Retinopathy in Pima Indians

Relationships to Glucose Level, Duration of Diabetes, Age at Diagnosis of Diabetes, and Age at Examination in a Population with a High Prevalence of Diabetes Mellitus

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SUMMARY

The occurrence of retinopathy and its relationship to diabetes in 1,640 Pima Indians age 15 and over has been determined. Eighteen per cent of those with two-hour postload plasma glucose levels of equal to or greater than 200 mg./dl. had some evidence of retinopathy. Of those with retinopathy and diabetes, 7 per cent were found to have proliferative or neovascular changes, the remainder having microaneurysms and/or exudates. The frequency of retinopathy increased from 3 per cent among newly diagnosed diabetics to 47 per cent among those with diabetes of 10 or more years duration. No relationship was found with sex, age at diagnosis of diabetes, or age at time of examination when duration of diabetes was taken into account. The occurrence of retinopathy was confined largely to those who fell into the second or hyperglycemic component of the frequency distribution of plasma glucose levels in the population, indicating the significance of the bimodal glucose tolerance frequency distribution. DIABETES *25*:554-60, July, 1976.

Epidemiologic studies of retinopathy among diabetics have dealt with the prevalence of retinopathy or the incidence of diabetic blindness and the increased mortality once the retinopathy develops. The populations under study have been drawn largely from diabetes clinics, which tend to see the more symptomatic patients, or from ophthalmology clinics, where patients with the later, more severe forms of retinopathy predominate. There are no previous reports of detailed investigations of retinopathy as it occurs in natural population groups, although such studies are well suited to provide much needed information about the earliest clinically detectable stages of this complication. Studies of the relationship of early retinopathy to other factors could be a logical step in providing clues to the etiology of retinopathy.

The Pima Indians of Arizona are an ideal natural population group for such a study, as they have the highest recorded prevalence of diabetes in the world.[1] The occurrence of retinopathy in this population was determined and the relationships of retinopathy to sex, age at time of examintion, glucose tolerance, duration, and age at diagnosis of diabetes were examined.

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METHODS

Between 1965 and 1969, 1,848 half- to full-blooded Pima Indians, aged 15 and older, received a

modified glucose tolerance test at the National Institutes of Health Clinic on the Gila River Indian Reservation in Arizona. The Indians tested represented slightly more than 92 per cent of the estimated population living on the Sacaton Service Unit area of the reservation.

An oral 75-gm. carbohydrate load‡ was given to each subject regardless of the time of the previous meal. Two hours later, venous blood was drawn into a tube containing sodium fluoride and the plasma glucose concentration was measured on an AutoAnalyzer by the modified Hoffman method.[2] Following the administration of 10 per cent phenylephrine hydrochloride and 0.5 per cent tropicamide ophthalmic drops, repeated until adequate pupillary dilatation was obtained, each subject underwent a careful funduscopic examination using a transformer-powered Bausch and Lomb direct ophthalmoscope in a darkened room by a single physician who had no knowledge of the glucose tolerance test result or the clinical history. The disc and macular areas of each eye were examined in detail, and each vessel coming off the disc was followed to the periphery as far as possible. This permitted the study of approximately 60 to 70 per cent of the total fundus area in the emmetropic eye. The presence or absence of each element of retinopathy —microaneurysms, exudates, and proliferative and neovascular changes—was separately recorded on a standard form, and if the physician could not determine with moderate certainty whether retinopathy was present or absent, the examination was declared inadequate. In attempting to develop simple standardized diagnostic criteria for an epidemiologic study, both "dot" and "blot" hemorrhages were included under "microaneurysms" and no distinction was made between "hard" and "soft" exudates.

The present analysis is confined to the first examination of the 1,640 Pima Indians aged 15 and over who had a plasma glucose determination and an adequate funduscopic examination.

Ophthalmoscopic evidence of retinopathy in either eye was used to determine the presence or absence of retinopathy in each subject and to determine the prevalence of each element of retinopathy in the population.

Subjects with "previously known diabetes" are those who had demonstrated—prior to the time of examination—unequivocal evidence of glucose intolerance. The duration of diabetes in these subjects was calculated from the time of the first documented evidence of glucose intolerance as indicated by blood or urine tests determined from a review of the medical records.

RESULTS

Table 1 shows the frequency of each element of retinopathy. In both males and females exudates were the most prevalent, followed by microaneurysms and proliferative and neovascular changes. No significant difference was found between the frequencies of microaneurysms and exudates in males ($\chi^2_R = 1.04$; $p>0.05$)§ or females ($\chi^2_R = 2.20$; $p>0.05$) or in both sexes combined ($\chi^2_R = 3.70$; $p>0.05$). Microaneurysms and exudates were each significantly more prevalent than proliferative and neovascular changes ($\chi^2_R > 25.0$; $p<0.001$). Approximately 5 per cent of all males and 6 per cent of all females were found to have one or more elements of retinopathy. This difference is not significant ($\chi^2 = 0.40$; $p>0.05$)¶, and, in fact, no significant differences were found between males and females in the frequencies of any element of retinopathy.

TABLE 1

Per cent of subjects with retinal abnormalities

	Males		Females		Both sexes
	No. exam.	per cent positive	No. exam.	per cent positive	per cent positive
Microaneurysms	737	3.1	903	3.5	3.4
Exudates	737	3.9	903	4.5	4.3
Prolif. and neovascular changes	737	0.1	903	0.4	0.3
One or more of the above elements of retinopathy	737	5.2	903	5.9	5.5

Table 2 shows the relationship of one or more elements of retinopathy to age, sex, and plasma glucose level. The frequency of retinal changes increased with age in males up through age 64 and in females up through age 74 regardless of the glucose level. The frequency of retinal changes was higher, however, in those with high glucose levels, especially beyond the age of 35 years.

‡Glucola, Ames, Elkhart, Indiana, or Dexcola, Custom Laboratories, Baltimore, Maryland.

§χ^2_R - Chi square for related samples.[3]

¶χ^2 - Chi square for unrelated samples.

TABLE 2

Distribution of subjects by age and plasma glucose levels and their relationship to one or more elements of retinopathy

Age at exam.	No. exam.	Two-hour plasma glucose (mg./100 ml.)							Per cent with one or more elements of retinopathy
		0-99	100-139	140-159	160-199	200-299	300-399	400+	
Males									
15-24	248	127	94	18	9	2	1	2	0
25-34	119	34	47	8(1)	7	8	4	11	8
35-44	126	30(1)*	38(1)	10	5	9(1)	13(1)	21(6)	7.9
45-54	91	13	35(2)	6	6	7(2)	12(4)	12(3)	12.1
55-64	72	13(1)	23(1)	10(2)	4(1)	5(3)	8(2)	9(1)	15.3
65-74	54	6	16(2)	4(1)	8	5	7(1)	8(1)	9.3
75+	27	3	11	3	4	3	1	2	0.0
Total	737								
Per cent with one or more elements of retinopathy		0.9	2.3	6.8	2.6	15.4	17.4	16.9	5.2
Females									
15-24	299	127	134	22	11	3	0	2	0.0
25-34	181	44(1)	81(2)	12	13	17	4	10(1)	2.2
35-44	181	14	64(2)	17	25	18	17(4)	26(2)	4.4
45-54	100	5	27(1)	9	14	15(2)	9(3)	21(5)	11.0
55-64	83	3	18	11(1)	5	12(1)	11(4)	23(11)	20.5
65-74	48	2(1)	11(2)	6	7(2)	6(1)	7(2)	9(4)	25.0
75+	11	0	5	0	0	3	2(1)	1	9.1
Total	903								
Per cent with one or more elements of retinopathy		1.0	2.1	1.3	2.7	5.4	28.0	25.0	5.9

*Number of subjects with one or more elements of retinopathy, for each age and plasma glucose range, is shown in parentheses.

Each element of retinopathy was more prevalent among those with elevated two-hour plasma glucose levels, especially among those with values in excess of 200 mg./dl. (table 3). A similar relationship was demonstrated by the distribution of subjects with one or more elements of retinopathy (table 2).

Figure 1 shows the frequency distributions of the two-hour plasma glucose levels in the 737 males and 903 females that comprise this sample. Superimposed on each two-hour plasma glucose frequency distribution is a graph of the per cent of subjects with one or more elements of retinopathy, calculated from moving averages at 0.1 $\log_{10}$ glucose intervals. The glucose distribution is clearly bimodal and typical of distributions previously reported of the Pima Indian population.[4] These distributions fit a mathematical model of two slightly overlapping Gaussian curves with an antimode around the 200-250-mg./dl. level. Below 200 mg./dl. the per cent of subjects with retinopathy increased only very gradually with increasing plasma glucose levels and the absolute values of the percentages were relatively low. Between 200 mg./dl. and 316 mg./dl. the per cent with retinopathy increased rapidly, but the slope again be-

TABLE 3

Percent of subjects with various elements of retinopathy and their relationship to plasma glucose levels

Two-hour plasma glucose (mg./100 ml.)	No. exam.	Micro-aneurysms Per cent positive	Exudates Per cent positive	Prolif. and neo-vascular changes Per cent positive
Males				
0- 99	226	0.4	0.4	0.0
100-199	361	1.1	2.2	0.0
200-299	39	5.1	15.4	0.0
300-399	46	17.4	15.2	2.2
400+	65	12.3	10.8	0.0
Females				
0- 99	195	0.5	0.5	0.0
100-199	492	0.4	1.8	0.0
200-299	74	5.4	4.1	1.4
300-399	50	18.0	18.0	2.0
400+	92	17.4	20.7	2.2
Both sexes				
1- 99	421	0.5	0.5	0.0
100-199	853	0.7	2.0	0.0
200-299	113	5.3	8.0	0.9
300-399	96	17.7	16.7	2.1
400+	157	15.3	16.6	1.3

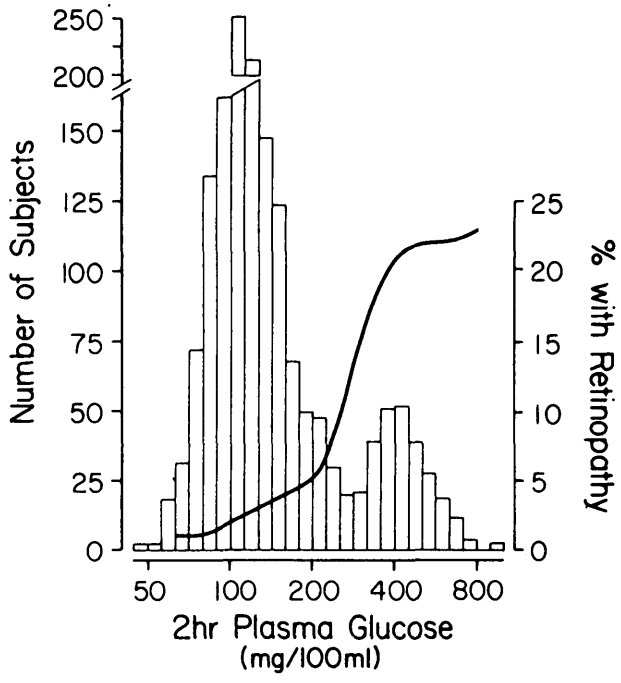

FIG. 1. Per cent of males and females with one or more elements of retinopathy (shown as continuous line) superimposed on the two-hour plasma glucose distribution (histogram). The per cent with retinopathy was calculated by using moving averages over three 0.1 $\log_{10}$ glucose intervals. The plasma glucose scale is in 0.1 $\log_{10}$ glucose intervals.

came more gradual above 316 mg./dl., where the absolute values of the percentages were considerably higher than below 200 mg./dl. In males and females retinopathy was approximately nine times more prevalent in all subjects with two-hour plasma glucose levels ≥200 mg./dl. than in those with levels <200 mg./dl.

The prevalence of each element of retinopathy was related to the duration of diabetes in males and females (table 4). Some 50 per cent of those with duration of 10 years or more had one or more elements of retinopathy as against about 11 per cent of those who had diabetes for less than five years. During the study, 128 males and females—without previously known diabetes—were found to have two-hour plasma glucose levels of ≥200 mg./dl. Of these subjects, four had one or more elements of retinopathy. Thus, the prevalence of retinopathy at time of diagnosis of diabetes was approximately 3 per cent.

No relationship was found between the frequency of retinopathy and the age at diagnosis of diabetes. In males and females who were at least 15 years old when the diagnosis was made (table 5), approximately 17 per cent had one or more elements of retinopathy. Too few people who had developed diabetes at less than 15 years of age were examined to make any meaningful statement about this group.

TABLE 4

Per cent of subjects* with various elements of retinopathy and their relationship to duration of diabetes

Duration of diabetes	No. exam.	One or more elements of retinopathy per cent positive	Microaneurysms per cent positive	Exudates per cent positive	Prolif. and neovascular changes per cent positive
Males					
Newly diagnosed†	57	5.3	3.5	5.3	0.0
0-4 years	53	18.9	11.3	13.2	0.0
5-9 years	29	24.1	17.2	17.2	0.0
10 years or more	21	38.1	28.6	33.3	4.8
Females					
Newly diagnosed	70	1.4	0.0	1.4	0.0
0-4 years	81	17.3	7.4	14.8	0.0
5-9 years	47	17.0	14.9	12.8	0.0
10 years or more	41	51.2	41.5	36.6	9.8
Both sexes					
Newly diagnosed	127	3.2	1.6	3.2	0.0
0-4 years	134	17.9	9.0	14.2	0.0
5-9 years	76	19.7	15.8	14.5	0.0
10 years or more	62	46.8	37.1	35.5	8.1

*Includes all persons with a previous diagnosis of diabetes mellitus regardless of plasma glucose level at time of examination.

†Includes only those persons, not previously diagnosed as diabetic, who were found to have two-hour plasma glucose levels of ≥200 mg./100 ml. at time of examination.

TABLE 5

Per cent of subjects* with various elements of retinopathy and their relationship to age at diagnosis of diabetes

Age at diagnosis of diabetes	No. exam.	One or more elements of retinopathy per cent positive	Microaneurysms per cent positive	Exudates per cent positive	Prolif. and neovascular changes per cent positive
Males					
15-24 years	10	0.0	0.0	0.0	0.0
25-34 years	33	15.2	12.1	9.1	0.0
35-44 years	44	25.0	20.5	18.2	2.3
45-54 years	34	17.6	8.8	17.6	0.0
55-64 years	21	23.8	9.5	19.0	0.0
65 years or more	19	5.3	5.3	5.3	0.0
Females					
15-24 years	10	20.0	10.0	0.0	10.0
25-34 years	48	12.5	10.4	8.3	2.1
35-44 years	69	18.8	17.4	15.9	2.9
45-54 years	61	16.4	8.2	14.8	0.0
55-64 years	34	32.4	17.6	23.5	0.0
65 years or more	15	13.3	6.7	13.3	0.0
Both sexes					
15-24 years	20	10.0	5.0	0.0	5.0
25-34 years	81	13.6	11.1	8.6	1.2
35-44 years	113	21.2	18.6	16.8	2.7
45-54 years	95	16.8	8.4	15.8	0.0
55-64 years	55	29.1	14.5	21.8	0.0
65 years or more	34	8.8	5.9	8.8	0.0

*Includes "newly diagnosed" diabetics and all persons with a previous diagnosis of diabetes mellitus regardless of plasma glucose level at time of examination—except for those diagnosed to have diabetes under age 15.[2]

The relationship of retinopathy to age among the diabetics is shown in table 6. Since the older subjects were likely to have had diabetes for a longer time, and since the prevalence of retinopathy was related to duration of diabetes (table 4), the data were stratified for duration of diabetes in order that the age associations could be examined independently of duration. Table 6 shows that no relationship was found between the frequency of one or more elements of retinopathy and age at time of examination in male and female diabetics with duration of 10 years or more. The same can probably be said of diabetics with duration of five to nine years. Though subjects 15-44 years of age had significantly less retinopathy than those 45-54 years of age ($\chi^2 = 11.50$; $p<0.01$), subjects 55-84 years of age also had significantly less retinopathy than those in the middle-age group ($\chi^2 = 5.72$; $p<0.02$) and no significant difference existed between those 15-44 and those 55-84 years of age ($\chi^2 = 1.44$; $p>0.05$). In subjects with duration of zero to four years, the per cent of diabetics with one or more elements of retinopathy was significantly less in those 15-44 years of age than in those 45-54 years of age ($\chi^2 = 4.19$; $p<0.05$) or in those 55-84 years of age ($\chi^2 = 12.49$; $p<0.01$). On the other hand, there was no significant difference in the frequency of retinopathy in these latter two age groups ($\chi^2 = 1.50$; $p>0.05$). Moreover, among the 127 newly diagnosed diabetics,

TABLE 6

Per cent of diabetic subjects with one or more elements of retinopathy and their relationship to age at examination and duration of diabetes

Age (yr.)	Duration of diabetes: Newly diagnosed		0-4 years		5-9 years		10 years or more	
	no. exam.	per cent positive	no. exam.	per cent positive	no. exam.	per cent positive	no. exam.	per cent positive
15-44	76	2.6	56	5.4	30	6.7	17	52.9
45-54	23	0.0	31	19.4	16	50.0	12	50.0
55-84	28	7.1	47	31.9	30	16.7	33	42.4

no significant difference was found between any of the age groups ($\chi^2 < 1.75$; $p > 0.05$).

DISCUSSION

Although there are many classifications of retinopathy among diabetics, there is no widely accepted, simple method of quantifying the observed abnormalities. We chose, in recording the data, to identify only the presence or absence of each element of retinopathy. No attempt was made to count the number of lesions or to record their locations in the fundus.

No significant sex difference was found in the per cent of subjects with retinopathy in the total population (table 1) or among the diabetics alone (table 4). This finding is consistent with previous studies that have been confined to diabetics.[5-8] The prevalence of each element of retinopathy and the per cent of subjects with one or more elements of retinopathy were approximately equal in both sexes.

Comparisons of the prevalence of retinopathy are hazardous because of considerable differences in methods. Examination precedures and diagnostic criteria vary from one study to another, as do the age groups examined and the distributions of the various durations of diabetes. As our sample was drawn from a natural population group, we identified many previously unrecognized diabetics and were, therefore, more likely to have seen the less symptomatic or asymptomatic, early stages of retinopathy. We believe that the relative frequencies shown in table 1 closely reflect the true ratio of each element of retinopathy as it occurred in the total population. Among the 72 previously known and newly diagnosed diabetic subjects with retinopathy, only 6.9 per cent were found to have proliferative and neovascular changes, the later, more severe form of retinopathy.

Table 2 shows that one or more elements of retinopathy were found in 25 males and females with two-hour plasma glucose levels <200 mg./dl. Of this group, six were previously diagnosed diabetics and one subject had a two-hour plasma glucose level of 168 mg./dl. Of the remaining 18 persons, four had known hypertension and one had decreased vision because of serious eye trauma. In nine additional persons, only exudates were discovered. There were four males and females with microaneurysms or retinal hemorrhages, one with accompanying exudates, for which there was no apparent explanation. These people will be further studied to document more fully their retinopathy and nondiabetic status and also to exclude other possible causes for the observed retinal changes.

In figure 1, a graph of the per cent of subjects with one or more elements of retinopathy is superimposed on the bimodal frequency distribution of the two-hour plasma glucose levels. The graph is divided into regions of high and low frequency of retinopathy separated by a transitional region that occurs between plasma glucose values of 200 mg./dl. and 316 mg./dl. and roughly corresponds to the area of overlap between the two components of the bimodal plasma glucose distribution. The second or hyperglycemic component appears to represent true diabetes mellitus among the Pima Indians, and its size is, therefore, indicative of the prevalence of diabetes in this population.[9] The finding of a consistently high frequency of retinopathy—a specific chronic vascular complication of diabetes—among the subjects who fell in the hyperglycemic component of the plasma glucose distribution and a consistently low frequency of retinopathy among those who fell in the normoglycemic component substantiates this theory and emphasizes the biologic and clinical significance of bimodality.

As in other populations, the frequency of retinopathy was related to the duration of diabetes. We have further demonstrated that the prevalence of each element of retinopathy was related to duration. Although microaneurysms and exudates each increased gradually with increasing duration, no proliferative or neovascular changes were found in known diabetics with duration less than 10 years. These trends have been previously reported by many other investigators (see discussion in Caird, Pirie, and Ramsell[10] and in Ballantyne and Michaelson[11]) and provide additional support to the premise that the retinopathy found in Pima Indians is essentially the same as that found in non-Indian populations.

Retinopathy at the time of diagnosis of diabetes has been reviewed by Soler, Fitzgerald, Malins, and Summers,[12] who found that the prevalence in different series varied from 4 to 15 per cent. The 3 per cent prevalence of retinopathy at time of diagnosis that we reported is at the lower end of this range.

No relationship was found between the frequency of retinopathy and the age at diagnosis of diabetes, confirming previously reported findings.[7] An apparent exception was the observation that proliferative and neovascular changes were confined to those males and females diagnosed to have diabetes under 45 years of age (table 5). Since this complication, however, occurs only with diabetes of long duration (10 years or more)

and as there were only 22 subjects who developed diabetes at beyond 45 years and survived 10 years or more thereafter, this observation is not unexpected. If we correct for duration of diabetes in subjects with age at diagnosis <45 years and in subjects with age at diagnosis ≥45, years, there is no significant difference in the frequency of proliferative and neovascular changes ($\chi^2 = 3.10$; $p>0.05$).

No relationship was found between the frequency of retinopathy and age at time of examination in subjects with durations of diabetes of five to nine years or 10 years or more. In those with durations of less than five years, younger people—15-44 years of age—had significantly less retinopathy than older people. It is quite likely, however, that our estimate of duration of diabetes was more accurate in younger people than in older people. Older people may also have had more nonspecific retinal changes. On the other hand, when older subjects developed diabetes, they may have developed retinopathy sooner than younger people, perhaps because of more susceptible vascular systems. We are inclined to believe, however, that no important relationship exists between retinopathy and age at examination and that other factors are more important in determining the presence or absence of retinopathy. Kornerup[5] and Nilsson and coworkers[13] reported similar findings among diabetics after adjusting for duration of diabetes.

The present study shows that the prevalence of retinopathy was related to duration of diabetes but not to sex, age at diagnosis of diabetes, or age at time of examination, confirming previously reported findings. A low frequency of retinopathy was found among subjects in the first, or normoglycemic component of the bimodal plasma glucose distribution, and a high frequency of retinopathy was found among subjects in the second, or hyperglycemic component. This substantiates the biologic and clinical significance of bimodality and supports the premise that the second component represents true diabetes mellitus among the Pima Indians.

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