

1   **Changes choroidal area following trabeculectomy: long-term effect of intraocular**  
2   **pressure reduction**

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23     **Abstract**

24     **Purpose:** To investigate the long-term effects of intraocular pressure (IOP) changes  
25     after trabeculectomy on the macular and peripapillary choroidal areas.

26     **Methods:** This prospective longitudinal study examined 30 eyes of 30 patients with  
27     glaucoma that was uncontrolled by medical therapy. At 1 day before and at 1 year after  
28     the trabeculectomy surgery, macular and peripapillary choroidal images were recorded  
29     by enhanced depth imaging optical coherence tomography (EDI-OCT). Luminal and  
30     interstitial areas were converted to binary images using the Niblack method. Factors  
31     influencing the macular choroidal and peripapillary area were examined by multivariate  
32     analysis.

33     **Results:** After trabeculectomy, the mean IOP was  $10.8 \pm 3.2$  mmHg compared to  
34      $17.8 \pm 7.2$  mmHg at baseline ( $P < 0.001$ ). The total macular choroidal area after the  
35     surgery increased from  $317,735 \pm 77,380$  to  $338,120 \pm 90,700 \mu\text{m}^2$ , while the interstitial  
36     area increased from  $108,598 \pm 24,502$  to  $119,172 \pm 31,495 \mu\text{m}^2$  (all  $P < 0.05$ ). The total  
37     peripapillary choroidal area after the surgery also increased from  $1,557,487 \pm 431,798$  to  
38      $1,650,253 \pm 466,672 \mu\text{m}^2$ , while the interstitial area increased from  $689,891 \pm 149,476$  to  
39      $751,816 \pm 162,457 \mu\text{m}^2$  (all  $P < 0.05$ ). However, there were no significant differences  
40     observed in the luminal area before and after the surgery. A decrease in the IOP was  
41     among the factors associated with the changes in the peripapillary choroidal area.

42     **Conclusions:** IOP reductions after trabeculectomy led to increases in the macular and  
43     peripapillary choroidal areas for at least 1 year postoperative. Increases in the interstitial  
44     areas were the primary reason for observed changes in the choroidal area after  
45     trabeculectomy.

## 46 **Introduction**

47 As metabolic support for the prelaminar portion of the optic nerve head is provided by  
48 the choroid,<sup>1-3</sup> this suggests that it may play an important role in glaucoma.<sup>4-6</sup> Even  
49 though indocyanine green angiography has traditionally been used to visualize  
50 choroidal vasculature,<sup>7</sup> other methods, such as optical coherence tomography (OCT)  
51 have also been used to study choroidal morphology. However, potential problems with  
52 these previous methods have led to the development of the enhanced depth imaging  
53 (EDI) spectral domain OCT method, which makes it possible to perform *in vivo*  
54 cross-sectional imaging of the choroid.<sup>8</sup>

55 The exact mechanism of glaucomatous optic neuropathy remains unknown,  
56 even though glaucoma is one of the leading causes of blindness worldwide. As it has  
57 been shown that progression of glaucoma is due to an elevated intraocular pressure  
58 (IOP), many studies have demonstrated the benefit of decreasing the IOP.<sup>9,10</sup> In order to  
59 reduce the IOP in glaucoma, trabeculectomy has been used and remains one of the most  
60 commonly performed filtration surgeries. Several investigations have reported increases  
61 in the subfoveal and peripapillary choroidal thicknesses in primary open-angle  
62 glaucoma (POAG) and in primary angle closure glaucoma (PACG) after  
63 trabeculectomy-caused IOP reductions.<sup>11-13</sup> Zhang et al.<sup>14</sup> recently found that the  
64 approximately equal increases in intravascular and extravascular compartments were  
65 related to increases in the choroidal thickness that occur after trabeculectomy.  
66 Measurements of the choroidal thicknesses in these previous studies were performed at  
67 1.7 mm superior, temporal, inferior, and nasal to the optic disc center and at 1 and 3 mm  
68 nasal, temporal, superior, and inferior to the fovea. However, our recent investigation  
69 examined a 1,500  $\mu$ m wide macular choroidal area and a 1.7 mm area around the optic  
70 nerve disc center in the peripapillary choroidal area.<sup>15,16</sup> In contrast to other previous  
71 studies, our use of an increased measurement area made it possible to collect greater  
72 amounts of information from the choroid. Furthermore, we recently found that the

73 increases that occurred at 2 weeks after trabeculectomy in the macular and peripapillary  
74 choroidal areas due to increases in the luminal areas were related to the reduction in the  
75 IOP that occurred after the surgery.<sup>15</sup> However, there is also the possibility that this  
76 increase could have been associated with inflammation. To definitively determine the  
77 effect of IOP changes on the choroidal area, a long-term follow-up is required.  
78 Therefore, the aim of our current study was to investigate the choroidal area changes  
79 that occurred at 1 year after the initial trabeculectomy.

80

## 81 **Materials and Methods**

### 82 **Subjects**

83 Between July 2016 and February 2017, this prospective longitudinal study evaluated the  
84 eyes of patients who underwent trabeculectomy treatments at Kagawa University  
85 Hospital. Written informed consent was provided by all enrolled subjects in accordance  
86 with the principles outlined in the Declaration of Helsinki. The Kagawa University  
87 Faculty of Medicine Institutional Review Board approved the study protocol. In  
88 addition, prior to patient enrollment, all patients signed the standard consent required  
89 for surgery and provided written informed consent to participate in this research study.

90 This study enrolled all glaucoma patients who had uncontrolled IOP while  
91 taking maximally tolerated medication. After enrollment, all subjects underwent visual  
92 examinations that included slit lamp, gonioscopy, refraction, and central and peripheral  
93 fields. Fornix-based trabeculectomy was performed in all of the patients by one surgeon  
94 (KH). Patients enrolled in the study were required to have a spherical refraction within  
95  $\pm 6.0$  diopters (D) and a cylinder within  $\pm 2.0$  D. Exclusion criteria included having any  
96 history of retinal diseases (e.g., diabetic retinopathy, macular degeneration, retinal  
97 detachment), having previously undergone laser therapy, exhibited poor image quality  
98 due to unstable fixation, or being found to have severe media opacities. Patients having  
99 a previous treatment history with medications known to affect retinal thickness

100 (intravitreal anti-VEGF therapy) were also excluded from the study. EDI-OCT  
101 examinations in all of the cases were performed by the same investigator.

102

### 103 **EDI-OCT**

104 At 1 day before and 1 year after the surgery, the Heidelberg Spectralis (Heidelberg  
105 Engineering, Heidelberg, Germany) with the EDI-OCT technique was used to obtain the  
106 macular or peripapillary choroidal images. Measurements were done between  
107 1300-1500 hours. To perform the macular region scans, seven horizontal lines of 30 ×  
108 10° through the center of the fovea were used. Scans of the peripapillary region used a  
109 360°, 3.4 mm diameter circle scan that was centered on the optic disc. To obtain each  
110 image, an eye tracking system was used, with the best quality image from at least three  
111 scans chosen for the subsequent analysis. The area found between the outer portion of  
112 the hyperreflective line that corresponded to the retinal pigment epithelium (RPE) and  
113 the inner surface of the sclera was defined as the choroidal thickness. In line with the  
114 methodology of our previous studies, a masked procedure was used for all of the  
115 measurements.<sup>15,16</sup> All eyes were examined without mydriasis.

116

### 117 **Binarization of the choroid EDI-OCT images**

118 After performing the EDI-OCT evaluation and masking the best images, these images  
119 were then displayed on a computer screen. Each of the images were evaluated by one of  
120 the authors (HK). Binarization of the choroidal area in each of the EDI-OCT images  
121 was performed using the previously described modified Niblack method.<sup>14</sup> Briefly, the  
122 EDI-OCT image was first analyzed using ImageJ software (version 1.47, NIH,  
123 Bethesda, MD). For this analysis, we examined a 1,500 μm wide area of the macular  
124 choroid that extended vertically to the fovea with 750 μm nasal and 750 μm temporal  
125 margins. The ImageJ ROI Manager determined the area to be analyzed, which included  
126 a 1.7 mm area that was located around the optic nerve disc center and spanned from the

127 retinal pigment epithelium to the chorioscleral border. After we randomly selected 3  
128 choroidal vessels with lumens  $> 100 \mu\text{m}$  through the use the Oval Selection Tool on the  
129 ImageJ tool bar, the reflectivities of the lumens were then averaged. The average  
130 reflectivity was set as the minimum value in order to reduce the noise in the OCT  
131 image. After conversion and adjustment of the image to 8 bits via the use of the Niblack  
132 Auto Local Threshold, the binarized image was once again converted to an RGB image.  
133 Both the binarization procedures and the automated calculations by the ImageJ software  
134 require conversions of the images. Determination of the hyporeflective area was  
135 performed using the Threshold Tool, with dark pixels defined as hyporeflective areas,  
136 while light pixels were defined as hyperreflective areas. In order to perform the  
137 automatic calculations of the hyperreflective and hyporeflective areas, it was necessary  
138 to first add data on the relationship between the distance on the fundus and the pitch of  
139 the pixels in the EDI-OCT images, which is dependent on the axial length.

140

## 141 **Statistical analysis**

142 All statistical analyses were performed using SPSS for Windows (SPSS Inc., Chicago,  
143 IL). A paired *t*-test was used to compare the preoperative and postoperative values.  
144 Pearson's correlation coefficient was used to evaluate the correlation between the  
145 choroidal area changes, and the correlations among the choroidal area, systolic blood  
146 pressure (SBP), diastolic blood pressure (DBP), IOP, age, and axial length. A  
147 subsequent multivariate regression analysis was performed using variables that had a  
148 Pearson's correlation coefficient value of  $P < 0.2$ . The choroidal area was defined as the  
149 dependent parameter for the multivariate analysis, while the independent parameters  
150 included the other parameters selected by the Pearson's correlation coefficient and the  
151 choroidal area.  $P < 0.05$  was considered statistically significant. All statistical values are  
152 presented as the mean  $\pm$  standard deviation (SD).

153

154 **Results**

155 Table 1 shows the clinical characteristics of the 30 eyes of 30 patients enrolled in the  
156 study. The mean age of the patients was  $68.9 \pm 9.0$  years (range: 50 to 87 years).

157

158 Table 1. Patient demographic and clinical data

Age (years)	$68.9 \pm 9.0$
Gender (M/F)	
Glaucoma type	
Primary-open angle glaucoma	12
Normal-tension glaucoma	9
Primary angle-closure glaucoma	4
Secondary glaucoma	3
Exfoliation glaucoma	2

159

160 The mean IOP decreased from  $17.8 \pm 7.2$  to  $10.8 \pm 3.2$  mmHg ( $P < 0.001$ ), while  
161 the mean OPP increased from  $45.2 \pm 11.3$  to  $57.0 \pm 9.2$  mmHg ( $P < 0.001$ ; Table 2) after  
162 the trabeculectomy. After the surgery, the axial length decreased from  $24.5 \pm 1.5$  mm  
163 before surgery to  $24.2 \pm 1.4$  mm after the surgery ( $P < 0.001$ ; Table 2).

164

165 Table 2. IOP, BP, OPP and axial length before and after trabeculectomy

	Before	After	P value
IOP (mmHg)	$17.8 \pm 7.2$	$10.8 \pm 3.2$	$<0.01$
BP (mmHg)			
Systolic	$127.5 \pm 19.8$	$138.2 \pm 17.8$	0.02
Diastolic	$78.0 \pm 13.9$	$84.5 \pm 13.2$	0.07
OPP (mmHg)	$45.2 \pm 11.3$	$57.0 \pm 9.2$	$<0.01$
Axial length (mm)	$24.5 \pm 1.5$	$24.2 \pm 1.4$	$<0.01$

166 IOP; intraocular pressure, BP; blood pressure,

167 OPP; ocular perfusion pressure

168

169 After the surgery, the macular choroidal area increased, with the total area  
170 increasing from  $317,735 \pm 77,380$  to  $338,120 \pm 90,700 \mu\text{m}^2$ , while the interstitial area  
171 increased from  $108,598 \pm 24,502$  to  $119,172 \pm 31,495 \mu\text{m}^2$  (all  $P < 0.05$ , Table 3). The

172 peripapillary choroidal area also exhibited increases after the surgery, with the total area increasing from  $1,557,487 \pm 431,798$  to  
173  $1,650,253 \pm 466,672 \mu\text{m}^2$ , while the interstitial area increased from  $689,891 \pm 149,476$  to  $751,816 \pm 162,457 \mu\text{m}^2$  (all  $P < 0.05$ ). However,  
174 no significant differences were noted for the luminal area before and after the surgery.

175

176 Table 3. Choroidal area observed on EDI-OCT images before and after surgery

	Macula			Peripapilla		
	Before	After	P value	Before	After	P value
Total area ( $\mu\text{m}^2$ )	$317,735 \pm 77,380$	$338,120 \pm 90,700$	0.03	$1,557,487 \pm 431,798$	$1,650,253 \pm 466,672$	0.03
Luminal area ( $\mu\text{m}^2$ )	$209,137 \pm 56,767$	$218,948 \pm 61,424$	0.15	$867,596 \pm 301,209$	$898,437 \pm 312,174$	0.28
Interstitial area ( $\mu\text{m}^2$ )	$108,598 \pm 24,502$	$119,172 \pm 31,495$	0.01	$689,891 \pm 149,476$	$751,816 \pm 162,457$	0.001

177

178 A positive correlation was observed for the magnitude of change between the macular choroidal area and the OPP ( $r = 0.44$ ,  $P =$   
179 0.02; Table 4). However, there was no observed correlation for the magnitude of the change between the macular choroidal area and the  
180 IOP reduction ( $r = -0.32$ ,  $P = 0.09$ ). In contrast, a negative correlation was observed for the magnitude of the change between the  
181 peripapillary choroidal area and the IOP reduction ( $r = -0.58$ ,  $P < 0.01$ ; Table 5).

182 Factors that could potentially influence the increases observed in the macular or peripapillary choroidal area were also  
183 investigated. Table 6 presents the results of the multivariate analyses for each parameter. These findings showed that there were no  
184 significant correlations observed for the changes in the macular choroidal area. However, our analyses did find that there was a  
185 significant association between the changes in the IOP and those in the peripapillary choroidal area (Table 7).

186 Table 4. Pearson's correlation between changes in the  
187 magnitude for the macular choroidal area and each factor

	r	P value
Age	-0.27	0.89
Changes in SBP	0.34	0.08
Changes in DBP	0.20	0.30
Changes in IOP	-0.32	0.09
Changes in AL	-0.33	0.11

188 SBP: Systolic blood pressure, DBP: Diastolic blood pressure,

189 IOP: Intraocular pressure, AL: Axial length

190

191 Table 5. Pearson's correlation between the magnitude  
192 change for the peripapillary choroidal area and each factor

	r	P value
Age	0.12	0.52
Changes in SBP	0.26	0.19
Changes in DBP	0.03	0.87
Changes in IOP	-0.58	<0.01
Changes in AL	-0.40	0.05

193 SBP: Systolic blood pressure, DBP: Diastolic blood pressure,

194 IOP: Intraocular pressure, AL: Axial length

195

196 Table 6. Multivariate analysis of the changes in the  
197 association in the subfoveal choroidal area and each factor

	$\beta$	P value
Choroidal area	-0.01	0.98
Changes in SBP	0.31	0.17
Changes in IOP	-0.31	0.19
Changes in AL	-0.26	0.28

198 SBP: Systolic blood pressure, IOP: Intraocular pressure,

199 AL: Axial length

200

201 Table 7. Multivariate analysis of the changes in the  
202 Associations in the peripapillary choroidal area and each factor

	$\beta$	P value
Choroidal area	-0.01	0.99
Changes in SBP	0.23	0.23
Changes in IOP	-0.53	0.02
Changes in AL	-0.19	0.36

203 SBP: Systolic blood pressure, IOP: Intraocular pressure,

204 AL: Axial length

205

## 206 Discussion

207 Our current study demonstrated that there were increases after trabeculectomy in the  
208 long-term subfoveal and peripapillary choroidal areas, with the trabeculectomy also  
209 leading to decreases in the IOP. In addition, we also determined that there were  
210 increases in both the macular and peripapillary choroidal areas, which led to an increase  
211 in the interstitium of the choroid.

212 Kara et al.<sup>11</sup> reported that at 1 month after trabeculectomy there was a large  
213 decrease in the IOP that subsequently led to choroidal thickening. Kadziauskiene et al.<sup>13</sup>  
214 additionally found that the increase in the subfoveal and peripapillary choroidal  
215 thickness that occurred after the trabeculectomy for at least 6 months postoperatively  
216 was correlated with greater IOP reduction and axial length shortening. Furthermore, we  
217 recently reported that the increases in the macular and peripapillary choroidal areas that  
218 were caused by the reduction in the IOP at 2 weeks after trabeculectomy were correlated  
219 with the subsequent changes in the IOP.<sup>15</sup> In contrast, although there were short-term (7  
220 days) increases in the choroidal thickness following trabeculectomy in PACG, these  
221 changes were found not to be related to either a decrease in the IOP or shortened axial  
222 length.<sup>12</sup> Usui et al.<sup>17</sup> additionally reported that while the choroid was thicker, the axial  
223 length was shorter, and the IOP was lower at 6 days after trabeculectomy, there was no  
224 correlation in POAG patients for the IOP changes and the changes in the choroidal  
225 thickness at the subfovea. Moreover, during the early stages following trabeculectomy,  
226 there was no significant change in the choroidal thickness in accordance with the  
227 decreasing IOP. However, for at least 1 year after the trabeculectomy, the increase in  
228 the choroidal area (thickness) that occurred after a large decrease in the IOP was  
229 correlated with the IOP reduction during the late stages.

230 We previously reported that increases in the luminal areas that led to increases  
231 in the macular and peripapillary choroidal areas were related to reductions in the IOP

232 that occurred at 2 weeks after trabeculectomy.<sup>15</sup> In the current study, however, increases  
233 in the interstitial areas that led to increases in the macular and peripapillary choroidal  
234 areas were due to a reduction in the IOP at 1 year after the initial trabeculectomy.  
235 Furthermore, our previous study showed that the rate of increase in the macular  
236 choroidal interstitial area or luminal area at 2 weeks after trabeculectomy was 111.2%  
237 or 118.6%, respectively, while the rate of increase for the peripapillary choroidal  
238 interstitial area or luminal area was 112.0% or 128.2%, respectively.<sup>15</sup> In contrast, the  
239 rate of increase in the macular choroidal interstitial area or luminal area at 1 year after  
240 trabeculectomy was 109.1% or 104.7%, respectively, while the rate of increase for the  
241 peripapillary choroidal interstitial area or luminal area was 109.0% or 103.5%,  
242 respectively. Zhang et al.<sup>14</sup> additionally reported that at 6 months after the  
243 trabeculectomy, choroidal thickness increases were observed in conjunction with  
244 decreasing IOP in both the large choroidal vessels and interstitium of the choroid.  
245 Furthermore, the luminal area returned to the originally observed size seen prior to the  
246 surgery even though the IOP reduction at 1 year after the trabeculectomy caused an  
247 increased choroidal area. Another recent study that examined choroidal vessels, also  
248 reported finding that the luminal area changed in accordance with the diurnal  
249 variation.<sup>18</sup> Thus, this suggests that changes could easily occur in the luminal area.  
250 Moreover, other studies have reported that the ocular blood flow increases seen after  
251 trabeculectomy can also potentially contribute to thickening of the choroid.<sup>11,19</sup>  
252 Therefore, the question that needs to be answered is, do increases in the ocular blood  
253 flow still occur even after a return of the luminal area to its pre-surgery size? However,  
254 since we did not measure the ocular blood flow, it was not possible to determine this in  
255 our current study. Further studies that examine the blood supply of the optic nerve disc  
256 after IOP reduction following trabeculectomy, especially in the peripapillary area, will  
257 need to be undertaken.

258 There were several limitations for our current study. First, this study only

259 examined a small number of subjects. Thus, a further study with a larger number of  
260 patients will need to be undertaken in order to address this issue. Second, since manual  
261 segmentation cannot achieve perfect reproducibility, a truly objective method would be  
262 preferable in this type of study.

263

## 264 **Conclusions**

265 The present study demonstrated that IOP reduction after trabeculectomy led to an  
266 increase in the macular and peripapillary choroidal areas, with these increases  
267 continuing for at least 1 year. These noted increases were found to be due to an increase  
268 in the interstitial areas. Thus, overall our findings demonstrated that changes in the IOP  
269 were significantly associated with changes in the peripapillary choroidal area.

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