

The Course of Diabetic Retinopathy

A Longitudinal Study

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SUMMARY

A prospective study was devoted to the spontaneous course of diabetic retinopathy. The retinas of 459 diabetics were photographed every two years for a total follow-up period, planned beforehand, of eight years.

For two-year intervals progression of retinopathy was found in 14 to 29 per cent, a stationary picture in 60 to 69 per cent, and amelioration in 7 to 17 per cent of cases. For four-year intervals these percentages were 32 to 39, 47 to 57, and 10 to 12, for six-year intervals 39-50, 40-47, and 10-14, respectively. During the total eight-year period, 48 per cent progressed, 38 per cent remained stationary, and 14 per cent improved. When the patients in whom retinopathy developed during the investigation were included, the percentages changed numerically without altering the general trend. The influence of the dropout of patients on the results is emphasized.

The results are compared with the results of other prospective studies. *DIABETES* 22:122-28, February, 1973.

Many aspects of diabetic retinopathy have been studied extensively, but until recently there have been few prospective studies of the spontaneous course. Yet knowledge of this course is indispensable, especially for evaluation of therapeutic results. This paper reports and discusses the findings of an eight-year study of the spontaneous course of diabetic retinopathy.

PATIENTS AND METHODS

From May 1960 until May 1962, 459 patients (200 men, 259 women) out of a population of about 1,200 diabetics, forming at that time the medical practice of the investigator, were selected for investigation without randomization. Only patients who had clear ocular media and were able to come to the clinic were considered eligible.

At the start of the investigation the mean age (\pm

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S.D.) was 54.2 years \pm 16.6 for the men and 58.1 years \pm 16.6 for the women. The mean duration of known diabetes was 8.4 years \pm 7.4 for the men and 8.9 years \pm 7.5 for the women. The mean ages at which diabetes was diagnosed were 45.7 years \pm 19.0 and 49.1 years \pm 18.0 for the men and women, respectively (table 1). Diabetes was diagnosed by typical signs and symptoms or by glucose tolerance test.

All subjects were treated for diabetes on an outpatient basis. The objectives of the treatment were freedom from complaints, normal diuresis, absence of ketonuria, normal body weight and, in children, normal body growth. When these requirements were met, the degree of glycosuria and the blood sugar levels at the regular check-ups were considered of minor importance.

The eyegrounds were photographed with a Zeiss fundus camera (30° objective, initially Kodachrome I and later Kodachrome II film) after full mydriasis. One photograph was made of each eye with the macula centered. This examination was repeated every two years until a maximum of five pairs of photographs was obtained. The investigation was scheduled to end in May 1970 but was completed in September 1970.

The photographs were always read by the author, who was aware of the names of the patients. The following classification of retinal changes was used:

Stage 0 = normal eyegrounds

Stage 1 = microaneurysms, i.e. small red dots.

Stage 2 = hemorrhages, with or without microaneurysms

Stage 3 = exudates, with or without signs of stage 2 retinopathy

Stage 4 = neovascularization, proliferative retinopathy

The findings were evaluated per patient; when one eye was more severely damaged than the other, the more advanced stage was recorded. To judge the changes in the retinas between two examinations, the following method was used. The photographic slides made of the same eye at these examinations were placed in

TABLE 1
 Frequency distributions of age at the first examination, age at the diagnosis of diabetes, and duration of known diabetes at the first examination

Yrs	Age						Age at diagnosis					
	men		women		men		women					
	n	%	n	%	n	%	n	%	n	%		
< 15	2	(1.0)	4	(1.5)	19	(9.5)	20	(7.7)				
15-19	7	(3.5)	4	(1.5)	7	(3.5)	6	(2.3)				
20-24	5	(2.5)	9	(3.5)	10	(5.0)	9	(3.5)				
25-29	5	(2.5)	10	(3.9)	3	(1.5)	6	(2.3)				
30-34	11	(5.5)	5	(1.9)	11	(5.5)	9	(3.5)				
35-39	8	(4.0)	9	(3.5)	14	(7.0)	8	(3.1)				
40-44	13	(6.5)	6	(2.3)	20	(10.0)	15	(5.8)				
45-49	16	(8.0)	12	(4.6)	18	(9.0)	25	(9.7)				
50-54	27	(13.5)	21	(8.1)	21	(10.5)	40	(15.4)				
55-59	16	(8.0)	30	(11.6)	26	(13.0)	36	(13.9)				
60-64	24	(12.0)	27	(10.4)	21	(10.5)	40	(15.4)				
65-69	29	(14.5)	49	(18.9)	12	(6.0)	26	(10.0)				
70-74	22	(11.0)	52	(20.1)	18	(9.0)						
75-79	8	(4.0)	15	(5.8)			19	(7.3)				
> 79	7	(3.5)	6	(2.3)								
Total	200	(100)	259	(100)	200	(100)	259	(100)				
Mean age	54.2		58.1		45.7		49.1					
± S.D.	16.6		16.6		19.0		18.0					

Yrs	Duration of known diabetes			
	men		women	
	n	%	n	%
< 5	64	(32.0)	83	(32.0)
5- 9	71	(35.0)	79	(30.6)
10-14	36	(18.0)	54	(20.8)
15-19	10	(5.0)	20	(7.7)
20-24	8	(4.0)	6	(2.3)
25-29	7	(3.5)	10	(3.9)
30-34	2	(1.0)	4	(1.5)
> 34	2	(1.0)	3	(1.3)
Total	200	(100)	259	(100)
Mean duration				
± S.D.	8.4 ± 7.4		8.9 ± 7.5	

small monocular viewers held before the eyes of the investigator, who obtained a single image by adjusting the position of the viewers. This method permits quick and easy evaluation of the differences between two slides. When the same stage (excluding stage 0), was indicated for both eyes of a patient in two successive examinations, subdivisions were added to indicate whether the signs of retinopathy had increased, decreased, or remained unaltered. It was not feasible to express these changes quantitatively.

The evaluation of the photographs was checked after three examinations; the investigator, unaware of the identity of the subjects, reevaluated the photographs of twenty-five patients selected at random. In one

case, one microaneurysm had been missed at the original reading in an otherwise normal fundus. In a second case the investigator had failed to see one microaneurysm at the second reading. For the remaining photographs, the second reading was identical with the first. A detailed description of the methods used and the composition of the patient material at the first four examinations has been published elsewhere.¹

DROPOUTS

The withdrawal of patients from a prospective study may seriously disturb evaluation of the findings. In the present investigation any patient who was not available for a scheduled examination was classified as a

dropout. It may be that such a patient returned to the investigation after having missed one or more examinations.

The reasons for dropping out in the periods between successive examinations were grouped under the following headings: death, cataract, glaucoma, change of residence, not examined for other reasons, terminated visits. A subdivision was made according to the presence or absence of retinopathy (table 2). No reminder was sent to patients who failed to appear for the regular checks.

The most frequent reasons for dropout were death and termination of check-up visits. The majority of deaths occurred in the age groups sixty years and over (74 per cent to 94 per cent at the various examinations). Those patients who terminated check-up visits left without giving reasons. The other headings comprise only a small number of patients compared to the two above mentioned categories.

For the present study it was argued that if the group of patients dropping out of the investigation in a given period could be judged a representative sample of the group remaining in the investigation, the influence on the results of their withdrawal should be negligible. This hypothesis was tested on the basis of the following variables: duration of known diabetes, sex, age, and age at the time of diagnosis of diabetes. This was done for patients both with and without retinopathy. The results are shown in table 3. As far as duration of known diabetes was concerned, no significant differences were found. With regard to sex, the difference was significant only in the period between the first and last examination among patients with retinopathy; more women than men dropped out. Differences were statistically signi-

ficant for age and age at diagnosis of diabetes. In all relevant periods there was a considerable dropping out of elderly patients, a fact already mentioned above and to be expected in a longitudinal study. Only in the first period was there no significant difference in this respect for patients with retinopathy, and in the last period there was no statistical significant difference for patients without retinopathy.

There was no statistically significant difference in dropping out between patients with and without retinopathy throughout the investigation (table 4).

RESULTS

A patient was judged to have retinopathy if it was found once either before the start of the investigation or during the investigation, even when it could not be demonstrated in a subsequent examination. The prevalence of retinopathy at the successive examinations is shown in table 5. Except at the first examination, when retinopathy was found more frequently in women than in men ($p < 0.05$), no significant differences in prevalence were found between the sexes.

The course of the retinopathy can be expressed as the change in composition of groups falling into stages 1 through 4. Crosstabes, arranged for the various intervals between subsequent examinations, are shown in table 6; the first horizontal row refers to intervals of two years, the second row to intervals of four years, and the third row to intervals of six years. The bottom table includes the entire eight years of the investigation. These intervals do not represent independent observation periods.

The percentages of change to a worse stage or a milder stage, and of no change in these intervals are

TABLE 2
Analysis of material lost during the study

Reason for dropout after:	First examination			Second examination			Third examination			Fourth examination		
	Total	R ⁺	R ⁻	Total	R ⁺	R ⁻	Total	R ⁺	R ⁻	Total	R ⁺	R ⁻
Death	36	15	21	27	17	10	24	10	14	16	13	3
Cataract	4	1	3	4	3	1	6	2	4	7	7	0
Glaucoma	2	1	1	1	0	1	1	1	0	4	1	3
Migration	6	0	6	4	2	2	4	3	1	4	4	0
Not examined for other reasons				1	0	1				1	0	1
Terminated visits	57	20	37	36	18	18	25	15	10	16	12	4
No 2nd examination	15	7	8									
No 3rd examination				2	0	2						
No 4th examination							6	4	2			
Total	120	44	76	75	40	35	66	35	31	48	37	11

R⁺ = retinopathy, R⁻ = no retinopathy

TABLE 3

Result of statistical analysis (X^2 test on contingency tables) carried out to detect differences between the patients dropping out of and those remaining in the investigation in the periods between successive examinations (underlined values are P values indicating statistical significance) (R⁺ = with retinopathy, R⁻ = without retinopathy)

Period	R ⁺ /R ⁻	Group	No. of pts.	Sex	Duration of diab.	Age at last ex.	Age at diag. of diab.
1-2	R ⁺	Dropouts	44	0.461	0.481	0.091	0.788
1-2	R ⁺	Remaining	94				
1-2	R ⁻	Dropouts	76	0.508	0.430	< 0.001	< 0.001
1-2	R ⁻	Remaining	245				
2-3	R ⁺	Dropouts	40	0.926	0.895	0.011	0.001
2-3	R ⁺	Remaining	120				
2-3	R ⁻	Dropouts	35	0.405	0.273	< 0.001	0.002
2-3	R ⁻	Remaining	144				
3-4	R ⁺	Dropouts	35	0.061	0.752	< 0.001	0.002
3-4	R ⁺	Remaining	123				
3-4	R ⁻	Dropouts	31	0.962	0.858	0.005	0.022
3-4	R ⁻	Remaining	90				
4-5	R ⁺	Dropouts	37	0.067	0.387	< 0.001	< 0.001
4-5	R ⁺	Remaining	119				
4-5	R ⁻	Dropouts	11	0.517	0.630	0.414	0.268
4-5	R ⁻	Remaining	48				
1-5	R ⁺	Dropouts	91	0.026	0.790	< 0.001	< 0.001
1-5	R ⁺	Remaining	47				
1-5	R ⁻	Dropouts	195	0.161	0.093	< 0.001	< 0.001
1-5	R ⁻	Remaining	126				

given in table 7. Between two-year intervals progression from a given stage to a worse stage occurred in 14 to 29 per cent of the cases, a stationary picture was found in

TABLE 4

Number of patients dropping out of or remaining in the investigation during intervals between successive examinations (R⁺ = with retinopathy, R⁻ = without retinopathy)

Interval	1-2		2-3		3-4		4-5	
	R ⁺	R ⁻	R ⁺	R ⁻	R ⁺	R ⁻	R ⁺	R ⁻
Dropouts	44	76	40	35	35	31	37	11
Remaining	94	245	120	144	123	90	119	48
P	0.07		0.22		0.49		0.42	

60 to 69 per cent, and regression of the retinopathy in 7 to 17 per cent. For the four-year intervals these percentages are 32 to 43, 47 to 57, and 10 to 12, respectively. For six-year intervals these values are 39 to 50 per cent, 40 to 47 per cent, and 10 to 14 per cent, respectively. In the over-all study, i.e. for the eight-year period, 48 per cent of the patients with retinal abnormalities showed progression, 38 per cent showed no change to another stage of retinopathy, and 14 per cent showed amelioration of the retinopathy. Findings pertaining to the course of the retinopathy were not essentially different for thirty-four patients who had diag-

TABLE 5

Prevalence of retinopathy at the successive examinations according to sex (R⁺ = retinopathy)

Examination Sex	1st		2nd		3rd		4th		5th	
	male	female	male	female	male	female	male	female	male	female
No. of patients	200	259	153	186	129	150	103	112	88	85
No. R ⁺ patients	50	88	65	95	67	91	71	85	70	70
% R ⁺ patients	25	34	43	51	52	61	69	76	79	85
P	0.038		0.11		0.14		0.25		0.63	

TABLE 6

Crosstabes showing changes, between various examinations, in composition of groups of patients with different degrees of retinopathy (see text for explanation)

		2nd Examination						3rd Examination						4th Examination						5th Examination					
		0	1	2	3	4	Dropout	0	1	2	3	4	Dropout	0	1	2	3	4	Dropout	0	1	2	3	4	Dropout
		Total						Total						Total						Total					
1st Examination	0	179	49	15	6		77	115	20	9	4		36	63	19	7	10		34	34	15	2	4		14
	1	4	16	8	9		6	6	28	11	10		10	4	27	3	11		7	6	27	6	2		6
	2	1		6	7	1	9	4	2	7	10		8	1	1	11	10		7	3	3	7	3	2	5
	3			2	34	1	27	1	1	33	1		20			2	35	8	16	1	5	1	40	3	17
	4					1	1					2	1					1	2					3	6
Dropout																									
Total		184	65	31	56	3	120	133	52	30	61	3	180	69	47	23	67	9	244	46	50	18	51	8	286
		3rd Examination						4th Examination						5th Examination											
1st Examination	0	127	40	18	20		121	57	28	11	18		70	40	28	5	10		60						
	1	3	11	6	16		7	2	16	6	18		20	5	18	6	11	1	11						
	2	2		4	5	1	12	2		4	8	2	15	1	4	7	4	2	12						
	3	1	1	2	20	1	39	1	1	21	6		27				25	4	32						
	4					1	1					1	2					1	2						
Dropout																									
Total		133	52	30	61	3	180	69	47	23	67	9	244	46	50	18	51	8	286						
		4th Examination						5th Examination																	
1st Examination	0	66	37	17	39	1	166	35	30	11	16	3	89												
	1	3	9	4	11	2	14	5	16	4	13	1	26												
	2			1	6		17	1	3	1	6	1	19												
	3		1	1	11	5	46			1	15	2	38												
	4					1	1					1	2												
Dropout																									
Total		69	47	23	67	9	244	46	50	18	51	8	286												
		5th Examination																							
1st Examination	0	43	41	11	29	5	197																		
	1	2	7	5	11	2	16																		
	2		2	1	3		18																		
	3	1		1	8		54																		
	4					1	1																		
Total		46	50	18	51	8	286																		

nosed diabetes before age twenty and who participated in the entire study.

If patients who showed no retinal abnormalities at the first examination are included, the percentages show remarkable similarity with those given above. Regression is less frequent since patients showing stage 0 retinas can only progress or remain stationary.

The above mentioned alterations concern changes from one stage of retinopathy to another. The changes in severity of retinopathy in cases that remained in the same stage for the various intervals have been calculated. Since these changes were not quantified and the numbers of patients involved are relatively small, the percentages are, of course, only rough estimates. But within these limitations the impression is gained that

the same trend exists here: deterioration of retinopathy is found more often when the interval between examinations is longer than when this interval is short. Furthermore, there is an important percentage of cases in which the severity of the retinopathy decreases.

DISCUSSION

Some comment on the reading of the photographs and on the dropouts is necessary before the results are discussed.

The reading of the photographs may be influenced by the knowledge of clinical information of the patient. The control reading of a random sample, with the investigator being unaware of the identity of the patients, showed, however, only minor deviations from

TABLE 7

Percentage changes from one stage of retinopathy to another in the classification used during the various observation periods

Retinopathy	Interval between examination			
	1-2	2-3	3-4	4-5
Progression	29	28	29	14
Stationary	63	60	64	69
Regression	8	12	7	17
Number of patients	90	116	114	112

Retinopathy	Interval between examination		
	1-3	2-4	3-5
Progression	39	43	32
Stationary	47	47	57
Regression	12	10	11
Number of patients	74	91	89

Retinopathy	Interval between examination	
	1-4	2-5
Progression	50	39
Stationary	40	47
Regression	10	14
Number of patients	55	70

Retinopathy	Interval between examination
	1-5
Progression	48
Stationary	38
Regression	14
Number of patients	44

the original reading. Furthermore, the four grades of retinal changes used were well defined and easy to recognize, a circumstance minimizing errors in classification. The evaluation of the changes in severity of the retinopathy within the various stages is open to subjectivity, however.

The withdrawal of patients from the investigation was caused mainly by death and termination of check-up visits. The majority of the deceased were over sixty years of age. The dropout rate due to discontinuation of regular check-up visits might have been reduced by sending reminders, but the unpredictability of the response to these reminders would be a new source for bias; therefore, no steps were taken to promote re-entry of these patients into the study group.

The influence of dropout on the findings can not be established. Since the distribution of the patients who dropped out in the intervals between the successive examinations did not differ from those who remained with regard to sex (with the exception of the interval between the first and the last examination) and the duration of known diabetes, it is assumed that the dropout rate did not influence the findings as far as these two criteria are concerned. A possible bias produced by differences in dropping out between the groups with and the groups without retinopathy could be ruled out. It should be borne in mind, however, that the assump-

tions are based on a theory on dropouts which is not proven to be true.

It is well known that the prevalence of diabetic retinopathy increases with increasing duration of diabetes. The present study confirms this point (table 5), and it seems reasonable that the withdrawal of patients did not influence this finding. In one period only was there a significant difference in prevalence between the sexes.

It was shown that the longer the interval between examinations the greater was the percentage of deteriorating retinopathy; the percentage of stationary retinopathy decreased concomitantly. This is consistent with the increasing prevalence of retinopathy with increasing duration of diabetes. However, the expected decrease in the percentage of regressing retinopathy was not found. This percentage was remarkably constant. Regression was noted in all stages of retinopathy with the exception of stage 4 (proliferative retinopathy). The constant percentage of regression could be the result of a special pattern of dropping out. Caird et al.² mention higher rates of regression in young than in old patients; it is conceivable that our high rate of dropping out among old patients led to a delicate balance resulting in the observed constancy. Statistical calculations, which would break the patient material up in small groups and, thereby, reduce the value of such analyses, have not been carried out.

Spontaneous regression of diabetic retinopathy has been reported by such authors as Caird et al.³ and Burditt et al.,⁴ while Keen et al.⁵ mention a high degree of spontaneous "activity," a term by which they express the appearance and disappearance of lesions.

Only a few investigations have been published in which the course of diabetic retinopathy was studied prospectively. In a small number of juvenile diabetics studied for ten years, Larsson et al.⁶ found progression in 56 per cent, a stationary picture in 27 per cent, and amelioration in 17 per cent. The classification of retinopathy was the same as that used in the present study.

In forty-one patients studied over seven years, Schlesinger et al.⁷ noted progression of two or more grades on the scale of Keith and Wagener in eight patients. The findings pertaining to stationary retinopathy are not given clearly, and regression is not mentioned.

Mikki et al.,⁸ who followed a group of 364 diabetics, also using Keith and Wagener's classification of diabetic retinopathy, found after two years of observation that 32 per cent of the initial cases of retinopathy had progressed to a higher grade, 50 per cent remained in the same grade, and 18 per cent had regressed to a lower

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¹¹Krall, L. P.: Communication at 7th Congress IDF, Buenos Aires, 1970.

grade. After four years these percentages were 46, 30, and 24 and after six years 59, 29, and 22, respectively. The similar percentages of regression of retinopathy are noteworthy.

Moriwaki et al.⁹ and Inoue et al.,¹⁰ who studied 190 patients, found after a follow-up of five years that 58 per cent of the patients with retinopathy did not show any change or showed regression and that after ten years this percentage was 47.

Krall¹¹ studied a group of 295 patients for about eleven years and found progression of retinopathy in 64 per cent and a stationary picture in 36 per cent.

Although these studies are hardly comparable because of differences in the composition of the patient material, the classification of the retinopathy, and the treatment of diabetes, data from some of them, together with the results of the present study, are given in table 8. None of the above mentioned studies give adequate information on dropout.

In view of the lack of comparability of these studies, the conformity of the results may be accidental. However, the possibility should not be overlooked that the spontaneous course of diabetic retinopathy is not influenced by such factors as population composition, classification of retinopathy, or even mode of treatment of diabetes. If this is actually the case, conformity could be expected.

The course of diabetic retinopathy seems to follow a definite pattern, knowledge of which is necessary for evaluating the effect of therapeutic measures aimed at influencing this course. Studies are also needed to determine which factors are indicative of a spontaneous favorable course (stationary and regressing retinopathy).

In any longitudinal study the dropout of patients will hamper the drawing of conclusions from the findings. This statement is certainly valid for the present study.

TABLE 8
Published data and present results concerning the course of diabetic retinopathy shown by prospective studies.

Authors	Follow up (yrs)	Progression (%)	Stationary (%)	Regression (%)
Larsson et al. ⁶	10	56	27	17
Mikki et al. ⁸	2	32	50	18
	4	46	30	24
	6	59	29	22
Moriwaki et al. ⁹	5	42	} 58	
Inoue et al. ¹⁰	10	53	} 47	
Krall ¹¹	11.2	64	} 36	
Present study	2	14-29	60-69	7-17
	4	32-43	47-57	10-12
	6	39-50	40-47	10-14
	8	48	38	14