Imaging of the optic disc and retinal nerve fiber layer: the effects of age, optic disc area, refractive error, and gender

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We cross-sectionally examined the relationship between age, optic disc area, refraction, and gender and optic disc topography and retinal nerve fiber layer (RNFL) measurements, using optical imaging techniques. One eye from each of 155 Caucasian subjects (age range 23.0–80.8 y) without ocular pathology was included. Measurements were obtained by using the Heidelberg Retina Tomography (HRT), the GDx Nerve Fiber Analyzer, and the Optical Coherence Tomograph (OCT). The effects of age were small ($R^2 < 17\%$) and were limited to specific HRT, GDx, and OCT parameters. Disc area was significantly associated with most HRT parameters and isolated GDx and OCT parameters. Refraction and gender were not significantly associated with any optic disc or RNFL parameters. Although effects of age on the optic disc and RNFL are small, they should be considered in monitoring ocular disease. Optic disc area should be considered when cross-sectionally evaluating disc topography and, to a lesser extent, RNFL thickness. © 2002 Optical Society of America

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1. INTRODUCTION

An important aspect of the clinical treatment of progressive eye diseases such as glaucoma is the clinician's ability to detect and monitor subtle change over time. Recently developed optic disc and retinal nerve fiber layer (RNFL) imaging techniques are promising tools for monitoring glaucomatous progression because of their ability to provide quantitative, reproducible measures of high resolution.[1–11] However, confounding information, including the normal physiological changes of the aging eye, may affect attempts to detect disease-related change over time in a late-onset and slowly progressing disease such as glaucoma. In particular, progressive loss of optic nerve fibers with age, suggested by some postmortem studies,[12,13] may influence the assessment of both the optic disc and the RNFL. It is important to estimate the effect of age on optic disc and RNFL imaging measures so that physiological changes will not be mistaken for disease progression when these methods are used.

The purpose of the present study was to cross-sectionally determine the effect of age on optic disc and RNFL measures in normal (healthy) human eyes by using confocal scanning laser ophthalmoscopy (CSLO), scanning laser polarimetry (SLP), and optical coherence tomography (OCT). Previous reports have been inconclusive regarding the effect of age on disc topography, RNFL thickness, and optic nerve fiber axon count.[12–23] Because other physiological factors may affect optic disc topography and RNFL measures, thus possibly confounding the effect of age, we also determined the relationship between optic disc area and refractive error on optic disc topography and RNFL thickness measures. Optic disc and RNFL measures also were compared between female and male subjects.

2. METHODS

A. Subjects

One eye from each of 155 healthy Caucasian subjects who had no history of diabetes or other systemic disease and no reported ophthalmological or neurological surgery or other diseases affecting visual fields or imaging of the optic disc or the RNFL was selected for study with use of the inclusion criteria presented below. Eyes were examined with CSLO, SLP, and OCT. Informed consent was obtained from each participant, and the University of California San Diego Human Subjects Committee approved all methodology.

All subject eyes had open angles by gonioscopy, best corrected acuity of 20/40 or better, sphere within ±5.0 diopters and cylinder within ±3.0 D at time of testing. Eyes had a measured intra-ocular pressure (IOP) of ≤22 mm Hg with no history of elevated IOP. Optic discs and RNFL appeared healthy on the basis of clinical examination (indirect slit-lamp biomicroscopy with a hand-held 78 D lens). Standard (achromatic) automated perimetry glaucoma hemifield test and corrected pattern standard deviation results were within normal limits. Standard automated perimetry tests were reliable (≤25% false positives, false negatives, and fixation losses) for all subjects, and all CSLO, SLP, and OCT images were judged to be of acceptable quality by experienced operators.

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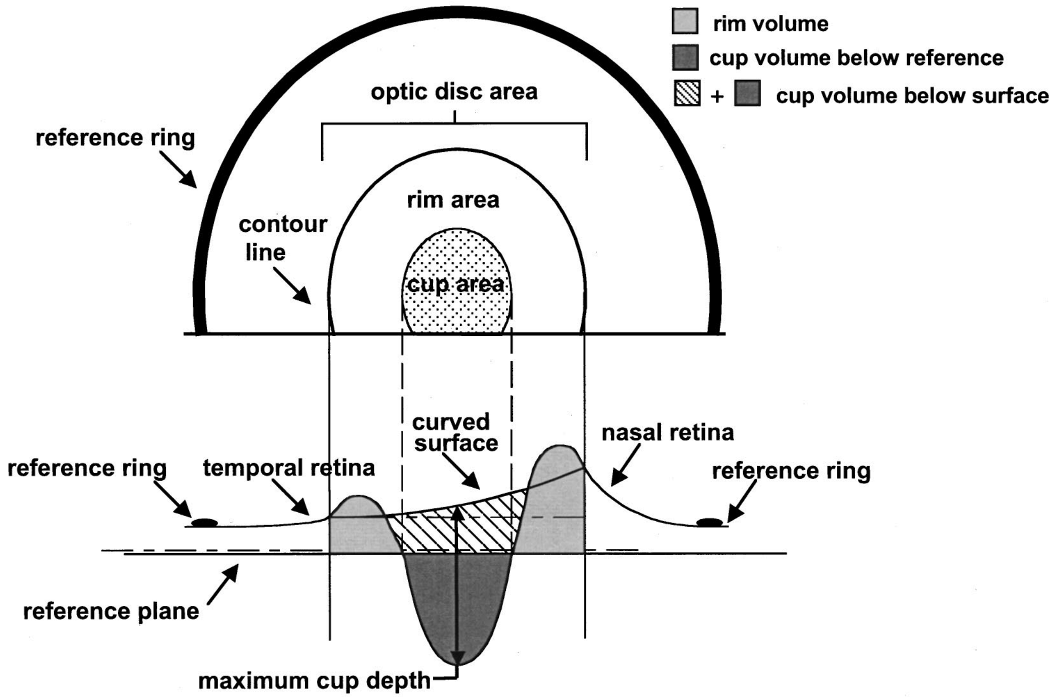

Fig. 1. Schematic depiction of HRT optic disc parameters. The reference plane is defined as a surface 50 μm posterior to the mean retinal height between 350 and 356 deg (temporal) along the operator drawn contour line delineating the optic disc margin. This region corresponds to the location of the papillo-macular nerve fiber bundle, the thickness of which is assumed to change only late in the course of progressive glaucoma.

Table 1. GDx Software Generated Parameters[a]

Parameter	Definition
Symmetry	Average of the thickest 1,500 pixels in superior quadrant ÷ average of the thickest 1,500 pixels in the inferior quadrant
Superior ratio	Average of the thickest 1,500 pixels in superior quadrant ÷ average of the median 1,500 pixels in the temporal quadrant
Inferior ratio	Average of the thickest 1,500 pixels in inferior quadrant ÷ average of the median 1,500 pixels in the temporal quadrant
Superior/nasal ratio	Average of the thickest 1,500 pixels in superior quadrant ÷ average of the median 1,500 pixels in the nasal quadrant
Maximum modulation	(Average of the thickest 1,500 pixels in the thickest quadrant − average of the median 1,500 pixels in the thinnest quadrant) ÷ average of the median 1,500 pixels in the thinnest quadrant
Superior maximum	Average of the thickest 1,500 pixels in the superior quadrant
Inferior maximum	Average of the thickest 1,500 pixels in the inferior quadrant
Average thickness	Average thickness of all pixels in the image outside of the user- defined optic disc margin
Ellipse modulation[b]	(Thickest pixel along the ellipse surrounding the optic nerve − thinnest pixel along the ellipse) ÷ thinnest pixel along the ellipse
Ellipse average[b]	Average thickness of all pixels around the ellipse
Superior Average[b]	Average thickness of all pixels around the superior quadrant of the ellipse
Inferior average[b]	Average thickness of all pixels around the inferior quadrant of the ellipse
Superior integral[b]	Total pixel volume under the ellipse in the superior quadrant
GDx LDF	$= -4.442655 - (0.156^*$ average thickness$) + (0.935^*$ ellipse modulation$) + (0.183^*$ ellipse average$)$

[a] GDx quadrants are defined as temporal (335–24 deg on unit circle), superior (25–144 deg), nasal (145–214 deg), and inferior (215–334 deg).
[b] Measured within a 10-pixel-wide ellipse 1.75 disc diameters distal to the user-defined optic disc margin.

B. Confocal Scanning Laser Ophthalmoscope

1. *Subjects and Instrumentation*

138 subjects (93 female, 45 male) were imaged with CSLO. Average (±SD) subject age was 55.7 (±15.3) yr. Age ranged from 23.0 yr to 80.8 yr with 50% of eyes over the age of 57.7 yr. There was no significant difference in age between female and male subjects ($p = 0.58$).

The CSLO [Heidelberg Retina Tomograph (HRT) Heidelberg Engineering, Heidelberg, Germany] employs confocal scanning laser technology to provide topographical measures of the optic disc and peripapillary retina. A topographical image is assembled from 32 optical sections at consecutive focal-depth planes. Each image consists of 256×256 pixels, with each pixel corresponding to retinal height at its location. Details of this instrument and descriptions of parameters have been reported elsewhere.[4,6,9] HRT software provided topographical parameters investigated in this study: disc area, cup area below reference, mean height contour, cup volume below surface, cup volume below reference, rim volume above reference, maximum cup depth, cup shape, mean cup depth, RNFL thickness, RNFL cross-sectional area, rim area, cup/disc area ratio, rim/disc ratio, HRT classification, and reference plane height. Disc area, cup area below reference, cup volume below surface, cup volume below reference, rim volume above reference, maximum cup depth, and rim area are illustrated in Fig. 1. RNFL thickness is defined as the mean height difference between the retinal surface along the operator-drawn contour line, and the reference plane. RNFL cross-sectional area is defined as the mean height difference between the retinal surface along the contour line and the reference plane, multiplied by the length of the contour line. Cup shape is defined as the third central moment of the frequency distribution of the depth values within the contour line and below the curved surface. HRT classification is the result of a linear discriminant function using age, cup shape, rim volume and height variation contour.[24]

2. *Procedure*

Three scans (10-deg field of view) centered on the optic disc were obtained for each eye. K values were recorded to correct for magnification. A mean topography image comprising these three scans was created using HRT software 2.01. The optic disc margin was outlined on the mean topographic image by a trained technician aided by viewing a simultaneous stereoscopic photograph of the fundus.

C. Scanning Laser Polarimetry

1. *Subjects and Instrumentation*

144 subjects were imaged by SLP. Of these eyes, 133 (84 female, 49 male) were included in the study. Eleven eyes

Table 2. Association between Age (yr) and Optic Disc Area (mm^2), and HRT Optic Disc Parameter Measures[a]

HRT Parameter		R^2 (%)	Slope	p
Disc Area	Age	0.85	−0.002	0.283
	Disc Area	N/A	N/A	N/A
Cup Area below Reference	Age	1.83	−0.003	0.114
	Disc Area	48.19	0.5300	**<0.0001**
Mean Height Contour	Age	0.03	0.0000	0.840
	Disc Area	14.64	0.0800	**<0.0001**
Cup Volume below Surface	Age	3.31	−0.002	0.033
	Disc Area	47.43	0.2800	**<0.0001**
Cup Volume below Reference	Age	3.79	−0.001	0.022
	Disc Area	37.54	0.1390	**<0.0001**
Rim Volume above Reference	Age	2.43	0.0004	0.566
	Disc Area	10.47	0.1100	**<0.0001**
Maximum Cup Depth	Age	6.29	−0.004	0.003
	Disc Area	20.78	0.2600	**<0.0001**
Cup Shape	Age	1.21	0.0005	0.199
	Disc Area	1.98	0.0300	0.100
Mean Cup Depth	Age	3.73	−0.001	0.023
	Disc Area	25.32	0.1100	**<0.0001**
RNFL Thickness	Age	1.19	−0.0004	0.203
	Disc Area	0.00	0.0000	0.978
RNFL Cross-Sectional Area	Age	0.02	−0.002	0.110
	Disc Area	19.41	0.3300	**<0.0001**
Rim Area	Age	0.02	0.0003	0.868
	Disc Area	43.01	0.4700	**<0.0001**
Cup/Disc Area Ratio	Age	2.20	−0.0010	0.083
	Disc Area	25.77	0.1730	**<0.0001**
Rim/Disc Ratio	Age	2.20	0.0010	0.083
	Disc Area	25.77	−0.1730	**<0.0001**
HRT Classification	Age	4.49	0.0210	0.012
	Disc Area	1.99	0.5830	0.099
Reference Plane Height	Age	0.51	−0.0005	0.405
	Disc Area	8.7	0.0788	0.0004

[a] $n = 138$, all ages included.

Table 3. Mean HRT Parameter Measures (95% C.I.) for Three Different Age Groups and All Age Groups Combined

HRT Parameter	23–43 yr ($n = 29$)	44–64 yr ($n = 64$)	>65 yr ($n = 45$)	$p(F)$	All Ages
Disc Area (mm^2)	1.90 (1.76–2.03)	1.76 (1.67–1.85)	1.78 (1.67–1.89)	0.24	1.80 (1.73–1.85)
Cup Area Below Reference (mm)	0.468 (0.367–0.570)	0.378 (0.309–0.446)	0.353 (0.271–0.435)	0.201	0.389 (0.341–.436)
Mean Height Contour (mm)	0.053 (0.025–0.080)	0.041 (0.023–0.060)	0.035 (0.013–0.057)	0.619	0.042 (00.029–0.054)
Cup Volume below Surface (mm^3)	0.261 (0.205–0.317)	0.216 (0.179–0.254)	0.182 (0.137–0.227)	0.097	0.214 (0.189–0.240)
Cup Volume below Reference (mm^3)	0.113 (0.075–0.150)	0.083 (0.061–0.103)	0.065 (0.044–0.085)	0.054	0.083 (0.069–0.097)
Rim Volume above Reference (mm^3)	0.374 (0.327–0.421)	0.375 (0.344–0.407)	0.402 (0.364–0.439)	0.507	0.383 (0.362–0.405)
Maximum Cup Depth (mm)	0.619 (0.543–0.696)	0.539 (0.488–0.591)	0.467 (0.406–0.528)	**0.009**[a]	0.533 (0.497–0.569)
Cup Shape	−0.230 (−0.259 to −0.205)	−0.209 (−0.226 to −0.193)	−0.210 (−0.230 to −0.191)	0.369	−0.214 (−0.225 to −0.203)
Mean Cup Depth (mm)	0.209 (0.179–0.238)	0.186 (0.167–0.206)	0.163 (0.140–0.187)	0.057	0.183 (0.170–0.197)
RNFL Thickness (mm)	0.254 (0.234–0.273)	0.261 (0.248–0.274)	0.247 (0.232–0.263)	0.411	0.255 (0.246–0.264)
RNFL Cross-Sectional Area (mm^2)	1.23 (1.13–1.33)	1.23 (1.16–1.29)	1.16 (1.08–1.25)	0.454	1.21 (1.16–1.25)
Rim Area (mm^2)	1.43 (1.33–1.53)	1.38 (1.32–1.45)	1.42 (1.35–1.50)	0.653	1.407 (1.362–1.452)
Cup/Disc Area Ratio	0.238 (0.192–0.284)	0.202 (0.171–0.232)	0.184 (0.147–0.221)	0.198	0.203 (0.182–0.225)
Rim/Disc Ratio	0.762 (0.716–0.808)	0.798 (0.767–0.829)	0.816 (0.779–0.853)	0.198	0.796 (0.775–0.818)
HRT Classification	1.28 (0.73–1.82)	1.39 (1.02–1.75)	2.16 (1.78–2.60)	**0.011**[b]	1.62 (1.36–1.87)
Reference Plane Height	0.306 (0.270–0.342)	0.302 (0.278–0.326)	0.282 (0.253–0.311)	0.492	0.296 (0.280–0.313)

[a] 23–43 yr significantly different from >65 yr.
[b] 23–43 yr 44–64 yr significantly different from >65 yr.

were excluded because of suspicious RNFL thickness profiles. In several subjects, examination of on-screen SLP images revealed that the RNFL "double-hump" pattern was shifted 90 deg so that temporal and nasal quadrant thickness was greater than inferior and superior quadrant thickness. To screen the exported data for this assumed artifact, we flagged any patients who had mean temporal or nasal thickness measures greater than mean inferior or superior measures. We then printed examination reports for each flagged patient and subjectively determined whether the RNFL thickness profile and retardation map appeared phase shifted. Nine patients were excluded. We suspect that the observed shift in thickness profile is a result of inadequate compensation of corneal polarization by the SLP corneal polarization compensator,[25] although this hypothesis was not tested.

Average (±SD) age of the included subjects was 55.6 (±14.9) yr. Age ranged from 23.0 to 80.8 yr with 50% of eyes over the age of 57.0 yr. There was no significant difference in age between female and male subjects ($p = 0.61$)

SLP (GDx Nerve Fiber Analyzer, Laser Diagnostic Technologies, San Diego, Calif.) uses scanning laser technology coupled with an integrated polarization modulator to measure retardation of light that has double-passed the birefringent fibers of the RNFL. Retardation measurements have been shown to correlate with RNFL thickness measurements. Details of this instrument and descriptions of parameters have been provided elsewhere.[4,20,22,26]

We examined 13 parameters automatically provided by GDx software (version 2.0.01) (Table 1). Parameters investigated were symmetry, superior ratio, inferior ratio, superior nasal ratio, maximum modulation, superior maximum, inferior maximum, average thickness, ellipse modulation, ellipse average, superior average, inferior average, and superior integral. These parameters were chosen because they are available to the clinician through the GDx examination report printout and are therefore most likely to be used in clinical settings. We also examined a previously reported linear discriminant function for discriminating between healthy and glaucomatous eyes (called GDx LDF).[26]

2. *Procedure*

Three scans (approximately 15-deg field of view) centered on the optic disc were obtained for each test eye. A mean retardation map comprising these three scans was created with GDx software. The optic disc margin was outlined on the mean retardation image by a trained technician.

D. Optical Coherence Tomography

1. *Subjects and Instrumentation*

99 subjects (66 female, 33 male) were imaged with OCT. Average (±SD) subject age was 56.9 (±15.4) yr. Age ranged from 22.7 to 80.8 yr with 50% of eyes over the age of 60.0 yr. There was no significant difference in age between female and male subjects ($p = 0.83$).

The optical coherence tomograph (Humphrey-Zeiss Instruments, Dublin, Calif.) employs low-coherence interferometry to assess peripapillary RNFL thickness. This instrument measures RNFL thickness by measuring the difference in temporal delay of backscattered light from the RNFL and a reference mirror. RNFL is differentiated from other retinal layers by use of an edge-detection algorithm (software: version A5X1). RNFL thickness is defined as the number of pixels between its anterior and posterior boundaries. Details of this instrument have been described elsewhere.[8,27]

Table 4. Association between Age (yr) and Optic Disc Area (mm^2) and GDx Parameter Measures[a]

GDx Parameter		R^2 (%)	Slope	p
Symmetry	Age	0.93	−0.001	0.35
	Disc Area	0.11	0.013	0.716
Superior Ratio	Age	3.49	−0.007	0.039
	Disc Area	0.075	−0.133	0.34
Inferior Ratio	Age	2.64	−0.006	0.055
	Disc Area	0.52	−0.104	0.529
Superior/Nasal Ratio	Age	4.62	−0.006	0.013
	Disc Area	8.15	−0.307	**0.001**
Maximum Modulation	Age	5.92	−0.008	**0.005**
	Disc Area	3.09	−0.240	0.051
Superior Maximum	Age	2.41	−0.164	0.066
	Disc Area	0.21	1.88	0.615
Inferior Maximum	Age	0.55	−0.077	0.312
	Disc Area	0.65	3.29	0.373
Average Thickness	Age	0.56	−0.056	0.391
	Disc Area	4.81	6.18	0.014
Ellipse Modulation	Age	10.49	−0.016	**0.001**
	Disc Area	0.8	−0.177	0.324
Ellipse Average	Age	1.16	−0.080	0.213
	Disc Area	1.63	3.6	0.158
Superior Average	Age	4.97	−0.203	0.01
	Disc Area	0.67	2.86	0.366
Inferior Average	Age	0.93	−0.087	0.269
	Disc Area	1.28	3.99	0.21
Superior Integral	Age	2.35	−0.0005	0.079
	Disc Area	16.93	0.048	**<0.001**
GDx LDF	Age	16.68	−0.024	**<0.0001**
	Disc Area	4.97	−0.47	0.013

[a] $n = 133$, all ages included.

OCT parameters investigated in this study were mean RNFL thickness (360-deg measure), temporal quadrant thickness (316–45-deg unit circle), superior quadrant thickness (46–135 deg), nasal quadrant thickness (136–225 deg), inferior quadrant thickness (226–315 deg), and thickness measures at 30-deg sectors corresponding to clock hours (called thickness 1:00, thickness 2:00, etc.). We also examined a modulation parameter defined as the difference between the thickest vertical OCT quadrant (superior, inferior) and the thinnest horizontal quadrant (temporal, nasal).[28] This parameter was designed to assess the amplitude of the characteristic double-hump pattern of RNFL thickness.

2. *Procedure*

Three circular scans of 3.4-mm diameter centered on the optic disc were obtained for each eye.[7] Mean RNFL thickness values were determined from the three scans obtained.

E. Analyses

The effects of age, optic disc area (defined by magnification-corrected HRT measurement) and refraction on optic disc topography and RNFL measures were investigated by linear regression analysis. To further examine the effect of age, patients were divided into three age groups: 23–43, 44–64, and 65 yr and older (defined arbitrarily as 20-yr bins). Measures were compared among these groups by analysis of variance and Tukey–Kramer HSD tests. The effect of gender on optic disc and RNFL measures was investigated with T tests.

3. RESULTS

A. Effect of Age on Optic Disc Topography and RNFL Thickness Measures

1. *HRT*

For the HRT, relatively weak correlations were found among age and topographic optic disc parameters. The

Table 5. Mean GDx Parameter Measures (95% C.I.) for Three Different Age Groups and All Age Groups Combined

GDx Parameter	23–43 yr ($n = 30$)	44–64 yr ($n = 59$)	65 yr ($n = 44$)	$p(F)$	All Ages
Symmetry	1.04 (0.97–1.10)	1.00 (0.97–1.04)	0.99 (0.94–1.03)	0.377	1.00 (0.98–1.03)
Superior Ratio	2.36 (2.15–2.57)	2.29 (2.14–2.43)	2.07 (1.91–2.23)	0.057	2.23 (2.13–2.33)
Inferior Ratio	2.32 (2.11–2.54)	2.30 (2.15–2.45)	2.10 (1.98–2.22)	0.104	2.24 (2.15–2.33)
Superior/Nasal Ratio	2.16 (2.01–2.32)	2.09 (1.99–2.18)	1.90 (1.78–2.02)	**0.012[a]**	2.04 (2.11–1.97)
Maximum Modulation	1.68 (1.49–1.86)	1.53 (1.40–1.66)	1.30 (1.16–1.45)	**0.006[a]**	1.49 (1.40–1.58)
Superior Maximum (μm)	93.18 (87.44–98.92)	95.05 (91.13–98.94)	90.27 (83.37–95.16)	0.318	93.04 (90.34–95.75)
Inferior Maximum (μm)	91.13 (85.53–96.74)	95.23 (91.36–99.09)	92.35 (87.44–97.26)	0.444	93.35 (90.68–96.03)
Average Thickness (μm)	65.49 (61.77–69.21)	68.03 (65.14–70.93)	66.25 (62.79–69.71)	0.54	66.87 (64.96–68.78)
Ellipse Modulation	2.92 (2.63–3.20)	2.59 (2.39–2.80)	2.20 (2.03–3.58)	**<0.001[b]**	2.53 (2.40–2.67)
Ellipse Average (μm)	69.21 (65.55–72.88)	71.94 (69.04–74.84)	69.39 (65.97–72.82)	0.403	70.48 (68.58–72.38)
Superior Average (μm)	80.16 (75.66–84.66)	82.15 (78.68–85.63)	76.34 (72.14–80.53)	0.098	79.78 (77.45–82.11)
Inferior Average (μm)	80.11 (75.65–84.58)	83.52 (80.09–86.96)	80.73 (76.52–84.95)	0.424	81.83 (79.53–84.13)
Superior Integral	0.220 (0.205–0.235)	0.257 (0.216–0.237)	0.211 (0.195–0.226)	0.208	0.220 (0.212–0.228)
GDxLDF	0.736 (0.495–0.977)	0.534 (0.335–0.733)	−0.026 (−0.231–0.180)	**<0.001[b]**	0.394 (0.260–0.528)

[a] 23–43 yr significantly different from >65 yr.

[b] 23–43 yr and 44–64 yr significantly different from >65 yr.

strongest correlations were between age and maximum cup depth ($R^2 = 6.3\%, p = 0.003$), HRT classification ($R^2 = 4.5\%, p = 0.012$), and cup volume below reference ($R^2 = 3.8\%, p = 0.022$). The associations (R^2 and associated probabilities and slopes) between age and all examined HRT parameters are shown in Table 2.

When patients were divided into three age groups (group 1, age 23–43 yr, $n = 29$; group 2, age 44–64 yr, $n = 64$; group 3, age 65 yr and over, $n = 45$), only two HRT parameters showed significant differences among the groups. The youngest group had significantly deeper cups (maximum cup depth parameter) than the oldest group, and the oldest group had more positive (less glaucomatous) HRT classification values than the two younger groups (all $p < 0.05$). Table 3 shows HRT parameter measures for each age group and for all subjects combined.

2. *GDx*

For GDx, the strongest correlations among age and RNFL thickness parameters were for GDx LDF ($R^2 = 16.7\%$, $p < 0.0001$), ellipse modulation ($R^2 = 10.5\%$, $p = 0.001$), and maximum modulation ($R^2 = 5.9\%$, $p = 0.005$). The associations (R^2 and associated probabilities and slopes) between age and all examined GDx parameters are shown in Table 4.

When patients were divided into different age groups (group 1, $n = 30$; group 2, $n = 59$; group 3, $n = 44$), the oldest group had a significantly lower GDx LDF value (more glaucomatous) than the two younger groups and a significantly lower ellipse modulation measurement than the two youngest groups. Further, superior/nasal ratio and maximum modulation measures were lower in the oldest group compared with the youngest group (all $p < 0.05$). Table 5 shows GDx parameter measures for each age group and for all subjects combined.

3. *OCT*

For OCT, the strongest correlations among age and RNFL thickness measures were for thickness 4:00 ($R^2 = 5.6\%$, $p = 0.018$), mean thickness ($R^2 = 5.2\%$, $p = 0.022$), and thickness 7:00 ($R^2 = 3.8\%$, $p = 0.053$). The associations (R^2 and associated probabilities and slopes) between age and all examined OCT parameters are shown in Table 6.

When patients were divided into different age groups (group 1, $n = 19$; group 2, $n = 40$; group 3, $n = 41$), the oldest group had thinner RNFL measures for 1:00, 2:00, 3:00 (nasal), 4:00, 12:00, nasal quadrant, inferior quadrant, superior quadrant measures and overall (mean) thickness than the second oldest group (all $p < 0.05$). No significant differences were found between the youngest group and the two older groups, possibly because of the relatively small number of patients in the former. Table 7 shows OCT parameter measures for each age group and for all subjects combined.

Because we found only weak relationships among age and HRT, GDx, and OCT measures, we also fitted second-order polynomial equations to the data. These fits were not significantly better than the linear fits, and the data are not shown. Figures 2–4 show linear regression relationships between age and optic disc area (see below) and representative HRT, GDx, and OCT parameters.

Table 6. Association between Age (yr) and Optic Disc Area, and OCT Parameter Measures[a]

OCT Parameter		R^2 (%)	Slope	p
Thickness 1:00	Age	1.87	−0.297	0.920
	Disc Area	11.13	23.74	**0.001**
Thickness 2:00	Age	1.34	−0.211	0.251
	Disc Area	1.48	9.27	0.244
Thickness 3:00 (nasal)	Age	0.89	−0.125	0.349
	Disc Area	0.14	5.81	0.306
Thickness 4:00	Age	5.60	−0.362	0.018
	Disc Area	5.48	14.93	0.023
Thickness 5:00	Age	0.86	−0.161	0.360
	Disc Area	0.28	3.86	0.614
Thickness 6:00 (inferior)	Age	1.37	−0.186	0.246
	Disc Area	1.66	−8.50	0.216
Thickness 7:00	Age	3.76	−0.330	0.053
	Disc Area	1.23	−7.87	0.287
Thickness 8:00	Age	2.12	−0.235	0.149
	Disc Area	5.17	−15.27	0.028
Thickness 9:00 (temporal)	Age	1.25	−0.153	0.268
	Disc Area	14.11	−21.33	**0.001**
Thickness 10:00	Age	1.61	−0.192	0.209
	Disc Area	12.42	−21.68	**0.001**
Thickness 11:00	Age	1.00	−0.154	0.322
	Disc Area	0.74	−5.14	0.411
Thickness 12:00 (superior)	Age	3.41	−0.320	0.067
	Disc Area	1.08	7.05	0.320
Nasal Quadrant Thickness	Age	3.01	−0.236	0.084
	Disc Area	2.21	8.43	0.153
Inferior Quadrant Thickness	Age	2.74	−0.212	0.100
	Disc Area	0.26	−2.79	0.621
Temporal Quadrant Thickness	Age	2.07	−0.194	0.153
	Disc Area	10.88	−18.29	**0.001**
Superior Quadrant Thickness	Age	3.61	−0.248	0.058
	Disc Area	2.03	7.16	0.171
Mean Thickness	Age	5.22	−0.216	0.022
	Disc Area	0.16	−1.54	0.706
Modulation	Age	0.27	0.05	0.611
	Disc Area	0.52	2.87	0.491

[a] $n = 99$, all ages included.

B. Effect of Optic Disc Area on Optic Disc Topography and RNFL-Thickness Measures

1. *HRT*

For HRT, associations among disc area and optic disc topography parameters were much stronger than associations among age and disc topography parameters. Disc area was significantly correlated with all parameters except cup shape, RNFL thickness, and HRT Classification.

The strongest correlations among disc area and disc topography parameters were for cup area ($R^2 = 48.2\%$, $p = < 0.0001$), cup volume ($R^2 = 47.5\%$, $p < 0.0001$), and rim area ($R^2 = 43.0\%$, $p < 0.0001$). The associations (R^2 and associated probabilities and slopes) between disc area and all examined HRT parameters are shown in Table 2.

2. GDx

For the GDx, relatively weak correlations were found among disc area and RNFL thickness parameters. The strongest correlations were between disc area and superior integral ($R^2 = 16.9\%$, $p < 0.001$), superior nasal ratio ($R^2 = 8.2\%$, $p < 0.001$), and GDx LDF ($R^2 = 5.0\%$, $p < 0.013$). The associations (R^2 and associated probabilities and slopes) between disc area and all examined GDx parameters are shown in Table 4.

3. OCT

For OCT, disc area was most strongly correlated with RNFL thickness 9:00 ($R^2 = 14.1\%$, $p = 0.001$), RNFL thickness 10:00 ($R^2 = 12.4\%$, $p = 0.001$), and RNFL thickness 1:00 ($R^2 = 11.1\%$, $p = 0.001$). The associations (R^2 and associated probabilities and slopes) between disc area and all examined OCT parameters are shown in Table 6.

For HRT, GDx, and OCT we used multivariate regression to examine, in one model, the combined effects of age, optic disc area, and refraction on optic disc topography and RNFL thickness measures. The contribution of age to the multivariate model was weaker (smaller R^2 contribution) than univariate analyses of age and weaker than that of disc area when both age and disc area were included in the model. These data are not shown.

C. Effect of Refractive Error on Optic Disc Topography and RNFL Thickness Measures

HRT, GDx, and OCT parameters were weakly correlated with refraction. The parameters correlated most strongly with refraction for each instrument were HRT rim area ($R^2 = 2.6\%$, $p = 0.06$), GDx superior nasal ratio ($R^2 = 3.1\%$, $p = 0.06$), and OCT thickness 10:00 ($R^2 = 5.1\%$, $p = 0.05$). Including refraction in multiple-regression models with age, disc area, or both did not improve R^2 values. Because R^2 values were small, their values and associated probabilities and slopes are not shown.

D. Effect of Gender on Optic Disc Topography and RNFL Thickness Measures

There were no HRT, GDx, or OCT parameters that differed significantly (T tests) between female and male subjects. For HRT all comparisons $p \geqslant 0.18$, for all GDx parameters $p \geqslant 0.08$, and for all OCT parameters $p \geqslant 0.14$. These data are not shown.

Table 7. Mean OCT Parameter Measures (95% C.I.) (μm) for Three Different Age Groups and All Age Groups Combined

OCT Parameter	23–43 yr ($n = 19$)	44–64 yr ($n = 40$)	>65 yr ($n = 41$)	$p(F)$	All Ages
Thickness 1:00	123.98 (112.88–135.09)	141.39 (133.74–149.05)	119.24 (111.68–126.80)	**0.0003**[a]	129.00 (123.79–134.21)
Thickness 2:00	103.79 (91.88–115.70)	118.54 (110.82–126.26)	100.87 (92.45–109.29)	**0.009**[a]	108.49 (103.10–113.89)
Thickness 3:00 (nasal)	77.82 (69.10–86.55)	86.95 (80.94–92.96)	75.28 (69.21–81.36)	**0.022**[a]	80.43 (76.52–84.35)
Thickness 4:00	90.46 (80.68–100.23)	100.89 (94.15–107.63)	82.28 (75.62–88.93)	**0.0008**[a]	91.28 (86.74–95.81)
Thickness 5:00	114.68 (103.03–126.34)	121.39 (113.36–129.42)	107.94 (100.01–115.87)	0.066	114.60 (109.43–119.77)
Thickness 6:00 (inferior)	146.51 (135.89–157.13)	153.58 (146.26–160.90)	140.85 (133.62–148.09)	0.053	147.02 (142.30–151.74)
Thickness 7:00	151.19 (139.81–162.58)	155.19 (147.34–163.04)	141.93 (134.19–149.69)	0.058	149.00 (143.94–154.06)
Thickness 8:00	103.11 (92.08–114.13)	96.82 (89.22–104.42)	95.56 (88.05–103.07)	0.521	97.50 (92.71–102.28)
Thickness 9:00 (temporal)	86.51 (77.15–95.87)	81.51 (75.06–87.96)	81.89 (75.52–88.27)	0.655	82.62 (78.56–86–67)
Thickness 10:00	109.72 (99.35–120.09)	106.83 (99.68–113.97)	104.78 (97.73–111.85)	0.735	106.54 (102.05–111.03)
Thickness 11:00	144.60 (134.09–155.10)	148.67 (141.43–155.91)	142.88 (135.73–150.03)	0.521	145.52 (140.96–150.01)
Thickness 12:00 (superior)	135.05 (123.76–146.34)	145.90 (138.12–153.68)	127.78 (120.10–135.47)	**0.006**[a]	136.41 (131.27–141.55)
Nasal Quadrant Thickness	90.33 (81.60–99.07)	101.37 (95.35–107.40)	85.65 (79.70–91.60)	**0.0015**[a]	92.83 (88.80–96.86)
Inferior Quadrant Thickness	137.61 (129.25–145.98)	144.62 (138.85–150.38)	131.33 (125.64–137.03)	**0.0066**[a]	137.84 (134.04–141.64)
Temporal Quadrant Thickness	98.58 (89.35–107.80)	95.07 (88.72–101.43)	93.26 (68.98–99.54)	0.64	95.00 (91.00–98.99)
Superior Quadrant Thickness	134.83 (126.50–143.15)	146.00 (140.26–151.74)	129.11 (124.25–135.58)	**0.006**[a]	137.28 (133.40–141.16)
Mean Thickness	115.76 (109.67–121.84)	121.52 (117.32–125.71)	110.51 (106.36–114.65)	**0.0016**[a]	115.91 (113.10–118.71)
Modulation	60.42 (53.52–67.32)	65.18 (60.42–69.93)	60.07 (55.38–64.77)	0.276	62.18 (59.16–65.20)

[a] 44–64 yr significantly different from >65 yr.

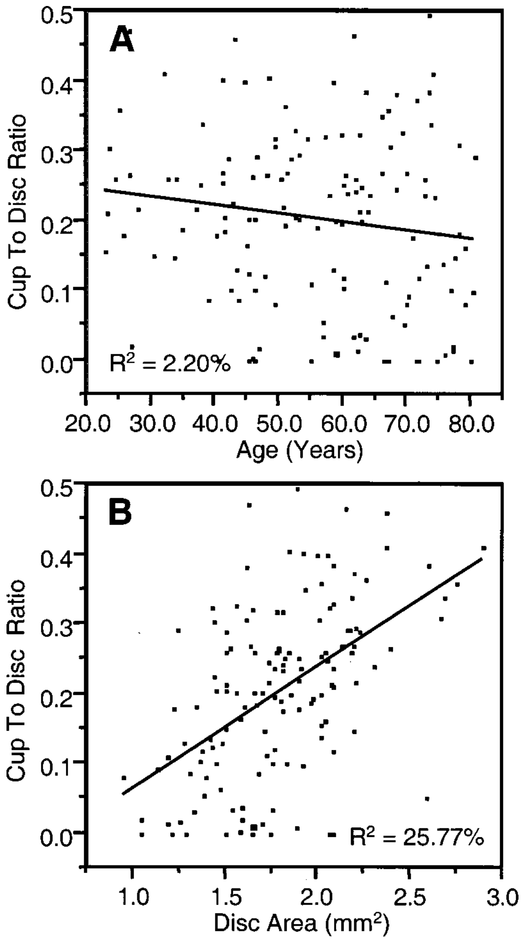

Fig. 2. Linear regression between (A) age (yrs) and (B) optic disc area (mm^2) and HRT-measured cup/disc area ratio.

4. DISCUSSION

Several studies have reported a relatively small but significant decrease in the number and density of optic nerve fibers with increasing age in humans.[12,13] To the degree that the number of optic never fibers are reflected in disc topography and RNFL thickness, it is likely that predictable changes in optic disc and RNFL topography measured by using optical imaging techniques also occur with age. Our results indicate that age is weakly correlated with HRT, GDx, and OCT parameters with maximum R^2 measures of 6.3%, 16.7%, and 5.6%, respectively. Although small, these effects should be nonetheless considered when attempting to detect subtle changes in optic disc and RNFL measures with these instruments.

Because increasing age results in fewer optic nerve fibers, we expected that HRT-measured mean and maximum cup depth would be increased in older subjects. Instead, we found that these measures decreased slightly by approximately 0.004 mm/year and 0.001 mm/year, respectively. The basis for this relationship is not known. Although optic disc topography is dependent on intraocular pressure,[29,30] we found no relationship between IOP and age ($R^2 = 0.0004$, $p = 0.82$), and no difference in IOP was identified among the three age groups ($p = 0.57$) in the current study. However, the range of IOP was small in this study because IOP measurements were all less than 22 mmHg. Alternatively, these results may be due to the generally larger (although not significantly larger) optic disc and optic cup in the youngest age group in this sample, or to chance statistical occurrence. It also is possible that these findings are an artifact of sample size.

Previous studies examining the relationship among HRT-measured optic disc topography and age have provided inconsistent results. For example, Garway-Heath and colleagues[15] showed a significant decline in neuroretinal rim area at a rate of approximately 1% every 2.5 yr (0.39%/yr) in subjects aged approximately 20–75 years. Further, cup/disc ratio increased by ~0.1 between ages 30 and 70 yr. Similar to the findings of the present study, multiple-regression analyses including both age and optic disc area showed that a significantly greater proportion of the variance was attributable to the disc area than to age. Nakamura and colleagues[18] observed a very small influence of age on mean RNFL thickness ($r = -0.001$) and RNFL cross-sectional area ($r = -0.005$) with the HRT. Similarly, Gunderson and colleagues[17] found no significant relationships among age and parameters examined (cup area and maximum cup depth).

Our results from GDx suggest that average RNFL thickness in the superior hemiretina decreases by approximately 0.2 μm/yr. This result is similar to a re-

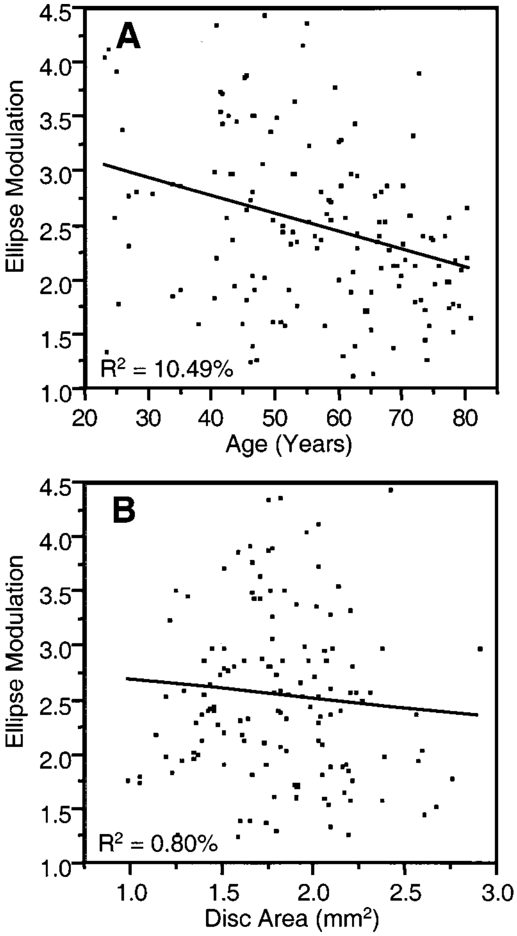

Fig. 3. Linear regression between (A) age (yrs) and (B) optic disc area (mm^2) and GDx-measured ellipse modulation.

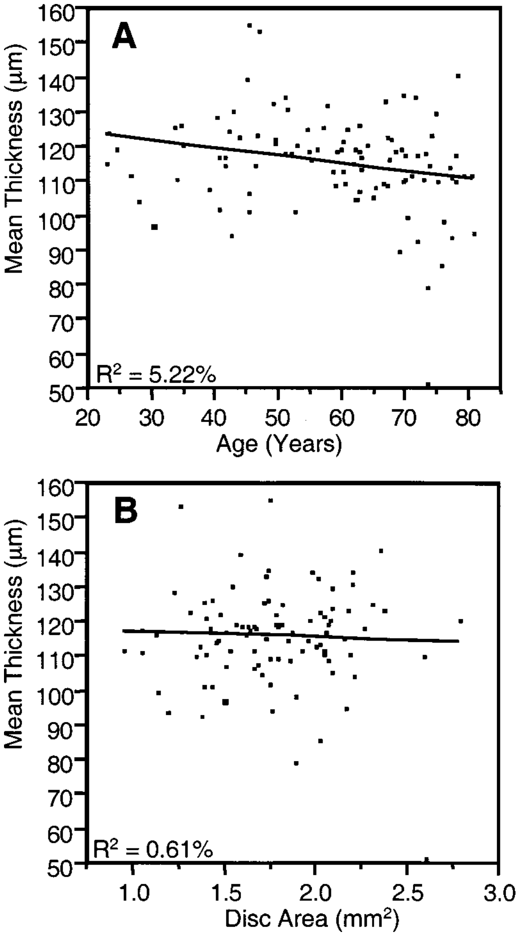

Fig. 4. Linear regression between (A) age (yrs) and (B) optic disc area (mm^2) and OCT-measured mean RNFL thickness (μm).

ported approximate decrease of average RNFL thickness of 0.38 μm/yr by Poinoosawmy and colleagues using the NFA I (prototype instrument; NFA II and GDx incorporate a modified polarization detector to reduce interoperator variability and dependence on the intensity setting of the NFA I).[20] Chi *et al.*, also using the NFA I, provided a different average RNFL thickness decrease estimate[14] of approximately 2.0 μm/yr. Weinreb *et al.*[23] also reported significant decreases in superior (and inferior) thickness with increasing age (using NFA I). In their study, age explained 11% of the RNFL thickness variation superiorly compared with ~5% in the current study.

We found small, but significant, relationships between age and GDx maximum modulation and ellipse modulation ($R^2 = 5.9\%$, $p = 0.005$ and $R^2 = 10.5\%$, $p = 0.001$, respectively), and significant differences in several ratio parameters were found among different age groups (decreases in older subjects), suggesting that the amplitude of the peripapillary retina thickness profile may decrease with increasing age. This finding may have implications for glaucoma diagnosis, because one hallmark of glaucoma is RNFL thinning of the superior and inferior quadrants compared with that of the temporal and nasal quadrants, resulting in decreased RNFL thickness amplitude.[31,32] Apparently a similar pattern of thinning occurs in normal aging eyes, although possibly not to the same extent. This finding is supported by those of Funaki and colleagues,[16] who (using the GDx-compatible NFA II) reported a decrease in total thickness/nasal thickness ratio as age increased, and Tjon-Fo-Sang and colleagues[22] and Özdek and colleagues,[19] who (using NFA I) reported decreases in inferior nasal and superior nasal thickness ratios as age increased. Özdek *et al.* suggested that the apparent effect of age in their study might be attributable to a reported significant correlation between degree of myopia and RNFL thickness ratios.[19] In the present study, we found no relationship between refractive error and any imaging parameters, although we examined only a restricted range of refractive error (-5 to $+5$ D), suggesting that the effect of age is not a refraction-related artifact.

Although we attempted to remove GDx subject data that were suspicious possibly as a result of inadequate corneal polarization compensation, this artifact still may have affected data from some subjects. In the current study we eliminated only subjects whose RNFL thickness profile was shifted 90 deg. Another effect of inadequate corneal polarization compensation is increased thickness measurements overall.[25] This artifact is harder to detect and therefore may be present in data from some eyes.

In the current study, we found no significant relationship between age and any measured OCT parameter. Alternately, Schuman and colleagues, using an OCT prototype device, reported a significant decrease in inferior quadrant, nasal quadrant, and average RNFL thickness in healthy and glaucoma eyes when controlling for variables associated with glaucoma.[33] Inspection of their data suggests a decrease with age of approximately 1.0 μm/yr.

In the current study, disc area was substantially correlated with almost all optic disc topography parameters but was, in general, weakly correlated with RNFL thickness parameters. This is a predictable finding that suggests that the size of the optic disc influences the distribution of optic nerve fibers within it.[34,35] The finding that RNFL thickness measures were less affected by disc area may suggest, indirectly, that the number and distribution of optic nerve fibers within the RNFL is somewhat independent of disc size (see also Jonas *et al.*[36]), although other sources have reported significant relationships between these variables with other methods.[37]

Other studies have also shown a relationship between optic disc size and various optic disc measures with the use of optical imaging techniques. For instance, Nakamura and colleagues[18] found positive correlations between disc area and cup area, cup/disc ratio, rim area, cup volume, mean cup depth, and cup shape (all $p < 0.001$). Studies evaluating stereoscopic disc photographs[34,35,38] and histological studies[36,39] have reported similar results with more general parameters such as RNFL thickness and rim area. These results combined suggest that optic disc area should be taken into consideration in the cross-sectional assessment of neuroretinal rim thinning, regardless of the methodology used.

Ideally, a study investigating the effect of age on optic disc and RNFL measures in healthy eyes should be a longitudinal one. However, with optical imaging technology in clinical use for less than one decade, a meaningful follow-up time in a large number of patients still is not available, in part because eyes examined are more frequently those of patients with known or suspected ocular disease rather than of healthy subjects.

Results from the present study suggest that although effects of age on optical imaging techniques are small, they should be considered in the diagnosis and longitudinal monitoring of the optic disc and RNFL. Because of the large effect of optic disc area on disc topography, we also suggest that optic disc area be considered when disc appearance is evaluated cross sectionally for diagnosis of glaucoma or other optic neuropathies, regardless of the methodology used. To a lesser extent, disc area also should be considered with the use of imaging techniques to evaluate RNFL thickness.

The authors have no commercial relationship/financial interest in any of the techniques described.

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