Factors Associated with Lamina Cribrosa Displacement After Trabeculectomy Measured by Optical Coherence Tomography in Advanced Primary Open Angle Glaucoma

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Abstract

Purpose: To investigate the relationship of lamina cribrosa displacement to corneal biomechanical properties and visual function after mitomycin C-augmented trabeculectomy.

Method: Eighty-one primary open angle eyes were imaged before and after trabeculectomy using an enhanced depth spectral-domain optical coherence tomography (SDOCT). Corneal biomechanical properties were measured with the Ocular Response Analyser before the surgery. The anterior lamina cribrosa (LC) was marked at several points in each of six radial scans to evaluate LC displacement in response to Intraocular pressure (IOP) reduction. A Humphrey visual field test (HVF) was performed before the surgery as well as three and six months postoperatively.

Results: Factors associated with a deeper baseline anterior lamina cribrosa depth (ALD) were cup-disc ratio (P=0.04), baseline IOP (P= 0.01), corneal hysteresis (P= 0.001), and corneal resistance factor (P= 0.001). After the surgery, the position of LC became more anterior (negative), posterior (positive) or remained unchanged. The mean LC displacement was -42 μm (P= 0.001) and was positively correlated with the magnitude of IOP reduction (regression coefficient: 0.251, P=0.02), and negatively correlated with age (regression coefficient: - 0.224, P= 0.04) as well as baseline cup-disk ratio (Regression coefficient: -0.212,P= 0.05) Eyes with a larger negative LC displacement were more likely to experience an HVF improvement of more than 3 dB gain in mean deviation (P= 0.002).

Conclusion: A lower SDOCT cup-disc ratio, younger age, and a larger IOP reduction were correlated with a larger negative LC displacement and improving HVF. Corneal biomechanics did not predict LC displacement.

Keywords: glaucoma, lamina cribrosa, optic nerve head, optical coherence tomography, corneal hysteresis, visual field, trabeculectomy

Introduction

Loss of visual function in glaucoma is secondary to axonal ganglion cell damage[1] initiated in and near the lamina cribrosa (LC).[2] Although a causative link between high intraocular pressure and optic nerve damage is well-established in glaucoma, the exact mechanism remains only partially understood.[3] High IOP and IOP fluctuations cause biomechanical stress and strain that compress, dislocate, stretch and shear the LC.[4] This leads to a mechanical failure of the load-bearing connective tissues of the ONH, to damage of nearby axons and compromise of the optic nerve head (ONH) blood supply.[2,4–6] The mechanical failure is followed by a posterior bowing and compaction of the LC.[4,7] Patient-specific properties of the LC may explain why some patients are more likely to develop glaucoma damage despite a similar IOP. The extracellular matrix that adds to the biomechanical properties of the LC is composed of collagens, elastins, and proteoglycans.[8,9] Collagen fibers primarily resist tensile forces and determine tissue elasticity while proteoglycans resist compressive forces and confer viscosity.[10]

The proteoglycans are similar in the cornea and LC despite different collagen types in these tissues.[11] Although an *in vivo* assessment of the biomechanical properties of the LC is not directly possible, the cornea can be readily analyzed with an ocular response analyzer (ORA, Reichert Instruments, Depew, NY). An examination of the biomechanical features of the cornea might serve as a substitute for the LC.[12,13] The ORA[14] uses a metered air jet to displace the cornea and determine its hysteresis. This variable can be described as the delay between a cause and an effect or in this case, the difference between the pressure at which the cornea bends posteriorly during an airjet-applanation and the pressure at which it moves anteriorly again. A larger CH can be interpreted as increased viscoelastic damping of stress-strain forces.

While the importance of the LC in glaucoma pathogenesis has been shown in mathematical models, and in *ex vivo* and *in vivo* studies,[1,5,15,16] high resolution in vivo assessment has only become available recently.[17,18] The association between corneal and ONH biomechanical properties had been explored in several studies in an attempt to propose easily measurable CH as a biomarker for LC biomechanical behaviour.[2,12,13,19]

The results remained contradictory: while some studies suggested a higher CH is associated with a greater anterior lamina cribrosa depth change (ALDC),[12,13] others observed an association with a low CH and thin corneal thickness.[2,20] A limitation of these studies was that the ALDC was measured in healthy eyes following an increase[13] in IOP or only a modest IOP reduction in glaucomatous eyes after initiating medical treatment.[12] The biomechanical properties of the LC in healthy eyes are different from eyes exposed to the chronic stress-strain deformation seen in glaucoma that leads to optic nerve head

remodelling.[21,22] In addition, the IOP reduction achieved by glaucoma eye drops only alters the stress (force per unit area) and strain (proportional deformation) within a limited range[12] given that the Young's modulus of the ONH is higher than other ocular tissues.[23]

In this study, we evaluated the relationship of biomechanical cornea properties to ONH parameters in eyes undergoing a trabeculectomy. We hypothesized that a higher CH would predict a larger ALDC.

Methods

Study design

The protocol of this study was approved by the institutional review board of the Shahid Beheshti University of Medical Science (protocol number: IR.SBMU.ORC.REC.95267) and adhered to the tenets of the Declaration of Helsinki. Informed written consent was obtained from each participant. Patients with uncontrolled primary open angle glaucoma (POAG) on maximum medical treatment and age above 25 years were enrolled in this study. The exclusion criteria consisted of a history of prior ocular surgery, need for a combined cataract procedure, ocular or systemic comorbidities that could affect the corneal biomechanics measurement including corneal opacities and dystrophies, keratectasia, connective tissue disease and uncontrolled diabetes, and pregnancy or nursing. Only one eye of each eligible patient was included chosen randomly by coin flip.

Clinical data acquisition

At baseline, all patients underwent a comprehensive ophthalmic examination including best-corrected visual acuity (BCVA), slit lamp examination, Goldmann applanation tonometry, gonioscopy, and fundus examination. Patients had at least two reliable (less than 33% fixation losses, false negatives, and false positives) on 24-2 standard automated perimetry visual fields (Humphrey visual field analyzer (HVF); model 750; Carl Zeiss Meditec, Dublin, California, USA) before the operation. We collected the mean deviation (MD) from the HVF. To detect any changes in visual function after surgery, we defined a 3 dB change in mean deviation (MD) as the cutoff point for detecting a change in the visual field.[24]
Baseline axial length and central corneal thickness were measured with a modified Michelson interferometer that uses infrared laser light (IOLMaster, Carl Zeiss Meditec, Dublin, California, USA).

Before the surgery, corneal biomechanical properties including CH and corneal resistance factor (CRF) were obtained by ORA. Three measurements were obtained for each eye, and the average of

these measurements was considered for final analysis. Measurements with a waveform score above 5 were included.

Spectral domain optical coherence tomography (SDOCT, Spectralis; Heidelberg Engineering, Heidelberg, Germany) measurements were performed after dilation with 1% tropicamide, using an enhanced depth mode by the same operator. The single line scan width produced by the Spectralis OCT is 8.9 mm long including 1024 A-scans per B-scan and 25 B-scan per second. Six high-resolution radial scans were centered on the ONH. Since the images had the fixed size but different magnification, all the exported images were rescaled to 1:1 pixel using a customized computer program developed in Matlab (R2010a, the MathWorks, Inc., Natick, MA). On each radial scan, Bruch's membrane opening (BMO) was identified and connected by a line as a reference line[25] and multiple points were marked on this line with an interval of 50 µm. We applied a subjective LC visibility grading[26] that describes the anterior LC as "grade 0" if no part is visible, "grade 1" if less than 25% is visible, "grade 2" for less than 50%, "grade 3" for less than 75%, and "grade 4" for greater than 75% is visible. Only scans with LCVG ≥ 3 were considered for inclusion. The mean of vertical lines from marked points on the reference line to the anterior surface of the LC was designated as the anterior lamina cribrosa depth (ALD). The difference between the pre- and postsurgical ALD was called LC displacement (ALDC). The prelaminar tissue thickness (PLTT) for each point was defined as the difference between the perpendicular distance from the reference line to the overlapping en face prelaminar tissue surface and anterior lamina cribrosa border. The LC thickness (ALD) was the difference between the perpendicular distance from anterior and posterior LC border at each point.

Surgical technique

After a peribulbar injection of 2 mL 2%lidocaine (Lignidic 2%, Caspian Tamin Pharmaceutical Co., Rasht, Iran), the cul-de-sacs was irrigated with povidone-iodine and normal saline solution followed by sterile draping and insertion of the lid speculum. 0.1 mL of mitomycin C 0.01% (MMC, Mitomycin C Kyowa, Kogyo Company, Tokyo, Japan) was injected into the subtenon space in the superior cul-de-sac and diffusely spread with a blunt spatula over the superior conjunctiva; a Weck-Cel was used to prevent anterior migration of the MMC limiting it to the area covered by the upper lid. The conjunctival peritomy was performed at the superior to superonasal quadrant for 1.5-2 clock hours followed by blunt dissection of Tenon's one minute after MMC injection. The operation field was copiously irrigated with balanced salt solution (BSS). A 3.0×4.0 mm trapezoidal half-thickness scleral flap was created using a crescent knife followed by lamellar dissection of the scleral flap 1 mm into clear cornea. After fashioning a sideport, the anterior chamber was entered underneath the scleral flap with

a keratome, and the incision was squared off with the sideport knife. An anterior tissue block that included clear cornea was removed with a Kelly punch, and a peripheral iridectomy was performed using Vannas scissors. The scleral flap was tied down with two 10-0 nylon releasable sutures, the knots were buried, and the conjunctiva was closed with two 10-0 nylon wing sutures. At the conclusion of surgery, 50mg cefazolin (Cefazolin 500, Exir pharmaceutical, Tehran, Iran) and 2mg of betamethasone (Betazone, Caspian Tamin Pharmaceutical., Rasht, Iran) were given into the inferior fornix. Postoperatively, patients were seen on a weekly basis for one month and then monthly up to three months. The comprehensive eye exam was performed at each postoperative visit. The EDI-OCT was repeated one month and visual field three and six months after the surgery.

Results

A total of 100 patients were enrolled in this study and 81 were included. Fourteen were excluded for a low LCVG and five lost to follow-up. All patients were phakic from the beginning to the end of the study. The mean age of study participants was 61.0±13.3 years, and 44 (54.3%) of the patients were male (P=0.901). The demographic data are presented in Table 1. The mean preoperative IOP was 22.8±5.1 mmHg on 3.1±0.9 medications and decreased to 8.6±2.5 mmHg at the three-month follow-up (Table 2, P <0.001). The baseline visual acuity was 0.5±0.5 logMAR and decreased to 0.6±0.5 logMAR at final follow-up (P <0.001) while the HVF MD changed from -17±5 dB at baseline to -16±6 dB at final follow-up (P=0.23). Lamina cribrosa thickness (LCT) and BMO remained unchanged (Ps= 0.398 and 0.234, respectively) but PLTT increased from 47±12 µm at baseline to 52±12 µm (p<0.001). Also, ALD decreased from 366±167 µm at baseline to 324±165 µm at the one-month follow-up (P=<0.001, Table 2). CH was correlated with CRF (regression coefficient: 0.918, P<0.001) as well as baseline HVF mean deviation (regression coefficient: -0.234, P= 0.041). There was no correlation between CH and other parameters like the baseline LCT, visual acuity, axial length, changes in IOP, ALDC, and changes in MD. Parameters associated with a deeper ALD were the cup-disk ratio (regression coefficient: 0.07, P= 0.04), baseline IOP (regression coefficient: -.276, P= 0.01), CH (regression coefficient: -0.523, P= 0.001), and CRF(regression coefficient: -0.509, P= 0.001). Scatter plots of relevant covariates significant correlations with ALDC are shown in Figure 1. ALDC was correlated to a younger age (regression coefficient: - 0.224, P=0.04), a larger IOP reduction (regression coefficient: 0.251, P=0.02), a lower baseline cup-disk ratio was correlated with larger LC displacement after the surgery (regression coefficient: -0.212, P= 0.05).

LC displacement was not associated with sex, corneal biomechanical properties, axial length, corneal thickness, and ALD (Figure 2). Highly hyperopic or myopic eyes were not included in this study. The range was 20 to 25 mm with a median of 23 mm.

Improvement of visual field was detected in eight (9.8%) eyes three months following the surgery. MD improvement was correlated with a more extensive ALDC (regression coefficient: -0.18, P= 0.04, Figure 1). As is presented in Table 3, only ALDC was significantly associated with improvement of the visual field.

Discussion

Our understanding of glaucomatous optic neuropathy has evolved to include complex biomechanical stress-strain cycle modeling.[4] The examination of IOP-induced lamina cribrosa movements is receiving increasing interest because they reveal important aspects of biomechanical LC properties[4,27] and can be measured *in vivo*.[17] CH is associated with the development and progression of glaucoma independent of corneal thickness and intraocular pressure.[28] The cornea and the sclera contain similar extracellular matrix proteoglycans with comparable viscosities although both are derived from different tissues during ocular development with different collagen fibers.[29] Eyes with a higher CH have been observed to experience a larger posterior LC dislocation with increasing IOP,[13] a larger ALDC following a medical IOP reduction,[12] and more ONH deformation during experimental IOP elevations.[20] We hypothesized that a higher CH would be representative of LC hysteresis and correlated to a larger post-trabeculectomy ALDC.[20] Surprisingly, we found this was not the case in our patients. Sigal discussed that the geometry and mechanical properties of the optic nerve head are highly complex and variably influence each other during IOP-induced stresses and strains.[30] The inclusion of normal participants with healthy loading-unloading cycles and Young's modulus[13] or a smaller, medical IOP reduction[12] may explain these differences. A lower CH has been reported to correlate with glaucoma progression,[31] possibly due to a reduced viscoelastic dissipation of mechanical forces that could harm axons passing through the LC. On the other hand, larger acute ALDCs have been observed with a large CH.[20] Glaucoma is a chronic condition that subjects the LC to the forces of IOP over a long time with an increasing deformation of the LC that becomes permanent. LC creep and tissue remodeling may contribute to the pathogenesis of glaucomatous optic neuropathy. The residual plastic biomechanical deformation affects the LC stress-strain curve and its displacement after IOP reduction,[32] which also corroborate with less displacement in higher baseline cup-disc ratio as observed in our study. As seen

before, we observed that patients with a larger IOP reduction had a greater ALDC[35–39] which inversely correlated with age.[35,40,41]

We saw an MD improvement in eight (9.8%) patients with a greater ALDC, comparable to previous reports.[24,42,43] Previous studies showed an improvement in HVF indices between first and second visual fields but not subsequent ones.[44,45] The extent of LCDC reflects the amount of IOP reduction,[35–39] but its clinical importance was not clear. Our study suggests that a negative ALDC may remove some of the strain on the ONH.

There are several limitations to our study. The baseline mean deviation and cup-disk ratio were -17±5 dB and 0.81±0.15, respectively, consistent with mostly advanced glaucoma. In advanced disease it becomes difficult to delineate the border[47] but by using several reference line points as well as the LCVG, we only had to discard 15% of images compared to other studies. [12,48,49]

In summary, age, baseline cup-disc ratio, and magnitude of IOP reduction were correlated to the extent of anterior lamina cribrosa displacement after trabeculectomy but corneal biomechanical properties were not. The visual field mean deviation improved more commonly after a larger anterior lamina cribrosa displacement.

Acknowledgements

We acknowledge support from NIH CORE Grant P30 EY08098 to the Department of Ophthalmology, from the Eye and Ear Foundation of Pittsburgh, and from an unrestricted grant from Research to Prevent Blindness, New York, NY

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Tables

Table 1

Table 1. Demographics and ocular characteristics

Parameter		Value
age	Mean±SD	61.98±13.28
sex	male	44 (54.3%)
	female	37 (45.7%)
Baseline medications	Mean±SD	3.14±0.85
	Median (range)	3 (1 to 4)
C/D ratio	Mean±SD	0.81±0.15
AL	Mean±SD	23±1
	Median (range)	23 (20 to 25)
CCT	Mean±SD	539±32
	Median (range)	542 (432 to 632)
CH	Mean±SD	11±2
	Median (range)	11 (6 to 14)
CRF	Mean±SD	10±1
	Median (range)	11 (7 to 14)

AL: axial length, CCT: central corneal thickness, C/D ratio: cup-disk ratio, CH: corneal hysteresis, CRF: CRF.

Table 2. Changes in study parameters after intervention

	Pre	Post		95% CI		
	Mean ± SD	Mean ± SD	Diff	Lower	Upper	P
BCVA (logMAR)	0.49 ± 0.52	0.55 ± 0.53	-0.06	-0.08	-0.04	<0.001
IOP (mmHg)	22.77 ± 5.14	8.56 ± 2.5	14.2	13	15.4	<0.001
MD (dB)	-17 ± 5	-16 ± 6	-1	-1	0	0.23
LCT (microns)	141 ± 17	142 ± 18	-1	-4	1	0.39
PLTT (microns)	47 ± 12	52 ± 12	1	1	2	<0.001
BMO (microns)	486 ± 57	485 ± 57	3	2	5	0.234
ALD (microns)	366 ± 167	324 ± 165	42	29	55	<0.001

BCVA: best corrected visual acuity, IOP: intraocular pressure, MD: mean deviation, LCT: lamina cribrosa thickness, PLTT: prelaminar tissue thickness, BMO: Bruch's membrane opening, ALD: anterior lamina cribrosa depth.

Table 3

Table 3. Study variables difference between two groups with and without 3 dB MD improvement

Parameter	Time	No MD improvement	MD improvement	Diff	95% CI		P
		Mean ± SD	Mean ± SD		Lower	Upper	
BCVA logMAR)	Pre	0.52 ± 0.56	0.39 ± 0.35	-0.13	-0.42	0.16	0.375
	Post	0.6 ± 0.57	0.45 ± 0.34	-0.14	-0.44	0.15	0.332
	Change	0.07 ± 0.1	0.06 ± 0.12	-0.01	-0.07	0.05	0.805
MD (dB)	Pre	-17 ± 5	-16 ± 7	1.01	-1.9	3.93	0.491
	Post	-17 ± 5	-12 ± 7	4.95	1.96	7.95	0.002
IOP (mmHg)	Pre	21.88 ± 4.9	22.23 ± 4.3	-1.35	-6.9	-1.71	0.542
	Post	10.56 ± 3.81	9.82 ± 1.5	0.74	-0.63	3.14	0.171
CCT (microns)	Pre	541 ± 34.1	528 ± 27.44	13.26	-4.7	31.22	0.146
AL (millimeters)	Pre	22.97 ± 0.99	23.73 ± 1.07	-0.75	-1.131	-0.2	0.008
CH	Pre	10.6 ± 1.59	10.09 ± 1.87	0.5	-0.4	1.4	0.27
LCT (microns)	Pre	139 ± 10	137 ± 11	-1.3	-14.76	4.15	0.267
	Post	142 ± 19	141 ± 12	-1.07	-10.21	8.82	0.885
BMO (microns)	Pre	488 ± 63	471 ± 34	-17.6	-49.1	14	0.271
	Post	485 ± 63	468 ± 33	-17.1	-48.6	14.4	0.284
ALD (microns)	Pre	348 ± 159	463 ± 176	115.9	26.86	204.98	0.011
	Post	324 ± 168	344 ± 173	19.4	-73.24	112.08	0.677
	Change	-23.2 ± 37.6	-119.7 ± 60.0	-96.5	-120.24	-72.75	<0.001

BCVA: best corrected visual acuity, MD: mean deviation, IOP: intraocular pressure, CCT: central corneal thickness, AL: axial length, CH: corneal hysteresis, LCT: lamina cribrosa thickness, BMO: Bruch's membrane opening, ALD: anterior lamina cribrosa depth.

Figures

Figure 1

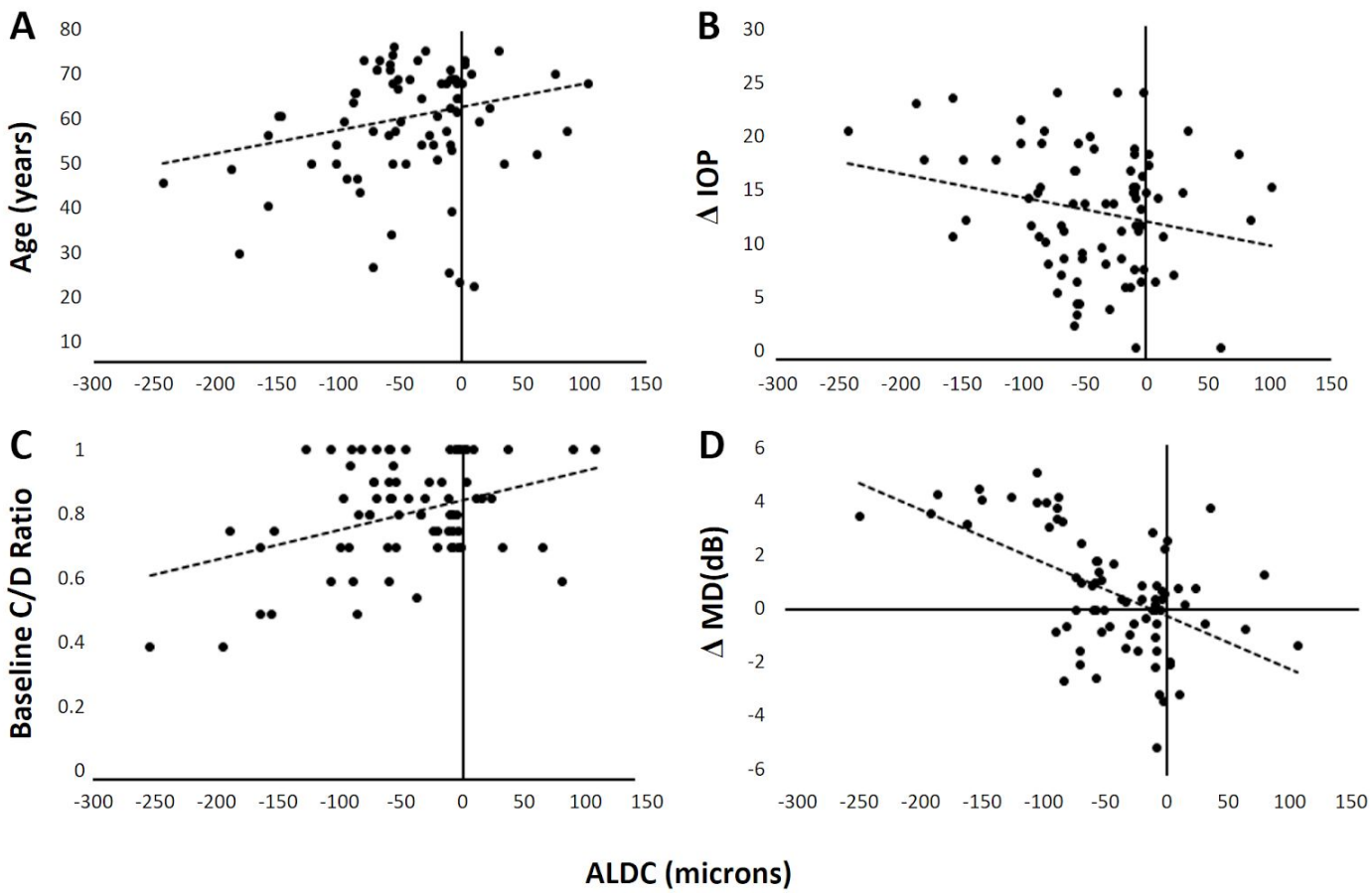

Figure 1: Scatter plot and regression line of following outcomes: A) lamina cribrosa displacement (ALDC) resulted negatively correlated to age, regression coefficient: - 0.224, P=0.04. B) ALDC was positively correlated with the amount of IOP reduction, regression coefficient: 0.251, P=0.02. C) ALDC was large in eyes with lower baseline cup-disk (C/D) ratio, regression coefficient: -0.212, P= 0.05. D) ALDC was positively associated with improvement in MD, regression coefficient: -0.18, P= 0.04.

Figure 2

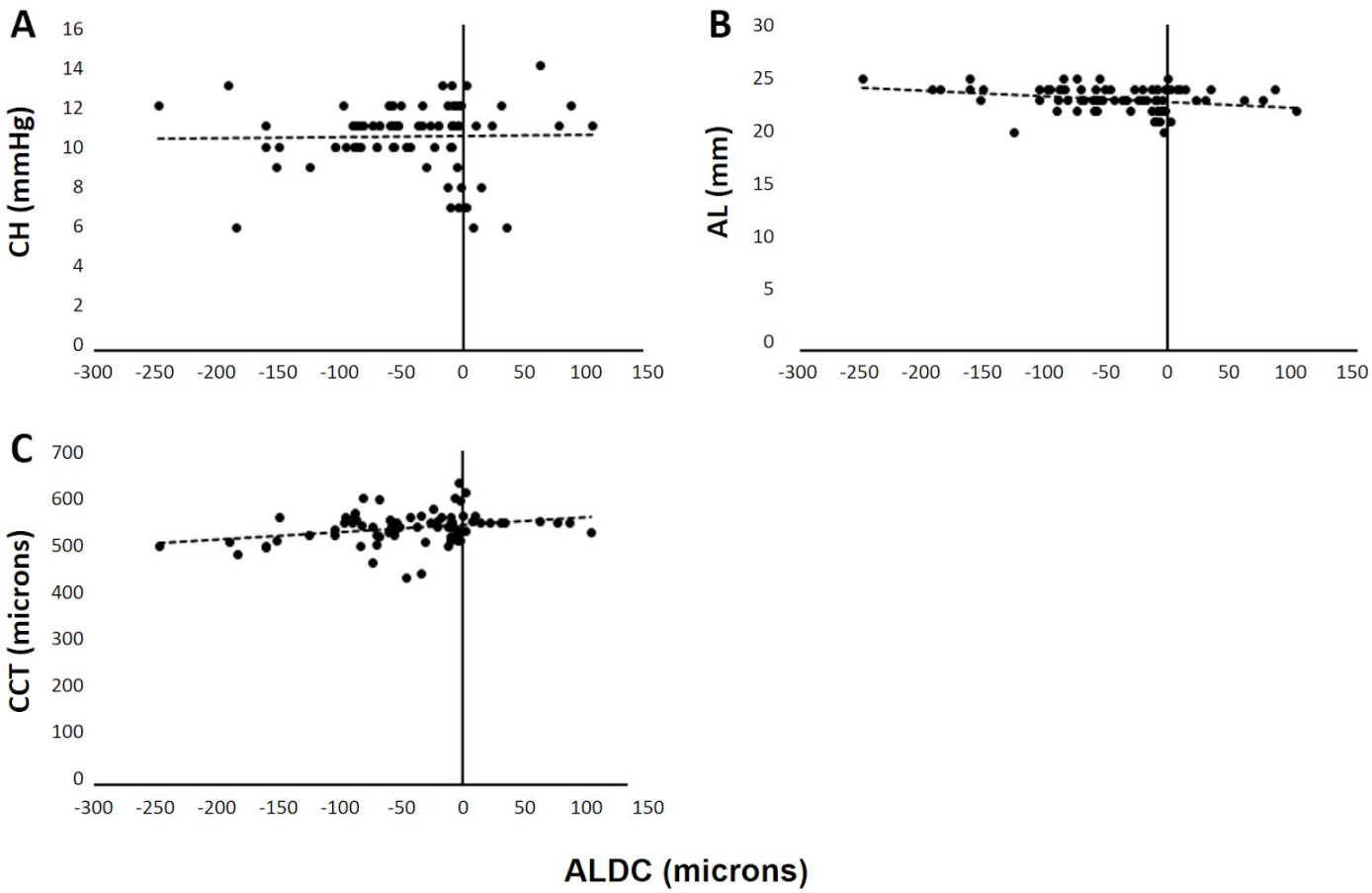

Figure 2: Scatter plot and regression line of following outcomes A) there was no correlation between ALDC and corneal hysteresis (CH), regression coefficient: 0.076, P=0.58. B) ALDC was not associated with baseline axial length of the eye, regression coefficient: -0.049, P= 0.69. C) there was no association between central corneal thickness (CCT) and ALDC, regression coefficient: 0.288, P= 0.09.