

Effect of aging on optic nerve appearance: a longitudinal study

Frank J Moya, Luca Brigatti, Joseph Caprioli

Abstract

Aim—To determine whether aging causes detectable changes in the appearance of the optic disc.

Methods—A retrospective longitudinal study was performed with quantitative and qualitative evaluations of digitised stereoscopic optic disc photographs of 224 eyes of 224 subjects. There were three groups: 100 normal subjects from the Framingham Eye Study, 68 glaucomatous patients followed longitudinally, and 56 normal subjects and glaucoma patients who had separate sets of disc photos taken on the same day. A disc was considered qualitatively worse if two of three experienced observers agreed that it was worse. Quantitative progression was defined as a >10% decrease in rim/disc area ratio measured with computer assisted planimetry.

Results—With quantitative evaluation, normal eyes (mean follow up 13 years) and same day eyes displayed no statistically significant difference in change of rim/disc area ratios ($p=0.095$), nor in the number of discs that progressed—five of 100 (5%) *v* two of 56 (4%) respectively. Glaucomatous eyes (mean follow up 9 years) showed a quantitative loss of disc rim in 24 of 68 (35%), and differed significantly from the normal eyes both in the change of rim/disc area ratio ($p<0.0005$) and number of discs that progressed ($p<0.0005$). With qualitative evaluation, the number of progressive discs in the glaucomatous eyes (31%) differed significantly ($p<0.0005$) from the normal eyes (3%) and the same day eyes (0%).

Conclusions—Over a period of follow up appropriate for long term outcome studies in glaucoma, there was no quantitatively or qualitatively detectable neuroretinal rim loss in normal aging optic nerves with stereoscopic optic disc photographs.

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Ophthalmologists monitor the appearance of the optic nerve head to obtain crucial information regarding the progression of a patient's glaucoma and the effectiveness of therapy.¹⁻⁶ It is often possible to appreciate changes in the optic nerve disc appearance before any visual field loss can be perceived by the patient or detected with visual field testing.^{7,8} Changes in optic disc appearance are caused by the death of retinal ganglion cells and the loss of their axons in the optic nerve; however, the exact mechanisms of damage remain unknown.⁹ The effect of aging on the appearance of the optic disc is not known with certainty. Aging is generally believed to

have little effect on disc rim area; however, most studies that have addressed this question have either been cross sectional or have had small numbers of subjects in longitudinal studies of relatively short duration. It is important to know whether aging alone can cause clinically detectable changes in optic disc appearance that may be mistaken for early glaucomatous progression over a long enough time period suitable for clinical glaucoma trials. The purpose of this study was to determine whether aging causes detectable changes in the appearance of the optic disc.

Methods

SUBJECTS

A total of 224 eyes of 224 subjects were evaluated. Included were 100 normal healthy subjects, and two control groups—one “positive” and one “negative”. These comprised 68 open angle glaucoma patients followed longitudinally (positive control group) and 56 subjects who had “sequential” disc photos taken on the same day (negative control group). The glaucomatous patients should have evidence of change in their optic disc appearance and therefore acted as the control for progression. These patients had intraocular pressures greater than 21 mm Hg on two or more separate occasions or a history of elevated intraocular pressure before treatment and typical, reproducible, early to moderate glaucomatous visual field defects. Typical glaucomatous visual field defects were defined in a reliably performed automated threshold field test as at least: (1) two or more adjacent points with a $p<0.01$ or more loss in the superior or inferior arcuate zones, compared with perimetry defined age matched normal values; (2) three or more adjacent points with $p<0.05$ or more loss at the superior or inferior arcuate areas; or (3) a 10 decibel difference across the nasal horizontal mid line in two or more adjacent locations. Patients with primary open angle glaucoma, pseudoexfoliation glaucoma, and pigment dispersion glaucoma were included. Patients with diseases capable of confounding the diagnosis or follow up of glaucoma (for example, optic neuritis or other neuro-ophthalmological conditions) were excluded. Patients were aged 29-79 years at baseline (mean age 56 (SD 14) years), and had a mean follow up of 9.0 years (range 6-19 years).

The 56 same day control group consisted of glaucoma, glaucoma suspect, and normal subjects who had four stereoscopic pairs of photographs taken on the same day at separate times. The fundus camera was reset after each sitting to simulate follow up conditions. Two different stereoscopic pairs randomly chosen for each patient were used as a control for no change in the rim/disc ratio.

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The 100 normal test subjects were from a randomly chosen subset of normal individuals from the Framingham Eye Study for which good quality baseline and follow up stereoscopic disc photos were available. All subjects had intraocular pressures between 11–18 mm Hg, the optic discs were not suspicious for glaucoma, none had a diagnosis nor a family history of glaucoma or diabetes. Patients were aged 52–85 years at the start of the study, and had a mean follow up of 13 years (range 9–16 years).¹⁰

Stereoscopic photographs were taken with standard telecentric fundus cameras, with a non-simultaneous technique and a non-standardised stereo base established by lateral camera shift. To enhance the stereoscopic effect and better appreciate three dimensional details, the stereoscopic base (or the distance between the “point of view” from which the left and right slide of the stereoscopic pair are taken) was always the widest allowed by the dilated pupil size. Every attempt was made to avoid parallax between baseline and follow up stereoscopic pairs. This occurs when the slides from two stereoscopic pairs are taken from two different positions so that the relative location of structures lying on different planes (for example, vessels and rim surface) appears shifted in the two stereoscopic pairs giving a false impression of change. Poor stereoscopic separation and parallax errors can be avoided by taking the left and right slides of the stereoscopic pair from the left most and right most position respectively, as close to the iris margin as possible.

The colour stereoscopic disc photo slide images were digitised onto Kodak photo compact discs (Eastman Kodak Company, Rochester, NY, USA). The optic disc images were then cropped with the image processing program, Adobe Photoshop 3.0 (Adobe Systems Inc, Mountain View, CA, USA) to 400×400 pixel, 16 bit, colour images that were then saved in a computer database. This database was prepared so that the bit map stereoscopic pair images were masked to diagnoses and chronology.

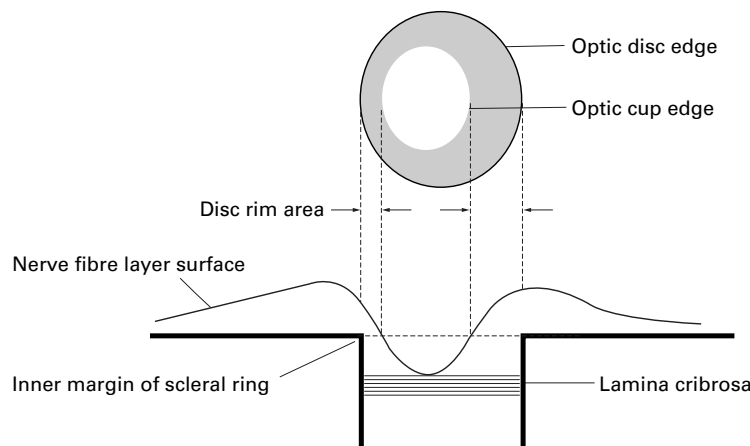


Figure 1 The disc rim is the area contained between the disc edge and the cup edge. The cup edge is where the surface of the nerve fibre layer intersects the imaginary plane established by the inner margin of the scleral ring.

QUANTITATIVE EVALUATION

A specially written computer planimetry program employing Microsoft Visual Basic 3.0 (Microsoft Corporation, Redmond, WA, USA) allowed the bit map stereoscopic images to be placed side by side on a computer screen as a full colour stereoscopic pair. A mirror stereoscopic viewer (VCH Verlagsgesellschaft, Weinheim, Germany) was used by the observer to provide stereoscopy. The observer used a mouse driven cursor to simultaneously trace the cup and disc margins directly onto both stereoscopic images, enabling the simultaneous viewing and tracing of what appeared as a single three dimensional image. The position of the cup was defined as the intersection of an imaginary plane that runs across the level of the scleral edge of the optic nerve outlet and the surface of the nerve head (Fig 1).¹¹ In cases where no rim remained, the cup edge and the disc edge were coincident. The slope of the rim was not taken into consideration. The planimetry program calculated the disc area, cup area, and rim area (disc minus cup area) in pixels, as well as the rim/disc area ratio. Rim/disc area ratio measurement was used for the study because each eye acted as its own control, negating the need for the correction of differences in refractive errors or differences in photographic magnification. The difference between the baseline and follow up rim/disc area ratios was calculated as the percentage of change between the two ratios.

One observer was trained on serial sets of 20 eyes, which included glaucoma, glaucoma suspect, and normal subject optic discs randomly chosen. Optic disc measurements of the same images were made on two separate days. Intraobserver variability was determined to have a 95% confidence interval of 9.8%; therefore, a change in the rim/disc area ratio greater than this was chosen to represent “real” change, significant both clinically and statistically.

QUALITATIVE EVALUATION

The baseline and follow up stereoscopic images were also evaluated by three expert observers who were masked to the diagnoses of the subjects, chronology of the images, and results of the other observers. They evaluated the images for evidence of change in the optic disc appearance. The images were prepared using Adobe Photoshop 3.0 (Adobe Systems Inc, Mountain View, CA, USA) by combining four 400×400 pixel bit map images that comprised two stereo pairs into an 800×800 pixel, 16 bit colour composite image. This image was displayed on a computer screen in a manner that enabled the observers to see both stereoscopic pairs with a stereoscopic viewer (VCH Verlagsgesellschaft, Weinheim, Germany). A disc's status of having changed or remained stable was determined by the agreement of at least two of three masked, experienced observers (fellowship trained glaucoma subspecialists).

STATISTICS

We calculated the statistical power of the study to find a 10% difference between the progression rates between the groups. The

Table 1 Quantitative progression

Study group	Total	Progressed (worse)			Improved (better)			
		Number	p value* (compared with same day)	p value* (compared with normal)	Number	p value* (compared with same day)	p value* (compared with Normal)	p value† (baseline v follow up)
Same day	56	2	—	—	3	—	—	0.978
Normal	100	5	0.30	—	1	0.12	—	0.939
Glaucoma	68	24	<0.0005	<0.0005	6	0.21	0.02	0.237

*Fisher's exact test; †one sample *t* test.

Table 2 Qualitative progression

Study group	Total	Progressed (worse)			Improved (better)		
		Number	p value* (compared with same day)	p value* (compared with normal)	Number	p value* (compared with same day)	p value* (compared with normal)
Same day	56	0	—	—	0	—	—
Normal	100	3	0.26	—	3	0.26	—
Glaucoma	68	21	<0.0005	<0.0005	2	0.30	0.35

*Fisher's exact test.

Kolmogorov–Smirnov test was to be used to determine the type of distributions of the glaucomatous, same day control, and normal eye data. The independent group's *t* test was to be used if the data were normally distributed. Otherwise, the Mann–Whitney U test was used. Fisher's exact testing was used to determine the independence between the discs that progressed or improved (defined as a rim/disc ratio that changed more than 10%) between the normal eyes and the other groups. In the qualitative arm of the study, Fisher's exact testing was used to determine the statistical significance between the number of discs that displayed progression or improvement in the glaucoma, normal, and same day subjects. One sample *t* test was used to compare baseline and follow up disc measure-

ments within each group (glaucoma, normal, and same day).

Results

The statistical power of the study to find a 10% difference between the progression rates between any of the groups (assuming $p=0.05$) was 0.98. In quantitative evaluation, the normal eyes (mean 13 year follow up) and the same day subjects displayed no statistically significant differences in the change of rim disc area ratios ($p=0.095$, Mann–Whitney U test), nor in the number of discs that progressed ($p=0.30$, Fisher's exact test), 5% (five of 100) v 4% (two of 56), respectively. The glaucomatous eyes (mean follow up 8.7 years, median follow up: 8.3 years) showed progressive loss of the disc rim area in 35% of subjects (24 of 68), differing significantly from both the same day and normal groups for change of rim disc area ratio ($p<0.0005$, Mann–Whitney U test) and number of discs that progressed ($p<0.0005$, Fisher's exact test). There were no statistically significant differences between number of discs that showed improvement among the normal and same day subjects, and the glaucoma and same day subjects ($p > 0.1$, Fisher's exact test) whereas between glaucoma and normal subjects the difference barely reached the significance level ($p = 0.02$, Fisher's exact test). Examination of the histograms for the three groups, in Figure 2, reveals differences between the distributions of the measurements of the glaucomatous and normal eyes. The number of patients that progressed, improved, or remained stable are shown in Table 1.

In the qualitative arm of the study, the number of progressing discs in the normal eyes, 3% (three of 100, Fisher's exact test), did not differ significantly from the same day eyes of which none showed progression ($p=0.25$, Fisher's exact test). However, the normal group differed significantly from the glaucomatous eyes in which 31% (21 of 68) showed change ($p<0.0005$, Fisher's exact test). The glaucomatous eyes also differed significantly from the same day group ($p<0.0005$, Fisher's exact test). There was no statistically significant difference among the groups for what concerns the number of improved discs

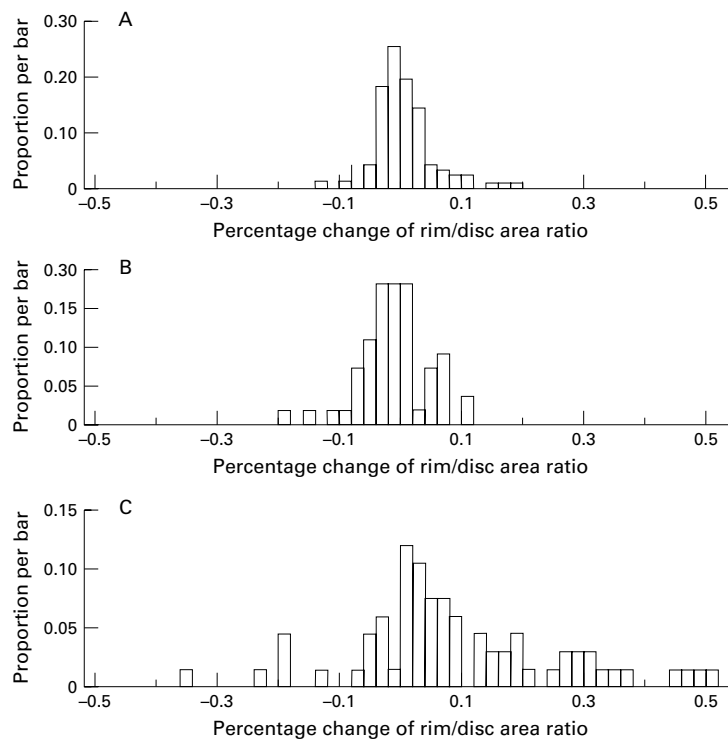


Figure 2 (A) Distribution of the percentage change of the rim/disc area ratio of the Framingham normal eyes. (B) Distribution of the percentage change of the rim/disc area ratio of the same day control eyes. (C) Distribution of the percentage change of the rim/disc area ratio of the glaucomatous eyes.

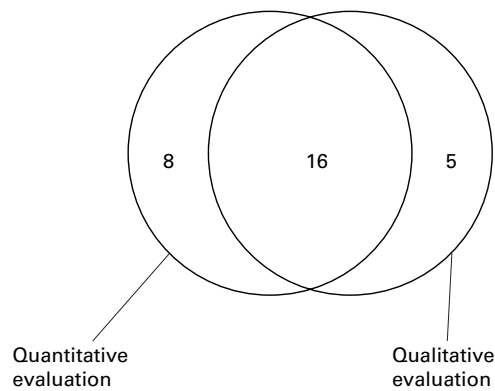


Figure 3 Venn diagram showing the relation between numbers of eyes progressing in the glaucoma group by quantitative and qualitative evaluations.

($p > 0.2$, Fisher's exact test). The numbers of patients that progressed, improved, or remained stable, are shown in Table 2.

When the qualitative and quantitative methods are combined, 29 glaucomatous discs progressed: of these 16 were evaluated as having progressed by both qualitative and quantitative methods, eight quantitatively alone, and five qualitatively alone (Figs 2 and 3). Eight eyes displayed improvement—six quantitatively alone, and two qualitatively alone. In the normal eyes, eight discs progressed—five quantitatively alone, and three qualitatively alone. Three eyes displayed improvement—one by both methods and two quantitatively alone. There continued to be a statistically significant difference in the total number of discs that progressed between the glaucomatous and normal ($p < 0.0005$, Fisher's exact test) and same day ($p < 0.0005$, Fisher's exact test) groups. No significant difference between the normal and the same day groups was evident ($p > 0.05$, Fisher's exact test).

The average difference in rim/disc area ratio between follow up and baseline measurements for the glaucoma, normal, and same day groups were 0.0136, -0.00071, and -0.000128 respectively. No statistically significant difference between base line and follow up disc measurements was found for the glaucoma ($p = 0.237$, one sample *t* test), normal ($p = 0.939$, one sample *t* test), or same day subjects ($p = 0.978$, one sample *t* test).

Discussion

Longitudinal studies of optic disc change in glaucoma do not generally have the benefit of parallel normal controls. It is important to know if the normal optic nerve changes in appearance secondary to the aging process alone, and to be able to correctly interpret any longitudinal changes identified in glaucomatous eyes. Study of normal optic discs over a period suitable for long term studies of glaucoma is required to provide appropriate controls for clinical trials and outcomes research.

Some histological studies support the idea that the number of axons decreases with age, while others yielded contrasting results. Dolman *et al* counted axons in histological sections of 300 cadaver eyes from 150 patients aged 0 to

96 years and found a general trend of axonal loss that became particularly noticeable from age 60 onward.⁸ Balazsi and coworkers also demonstrated a statistically significant inverse correlation between age and axon count in 16 normal optic nerves from patients aged 3.5–82 years, estimating a yearly loss of 5637 axons.⁹ However, the correlation lost significance after eliminating the eyes that suffered long delays before fixation. Johnson *et al* analysed 13 optic nerves from patients aged 31–86 years, and were able to find a statistically significant loss of axons with age.¹² Repka and Quigley performed a histological study of 19 normal eyes from patients aged 4–84, and found only a slight decrease of optic nerve axons, approximately 500 per year or about 6% over 75 years; they were not able to establish a statistically significant relation between nerve fibre loss or rim area with age.¹³

Cross sectional studies performed in vivo have attempted to relate optic disc appearance with age, again yielding contrasting results. Carpel and Engstrom estimated the cup/disc diameter ratio in 580 normal individuals with the Hruby lens and found the cup/disc ratios significantly larger in older patients.¹⁴ Bengtsson examined the monoscopic photos of 2274 normal eyes and found that the disc and cup diameters were larger and the rim breadth was smaller in older patients.¹⁵ Healey and coworkers examined the pictures of 6579 eyes and found that, after adjusting for disc size and intraocular pressure, the cup diameter increased by 0.01 mm, the rim width decreased by 0.01 mm and the cup/disc ratio increased by 0.01 per every decade of age increase.¹⁶ Britton and coworkers studied 113 normal eyes from 113 patients aged 20–81 with stereoscopic planimetry and determined that there was no correlation between age and rim area.¹⁷ Jonas and coworkers found no correlation between disc rim area and age.¹⁸ Funk and coworkers used the Rodenstock optic disc analyser to study 194 eyes of 122 normal subjects aged 7–84 years.¹⁹ They concluded that there was no significant difference between the mean rim area of any age group that they studied. Conversely, Tsai and coworkers, used the Rodenstock optic disc analyser to study the optic disc variables of a group of normal patients (aged 18–87 years) and found that rim area statistically significantly declined with age.²⁰ Varma and coworkers analysed simultaneous stereoscopic optic disc photographs from 3387 healthy individuals (40 years old or older) using the Topcon image analyser and reported that no progressive age related decline in neural rim area was detectable.²¹ Kee and coworkers evaluated 14 topographic optic disc variables of 104 normal Asian adults of both sexes aged 40–68 using a confocal scanning laser ophthalmoscope. They found that age did not have any significant influence on optic disc variables ($p > 0.1$).²² Schwartz and associates studied six patients with various diagnoses over variable periods, assessing changes in cup/disc ratios and disc pallor.²³ Included in the study were one normal patient with 18 month follow up and an open angle glaucoma patient with a

7.3 year follow up. Neither patient showed any trend of change in optic disc measurements over time. Airaksinen and co-workers used planimetry to study stereoscopic photographs of five normal, 54 exfoliative glaucoma, 61 primary open angle glaucoma, and 50 normal tension glaucoma patients who had a mean follow up of 10 years (range 5–15 years).²⁴ It was found that the rate of rim loss was the same for glaucomatous and glaucoma suspect patients, and that the mean values of the exfoliative glaucoma and primary open angle glaucoma eyes did not differ significantly. The yearly rim loss was 0.23% in the five normal eyes, 0.47% and 2.75% in stable and deteriorating glaucoma suspect patients, and 3.47% in glaucoma patients. The paper did not provide confidence intervals for observer variability. Airaksinen commented that the measurement variation of his method exceeded the 1.2% yearly rate of rim loss of OHT patients with visible change and that it would take years to distinguish between true rim loss or measurement variation.

In our study the change of rim disc area ratio of normal eyes was not found to be statistically significantly different from that of the same day controls. This implies that the rim disc area ratio of the normal eyes remains relatively constant over long periods. As the number of discs that qualitatively displayed progression between the two groups also was not statistically significantly different, it is reasonable to conclude that the appearance of the normal optic nerve also remains relatively unchanged. This was even more obvious when the normal and same day groups displayed a strongly significant difference when compared with the glaucomatous eyes both in the evaluation of rim disc area ratio change and qualitative progression. These data indicated that there was a strongly significant difference in the loss of neuroretinal rim area between normal and glaucomatous optic nerves.

That progression between the normal eyes, same day, and glaucoma groups was found to be highly statistically significant with glaucoma, reaffirmed that progressive rim loss occurs at a measurable rate in glaucoma. The rate of disc “improvement” in the normal eyes and in the same day eyes indicates the magnitude of the “noise” of the method. The borderline statistically significant difference between improved glaucoma discs and improved normal discs is probably an effect of the noise, particularly considering that the difference was not statistically significant when improved glaucoma were compared with same day discs.

t Test analysis failed to display a statistically significant difference between base line and follow up disc measurements for the normal ($p=0.939$, one sample *t* test), and same day subjects ($p=0.978$, one sample *t* test). The lack of a significant difference between the glaucoma baseline and follow up measurements ($p=0.237$, one sample *t* test), may be explained by the fact that most glaucomatous discs, even those that changed more than 10%, as a group displayed little change; thereby, the discs that progressed were “diluted” among the discs that did not progress. That the *p* value of the glau-

coma group is much smaller than that of the other two groups may indicate a trend of progression that may have been borne out with a larger number of patients.

The diagnostic value of qualitative disc evaluation has been shown²⁵; however, this study describes a new computerised planimetry program and displayed some interesting results. An indication of the noise of the method may be suggested by the lack of significant difference among the groups in the number of optic discs improving over time. None the less, this method can show a quantitative change in glaucomatous discs, while at the same time not showing a quantitative change in normal discs. This suggests the value of this approach. One limitation of this quantitative method is that it can only reliably detect changes in rim/disc area ratio of greater than 10%. Since the normal subjects did not show, as a group, a change of this magnitude in 13 years it can be inferred that up to 0.8% change per year may have occurred undetected. This value may be considered the “upper limit” of detectable change. That some discs were found to progress only qualitatively or quantitatively may indicate the type of neuroretinal rim loss. Broad diffuse loss is found more readily with planimetry, while focal defects may be seen qualitatively, but without sufficient rim loss to qualify as quantitative progression.

The literature is sparse on long term cohort studies of normal optic discs. This study is believed to be the first to look at a large group of normal patients over a long follow up period. The one study described above that most closely resembled ours was performed by Airaksinen and co-workers. Although the two studies measure different variables (rim disc area ratio versus rim area), the significant differences found between normal and glaucomatous progression were similar.

Our study masked the observer to the chronology of the disc pairs. This removed a potential bias for the observer to ensure that disc measurements “made sense” by not having any disc with improvement, while suggesting a measure of the “noise” of the new method by the number of discs that showed “improvement”. No attempt was made to quantify rim disc area ratio progression as a percentage per year, because, except for glaucoma, the majority of the data fell within our 10% confidence interval. Any change in this area was not detectable above the “noise” of the method. The calculated progression rate for data outside of the confidence interval would be artificially high because much of the data for change is lost within the “noise” of the method.

It may be concluded that disc area loss secondary to aging is not sufficient to be mistaken for glaucomatous progression. Therefore, a clinician following a patient with glaucoma may feel confident that any progression noticed in the optic nerve head, over at least a 13 year span, is actually progression of disease and not age related neuroretinal degeneration. These findings also imply that in long term clinical glaucoma studies, age related degeneration of the optic disc should not be

considered an important confounding factor when rim loss is detected.

For future quantitative studies employing computer aided planimetry, it seems reasonable to develop different confidence limits for different groups with different disc characteristics. If the initial rim/disc ratio is responsible for the degree of variability, another approach would be to stratify the discs for baseline rim/disc ratio and develop different confidence limits accordingly, then apply the confidence limit that corresponds to the baseline rim/disc ratio of the disc that is being considered.

Potential bias in our study comes from its retrospective nature and from the availability of follow up pictures. Subjects available for follow up may have had particular characteristics that could have influenced the outcome. Social, health, and other variables may have affected both availability for follow up and the rate of aging.

What may be done in the future to further address this question? While computer aided planimetry of stereoscopic images is a sound method of disc analysis, there remains a certain degree of subjectivity when measuring disc variables. Therefore, as newer technologies, including the confocal scanning laser,²⁶ nerve fibre layer polarimetry,²⁷ and optical coherence tomography,²⁸ come to the forefront of glaucoma management and monitoring, a longitudinal study with these more objective modalities must be undertaken. Unfortunately, owing to the relatively recent appearance of these machines in the field, follow up is not yet nearly as long as is desirable for definitive studies. We were fortunate to have such a rich data base of normal eyes with lengthy follow ups from the Framingham Eye Study. It is highly desirable for ophthalmologists to locate another such study and gather normal optic disc data using the newer technologies for further study.

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