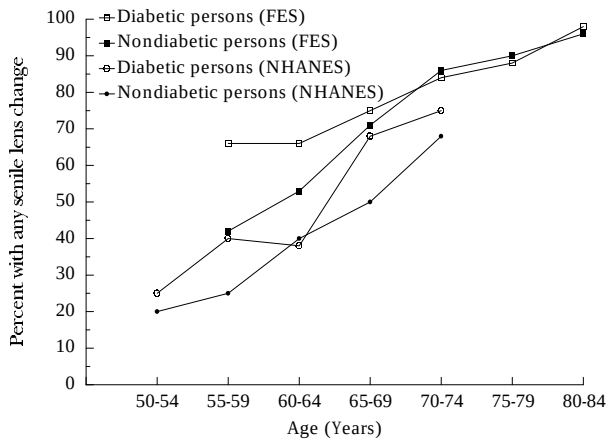
Figure 14.21
Prevalence of Self-Reported History of Cataracts According to Diabetes Status, U.S., 1976-80



Undiagnosed diabetes determined by oral glucose tolerance test; nondiabetic status ascertained by medical history and oral glucose tolerance test.

Source: Harris MI: National Diabetes Data Group. Unpublished data from the 1976-80 Second National Health and Nutrition Examination Survey

Figure 14.22
Prevalence of Senile Lens Changes in Diabetic and Nondiabetic Persons According to Age



FES, Framingham Eye Study; NHANES, 1970-75 First National Health and Nutrition Examination Survey.

Source: Reference 143

relative importance of age and diabetes status (Figure 14.21 and Table 14.36).

Rates of cataract determined at an ophthalmologic examination in the NHANES I and the FES populations also increased with increasing age (Figure 14.22 and Table 14.37)[143]. In the FES, rates for diabetic persons in the youngest age group were higher than for nondiabetic persons; there was little difference in older persons. In the NHANES I population, rates in diabetic persons were higher than in nondiabetic persons.

In the WESDR, cataract was determined by slip lamp examination and graded by comparison with standard photographs[144]. In the younger- and older-onset persons, rates of cataract in females were slightly higher than in males (Table 14.38).

Lens opacities of any sort are often referred to as cataract, despite the fact that different anatomic locations in the lens may be involved. There appear to be differences in the frequencies and severity of specific lens opacities in people with diabetes. In the Beaver Dam Eye Study, lenses were photographed with cameras specifically designed to image specific sites of lens opacities[145]. Photographs were graded according to standard protocols and graders were masked to subject characteristics. In that study, after adjusting for age and sex, cortical opacities were significantly

Table 14. 36
Prevalence of Self-Reported Cataracts and Glaucoma by Diabetes Status, U.S., 1989

	All adults with diabetes		IDDM		NIDDM		Adults without diabetes	
	No.	%	No.	%	No.	%	No.	%
Age ≥18 years								
Cataracts	2,372	22.42	123	5.77	2,239	23.40	3,364	3.30
Glaucoma	2,376	6.98	122	2.23	2,244	7.29	3,364	0.85
Age 18-44 years								
Cataracts	351	3.80	101	5.19	246	3.24	1,888	0.48
Glaucoma	352	1.85	101	2.66	247	1.51	1,888	0.09
Age 45-64 years								
Cataracts	972	11.92	19	0.00	949	12.09	836	1.58
Glaucoma	969	4.30	18	0.00	947	4.40	836	0.78
Age ≥65 years								
Cataracts	1,049	38.37	3		1,044	38.27	640	16.56
Glaucoma	1,055	11.18	3		1,055	11.23	640	3.79

Source: Harris MI: National Diabetes Data Group. Unpublished data from the National Health Interview Survey, 1989

more common among people with older-onset diabetes compared with the rest of the Beaver Dam population (Table 14.39)[145].

Posterior subcapsular cataract was also more common in people with diabetes, but the increase was not significant in all age groups. Longer duration of diabetes was associated with increased odds of all kinds of age-related cataract but was significant only for cortical opacity (Table 14.40).

With regard to risk factors for prevalent cataract in people with diabetes in the WESDR, multivariate analyses indicated that age or duration of diabetes were the most important risk factors[144] (Table 14.41), with the severity of diabetic retinopathy associated with a small but significant further increase in risk. In younger-onset persons, diuretic use and glycosylated hemoglobin were also associated with increased risk. In older-onset persons, diuretic use, intraocular pressure, smoking status (current, ex-, or never smokers) and diastolic blood pressure were associated with increased risk of cataract.

Cataract extraction with lens implant (pseudophakia) or without (aphakia) is a frequent occurrence in people with diabetes. In prevalence data from the WESDR, 3.6% of younger-onset and 8.7% of older-onset persons had had such surgery[144] (Table 14.42). Rates increased with current age. In the Beaver Dam Eye Study, there were higher frequencies of past cataract surgery in people with diabetes in each age group[145] (Table 14.43).

Table 14.38
Rates of Cataract* for Younger- and Older-Onset Diabetic Persons by Sex and Age, WESDR, 1980-82

Age (years)	Females %	Females No.	Males %	Males No.
Younger-onset				
0-19	4.8	6/126	2.1	3/140
20-29	15.2	22/145	13.4	20/149
30-44	39.4	54/137	29.4	42/143
≥45	87.1	61/70	92.4	61/66
Total	29.9	143/478	25.3	126/498
Older-onset				
30-54	60.8	62/102	56.7	59/104
55-64	86.9	159/183	76.3	132/173
65-74	94.7	233/246	94.0	202/215
≥75	98.5	192/195	97.8	133/136
Total	89.0	646/726	83.8	526/628

* Includes cases of surgical aphakia. WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy; younger-onset, diabetes diagnosed at age <30 years.; older-onset, diabetes diagnosed at age ≥30 years.

Source: Reference 144

Table 14.37
Lens Changes by Age and Diabetic Status in Two Study Populations

Lens change	Framingham, MA: With diabetes No.	Framingham, MA: With diabetes %	Framingham, MA: Without diabetes No.	Framingham, MA: Without diabetes %	NHANES I: With diabetes No.	NHANES I: With diabetes %	NHANES I: Without diabetes No.	NHANES I: Without diabetes %
Age 50-64 years								
All persons	97	100.0	1,091	100.0	79	100.0	930	100.0
No senile lens change	36	37.1	593	54.4	52	65.8	678	72.9
Any senile lens change	61	62.9	498	45.6	27	34.2	252	27.1
Aphakia	3	3.1	14	1.3	2	2.5	8	0.9
Cataract†	4	4.1	11	1.0	8	10.1	31	3.3
Pre-cataract	54	55.7	473	43.4	17	21.5	213	22.9
Age 65-74 years								
All persons	87	100.0	666	100.0	162	100.0	1,476	100.0
No senile lens change	19	21.8	151	22.7	48	29.6	635	43.0
Any senile lens change	68	78.2	515	77.3	114	70.4	841	57.0
Aphakia	2	2.3	13	2.0	13	8.0	47	3.2
Cataract†	6	6.9	49	7.4	52	32.1	299	20.3
Pre-cataract	60	69.0	453	68.0	49	30.2	495	33.5
Age 75-85 years								
All persons	49	100.0	327	100.0				
No senile lens change	4	8.2	27	8.3				
Any senile lens change	45	91.8	300	91.7				
Aphakia	4	8.2	30	9.2				
Cataract†	13	26.5	72	22.0				
Pre-cataract	28	57.1	198	60.5				

The youngest Framingham subject was age 52 years; NHANES I, 1970-75 National Health and Nutrition Examination Survey; diabetes determined by medical history in both populations. † Excluding aphakia.

Source: Reference 143

Table 14.39
Prevalence of Lens Opacity from Gradings of Photographs by Diabetes Status, Beaver Dam Eye Study, 1988-90

Age (years)	Type of lens opacity	No diabetes (%)	Diabetes (%)	RR (95% CI)
		(n=1,441)	(n=66)	
43-54	Cortical	1.3	6.1	4.7 (1.6-13.4)
	Posterior subcapsular	1.7	0.0	
	Nuclear	0.4	3.4	15.3 (4.4-53.2)
		(n=1,168)	(n=120)	
55-64	Cortical	10.4	16.7	1.6 (1.0-2.5)
	Posterior subcapsular	3.9	8.3	2.1 (1.1-4.1)
	Nuclear	8.0	6.3	0.8 (0.4-1.6)
		(n=1,077)	(n=39)	
65-74	Cortical	24.6	31.7	1.3 (1.0-1.7)
	Posterior subcapsular	8.1	10.8	1.3 (0.8-2.2)
	Nuclear	40.7	38.2	0.9 (0.8-1.2)
		(n=611)	(n=76)	
≥75	Cortical	41.7	52.6	1.3 (1.0-1.6)
	Posterior subcapsular	14.1	15.8	1.1 (0.7-2.0)
	Nuclear	81.3	76.0	0.9 (0.8-1.1)

RR, relative risk; CI, confidence interval.

Source: Reference 145

Long-term incidence data are sparse with regard to cataract surgery among diabetic patients. Table 14.44 indicates the 10-year incidence of such surgery in subjects in the WESDR[146]. Current age is systematically associated with increased frequency of surgery (Table 14.45). The data show the high frequency of cataract surgery in diabetic subjects.

Multivariate analyses of risk factors for incidence of cataract surgery were performed on data from the WESDR[146] (Table 14.46). For younger-onset persons, older age, past history of laser therapy, presence of proteinuria, higher glycosylated hemoglobin, and taking aspirin daily were associated with increased risk of cataract surgery. For older-onset persons, aside from older age, only use of insulin was associated with increased risk of cataract surgery.

Table 14.40
Relationship of Lens Opacity in Either Eye to Duration of Diabetes and Glycosylated Hemoglobin in Diabetic Subjects, Beaver Dam Eye Study, 1988-90

	Cortical		Posterior subcapsular		Nuclear	
	OR	CI	OR	CI	OR	CI
Duration of diabetes, 5 years	1.15	1.03,1.29	1.12	0.97,1.28	1.08	0.95,1.22
Glycosylated hemoglobin, %	0.99	0.92,1.07	0.98	0.87,1.09	0.97	0.89,1.06

OR, odds ratio; CI, 95% confidence interval. Data are from logistic regression adjusted for age.

Source: Reference 145

In summary, there is evidence of increased risk of cataracts or lens opacities and of cataract surgery in people with diabetes. Although some data suggest a relationship between level of glucose control and risk of cataract surgery, it is unlikely that even if tighter glycemic control were feasible, risk would be reduced to the usual age-related rates. Thus, it is necessary for

Table 14.41
Logistic Regression of Risk Factors for Cataract, WESDR, 1980-82

	Entropy*	Change in entropy
Younger-onset		
Duration	0.38	0.38
Age at exam	0.41	0.03
Retinopathy	0.43	0.02
Diuretic (never, ex-user, current user)	0.43	0.01
Glycosylated hemoglobin	0.44	0.01
Older-onset		
Age at exam	0.20	0.20
Retinopathy	0.22	0.02
Diuretic (never, ex-user, current user)	0.23	0.01
Intraocular pressure	0.24	0.01
Smoking	0.25	0.01
Diastolic blood pressure	0.25	0.003

Younger-onset, diabetes diagnosed at age <30 years; 618 no cataract, 219 with cataract; older-onset, diabetes diagnosed at age ≥30 years, 145 no cataract, 968 with cataract; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy. * In order to evaluate the goodness of fit of the model to the data, an index, "entropy" is used. Entropy is a function of the log likelihood of the current model compared with a model in which no variables had been considered, i.e., the prevalence. This index is analogous to the R^2 values for multiple linear regression.

Source: Reference 144

Table 14.42

Prevalence of Surgical Aphakia in Either Eye by Age and Sex, WESDR, 1980-82

	Age (years)									
	0-19		20-29		30-44		≥45		Total	
	%	No.	%	No.	%	No.	%	No.	%	No.
Younger-onset										
Female	1.6	2/126	0.7	1/149	5.0	7/139	17.1	12/70	4.5	22/484
Male	0	0/146	1.3	2/152	3.4	5/146	10.4	7/67	2.7	14/511
Total	0.7	2/272	1.0	3/301	4.2	12/285	13.9	19/137	3.6	36/995
	30-54		55-64		65-74		≥75		Total	
	%	No.	%	No.	%	No.	%	No.	%	No.
Older-onset										
Female	1.9	2/106	6.0	11/184	10.4	26/249	14.7	29/197	9.2	68/736
Male	3.8	4/104	4.0	7/174	11.0	24/219	11.7	16/137	8.0	51/634
Total	2.9	6/210	5.0	18/358	10.7	50/468	13.5	45/334	8.7	119/1,370

Younger-onset, diabetes diagnosed at age <30 years; older-onset, diabetes diagnosed at age ≥30 years; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

Source: Reference 144

Table 14.43

Frequency of Cataract Surgery in Either Eye by Age and Diabetes Status, Beaver Dam Eye Study, 1988-90

Age (years)	No diabetes		Diabetes		
	No.	%	No.	%	RR (95% CI)
43-54	1,454	0.8	66	1.5	1.9 (0.3, 14.4)
55-64	1,188	1.7	128	5.5	3.2 (1.4, 7.5)
65-74	1,130	4.1	153	9.8	2.4 (1.4, 4.2)
≥75	709	14.2	98	24.4	1.7 (1.2, 2.5)

RR, relative risk; CI, confidence interval.

Source: Reference 145

Table 14.44

Ten-Year Incidence of Cataract Surgery in Diabetic Persons, WESDR, 1980-92

	No.	%	95% CI
Younger-onset (age ≥18)	685	8.5	6.2, 10.8
Older-onset	925	24.9	21.3, 28.5

Younger-onset, diabetes diagnosed at age <30 years; older-onset, diabetes diagnosed at age ≥30 years; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy; CI, confidence interval.

Source: Reference 146

Table 14.45

Ten-Year Incidence of Cataract Surgery in Diabetic Persons by Age, WESDR, 1980-92

Age (years)	No.	Incidence (%)
Younger-onset		
18-24	218	3.7
25-34	262	6.1
35-44	113	9.7
≥45	92	27.6
Older-onset		
30-54	184	14.7
55-64	283	21.0
65-74	309	31.7
≥75	149	44.3

Test for trend with age: younger-onset (diabetes diagnosed at age <30 years), p<0.0001, older-onset (diabetes diagnosed at age ≥30 years), p<0.0005. WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

Source: Reference 146

Table 14.46

Odds Ratio for 10-Year Incidence of Cataract Surgery for a Specified Change in Baseline Characteristic, WESDR, 1980-92

Characteristic	Change	p	Odds ratio	95% CI
Younger-onset				
Age	10 years	<0.0001	2.35	1.73, 3.20
Laser history	present	<0.005	3.28	1.44, 7.45
Proteinuria	present	<0.005	3.21	1.43, 7.20
Glycosylated hemoglobin	1%	<0.05	1.21	1.02, 1.45
Aspirin/day	taking	<0.05	2.44	1.02, 5.84
Older-onset				
Age	10 years	<0.0001	1.79	1.47, 2.18
Insulin	taking	<0.0005	2.11	1.43, 3.11

CI, confidence interval; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy; younger-onset, diabetes diagnosed at age <30 years; older-onset, diabetes diagnosed at age ≥30 years.

Source: Reference 146

health care planners to be mindful of the costs and services associated with increased rates of cataract surgery and post-surgical rehabilitation (post-operative recovery time, new spectacles, etc.) in people with diabetes.

GLAUCOMA

Glaucoma is a condition in which there is evidence of optic nerve damage attributed to intraocular pressure that is presumably too high for a particular eye. Data from the NHANES II indicate that diabetic persons age ≥35 years reported substantially higher rates of glaucoma than did the nondiabetic U.S. population (Figure 14.23). Rates of glaucoma increased with increasing age, with the highest reported rates occurring in persons age ≥55 years. Similar relationships were found for diabetic subjects in the 1989 NHIS (Table 14.36).

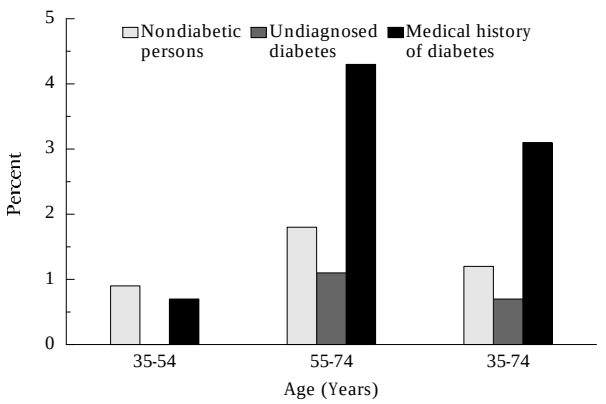
Glaucoma has been defined in different ways in different studies. Some researchers include as cases all those with a history of glaucoma irrespective of treatment status. Some include only those with a history of medical or surgical intervention, while others depend on defined objective criteria. Another consideration to bear in mind when reviewing published data is that some studies make no distinction between the various types of glaucoma (open angle, closed angle, rubeotic, or other primary or secondary types of glaucoma).

In the Beaver Dam Eye Study, definite glaucoma was defined by the presence of at least two of the following three characteristics: abnormal visual field, large or asymmetric cupping of the optic nerve, and an intraocular pressure greater than 21 mmHg[147]. Probable glaucoma was defined as a history of medical treatment or surgery for glaucoma with fewer than two of the above criteria. In a multiple logistic regression model, after controlling for age and sex, the relationship of the presence of older-onset diabetes to glaucoma was evaluated. Diabetes was associated with a modest increase in risk of definite and probable glaucoma that was only statistically significant for definite glaucoma (controlling for age and sex) (Table 14.47)[147].

In the WESDR, self-reported incidence of glaucoma was evaluated in both younger- and older-onset diabetes. Follow-up evaluations were done 4 and 10 years after the original evaluation. Using the product limit method to adjust for study attrition, the 10-year incidence of glaucoma in the younger-onset group was estimated to be 3.7% (95% CI 2.3,5.1). The estimated incidence in the older-onset group not taking insulin was 6.9% (95% CI 3.9,9.8); in those taking insulin it was 11.8% (95% CI 7.9,15.7) (Klein BEK et al., unpublished data).

The 10-year incidence of glaucoma varied with age (Figure 14.24). In older- as well as younger-onset persons, rates increased with age, although only in the latter group was the relationship significant. The decrease noted at the oldest age in older-onset persons may be the result of mortality in these people (Klein BEK et al., unpublished data).

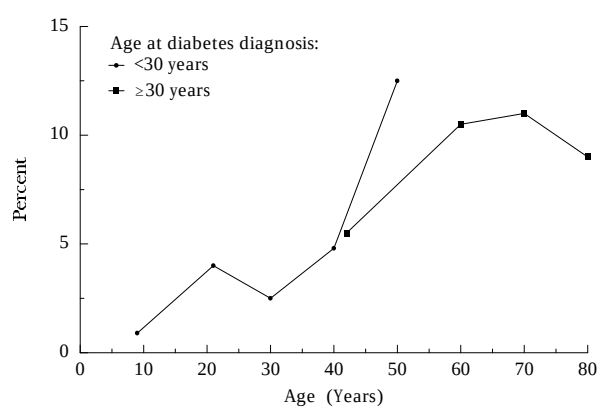
Figure 14.23
Prevalence of Self-Reported History of Glaucoma According to Diabetes Status, U.S., 1976-80



Undiagnosed diabetes determined by oral glucose tolerance test; nondiabetic status ascertained by medical history and oral glucose tolerance test.

Source: Harris MI: National Diabetes Data Group. Unpublished data from the 1976-80 Second National Health and Nutrition Examination Survey

Figure 14.24
Ten-Year Incidence of History of Glaucoma for Persons with Diabetes Diagnosed at Age <30 or ≥30 Years, by Age



Test for trend: p<0.005, age <30 years; p=0.88, age ≥30 years.

Source: Klein BEK: Unpublished data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy

Table 14.47

Frequency of Glaucoma in Older-Onset Diabetic Subjects, Beaver Dam Eye Study, 1988-90

Older-onset diabetes status	No. at risk	Definite glaucoma %	p	Probable glaucoma %	p	Combined %	p
Both sexes							
No diabetes	4,420	2.0	0.004	1.9	0.031	3.9	0.0005
Diabetes	426	4.2		3.5		7.8	
Women							
No diabetes	2,480	2.0	0.009	2.5	0.133	4.4	0.002
Diabetes	240	5.0		4.2		9.2	
Men							
No diabetes	1,940	1.9	0.266	1.2	0.091	3.1	0.052
Diabetes	186	3.2		2.7		5.9	
Both sexes							
43-54 years							
No diabetes	1,443	1.0	0.44	0.2	1.00	1.2	0.504
Diabetes	57	1.8		0.0		1.8	
55-64 years							
No diabetes	1,171	1.4	1.00	1.3	0.244	2.7	0.768
Diabetes	124	0.8		2.4		3.2	
65-74 years							
No diabetes	1,108	2.3	0.014	2.4	0.110	4.7	0.005
Diabetes	149	6.0		4.7		10.7	
≥75 years							
No diabetes	698	4.4	0.207	5.6	1.00	10.0	0.474
Diabetes	96	7.3		5.2		12.5	

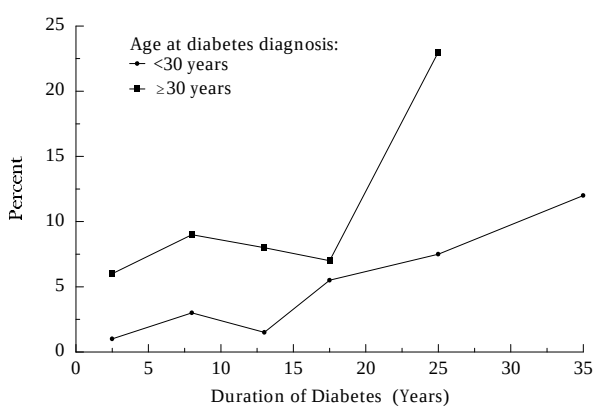
Multiple logistic analyses of glaucoma and diabetes	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Diabetes	1.84	1.09, 3.11	0.02	1.47	0.83, 2.59	0.184	1.68	1.14, 2.50	0.01

Univariate significance tested by chi-square test. Multivariate analysis was controlled for age and sex. Definite glaucoma and probable glaucoma are defined in the text. CI, confidence interval; OR, odds ratio.

Source: Reference 147

Figure 14.25

Ten-Year Incidence of History of Glaucoma in Persons with Diabetes Diagnosed at Age <30 or ≥30 Years, by Diabetes Duration



Test for trend: p<0.001, age <30 years; p<0.005, age ≥30 years.

Source: Klein BEK: Unpublished data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy

The relationship of duration of diabetes to glaucoma is seen in Figure 14.25. The relationship is significant in both groups. To evaluate the effects of several characteristics on the presence of glaucoma, multiple logistic regression analyses were used. The variables included were age, sex, glycosylated hemoglobin, duration of diabetes, systolic blood pressure, diastolic blood pressure, body mass index, and presence of proteinuria. In younger-onset persons, only age was significantly related to glaucoma; the odds ratio was 1.7 (95% CI 1.2,2.3) for 10 years of age. For older-onset persons, only duration of diabetes was associated with a significantly increased risk (odds ratio 1.8, 95% CI 1.3,2.6) for each 10 years duration (Klein BEK et al., unpublished data).

In summary, these data suggest an increased risk of open angle glaucoma associated with diabetes. In addition, among people with older-onset diabetes, increasing duration is associated with increased risk. Although some of this excess may be related to greater surveillance of people with diabetes, it is unlikely to be the entire explanation.

RESEARCH NEEDS

Pathologic mechanisms responsible for increased glaucoma risk should be investigated. Population-based incidence data using objective diagnostic criteria are needed to evaluate the actual incidence of glaucoma so as to anticipate the need for care. This will also permit an estimate of rates that are not from self reports and can therefore be relatively free of surveillance bias.

CORNEAL DISEASE

Epidemiologic data concerning corneal problems in diabetic persons is lacking. In a study of 81 insulin-dependent patients attending a university hospital outpatient clinic, diabetic patients had significantly greater mean corneal thickness, measured by pachometry, than a nondiabetic group[148]. Among diabetic patients, those with proliferative retinopathy had higher mean values than patients without retinopathy or those without proliferative changes. There were a similar number of corneal endothelial cells in diabetic and nondiabetic persons. In 89 diabetic patients followed at a university eye clinic, corneal epithelial defects were found in 64% of the patients, with lesions occurring more frequently in NIDDM compared with IDDM patients[149]. Forty-seven percent of eyes were said to have "decreased" tear production and 23% had "reduced" corneal sensation. Data were not provided for a matched nondiabetic control group.

In the Beaver Dam Eye Study, all persons were examined for the possibility of corneal abnormalities, including current corneal (and conjunctival) infections, scars, and other abnormalities. There was no difference between those with and without diabetes with regard to these findings (Klein BEK et al., unpublished data).

RESEARCH NEEDS

It is important to determine the risk of corneal infections (corneal ulcers), scar formation, and degeneration that may follow surgical treatment (cataracts, vitreal and retinal surgery), and that may, themselves, lead to visual impairment.

HEALTH CARE DELIVERY

In the 1973 NHIS, participants age >40 years were asked, "How long has it been since you had a test for glaucoma?" No distinction was made between care by an ophthalmologist or an optometrist. Diabetic persons were more likely to have had a glaucoma test than nondiabetic persons (Table 14.48). Over 32% of diabetic patients stated that they had never had an eye pressure test.

In the 1989 NHIS, participants age ≥18 years were asked if they had a dilated eye examination in the past year. Only 49% (57% of people with IDDM, 55% of insulin-treated people with NIDDM, and 44% of people with NIDDM not treated with insulin) reported a dilated eye examination within a year of the interview (Table 14.49)[5]. People with NIDDM were more likely to have had a dilated eye examination if they were older, had a higher socioeconomic status, and had attended a diabetes education class. Receiving a dilated eye examination was not related to race, duration of diabetes, frequency of physician visits for diabetes, or health insurance.

In the 1989 NHIS, 69% of people with IDDM and 61% of people with NIDDM reported that they had an eye examination within one year of the survey (Table 14.49). Of all adults with diabetes, 45% reported they had seen an ophthalmologist in the past 12 months.

In the WESDR, participants were queried as to whether they had been seen by an ophthalmologist,

Table 14.48
Frequency of Vision Tests, U.S., 1973

	Age 40-64		Age ≥65	
Frequency of test	Diabetic %	Non-diabetic %	Diabetic %	Non-diabetic %
Last glaucoma test				
Never had a test	35.7	38.5	32.6	40.0
Test within the past year	29.1	23.7	31.0	24.5
Within past 2 years	39.6	34.6	41.3	33.4
2-5 years ago	16.2	17.4	15.0	15.9
>5 years ago	4.4	4.2	6.8	5.8
Last eye exam				
Never had a test	3.1	4.1	2.0	3.4
Test within the past year	39.4	35.9	37.5	33.5
Within past 2 years	56.8	54.4	52.4	48.1
2-5 years ago	29.1	30.1	27.3	30.7
>5 years ago	9.3	9.0	15.6	15.1

Source: Drury, TF: Unpublished data from the 1973 National Health Interview Survey, National Center for Health Statistics

Table 14.49
Frequency of Ophthalmic Care, U.S., 1989

Frequency of test	Age group (years)	All people with diabetes		IDDM		NIDDM	
		No.	%	No.	%	No.	%
Ever had photos	≥18	2,121	27.53	115	40.07	1,996	26.68
taken of retina	18-44	317	25.75	93	34.96	220	21.43
	45-64	881	25.68	19	61.59	858	24.73
	≥65	923	29.90	3		918	29.74
Ever had laser treatment	≥18	2,296	6.57	122	19.22	2,164	5.67
	18-44	348	8.08	100	18.50	244	3.00
	45-64	946	6.75	19	20.80	923	6.25
	≥65	1,002	5.88	3		997	5.80
Seen ophthalmologist	≥18	2,386	44.72	123	54.35	2,253	44.14
in past 12 months	18-44	352	40.94	101	55.08	247	34.71
	45-64	973	41.83	19	58.04	950	41.44
	≥65	1,061	48.63	3		1,056	48.76
Dilated eye examination:							
≤12 months	≥18	2,282	48.51	120	56.93	2,153	47.96
	18-44	346	45.06	98	57.38	244	39.52
	45-64	935	45.81	19	62.63	913	45.38
	≥65	1,001	52.23	3		996	52.38
13-24 months	≥18	2,282	17.41	120	22.51	2,153	17.17
	18-44	346	16.87	98	23.87	244	14.05
	45-64	935	20.59	19	13.73	913	20.82
	≥65	1,001	14.68	3		996	14.66
≥24 months	≥18	2,282	20.91	120	13.26	2,153	21.30
	18-44	346	20.84	98	14.61	244	24.26
	45-64	935	18.42	19	14.13	913	18.45
	≥65	1,001	23.21	3		996	23.13
Any eye examination:							
≤12 months	≥18	2,399	61.39	124	68.93	2,265	60.97
	18-44	355	57.29	102	68.44	249	52.34
	45-64	977	60.73	19	81.68	954	60.33
	≥65	1,067	63.39	3		1,062	63.59
13-24 months	≥18	2,388	17.96	123	21.03	2,255	17.84
	18-44	353	20.06	101	21.08	248	19.77
	45-64	974	19.40	19	13.97	951	19.59
	≥65	1,067	15.94	3		1,062	15.84
≥24 months	≥18	2,388	20.38	123	9.48	2,255	20.93
	18-44	353	22.35	101	9.81	248	27.70
	45-64	974	19.69	19	4.35	951	19.90
	≥65	1,061	20.32	3		1,062	20.22

Source: Harris, MI, from the 1989 National Health Interview Survey; Reference 5

and, if so, when they were last seen[150]. Those who were never seen by an ophthalmologist were asked if they had received optometric care. Sixty-three percent of younger-onset and 50% of older-onset diabetic persons had seen an ophthalmologist within the past 2 years; 25% of younger- and 36% of older-onset persons had never had an ophthalmologic examination (Table 14.50). Approximately 90% of younger-onset and 93% of older-onset persons with DRS high-risk characteristics for visual loss had been examined in the 2 years prior to the survey.

Because proliferative retinopathy is usually initially asymptomatic and may require treatment to prevent severe visual loss, it is necessary that it be diagnosed correctly. Internists, diabetologists, and senior medical residents were found to correctly diagnose the presence of proliferative retinopathy in 49% of cases they examined, whereas ophthalmologists and retinal specialists correctly diagnosed its presence in 96% of cases (Table 14.51)[151]. Using direct and indirect ophthalmoscopy, well-trained nonophthalmologists and an ophthalmologist specializing in retinal diseases were found to have a high rate of detection of proliferative retinopathy[152].

The accuracy of detection of retinopathy by 1) well-trained diabetologists and endocrinology fellows using ophthalmoscopy through an undilated pupil, 2) ophthalmologists using ophthalmoscopy through a dilated pupil, and 3) grading of nonmydriatic photographs was compared with detection of retinopathy by

Table 14.50
Frequency of Eye Care for Diabetic Persons in Southern Wisconsin, WESDR, 1980-82

	Younger-onset		Older-onset	
	No.	%	No.	%
Eye care for diabetic patients				
Ophthalmologic examination				
Within 2 Years	632	63.0	685	50.0
>2 Years	108	11.0	170	12.0
Never saw ophthalmologist				
Optometric examination	172	17.0	456	33.0
No optometric examination	81	8.0	40	3.0
Questionable status	2	0	19	1.0
Eye care for persons with proliferative diabetic retinopathy with DRS HRC				
Ophthalmologic examination				
Within 2 Years	43	90.0	25	93.0
>2 Years	2	4.0	1	4.0
Never saw ophthalmologist				
Optometric examination	3	6.0	1	4.0
No optometric examination	0	0	0	0
Questionable status	0	0	0	0

WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy; younger-onset, diabetes diagnosed at age <30 years; older-onset, diabetes diagnosed at age ≥30 years; DRS HRC, Diabetic Retinopathy Study high-risk characteristics for visual loss.

Source: Reference 150

Table 14.52
Recommendation for Eye Care for Diabetic Patients

Primary-care physician informs patient at time of diagnosis of diabetes that:

- Ocular complications are associated with diabetes and may threaten sight
- Timely detection and treatment may reduce the risk of decreased vision

Referral to an eye doctor competent in ophthalmoscopy:

- Patients age 10-30 years with diabetes duration ≥5 years: annual referral
- Patients diagnosed at age ≥30 years: referral at the time of diagnosis or shortly thereafter

Referral to an ophthalmologist:

- All women with IDDM planning pregnancy within 12 months, in the first trimester, and thereafter at the discretion of the ophthalmologist
- Patients found to have reduced corrected visual acuity, elevated intraocular pressure, and any other vision-threatening ocular abnormalities

Source: Reference 160

grading of seven field stereoscopic fundus photographs[153]. Nonophthalmologists missed all cases of macular edema and most cases of proliferative retinopathy; however, they did detect other lesions that accompany severe retinopathy. Nonmydriatic photography was similar to direct ophthalmoscopy. In both this study and another[154], the most sensitive method for detection of retinopathy was fundus photography. For this reason, it was suggested that if any signs of retinopathy are detected or if visual acuity is worse than 20/30, referral to an ophthalmologist be required[153]. Fundus photography was advised because it is the "most sensitive means of detecting clinically significant retinopathy." Data from a number of studies suggest that, in the absence of trained ophthalmoscopists or ophthalmologists, nonmydriatic cameras may provide an alternative screening approach for detection of retinopathy in people with diabetes[152,155]. Current guidelines for detection of diabetic retinopathy are presented in Table 14.52.

Prevalence rates of reported photocoagulation in the

Table 14.51
Characteristics of Diagnosis During Ophthalmoscopic Examination for Proliferative Diabetic Retinopathy, by Physician Specialty

	% correctly diagnosed as having proliferative retinopathy (Mean ± SD)	% correctly diagnosed as not having proliferative retinopathy (Mean ± SD)	Predictive value* (%)	
			Positive	Negative
Internists, diabetologists, and senior medical residents	49 ± 5	84 ± 5	9	98
Ophthalmologists and retinal specialists	96 ± 2	93 ± 3	29	99
Statistical significance	p<0.001	p=0.057		

* The predictive value of the positive statement is the probability of physicians who say proliferative diabetic retinopathy is present when it is; the negative value is those who say it is not present when it is not. Assumes the prevalence of proliferative retinopathy to be 3%, which is an estimate of the actual prevalence of this diagnosis in diabetic patients.

Source: Reference 151

Table 14.53
History of Photocoagulation Treatment by Sex in Insulin-Taking Persons Diagnosed at Age <30 Years, WESDR, 1980-82

	History of photocoagulation					
	Males			Females		
Age (years)	No.	No	Yes	No.	No	Yes
<15	61	100.0	0	52	100.0	0
15-44	384	83.3	16.7	362	87.6	12.2
≥45	66	68.2	31.8	70	78.6	21.4
Total	511	83.4	16.6	484	87.6	12.2

The history of photocoagulation was uncertain in 0.2 percent of females. WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

Source: Klein R. WESDR. Unpublished data, 1980-82

Table 14.54
History of Photocoagulation Treatment in Persons Diagnosed at Age ≥30 Years, WESDR, 1980-82

	History of photocoagulation		
Age (years)	No.	No	Yes
30-44	49	98.1	1.9
45-64	519	94.4	5.1
65-84	738	96.6	2.8
≥85	64	91.8	5.8
Total	1,370	95.6	3.8

The history of photocoagulation treatment was uncertain in 0.6 percent of persons. WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

Source: Klein R. WESDR. Unpublished data, 1980-82

WESDR are presented in Tables 14.53 and 14.54[156,157]. In younger-onset patients, the rates of photocoagulation treatment increased with increasing current age and were higher in males than in females. In older-onset persons, the reported rate for the group was 3.8%.

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Appendix 14.1

Resource Materials for Visually Impaired Diabetic Persons

Blindness and Diabetes. American Foundation for the Blind, Inc. Publications Division, 15 West 16th Street, New York, NY 10011

Diabetic control: Equipment for use with vision loss. *Aids and Appliances Review*, Issue No. 6, June 1982. The Carroll Center for the Blind, 770 Centre Street, Newton, MA 02158, Tel. 617-969-6200

Diabetes Teaching Guide; George P. Kozak, MD. The Joslin Clinic, One Joslin Place, Boston, MA 02215, Tel. 617-732-2539

Materials and Aids for the Visually Impaired Diabetic. National Diabetes Information Clearinghouse, Box NDIC, Bethesda, MD 20205, Tel. 202-842-7630

Special Devices and Equipment for the Visually Impaired Diabetic; Keith Campbell. American Pharmacy Association. Vision Foundation, Inc., 2 Mt. Auburn Street, Watertown, MA 02172, Tel. 800-852-3029 or 617-926-4232

Teaching Guides for Diabetes Education Programs: Selected Annotations. National Diabetes Information Clearinghouse, Box NDIC, Bethesda, MD 20205 Tel. 202-842-7630

You, Your Eyes and Your Diabetes; Donna L. Johnson. The Hadley School for the Blind, 700 Elm Street, Winnetka, IL 60093, Tel. 800-323-4238 or 800-942-4193 (Illinois residents)

Regional libraries for the blind and physically handicapped can be consulted for information, or contact the Library of Congress, Division for the Blind and Physically Handicapped, 1291 Taylor Street, NW, Washington, DC 20542

Other References of Interest on Visual Impairment

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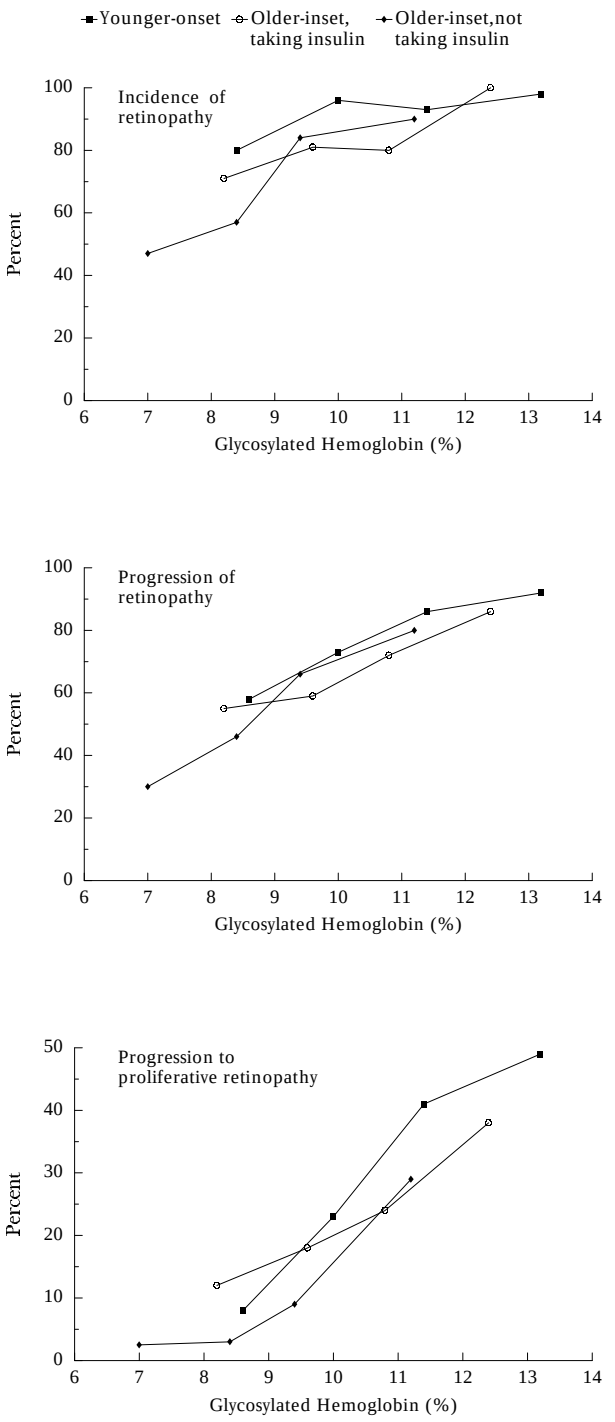
Keegan DL, Greenaugh T: Blindness: Some psychological and social implications. *Can Psychiatr Assoc J* 21:333-40, 1976

Kirchner C: *Data on blindness and visual impairment in the U.S*. A resource manual on social demographic characteristics, education, employment and income, and service delivery. 2nd Edition, American Foundation for the Blind. New York, NY 1988

Appendix 14.2

The 10-Year Incidence, Progression, and Progression to Proliferative Retinopathy, by Glycosylated Hemoglobin at Baseline, WESDR, 1980-92



WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy. Abscissa values for each group are the median glycosylated hemoglobin for each quartile of the group.

Source: Reference 161