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Neuroretinal Rim Area in Diabetes Mellitus

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Neuroretinal rim area (NRA) may indicate the amount of viable optic nerve tissue. Changes in the NRA have been found to occur in people with glaucoma. We sought to determine whether there were effects of retinopathy and intraocular pressure (IOP) on NRA in eyes of people with diabetes. Measurements of optic discs and cups were taken from 35-mm stereoscopic slides taken with a Zeiss fundus camera. The photographs were taken during a population-based study. The difference between disc and cup area was taken to be the NRA. Median photographic NRA from 2085 right eyes was 10.5 mm^2. In younger- and older-onset persons, NRA showed a tendency to increase with age and, inconsistently, with the severity of diabetic retinopathy; it decreased with increasing IOP in older-onset persons not taking insulin. The cohort was reevaluated 4 yr later. NRA increased in all groups. Measurements from photographs taken of a nondiabetic comparison group showed no change over the same interval. These data suggest that NRA may be affected by diabetes. This could be due to nerve swelling. Invest Ophthalmol Vis Sci 31:805–809, 1990

It has been suggested by some investigators that neuroretinal rim area (NRA) may be an indicator of viable nerve tissue comprising the optic disc,[1-5] and therefore, may be decreased in people with glaucoma. NRA may not be a good measure of viable nerve tissue when other disease processes such as overt papilledema or pseudo-tumor cerebri are present. In these conditions, swelling of the nerve and estimates of NRA might indicate enlargement compared to estimates made before the onset of the condition.

Diabetes mellitus is a condition with manifestations in the retina, the lens, and the optic nerve (diabetic papillopathy).[6] Therefore, we sought to evaluate the effects of age and intraocular pressure (IOP) as well as retinopathy in persons with diabetes.

Materials and Methods

Case identification procedures have been described in detail in previous reports.[7-9] A brief relevant description is provided below.

Population

A sample of 2990 diabetic persons from an 11-county area in south central Wisconsin was selected for the study. The sample was composed of two groups. The first group consisted of all persons who were diagnosed to have diabetes before they reached their 30th birthday, and who took insulin (n = 1210); this group will be referred to as "younger-onset." The second group consisted of a probability sample of people who were diagnosed to have diabetes at 30 yr of age or older and who had the diagnosis confirmed by a casual or postprandial serum glucose level of at least 11.1 mmol/l or a fasting serum glucose of at least 7.8 mmol/l on at least two occasions (n = 1780); this group will be referred to as "older-onset." The baseline examination occurred in 1980–1982. A follow-up study was done in 1984–1986.

Procedures

The examinations, medical history, ocular examination, and photography were performed in a mobile examining van which was located in the communities in which the participants lived. Informed consent was obtained from each subject. The stereoscopic photographs were sent for processing and were mounted at the study office. Grading for diabetic retinopathy was done at the Fundus Photograph Reading Center of the University of Wisconsin (Madison, WI).

The stereoscopic photographs of the optic nerve head were graded for disc and cup size directly from the photographs according to a standard protocol using a measuring template. Details of the grading scheme have been published elsewhere.[10-13] Each photograph was measured independently by two graders. The formula for the area of an ellipse was applied to the measured diameters of cup and disc. The cup and disc measurements used were the means

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Table 1. Distribution of neuroretinal rim area for right and left eyes

Neuroretinal rim area (mm^2)	Right eyes: Younger-onset n	Right eyes: Younger-onset %	Right eyes: Older-onset, insulin n	Right eyes: Older-onset, insulin %	Right eyes: Older-onset, no insulin n	Right eyes: Older-onset, no insulin %	Left eyes: Younger-onset n	Left eyes: Younger-onset %	Left eyes: Older-onset, insulin n	Left eyes: Older-onset, insulin %	Left eyes: Older-onset, no insulin n	Left eyes: Older-onset, no insulin %
<5	0	0.0	1	0.2	2	0.3	1	0.1	0	0.0	0	0.0
5 < 6	3	0.3	4	0.7	2	0.3	1	0.1	1	0.2	5	0.8
6 < 7	19	2.1	9	1.6	5	0.8	20	2.3	4	0.7	6	1.0
7 < 8	97	10.9	29	5.1	28	4.4	74	8.6	27	4.8	26	4.3
8 < 9	164	18.4	67	11.9	52	8.2	182	21.2	67	12.0	63	10.4
9 < 10	210	23.6	91	16.1	94	14.9	198	23.1	102	18.2	98	16.1
10 < 11	154	17.3	111	19.7	125	19.8	145	16.9	96	17.1	115	18.9
11 < 12	115	12.9	106	18.8	126	20.0	108	12.6	105	18.8	93	15.3
12 < 13	70	7.9	65	11.5	85	13.5	60	7.0	82	14.6	82	13.5
13 < 14	32	3.6	41	7.3	57	9.0	39	4.6	30	5.4	55	9.1
14 < 15	12	1.3	13	2.3	22	3.5	15	1.8	20	3.6	32	5.3
15 < 16	8	0.9	12	2.1	12	1.9	9	1.1	13	2.3	17	2.8
16 < 17	4	0.4	9	1.6	11	1.7	3	0.4	7	1.2	5	0.8
17+	2	0.2	6	1.1	10	1.6	2	0.2	6	1.1	10	1.6
	890		564		631		857		560		607	

from the two graders. The NRA for each eye was calculated by subtracting the area for the cup from the area for the disc.

Numbers within and between tables vary. This variation is due to the following circumstances: photographs could not be taken of all study participants; some photographs could not be graded, because of obscuration by diabetic retinopathy; in some cases stereoscopic effect was lacking or photographic quality was poor; and data occasionally were missing for the other variables involved in the specific analyses.

Data Handling and Analysis

Wisconsin Storage and Retrieval (Madison, WI), an information-processing software system, was used for processing all subject files.[14] Statistical Analysis System (Cary, NC) was used for calculating the student t-test and multiple linear regression.[15]

Results

Table 1 describes the frequency distributions of NRA for right and left eyes of study subjects. Data for older-onset persons who reported taking insulin are given separately from the data for those not taking insulin. Younger-onset people have smaller NRAs than older-onset people, as seen in Table 1 and as confirmed by student t-tests on mean NRA ($P < 0.0001$). Distributions are similar for right and left eyes. Pearson correlation coefficients for NRAs of right and left eyes were 0.79 for younger-onset people, 0.75 for older-onset insulin-takers, and 0.76 for older-onset people not taking insulin. Because of these findings, and because relationships of NRA to other variables did not differ systematically between the eyes, the analyses presented in this paper are for the right eye only except when there were differences between the eyes. In addition, because of the effect on

Table 2. Neuroretinal rim area of right eyes by age at baseline examination

Age (yr)	Younger-onset n	Younger-onset Mean (mm^2)	Younger-onset SD	Older-onset, insulin n	Older-onset, insulin Mean (mm^2)	Older-onset, insulin SD	Older-onset, no insulin n	Older-onset, no insulin Mean (mm^2)	Older-onset, no insulin SD
0–9	24	9.9	1.8						
10–19	212	9.7	1.7						
20–29	211	10.0	2.0						
30–44	191	10.4	1.9						
45+	86	10.9	1.9						
30–44				22	9.8	1.8	15	10.4	1.6
45–54				79	10.6	1.7	48	10.9	2.5
55–64				134	10.9	2.0	146	11.1	1.9
65–74				158	11.3	2.2	182	11.2	2.1
75+				68	11.7	2.3	124	11.9	2.6
P*		<0.0001			<0.0001			<0.01	

* Based on linear regression.

Table 3. Neuroretinal rim area of right eyes by duration of diabetes at baseline examination

	Younger-onset			*Older-onset, insulin*			*Older-onset, no insulin*		
Duration (yr)	*n*	*Mean (mm^2)*	*SD*	*n*	*Mean (mm^2)*	*SD*	*n*	*Mean (mm^2)*	*SD*
0–4	146	9.5	1.6	77	10.3	1.9	196	11.2	2.3
5–9	195	9.8	1.8	86	11.1	2.0	177	11.3	2.1
10–14	139	10.2	2.0	80	11.1	2.4	55	11.4	1.8
15–19	81	10.5	1.8	109	11.2	2.1	53	11.3	2.3
20+	163	10.8	1.9	109	11.2	2.0	34	11.8	3.0
*P**		<0.0001			<0.05			>0.10	

* Based on linear regression.

magnification of the image, those eyes with refractive errors of 3 diopters or more are excluded from these analyses.

The mean NRAs increased modestly with age (Table 2). This was true for all three groups. The relationship of NRA with duration of diabetes is shown in Table 3. A significant positive relationship was found in younger-onset and older-onset insulin-taking persons. In the latter group, the association was not significant for left eyes.

We examined the relationship between IOP and NRA (Table 4). There was a modest inverse association, which was significant only in right eyes of older-onset people who did not use insulin.

During the interviews, participants were asked whether or not they had glaucoma. NRA was not significantly associated with glaucoma in the small number (n = 48) of people with a positive history.

Because of a possible effect of the severity of diabetic retinopathy on NRA, we grouped right eyes by level of retinopathy (Table 5). There was a positive association in all three groups. The relationship was significant in right and left eyes of younger-onset persons, in left eyes of older-onset persons using insulin, and in right eyes of older-onset persons not using insulin.

We were able to evaluate whether there was a change in NRA 4 yr later. Overall, mean NRAs tended to increase at the 4-yr examination compared to the mean NRAs found at the prevalence examination in all groups (Table 6). The change in NRA was the result of larger discs and smaller cups. NRA increased with an increasing level of glycosylated hemoglobin in the younger-onset group only. Age and duration of diabetes at the baseline examination were not associated with increased NRA at follow-up in any group.

The initial measurements of cup and disc were performed during the course of a large field study. Thus, the grading spanned several years. In order to be certain that the differences in gradings were not the result of temporal trends in grading, we selected photographs of right eyes of 50 persons for whom we had baseline and follow-up stereoscopic photographic pairs. The pairs were randomized and graded in masked fashion on 2 consecutive days by one of the original graders. The mean increase in the NRA was 0.37 mm^2. This difference was statistically significant (P = 0.003). Similarly, we graded optic discs and cups of 60 people who were free of diabetes and who had been seen and photographed contemporaneously with the diabetic subjects. There was no significant difference in NRA between two sets of photographs for this group (P = 0.29).

Discussion

A potential explanation for the change in NRA could have been a systematic increase in magnification of the follow-up photographs. If this were true,

Table 4. Neuroretinal rim area of right eyes by IOP at baseline examination

	Younger-onset			*Older-onset, insulin*			*Older-onset, no insulin*		
IOP (mmHg)	*n*	*Mean (mm^2)*	*SD*	*n*	*Mean (mm^2)*	*SD*	*n*	*Mean (mm^2)*	*SD*
0–13	187	10.4	2.0	100	11.4	2.1	115	11.5	2.1
14–15	136	10.2	1.9	92	11.0	2.1	109	11.5	2.3
16–18	207	9.8	1.9	138	10.9	2.2	146	11.5	2.5
19+	183	10.1	1.8	126	11.0	2.0	141	10.8	1.8
*P**		>0.10			<0.10			>0.05	

* Based on linear regression.

Table 5. Neuroretinal rim area of right eyes by retinopathy at baseline examination

Severity of diabetic retinopathy	*Younger-onset*			*Older-onset, insulin*			*Older-onset, no insulin*		
	n	*Mean (mm^2)*	*SD*	*n*	*Mean (mm^2)*	*SD*	*n*	*Mean (mm^2)*	*SD*
10	269	9.5	1.6	174	10.9	2.1	360	11.2	2.1
20	143	10.4	2.0	68	10.6	1.8	61	11.3	1.8
30	98	10.3	1.7	75	11.5	2.2	51	11.8	2.4
40	124	10.2	1.9	106	11.2	2.2	38	11.7	3.0
50	3	10.8	1.5	4	11.2	2.8	—	—	—
60	87	11.0	2.1	34	11.1	1.8	5	14.2	1.9
*P**		<0.0001			>0.10			<0.005	

* Based on linear regression.

both the disc and the cup would have been larger. However, this was not the case. The increase in NRA resulted from larger discs and smaller cups. Therefore, the finding is unlikely to be spurious.

Swelling of the optic disc, as in papilledema, usually is believed to be due to a disturbance in the pressure gradient across the lamina cribrosa. Thus, it commonly is considered to occur with increased intracranial pressure, malignant hypertension, and orbital disease, with the histologic counterpart being intraaxonal distension involving the prelaminar region of the optic nerve.[16] Overt diabetic papillopathy occurs infrequently. Little is known about the etiology, pathophysiology, and histology of this clinical syndrome.[6] In the current study, no eyes with overt diabetic papillopathy were encountered. The findings of larger rim areas with increasing age and duration of diabetes in the prevalence data, and the increase in rim areas at follow-up, suggest a subtle but consistent relationship of diabetes with NRA. Studies of peripheral nervous tissue of diabetic persons and experimental animals suggest that accumulation of sugar alcohols and increased endoneurial fluid pressure may be an early manifestation of diabetes.[17-20] It may be that the finding of a positive relationship of glycosylated hemoglobin and increased NRA is a manifestation of this proposed mechanism. In a few studies in diabetic patients, very early functional abnormalities suggestive of central nervous system tract dysfunction have been found.[21-22] There are some reports of decreased visual evoked potential in persons with diabetes.[23-25] We are not aware of any histologic studies to correlate with these functional measures. Our findings, however, are suggestive of an anatomic change.

Hernandez et al[26] have reported a change in extracellular matrix, and Ogden et al[27] have reported more interpore tissue in the lamina cribrosa with age. Balazsi et al[28] have suggested a possible decrease in the number of axons with increasing age, but their data were inconclusive, as were those of Repka and Quigley.[29] The findings of these investigators may be consistent if there were a large enough increase in connective tissue volume and swelling of (remaining) nerve fibers. Further investigation in other populations is needed to confirm the finding of increased NRA with age, as found in the current study.

In computations of NRA, a correction for the magnification of the photographic image frequently is made. The correction takes into account the refraction and corneal power or the axial length.[1,5] The correlation between "corrected" rim area and direct measurements of neuroretinal rim area was found to be 0.82.[5] Significant deviation from a linear relationship was only found for eyes with greater than 3 diopters of ametropia. In the current study, neither keratometry nor axial length measurements were performed. Therefore, no attempt was made to correct for these. In all analyses, except when comparing right and left eyes, we excluded eyes with a refractive

Table 6. Change in area of optic discs, optic cups, and neuroretinal rim areas of right eyes between baseline and follow-up

	Younger-onset		*Older-onset, insulin*		*Older-onset, no insulin*	
	Area (mm^2)	*P*	*Area (mm^2)*	*P*	*Area (mm^2)*	*P*
Change in optic disc (mm^2)	0.32	<0.0001	0.26	<0.0001	0.35	<0.0001
Change in optic cup (mm^2)	−0.13	<0.0001	−0.17	<0.0001	−0.07	<0.10
Mean increase in NRA (mm^2)	0.45	<0.0001	0.43	<0.0001	0.42	<0.0001
n	610		248		311	

error that equaled or exceeded 3 diopters. Using "uncorrected" areas might also create some disparity when comparing our rim areas to those that were calculated in studies making this correction. Our uncorrected areas are similar to those of Balazsi and colleagues.[5] Were a comparison to be made, other authors could use their uncorrected data to compare with ours, assuming that the distribution of refractive errors was the same.

Another source of variation when comparing studies is that different investigators have used different methods of imaging the discs before taking their measurements. Jonas et al[2] and Balazsi et al[5] projected stereoscopic photographs taken with a 2× magnification adapter. The projected image was magnified to 20–25× the photographic image, and the contour then was traced. An image analysis system was used to compute the rim area based on the tracings. Airaksinin et al used enlarged prints made from stereoscopic photographs, measured disc and cup with a planimeter, and took the difference in measurements as the rim area.[4] Caprioli and Miller[1] used a computerized image analysis system which provides a videographic image of the disc. We have measured cups and discs directly from the stereoscopic photographs. Differences in findings between studies can also be due to using even slightly different landmarks to define discs or cups.[3] These differences in technique do not effect results when computing changes in rim area within one study.

Key words: neuroretinal rim area, optic cup and disc measurements, diabetes, longitudinal studies

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