Foveal Structure and Thickness of Retinal Layers Long-Term after Surgical Peeling of Idiopathic Epiretinal Membrane

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PURPOSE. To better understand the long-term effect of idiopathic epiretinal membrane peeling on retinal anatomy, the foveal structure and the thickness of individual retinal layers were analyzed with frequency-domain optical coherence tomography (fdOCT). The long-term postoperative course of macular thickness was followed.

METHODS. fdOCT scans were obtained from the horizontal midline in 33 eyes long-term (mean 46 ± 13 months) after surgery and in 30 eyes of age-matched controls. Raw images were exported, and the thickness of retinal layers was measured with a manual segmentation procedure aided by a customized computer program. Macular thickness was quantified over time with the time-domain (td) OCT Fast Macular Thickness program.

RESULTS. Thickness of retinal layers between the outer nuclear and the ganglion cell plus inner plexiform layers in the horizontal midline of the fovea and the nasal parafovea was greater than normal, whereas that of the RPE, photoreceptor, and retinal nerve fiber layers was not different from controls. Twelve of 33 eyes had a foveal pit though the median foveal shape was distorted. Central macular thickness quantified with tdOCT remained increased, whereas the decrease of nasal macular thickness toward normal values was incomplete and delayed to 35 months after surgery. Superior, temporal, and inferior macular thickness returned to normal 12 to 14 months after surgery.

CONCLUSIONS. Long-term after surgery, the fovea and the nasal parafovea remain thickened between the outer nuclear layer and the ganglion cell layer, whereas the superior, temporal, and inferior macular thickness returns to normal. Long-term observations are required in the assessment of macular recovery from mechanical stress.

OPTICAL coherence tomography (OCT) studies have added to the understanding of the morphologic alterations in IEM. Time-domain OCT (tdOCT) has demonstrated increased retinal thickness of the macula, which decreased significantly after surgical membrane peeling; However, macular thickness after surgery was thicker in the operated compared with the normal unoperated fellow eyes or normal control eyes. Masini et al. found that macular thickness returned to normal in only 3 of 62 eyes and that a foveal pit reappeared in 20 of 62 eyes 3 months after surgery. Absence of a foveal pit did not preclude satisfactory postoperative visual acuity, whereas others found that recovery of a normal foveal contour was associated with good visual acuity 3 months after surgery. It seems clear that after surgery visual acuity continues to improve and retinal thickness decreases over an extended period, but reports on the outcome of surgery are inconsistent. Pesin et al. found that visual acuity continued to improve over a period of slightly less than 1 year after membrane peeling. Others describe improvement of visual acuity during the entire follow-up period of 24 months, but it is unclear whether 24 months is the end point of postoperative recovery. In a retrospective analysis of 16 eyes, the length of time of postoperative foveal thickness decrease was calculated to 109 days. However, previous studies have measured overall macular thickness with tdOCT without detailed investigations of retinal anatomy, and there are no OCT studies with follow-up of more than 1 year. Hence, it is unknown when and to what extent retinal changes caused by IEM eventually return toward a normal anatomy after surgical membrane peeling.

Besides the measurement of total retinal thickness it is now possible to better visualize details of retinal structure and measure individual retinal cellular layers with the newer frequency-domain OCT (fdOCT) technology, which has greater spatial resolution than tdOCT. For example, recently Hood et al. measured the thickness of individual retinal layers in retinitis pigmentosa patients using a similar methodology as in the present study, and reported that retinal nerve fiber layer thickness was greater than normal in retinitis pigmentosa.

To better understand the long-term effect of surgical peeling of IEM on retinal anatomy, we included patients who underwent surgery at least 25 months before testing. We assessed best-corrected visual acuity (BCVA) and used tdOCT to measure macular thickness preoperatively and during the postoperative course. We used fdOCT to measure the long-term postoperative thickness of individual retinal layers and total retinal thickness along the horizontal meridian. Normal eyes of age-matched patients served as controls. Foveal structure was analyzed and compared with BCVA.
Patients, Subjects, and Methods

Preoperative and postoperative BCVA and OCT scans of 33 eyes of 32 patients with IEM and OCT scans of 30 eyes of 29 subjects with normal, healthy vision as an age-matched control group were analyzed. A random selection of patients with IEM who underwent surgery between 2003 and 2007 were scheduled for a visit and tested at the Department of Ophthalmology of the University Medical Center Schleswig-Holstein in Kiel, Germany. The tenets of the Declaration of Helsinki were followed, and all subjects gave written informed consent after a full explanation of the procedures. Approval was obtained from the Institutional Review Board of the University Medical Center Schleswig-Holstein in Kiel, Germany. All subjects were pseudophakic and had clear optical media at the time of testing. Patients were excluded if they had corneal opacities, posterior capsular opacification, glaucoma or other optic nerve diseases, nonidiopathic epiretinal membrane, any maculopathy other than IEM, or a refractive error before cataract surgery greater than ± 6.0 diopters spherical or ± 2.0 diopters cylindrical. Mean ± SD patient age was 75 ± 6 (range, 57–84) years of age. Mean ± SD age of control subjects was 72 ± 6 (range, 59–85) years of age. Mean ± SD last follow-up was 46 ± 13 (range, 25–80) months after surgery. All patients and subjects underwent complete ophthalmic examination, including refraction and BCVA, anterior segment examination, and indirect ophthalmoscopy.

Frequency-Domain OCT

To analyze foveal structure and thickness of individual retinal layers, all patients and subjects were scanned with fdOCT (Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany) using the eye-tracking feature. All patients were scanned at last follow-up. High-resolution macular volume scans were acquired with 19 horizontal 6-mm B-scans (1536 A-scans per B-scan) with a distance of 240 μm. Each B-scan was averaged from 51 automated real-time scans. We segmented a scan along the horizontal meridian chosen from among the scans for each person. Each person had one or more horizontal scans through the midline as a 6-mm scan as part of the macular volume scan. If more than one scan was available, the scan of the highest quality was chosen. The segmentation data are shown for 6-mm volume scan. If more than one scan was available, the scan of the highest quality was chosen. The segmentation data are shown for 6-mm volume scan. If more than one scan was available, the scan of the highest quality was chosen.

Segmentation Procedure

A digital image (.png) of the foveal scan was exported from the analysis window of the fdOCT machine. Segmentation of the retinal layers was made by hand (aided by a program written in C+++, using wxWidgets GUI library and SQLite database). The experienced operators (FT and NW) marked the boundaries of the layers by clicking on points along the boundaries of interest. The program drew a curve through these points using either linear or cubic spline interpolation. The two operators (FT and NW) segmented each scan. After a training period in which the two operators (FT and NW) discussed the boundaries of a sample set of scans with the senior author, they independently marked the boundaries of the layers. There was good agreement between the two measurements.

Segmentation of Retinal Layers

Eight boundaries labeled a through g (Figs. 1B, 1C) were identified and labeled as follows: a, vitreous/retinal nerve fiber layer (RNFL); b, RNFL/retinal GCL; c, IPL/inner nuclear layer (INL); d, INL/OPL; e, OPL/outer nuclear layer (ONL); f, ONL/external limiting membrane (ELM); g, Bruch’s membrane/choroid. Using the locations of these boundaries, we identified six retinal layers and total retinal thickness: total retinal thickness is the distance between a and g; RNFL is the distance between a and b; retinal GCL plus IPL (RGC+IPL) is the distance between b and c; INL is the distance between c and d; OPL is the distance between d and e; ONL is the distance between e and f; photoreceptor inner and outer segment plus retinal pigment epithelium (RPE)-Bruch’s membrane (IS/OS+RPE) is the distance between f and g.

The thickness of the six layers and the total retinal thickness were calculated by computing software evaluating the interpolated boundary curves at 100 equidistant positions and calculating the vertical differences of successive boundaries.

Time-Domain OCT

tdOCT was used only for the postoperative longitudinal analysis of macular thickness. Scanning was performed (Stratus OCT III; Zeiss, Jena, Germany) before surgery and at various times for up to 80 months after surgery.

The scanning protocol used for this study was the standard Fast Macular Thickness program used in clinical practice, which creates a retinal map algorithm consisting of six radiating cross-sectional scans, each 6 mm long, and produces a circular plot in which the foveal area is a central circular field of 1-mm diameter. Superior, nasal, inferior, and temporal parafoveal zones represent annular bands in these respective sectors. There are two concentric fields, the first with a diameter of 3 mm and the second with a diameter of 6 mm. The nine OCT zones have been called Early Treatment Diabetic Retinopathy Study (ETDRS)-type regions because of their similarity to the grading template of photographs used in the ETDRS. For the purpose of this study, the first concentric field was analyzed (Fig. 2F). Retinal thickness data were averaged by computer in all five subfields.

Surgical Procedure

The standardized surgical procedure consisted of standard 20-gauge, 3-port pars-plana vitrectomy including the induction of a posterior

Figure 1. Segmentation of the retinal layers. (A) fdOCT fundus image showing 6-mm horizontal single scan line. The scan through the fovea (red) was chosen for analysis. (B) Horizontal scan of a control eye demonstrating the normal anatomy of the retinal layers. (C) The same scan as in (B) showing the segmentation of the retinal layers for analysis: (a) vitreous/RNFL; (b) RNFL/retinal GCL; (c) IPL/INL; (d) INL/OPL; (e) OPL/ONL; (f) ONL/ELM; (g) Bruch’s membrane/choroid.
vitreous detachment. Balanced salt solution (Alcon, Fort Worth, TX) was used as an irrigation solution. All patients underwent surgery without the aid of vital stains. The IEM was engaged with intraocular forceps to create a flap and then was peeled in a circular capsulorrhexis fashion in the entire macula. After removal of the IEM, the internal limiting membrane (ILM) was identified and peeled in all eyes. Four eyes were pseudophakic at the time of surgery; 24 phakic eyes underwent concomitant standard small-incision phacoemulsification cataract surgery with implantation of an acrylic intraocular lens (Sensar AR40e; AMO, Abbott Park, IL), and five eyes underwent standard cataract surgery 1 to 16 months after vitrectomy.

Statistical Analysis

Reference values from normal control eyes were described by quantiles (3%, 50%, 97%; Figs. 3, 4). Differences of thickness were considered significant in areas in which the CIs did not overlap (Fig. 5). Longitudinal data of retinal thickness in each subfield of the tdOCT Fast Macular Thickness program were analyzed by nonlinear mixed-model regression before surgery and for up to 48 months after surgery. A reference interval (Fig. 2) was derived from box-whisker analysis of the normal control eyes (median value and the lowest/highest value within 1.5 times the interquartile range of the lower/upper quartile). Arrows: time points when the regression entered the reference interval. (A) Retinal thickness of the central subfield did not return to normal during the entire follow-up period. (B) Retinal thickness of the nasal subfield entered the reference interval 35 months after surgery, whereas several eyes remained thickened during the entire follow-up period. (C–E) Thickness of the superior, temporal, and inferior subfield entered the reference interval 12 to 14 months after surgery and returned to normal during the after months. (F) Five subfields of the Fast Macular Thickness program.

RESULTS

Foveal Structure

The preoperatively obtained tdOCT Fast Macular Thickness program showed diffuse retinal thickening (Figs. 2A–E, 0 months) without a foveal pit in all patients. tdOCT scans of the horizontal meridian obtained at last follow-up showed a foveal pit in 12 of 33 eyes. Photoreceptor layers and the junction between the photoreceptor inner segment and outer segment were intact in all patients. Retinal layers between the RNFL and the ONL appeared irregularly shaped or thickened to varying degrees in 27 of 33 eyes (Fig. 6). Twenty-five months after surgery, cystoid macular edema temporal to the fovea was observed in one eye, but no macular edema was observed as excessive intraretinal accumulation of fluid in the other eyes. We found minimal excentric persistent or recurrent IEM in two eyes. Figures 4 and 5 show that in most eyes the shape of the fovea remains abnormal long-term after surgery.

Retinal Layers along Horizontal Meridian

Long-term after Surgery

Figure 3 shows the thickness of the six retinal layers and total retinal thickness as measured with the customized software algorithm for the 30 control eyes. All fdOCT scans of the horizontal meridian obtained at last follow-up showed a foveal pit in 12 of 33 eyes. The preoperatively obtained tdOCT Fast Macular Thickness program before and after membrane peeling. Longitudinal data of retinal thickness in each subfield analyzed by nonlinear mixed-model regression before surgery (0 months) and after surgery. Horizontal lines: reference interval derived from box-whisker analysis of the normal control eyes (median value and the lowest/highest value within 1.5 times the interquartile range of the lower/upper quartile). Arrows: time points when the regression entered the reference interval. (A) Retinal thickness of the central subfield did not return to normal during the entire follow-up period. (B) Retinal thickness of the nasal subfield entered the reference interval 35 months after surgery, whereas several eyes remained thickened during the entire follow-up period. (C–E) Thickness of the superior, temporal, and inferior subfield entered the reference interval 12 to 14 months after surgery and returned to normal during the after months. (F) Five subfields of the Fast Macular Thickness program.
temporal retina is to the right, with 0 on the x-axis indicating the center of the fovea. There is reasonable agreement among the controls. The data of the controls agree with known retinal anatomy. For example, the RNFL is thin in the temporal retina and increases in thickness in the nasal retina as it approaches the optic disc. Furthermore, the RGC/IPL and the INL approach zero in the center of the fovea, whereas the thickness of the IS/OS+RPE complex increases in this area.

Data for the individual patient eyes are shown in Figure 4. The bold black curves represent the quantiles (3%, 50%, and 97%) of the control eyes. Figure 4 also illustrates the key findings. The IS/OS+RPE and RNFL curves of the great majority of patients do not deviate from the 3% and 97% quantile limits. Total retinal thickness, ONL, OPL, INL, and RGC/IPL are significantly thicker than normal, with a shift of maximum thickness to the nasal side. In the nasal parafovea, the INL is significantly thicker than normal (Fig. 5). The median RGC/IPL was thinner than normal on the temporal side of the

Median curves for the controls in Figure 3 are shown in Figure 5 as the central blue line. The additional blue lines above and below the central blue line represent the 95% CIs. Median and 95% CIs for the 33 patient eyes are shown as red lines. Consistent with the results of the Fast Macular Thickness program, which showed thickened central and nasal subfields (Fig. 2), total retinal thickness was increased in the fovea and in the nasal parafovea. Of interest here is the distorted median foveal shape and the maximum retinal thickness in the nasal fovea (Fig. 5G). Also of interest is the analysis of the individual retinal layers. IS/OS+RPE and RNFL are not significantly different from controls. In the fovea, ONL, OPL, INL, and RGC+IPL are significantly thicker than normal, with a shift of maximum thickness to the nasal side. In the nasal parafovea, the INL is significantly thicker than normal (Fig. 5). The median RGC+IPL was thinner than normal on the temporal side of the

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**Figure 3.** Thickness of retinal layers in normal controls. RNFL (A), RGC+IPL (B), INL (C), OPL (D), ONL (E), IS/OS+RPE (F), and total retina (G) thickness curves are shown for 30 normal control eyes (colored lines). The bold lines are the 3%, 50%, and 97% quantiles.

**Figure 4.** Thickness of retinal layers in patient eyes. RNFL (A), RGC+IPL (B), INL (C), OPL (D), ONL (E), IS/OS+RPE (F) and total retina (G) thickness curves are shown for 33 patient eyes (colored lines). For comparison, the bold lines are the 3%, 50%, and 97% quantiles of normal control eyes from Figure 3.
The retinal thickness of the superior, temporal, and inferior subfields entered the reference interval 12 to 14 months after surgery and returned to normal during the following months. Results from controls were consistent with known anatomy (Fig. 2).

**BCVA and Foveal Structure**

High-level BCVA of logMAR (Snellen equivalent) 0.05 (20/22.5) to 0.0 (20/20) was achieved at last follow-up by four eyes with foveal pit and by eight eyes without foveal pit. More pronounced irregularities of retinal layers, as shown in Figure 3B, were found in five eyes with BCVA at the last follow-up of 0.18 (20/30) to 0.4 (20/50).

**DISCUSSION**

The long-term effect of IEM peeling is only partly understood. Previous investigations were undertaken relatively short-term after surgery, and persistent retinal thickening was not precisely localized either within the macular area or among the individual retinal layers.\(^2\)\(^-\)\(^5\)\(^-\)\(^9\)\(^-\)\(^10\)

The detailed analysis of persistently thickened retina within the macula with tdOCT and fdOCT constitutes the main findings of this study. We chose an age-matched control group because age-related retinal thinning in normal eyes measured by tdOCT has been described.\(^15\) Using the tdOCT Fast Macular Thickness Program, we found that thickness continuously decreased nonlinearly over an extended postoperative period in all macular subfields. The analysis of the thickness measurements derived from the relatively small number of 33 operated eyes allows the observation of trends. Long-term after surgery, the retinal thickness of the superior, inferior, and temporal macula returned to normal while the central macula clearly remained thickened. The decrease of thickness of the nasal macula toward normal values was incomplete and delayed (Fig. 2). Our findings of postoperative macular thickness as a function of time demonstrate that anatomic recovery after IEM peeling differs within the macula and it may take longer than previously thought.\(^5\)\(^-\)\(^9\)\(^-\)\(^10\)

The discrepancy may have been caused by a regression analysis derived from a smaller number of eyes (\(n = 16\)), of a comparatively short median follow-up period of 360 days, and because the foveal thickness and macular volume parameters do not differentiate between different macular subfields.\(^9\)

The fovea has been defined as a circular area with a diameter of 1.5 mm centered on the 0.2-mm diameter circular foveola and the parafovea as a 0.5-mm rim around the fovea.\(^16\)

To analyze the morphology of the retina more specifically in the different zones of the macula and to depict the median structure of the fovea we used fdOCT scans obtained from the horizontal midline. FdOCT showed in line with the results of normal control eyes 35 months after surgery, whereas the retinas of several eyes remained thickened during the entire follow-up period. The thickness of the superior, temporal, and inferior subfields entered the reference interval 12 to 14 months after surgery and returned to normal during the following months. Results from controls were consistent with known anatomy (Fig. 2).

**Postoperative Course of Macular Thickness**

All five macular subfields of the td OCT Fast Macular Thickness program were equally thickened before surgery (Figs. 2A–E, 0 months). After surgery, retinal thickness decreased nonlinearly in all subfields. Nonlinear mixed model regression showed different trends in the central and nasal subfields compared with the superior, temporal, and inferior subfields. Retinal thickness of the central subfield did not return to normal during the entire follow-up period. Retinal thickness of the nasal subfield entered the reference interval derived from the fovea (Fig. 5B). This effect was probably caused by circumscribed areas of thinning or indentation of this layer on the temporal side of the fovea, as observed to varying degrees in 13 of 33 eyes (Figs. 6D, 6F).

### FIGURE 5.

Median thickness of retinal layers in normal controls and in patients. **Blue lines:** median ± 95% CIs for the 30 normal controls of Figure 3. **Red lines:** median ± 95% CIs for the 33 patient eyes of Figure 4. As in Figures 3 and 4, RNFL (A), RGC+IPL (B), INL (C), OPL (D), ONL (E), IS/OS+RPE (F), and total retina (G) thickness curves are shown in separate panels.
the tdOCT Fast Macular Thickness Program that long-term after surgery total retinal thickness along the horizontal meridian in the fovea and the nasal parafovea remained increased with a maximum of thickness in the nasal fovea (Figs. 4G, 5G). The thickness of individual layers was increased in the fovea between the outer nuclear and the ganglion cell plus IPL while the thickness of RPE and photoreceptor, and RNFL layers did not differ from normal anatomy (Fig. 5). In most, but not all, eyes, the thickness of the layers between the outer nuclear and the ganglion cell plus IPL deviated from the median with Cs of normal eyes (Fig. 4). The difference of total retinal thickness in the fovea between patients and controls was mainly caused by the absence of a normally structured foveal pit in the majority of patients (Figs. 4, 5). The greater than normal thickness of the nasal parafovea may be mainly caused by persistent thickening of the INL, as well as, in accordance with other studies,4,17 the absence of a foveal pit did not preclude favorable long-term postoperative visual acuity (Fig. 6). Others have described disruptions of the junction between the photoreceptor inner segment and outer segment associated with poor visual acuity after surgical peeling of IEM17 that we did not observe. Overall, in this study, visual acuity continuously improved after surgery and reached very good levels at last follow-up in most patients. Earlier measurements of parafoveal retinal thickness taken from histologic horizontal cross-sections of normal human eyes described an equal thickness of the nasal and temporal parafovea of 0.23 mm.18 By contrast, according to our measurements, the normal parafovea was slightly thicker on the nasal side than on the temporal side (Figs. 3G, 5G). This is in agreement with ultrahigh-resolution OCT19 and other fdOCT studies.34 The normally greater total retinal thickness on the nasal side of the fovea is caused primarily by a thicker RNFL and perhaps, to a small degree, by slightly thicker RGC+IPL, INL, and OPL (Figs. 3, 5).

It is unclear why long-term after surgery the nasal parafoveal retina remained thickened (Figs. 2, 4G, 5G) though the thickness of the superior, inferior, and temporal macula returned to normal (Fig. 2). The mean follow-up time in the present study of 46 months was considerably longer than in other reports.2–7,9,10 However, further postoperative decreases of central and nasal macular thickness after the follow-up period of this study cannot be excluded. To our knowledge, no experimental data describing the response of retinal tissue to mechanical traction and shear stress and how the tissue recovers after temporary traction have been published. Because of the course of the nerve fibers toward the optic nerve, in the papillomacular bundle nerve fibers, ganglion cells, and other retinal cells are packed very closely together, perhaps more so than elsewhere in the parafoveal region. It can be hypothesized, therefore, that the nasal side of the fovea is more vulnerable to traction and shear stress exerted by IEM and recovers more slowly and to a lesser degree long-term after surgery. Perhaps because of its greater thickness, the RNFL on the nasal side of the fovea cannot fully relax back to its normal static length because of the mechanical shearing forces exerted on the macula by IEM and may recover incompletely. It is not possible, with existing data, to distinguish between this hypothesis and other possible alternatives. However, the data show that long-term observations are required to gain a better understanding of macular recovery from mechanical stress. The present results may be helpful in future studies of macular recovery after IEM or ILM peeling with new, potentially toxic vital stains, correlation of anatomy and visual function in clinical studies, or investigation of new techniques of macular surgery.

References


