Longitudinal Stability of Optical Coherence Tomography Measures of Peripapillary Retinal Nerve Fiber Layer Thickness, Macular Thickness, and Macular Volume in Control and Glaucomatous Eyes of Children

By

Dana M. Hornbeak

A Master's Paper submitted to the faculty of
the University of North Carolina at Chapel Hill
In partial fulfillment of the requirements for
the degree of Master of Public Health in
the Public Health Leadership Program.

Chapel Hill

June 2008

_____
Advisor (Sharon Freedman, MD, Duke)

_____
Second Reader (Margaret Gourlay, MD, MPH, UNC)

_____
Date

MANUSCRIPT:

(Submitted for publication to the British Journal of Ophthalmology in June 2008)

ABSTRACT:

Background/Aims:

To document baseline and longitudinal values for peripapillary retinal nerve fiber layer (RNFL) thickness, macular thickness, and macular volume as measured by optical coherence tomography(OCT) in glaucomatous and control eyes of children, followed prospectively for a mean of 2.4 years (range 0.5-5.3 years).

Methods:

OCT measurements (Fast RNFL 3.4 Thickness, Fast RNFL Map, and Fast Macular Thickness Map protocols; StratusOCT, Carl-Zeiss-Meditech, Dublin,CA) were obtained at baseline and on follow-up in 27 control and 19 glaucoma participants at the Duke University Eye Center Pediatric Clinic. Longitudinal changes were compared between groups with a two-sample-t-test and multiple linear regression analysis of covariance model adjusting for age, race, and baseline refractive error.

Results:

Eyes with glaucoma exhibited reduced baseline macular thickness, macular volume, and RNFL thickness, and increased myopia, compared to control eyes (eg. macular volume 6.54 vs. 7.03 mm^3, p=0.006; RNFL 3.4 thickness 87.8 vs. 110.6µm, p=0.02). All OCT parameters studied showed minimal change over time, and rates of change were similar between groups.

Conclusion:

Baseline differences and longitudinal stability of OCT parameters were seen in normal and clinically stable glaucomatous eyes of children. These findings support continued study of OCT as an easily performed clinical adjunct in evaluation and management of children with glaucoma.

INTRODUCTION:

Pediatric glaucoma causes an estimated 9.5-10.8% of childhood visual impairment.[1, 2] If treated surgically and/or medically at an appropriately early stage, juvenile glaucoma's negative effects can be lessened substantially. If untreated, glaucoma can result in irreversible blindness. Thus objective, sensitive ocular measurements are extremely valuable for early diagnosis, treatment, and measurement of disease progression in children with glaucoma.

Optical Coherence Tomography (OCT), a rapid, non-invasive imaging technique, has been studied extensively in adult eyes with glaucoma and to a lesser extent in children. It has been shown to have high inter-operator reproducibility,[3] reliably distinguish glaucomatous eyes from normals,[4] match the diagnostic efficacy of ONH stereophotography in early glaucoma,[5] have high sensitivity and specificity in measuring RNFL thickness,[6] predict future glaucomatous change,[7] and provide earlier detection of glaucomatous damage.[8] Baseline OCT and refractive error measurements have been studied in adult[7, 9] and pediatric[10, 11] glaucoma patients; longitudinal progression of OCT measurements[7, 12, 13] has been examined only in adults. Baseline cross-sectional studies in adults have shown a correlation between glaucoma and decreased baseline RNFL, macular thickness, and macular volume;[6, 9, 14] between increased myopia and decreased RNFL thickness[15] and between baseline RNFL thinning and future glaucomatous change.[7] In children, glaucoma has been correlated with reduced baseline macular thickness and macular volume, increased myopia, and reduced RNFL thickness, particularly in the inferior quadrant.[10, 11, 16] Longitudinal OCT monitoring in adults has shown either no difference,[12] or a slightly greater rate of RNFL thickness reduction,[13] in glaucomatous vs. control eyes in adults over time. OCT measurements also have been shown to be affected by race, refractive error, axial length, and age: for example, decreased macular and RNFL thickness[17] in African American than

Caucasian individuals; thinner RNFL in Caucasian than Hispanic or Asian individuals;[18] and decreased RNFL thickness with increased age, axial length, and myopia.[18, 19] Most studies in adults, and all studies in children, have been cross-sectional. Prospective longitudinal OCT measurements have not been studied in children, nor has the longitudinal relationship between pediatric glaucoma and RNFL thinning been examined.

We conducted a 6-year prospective study of 46 children aged 2 to 16 years old recruited from a pediatric ophthalmology clinic at a large academic medical center. Our objective was to document longitudinal changes in OCT measurements of peripapillary RNFL thickness, macular thickness, and macular volume in glaucomatous vs. control eyes of children.

MATERIALS AND METHODS:

Study Participants:

OCT measurements were completed in both eyes of 21 control participants, 6 participants with uniocular glaucoma (whose normal eyes were included in the control group), and 19 participants with bilateral glaucoma, selected from the Duke University Eye Center Pediatric Clinic between December 2002 and August 2006. Selection was by the attending physician caring for the patient (SFF). Patients with glaucoma receiving OCT as part of their regular clinical care signed a consent allowing their measurements to be used in the study; control participants were patients with large physiological cups or normal volunteers who agreed to receive OCT measurements. Inclusion criteria for the glaucoma group included clinical diagnosis of glaucoma (elevated intraocular pressure, visual field loss, and optic nerve damage) and high quality of baseline and repeat scans; patients were excluded if they had media opacities, were unable to fixate, or had severe myopia (-4.0 diopters or greater). Control participants were patients with normal intraocular pressure and no optic nerve damage or visual field loss. The

study was approved by the Duke University Medical Center Institutional Review Board; informed consent was obtained from the legal guardian of each child before study enrollment.

Measures:

OCT protocols performed included Fast RNFL 3.4 Thickness, Fast RNFL Map, and Fast Macular Thickness Map.(Figure 1) Measurements were obtained at baseline and at one to four clinically-indicated visits for glaucoma or routine eye care during a mean 2.4 years of follow-up (range 0.5-5.3 years); demographic data and refractive error measurements were also recorded. The baseline and most recent measurements from the right eye of normal and bilateral glaucoma participants, and from the normal eye of uniocular glaucoma participants, were used for analysis. To account for unequal lengths of follow-up, and to provide a clinical context for each patient's progression, outcomes were expressed as rates: percent change per year (of each eye's baseline value) and absolute change per year. Three OCT machines were used (Stratus OCT, Carl-Zeiss-Meditech, Dublin, CA); they are located in the Duke University Eye Center Photography Department and are frequently calibrated by the Department to minimize variability.

Analysis:

First the unadjusted outcomes [absolute and percent change per year in average RNFL 3.4 thickness (μm), RNFL inner- and outer-ring thickness (μm), macular inner- and outer-ring thickness (μm), and macular volume (mm^3)] were compared between glaucomatous and control eyes, using a two-sample t-test. A multiple linear regression analysis of covariance (ANCOVA) model was then constructed for each outcome, adjusted for age (years), parent-reported race (white/black/other), and baseline refractive error (spherical equivalents).

Since the eye expands and refractive error naturally increases with age in childhood, and some analyses have shown no effect of age after controlling for refraction,[19] a Pearson's correlation coefficient was calculated between age and baseline refractive error within the model.

To determine whether OCT parameters were affected by length of follow-up, Pearson's correlation coefficients were calculated between each outcome and follow-up time within the regression model. To determine whether RNFL thickness was correlated with baseline refractive error as has been observed previously in adults,[15] a Pearson's correlation coefficient was calculated between these two values within the regression model.

RESULTS:

Of the study's 27 control participants, 6 (22%) had glaucoma in the other eye, 18 (67%) had large cups, and 3 (11%) had small cups. Of the study's 19 participants with glaucoma, 13 (69%) had juvenile open-angle glaucoma (JOAG), 5 (26%) had congenital glaucoma, and 1 (5%) had secondary pseudophakic glaucoma. All patients with glaucoma have been clinically stable during follow-up, established by optic nerve examination and visual field testing when possible.

Mean age at baseline was 10.5 and 8.9 years for the glaucoma and control groups, respectively; racial and gender makeup of the two groups was comparable. Mean follow-up was 2.3 and 2.5 years for the glaucoma and control groups, respectively.(Table 1). Baseline average RNFL 3.4 thickness, macular inner- and outer-ring thicknesses, and macular volume were significantly lower, and baseline refractive error was significantly greater, in glaucomatous vs. control eyes. Baseline RNFL inner- and outer-ring thicknesses were reduced in glaucomatous vs. control eyes, but the difference was not significant.(Table 2).

FIGURE 1.
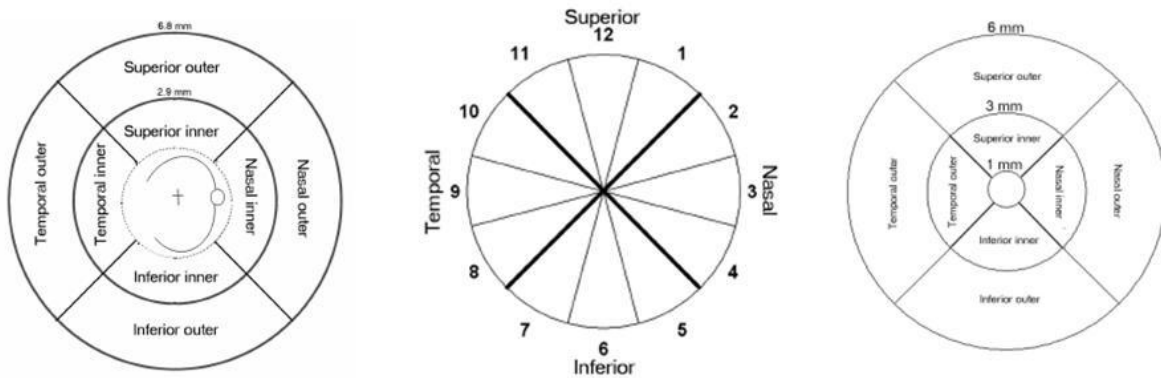
A. Fast Retinal Nerve Fiber Layer (RNFL) Map protocol, right eye. This figure illustrates the optical coherence tomography (OCT) scan area and labeling for the right eye, using the Fast RNFL Map protocol. The StratusOCT scan computes a combined average for the three inner and three outer concentric rings for each of the eight pie sections. We averaged the four inner and four outer readings to comprise the RNFL Inner Ring and RNFL Outer Ring used in analysis.

B. Fast RNFL Thickness (3.4) protocol, right eye. This figure illustrates the OCT scan area and labeling for the right eye, using the RNFL 3.4 protocol. For each eye, RNFL thickness is measured in twelve 30-degree segments and displayed for four quadrants (superior, nasal, inferior, temporal). One average thickness value is used for analysis, corresponding to a ring with 3.4mm diameter.

C. Fast Macular Thickness Map protocol, right eye. This figure illustrates the OCT scan area and labeling for the right eye, using the Fast Macular Thickness Map protocol. Results were recorded as average thickness values within four quadrants (superior, temporal, inferior, nasal); these were averaged to yield one value for macular volume used for analysis.

TABLE 1.

Participant characteristics: control and glaucomatous eyes (1 eye/participant)

	Control	Glaucoma	p-value
Number of participants (n)	27	19	
Mean age at baseline (years) (95% CI)	8.9 (7.8,10.0)	10.5 (9.0, 12.0)	0.07
Mean follow-up (years) (95% CI)	2.5 (2.04, 2.92)	2.3 (1.65, 2.98)	0.67
Gender (male:female %)	44:56	42:58	0.88
Race/Ethnicity (% white: black: other)	63:33:4	53:42:5	0.49 : 0.55 : 0.80

TABLE 2.

Mean and 95% confidence interval of baseline ocular parameters: control and glaucomatous eyes

Baseline ocular parameter	Control	Glaucoma	p-value
Mean peripapillary RNFL thickness [μm, Fast RNFL 3.4 Thickness]	110.6 (104.0, 117.2) (n=15)	87.8 (60.1, 115.4) (n=7)	0.02
Mean RNFL Thickness, Inner Ring [μm, Fast RNFL Map]	89.2 (78.4, 99.9) (n=11)	81.3 (67.5, 95.1) (n=14)	0.36
Mean RNFL Thickness, Outer Ring [μm, Fast RNFL Map]	69.3 (59.5, 79.1) (n=11)	62.6 (50.2, 75.0) (n=13)	0.38
Mean macular thickness, Inner Ring [μm, Fast Macular Thickness Map]	271.2 (263.2, 279.2) (n=27)	257.8 (247.1, 268.4) (n=19)	0.04
Mean macular thickness, Outer Ring [μm, Fast Macular Thickness Map]	243.2 (235.2, 251.3) (n=27)	225.3 (215.1, 235.5) (n=19)	0.006
Mean macular volume [mm^3, Fast Macular Thickness Map]	7.03 (6.81, 7.25) (n=27)	6.54 (6.27, 6.82) (n=19)	0.006
Mean refractive error [spherical equivalents]	-0.10 (-0.78, 0.57) (n=27)	-1.51 (-2.21, -0.81) (n=19)	0.006

n=number of participants (1 eye/participant) for each OCT scan protocol.

During a mean 2.4 years of follow-up, the six OCT parameters changed little, and rates of change between glaucomatous and control eyes were similar.(Table 3) Age was significantly correlated with baseline refractive error (correlation coefficient -0.32, p = 0.03), so the ANCOVA regression model was run with both age and refractive error, and with refractive error only, in addition to race. Results were similar; the model with all covariates is reported.(Table 3)

TABLE 3.

Adjusted mean and range of OCT changes in control and glaucomatous eyes during a mean 2.4 years of follow-up (ANCOVA regression model, adjusted for age, race, and baseline refractive error)

Adjusted OCT parameter	Absolute change (μm) per year (95% CI)		Percent change per year from baseline (95% CI)		p-value*
	Control	Glaucoma	Control	Glaucoma	
Mean peripapillary RNFL thickness [μm, Fast RNFL 3.4 Thickness]	-0.4 (-3.5, 2.7) (n=14)	4.3 (-0.3, 8.9) (n=7)	-0.1 (-3.3, 3.0) (n=14)	3.5 (-1.2, 8.2) (n=7)	0.25
Mean RNFL Thickness, Inner Ring [μm, Fast RNFL Map]	2.6 (-1.4, 6.6) (n=11)	0.03 (-3.6, 3.6) (n=13)	3.4 (-2.1, 9.0) (n=11)	0.2 (-4.8, 5.2) (n=13)	0.47
Mean RNFL Thickness, Outer Ring [μm, Fast RNFL Map]	2.4 (-3.3, 8.1) (n=11)	-2.3 (-7.7, 3.0) (n=12)	5.3 (-3.8, 14.5) (n=11)	-1.0 (-9.7, 7.6) (n=12)	0.39
Mean macular thickness, Inner Ring [μm, Fast Macular Thickness Map]	1.4 (-0.9, 3.6) (n=27)	0.7 (-2.1, 3.5) (n=18)	0.5 (-0.4, 1.4) (n=27)	0.3 (-0.8, 1.3) (n=18)	0.73
Mean macular thickness, Outer Ring [μm, Fast Macular Thickness Map]	-0.4 (-1.8, 0.9) (n=27)	1.7 (-0.05, 3.4) (n=18)	-0.2 (-0.7, 0.4) (n=27)	0.7 (-0.02, 1.4) (n=18)	0.08
Mean macular volume [mm^3, Fast Macular Thickness Map]	-0.02 (-0.06, 0.03) (n=27)	0.05 (-0.004, 0.1) (n=18)	-0.2 (-0.8, 0.4) (n=27)	0.7 (-0.1, 1.5) (n=18)	0.10

n=number of participants (1 eye/participant) for each OCT scan protocol.

* p-value for difference between glaucomatous and control eyes, in percent change per year from each eye's baseline.

There was no significant correlation between the rate of change in any of the 6 OCT parameters and follow-up time in the regression model. There was also no significant relationship between average RNFL 3.4 thickness and baseline refractive error (correlation coefficient 0.35, p=0.11).

DISCUSSION:

In this prospective study of children aged 2 to 16 with glaucoma, glaucomatous eyes exhibited reduced baseline RNFL thickness, macular thickness, and macular volume, and increased baseline myopia, compared to control eyes. During a mean 2.4 years of follow-up, OCT measurements in control and glaucomatous eyes changed minimally. Annual changes ranged from -0.4μm/year (for macular outer-ring thickness) to 4.3μm/year (for average RNFL 3.4 thickness), clinically modest amounts in the context of OCT's intra-eye variability of 3.14μm for Fast Macular Thickness protocol and 2.68μm for Fast RNFL 3.4 Thickness protocol.[3] To our knowledge, this is the first study to prospectively analyze longitudinal changes in OCT measurements of peripapillary RNFL thickness, macular thickness, and macular volume in children with and without glaucoma.

The rates of change for the six OCT parameters were similar between control and glaucomatous eyes, adjusted for age, race, and baseline refractive error. There was also no correlation between change in OCT parameters and length of follow-up (i.e. participants with long and short follow-up showed similar rates of change). Furthermore, since the expected axial length increase in children older than 10 years is 0.4-0.5mm over 8 years (10-18 years old),[20] and average RNFL thickness decreases by 2.2μm for every 1mm increase in axial length,[18, 21] adolescent axial length increase would be expected to account for no more than about 1.1 μm decrease in OCT measurements of average RNFL thickness over 8 years.

The present study is consistent with previous published studies reporting decreased baseline RNFL thickness, macular thickness, macular volume, and increased baseline myopia in glaucomatous vs. control eyes.[6, 9-12, 15] Consistent with longitudinal findings in adults,[12] longitudinal changes in RNFL thickness, macular thickness, and macular volume were similar in glaucomatous and control eyes in our population. However, unlike in previous adult findings,[7]

decreased baseline RNFL thickness in our population was not predictive of future RNFL thinning. There are several potential explanations for our findings.

The limited length of time between baseline and subsequent OCT measurements in our study might be insufficient to detect ongoing glaucomatous changes in OCT parameters such as RNFL and macular thickness. Second, the present study included eyes of children whose glaucoma was clinically stable; the stable OCT measurements in these eyes would seem to confirm the clinical impression of disease control over the study period. Third, and likely most important, the limited number of eyes in the present study limits its power to detect small differences between study groups. Additionally, many eyes in the control group had been referred to our practice as glaucoma suspects based upon optic nerve cups, biasing the study toward more similarity between glaucoma and control groups than otherwise might be observed. Furthermore, many children with severe glaucoma could not be included in the study because of media opacities or poor fixation. These eyes with severe glaucoma might have demonstrated higher rates of decline in OCT parameters than the stable glaucomatous eyes included in the study.   This is particularly important given the potentially proportional relationship between disease progression and ocular changes, as has been shown with macular volume.[18]

There are several additional limitations to the present study. The patients attending the Duke University Eye Center, a research-focused tertiary care center, may not be representative of the general population, thus reducing generalizability of results. Data were collected as part of normal clinic visits, so participants, clinicians, and data collectors were unmasked. Baseline and repeat OCT measurements were completed by different operators, introducing potential measurement bias, although such bias is likely small due to OCT's high inter-operator reproducibility[4] and frequent on-site calibration.   The study would have been stronger if it included more patients, OCT reproducibility data, and axial-length measurements.

The present study has examined longitudinal changes in OCT measurements of peripapillary RNFL thickness, macular thickness, and macular volume in children with and without glaucoma. While confirming previously reported baseline differences between glaucomatous and control eyes in children,[10, 11] we found that longitudinal OCT parameters were essentially stable in both groups, with similar, minimal rates of change over a relatively short time period. Despite its limitations, our findings support continued study of OCT as an easily performed clinical adjunct in the evaluation and management of children with glaucoma.

REFERENCES:

1. Robaei D, Huynh SC, Kifley A, Mitchell P. Correctable and non-correctable visual impairment in a population-based sample of 12-year-old Australian children. Am J Ophthalmol 2006;142:112-118.

2. Haddad MA, Sei M, Sampaio MW, Kara-Jose N. Causes of visual impairment in children: a study of 3,210 cases. J Pediatr Ophthalmol Strabismus 2007;44:232-40.

3. Paunescu LA, Schuman JS, Price LL, Stark PC, Beaton S, Ishikawa H, et al. Reproducibility of nerve fiber thickness, macular thickness, and optic nerve head measurements using StratusOCT. *Invest Ophthalmol Vis Sci.* 2004;45:1716-1724.

4. Leung CK, Chan WM, Yung WH, et al., Comparison of macular and peripapillary measurements for the detection of glaucoma: an optical coherence tomography study. *Ophthalmology*. 2005;112:391-400.

5. Badala F, Nouri-Mahdavi K, Raoof DA, Leeprechanon N, Law SK, Caprioli J. Optic disk and nerve fiber layer imaging to detect glaucoma. *Am J Ophthalmol.* 2007;144:724-732.

6. Liu X, Ling Y, Luo R, Ge J, Zheng X. Optical coherence tomography in measuring retinal nerve fiber layer thickness in normal subjects and patients with open-angle glaucoma. *Chin Med J (Engl).* 2001;114:524-529.

7. Lalezary M, Medeiros FA, Weinreb RN, et al. Baseline optical coherence tomography predicts the development of glaucomatous change in glaucoma suspects. *Am J Ophthalmol*. 2006;142:576-582.

8. Jonas JB, Grundler AE. Correlation between mean visual field loss and morphometric optic disk variables in the open-angle glaucomas. *Am J Ophthalmol.* 1997;124:488-497.

9. Guedes V, Schuman JS, Hertzmark E, et al. Optical coherence tomography measurement of macular and nerve fiber layer thickness in normal and glaucomatous human eyes. *Ophthalmology*. 2003;110:177-189.

10. Hess DB, Asrani SG, Bhide MG, Enyedi LB, Stinnett SS, Freedman SF. Macular and retinal nerve fiber layer analysis of normal and glaucomatous eyes in children using optical coherence tomography. *Am J Ophthalmol*. 2005;139:509-517.

11. Mrugacz M, Bakunowicz-Lazarczyk A. Optical coherence tomography measurement of the retinal nerve fiber layer in normal and juvenile glaucomatous eyes. *Ophthalmologica*. 2005;219:80-85.

12. Wollstein G, Schuman JS, Price LL, et al. Optical coherence tomography longitudinal evaluation of retinal nerve fiber layer thickness in glaucoma. *Arch Ophthalmol.* 2005;123:464-470.

13. Tsai JC, Lin PW, Teng MC, Lai IC. Longitudinal changes in retinal nerve fiber layer thickness after acute primary angle closure measured with optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2007;48:1659-1664.

14. Lederer DE, Schuman JS, Hertzmark E, et al. Analysis of macular volume in normal and glaucomatous eyes using optical coherence tomography. *Am J Ophthalmol.* 2003;135:838-843.

15. Leung CK, Mohamed S, Leung KS, et al. Retinal nerve fiber layer measurements in myopia: An optical coherence tomography study. *Invest Ophthalmol Vis Sci.* 2006;47:5171-5176.

16. Quinn GE, Berlin JA, Young TL, Ziylan S, Stone RA. Association of intraocular pressure and myopia in children. *Ophthalmology*. 1995;102:180-185.

17. Asefzadeh B, Cavallerano AA, Fisch BM. Racial differences in macular thickness in healthy eyes. *Optom Vis Sci.* 2007;84:941-945.

18. Budenz DL, Anderson DR, Varma R, et al. Determinants of normal retinal nerve fiber layer thickness measured by Stratus OCT. *Ophthalmology*. 2007;114:1046-1052.

19. Salchow DJ, Oleynikov YS, Chiang MF, et al. Retinal nerve fiber layer thickness in normal children measured with optical coherence tomography. *Ophthalmology*. 2006;113:786-791.

20. Fledelius HC. Ophthalmic changes from age of 10 to 18 years. A longitudinal study of sequels to low birth weight. IV. Ultrasound oculometry of vitreous and axial length. *Acta Ophthalmol*. 1982;60:403-411.

21. Huynh SC, Wang XY, Rochtchina E, Mitchell P. Peripapillary retinal nerve fiber layer thickness in a population of 6-year-old children: findings by optical coherence tomography. *Ophthalmology.* 2006;113:1583-1592

NON-MANUSCRIPT ADDENDA, UNC MPH THESIS:

Research Question:

Do children with glaucoma exhibit greater changes in peripapillary RNFL thickness, macular thickness, and macular volume [as measured by Optical Coherence Tomography (OCT)] compared to non-glaucomatous children during a mean 2.4 years of follow-up?

Hypothesis:

We expect OCT measurements of ocular parameters to reflect those in the adult population: that is, to show an association between glaucoma and reduced baseline and longitudinal RNFL thickness, reduced baseline and longitudinal macular volume, and greater baseline refractive error. Thus we hypothesize that our study's participants with glaucoma will have lower baseline RNFL thickness, macular inner- and outer-ring thicknesses, and macular volume, and higher baseline refractive error, than control participants. During follow-up, we expect glaucomatous eyes to exhibit greater decreases in peripapillary retinal nerve fiber layer (RNFL) thickness, inner- and outer-ring retinal thicknesses, inner- and outer-ring macular thicknesses, and macular volume than control participants.

Addendum to Abstract (see page 1):

Background/Aims:

This study documents baseline and longitudinal OCT measurements in control and glaucomatous eyes of children. If clinically meaningful inter-group differences exist, this would support the use of OCT to assist with noninvasive baseline glaucoma diagnosis, and/or to monitor subclinical glaucoma progression over time. If we identify longitudinal stability, this could suggest the use of OCT in monitoring maintenance of RNFL over time, the ability of attentive medical

management to prevent retinal thinning in children with glaucoma, or the limitations of the study's small sample size.

Addendum to Introduction (see page 2):

Burden of Disease:

Glaucoma is the leading cause of preventable blindness in the United States, and the second leading cause of bilateral blindness in the world. [1, 2] One form of the disease, pediatric glaucoma, causes an estimated 9.5%-10.8% of childhood visual impairment [3, 4] and occurs as congenital glaucoma or juvenile open-angle glaucoma (JOAG), or can be secondary to syndrome complexes, medications, chemical and physical trauma, cataract surgery and pseudophakia, or other ocular pathologies.

High intraocular pressure can permanently damage the optic nerve, and can distend and thin the cornea and sclera.[5, 6] Due to more elastic ocular collagen, corneal and scleral thinning are even more pronounced in children younger than 3 years of age, making early diagnosis even more important in these children. 40% of patients with infantile glaucoma have symptoms at birth, and 86% by 1 year of age;[7] however, the age of medical diagnosis for children with later-onset JOAG ranges from birth until late childhood.

Disease Etiology:

The etiology of congenital and juvenile open-angle glaucoma, like adult glaucoma, remains unclear. These progressive conditions can be caused by abnormal fetal development of ocular angle structures, leading to impaired drainage of the aqueous fluid and elevated intraocular pressure (IOP). The disease is also thought to be highly influenced by additive genetic effects, with heritability estimates of 35% for IOP, 48% for RNFL thickness, and 39% for neuroretinal rim area, and nongenetic factors accounting for only 13% of the variance in

these traits.[8] Mutations in genes affecting angle development, such as in CYP1B1 (a member of

the cytochrome P450 superfamily of enzymes), have been correlated with the degree of angle

dysgenesis, age of onset, and difficulty of achieving intraocular pressure control.[8]   In some

populations, mutations in this gene accounted for 37.5-70% of primary congenital glaucoma

cases.[9-11]

     Pediatric glaucoma can also occur secondary to syndrome complexes, medications,

chemical and physical trauma, cataract surgery and pseudophakia, or other ocular pathologies. A

prime example of glaucoma within a syndrome complex is Sturge-Weber syndrome (also known

as encephalotrigeminal angiomatosis), a rare congenital neurological and skin disorder caused by

a cerebral arteriovenous malformation. Most often unilateral, it is associated with glaucoma,

port-wine stains of the face, mental retardation, seizures, and leptomeningeal angioma. Many

medications (eg. topical steroid eye drops) can reduce aqueous humor drainage and thereby

cause ocular hypertension and raise an individual's risk of developing glaucoma; infants and

very young children are particularly sensitive to this pressure rise.[12] Chemical or physical

trauma can cause corneal inflammation, hemorrhage, or lens dislocation or rupture, all producing

a secondary pressure increase. Cataract surgery in pediatric patients, with or without intraocular

lens implant (pseudophakia and aphakia, respectively), is associated with glaucoma.[13] In

particular, early surgery (at <9 months of age) has a 7.2-fold increased risk of glaucoma

compared with later surgery (≥9 months of age), a higher risk that continues for more than 10

years after cataract surgery.[14] Other ocular pathologies such as tumors (eg. retinoblastoma),

uveitis, iridocyclitis, or Coats' Disease also can affect aqueous drainage and raise intraocular

pressure. [15-17]

Tools for Glaucoma Diagnosis and Management:

The three most commonly used glaucoma diagnostic techniques are visual field testing, optic nerve head (ONH) stereophotography, and measurement of intraocular pressure (IOP) (see page 2). Visual field testing takes 7-10 minutes per eye and requires significant concentration from the patient, making it unreliable in young children and those with nystagmus; in addition, it only shows changes in advanced stages of the disease.[18] ONH stereophotography (the gold standard in adults) has high inter-observer variability.[19] IOP measurements are completed via applanation or indentation tonometry, can vary substantially within one day in the same patient, and provide no information about retinal thinning or optic nerve damage. In addition, applanation measurements are dependent upon central corneal thickness (CCT),[20] yielding IOP deviation up to 7 mm Hg from the true IOP for every 100-µm variation in CCT from the normal CCT of 520 µm for which the tonometer is calibrated.[20, 21] This biases toward glaucoma overdiagosis in patients with thicker CCT, and underdiagnosis of patients with thinner CCT.

In addition to the above three modalities, several imaging techniques have emerged for evaluating and managing glaucoma, including optical coherence tomography (OCT), Heidelberg retinal tomography, and scanning laser polarimetry. Since its introduction into adult and pediatric clinical practice in the past two decades,[22] OCT has rapidly become a valuable tool for providing high-resolution cross-sectional tomographic images of the ocular microstructure (see page 2).

First devised with 30µm axial resolution by Huang et al. in 1991, OCT's initial application was in diagnosing and monitoring glaucoma;[23] today OCT has sub-micrometer resolution and is used for other ophthalmic pathologies in addition to glaucoma, such as macular degeneration, retinal capillary hemangioma, macular edema in diabetes or retinal vein occlusion, retinal thinning in drug-induced retinal toxicity, central corneal thickness changes, and foveal and retinal detachment. Studies have shown OCT to yield accurate, reproducible results when

used independently and/or in conjunction with other ophthalmic diagnostic technologies such as stereoscopic fundus photography, visual field testing, static automated pachymetry (SAP), and biomicroscopy.[24-26] Other ophthalmic variations of traditional OCT technology include the OCT ophthalmoscope for en face OCT images of retinal diseases,[27] and anterior segment OCT for evaluation of the cornea and anterior segment before and after lamellar transplantation surgery.[28] OCT is also used in non-ophthalmic tissue imaging requiring micrometer resolution and millimeter penetration depth: for example, hard and soft dental tissues;[29] skin layers in inflammatory dermatologic disorders such as contact dermatitis and psoriasis;[30] and preneoplastic lesions and epithelial changes in the esophagus, esophagogastric junction, duodenum, colon, and pancreatico-biliary ductal system.[31] Currently it is also being investigated for use in imaging allergic and infectious changes in nasal mucosa;[32] proximal airway microstructure changes in adult respiratory diseases;[33] normal and pathologic features of the pediatric airway;[34] and features of atherosclerotic plaques that predict plaque rupture, including fibrous cap thickness, lipid core size, and percentage of lipid content.[35, 36] Outside medicine, OCT is used in art conservation projects to non-invasively analyze different layers of underdrawings in museum paintings.[37]

Despite the promise of OCT as a useful adjunct in the clinical management of glaucoma, several potential problems exist. These include variable reproducibility of measurements depending on quadrant measured,[38] variable inter-individual reproducibility depending on protocol applied,[22] and differences in measurements depending on OCT instrument used (eg. OCT 2000 vs. Stratus OCT/OCT3).[39] In addition, although OCT performed better than ONH stereophotography in early detection of glaucomatous damage in perimetrically normal eyes of primary open-angle glaucoma patients (sensitivity 61% vs. 28%, respectively, with 95% specificity), 61% is still far from an optimal sensitivity value.[40] As with any technology, OCT

imaging may fail to identify true positives or may falsely identify glaucoma and its progression; thus clinicians should not make treatment decisions based on the results of a single test or technology. Due to OCT's relatively recent introduction into clinical practice, the efficacy of OCT in monitoring long-term disease progression has not been thoroughly demonstrated. In addition, although OCT has shown to be an extremely safe, noninvasive imaging modality, there may be unforeseen adverse consequences of multiple ocular exposures to ultrasound over time; such consequences may only become apparent after several decades of routine OCT use.

Glaucoma Treatment:

Treatment for pediatric glaucoma can be medical and/or surgical, with medications (typically given as eye drops) usually tried before surgery. The objective of most medications is to decrease intraocular pressure, the only treatment that has been proven effective in preventing the onset or progression of glaucoma.[41] Medications achieve IOP reduction either by reducing aqueous humor production or increasing uveoscleral or transcanalicular aqueous humor outflow. The vast majority of medication data are from adult studies, and almost all of the drugs are not officially licensed for use in children,[42] nor do they have pediatric safety labeling information.[43] However, most topical drugs have shown to be safe and well-tolerated in children. These drugs include beta-blockers (eg. timolol), adrenergic α_2-receptor agonists, and carbonic anhydrase inhibitors (e. acetazolamide), which inhibit aqueous humor formation; prostaglandin analogs (eg. latanoprost) and adrenergic a1-receptor antagonists, which increase uveoscleral aqueous humor outflow; and miotics (eg. pilocarpine), which increase transcanalicular aqueous humor outflow.[44, 45] A notable exception to medication safety is the selective α_2-receptor agonist brimonidine, a commonly used and well-tolerated glaucoma medication in adults, which can produce systemic effects such as apnea, bradycardia, bronchospasm, and hypotension in children under two years of age.[42, 46]

The impact of IOP reduction (via IOP-lowering medication) on RNFL thickness in newly-diagnosed adult glaucomatous patients has been equivocal, varying from no effect to a significant protective effect on RNFL thickness.[47, 48] The relationship between IOP reduction by different ophthalmic medications and degree of RNFL thinning has been examined in adults, with brimonidine appearing to have a more protective effect on RNFL thickness compared to timolol.[49] Studies have differed in their findings of the effect of IOP reduction on optic nerve topography, showing that IOP reduction either has no effect on optic nerve topography changes,[50] or that it moderately increases optic rim area and reduces optic cup area, cup volume, and cup-to-disk ratio.[51]

In addition to established glaucoma medications, novel classes are currently under investigation. For example, selective Rho-associated coiled coil-forming protein kinase (ROCK) inhibitors, are the first medications to act directly on the trabecular meshwork; these medications inhibit formation of actin stress fibers and focal adhesions, thereby improving aqueous outflow.[45] A forefront example is the ophthalmic solution SNJ-1656, currently in its Phase 1 clinical trial. This medication has demonstrated effective reduction of intraocular pressure, but is associated with post-instillation hyperemia of the bulbar and palpebral conjunctiva,[45] which may limit its use in both adults and children.

If intraocular hypertension is unresponsive to medical therapy, it can cause increased retinal thinning and necessitate surgical treatment. First-line procedures usually include trabeculotomy (surgical opening of the canal of Schlemm to treat glaucoma), trabeculectomy (removal of part of the trabecular meshwork to relieve high intraocular pressure), or trabeculoplasty (laser photocoagulation of the trabeular meshwork). In some patients, variations of these procedures have also been successful, such as nonpenetrating external trabeculectomy, which has fewer risks and postoperative complications than traditional trabeculectomy;[52]

combined trabeculotomy-trabeculectomy, which has shown efficacy in reducing intraocular pressure in surgery-naïve patients;[53] and viscotrabeculotomy (use of viscoelastic materials during trabeculectomy), which has shown higher success rates than classical trabeculotomy due to its reduction of postoperative hemorrhage, adhesion of incision lips, or fibroblastic proliferation.[54] Further surgical treatment can include implantation of an Ahmed glaucoma valve (New World Medical, Inc, Rancho Cucamonga, California, USA), which has been shown to reduce intraocular pressure and number of necessary ophthalmic medications in patients with refractory pediatric glaucoma,[55] and has shown long-term success (particularly when combined with glaucoma medications) in patients with uveitic glaucoma.[56]

Addendum to Materials and Methods (see page 4):

Measures:

Optical coherence tomography (OCT) provides a non-contact measurement of retinal thickness using optical ultrasound. It is less sensitive to opacities in the media than the earlier-used retinal thickness analyzer (RTA), and may allow changes to be detected earlier in certain patients; it also provides quantitative measurements such as retinal nerve fiber layer thickness. OCT analysis itself involves pupil dilation (part of routine eye exam) followed by obtaining several cross-sectional retinal images by asking the patient to look into the instrument at different internal fixation targets. Each cross-sectional set of images takes 200 msec to perform, and the total time required for the entire examination is approximately 2 minutes. An example of an OCT report is shown below.[57]
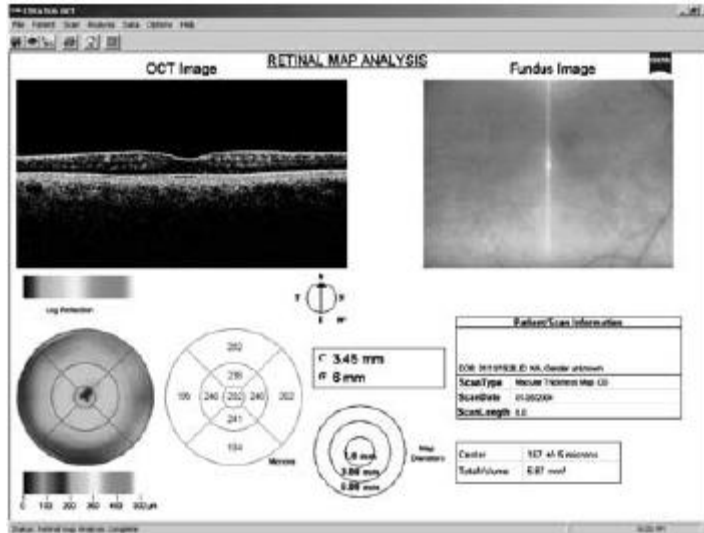
To account for unequal lengths of follow-up between participants, and to address both statistical and clinical significance of OCT changes, outcomes were expressed as percent change per year (of each eye's baseline value) in addition to absolute change per year. This provides a clinical context for each patient's progression; for example, a thinning of 10μm is more clinically concerning in a patient with baseline RNFL thickness of 50μm than in a patient with baseline RNFL thickness of 120μm.

In interpreting the results of our study, there are three potential outcomes: statistical and clinical significance, statistical significance but clinical insignificance, and statistical and clinical insignificance. Given the absence of longitudinal research in pediatric glaucoma, all three scenarios – including a null outcome - are helpful, as they help us document expected values for change over time in glaucomatous and non-glaucomatous children. A finding of statistical and clinical significance would support OCT's use in providing reliable baseline glaucoma diagnosis as well as monitoring longitudinal disease progression. In cases of statistical significance but clinical insignificance, we can conclude that the study had adequate power to detect small differences in ocular outcomes, but that these differences were not clinically meaningful. A finding of statistical and clinical insignificance indicates no difference in ocular outcomes

between glaucomatous and control participants; such a finding could have several implications, including a different etiologic mechanism for pediatric and adult glaucoma, an opportunity for medical management to halt glaucomatous damage, a limited sample size, bias toward similarity between control and glaucomatous participants, or longitudinal regression to the mean.

Analysis:

The inclusion of age, race, and baseline refractive error as covariates in the ANCOVA regression model was due to the known effect of these factors on OCT measurements (see page 2); it also results in a thorough yet parsimonious model, remaining consistent with the advised limitation of number of model parameters per study case.[58]

Addendum to Results (see page 8):

TABLE 4.
Unadjusted mean and range of OCT changes in control and glaucomatous eyes during a mean 2.4 years of follow-up (two-sample t-test)

Unadjusted OCT parameter	Absolute change (µm) per year (95% CI)		Percent change per year from baseline (95% CI)		p-value*
	Control	Glaucoma	Control	Glaucoma	
Mean peripapillary RNFL thickness [µm, Fast RNFL 3.4 Thickness]	-0.6 (-3.7, 2.5) (n=14)	4.7 (0.4, 9.1) (n=7)	-0.3 (-3.3, 3.0) (n=14)	3.9 (-0.6, 8.5) (n=7)	0.15
Mean RNFL Thickness, Inner Ring [µm, Fast RNFL Map]	2.0 (-2.3, 6.2) (n=11)	2.1 (-1.7, 5.8) (n=14)	3.0 (-2.7, 8.6) (n=11)	2.5 (-2.5, 7.5) (n=14)	0.91
Mean RNFL Thickness, Outer Ring [µm, Fast RNFL Map]	0.7 (-4.5, 5.9) (n=11)	-0.3 (-5.1, 4.5) (n=13)	2.2 (-5.9, 10.3) (n=11)	2.4 (-5.0, 9.8) (n=13)	0.97
Mean macular thickness, Inner Ring [µm, Fast Macular Thickness Map]	1.7 (-0.4, 3.7) (n=27)	0.3 (-2.2, 2.7) (n=19)	0.6 (-0.2, 1.4) (n=27)	0.1 (-0.8, 1.0) (n=19)	0.41
Mean macular thickness, Outer Ring [µm, Fast Macular Thickness Map]	0.1 (-1.2, 1.5) (n=27)	0.9 (-0.7, 2.5) (n=19)	0.1 (-0.5, 0.6) (n=27)	0.4 (-0.3, 1.1) (n=19)	0.49
Mean macular volume [mm³, Fast Macular	-0.002 (-0.04, 0.04)	0.02 (-0.03, 0.1)	0.03 (-0.6, 0.6)	0.3 (-0.4, 1.1)	0.55

Thickness Map]	(n=27)	(n=19)	(n=27)	(n=19)	

n=number of participants (1 eye/participant) for each OCT scan protocol.

* p-value for difference between glaucomatous and control eyes, in percent change per year from each eye's baseline.

Methods for Systematic Review of the Literature:

We searched the MEDLINE/PubMed database (August 1983 to May 2008) using the following search terms: "childhood blindness U.S." and "congenital glaucoma prevalence" for articles on congenital glaucoma's burden of disease; "congenital glaucoma retina," "congenital glaucoma refractive error," and "infantile glaucoma" for articles on baseline ocular characteristics of pediatric glaucoma patients; "glaucoma optical coherence tomography," "congenital glaucoma diagnosis," and "glaucoma diagnosis retinal thickness" for articles on congenital glaucoma diagnosis; "glaucoma treatment," "congenital glaucoma treatment," "congenital glaucoma treatment trabeculectomy," "congenital glaucoma medication," "glaucoma medication," and "glaucoma drugs" for articles on medical and surgical management of glaucoma; "glaucoma progression retinal thickness," "glaucoma progression macular thickness," "congenital glaucoma outcome," "glaucoma progression optical coherence tomography," and "RNFL decrease OCT" for articles on longitudinal glaucoma progression; "intraocular pressure medications retinal thickness," "intraocular pressure retinal thickness," "glaucoma retinal nerve fiber layer thickness," "glaucoma macular thickness," and "glaucoma retinal thickness OCT" for articles on the relationship between glaucoma and baseline RNFL and macular thickness; "optical coherence tomography uses" and "optical coherence tomography diagnosis accuracy" for articles on clinical uses and diagnostic reliability of OCT; "optical coherence tomography problem," "optical coherence tomography resolution," "optical coherence tomography resolution glaucoma," "optical coherence tomography glaucoma adverse," "optical coherence tomography

safety," and "optical coherence tomography risk" for articles on potential problems with OCT technology; "secondary glaucoma children" and "secondary glaucoma children medication" for articles on the etiology of non-congenital glaucoma in children; "congenital glaucoma corneal thickness" for articles on the effect of glaucoma on corneal and scleral thickness; "congenital glaucoma gene" for articles on the molecular etiologies of glaucoma; "pediatric spherical equivalent change" for articles on eye development over time; "race retinal thickness", "age retinal thickness", and "refractive error retinal thickness" for articles on the influence of participant characteristics (covariates) on retinal thickness.

We reviewed abstracts for citations in peer-reviewed journals, using the limits of age (Infant-18 years old), language (English), and subjects (human) for the majority of searches; for the OCT-problems, OCT-uses, OCT-accuracy, and some of the longitudinal OCT-parameters searches, no limits were applied. For a detailed list of systematic search terms and limits, please refer to Table 5 in the Appendix. We excluded the following: studies of insufficient length to assess change in ocular outcomes (two months or less), studies that did not adjust for confounding variables (age, race), studies that did not include follow-up measures, and studies with a lack of glaucoma-related ocular outcomes. Due to the small number of studies on pediatric ophthalmology patients, we considered all study designs except case reports and case series, and included articles with adult ophthalmology patients. We then used a checklist, modified from two established quality assessment guidelines,[59, 60] to evaluate the internal validity of scientific studies, systematic reviews, and meta-analyses that met the eligibility criteria. For evidence grading checklist, please see Table 6 in the Appendix.

In addition, we read several studies recommended to us by clinical or research professors. These included 3 articles on central corneal thickness and applanation tonometry, 1 article on glaucoma development after pediatric cataract surgery, 3 articles on the relationship between

axial length and retinal thickness, 2 articles including OCT reproducibility data, 1 article on

ROCK inhibitors, 3 articles on translaminal pressure and glaucoma, 1 article on modeling and

variable selection in epidemiologic analysis, 1 article including images of OCT reports, and 2

articles on quality assessment guidelines.

Addendum to Discussion (see page 9):

Limitations:

The present study has limited generalizability due to the tertiary-care, clinically complex

patient population attending the Duke Eye Center, as discussed previously (see page 10). In

addition, it may be limited by selection bias, necessitating a discussion of the participant

selection process. Participants with glaucoma were selected sequentially; every patient with

glaucoma between 2002 and 2006 who was able to fixate and had no media opacities was

included in the study. Control participants with large physiologic cups or uniocular glaucoma

were also selected sequentially. All control participants with normal cups were approached to

participate in the study, and were included if they were willing to receive baseline and repeat

OCT scans. Since the Clinic sees relatively few patients with normal cups, and since selection

largely depended upon the guardians' willingness to allow their children to participate, these

participants constitute somewhat of a "convenience sample." This could reduce the

generalizability of the study findings, although this limitation is likely small considering that the

control group only contained 3 participants (11% of group) with normal cups (see page 5).

There are several factors that the present study was unable to evaluate as in previous

studies (see page 2). Since participants had longstanding diagnoses of glaucoma, the effect of

IOP reduction on RNFL thickness in newly-diagnosed glaucoma could not be examined as has

been done in previous studies.   Glaucoma treatment was not divided into separate IOP-lowering

medications, and thus the effect of specific medications on retinal thinning was not evaluated. Confocal scanning laser tomography was not completed in participants, so baseline and longitudinal changes in optic nerve topography could not be reported. There were no previous studies of longitudinal change in macular thickness and macular volume, so we could not determine whether our findings were consistent with previously observed results.

Specific to longitudinal studies of OCT measurements, it is important to consider both glaucomatous thinning and normal age-related eye growth. Potential effects of the latter must be discerned from the former, through inclusion of age in regression analysis (see page 7), through demonstration of independence between outcome and follow-up time (see page 8), and/or through interpreting the results in the context of normal pediatric axial length increases (see page 9).

Increased axial length has been shown to be correlated with increased foveal thickness (in the central retina) and decreased parafoveal thickness;[61, 62] these trends are present in both Caucasian and African American individuals, although they are more prominent in the latter, for unknown reasons.[63] Thus it is not entirely surprising for our study to show a longitudinal increase in macular volume and macular inner-ring thickness in participants with increased refractive error (and presumably increased axial length) at baseline, i.e. in our study population's participants with glaucoma (see page 8).

Broader Implications:

In analyzing the results of any study, it is important to evaluate the immediate hypothesis in question, but it is also imperative to think "outside the box" about potential explanations we had not previously considered. For example, there are three main hypotheses of glaucoma etiology, each of which has developed out of innovative analysis and warrant further discussion in relation to our study findings. One hypothesis is that the initial insult in glaucoma is optic

nerve damage, and that intraocular hypertension, retinal thinning, and increased refractive error

are signs independently associated with this insult; this definition has led to the use of the phrase

"optic neuropathy" to describe glaucoma, and helps explain why glaucoma occurs across the

entire spectrum of intraocular pressure and often progresses despite normalization of IOP.[64]

This hypothesis would account for the baseline differences in RNFL and macular thickness,

macular volume, and refractive error seen between control and glaucomatous individuals in our

study. The lack of change in OCT parameters over time in our study counter this hypothesis, as

an initial optic nerve insult would be expected to result in decreased OCT values in

glaucomatous participants despite attainment of intraocular pressure control; however, since

average follow-up was relatively short (2.4 years), it is difficult to say that a difference would not

have been observed if the sample were followed for a longer time period.

A second hypothesis, illustrated in a recent population-based case-control study,

demonstrates a "tipping point" or paradigm shift in our understanding of glaucoma.[64] The study

showed that cerebrospinal fluid (CSF) pressure is significantly lower in patients with primary

open-angle glaucoma, supporting the novel hypothesis that translaminal pressure difference –

rather than absolute pressure values - may play an important role in the mechanism by which

increased intraocular pressure causes optic nerve damage.[65] The optic nerve is exposed to two

different pressurized regions (intraocular space anteriorly, average IOP pressure 10-21 mmHg,

and subarachnoid space posteriorly, average CSF pressure 5-15 mmHg), with the lamina cribrosa

separating the two regions.[66] If elevated, the pressure difference between them (the translaminar

pressure difference) can cause optic nerve head swelling or optic nerve cupping: the former

occurs when CSF pressure is elevated relative to IOP (eg. due to high CSF pressure in

pseudotumor cerebri or low IOP in hypotony),[51, 67] and the latter when IOP pressure is elevated

relative to CSF (as in glaucoma).[68]

Indeed, the study showed that IOP, CSF pressure, and translaminal pressure difference all correlate with cup-to-disc ratio.[65] It is also suggested that the high translaminar pressure gradient disrupts retinal ganglion cell axoplasmic flow, leading to retinal ganglion cell apoptosis and visual loss.[64] This is supported by the observed kinking of retinal ganglion cell axons as they pass through the lamina cribrosa in the setting of elevated translaminal pressure difference, and the observation of reduced axonal transport at the lamina cribrosa in glaucoma models.[65] It is also supported by the thinning and posterior bowing of the lamina cribrosa observed in glaucomatous human eyes.[69, 70] The importance of pressure differences, rather than absolute values, in glaucoma pathogenesis is further underscored by studies in rabbits, which have shown that peripheral nerves can withstand high absolute pressures of 3800 mmHg, but show reduced axonal transport in the presence of a pressure gradient of only 4.5 mmHg.[71]

Relating the above findings to our study, it is possible that the higher translaminal pressure difference seen in glaucoma – rather than the intraocular pressure alone – is the important factor in affecting the macula and retinal nerve fiber layer; this could account for the finding of lower baseline RNFL and macular thicknesses in glaucomatous than control participants. It also could help explain the absence of longitudinal differences between the two groups: since glaucomatous participants' intraocular pressure was kept at a near-healthy level with IOP-lowering medications, the translaminal pressure gradients of glaucomatous and control participants were likely quite similar. Thus only the participants with inherently low CSF pressure would retain an elevated translaminal pressure gradient despite IOP reduction, and their results would likely be diluted within the aggregate glaucoma sample, thereby allowing the glaucomatous group's change over time to remain similar to the control group's change over time.   Although this hyopthesis is plausible, a more likely explanation is that the study's sample

size was not large enough, and the follow-up period not long enough, to detect longitudinal differences between groups.

A third hypothesis reflects an even broader view: it is possible that retinal thinning, refractive error, and elevated IOP are all downstream manifestations of a common disease process involving innate differences in connective tissue makeup between glaucomatous and non-glaucomatous individuals. Such differences suppose the ocular (and perhaps subarachnoid) connective tissue of the former to be more readily deformable than that of the latter. This upstream mechanism could account for our study's findings as well as for the aforementioned lower CSF pressure, elevated rates of myopia, lower central corneal thickness (CCT), and lower corneal hysteresis observed in glaucoma.

The reasoning behind this hypothesis is as follows. Corneal hysteresis is determined by the viscoelastic properties of the corneoscleral shell and thus is a useful indicator of the biomechanical properties of the eye; lower values are associated with more easily deformable corneoscleral coats, and have been reported to be associated with higher risk of glaucoma progression.[72] A recent study in Chinese schoolchildren also showed a significant correlation between lower corneal hysteresis and longer axial length;[73] the mean corneal hysteresis observed in the study was significantly lower than that previously reported in Caucasian children.[74] This finding could help explain the higher prevalence and faster progression of myopia in Asian children than Caucasian children, since increased axial length is a major determinant of myopia development. It also could explain the observed association between myopia and glaucoma,[75] as a more compliant ocular coat could predispose individuals to axial elongation as well as provide less physical support for the optic nerve (and thus predispose to glaucoma progression).

This more mechanical, rather than pressure-related, explanation for glaucomatous damage to the optic nerve is consistent with the fact that primary open-angle glaucoma occurs

across the entire spectrum of intraocular pressure, and that it often progresses despite normalization of IOP.[64]   It also could help explain why certain patients experience much greater optic nerve damage and visual field loss than other patients, despite having similar intraocular pressures.

This third view counters the first hypothesis that optic neuropathy is the initial insult predisposing to elevated IOP, myopia, and retinal thinning. It is consistent with the second hypothesis that an increased translaminar pressure gradient could lead to glaucoma, although it differs in its placement of that gradient along the causative disease pathway. In contrast to the second hypothesis, increased IOP, axial elongation, myopia, and retinal thinning all could be manifestations of the same upstream mechanism in glaucomatous eyes – that of more pliable connective tissue makeup. The lower CCT seen in glaucomatous eyes could be an additional manifestation of this increased biomechanical pliability.

The finding by Berdahl et al. of lower CSF pressure and higher cup-to-disc ratio in glaucomatous vs. control individuals could be yet another downstream result of connective tissue differences. It is possible that different biomechanical properties are reflected in subarachnoid drainage mechanics as well. If this is the case, we would expect CSF protein and glucose levels to be similar in cases and controls, thereby indicating that CSF pressure differences are due to mechanics rather than metabolic processes involving CSF production by the cerebral ventricles or absorption by the arachnoid granulations over the venous sinuses. Indeed, the study found this to be the case, hence supporting a mechanical rather than metabolic hypothesis. This third hypothesis is consistent with the elevated rates of myopia, lower central corneal thickness (CCT), higher translaminar pressure difference, and lower corneal hysteresis observed in glaucoma, as well as the higher prevalence of myopia in the Asian population, and the association between lower corneal hysteresis and axial elongation. Although plausible in adults,

it is necessary to demonstrate support for this hypothesis in children, whose ocular collagen is naturally more elastic than that in adults, and whose glaucoma etiology may be significantly different than that of adult glaucoma. Unfortunately, to prove such a hypothesis, it would be necessary to measure CSF pressure and sample intraocular connective tissue concurrently with taking ocular measures, both of which are clinically impractical propositions.

Public Health Application:

In many cases a research study will apply to the general population and thus allow for public health interventions. Given the rare incidence of pediatric glaucoma, population-based interventions are unlikely; however, the study's results are very significant to the entire subpopulation of pediatric patients with glaucoma. This includes patients with congenital glaucoma as well as JOAG and secondary glaucoma, since RNFL thinning is expected in all. The Duke University Eye Center Pediatric Clinic is a tertiary-care, referral-heavy institution, and thus sees a substantial number of the eastern U.S.'s pediatric glaucoma patients. This referral pattern means that study participants are from varied regions across the Eastern U.S., which improves applicability to the general population; however, it also means that the study population likely has more complex glaucoma cases, more proactive families, and slightly higher socioeconomic status than that of the general pediatric glaucoma population. In addition, Duke's location in the Southeast gives the study a racial makeup of primarily African American and Caucasian individuals, thereby preventing direct comparison to demographically different populations, such as the Caucasian/Hispanic/Asian makeup of the U.S. West Coast.

Future Studies:

The relative paucity of research in pediatric ophthalmology is both daunting and exciting. Several short- and long-term steps in clinical research are needed to help us better understand pediatric glaucoma and improve care for patients. The rare incidence of pediatric glaucoma

makes a randomized controlled trial unrealistic; however, prospective and retrospective case-control study designs, such as in this study, would be both reasonable and cost-effective.

Immediately, this study's cohort could continue to be followed for several additional years; this would provide further information on longitudinal changes in RNFL and macular thicknesses and macular volume in children with and without glaucoma, and potentially establish reference ranges for expected OCT changes in patients with well-controlled glaucoma. In addition, pharmaceutical companies could begin clinical trials on glaucoma medications in children, given that the vast majority of data are from adult studies and almost all the drugs are not licensed for use in children. Pediatric use of adult medications is a major problem because ocular dosing is not weight-adjusted (thus giving children a much higher dose than is likely needed), infants' incompletely-developed ocular apparatus cannot efficiently metabolize the medication, and drugs can more easily access the brain due to an immature blood-brain barrier.[42] Lower doses are likely just as efficacious and have a lower incidence of complications, such as the successful use of less-concentrated mitomycin-C in congenital glaucoma post-trabeculotomy patients.[76] However, such studies are needed for other glaucoma medications commonly used in the pediatric population.

A longer-term research step could include completing a similar prospective longitudinal study of RNFL thickness, macular thickness, and macular volume change over time in a demographically distinct population: for example, with a primarily Hispanic, Asian, and Caucasian population on the U.S. West Coast. Although we know that Hispanic and Asian individuals on average have higher RNFL thickness than Caucasians,[77] longitudinal change has not yet been studied. A second possibility would be to study longitudinal retinal thickness change in a highly myopic population, such as that of the Singapore Cohort study Of the Risk factors for Myopia (SCORM), a 1,250-participant study of the genes, genetic loci, and gene-

environment interactions responsible for myopia in Singaporean children, who have some of the highest rates of myopia in the world. Study of this cohort has shown a correlation between increased axial myopia and decreased retinal thickness at baseline;[78] however, longitudinal changes have not been established for either the SCORM cohort or many other Asian study populations. The Asian eye differs structurally from the Caucasian eye, as evidenced by the increased frequency, severity, and progression of myopia in the Asian population;[79-81] the abovementioned difference in retinal thickness;[78] and the earlier and more prevalent incidence of primary angle-closure glaucoma in Asian than in Caucasian individuals.[4, 82, 83] These differences make Asia an opportune location for clinical trials on pediatric glaucoma. In addition, previously identified myopia-related genes or newly-identified genes from the SCORM trial could be examined in future glaucoma studies, to determine if there is a common molecular etiology to both myopia and glaucoma in Asian and/or Caucasian populations.

If greater retinal thinning over time is correlated with decreased visual acuity in patients with myopia, then OCT measurements potentially could be used as predictive biomarkers for vision loss. This use of OCT would be relatively easy to implement, given that OCT is already widely used in the clinical setting for patients with various ocular pathologies; ophthalmologists would only have to incorporate its use for myopia in addition to these pathologies. The approval of glaucoma medications for pediatric patients, once proven safe in pharmaceutical clinical trials, would necessitate FDA oversight and removal of the "NR" (not recommended) safety label from approved drugs. Implementation of these medications will likely not alter clinical practice, given that they have been in use for many years without formal approval. However, determination of proper weight-adjusted medication dosages for children, documentation of adverse systemic and ocular effects of certain drugs, and removal of unsafe medications from the market, would significantly improve clinical care by reducing complications in pediatric glaucoma patients.

ACKNOWLEDGEMENTS:

TABLE 5. Systematic Review Literature Searches

Date	Database	Main search terms	Modifiers	Yield (articles)	Used search?
2/11/08	PubMed	Congenital glaucoma retina	English	60	yes
2/11/08	PubMed	Congenital glaucoma retinal thinning	English	2	no
2/11/08	PubMed	Congenital glaucoma	English	1208	no
2/11/08	PubMed	Glaucoma optical coherence tomography	English	367	yes
2/11/08	PubMed	Congenital glaucoma progression	English	10	maybe
2/11/08	PubMed	Glaucoma progression retinal thickness	English	66	yes
2/11/08	PubMed	Glaucoma diagnosis retinal thickness	English	531	yes
2/11/08	PubMed	Congenital glaucoma refractive error	English	40	yes
2/11/08	PubMed	Congenital glaucoma diagnosis	English	608	no
2/13/08	PubMed	Childhood blindness U.S.	English	60	yes
2/13/08	PubMed	Congenital glaucoma prevalence	English	86	yes
2/16/08	PubMed	Infantile glaucoma	English, Infant-18 yrs	135	yes
2/16/08	PubMed	Congenital glaucoma outcome	English, Infant-18 yrs	73	yes
2/16/08	PubMed	Glaucoma optical coherence tomography	English, Infant-18 yrs	248	yes
2/16/08	PubMed	Glaucoma progression optical coherence tomography	English, Infant-18 yrs	21	yes
2/16/08	PubMed	Congenital glaucoma diagnosis	English, Infant-18 yrs	310 (first 100 reviewed)	yes
2/16/08	PubMed	Congenital glaucoma refractive error	English, Infant-18 yrs	22	no
2/16/08	PubMed	Glaucoma diagnosis retinal thickness	English, Infant-18 yrs	383 (first 60 reviewed)	yes
2/22/08	PubMed	Childhood myopia treatment glasses	English, Infant-18 yrs	12	yes

3/1/08	PubMed	Optical coherence tomography problem	None	32	yes
3/1/08	PubMed	Optical coherence tomography resolution	None	850	no
3/1/08	PubMed	Optical coherence tomography resolution glaucoma	None	51	yes
3/1/08	PubMed	Optical coherence tomography glaucoma adverse	None	33	no
3/1/08	PubMed	Optical coherence tomography safety	None	134 (first 60 reviewed)	no
3/1/08	PubMed	Optical coherence tomography risk	None	161 (first 40 reviewed)	no
4/21/08	PubMed	Secondary glaucoma children	Humans, English, Infant-18 yrs	324 (first 40 reviewed)	yes
4/21/08	PubMed	Secondary glaucoma children medication	Humans, English, Infant-18 yrs	26	yes
4/21/08	PubMed	Congenital glaucoma corneal thickness	Humans, English, Infant-18 yrs	6	yes
4/21/08	PubMed	Congenital glaucoma gene	Humans, English, Infant-18 yrs	63	yes
4/26/08	PubMed	Pediatric spherical equivalent change	None	8	yes
4/26/08	PubMed	Race retinal thickness	None	49	yes
4/26/08	PubMed	Age retinal thickness	Humans, English, Infant-18 yrs	115	yes
4/26/08	PubMed	Refractive error retinal thickness	None	31	yes
4/27/08	PubMed	Glaucoma treatment	Humans, English, Infant-18 yrs	2243 (first 40 reviewed)	yes
4/27/08	PubMed	Congenital glaucoma treatment	Humans, English, Infant-18 yrs	237	yes
4/27/08	PubMed	Congenital glaucoma treatment trabeculectomy	Humans, English, Infant-18 yrs	100	yes
4/27/08	PubMed	Congenital glaucoma	Humans,	24	no

		medication	English, Infant-18 yrs		
4/27/08	PubMed	Glaucoma medication	Humans, English, Infant-18 yrs	317	yes
4/27/08	PubMed	Glaucoma drugs	Humans, English, Infant-18 yrs	206	yes
4/28/08	PubMed	Closed angle glaucoma Asia prevalence	Humans, English, Infant-18 yrs	91	yes
4/28/08	PubMed	Intraocular pressure retinal thinning	Humans, English, Infant-18 yrs	12	yes
4/28/08	PubMed	SCORM	Humans, English, Infant-18 yrs	12	yes
5/04/08	PubMed	Optical coherence tomography diagnosis accuracy	None	109	yes
5/04/08	PubMed	Optical coherence tomography uses	None	91	yes
5/10/08	PubMed	Intraocular pressure medications retinal thickness	None	17	yes
5/10/08	PubMed	Intraocular pressure retinal thickness	None	436 (first 60 reviewed)	yes
5/11/08	PubMed	Glaucoma retinal nerve fiber layer thickness	Humans, Infant-18 yrs	42	yes
5/11/08	PubMed	Glaucoma macular thickness	Humans, Infant-18 yrs	11	yes
5/11/08	PubMed	Glaucoma macular volume	Humans, Infant-18 yrs	5	yes
5/11/08	PubMed	Glaucoma retinal thickness OCT	Humans, Infant-18 yrs	18	yes
5/11/08	PubMed	Glaucoma progression retinal thickness	Humans, Infant-18 yrs	7	yes
5/11/08	PubMed	Glaucoma progression macular thickness	Humans, Infant-18 yrs	0	no
5/11/08	PubMed	Glaucoma progression	Humans, Infant-18 yrs	136 (first 40 reviewed)	no
5/11/08	PubMed	Myopia glaucoma risk	None	144	yes
5/11/08	PubMed	Myopia glaucoma association	None	48	yes

5/26/08	PubMed	OCT error	None	94	yes
5/29/08	PubMed	RNFL decrease OCT	None	23	yes
5/29/08	PubMed	Macular volume increase OCT	None	10	no

TABLE 6. Evidence Quality Scoring Checklist, modified from two established quality assessment guidelines[59, 60]

Level of review: _____ Title _____ Abstract _____ Article
Study authors, citation, year:
Type of Study:
1. Is there description of the source population, including basic demographic and prognostic information? _____ YES (1) _____ NO (0)
2. Is the study population representative of the source population? _____ YES (1) _____ NO (0)
3. Is the measurement described and reliably ascertained? _____ YES, both (2) _____ YES, described or ascertained (1) _____ NO (0)
4. Were case and control groups comparable on important confounding factors (age, race)? _____ YES (1) _____ NO (0)
5. Was there adjustment for the effects of these confounding variables? _____ YES (1) _____ NO (0)
6. Was follow-up long enough for outcomes to occur (more than 2 months)? _____ YES (1) _____ NO (0)
7. Were the data collectors identified and masked? _____ YES, both (2) _____ YES, identified or masked (1) _____ NO (0)
8. Was statistical analysis completed?

_____ YES (1)　　　_____ NO (0)

9. Were results reported thoroughly, including p-values and confidence intervals?
   _____ YES (1)　　　_____ NO (0)

OVERALL QUALITY SCORE (maximum 11 points):

APPENDIX ITEM 3:

British Journal of Ophthalmology Submission Requirements:

Original articles:
1. Clinical Science: up to 2500 words, 5 images and tables, 25 references

All types of original article should include the following:
1. Title
2. Keywords (up to four)
3. Addresses and which author address for correspondence
4. Structured abstract
   (200 words, headings, "Background/aims", "Methods", "Results", and "Conclusion")
5. Introduction
6. Materials and methods
7. Results
8. Discussion
9. References and acknowledgements
10. Legends for display items (Figures and Tables)"

Manuscript format:
The manuscript format must be presented in the following order:
1. Title page
2. Abstract (or summary for case reports)
3. Main text (tables should be inserted where cited in the text; images must be uploaded as separate files)
4. Acknowledgments • Competing interests • Funding
5. References
6. Appendices

Do not use the automatic formatting features of your word processor such as endnotes, footnotes, headers, footers, boxes etc.

Provide appropriate headings and subheadings as in the journal. We use the following hierarchy: BOLD CAPS, bold lower case, Plain Text, Italics.

Cite illustrations in numerical order (fig 1, fig 2 etc) as they are first mentioned in the text.

Tables must be embedded where cited in the text.

Images must not be embedded in the text file, but submitted as individual files.

Statistics:

Statistical analyses must explain the methods used.

Tables:

Tables should be submitted in the same format as your article and embedded in the main body of the article. Please note: Bench>Press cannot accept Excel files. If your table(s) are in Excel, copy and paste them into the manuscript file (where cited is preferable). In extreme circumstances, Excel files can be uploaded as supplementary files; however, we advise against this as they will not be acceptable if your article is accepted for publication. Tables should be self-explanatory, and the data they contain must not be duplicated in the text or figures.

References:

Authors are responsible for the accuracy of references cited: these should be checked against the original documents before the paper is submitted. It is vital that the references are styled correctly so that they may be hyperlinked.

In the text:

References must be numbered sequentially as they appear in the text. References cited in figures or tables (or in their legends and footnotes) should be numbered according to the place in the text where that table or figure is first cited. Reference numbers in the text must be given in square brackets immediately after punctuation (with no word spacing) - for example, .[6] not [6].

Where more than one reference is cited, separate by a comma - e.g. [1, 4, 39]. For sequences of consecutive numbers give all numbers without spaces - for example, [22-25]. References provided in this format are translated during the production process to superscript type, which act as hyperlinks from the text to the quoted references in electronic forms of the article.

References:

1.	Leske MC. The epidemiology of open-angle glaucoma: a review. Am J Epidemiol 1983;118:166-91.

2.	Quigley HA. Number of people with glaucoma worldwide. Br J Ophthalmol 1996;80:389-93.

3.	Haddad MA, Sei M, Sampaio MW, Kara-Jose N. Causes of visual impairment in children: a study of 3,210 cases. J Pediatr Ophthalmol Strabismus 2007;44:232-40.

4.	Robaei D, Huynh SC, Kifley A, Mitchell P. Correctable and non-correctable visual impairment in a population-based sample of 12-year-old Australian children. Am J Ophthalmol 2006;142:112-118.

5.	Wygnanski-Jaffe T, Barequet IS. Central corneal thickness in congenital glaucoma. Cornea 2006;25:923-5.

6.	Henriques MJ, Vessani RM, Reis FA, de Almeida GV, Betinjane AJ, Susanna R, Jr. Corneal thickness in congenital glaucoma. J Glaucoma 2004;13:185-8.

7.	Yanoff M, Fine BS. Ocular pathology, 5th ed. Philadelphia: Mosby, 2002:xxi, 761 p.

8.	van Koolwijk LM, Despriet DD, van Duijn CM, et al. Genetic contributions to glaucoma: heritability of intraocular pressure, retinal nerve fiber layer thickness, and optic disc morphology. Invest Ophthalmol Vis Sci 2007;48:3669-76.

9.	Stoilov IR, Costa VP, Vasconcellos JP, et al. Molecular genetics of primary congenital glaucoma in Brazil. Invest Ophthalmol Vis Sci 2002;43:1820-7.

10.	Chitsazian F, Tusi BK, Elahi E, et al. CYP1B1 mutation profile of Iranian primary congenital glaucoma patients and associated haplotypes. J Mol Diagn 2007;9:382-93.

11.	Reddy AB, Kaur K, Mandal AK, et al. Mutation spectrum of the CYP1B1 gene in Indian primary congenital glaucoma patients. Mol Vis 2004;10:696-702.

12.	Hutcheson KA. Steroid-induced glaucoma in an infant. J Aapos 2007;11:522-3.

13.	Trivedi RH, Wilson ME, Jr., Golub RL. Incidence and risk factors for glaucoma after pediatric cataract surgery with and without intraocular lens implantation. J Aapos 2006;10:117-23.

14.	Haargaard B, Ritz C, Oudin A, et al. Risk of glaucoma after pediatric cataract surgery. Invest Ophthalmol Vis Sci 2008;49:1791-6.

15.	Sijssens KM, Rothova A, Berendschot TT, de Boer JH. Ocular hypertension and secondary glaucoma in children with uveitis. Ophthalmology 2006;113:853-9 e2.

16.   Foster CS, Havrlikova K, Baltatzis S, Christen WG, Merayo-Lloves J. Secondary glaucoma in patients with juvenile rheumatoid arthritis-associated iridocyclitis. Acta Ophthalmol Scand 2000;78:576-9.

17.   Han ES, Choung HK, Heo JW, Kim SJ, Yu YS. The effects of external subretinal fluid drainage on secondary glaucoma in Coats' disease. J Aapos 2006;10:155-8.

18.   Hess DB, Asrani SG, Bhide MG, Enyedi LB, Stinnett SS, Freedman SF. Macular and retinal nerve fiber layer analysis of normal and glaucomatous eyes in children using optical coherence tomography. Am J Ophthalmol 2005;139:509-17.

19.   Hermann MM, Garway-Heath DF, Jonescu-Cuypers CP, et al. Interobserver variability in confocal optic nerve analysis (HRT). Int Ophthalmol 2005;26:143-9.

20.   Johnson TV, Toris CB, Fan S, Camras CB. Effects of central corneal thickness on the efficacy of topical ocular hypotensive medications. J Glaucoma 2008;17:89-99.

21.   Ehlers N, Bramsen T, Sperling S. Applanation tonometry and central corneal thickness. Acta Ophthalmol (Copenh) 1975;53:34-43.

22.   Kamppeter BA, Schubert KV, Budde WM, Degenring RF, Jonas JB. Optical coherence tomography of the optic nerve head: interindividual reproducibility. J Glaucoma 2006;15:248-54.

23.   Huang D, Swanson EA, Lin CP, et al. Optical coherence tomography. Science 1991;254:1178-81.

24.   Virgili G, Menchini F, Dimastrogiovanni AF, et al. Optical coherence tomography versus stereoscopic fundus photography or biomicroscopy for diagnosing diabetic macular edema: a systematic review. Invest Ophthalmol Vis Sci 2007;48:4963-73.

25.   Madgula IM, Kotta S. Stratus optical coherence tomogram III: a novel, reliable and accurate way to measure corneal thickness. Indian J Ophthalmol 2007;55:301-3.

26.   Hood DC, Harizman N, Kanadani FN, et al. Retinal nerve fibre thickness measured with optical coherence tomography accurately detects confirmed glaucomatous damage. Br J Ophthalmol 2007;91:905-7.

27.   van Velthoven ME, Verbraak FD, Yannuzzi LA, Rosen RB, Podoleanu AG, de Smet MD. Imaging the retina by en face optical coherence tomography. Retina 2006;26:129-36.

28.   Lim LS, Aung HT, Aung T, Tan DT. Corneal imaging with anterior segment optical coherence tomography for lamellar keratoplasty procedures. Am J Ophthalmol 2008;145:81-90.

29.   Kakuma H, Ohbayashi K, Arakawa Y. Optical imaging of hard and soft dental tissues using discretely swept optical frequency domain reflectometry optical coherence tomography at wavelengths from 1560 to 1600 nm. J Biomed Opt 2008;13:014012.

30. Welzel J, Bruhns M, Wolff HH. Optical coherence tomography in contact dermatitis and psoriasis. Arch Dermatol Res 2003;295:50-5.

31. Testoni PA. Optical coherence tomography. ScientificWorldJournal 2007;7:87-108.

32. Mahmood U, Ridgway J, Jackson R, et al. In vivo optical coherence tomography of the nasal mucosa. Am J Rhinol 2006;20:155-9.

33. Han S, El-Abbadi NH, Hanna N, et al. Evaluation of tracheal imaging by optical coherence tomography. Respiration 2005;72:537-41.

34. Ridgway JM, Ahuja G, Guo S, et al. Imaging of the Pediatric Airway Using Optical Coherence Tomography. Laryngoscope 2007;117:2206-2212.

35. Cilingiroglu M, Oh JH, Sugunan B, et al. Detection of vulnerable plaque in a murine model of atherosclerosis with optical coherence tomography. Catheter Cardiovasc Interv 2006;67:915-23.

36. Low AF, Tearney GJ, Bouma BE, Jang IK. Technology Insight: optical coherence tomography--current status and future development. Nat Clin Pract Cardiovasc Med 2006;3:154-62; quiz 172.

37. Liang H CM, Cucu R, Dobre G, Podoleanu A, Pedro J, Saunders D. En-face optical coherence tomography: a novel application of non-invasive imaging to art conservation. Optics Express 2005;13:6133-6144.

38. Lalezary M, Medeiros FA, Weinreb RN, et al. Baseline optical coherence tomography predicts the development of glaucomatous change in glaucoma suspects. Am J Ophthalmol 2006;142:576-82.

39. Bourne RR, Medeiros FA, Bowd C, Jahanbakhsh K, Zangwill LM, Weinreb RN. Comparability of retinal nerve fiber layer thickness measurements of optical coherence tomography instruments. Invest Ophthalmol Vis Sci 2005;46:1280-5.

40. Caprioli J, Nouri-Mahdavi K, Law SK, Badala F. Optic disc imaging in perimetrically normal eyes of glaucoma patients with unilateral field loss. Trans Am Ophthalmol Soc 2006;104:202-11.

41. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol 2002;120:701-13; discussion 829-30.

42. Levy Y, Zadok D. Systemic side effects of ophthalmic drops. Clin Pediatr (Phila) 2004;43:99-101.

43. Chung I, Buhr V. Topical ophthalmic drugs and the pediatric patient. Optometry 2000;71:511-8.

44.   Moore W, Nischal KK. Pharmacologic management of glaucoma in childhood. Paediatr Drugs 2007;9:71-9.

45.   Tanihara H, Inatani M, Honjo M, Tokushige H, Azuma J, Araie M. Intraocular pressure-lowering effects and safety of topical administration of a selective ROCK inhibitor, SNJ-1656, in healthy volunteers. Arch Ophthalmol 2008;126:309-15.

46.   Daubert GP. Is brimonidine ophthalmic a safe therapy for infants? J Clin Pharm Ther 2006;31:289-92.

47.   Avelino RR, Luis PA, Medeiros M, Costa VP. [The influence of intraocular pressure reduction with medication on retinal nerve fiber layer thickness measurements obtained with scanning laser polarimetry in glaucomatous and hypertensive eyes]. Arq Bras Oftalmol 2006;69:655-9.

48.   Meredith SP, Swift L, Eke T, Broadway DC. The acute morphologic changes that occur at the optic nerve head induced by medical reduction of intraocular pressure. J Glaucoma 2007;16:556-61.

49.   Tsai JC, Chang HW. Comparison of the effects of brimonidine 0.2% and timolol 0.5% on retinal nerve fiber layer thickness in ocular hypertensive patients: a prospective, unmasked study. J Ocul Pharmacol Ther 2005;21:475-82.

50.   Nicolela MT, Soares AS, Carrillo MM, Chauhan BC, LeBlanc RP, Artes PH. Effect of moderate intraocular pressure changes on topographic measurements with confocal scanning laser tomography in patients with glaucoma. Arch Ophthalmol 2006;124:633-40.

51.   Bowd C, Weinreb RN, Lee B, Emdadi A, Zangwill LM. Optic disk topography after medical treatment to reduce intraocular pressure. Am J Ophthalmol 2000;130:280-6.

52.   Roche O, Beby F, Parsa A, Orssaud C, Dufier JL, Parsa CF. Nonpenetrating external trabeculectomy for congenital glaucoma: a retrospective study. Ophthalmology 2007;114:1994-9.

53.   Costa LS, Costa RM. Combined trabeculotomy-trabeculectomy as a first surgical procedure for primary congenital glaucoma. Ann Ophthalmol (Skokie) 2006;38:25-7.

54.   Tamcelik N, Ozkiris A. Long-term results of viscotrabeculotomy in congenital glaucoma: comparison to classical trabeculotomy. Br J Ophthalmol 2008;92:36-9.

55.   Souza C, Tran DH, Loman J, Law SK, Coleman AL, Caprioli J. Long-term outcomes of Ahmed glaucoma valve implantation in refractory glaucomas. Am J Ophthalmol 2007;144:893-900.

56.   Papadaki TG, Zacharopoulos IP, Pasquale LR, Christen WB, Netland PA, Foster CS. Long-term results of Ahmed glaucoma valve implantation for uveitic glaucoma. Am J Ophthalmol 2007;144:62-69.

57.   Biro Z, Balla Z, Kovacs B. Change of foveal and perifoveal thickness measured by OCT after phacoemulsification and IOL implantation. Eye 2008;22:8-12.

58.   Greenland S. Modeling and variable selection in epidemiologic analysis. Am J Public Health 1989;79:340-349.

59.   Mulrow CD, Cook D, American College of Physicians. Systematic reviews : synthesis of best evidence for health care decisions. Philadelphia, Pa.: American College of Physicians, 1998:x, 117 p.

60.   Khalid S Khan GtR, Jennie Pepay, John Nixon, Jos Kleijnen. Phase 5: Study quality assessment. In: Stewart L, editor. Undertaking systematic reviews of research on effectiveness: CRD's guidance forthose carrying out or commissioning reviews. York, UK: Centre for Reviews and Dissemination, University of York, 2001:1-20.

61.   Lim MC, Hoh ST, Foster PJ, et al. Use of optical coherence tomography to assess variations in macular retinal thickness in myopia. Invest Ophthalmol Vis Sci 2005;46:974-8.

62.   Wong AC, Chan CW, Hui SP. Relationship of gender, body mass index, and axial length with central retinal thickness using optical coherence tomography. Eye 2005;19:292-7.

63.   El-Dairi M, Asrani S, Holgado S, Enyedi L, Freedman S. Optical coherence tomography: difference in optic nerve, macular and nerve fiber layer thickness in black versus white children. Washington, DC: American Association of Pediatric Ophthalmology and Strabismus, 2008.

64.   Pasquale LR. Low intracranial pressure: a tipping point in our understanding of primary open-angle glaucoma? Ophthalmology 2008;115:761-2.

65.   Berdahl JP, Allingham RR, Johnson DH. Cerebrospinal fluid pressure is decreased in primary open-angle glaucoma. Ophthalmology 2008;115:763-8.

66.   Morgan WH, Yu DY, Alder VA, et al. The correlation between cerebrospinal fluid pressure and retrolaminar tissue pressure. Invest Ophthalmol Vis Sci 1998;39:1419-28.

67.   Hayreh SS. Optic disc edema in raised intracranial pressure. VI. Associated visual disturbances and their pathogenesis. Arch Ophthalmol 1977;95:1566-79.

68.   Azuara-Blanco A, Harris A, Cantor LB, Abreu MM, Weinland M. Effects of short term increase of intraocular pressure on optic disc cupping. Br J Ophthalmol 1998;82:880-3.

69.   Jonas JB, Berenshtein E, Holbach L. Anatomic relationship between lamina cribrosa, intraocular space, and cerebrospinal fluid space. Invest Ophthalmol Vis Sci 2003;44:5189-95.

70.   Jonas JB, Berenshtein E, Holbach L. Lamina cribrosa thickness and spatial relationships between intraocular space and cerebrospinal fluid space in highly myopic eyes. Invest Ophthalmol Vis Sci 2004;45:2660-5.

71.   Hahnenberger RW. Inhibition of fast anterograde axoplasmic transport by a pressure barrier. The effect of pressure gradient and maximal pressure. Acta Physiol Scand 1980;109:117-21.

72.   Congdon NG, Broman AT, Bandeen-Roche K, Grover D, Quigley HA. Central corneal thickness and corneal hysteresis associated with glaucoma damage. Am J Ophthalmol 2006;141:868-75.

73.   Song Y, Congdon N, Li L, et al. Corneal Hysteresis and Axial Length Among Chinese Secondary School Children: The Xichang Pediatric Refractive Error Study (X-PRES) Report No. 4. Am J Ophthalmol 2008;145:819-826 e1.

74.   Kirwan C, O'Keefe M, Lanigan B. Corneal hysteresis and intraocular pressure measurement in children using the reichert ocular response analyzer. Am J Ophthalmol 2006;142:990-2.

75.   Wong TY, Klein BE, Klein R, Knudtson M, Lee KE. Refractive errors, intraocular pressure, and glaucoma in a white population. Ophthalmology 2003;110:211-7.

76.   Agarwal HC, Sood NN, Sihota R, Sanga L, Honavar SG. Mitomycin-C in congenital glaucoma. Ophthalmic Surg Lasers 1997;28:979-85.

77.   Budenz DL, Anderson DR, Varma R, et al. Determinants of normal retinal nerve fiber layer thickness measured by Stratus OCT. Ophthalmology 2007;114:1046-52.

78.   Luo HD, Gazzard G, Fong A, et al. Myopia, axial length, and OCT characteristics of the macula in Singaporean children. Invest Ophthalmol Vis Sci 2006;47:2773-81.

79.   Heng LS, Khoo CY. Can contact lenses control the progression of myopia? Singapore Med J 1994;35:367-70.

80.   Murthy GV, Gupta SK, Ellwein LB, et al. Refractive error in children in an urban population in New Delhi. Invest Ophthalmol Vis Sci 2002;43:623-31.

81.   Seet B, Wong TY, Tan DT, et al. Myopia in Singapore: taking a public health approach. Br J Ophthalmol 2001;85:521-6.

82.   Das J, Bhomaj S, Chaudhuri Z, Sharma P, Negi A, Dasgupta A. Profile of glaucoma in a major eye hospital in north India. Indian J Ophthalmol 2001;49:25-30.

83.   He M, Foster PJ, Ge J, et al. Prevalence and clinical characteristics of glaucoma in adult Chinese: a population-based study in Liwan District, Guangzhou. Invest Ophthalmol Vis Sci 2006;47:2782-8.