의학박사 학위논문

Reversal of the Optic Nerve Head Tissues after Intraocular Pressure Lowering Treatment in Open Angle Glaucoma

-Reversal of the Optic Nerve Head

in Open Angle Glaucoma-

개방각녹내장 환자에서 안압하강치료 후 시신경유두조직의 복원 관찰

- 개방각녹내장 환자에서

시신경유두조직의 복원 관찰-

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서울대학교 대학원

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Abstract

Introduction

Glaucoma is a progressive optic neuropathy which affects as many as 3.5% of Korean population aged 40 years or more. Lowering of intraocular pressure (IOP) has been the mainstay of glaucoma treatment, and is the only possible intervention that could be actually done to glaucoma patients. However, many glaucoma patients are still suffering from visual loss despite of IOP lowering. This suggests that IOP lowering may not be equally effective in all glaucoma patients, and that factors other than IOP are involved in glaucoma pathogenesis. However, it remained to be determined how IOP lowering has influences on the glaucomatous optic nerve.

Recently, in vivo visualization of the optic nerve head tissues became possible with the emergence of spectral domain optical coherence tomography (SD-OCT), which enabled the evaluation of changes of the optic nerve head tissues including the lamina cribrosa (LC) after IOP lowering in glaucoma. The reversal of the optic nerve tissues according to IOP lowering treatment might be a sign of released strain and stress at the level of the LC which may give relief to the compressed nerve fibers or laminar capillaries. On the other hand, if the LC reversal is not observed, other pathogenic factor other than IOP could be suspected for the mechanism of glaucomatous damage.

Purpose

The purpose of the study was to investigate the change of the optic nerve tissues including the LC after IOP lowering treatment in open angle glaucoma (OAG) patients, using enhanced depth imaging SD-OCT. and to evaluate the factors associated with the optic nerve changes. By accomplishing this purpose, the study further aimed to contemplate the effect and meaning of IOP lowering treatment in each eye, and to understand primary mechanism of glaucomatous optic neuropathy in individual glaucoma patients.

This study was performed under three specific aims; First, investigation of

short-term change in the optic nerve head tissues in high-tension OAG after surgical IOP lowering. Second, comparison of the short-term change in the optic nerve head tissues in high- and low-tension OAG after IOP lowering treatment. Third, investigation of long-term change in the optic nerve head tissues in high-tension OAG after surgical IOP lowering.

Methods

Optic nerves of OAG patients who underwent surgical or medical IOP-lowering treatment were scanned using enhanced depth imaging SD-OCT before treatment and after treatment during the serial follow-up. The pre- and post- treatment SD-OCT images were compared. The LC depth (the distance from the Bruch's membrane opening plane to the level of the anterior LC surface), and the thickness of the LC and prelaminar tissue were measured in each scan. The change in the optic nerve tissues after IOP lowering was observed, and the factors associated with the amount of change were investigated.

Results

1. Reversal of lamina cribrosa displacement and thickness after trabeculectomy in glaucoma

- Until 6 months after trabeculectomy, decrease in the LC depth (reversal of the LC), and increase in the thickness of the LC and prelaminar tissue was observed in 35 OAG patients with IOP lowering. The magnitude of the reduction in the LC displacement was significantly associated with younger age, greater percent IOP reduction, and greater preoperative LC displacement.

2. Reversal of the lamina cribrosa displacement after intraocular pressure reduction in open angle glaucoma

- The LC reversal was observed in 100 open angle glaucoma patients until 6 months after surgical or medical IOP lowering. Although the reversal was of larger amount in high-tension OAG, the LC reversal was also observed in a focal plane in low-tension OAG patients. The magnitude of LC reversal was associated with younger age, higher untreated IOP, higher baseline IOP, and greater percent of IOP reduction.

3. Variation of lamina cribrosa depth following trabeculectomy

- The change of the LC was observed at 6 months and ≥2 years postoperatively in 28 OAG patients who underwent trabeculectomy. The postoperative reversal of the LC that was observed 6 months after surgery was not maintained in 9 eyes after postoperative 2 years. The degree of LC depth increase after 6 months was significantly associated with younger age, higher IOP at final follow-up, greater IOP fluctuation, and higher mean follow-up IOP from 6 months to final follow-up.

Conclusions

Reversal of the LC after IOP lowering treatment was observed in open angle glaucoma patients using enhanced depth imaging SD-OCT. The short-term LC reversal was associated with younger age and larger amount of IOP reduction. Although the reversal was more prominent in eyes with high-tension OAG, the LC reversal was also observed in a focal plane in low-tension OAG patients. In the long-term, the reversed LC was not maintained and returned to pre-treatment level in some OAG eyes. The return was likely to occur in patients who were younger and who had higher IOP and IOP fluctuation during the postoperative follow-up.

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keywords : Lamina cribrosa, Spectral-domain optical coherence tomography, Open angle glaucoma, Intraocular pressure lowering

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Chapter 1

Reversal of Lamina Cribrosa Displacement and Thickness after Trabeculectomy in Glaucoma

- Reversal of the LC after Trabeculectomy -

녹내장 환자에서 섬유주절제술 후 사상판 깊이와 두께의 복원 관찰

- 섬유주절제술 후 사상판의 복원 관찰 -

Abstract

Purpose: To investigate the response of the lamina cribrosa (LC) and prelaminar tissue to glaucoma surgery using spectral-domain optical coherence tomography (SD-OCT) and to determine the factors influencing such responses.

Methods: This is an observational case series on 35 eyes of 35 primary open-angle glaucoma patients who underwent trabeculectomy. Patients were imaged using a 10 x 15-degree rectangle covering the optic disc using SD-OCT. About 65 B-scans covering the optic discs were obtained using enhanced depth imaging SD-OCT before surgery, after 1 week, and 1, 3, and 6 months postoperatively. The pre- and postoperative magnitude of the LC displacement (distance from the Bruch’s membrane opening plane to the level of anterior LC surface) and the thickness of LC and prelaminar tissue were determined on 7 to 13 selected B-scan images in each eye. The amount of reduction in the LC displacement and changes in the thickness of LC and prelaminar tissue was assessed at each follow-up.

Results: Intraocular pressure (IOP) was decreased from 27.2 ± 8.9 mmHg (range, 14–47) to 10.5 ± 3.4 mmHg (range, 6–21) at postoperative month 6. The amount of posterior displacement of the LC was significantly decreased from a mean preoperative level of 614.58 ± 179.57 to 503.90 ± 142.67 μm at postoperative month 6 ($P < 0.001$). The thicknesses of the LC and prelaminar tissue were significantly increased at postoperative month 6 ($P < 0.001$ and $P = 0.048$, respectively). The magnitude of the reduction in the LC displacement was significantly associated with younger age ($P < 0.001$), greater percent IOP reduction ($P = 0.019$), and greater preoperative LC displacement ($P = 0.024$). None of the factors was associated with the amount of LC or prelaminar tissue thickening.

Conclusions: A significant reduction in the posterior displacement and increase in the thickness of the LC and prelaminar tissue were demonstrated after glaucoma surgery using enhanced depth imaging SD-OCT of the optic nerve head. The amount of reduction in the LC displacement was associated with younger age, larger baseline LC displacement, and greater IOP reduction.

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Keywords: Lamina Cribrosa, Spectral-domain Optical Coherence Tomography, Open Angle Glaucoma, Trabeculectomy

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초 록

목적: 녹내장 수술에 따른 사상판과 사상판앞조직의 변화를 스펙트럼영역 빛간섭단층촬영(Spectral-domain optical coherence tomography, SD-OCT)을 통해 관찰하고, 이러한 변화에 영향을 미치는 인자들을 알아보고자 한다.

방법: 본 연구는 섬유주절제술을 시행받은 35명 35안의 일차개방각녹내장안을 대상으로 한 관찰연구이다. Enhanced depth imaging SD-OCT 를 이용하여 시신경을 포함하는 10 x 15도 사각형영역에서 약 65개의 연속스캔이미지를 얻었고, 수술 전과 수술 후 1주, 1개월, 3개월, 6개월째 반복 시행하였다. 각 검사에서 선택된 7~13개의 스캔이미지에서 수술 전과 후의 사상판의 깊이(브루크막 개구부에서 사상판의 앞경계까지의 거리), 사상판과 사상판앞조직의 두께를 측정하여 수술 전후의 변화를 알아보았다.

결과: 수술 후 6개월째 안압은 27.2 ± 8.9 (14-47) mmHg 에서 10.5 ± 3.4 (6-21) mmHg 로 감소하였다. 수술 후 6개월째 사상판의 깊이는 수술 전 614.58 ± 179.57 μm 에서 503.90 ± 142.67 μm 로 유의하게 감소하였고(P < 0.001), 사상판과 사상판앞조직의 두께 또한 유의하게 감소하였다 (각각 P < 0.001, P = 0.048). 사상판 깊이의 복원 정도는 나이가 젊을수록(P <0.001), % 안압하강율이 클수록(P = 0.019), 그리고 수술 전 사상판의 깊이가 깊을수록(P = 0.024) 더 큰 것으로 나타났다. 사상판과 사상판앞조직의 두께 변화와 관련된 인자는 없었다.

결론: Enhanced depth imaging SD-OCT 시신경이미지를 이용하여

녹내장 수술 후 사상판의 깊이가 감소하고 사상판/사상판앞조직의 두께가 증가하는 현상을 관찰하였다. 사상판 깊이의 복원은 나이, 수술 전 사상판 깊이, 안압하강정도와 유의한 관계를 가졌다.

* 본 내용은 *Ophthalmology* (*Ophthalmology*. 2012 Jul;119(7):1359-66)에 출판 완료된 내용임

주요어: 사상판, 스펙트럼영역 빛간섭단층촬영, 개방각녹내장, 섬유주절제술

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INTRODUCTION

Reversal of optic disc cupping following intraocular pressure (IOP) lowering treatment has been documented by a number of studies. Reduction in cup size based on stereoscopic disc photography[1-4] and changes in optic disc topography as assessed by scanning laser tomography[5-11] or optic nerve head analyzer[12-14] have both been reported. The mechanism of reversal, however, remains to be determined. One hypothesis is that reversal of cupping may be the result of reduction in the posterior bowing of the lamina cribrosa (LC).[1, 15, 16] Alternatively, it has been speculated that reversal of cupping represents thickening of the prelaminar tissue; this might result from several etiologies, including redistribution of axonal fluid or long-term prelaminar glial proliferation.[4, 17] However, neither the reduction in the posterior bowing of LC nor the thickening of the prelaminar tissue after IOP lowering has ever been confirmed, perhaps due to an inability to clinically visualize the deep optic nerve head structures.

It recently has been demonstrated that spectral domain optical coherence tomography (SD-OCT) can image the LC.[18-20] Inoue et al[20] demonstrated that the LC was discernable on longitudinal sections of SD-OCT images; each longitudinal section clearly showed changes in reflectivity at the anterior and posterior borders of the LC. Srinivasan et al[18] also visualized the human LC using ultrahigh speed OCT with 1060 nm wavelength light. Previously, we demonstrated that visualization of the LC may be improved using enhanced depth imaging.[21] This technique was originally developed to visualize the full thickness of the choroid.[22] It improves the sensitivity of a more posteriorly located tissue via delivering the most tightly focused position of the illumination at the level of the tissue.[22] Applying this technique to LC imaging, we could obtain a larger depth of signal and better image contrast, which facilitated the delineation of full thickness of the LC.

The purpose of the present study was to evaluate the structural changes in the deep optic nerve head after IOP lowering by trabeculectomy using enhanced depth imaging SD-OCT, focusing on the amount of LC displacement and the thickness of LC and prelaminar tissue. By doing this, we hoped to elucidate whether the reversal of cupping previously demonstrated by photographic and topographic analysis, is mainly attributable to LC change or prelaminar tissue change. We also sought the factors influencing the observed changes. This study should help understand the phenomenon of cupping reversal after glaucoma surgery.

METHODS

This study was approved by the Seoul National University Bundang Hospital Institutional Review Board and conformed to the Declaration of Helsinki. Informed written consent was obtained from all subjects.

Consecutive patients with primary open angle glaucoma (POAG) were recruited into the study. Indications for trabeculectomy were: IOP deemed to be associated with a high risk for progression or glaucomatous progression of the visual field or optic disc in spite of maximally tolerated medications.

Prior to the study, each patient underwent a complete ophthalmic examination including visual acuity assessment, refraction test, slit-lamp biomicroscopy, gonioscopy, Goldmann applanation tonometry, dilated stereoscopic examination of the optic disc. They also underwent central corneal thickness measurement (Orbscan II, Bausch & Lomb Surgical, Rochester, NY, USA), SD-OCT and standard automated perimetry

(Humphrey Field Analyzer II 750; 24-2 Swedish interactive threshold algorithm; Carl-Zeiss Meditec, Dublin, CA, USA).

To be included, subjects were required to have POAG, a best corrected visual acuity of ≥ 20/40, spherical refraction of -8.0 to +5.0 diopters and cylinder correction within ±3.0 diopters, and clear ocular media (up to grade 3 for nuclear opalescence, nuclear color and cortical changes (NO1–3, NC1–3, C1–3) and up to grade 2 for posterior subcapsular change (P1-2) on Lens Opacities Classification System III).[23] POAG was defined as the presence of glaucomatous optic nerve damage and associated visual field defect without ocular disease or conditions that may elevate the IOP. A glaucomatous visual field change was defined as (1) outside normal limit on glaucoma hemifield test; or (2) three abnormal points with $P < 5\%$ probability of being normal, one with $P < 1\%$ by pattern deviation; or (3) pattern standard deviation of 5% if the visual field was otherwise normal, confirmed on two consecutive tests. A visual field measurement was considered as reliable when false-positive/negative results were < 25% and fixation losses were <20%.

Eyes that had undergone previous intraocular surgery or that had coexisting retinal or neurological diseases that could have affected the visual field were excluded from this study. Eyes were also excluded when a good quality image (i.e. quality score > 15) could not be obtained at more than 5 sections. When the quality score does not reach 15, the image acquisition process automatically stops and images of the respective sections are not obtained.

All the ocular hypotensive medications were continued up to the time of surgery. The preoperative IOP was defined as the average of the 2 measurements within two weeks before trabeculectomy.

Optic discs were examined using Spectralis OCT (Heidelberg Engineering GmbH, Heidelberg, Germany) at 1 day before surgery, and 1 week, 1, 3 and 6 months postoperatively. IOP measurements by Goldmann applanation tonometry were also recorded at each follow up visit.

Enhanced Depth Imaging Optical Coherence Tomography of the Optic Disc

The optic nerve was imaged using the enhanced depth imaging technique. This technique was originally developed by Spaide et al. to visualize the full thickness of the choroid.[22] The detail and advantage of this technology to evaluate the LC has been described previously.[21] In brief, the device was positioned close enough to the eye to create an inverted image near the top of the display. Enough separation from the top of the display was used to avoid image ambiguity from image folding with respect to zero depth. We found that this technique provides images having a larger amount of signal and better image contrast in the deep optic nerve head tissue compared to the conventional imaging technique. [21] Patients were imaged through undilated pupils using a 10x15-degree rectangle covering the optic disc. This rectangle was scanned with approximately 65 sections, which were 30 to 34 μm apart (the scan line distance is determined automatically by the machine). Each section had 42 OCT frames averaged. As reported previously, this protocol provided the best trade off between image quality and patient cooperation.[21]

Quantification of the Posterior Displacement of the Lamina Cribrosa

The LC displacement was quantified using the 3-dimensional OCT data set which was reconstructed from the SD-OCT B-scan images using image processing software (Amira 5.2.2, Visage Imaging, Berlin, Germany). To do this, B-scans were selected equidistantly (one from every 4 scans) from the 3-dimensional image data set. In the peripheral scans near the superior and inferior poles of the optic disc, the full thickness LC often was not visualized. Those B-scans were not included in the analysis. With this approach, 7 to 13 B-scans were selected from the central 2/3 to 3/4 of the optic disc (Figure 1.1A, 1.1B). The number of the selected B-scans was dependent on the disc size as well as the visibility of the LC in the peripheral optic nerve.

In each B-scan, the distance from the reference line connecting the 2 termination of the Bruch's membrane to the level of anterior border of LC was measured at 3 points; the maximally depressed point and two additional points (100 and 200 μm apart from the maximally depressed point to temporal direction). Only the temporally adjacent points were selected because the maximally depressed point was often close to the central vessel trunk of which the shadow obscured the LC. In addition, the full thickness LC often was not clearly discernable at the temporal periphery. Thus, data were collected from only 2 additional points.

The distance was measured on the line perpendicular to the reference line using a manual caliper tool of the Amira 5.2.2 software (Figure 1.1C). The average of the 3 measurements (from the 3 points) was considered the LC displacement of the each selected B-scan. Then, the 7 to 13 values obtained from each of the selected B-scans were averaged and defined as the magnitude of LC displacement for the eye.

For the follow-up measurement, the sets of B-scans were selected to correspond to those that had been selected for the baseline measurements. To do this, en face images were used (Figure 1.1 B). The low reflective shadow within the LC was also examined to confirm the correspondence of the B-scan image series between preoperative and postoperative images.

Measurement of Prelaminar Tissue and Lamina Cribrosa Thickness

The thicknesses of the prelaminar tissue and LC were determined by additionally measuring the distance from the reference line to the optic cup surface (Figure 1.1D) and to the posterior LC surface (Figure 1.1E) at the same 3 points where the LC displacement was measured. Again, the distances were measured on the line perpendicular to the reference line. The prelaminar tissue thickness was defined as the difference between the distance from the reference line to the optic cup surface and that to the anterior LC surface. The LC thickness was defined as the difference between the distance from the reference line to the anterior LC surface and that to the posterior LC surface. The average of the measurements obtained from the 3 points was considered the thicknesses of the prelaminar tissue and LC in each selected B-scan. The mean of the 7 to 13 values obtained from the selected B-scans were defined as the prelaminar tissue or LC thickness of the eye. When the posterior border of the LC was not definite on a particular B scan image, the neighboring B-scans were evaluated to estimate the posterior border of the LC on the B-scan.

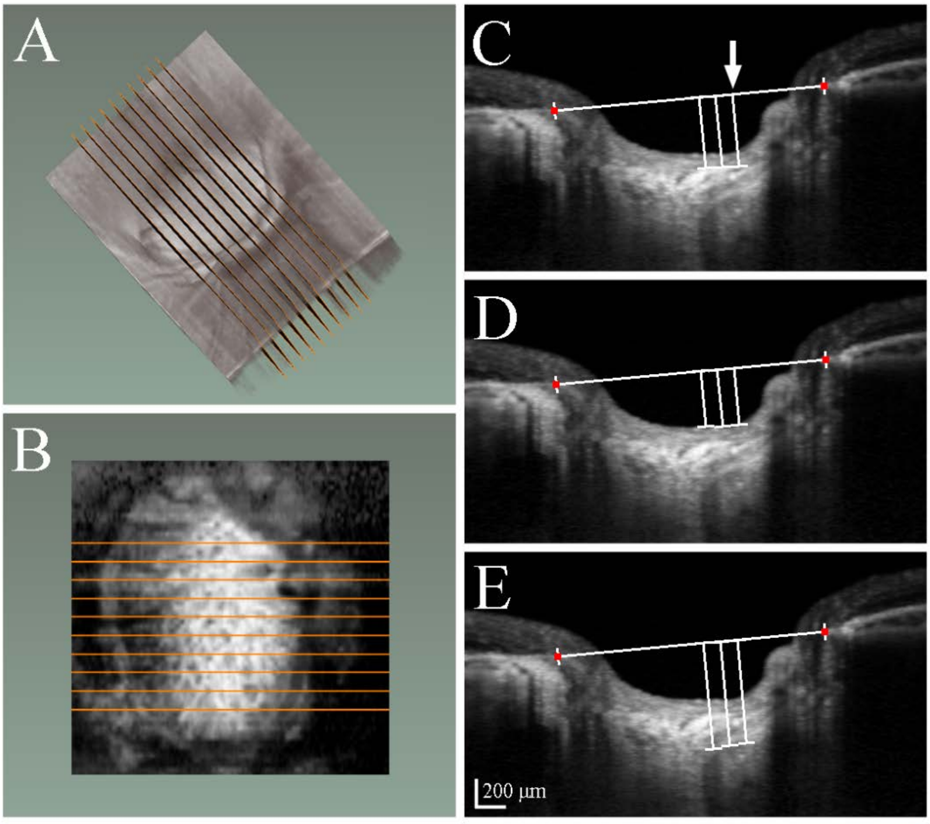

Figure 1.1. A, Three-dimensional, volume-rendered image reconstructed from B-scan images obtained using spectral-domain optical coherence tomography. **B,** En face image of the same eye at the lamina cribrosa (LC) level. Seven to 13 equidistantly located B-scans were selected from the 3-dimensional image data set depending on the disc size and the visibility of the LC at the peripheral B-scans (orange lines; 10 B-scans in this eye). The magnitude of the LC displacement and thicknesses of the LC and prelaminar tissue were determined by averaging the values measured at each selected B-scan. **C**–**E**, The distances from the reference line (straight line connecting the 2 terminations of the Bruch's membrane; red dots) to the anterior laminar surface (**C**), to the cup surface (**D**), and to the posterior laminar surface (**E**) were measured at 3 points: the maximally depressed point (white arrow) and 2 additional points 100 and 200 _m apart from the maximally depressed point to

temporal direction. The distance was measured on the line perpendicular to the reference line using a manual caliper tool of the Amira 5.2.2 software. The distance from the reference line to the anterior LC surface was defined as the displacement of the LC. The difference between the distance from the reference line to the optic cup surface and that to the anterior LC surface was defined as the prelaminar tissue thickness. The difference between the distance from the reference line to the posterior LC surface and that to the anterior LC surface was defined as the laminar tissue. The average of the 3 measurements obtained from the 3 points was considered the respective value at the selected B-scan.

Measurement of the Neural Canal Opening Diameter

To observe the stability of the reference line, the size of neural canal opening, the diameter of the Bruch's membrane opening (BMO) was measured at the mid-horizontal plane of the optic nerve head at each time point using a manual caliper tool of the Amira software. The preoperative and postoperative values were measured at the same plane.

The laminar displacement and the thicknesses of the LC and the prelaminar tissue were measured by an observer (EJL) who was masked to the clinical information including IOP and the time point of scanning for the follow-up OCT images. To evaluate the interobserver reproducibility of our measuring method, 15 randomly selected SD-OCT datasets were evaluated by 2 independent examiners (EJL, TWK) and the intraclass correlation coefficient (ICC) was calculated.

Data Analysis

The preoperative and postoperative amount of posterior displacement of the LC, the thickness of the prelaminar tissue and LC, and the mid-horizontal BMO diameter were compared using repeated measures analysis of variance. Logistic regression analysis was used to determine the factors associated with the change in the posterior displacement or LC thickness. Statistical analyses were performed using SPSS 17.0 software (SPSS Inc, Chicago, IL). A P value of less than 0.05 was considered statistically significant.

RESULTS

Thirty eight patients with POAG who underwent trabeculectomy were included. Of these, 3 patients were excluded due to poor image quality (more than 5 missing sections, n=2) and extremely low postoperative IOP which might cause measurement error due to decreased axial length and changes in corneal curvature (IOP=4 mmHg at postoperative 6 months, n=1). Serial OCT images were of good quality and the LC was readily discernable at the majority of the B-scans in the remaining 35 patients at all time points. The mean age was 52.6±17.9 years (range, 15 to 80 years). Fourteen subjects were women and 21 were men. The visual acuity ranged from 20/40 to 20/20 and the mean refractive error (spherical equivalent) was -1.73±2.61 diopters (range, -7.00 to +3.00 diopters). The visual field mean deviation was -15.52±10.10 dB (range, -31.79 to -0.45 dB) (Table 1.1).

Table 1.1. Patient clinical demographics (n=35)

Variables	
Age (years)*	52.6±17.9
Male / Female	21 / 14
Spherical equivalent (D)*	-1.73±2.61
Central corneal thickness (μm)*	558.3±46.9
Axial length (mm)*	24.4±1.1
Visual field MD (dB)*	-15.52±10.10
Visual field PSD (dB)*	8.20±4.30

D = diopters; MD = mean deviation; PSD = pattern standard deviation.

* Values are shown in mean ± standard deviation.

IOP decreased from 27.2±8.9 mmHg (range, 14 to 47 mmHg) to 10.5±3.4 mmHg (range, 6 to 21 mmHg) at postoperative 6 months. The interobserver ICCs for the measurement of LC displacement, LC thickness, prelaminar tissue thickness and BMO diameter were 0.998, 0.818, 0.886, and 0.995, respectively. The amount of posterior displacement of the LC was significantly decreased from a mean preoperative level of 614.58±179.57 μm to 503.90±142.67 μm at 6 month postoperatively ($P<0.001$). Both LC thickness and prelaminar tissue thickness significantly increased at postoperative 6 months (LC thickness; 169.39±24.70 μm preoperatively, and 204.75±26.43 μm at 6 month postoperatively, $P < 0.001$, prelaminar tissue thickness; 95.77±40.97 μm preoperatively, and 101.71±42.06 μm at 6 month postoperatively, $P=0.048$) (Table 1.2, Figure 1.2, 1.3, Video clip 1.1, 1.2: available at http://aaojournal.org).

Table 1.2. Pre- and postoperative (6 month) measurements of intraocular pressure, the amount of posterior displacement of lamina cribrosa, and the thickness of the prelaminar tissue and the lamina cribrosa

	Preoperative	Postoperative 6 month	P-value
Intraocular pressure (mmHg)	27.2±8.9	10.5±3.4	<0.001
Posterior displacement of lamina cribrosa (μm)	614.58±179.57	503.90±142.67	<0.001
Prelaminar tissue thickness (μm)	95.77±40.97	101.71±42.06	0.048
Lamina cribrosa thickness (μm)	169.39±24.70	204.75±26.43	<0.001

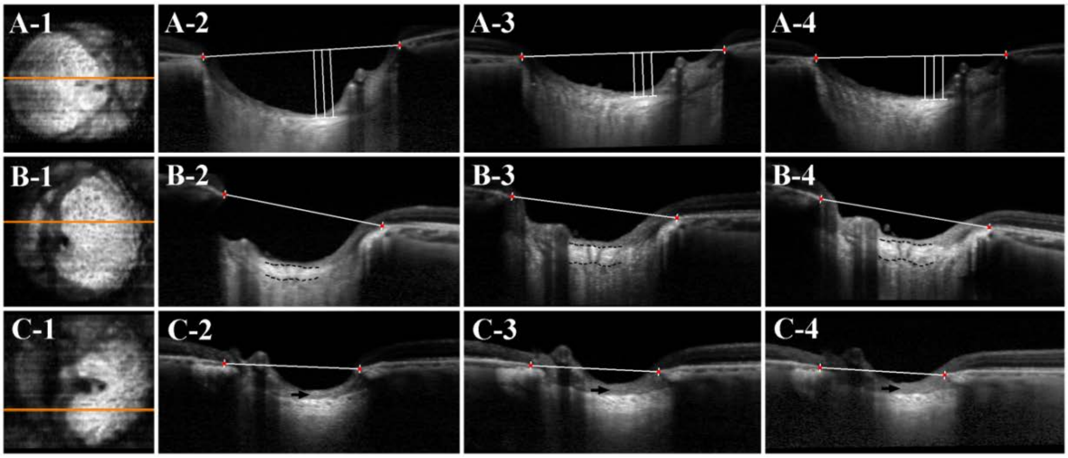

Figure 1.2. En face (**A-1**, **B-1**, **C-1**) and B-scan images obtained preoperatively (**A-2**, **B-2**, **C-2**) and at 1 (**A-3**, **B-3**, **C-3**) and 6 (**A-4**, **B-4**, **C-4**) months postoperatively in 3 cases that underwent trabeculectomy. A reference line was set by connecting the termination of Bruch's membrane (red dots). **A**, Right eye of a 15-year-old female patient. The intraocular pressure (IOP) decreased from 30 to 15 mmHg. Note that the magnitude of the lamina cribrosa (LC) displacement (vertical white lines) decreased in the postoperative images. **B**, Left eye of a 17-year-old female patient. The IOP decreased from 37 to 6 mmHg. Note the thickening of the LC (black dashed lines) in the postoperative images. **C**, Left eye of an 80-year-old woman where the IOP decreased from 17 to 6 mmHg. Note the thickening of the prelaminar tissue (arrows) in postoperative images. The reduction of the laminar displacement is noticeable in **B** and **C** as well. The prelaminar tissue thickness was slightly decreased at postoperative month 6 when compared with the 1-month postoperative image.

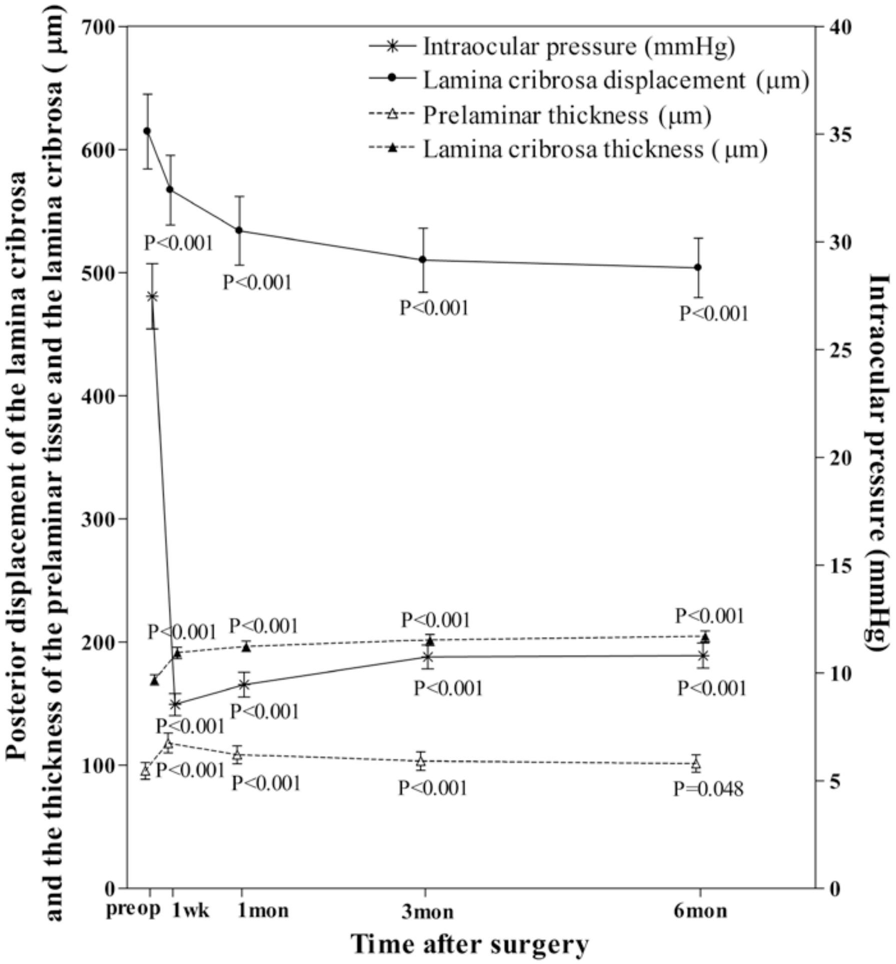

Figure 1.3. The mean magnitude of the posterior displacement of the lamina cribrosa (LC), the mean thickness of the LC and the prelaminar tissue, and mean intraocular pressures measured at each follow-up visits in 35 eyes that underwent trabeculectomy. *P* values are based on the repeated measures analysis of variance. Each error bar indicates ±1 standard deviation.

The diameter of BMO at baseline and postoperative 1 week, 1 month, 3 months and 6 months were 1697.33±304.65, 1670.12±298.17, 1660.83±281.46, 1683.50±285.86 and 1674.80±289.00 μm, respectively. There were significant differences between the baseline and postoperative images at all time point (all Ps < 0.05).

The majority of the reduction in the posterior displacement of the LC and the thickening of the LC observed during the study period occurred at the early postoperative period. The amount of additional changes observed at each time point after postoperative 1 week decreased gradually. The prelaminar thickness increased at postoperative 1 week and slowly decreased thereafter, but remained significantly thicker than baseline values until postoperative 6 months (Figure 1.2C, 1.3).

Linear regression showed significant influence of younger age ($P<0.001$), greater percent IOP reduction ($P=0.022$), larger posterior displacement of the LC ($P<0.001$) and larger diameter of the BMO at preoperative examination ($P=0.009$), and greater amount of decrease in the BMO diameter ($P=0.049$) on the magnitude of reduction in the LC displacement (Table 1.3, Figure 1.4). In the multivariate analysis, age ($P<0.001$), percent IOP reduction ($P=0.019$), and preoperative amount of LC displacement ($P=0.024$) were statistically significant. None of the factors were significantly associated with the thickening of the LC and prelaminar tissue (Table 1.3).

Table 1.3. Factors associated with the reduction of posterior displacement and thickening of the lamina cribrosa and prelaminar tissue

	Reduction of the LC displacement P-value		Thickening of the LC P-value		Thickening of the prelaminar tissue P-value	
	Univariate	Multivariate*	Univariate	Multivariate	Univariate	Multivariate
Age (years)	**<0.001**	**<0.001**	0.090		0.387	
Female gender	0.579		0.105		0.112	
Preoperative IOP (mmHg)	0.147		0.170		0.714	
% IOP reduction	**0.022**	**0.019**	0.559		0.189	
Baseline prelaminar tissue thickness (μm)	0.632		0.827		0.735	
Baseline LC thickness (μm)	0.986		0.839	N/A	0.542	N/A
Baseline LC displacement (μm)	**<0.001**	**0.024**	0.864		0.878	
Baseline BMO diameter (μm)	**0.009**	0.108	0.187		0.618	
Decrease in BMO diameter (μm)	**0.049**	0.937	0.891		0.369	
Central corneal thickness (μm)	0.952		0.769		0.562	
Axial length (mm)	0.606		0.375		0.668	
Visual field MD (dB)	0.931		0.801		0.128	

LC= lamina cribrosa; IOP = intraocular pressure; BMO=Bruch's membrane opening; MD = mean deviation.

Statistically significant values are shown in bold.

* Only variables with a *P* value of less than 0.1 in the univariate analysis were included in the multivariate model.

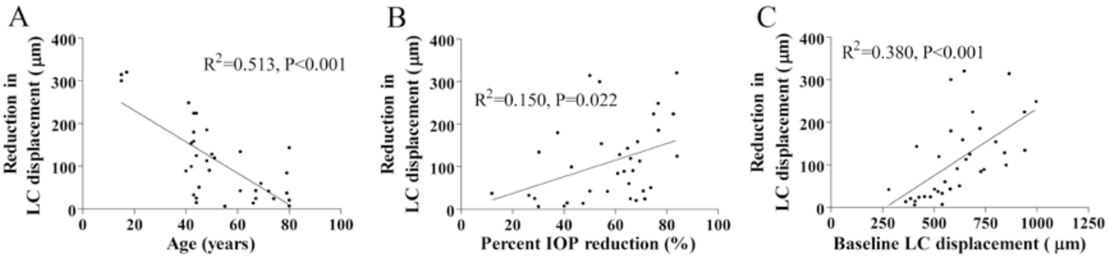

Figure 1.4. Relationship between the age (**A**), percent intraocular pressure (IOP) reduction (**B**), and baseline lamina cribrosa (LC) displacement (**C**) and the amount of reduction in the LC displacement.

DISCUSSION

Our results demonstrate the anterior movement of the LC and thickening of the LC and prelaminar tissue following the reduction of IOP in glaucomatous eyes. To our knowledge, this is the first report to visualize the structural change in the deep optic nerve tissues after glaucoma surgery.

A change of optic nerve head topography with changes of IOP has been described previously. Decrease of cup area, cup volume, cup depth and cup-to-disc ratio, and increase of rim area were demonstrated in glaucoma patients undergoing glaucoma filtering surgery[5, 8] or medical treatment.[24] Whether such topographic changes resulted from the alteration in LC position or changes of the prelaminar tissue thickness has not been elucidated.[4, 17] Our data suggest that the reversal is attributable to the reduced posterior displacement of the LC as well as the thickening of both LC and prelaminar tissue. When the magnitude of changes is considered, it appears that posterior displacement is likely to be mainly responsible for the reversal and the restoration of the prelaminar tissue and LC thickness contributes less.

Recently, Agoumi et al visualized the change of optic nerve head structure in human eyes following acute IOP elevation using SD-OCT.[25] They demonstrated a significant prelaminar tissue displacement in those eyes. However, the LC displacement was negligible in their study. These results are contradictory to those of the current study. The discrepancy between the two studies may be attributable to several factors. First, the degree of IOP elevation was maintained for a relatively short period (approximately 2 minutes) in Agoumi et al's study. Second, the amount of IOP change differs between the studies. In Agoumi et al's study, the mean IOP elevation was 12.4 mmHg. In contrast, the mean IOP reduction was 17.5 mmHg at 6 month postoperatively in our study. Thirdly, the majority of study subjects were healthy subjects in Agoumi et al's study while all of our subjects were glaucoma patients. Lastly, we examined the behavior of the optic nerve after lowering IOP while Agoumi et al did it during the elevation of IOP. It remains uncertain whether the mechanisms responsible for the laminar change following IOP reduction are equivalent to those following IOP elevation.

The length of the reference line measured at the mid-horizontal plane (BMO diameter) was significantly reduced postoperatively, although the amount of decrease was of small degree (maximum mean decrease=5.6%). This finding is in line with previous observations that the optic disc size may be reduced with IOP lowering.[26-27] In addition, the decrease of the BMO diameter was significantly associated with the reversal of the LC displacement in the univariate analysis. However, we do not consider that the decrease of the BMO diameter (shrinkage of the optic disc) is a causal factor of the LC reversal. It has been demonstrated that elevated IOP results in canal expansion, which in turn induces anterior movement of the LC.[17, 28] Based on this finding, it may be speculated that the shrinkage of the scleral canal following IOP lowering should cause posterior movement of the LC, which is the opposite of our finding. Corresponding to this idea, the association of decreased BMO diameter with reversal of LC displacement became insignificant in the multivariate analysis. We consider that the reversal of LC displacement and the reduction of BMO diameter are collateral findings occurring together as the IOP decreases.

Age was found to be a significant factor affecting the reduction in the LC displacement. This finding is in line with Albon et al's ex vivo study.[29] They demonstrated decreased mechanical compliance of the human LC with age using cadaver eyes. The decreased resilience of the LC with age may be related to a higher risk of disease progression in older glaucoma patients.[30-32] We speculate that the deformed LC is more likely to remain permanent or less restored despite IOP lowering treatment in older age, exerting compressive stress continuously on the optic nerve axons or laminar capillaries. On the other hand, the possibility cannot be denied that a stiffer LC with age could serve as a protective mechanism to counter age-related susceptibility.

The amount of anterior LC movement was significantly associated with percent IOP reduction. This finding accords with previous reports.[3, 5, 8, 10, 15] Katz et al[3] reported that the improved optic disc cupping was seen in one third of glaucomatous eyes (16 of 51 eyes) in which IOP decreased by at least 30%. Irak et al[5] and Lesk et al[8] have examined reversal of cupping after glaucoma surgery using the confocal scanning laser ophthalmoscope and also found a good correlation between the amount of IOP reduction and the changes in optic disc parameters.

None of the factors was found to be significantly associated with an increase of both LC and prelaminar tissue thickness after trabeculectomy. One may hypothesize that the thickness reversal is related to stiffness of the tissue. However, the stiffness is not measurable currently. Meanwhile, it is notable that younger age was marginally associated with the thickening of LC in the current study. This finding is consistent with several experimental studies which suggested that the LC is likely to be stiffer in an aged optic nerve head.[29, 33-36]

The present study included 12patients who had preoperative IOPs within normal range (18.2±1.9 mmHg, range, 14 to 20 mmHg). These patients received surgery because of the progressive glaucomatous change in spite of maximal medical treatment. Significant reduction in the LC displacement (580.82±160.87 μm to 507.81±140.60 μm, P=0.002) and increase of the LC thickness (173.52±20.89 μm to 203.58±26.54 μm, P<0.001) were also observed in these patients, while the increase in the prelaminar tissue thickness was not statistically significant (89.30±37.42 to 98.16±41.73 μm, P=0.129) (data not presented). This finding suggests that LC may still suffer from IOP induced stress and strain even by IOP within normal range in some glaucoma patients.

The importance and influence of the LC reversal on the disease prognosis remains to be determined. However, based on the current understanding of the role of LC displacement in the pathogenesis of glaucomatous damage (i.e., backward bowing of the LC may cause the mechanical or vascular damage to the ganglion cell axons), it may be proposed that LC reversal might be a sign of released strain at the level of the LC which may give relief to the compressed nerve fibers or laminar capillaries. This conception is supported by Harju et al's observation[11] that cup reversal as measured by confocal scanning laser ophthalmoscope was negatively associated with glaucoma progression in patients with exfoliation glaucoma and ocular hypertension combined with exfoliation syndrome.

Study Limitations

Our study has some limitations. First, patients were observed for only up to 6 months following trabeculectomy. This was mainly because the IOP not uncommonly re-elevates after this period. It is possible that reversal of the changes within the LC may persist after this period if IOP remained well-controlled. However, our data demonstrated that reduction of the LC displacement occurred largely before postoperative 3 months. Thus, we believe that evaluation of the LC change at postoperative 6 months may be sufficient to evaluate the resilience of the LC.

Secondly, the preoperative and postoperative images were acquired independently. Although Spectralis has a “follow-up” mode which allows serial images to be registered from the same location, it did not work well in our patients. This may be attributable to the changes of the vascular contour on the optic nerve head after the surgery. Given the substantial LC movement, significant changes in the vascular contour on the optic nerve head could be induced. Due to this limitation, it is possible that the images would not be aligned appropriately. However, as the scan line distance is about 30 to 34μm, the maximum misalignment could not exceed 15 to 17 μm. Thus, the measurement error appears small.

Thirdly, although the angle of the reference line mostly showed minimal variation among images at different time point, it varied substantially (up to 15 degree) in some patients. One may consider that the different angle of the reference line may induce a measurement error. However, we measured the LC displacement and the thicknesses on the line perpendicular to the reference line to remove the measurement error. Thus, the influence of the different angle of the reference line may be negligible.

Forthly, peripheral B-scans were not included in the analysis because the LC often was not clearly visible in the peripheral scans (especially the posterior border of the LC). However, it may be assumed that the reversal of the lamina may largely occur in the central region, given the posteriorly bowed nature of the LC. Thus, we think that evaluation of the central LC may be an effective way to demonstrate the changes occurring with the IOP lowering treatment. The same rational may be applied to the evaluation at only 3 points in each B-scan.

Fifthly, the posterior LC was not clearly identified in one or 2 selected B-scans in 70% of the images. In such cases, the level of posterior LC in the B-scan was estimated by examining the neighboring B-scans. This method allowed comparable or better interobserver agreement than previously reported using en face image.[20-21]

Lastly, as described earlier, parameters potentially relevant to the resilient response of the LC such as material properties of the laminar and peripapillary scleral connective tissue were not considered in our study. Unfortunately, those parameters are not currently measurable. It is possible such factors may play a significant role for the reduction of LC displacement and the increase in the thickness of the LC and prelaminar tissue.

In conclusion, we demonstrated the reversal of displacement and thickness of the LC following trabeculectomy in patients with glaucoma. Our data show that the previously known reversal of the optic disc cupping is likely to mainly result from the anterior movement of the LC. It appears that the de-compression of the LC and restoration of the prelaminar tissue also contribute to the cupping reversal. The reduction in the LC displacement was affected by age, amount of baseline LC displacement and the magnitude of IOP lowering. Further study is needed to determine the influence of the LC reversal after IOP reduction on disease prognosis.

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Chapter 2

Reversal of Lamina Cribrosa Displacement after Intraocular Pressure Reduction in Open Angle Glaucoma

- Reversal of LC after IOP Reduction -

개방각녹내장 환자에서 안압하강치료 후 사상판 깊이의 복원 관찰

- 안압하강치료에 따른 사상판의 복원 관찰-

Abstract

Purpose: To compare the change in lamina cribrosa (LC) displacement in response to intraocular pressure (IOP) lowering in patients with open-angle glaucoma (OAG) using spectral-domain optical coherence tomography (SD-OCT).

Methods: This is an observational case series of 100 eyes of 100 patients with OAG in whom IOP at the follow-up examination had decreased by at least 20% compared with the baseline IOP. Serial horizontal B-scan images of the optic nerve head (ONH) were obtained from each eye using enhanced depth imaging SD-OCT. Approximately 65 B-scans covering the optic discs were obtained before and 3 to 6 months after lowering IOP. The baseline and follow-up LC depths (the distance from the Bruch's membrane opening plane to the level of the anterior LC surface) were measured in B-scan images from each eye. The mean and maximum amount of reductions in LC depth were determined in the 7 selected B-scan images in each eye.

Results: Intraocular pressure decreased from 21.2 ± 9.1 to 10.5 ± 2.6 mmHg. The percent of IOP reduction was significantly related to the untreated IOP ($P < 0.001$). There was a significant decrease in the LC depth at the follow-up examination compared with the baseline value ($P < 0.001$). The magnitude of LC depth reduction was significantly associated with younger age, higher untreated IOP, higher baseline IOP, and greater percent of IOP reduction (all $P < 0.02$).

Conclusions: Reversal of the LC displacement was observed after IOP-lowering treatment in OAG. The degree of LC displacement reversal was related to the amount of IOP lowering.

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Keywords: Lamina Cribrosa, Spectral-domain Optical Coherence Tomography, Open Angle Glaucoma, Intraocular Pressure Lowering

Student Number: 2011-31129

초 록

목적: 개방각녹내장 환자에서 안압하강치료에 따른 사상판 깊이의 변화를 스펙트럼영역 빛간섭단층촬영(Spectral-domain optical coherence tomography, SD-OCT)을 통해 비교 · 관찰하고자 한다.

방법: 본 연구는 안압하강치료 후 안압이 20% 이상 하강한 100명 100안의 일차개방각녹내장안을 대상으로 한 관찰연구이다. 각 눈을 대상으로 Enhanced depth imaging SD-OCT 를 이용하여 시신경유두를 횡단하는 약 65개의 연속스캔이미지를 얻었고, 안압하강 전과 후 3개월, 6개월째 반복 시행하였다. 각 검사에서 7개의 스캔이미지를 선택하여 안압하강 전 · 후의 사상판의 깊이(브루크막 개구부에서 사상판의 앞경계까지의 거리)를 측정하여 비교하였다. 사상판 깊이의 평균 복원 정도와 복원이 가장 많이 일어난 지점의 복원 정도를 알아보았다.

결과: 안압은 21.2 ± 9.1 mmHg 에서 10.5 ± 2.6 mmHg 로 감소하였다. 안압하강의 정도(%)는 치료 전 안압과 유의한 관계를 보였다($P < 0.001$). 사상판의 깊이는 안압하강 전에 비해 안압하강 후 유의하게 감소하였다($P < 0.001$). 사상판의 깊이의 복원 정도는 나이가 젊고, 치료 전 안압이 높으며, 안압하강 정도(%)가 클수록 더 큰 것으로 나타났다(all $P < 0.02$).

결론: 개방각녹내장 환자에서 안압하강치료 후 사상판 깊이의 복원이 관찰되었다. 사상판 깊이의 복원은 안압하강의 정도와 관련있는 것으로 나타났다.

* 본 내용은 *Ophthalmology* (*Ophthalmology*. 2013 Mar;120(3):553-

9)에 출판 완료된 내용임

주요어: 사상판, 스펙트럼영역 빛간섭단층촬영, 개방각녹내장, 안압하강치료

학 번: 2011-31129

INTRODUCTION

Lowering intraocular pressure (IOP) is the mainstay of glaucoma treatment. However, little is currently known about the effect of IOP reduction on the optic nerve tissue in glaucoma. We have recently shown that displacement and compression of the lamina cribrosa (LC) may be reversed after trabeculectomy in eyes with primary open angle glaucoma (POAG).[1] This finding suggests that the reversal of LC displacement and deformation is related to the slower rate of disease progression associated with IOP reduction.[2, 3] Since deformation and compression of the LC may induce shearing stress in the axons passing through the laminar pores and possible occlusion of the laminar capillaries, it is reasonable to postulate that the reversal of such pathologic changes would provide relief to compressed nerve fibers or laminar capillaries.[1]

In our previous study,[1] all patients had high (i.e., >21 mmHg) untreated IOP, although some did have low IOP with IOP-lowering medication prior to the trabeculectomy. Thus, it remains to be determined whether the reversal of LC also occurs in glaucomatous eyes with lower levels of untreated IOPs. It is well known that IOP reduction is beneficial in open angle glaucoma regardless of the baseline IOP[2, 4] Moreover, the results of studies using finite element modeling suggest that the IOP-related stress within the connective tissues of the optic nerve head (ONH) is substantial even at low levels of IOP, depending on the geometry of the eyeball.[5, 6] Thus, it is highly likely that IOP lowering would also induce reversal of the LC displacement in eyes with low IOP.

The purpose of the present study was to determine whether reversal of the LC displacement that occurs when the IOP is lowered in OAG patients with IOP> 21 mmHg is also observed in OAG with low IOP.

METHODS

This study was approved by the Seoul National University Bundang Hospital Institutional Review Board and conformed to the Declaration of Helsinki.

Study Subjects

Patients with POAG were enrolled during the period of December 2009 to January 2012 from the Glaucoma Clinic of Seoul National University Bundang Hospital.

All subjects received comprehensive ophthalmic examinations that included visual acuity measurement, Goldmann applanation tonometry, measurement of best –corrected visual acuity, slit-lamp biomicroscopy, gonioscopy, and dilated stereoscopic examination of the ONH. They also underwent central corneal thickness measurement (Orbscan II, Bausch & Lomb Surgical, Rochester, NY, USA), axial length measurement (IOL Master ver. 5, Carl-Zeiss Meditec, Dublin, CA, USA), disc area measurement (Spectralis HRA, Heidelberg Engineering, Heidelberg, Germany), spectral-domain optical coherence tomography (SD-OCT; Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany), and standard automated perimetry (Humphrey Field Analyzer II 750; 24-2 Swedish interactive threshold algorithm; Carl-Zeiss Meditec).

To be included, eyes were required to have been diagnosed with POAG, and to have a best corrected visual acuity of ≥ 20/40 with spherical refraction of –8.0 to +5.0 diopters and cylinder correction within ±3.0 diopters, and clear ocular media; up to grade 3 for nuclear opalescence, nuclear color, and cortical changes (NO1–3, NC1–3, C1–3, respectively) and up to grade 2 for posterior subcapsular changes (P1–2) of the Lens Opacities Classification System III.[7] POAG was defined as having an open angle on gonioscopy, glaucomatous optic nerve damage (i.e., the presence of focal thinning of the neuroretinal rim or notching), and associated visual field defect without ocular disease or conditions that may elevate the IOP. A glaucomatous visual field change was defined as (1) outside normal limits on the Glaucoma Hemifield Test; (2) three abnormal points with a <5% probability of being normal, one with P<1% by pattern deviation; or (3) a pattern standard deviation of <5% if the visual field was otherwise normal, confirmed on two consecutive tests.

The patients included were either newly diagnosed glaucoma patients or patients who received surgical treatment (trabeculectomy), which was considered when the IOP was deemed to be associated with a high risk for progression or glaucomatous progression of the visual field or optic disc, despite maximally tolerated medications. All ocular hypotensive medications were continued up to the time of the surgery.

Baseline optic disc scanning were performed at 1 day before initiation of topical IOP-lowering treatment or 1 day prior to trabeculectomy. Follow up optic disc scanning was performed 4 to 6 months after the medical treatment (at least 3 months after confirming a 20% IOP reduction) or 3 months after trabeculectomy. IOP measurements using Goldmann applanation tonometry were also recorded at follow-up visits.

The untreated IOP was defined as the average of at least two measurements made within 2 weeks before initiation of IOP-lowering treatment.IOP*b* and IOP*f* were defined as the IOPs measured at the time of baseline and follow up optic disc scanning, respectively.

Eyes for which the IOP*f* decreased <20% from the IOP*b* were excluded, as were eyes that had undergone previous intraocular surgery or coexisting retinal or neurologic diseases that could affect the visual field.

Enhanced Depth Imaging SD-OCT of the Optic Disc

The ONH was imaged using the Spectralis OCT with the enhanced depth imaging technique. The details and advantages of this technology for evaluating the LC have been described previously.[8, 9] In brief, the device was positioned sufficiently close to the eye to create an inverted image near the top of the display. Enough separation from the top of the display was implemented to avoid image ambiguity from image folding with respect to zero depth. Approximately 65 B-scan section images covering the ONH, 30–34 μm apart (the scan line distance being determined automatically by the machine), were obtained from each eye. Each section had 42 OCT frames averaged, which provided the best trade-off between the image quality and patient cooperation.[9]

Images are obtainable using the Spectralis OCT only when the quality score is higher than 15. When the quality score does not reach 15, the image acquisition process automatically stops and the image of the respective section is excluded. Only acceptable scans with a good-quality image (i.e., quality score >15) obtained for more than 60 sections, and that allowed clear delineation of the anterior and posterior borders of the LC, were included.

Measurement of the Lamina Cribrosa Depth

The depth of the LC was measured on the initial and follow-up B-scan images. The LC depth was determined by measuring the distance from the Bruch's membrane opening plane to the level of the anterior LC surface. To this end, a reference line connecting the two termination points of Bruch's membrane was drawn in each B-scan. Then, the distance from the reference line to the level of anterior border of LC was measured at 3 points; the maximally depressed point and two additional points (100 and 200 μm apart from the maximally depressed point to temporal direction). Only the temporally adjacent points were selected because the maximally depressed point was often close to the central vessel trunk of which the shadow obscured the LC. In addition, the full thickness LC often was not clearly discernible at the temporal periphery. Thus, data were collected from only 2 additional points.

The distance was measured on the line perpendicular to the reference line using the manual caliper tool of the Amira 5.2.2 software. The average of these three values was defined as the LC depth of the B-scan.

To determine the mean LC depth, seven B-scan images that divided the optic disc diameter into eight equal parts vertically were selected in each eye from the three-dimensional image data set, as described previously.[1] The LC depth was measured in each B-scan as described above and the average of the measurements was defined as the mean LC depth of the eye.

For the follow-up measurement, the sets of B-scans were selected to correspond to those that had been selected for the baseline measurements. En-face images as well as the low reflective shadow within the LC shown in B-scan images were used to confirm the correspondence of the selected B-scans between pre- and post-treatment images.[1]

The difference in the mean LC depth between the initial and follow-up measurements was defined as the mean LC depth reduction. The amount of LC depth reduction at the location where the greatest reduction was observed was defined as the maximum LC depth reduction.

Data Analysis

The inter-session variability was obtained from 30 stable glaucoma patients who were separately recruited among patients who had received treatment and whose IOP had been less than 18 mmHg with IOP fluctuation < 2 mmHg during the last 6 months follow up. The scan was repeated on a different day within a 1-week period in these patients, and the intraclass correlation coefficient (ICC), coefficient of variation (CV), and inter-session standard deviation were calculated. A statistically significant change was accepted with an inter-session standard deviation of 1.96 times because it corresponds to the 95% confidence interval for the true value of the measurement.[10]

The independent-samples *t*-test and chi-squared test were used to compare the data between the groups. Regression analysis was used to determine the factors associated with the change in the LC depth. Statistical analyses were performed using SPSS 17.0 software (SPSS, Chicago, IL, USA) and the R Language and Environment for Statistical Computing (version 2.12.1, www.r-project.org). The level of statistical significance was set at $P<0.05$.

RESULTS

Of the 130 POAG patients who were initially enrolled, 17 were excluded due to an IOP reduction of <20% (n=15) or an extremely low IOP*f* (5 mmHg, n=2), which may have resulted in measurement error because of the decreased axial length and change in the corneal curvature. A further 13 subjects were excluded due to poor scan image quality (more than 5 missing sections out of an average of 65 sections). The LC, and especially its anterior surface, was readily discernible in most of the B-scans at both baseline and follow-up examinations in the remaining 100 patients.

Of the 100 POAG subjects, 62 eyes were newly diagnosed and were treated with medical therapy. The remaining 38 eyes had been treated with maximally tolerated IOP-lowering medication and then underwent trabeculectomy, as previously noted.

The patients were aged 54.1±16.8 years (range, 15 to 82 years), and 44 were women and 56 were men. Their visual acuity ranged from 20/40 to 20/16 and the refractive error (spherical equivalent) was –1.49±2.93 diopters (range, –8.00 to +3.13 diopters). The untreated IOP, measured before initiation of any IOP-lowering medication, was 22.4±9.7 mmHg (range, 10 to 50 mmHg). The visual field mean deviation (MD) was –9.61±8.69 dB (range, –31.79 to –0.25 dB) (Table 2.1).

Table 2.1. Patients clinical demographics

Variables	
Age (years)	54.1 ± 16.8
Male / Female	56 / 44
Spherical equivalent (D)	-1.49 ± 2.93
Untreated IOP (mmHg)	22.4 ± 9.7
Visual field MD (dB)	-9.61 ± 8.69
Central corneal thickness (μm)	557.5 ± 37.4
Axial length (mm)	24.3 ± 1.5
Disc area (mm^2)	2.2 ± 0.5

D = diopters; IOP = intraocular pressure; MD = mean deviation.

Values are shown in mean ± standard deviation.

The inter-session reproducibility determined based on the LC depth measurements of the 30 stable glaucoma patients was excellent (ICC=0.991, CV=1.98%); 1.96 times the inter-session standard deviation was 23.3 μm.

In all 100 subjects, the IOP decreased from 21.2±9.1 mmHg (range, 10 to 50 mmHg) to 10.5±2.6 mmHg (range, 6 to 17 mmHg; P<0.001) (Table 2.2).

The percent IOP reduction was significantly associated with untreated (R^2=0.71, P<0.001) and baseline IOP (R^2=0.66, P<0.001) (Figure 2.1).

Table 2.2. Intraocular pressure and lamina cribrosa depth at the baseline and follow up optic disc examinations

	Baseline	Follow up	*P* value*
Intraocular pressure (mmHg)	21.2±9.1	10.5±2.6	**<0.001**
Mean LC depth (µm)	584.73±160.52	529.18±137.18	**<0.001**
LC depth at the location of maximum LC depth reduction (µm)	603.08±169.09	522.70±143.83	**<0.001**

LC = lamina cribrosa

Values are shown in mean±standard deviation.

Statistically significant values are shown in bold.

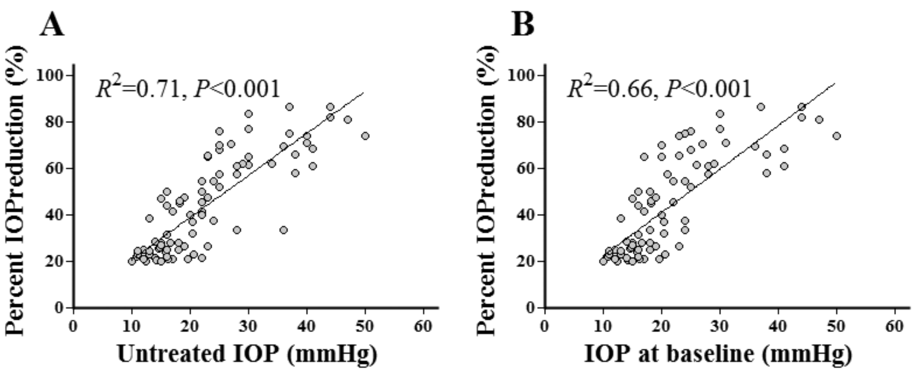

Figure 2.1. Relationship between untreated intraocular pressure (IOP) and percent IOP reduction (**A**) and between IOP at baseline and percent IOP reduction (**B**) (n=100).

The magnitude of mean and maximum LC depth at the follow-up examination was also significantly decreased from the baseline (Figure 2.2,

Table 2.2). Overall, there was a significant relationship between the untreated IOP and the mean amount of LC depth reduction: the relationship was better explained by an exponential curve (R^2=0.51, P<0.001) than a linear curve (R^2=0.45, P<0.001) (Figure 2.3A). There was also a significant relationship between the maximum LC depth reduction and the untreated IOP: the relationship was again better explained by an exponential curve (R^2=0.49, P<0.001) than a linear curve (R^2=0.45, P<0.001) (Figure 2.4A).

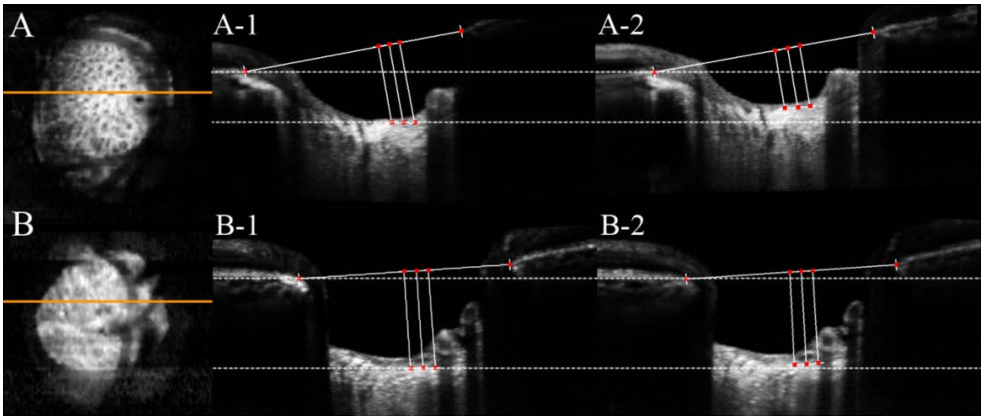

Figure 2.2. En-face and B-scan images obtained at baseline (**A**-1, **B**-1) and follow-up (**A**-2, **B**-2) in an eye with high-tension glaucoma **(A)** and an eye with normal-tension glaucoma **(B)**. The upper and lower *dashed lines* in each case are set at the level of the termination point of temporal Bruch's membrane and at the level of the anterior border of the lamina cribrosa (LC) at baseline, respectively. **A,** The right eye of a 17-year-old female patient. The intraocular pressure (IOP) had decreased from 41 to 13 mmHg 4 months after starting topical antiglaucoma medication. Note that the magnitude of the LC depth decreased considerably in the follow-up image. **B,** The right eye of a 45-year-old male patient. The IOP had decreased from 19 to 10 mmHg 5 months after starting topical medication. A small but noticeable LC depth reduction was observed in this patient.

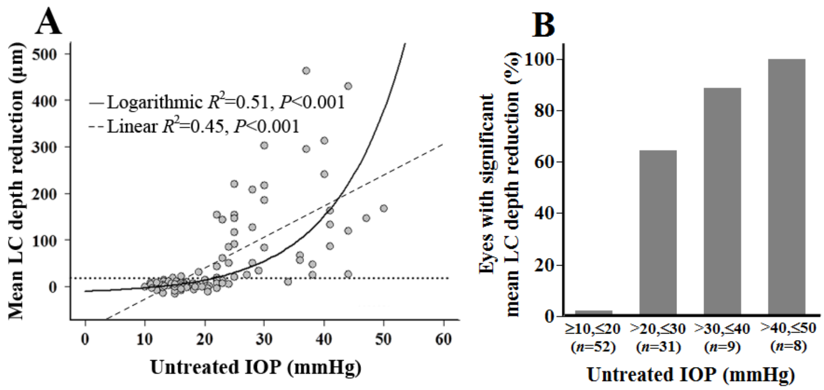

Figure 2.3. Untreated intraocular pressure (IOP) and mean lamina cribrosa (LC) depth reduction (n = 100). **A,** Relationship between untreated IOP and mean LC depth reduction. The *dotted line* indicates 1.96 times the intersession standard deviation (23.3 μm). **B,** Percentage of eyes with a mean LC depth reduction exceeding the intersession variability in various untreated IOP ranges.

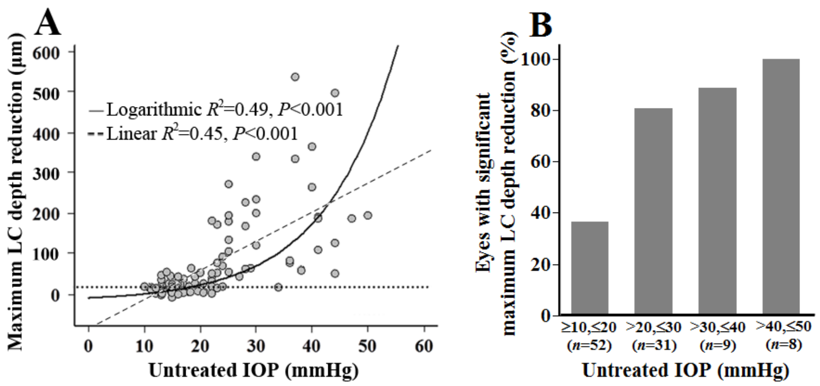

Figure 2.4. Untreated intraocular pressure (IOP) and maximum lamina cribrosa (LC) depth reduction (n = 100). **A,** Relationship between untreated IOP and maximum LC depth reduction. The *dotted line* indicates 1.96 times the intersession standard deviation (23.3 μm). **B,** Percentage of eyes with a maximum LC depth reduction exceeding the intersession variability in various untreated IOP ranges.

Figures 2.5, 2.6, and 2.7 show the relationships between the mean LC depth reduction and percent IOP reduction, age, IOP*b*, respectively.

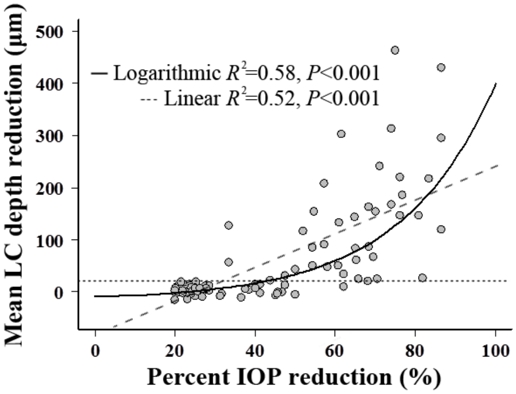

Figure 2.5. Relationship between percent intraocular pressure (IOP) reduction and mean lamina cribrosa (LC) depth reduction (n=100). The dotted line indicates 1.96 times the inter-session standard deviation (23.3 µm).

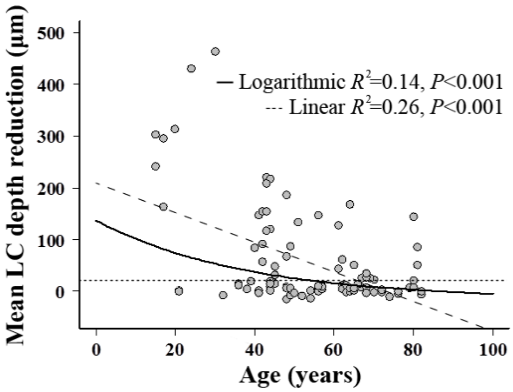

Figure 2.6. Relationship between age and mean lamina cribrosa (LC) depth reduction (n=100). The dotted line indicates 1.96 times the inter-session standard deviation (23.3 µm).

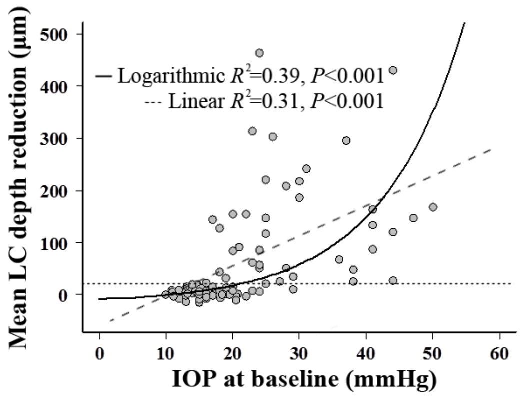

Figure 2.7. Relationship between intraocular pressure (IOP) at baseline and mean lamina cribrosa (LC) depth reduction (*n*=100). The dotted line indicates 1.96 times the inter-session standard deviation (23.3 μm).

Univariate analysis revealed that the log-transformed mean LC depth reduction was significantly associated with younger age, higher untreated IOP, higher IOP*b*, greater percent IOP reduction, and larger magnitude of LC depth at baseline examination (all P<0.001, Table 2.3). Visual field MD was also significantly associated (P<0.05, Table 2.3). As the untreated IOP, IOP*b* and percent IOP reduction had a high variance inflation factor, multivariate analysis was performed in 3 ways to avoid the multicollinearity. Multivariate analysis revealed statistically significant associations of untreated IOP (P<0.001), IOP*b* (P<0.001) and percent IOP reduction (P<0.001). Age was significantly associated in the model including IOP*b* and percent IOP reduction (P<0.05) and marginally significantly associated in the model including untreated IOP (Table 2.4).

Table 2.3. Univariate analysis on the factors associated with the mean amount of reduction of the lamina cribrosa depth* (*n*=100)

	Beta [95% CI]	*P* value	VIF
Age (per 10 years older)	-0.26 [-0.39, -0.14]	**<0.001**	1.28
Female gender	-0.17 [-0.64, 0.30]	0.479	1.12
Untreated IOP (per 5 mmHg increase)	0.43 [0.35, 0.52]	**<0.001**	13.06
IOP at baseline (per 5 mmHg increase)	0.40 [0.30, 0.50]	**<0.001**	11.35
% IOP reduction (per 10% reduction)	0.42 [0.30, 0.50]	**<0.001**	3.56
LC depth at baseline (per 100 μm deeper)	0.32 [0.19, 0.45]	**<0.001**	1.33
Disc area (per 1 mm^2 larger)	0.32 [-0.11, 0.75]	0.151	N/A
Central corneal thickness (per 100 μm thicker)	-0.14 [-0.81, 0.52]	0.666	N/A
Axial length (per 1 mm longer)	0.001 [-0.18, 0.18]	0.994	N/A
Visual field MD (per 1 dB better)	-0.03 [-0.05, 0.001]	**0.043**	1.34

VIF = variance inflation factor; LC = lamina cribrosa; CI = confidence interval; IOP = intraocular pressure; MD = mean deviation.

Statistically significant values are shown in bold.

*The amount of LC depth reduction was log-transformed to correct non-linearities between the data. Thus, the beta value indicates that mean LC depth reduction increases Exp (beta) folds for unit increase of the independent variables.

Table 2.4. Multivariate analysis on the factors associated with the mean amount of reduction of the lamina cribrosa depth* (*n*=100)

	Multivariate 1		Multivariate 2		Multivariate 3	
	Beta [95% CI]	*P* value	Beta [95% CI]	*P* value	Beta [95% CI]	*P* value
Age (per 10 years older)	-0.09 [-0.20, 0.01]	0.088	-0.14 [-0.25, -0.02]	**0.018**	-0.13 [-0.23, -0.04]	**0.006**
Female gender	0.18 [-0.16, 0.51]	0.292	0.13 [-0.24, 0.49]	0.486	0.23 [-0.07, 0.53]	0.132
Untreated IOP (per 5 mmHg increase)	0.40 [0.29, 0.50]	**<0.001**				
IOP at baseline (per 5 mmHg increase)			0.35 [0.24, 0.47]	**<0.001**		
% IOP reduction (per 10% reduction)					0.41 [0.33, 0.49]	**<0.001**
LC depth at baseline (per 100 μm deeper)	0.08 [-0.04, 0.20]	0.199	0.09 [-0.04, 0.22]	0.174	0.07 [-0.03, 0.18]	0.171
Visual field MD (per 1 dB better)	0.01 [-0.02, 0.03]	0.574	0.001 [-0.02, 0.02]	0.929	0.01 [-0.01, 0.03]	0.242

VIF = variance inflation factor; LC = lamina cribrosa; CI = confidence interval; IOP = intraocular pressure; MD = mean deviation.

Statistically significant values are shown in bold.

*The amount of LC depth reduction was log-transformed to correct non-linearities between the data. Thus, the beta value indicates that mean LC depth reduction increases Exp (beta) folds for unit increase of the independent variables.

DISCUSSION

In the current study, we observed a reversal in LC depth with IOP-lowering in eyes with OAG. The degree of reversal of the LC was related to the age, untreated IOP, baseline IOP, and amount of IOP lowering.

The magnitude of reduction of LC depth was significantly less in eyes with lower untreated IOP than in eyes with higher IOP. We speculate that this finding is mainly attributable to less IOP reduction in patients with lower IOP than in patients with higher IOP. Alternatively, one may argue that the LC of eyes with lower untreated IOP was less displaced from a baseline than eyes with higher untreated IOP. It would have been ideal if the amount of IOP reduction was comparable in all subjects included. In this scenario, the LC reversal with the same amount of IOP reduction might be less in eyes with lower IOP than in those with higher IOP. This possibility, however, cannot be evaluated with the current data because of the difference in IOP reduction among patients.

In all included eyes, the IOP reduction was reduced by at least 20%. It has been shown that over 20% IOP reduction often is effective for preventing visual field progression in glaucoma, including eyes with normal pressure.[11] In the present study, only a minority has shown significant reversal of the LC among patients with low IOP. These data suggest that the preventing disease progression by IOP reduction in those patients may be largely dependent on the factors other than the mechanical stress in the ONH.

Our data also demonstrate that the LC displacement is reversed after IOP lowering in some patients with low IOP. A recently proposed biomechanical paradigm suggests that posterior deformation of the LC depends not only on the IOP but also on the geometry and material properties (i.e., thickness, compliance, or rigidity) of the ONH and the peripapillary scleral tissue.[12] This indicates that the IOP-induced stress imposed on the ONH may be substantial even at normal levels of IOP.[12] The reversal of the LC observed after IOP lowering in eyes with low IOP is in line with this paradigm.

LC reversal was not observed in any selected B-scan image in 41% of eyes. Several factors may explain this. First, it is possible that the LC was not posteriorly displaced at baseline. This may be related not only to the level of IOP but also to the individual ONH susceptibility to the IOP, which is affected by various biomechanical factors including laminar and peripapillary scleral connective tissue geometry and material properties (strength, stiffness, rigidity, compliance, and nutrient diffusion capabilities).[5, 13] Second, the LC may have lost the elasticity that is required to resume its original configuration. This may be due to IOP-induced connective tissue changes or age-related LC rigidity/stiffness. Finally, the amount of IOP reduction may have been less than the amount needed to induce LC reversal in those particular patients.

Overall, age was found to be a significant factor affecting the reduction in LC depth, as we reported previously.[1] This may be related to the decrease in the mechanical compliance of the LC with age.[14, 15]

Study Limitations

This study has several limitations. First, it is of interest to know whether the LC reversal is influenced by the treatment modality. However, we could perform only a limited analysis on this matter due to the preponderance of specific treatments in each group; while 84.4% of patients with IOP ≥ 22mmHg received trabeculectomy, all patients with IOP <22mmHg received medical treatment. In an analysis including only patients with IOP ≥ 22mmHg, it appeared that the mean LC depth reduction in those who received medical treatment was comparable or smaller than in those who received trabeculectomy (Figure 2.8). This finding suggests that trabeculectomy could be influencing the reversal of the laminar displacement by an effect that goes beyond the IOP level measured at the time of follow up imaging. Further study is needed to address this matter.

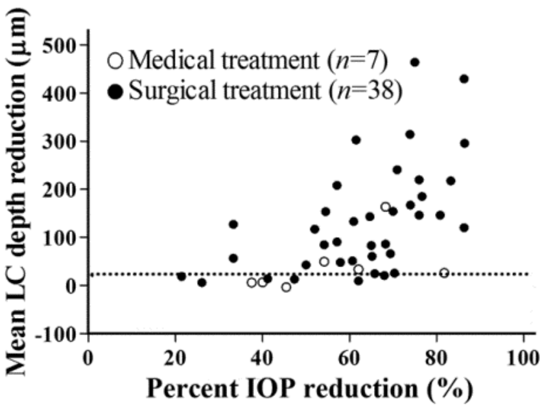

Figure 2.8. Relationship between percent intraocular pressure (IOP) reduction and mean lamina cribrosa (LC) depth reduction in eyes with untreated IOP ≥ 22mmHg (n=45), who were separated into two groups based on the treatment modality. The dotted line indicates 1.96 times the inter-session standard deviation (23.3 µm).

Second, we did not consider the LC thickness. This decision was based mainly on our previous investigation that the reversal of the LC displacement was far more evident than the LC thickness reversal after trabeculectomy.[1] Moreover, in most of our subjects the change in LC thickness was less than the inter-session variability (data not presented). Therefore, we instead focused on the LC depth change.

Third, patients were observed for up to 6 months. The LC depth reduction may persist after this period if the IOP remains well controlled. However, we have demonstrated previously that reduction of the LC displacement largely occurs within 3 months.[1] Thus, the follow-up period of 3 to 6 months may not have greatly influenced the results of our study.

Forth, the LC depth was measured at only the central three points in each B-scan. However, given the posteriorly bowed nature of the LC, the reversal of the LC may occur largely in the central region. Thus, evaluation of the central LC may indeed represent the main changes that occur with IOP reduction.

Finally, the material properties of the laminar and peripapillary scleral connective tissue were not considered in the present study. These factors might have partly contributed to the resilient response of the LC. Further investigation of the behavior of the LC under various mechanical conditions is required once it becomes possible to evaluate these factors in vivo.

In summary, reversal of the LC displacement was observed after IOP-lowering treatment in eyes with POAG. The degree of LC displacement reversal was associated with the amount of IOP lowering.

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Chapter 3

Variation of Lamina Cribrosa Depth Following Trabeculectomy

- Lamina Cribrosa Depth Variation -

녹내장 환자에서 섬유주절제술 후 사상판 깊이의 장기 추적 관찰

- 섬유주절제술 후 사상판 깊이의 장기 변화 관찰 -

Abstract

Purpose: To investigate the long-term changes in lamina cribrosa (LC) depth following trabeculectomy.

Methods: Serial horizontal B-scan images of the optic nerve head were obtained using spectral-domain optical coherence tomography from 28 primary open-angle glaucoma patients who underwent trabeculectomy and were followed up for at least 2 years. Approximately 65 B-scans covering the optic discs were obtained before surgery and at 6 months and ≥2 years postoperatively. The pre- and postoperative LC depth (the distance from the opening plane of Bruch's membrane to the level of the anterior LC surface) was determined on seven selected B-scan images from each eye and averaged (mean LC depth).

Results: The intraocular pressure (IOP) decreased from 27.4 ± 9.0 (mean ± SD) to 9.7 ± 3.1

mmHg at postoperative 6 months ($P < 0.001$) and subsequently increased to 12.7 ± 5.1 mmHg at a mean final follow-up of 27.1 ± 3.3 months ($P = 0.001$). The mean LC depth was reduced from 625.6 ± 186.3 to 499.6 ± 140.6 μm at postoperative 6 months ($P < 0.001$). A subsequent slight, but nonsignificant, increase in the LC depth was noted at final follow-up. The degree of LC depth increase after 6 months was significantly associated with younger age, higher IOP at final follow-up, greater IOP fluctuation, and higher mean follow-up IOP from 6 months to final follow-up (all $P < 0.05$).

Conclusions: The postoperative reduction in the LC depth that was observed 6 months after surgery was not maintained in some eyes. The redisplacement of the LC after postoperative 6 months appeared more likely to occur in patients who were younger and who had higher IOP and IOP fluctuation during the postoperative follow-up.

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Keywords: Lamina Cribrosa, Spectral-domain Optical Coherence Tomography, Open Angle Glaucoma, Trabeculectomy

Student Number: 2011-31129

초 록

목적: 섬유주절제술 후 사상판 깊이의 장기 변화를 알아보고자 한다.

방법: 섬유주절제술을 시행받은 후 2년 이상 추적관찰된 28명의 일차개방각녹내장 환자를 대상으로 스펙트럼영역 빛간섭단층촬영을 이용한 시신경유두횡단면의 연속스캔이미지를 얻었다. 각 눈에서 시신경영역을 포함하는 약 65개의 이미지를 얻었는데, 수술 전, 수술 후 6개월째, 수술 2년 이후 각각 반복하여 시행하였다. 각 검사에서 선택된 7개의 스캔이미지에서 수술 전과 후의 사상판의 깊이(브루크막 개구부에서 사상판의 앞경계까지의 거리)를 측정하여 이의 평균을 얻었다(사상판의 평균 깊이).

결과: 안압은 수술 후 6개월째 27.4 ± 9.0 mmHg 에서 9.7 ± 3.1 mmHg 로 감소하였고($P < 0.001$), 마지막 추적관찰시인 수술 후 27.1 ± 3.3개월째에는 12.7 ± 5.1 mmHg 로 증가하였다($P = 0.001$). 사상판의 평균 깊이는 수술 전 625.6 ± 186.3 μm 에서 수술 후 6개월째 499.6 ± 140.6 μm 로 감소하였고($P < 0.001$), 이후 마지막 추적관찰시에는 다소 증가하였지만, 통계적으로 유의하지는 않았다. 수술 6개월 이후에 관찰된 사상판 평균 깊이의 증가는 나이가 젊고, 마지막 관찰시 안압이 높을수록, 수술 6개월 이후부터 마지막 관찰까지의 안압 변동폭이 크거나, 해당기간 동안 평균안압이 높을수록 더 큰 폭으로 나타났다(all $P < 0.05$)

결론: 수술 후 6개월째 관찰되었던 사상판 깊이의 복원은 일부 녹내장안에서는 유지되지 않고 다시 깊어지는 현상을 보였다. 이러한 현상은 젊고, 수술 후 안압이 높거나 그 변동폭이 큰 환자에서 나타나는 것으로 보인다.

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주요어: 사상판, 스펙트럼영역 빛간섭단층촬영, 개방각녹내장, 섬유주절제술

학 번: 2011−31129

INTRODUCTION

Glaucoma is a multifactorial disease, and lowering the intraocular pressure (IOP) has been the mainstay treatment. According to the recently suggested biomechanical paradigm, IOP plays a central role in the pathogenesis of optic nerve damage in glaucoma.[1] The IOP related stress, which can be substantial even at low levels of IOP,[2] may generate the strain on the optic nerve. The resulting tensile strain within the lamina cribrosa (LC) would provide shearing stress on the axons passing through the laminar pores. In addition, the LC deformation may also be relevant with optic nerve ischemia because the strain within the LC can compress the laminar capillaries, which is contained in the laminar trabeculae.[1] Thus, to image the LC and to determine factors associated with LC deformation may not only expand our understanding on the pathogenesis of glaucomatous damage but also help to develop better strategy in treating glaucoma.

Until now, however, little observation has been made about the biomechanical behavior of the LC. This may be largely due to the lack of imaging technology which can capture the LC in patients. With the emergence of spectral-domain (SD) optical coherence tomography (OCT), it became possible to obtain images of the LC, especially with enhanced depth imaging technique (EDI). Using this technique, we recently have demonstrated that displacement and compression of the LC may be reversed after trabeculectomy in eyes with primary open-angle glaucoma (POAG).[3] This finding gives an explanation about how IOP lowering can be beneficial to prevent or slow glaucoma progression from the biomechanical perspective. Since deformation and compression of the LC may induce shearing stress in the axons passing through the laminar pores and possible occlusion of the laminar capillaries,[4-8] it can be postulated that reversal of the LC deformation would provide relief to the compressed nerve fibers or laminar capillaries.[3, 9]

In a previous study[3] we described the changes in the LC depth up to 6 months after trabeculectomy. The reversal of the LC occurred rather rapidly, and then continued gradually up to 6 months, and the amount of reversal was associated with percent degree of IOP lowering. The purpose of the current study was to elucidate the longer-term changes in the LC depth (i.e., later than 6 months after surgery). As it is not uncommon that IOP re-elevates after 2 years in trabeculectomized eyes, the long-term follow-up observation would provide a window of opportunity to examine the effect of varying IOP on the LC configuration.

METHODS

The study included POAG patients who were followed up for at least 2 years after trabeculectomy. The study was approved by the Seoul National University Bundang Hospital Institutional Review Board and conformed to the Declaration of Helsinki. Informed written consent to participate was obtained from all subjects.

The preoperative examinations and criteria for inclusion and exclusion have been described in detail elsewhere.[3] In brief, all of the patients underwent a complete ophthalmic examination including visual acuity assessment, refraction test, slit-lamp biomicroscopy, gonioscopy, Goldmann applanation tonometry, dilated stereoscopic examination of the optic disc. They also underwent central corneal thickness measurement (Orbscan II, Bausch & Lomb Surgical, Rochester, NY, USA), spectral-domain optical coherence tomography (SD-OCT), and standard automated perimetry (24-2 Swedish interactive threshold algorithm; Humphrey Field Analyzer II 750, Carl-Zeiss Meditec, Dublin, CA, USA).

The inclusion criteria were a diagnosis of POAG, a best corrected visual acuity of ≥20/40, a spherical refraction of –8.0 to +5.0 diopters, and cylinder correction within ±3.0 diopters. POAG was defined as the presence of glaucomatous optic nerve damage and associated visual field defects without ocular disease or conditions that may elevate the IOP. Indications for trabeculectomy were IOP deemed to be associated with a high risk for progression, or glaucomatous progression of the visual field or optic disc in spite of maximally tolerated medications.

Eyes that had undergone previous intraocular surgery or that had coexisting retinal or neurological diseases that could have affected the visual field were excluded from this study. Eyes were also excluded when a good quality image (i.e., quality score >15) could not be obtained at more than five sections (when the quality score does not reach 15, the image-acquisition process automatically stops and images of the respective sections are not obtained).

For this study, the follow-up period was divided into an initial 6-month follow-up (initial follow-up) and a subsequent follow-up of up to 2~3 years after surgery (subsequent follow-up). Measurements made at the patient’s last follow-up appointment (at least 2 years after surgery) are hereafter referred to as the ‘final’ follow-up.

Optic discs were examined using SD-OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany) at 1 day before surgery and at 6 months and approximately 2 or 3 years postoperatively (final follow-up). The preoperative IOP was defined as the average of the two measurements within 2 weeks before trabeculectomy. The IOP was recorded every 3 months during the subsequent follow-up period, and the average and the standard deviation (SD) of the follow-up IOP measurements were defined as the mean follow-up

IOP and the IOP fluctuation, respectively. When patients underwent an additional IOP-lowering procedure such as bleb needling, additional trabeculectomy, or glaucoma drainage device implantation, the IOPs measured within 3 months post-treatment were not included in the calculation.

Enhanced Depth Imaging Optical Coherence Tomography of the Optic Disc

The optic nerve head (ONH) was imaged using the Spectralis OCT device with the EDI technique. The details and advantages of this technology for evaluating the LC have been described previously.[10-13] Approximately 65 B-scan section images covering the ONH, 30–34 μm apart (the scan line distance being determined automatically by the machine), were obtained from each eye. Forty-two OCT frames averaged for each section, which provided the best trade-off between the image quality and patient cooperation.[10] Images are obtainable using the Spectralis OCT device only when the quality score is higher than 15. When this criterion is not fulfilled the image acquisition process automatically stops and the image of the respective section is excluded. Only acceptable scans with a good-quality image (i.e., quality score >15) obtained for more than 60 sections and that allowed clear delineation of the anterior and posterior borders of the LC were included.

Quantification of the Lamina Cribrosa Depth

The depth of the LC was measured on the pre- and postoperative B-scan images. The details of this measurement method have been described previously.[3, 9] An excellent inter-observer reproducibility in measuring the LC depth has been reported (intraclass correlation coefficient =0.998).[3] The LC depth was determined by measuring the distance from the opening plane of Bruch's membrane to the level of the anterior LC surface. To this end, a reference line connecting the two termination points of Bruch's membrane was drawn in each B-scan. The distance from the reference line to the level of anterior border of LC was then measured at three points: the maximally depressed point and two additional points (100 and 200 μm apart from the maximally depressed point in the temporal direction). Only the temporally adjacent points were selected because the maximally depressed point was often close to the central vessel trunk, the shadow of which obscured the LC. In addition, the full-thickness LC was often not clearly discernible at the temporal periphery. Thus, data were collected from only two additional points. The distance was measured on the line perpendicular to the reference line using the manual caliper tool of Amira software (version 5.2.2, Visage Imaging, Berlin, Germany). The average of these three values was defined as the LC depth of the B-scan.

To determine the mean LC depth, seven B-scan images that divided the optic disc diameter into eight equal parts vertically were selected in each eye from the three-dimensional image data set, as described previously.[9] The LC depth was measured in each B-scan as described above, and the average of the measurements was defined as the mean LC depth of the eye.

For follow-up measurements, the sets of B-scans were selected to correspond to those that had been selected for the baseline measurements. En-face images as well as the low reflective shadow within the LC shown in B-scan images were used to confirm the correspondence of the selected B-scans between pre- and postoperative images.[3, 9]

The difference in the mean LC depth between each follow-up examination was defined as the mean LC depth decrease. A statistically significant change was accepted with an intersession SD of 1.96 times, since this corresponds to the 95% confidence interval for the true value of the measurement. The intersession reproducibility in the LC depth measurements (ICC=0.991) and 1.96 times the intersession SD (23.3 μm) have been reported previously.[9]

The LC depth was measured by an observer (E.J.L.) who was blind to the clinical information including the IOP and the time point of the scanning for the follow-up OCT images.

Data Analysis

The LC depths measured preoperatively and at 6 and 24 months postoperatively were compared using repeated-measures analysis of variance. Linear regression analysis was used to determine the factors associated with the change in the LC depth during the subsequent follow-up. Statistical analyses were performed using PASW Statistics software (version 18.0.0, SPSS, Chicago, IL, USA). The level of statistical significance was set at $P<0.05$.

RESULTS

Thirty-five POAG patients who underwent trabeculectomy were included. Of these, 7 patients were lost to follow-up; the remaining 28 patients were followed up for 27.1±3.3 months (mean±SD; range, 23–34 months).

The age was 48.6±17.2 years (range, 15–80 years), and 10 subjects were women and 18 were men. The visual acuity ranged from 20/40 to 20/20 and the refractive error (spherical equivalent) was –2.9±2.8 diopters (range, –7.00

to +2.25 diopters). The visual field mean deviation was –14.5±9.9 dB (range, –31.79 to –1.41 dB) (Table 3.1).

Table 3.1. Patient clinical demographics (*n*=28)

Variable	
Age, *y*	48.6±17.2
Gender, *male/female*	18/10
Spherical equivalent, *diopter*	–2.9±2.8
Central corneal thickness, *μm*	546.0±55.2
Axial length, *mm*	25.0±1.7
Visual field MD, *dB*	–14.5±9.9
Visual field PSD, *dB*	8.3±4.1

MD, mean deviation; PSD, pattern standard deviation.

Values are shown in mean ± standard deviation.

Eleven of the 28 eyes required a total of 15 additional surgical interventions during the subsequent follow-up period. Three eyes required needling of an encapsulated bleb with adjunctive 5-fluorouracil delivered by subconjunctival injection (2, 2, and 5 times, for each eye). Five eyes underwent an additional trabeculectomy at 8, 11, 16, 26, and 29 months after initial surgery. Of these five eyes, one also had glaucoma drainage implantation surgery.

Table 3.2 lists the IOP and LC depth at each follow-up visit. The IOP decreased from 27.4±9.0 mmHg (range, 14–47 mmHg) to 9.7±3.1 mmHg (range, 6–16 mmHg) at postoperative 6 months (P<0.001) and to 12.7±5.6 mmHg (range, 6–30 mmHg) at the final follow-up (P<0.001). None of the patients had signs of ocular hypotony in terms of reduced visual acuity or retinal folds at the time of SD-OCT. The mean LC depth decreased significantly from a preoperative level of 625.6±186.3 μm to 499.6±140.6 μm at 6 month postoperatively (*P*<0.001), and to 519.0±133.4 μm at final follow-up (P<0.001).

Table 3.2. Intraocular pressure and the mean lamina cribrosa depth at each follow-up visit

	Preop	Postop 6 month	*P**	Final	*P**	*P*†
IOP, *mmHg*	27.4±9.0	9.7±3.1	**<0.001**	12.7±5.1	**<0.001**	**0.001**
Mean LC depth, *μm*	625.6±186.3	499.6±140.6	**<0.001**	519.0±133.4	**<0.001**	0.116

IOP, intraocular pressure; LC, lamina cribrosa

P values are based on the repeated measures analysis of variance.

* *P* values comparing between the postoperative and preoperative measurements.

† *P* values comparing between the final and postoperative 6 months' measurements.

Values are shown in mean ± standard deviation (μm).

Values with statistical significance are shown in bold.

At the end of the initial follow-up (i.e., 6 months after surgery), significant LC reversal was observed in 23 of the 28 eyes. In 8 of the 23 eyes (34.8%), LC depth increased again and exceeded the intersession variability (491.9±171.7 to 585.6±159.2 μm, *P*=0.012, Wilcoxon signed-rank test), while 4 eyes (17.4%) exhibited a further reversal of the LC to a significant level during the subsequent follow-up (632.1±138.5 to 569.0±109.0 μm, *P*=0.068, Wilcoxon signed-rank test). The change in the mean LC depth during the subsequent follow-up period in the remaining 11 eyes (47.8%) was not statistically significant (494.9±122.7 to 495.8±125.6 μm, *P*=0.594, Wilcoxon signed-rank test). (Figure 3.1A).

Of the five eyes in which significant LC reversal was not observed during the initial follow-up, an increase in the mean LC depth was observed in one eye during the subsequent follow-up. In another eye, a significant LC reversal was observed at the subsequent follow-up. In the remaining three eyes, there was no change in the mean LC depth during the subsequent follow-up (Figure 3.1B)

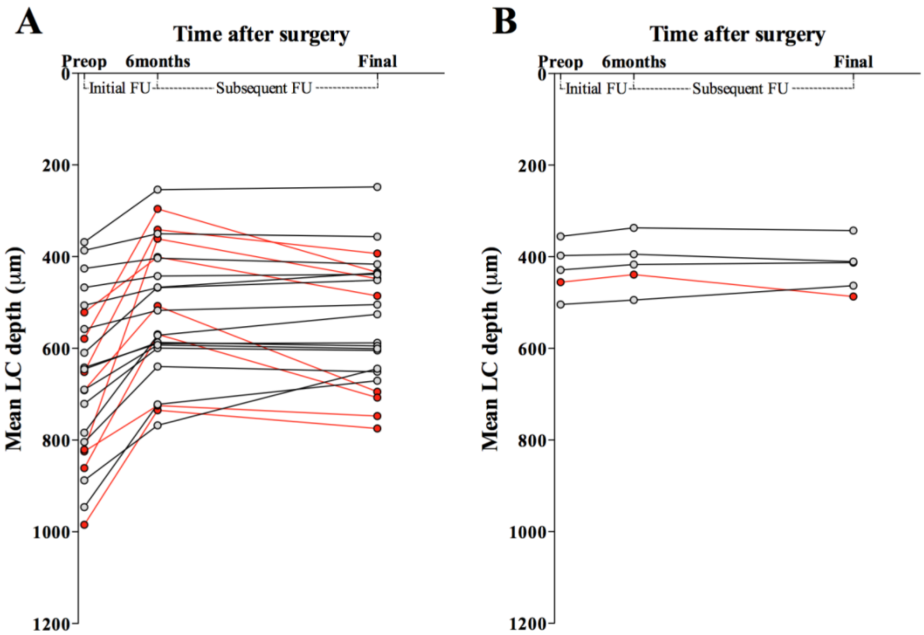

Figure 3.1. Mean lamina cribrosa (LC) depth at each follow-up in eyes where a significant LC reversal was observed (**A**, *n*=23) or not observed (**B**, *n*=5) during the initial follow-up. Of the 23 eyes in which a significant reversal was observed at the postoperative 6 months, 8 showed redisplacement of the LC at the end of the subsequent follow-up (red lines with red circles). Of the five eyes in which significant LC reversal was not found during the initial follow-up, an increase in the mean LC depth was observed in one eye during the subsequent follow-up.

Eyes in which the LC depth increased again after the 6 month follow-up were observed in patients who were younger (*P*=0.001) and had a higher IOP at final follow-up (*P*=0.035), a greater IOP fluctuation (*P*=0.007), and a higher mean follow-up IOP from 6 months after surgery (*P*=0.022). There was no significant difference in the reduction of the VF MD between eyes with LC re-displacement and eyes without LC re-displacement (*P*=0.951). (Table 3.3)

Table 3.3. Comparison between eyes with and without a significant redisplacement of the lamina cribrosa during the subsequent follow-up.

	Eyes with significant LC re-displacement (*n*=9)	Eyes without significant LC re-displacement (*n*=19)	*P**
Age, *y*	34.3±14.6	55.4±14.1	**0.001**
Gender, *male/female*	4/5	14/5	0.132†
IOP at baseline, *mmHg*	31.0±10.1	25.7±8.1	0.147
IOP at postoperative 6mo, *mmHg*	10. 3±4.0	9.4±2.6	0.461
IOP at final follow-up, *mmHg*	16.6±6.6	10.9±2.9	**0.035**
%IOP reduction from 6mo, *%*	-84.7±122.3	-19.6±26.1	0.151
IOP fluctuation, *SD*	4.9±2.4	2.0±1.1	**0.007**
Mean follow-up IOP, *mmHg*	14.3±4.5	10.9±2.8	**0.022**
Mean LC depth at baseline, *μm*	710.0±175.0	585.6±182.3	0.10
Mean LC depth at 6mo, *μm*	486.0±161.6	506.0±133.8	0.732
Global RNFL thickness, *μm*	61.6±15.7	53.3±14.4	0.178
Visual field MD at baseline, *dB*	-13.7±11.6	-14.9±9.3	0.769
Visual field MD at final follow-up, *dB*	-15.3±12.2	-16.6±9.8	0.768
Amount of visual field MD deterioration, *dB*	-1.6±2.0	-1.7±3.0	0.951
Central corneal thickness, *μm*	548.0±67.9	545.4±53.4	0.928
Axial length, *mm*	25.0±1.4	25.1±1.9	0.908
Spherical equivalent, *diopter*	-4.6±3.1	-3.1±4.7	0.390
Follow-up duration, *month*	25.0±4.2	26.9±4.8	0.321

LC, lamina cribrosa; IOP, intraocular pressure; SD, standard deviation; RNFL, retinal nerve fiber layer; MD, mean deviation.

*Except where indicated otherwise, the comparison was performed using independent-samples *t*-test.

†Comparison was performed using chi-squared test.

Values with statistical significance are shown in bold.

The factors associated with the increase of LC depth during the subsequent follow-up period were assessed using linear regression analysis. In the univariate analysis, younger age (P=0.012), female gender (P=0.016), higher IOP at the final follow-up (P=0.004), smaller percentage IOP reduction from 6 months to the final follow-up (P=0.049), greater IOP fluctuation (P<0.001), and higher mean follow-up IOP (P=0.005) after postoperative 6 months were significantly associated with an increase of LC depth in the subsequent follow-up period. Since the IOP-related factors had high variance inflation factors, multivariate analysis was performed in four ways to avoid multicollinearity; this revealed significant associations with younger age (*Ps*<0.05), IOP at final follow-up (P=0.029), greater IOP fluctuation (P<0.001), and higher mean IOP during the subsequent follow-up period (P=0.034). (Tables 3.4 and 3.5, Figure 3.2).

Table 3.4. Univariate analysis of the factors associated with increasing depth of the lamina cribrosa more than 6 months postoperatively.

	Univariate analysis		
	Beta (95% CI)	*P*	VIF
Age, *per 1 year older*	**–1.73 (–3.03 to –0.42)**	**0.012**	1.33
Female gender	**58.62 (12.05 to 105.19)**	**0.016**	1.85
IOP at baseline, *per 1 mmHg increase*	1.75 (–0.99 to 4.50)	0.201	
IOP at postoperative 6 months, *per 1 mmHg increase*	2.68 (–5.55 to 10.90)	0.510	
IOP at final follow-up, *per 1 mmHg increase*	**6.47 (2.21 to 10.73)**	**0.004**	9.07
%IOP reduction from 6mo, *per 10% reduction*	**–3.10 (–6.19 to –0.01)**	**0.049**	8.00
IOP fluctuation, *per 1 SD increase*	**22.80 (15.08 to 30.53)**	**<0.001**	4.44
Mean follow-up IOP, *per 1 mmHg increase*	**8.80 (2.92 to 14.69)**	**0.005**	12.37
Mean LC depth at baseline, *per 100 μm deeper*	0.64 (–13.03 to 14.32)	0.924	
Mean LC depth at 6 month, *per 100 μm deeper*	–15.09 (–32.17 to 1.99)	0.081	1.84
Global RNFL thickness, *per 1 μm thicker*	1.06 (–0.58 to 2.70)	0.195	
Visual field MD, *per 1 dB worse*	–0.16 (–2.95 to 2.63)	0.907	
Central corneal thickness, *per 1 μm thicker*	0.31 (–0.15 to 0.76)	0.176	
Axial length, *per 1 mm longer*	3.25 (–14.77 to 21.27)	0.712	
Follow-up duration (per 1 month longer)	–0.85 (–104.61 to 188.21)	0.752	

95% CI, 95% confidence interval; VIF, variance inflation factor; IOP, intraocular pressure; SD, standard deviation; LC, lamina cribrosa; MD, mean deviation.

Values with statistical significance are shown in bold.

Table 3.5. Multivariate analysis of the factors associated with increasing depth of the lamina cribrosa more than 6 months postoperatively.

	Multivariate 1		Multivariate 2		Multivariate 3		Multivariate 4	
	Beta (95% CI)	*P*	*Beta* (95% CI)	*P*	*Beta* (95% CI)	*P*	*Beta* (95% CI)	*P*
Age, *per 1 year older*	**–1.51 (–2.65 to –0.38)**	**0.011**	**–1.48 (–2.71 to –0.25)**	**0.021**	**–1.34 (–2.18 to –0.50)**	**0.003**	**–1.64 (–2.76 to –0.52)**	**0.006**
Female gender	24.95 (–18.98 to 68.88)	0.252	43.79 (–3.85 to 91.42)	0.070	11.67 (–21.57 to 44.92)	0.475	13.51 (–33.58 to 60.60)	0.559
IOP at final follow-up, *per 1 mmHg increase*	**4.26 (0.48 to 8.05)**	**0.029**						
%IOP reduction from 6 month, *per 10% reduction*			–2.24 (–5.03 to 0.55)	0.111				
IOP fluctuation, *per 1 SD increase*)					**18.03 (11.04 to 25.01)**	**<0.001**		
Mean follow-up IOP, *per 1 mmHg increase*							**5.99 (0.49 to 11.49)**	**0.034**
Mean LC depth at 6 month, *per 100 μm deeper*	–12.42 (–27.64 to 2.81)	0.105	–8.38 (–25.63 to 8.86)	0.325	–10.42 (–21.77 to 0.93)	0.070	–14.59 (–29.90 to 0.71)	0.061

95% CI, 95% confidence interval; IOP, intraocular pressure; SD, standard deviation; LC, lamina cribrosa.

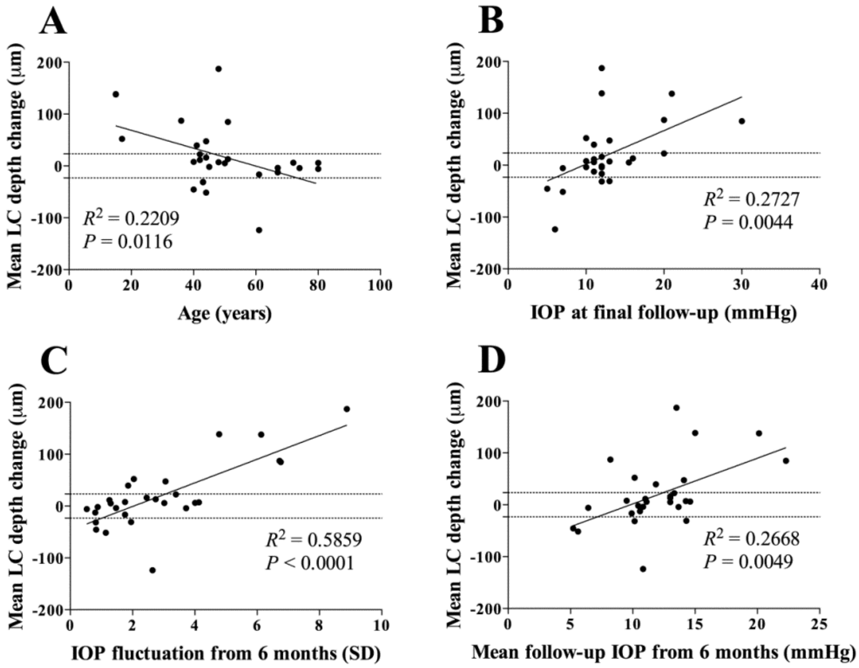

Figure 3.2. Relationship between the change in the mean lamina cribrosa (LC) depth from postoperative 6 months to the end of the subsequent follow-up period and age (**A**), intraocular pressure (IOP) at the final follow-up (**B**), IOP fluctuation (**C**), and mean follow-up IOP from 6 months after surgery (**D**). The dotted line indicates 1.96 times the intersession standard deviation (SD; 23.3 μm). Positive and negative values indicate LC redisplacement and further LC depth reduction, respectively.

Representative Cases

Figure 3.3 shows two cases with POAG in whom there was further LC reversal and increase in the LC depth during the subsequent follow-up period. In case A, the LC depth continued to decrease after 6 months (Figure 3.3A-3). However, the LC depth in case B increased at the final follow-up compared with the 6 month LC depth (Figure 3.3B-3).

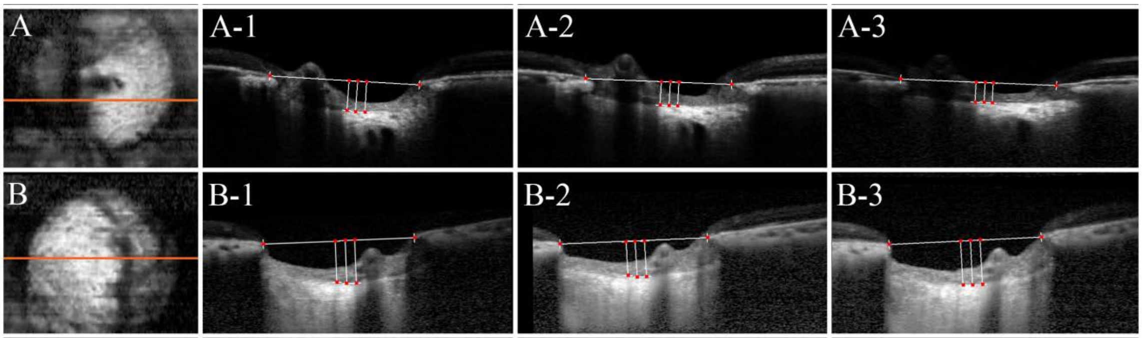

Figure 3.3. En-face (**A, B**) and B-scan images obtained at baseline (**A-1, B-1**), postoperative 6 months (**A-2, B-2**), and final follow-up (**A-3, B-3**) in two eyes with primary open angle glaucoma who underwent trabeculectomy. (**A)** The left eye of an 81-year-old female patient. The IOP had decreased from 17 to 6 mmHg at 6 months and was 7 mmHg at 25 months after surgery. Note that the magnitude of the LC depth continuously decreased throughout the entire follow-up period. (**B)** The right eye of a 51-year-old female patient. The IOP had decreased from 41 to 16 mmHg at postoperative 6 months, but had increased to 30 mmHg at 23 months. Note that there was a clear LC depth reduction and then increase in the LC depth at 6 months and final follow-ups, respectively.

DISCUSSION

In the current study we investigated the long-term changes in the LC depth after trabeculectomy in eyes with POAG. Six months after surgery (i.e., the initial follow-up), significant LC depth reduction was observed in most of the eyes. This reversal of LC displacement exhibited a variable course thereafter, either remaining stable, further being reversed, or increasing in depth again.

This is the first study to investigate the long-term changes of the LC following IOP-lowering surgery.

The present study found a significant increase of the LC depth during the subsequent (i.e., post-6-month) follow-up after IOP-lowering surgery in 9 of 28 eyes (32.1%). These eyes exhibited a higher IOP at final follow-up, a greater IOP fluctuation, and a higher mean IOP over the subsequent follow-up period. This finding suggests that sustained reduction of the IOP is important for maintenance of the reversed LC displacement that occurs after trabeculectomy.

The deepening of the LC over the subsequent follow-up period in eyes with unstable IOP is in line with those of previous experimental studies. Burgoyne et al.[14]and Yang et al. [15, 16] showed that the LC was posteriorly displaced according to IOP elevation in monkey eyes with early experimental glaucoma. Similar finding was demonstrated in Bellezza et al's study,[17] where the LC displacement was observed at the onset of ONH surface change detected by confocal scanning laser tomography. Recently, Strouthidis et al[18] showed that the IOP-induced LC displacement was also detectable using longitudinal SD-OCT images in early glaucomatous monkey eyes. Although the current study involved eyes which received trabeculectomy, our observation confirms that displacement of LC according to IOP elevation, which has been demonstrated in previous experimental studies, is a realistic finding in the clinical situation.

Several clinical trials emphasized the importance of IOP control for disease prognosis within the glaucoma continuum. The European Glaucoma Prevention Study showed that the mean IOP over time was an important factor for the development of open-angle glaucoma.[19] In the Advanced Glaucoma Intervention Study, both higher mean follow-up IOP and greater IOP fluctuation were associated with an increased risk of visual field progression.[20] Others[21, 22] have also demonstrated a significant influence of mean IOP and fluctuation of IOP over the follow-up period on visual field progression. We propose that increased LC depth indicates an increased IOP-related stress on the ONH, which is likely to be related to a worse disease prognosis. In the present study, however, there was no difference in the reduction of the VF MD between the groups with LC re-displacement and without LC re-displacement during the study period. However, it is well known that VF data fluctuate considerably and that VF changes should therefore be compared only with multiple examinations. Further, the LC displacement group in the current study included only 9 patients, and thus, the comparison between the 2 groups had only limited power to detect group difference. The current study was not designed to investigate the influence of LC change on future visual field changes and this relationship remains to be elucidated. A longitudinal study is currently underway to investigate the relationship between the reversal of the LC displacement and the rate of disease progression.

In the present study, BMO level was used as the reference plane. Although the BMO opening is a solid structure that can be identified consistently among patients, there is a possibility that the BMO level moves due to choroidal thickness change or retinal edema. In eyes with long lasting hypotony, potential thickening of the choroid may move the BMO anteriorly, resulting in an artefactual increase of LC depth. Such effect can be more significant in patients with younger age who are more susceptible to hypotony maculopathy or edema at low IOP. Thus, the association of LC redisplacement with younger age may be partly attributable to this artifact. However, we believe that such artifact was not a major component of LC depth increase seen in our patients for the following reasons. First, none of the eyes included had signs of ocular hypotony at the time of SD-OCT scanning. Second, the degree of LC re-displacement was generally of much larger extent than the potentially overlooked choroidal thickness change as shown in sample figures (Figure 3.3). Third, the IOP at postoperative 24 months of the 9 patients who displayed LC re-displacement were equal to or higher than the measurement at postoperative 6 months, ranging from 10 to 30 mmHg (data not presented).

In the present study, younger patients were more susceptible to LC redisplacement. This finding can be attributable to following factors. First, LC is probably less stiff in younger patients, and thus the LC responses to varying IOP may be of larger extent. Second, as described above, there is a higher likelihood that the choroid thickens in eyes with long lasting low IOP, leading to anterior displacement of the BM. This may increase the distance between the BMO and the anterior LC surface.

This study was subject to some limitations. First, the LC depth was measured in the central area because the LC was often not clearly visible in the peripheral area. However, it may be assumed that given the posteriorly bowed nature of the LC, the reversal of the LC may actually occur largely in the central region. Thus, we believe that evaluation of the central LC area may be an effective way of demonstrating the changes occurring with IOP variation.

Second, parameters potentially relevant to the resilient response of the LC, such as the material properties of the laminar and peripapillary scleral connective tissue,[1, 15, 17, 23] were not considered in this study. Unfortunately, those parameters are not currently measurable. It is possible such factors play a significant role in the reduction of LC displacement and the increase in the thickness of the LC and prelaminar tissue.

Lastly, our study included many young, myopic patients with high preoperative IOP. It is possible that the LC response in these patients may be different from those in elderly patients with modestly high IOP who comprise typical OAG patients who underwent trabeculectomy.

In conclusion, we have described herein the long-term follow-up outcome of trabeculectomy on the LC depth in 28 patients with POAG. The LC depth change after the initial 6 months after surgery varied among the patients; younger age, higher IOP at final follow-up, greater IOP fluctuation, and a higher mean follow-up IOP were associated with an increase in LC depth during the longer-term postoperative follow-up period. Further studies should determine the influence of the reversal of LC displacement that occurs following IOP reduction on disease prognosis.

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국 문 초 록

서론

녹내장은 점진적으로 시신경손상이 일어나는 질환으로서 우리나라 40세 이상 성인인구의 3.5%에서 발병하는 상당히 유병률이 높은 질환이다. 현재 녹내장의 치료는 안압을 낮추는 것이 사실상 유일한 치료인데, 치료에도 불구하고 여전히 많은 녹내장 환자들이 시야결손 진행으로 시력을 잃고 있다. 이는 안압하강치료가 모든 환자에서 같은 효과를 미치지 못할 가능성을 시사하며, 한 편으로는 안압 이외의 다른 인자가 녹내장의 병인에 관여하고 있다는 사실을 의미할 수 있겠다. 그러나 현재까지 안압하강이 실제로 시신경에 어떤 영향을 미치는 지는 알려져 있지 않다.

최근 spectral domain optical coherence tomography (SD-OCT)를 이용하여 시신경유두조직을 생체에서 관찰할 수 있는 방법이 개발됨에 따라 실제 녹내장 환자에서 안압하강치료 후에 사상판을 비롯한 시신경유두에 일어나는 변화를 관찰할 수 있게 되었다. 안압하강 치료에 따라 시신경이 복원되는 현상은 녹내장 환자에서 안압에 의해 시신경과 모세혈관에 가해지고 있던 스트레스의 완화를 의미할 수 있겠으며, 이에 따라 차단되었던 축삭흐름과 혈류가 회복될 것으로 예상할 수 있겠다. 한 편, 복원이 관찰되지 않는다면 이는 안압 이외의 다른 인자가 녹내장의 병인에 관여하고 있을 가능성을 시사한다 하겠다.

목적

안압하강치료를 받은 개방각녹내장 환자를 대상으로 시행한 enhanced depth imaging SD-OCT 시신경이미지를 이용하여 치료 후 사상판을 비롯한 시신경유두조직에 일어나는 변화를 관찰하고, 이러한 변화에 영향을 미치는 인자들을 알아봄으로써 개개 녹내장 환자에서 안압하강 치료의 효과와 의미를 고찰하고, 궁극적으로는 각

환자에서 녹내장의 주된 발병기전을 이해하고자 하였다.

본 연구는 세 가지 세부목표하에 시행되었다. 첫째, 고안압 개방각녹내장에서 수술적치료 후 시신경유두조직에 나타나는 단기변화 관찰, 둘째, 고안압과 저안압 개방각녹내장에서 안압하강치료 후 시신경유두조직에 나타나는 단기변화 비교 관찰, 셋째, 고안압 개방각녹내장에서 수술적치료 후 시신경유두조직 변화의 장기 추적관찰.

방법

녹내장 수술 또는 안약 치료로 안압이 하강된 개방각녹내장 환자를 대상으로 치료 전후 enhanced depth imaging SD-OCT 시신경유두스캔을 시행, 치료 전 얻은 시신경이미지와 치료 후 추적관찰기간동안 연속적으로 얻은 시신경이미지를 비교하였다. 각 이미지에서 사상판의 깊이(브루크막 개구부에서 사상판의 앞경계까지의 거리)와 사상판의 두께, 사상판앞조직의 두께를 측정하였다. 안압하강 전후의 시신경유두조직의 변화를 관찰하고, 이에 영향을 미치는 인자들을 알아보았다.

결과

1. 녹내장 환자에서 섬유주절제술 후 사상판 깊이와 두께의 복원 관찰

- 섬유주절제술을 시행받은 35명의 개방각녹내장 환자에서 안압하강에 따라 수술 후 6개월째까지 사상판 깊이의 감소(사상판의 복원)와 사상판/사상판앞조직의 증가를 관찰할 수 있었다. 사상판의 복원은 나이가 젊고, 안압하강율이 크며, 수술 전 사상판 깊이가 깊을수록 더 많이 일어났다.

2. 개방각녹내장 환자에서 안압하강치료 후 사상판 깊이의 복원 관찰

- 섬유주절제술 또는 안압하강제 치료를 받은 100명의 개방각녹내장 환자에서 치료 후 6개월째까지 사상판의 복원을 관찰할 수 있었으며, 이는 치료 전 안압이 높은 환자에서 더 큰 폭으로 관찰되었으나, 치료 전 안압이 낮은 환자에서도 국소적으로는

복원이 일어났다. 복원과 관련된 인자로는 젊은 나이, 높은 치료 전 안압과 안압하강 정도로 나타났다.

3. 녹내장 환자에서 섬유주절제술 후 사상판 깊이의 장기 추적관찰

- 섬유주절제술을 받은 28명의 개방각녹내장 환자에서 수술 후 6개월째와 2년 이후 사상판의 복원 여부를 관찰하였다. 수술 후 6개월째까지 관찰되었던 감소되었던 사상판 깊이는 수술 2년 이후 9명에서 다시 증가하는 양상을 보였다. 수술 6개월 이후에 관찰된 사상판 평균 깊이의 증가는 나이가 젊고, 마지막 관찰시 안압이 높을수록, 수술 6개월 이후부터 마지막 관찰까지의 안압 변동폭이 크거나, 해당기간 동안 평균안압이 높을수록 더 큰 폭으로 나타났다.

결론

Enhanced depth imaging SD-OCT 시신경이미지를 이용하여 개방각녹내장에서 안압하강치료 후 사상판의 복원을 관찰하였다. 사상판의 단기 복원은 나이가 젊고, 안압을 많이 떨어뜨릴수록 더 많이 일어났으며, 치료 전 안압이 높은 개방각녹내장 환자에서 더 현저하였으나, 안압이 낮은 환자에서도 국소적으로는 복원이 일어나는 것으로 나타났다. 장기적으로는 복원된 사상판이 유지되지 않고 다시 안압하강치료 전으로 되돌아가는 환자도 있었는데, 이는 젊고, 수술 후 안압이 높거나 안압의 변동폭이 큰 환자에서 나타나는 것으로 관찰되었다.

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주요어 : 사상판, 스펙트럼영역 빛간섭단층촬영, 개방각녹내장, 안압하강치료

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