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Macular fluid reduces reproducibility of choroidal thickness measurements on enhanced depth optical coherence tomography

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Abstract

Purpose—To determine if different types of retinal fluid in the central macula affect the reproducibility of choroidal thickness (CT) measurements on enhanced depth imaging optical coherence tomography (EDI-OCT)

Design—retrospective, reliability analysis

Methods—EDI-OCT images were obtained and the choroidal-scleral junction was analyzed through semi-automated segmentation. CT was measured at the fovea and averaged across the central 3 mm horizontal segment. Demographic data, central macular thickness and type of fluid present were recorded. Intragrader and intergrader repeatability were assessed using the intraclass correlation coefficient (ICC) and coefficient of repeatability (CR).

Results—Of 124 eyes analyzed, 60 (48.4%) had diabetic macular edema, 32 (25.8%) had neovascular age-related macular degeneration, and 32 (25.8%) had other causes of fluid. Intergrader ICC (CR) were 0.95 (74.1 μm) and 0.96 (63.9 μm) for subfoveal and average CT, respectively. CR were similar across various causes of retinal fluid, but were worst for subretinal fluid compared to intraretinal or sub-retinal pigment epithelial fluid. CR also worsened with

increasing choroidal thickness, but was not affected by retinal thickness. Intragrader repeatability was generally greater than intergrader values, and followed the same trend.

Conclusions—The presence of macular fluid reduces CT measurement reproducibility, particularly in eyes with subretinal fluid and greater choroidal thickness. A difference of 74.1 μm in subfoveal CT or 63.9 μm in average CT may be necessary to detect true clinical change in eyes with macular fluid.

Introduction

The choroid is the primary vascular supply for the outer retina and has been implicated to play a role in a variety of ocular and systemic diseases.[1] Recent studies have shown that the thickness of the choroid may be affected in retinal conditions such as diabetic retinopathy, age-related macular degeneration (AMD), vascular occlusive diseases, uveitis, and pachychoroid entities.[2–5] In some conditions, choroidal thickness (CT) may be used as a marker of disease activity or treatment response, although intravitreal pharmacotherapies and laser treatments may cause additional alterations to CT.[6–12]

Enhanced depth imaging optical coherence tomography, or EDI-OCT, improves visualization of the deeper tissue structures, allowing the choroidal-scleral interface to be more easily observed and CT to be measured.[13] CT measurements may be affected by shadowing from overlying retinal pathology, especially in the presence of macular fluid. The deeper location of the choroid inherently limits its visibility, and a thicker choroid reduces measurement reliability.[14,15] Finally, there is also variability in how the posterior boundary of the choroid is defined, which may include the border of the vessel lumena, the choroid stroma, or the sclera, and particularly when the suprachoroidal layer is visible. Recent studies suggest that the repeatability of CT measurements may be optimized at the stromal border.[16] These factors all serve to make CT estimation imprecise, necessitating reproducibility studies to guide analysis.

Most studies to date have assessed CT measurement repeatability in healthy eyes,[16–23] with a few studies examining CT in diabetic retinopathy and AMD.[15,24–27] We hypothesize that the reliability of CT measurements may be less determined by the pathophysiology of particular conditions, than by the type or quantity of overlying retinal fluid in the macula. In this study, we provide a practical context to CT analysis by determining if CT measurements are affected by the presence and type of macular fluid.

Methods

Subject Selection

After obtaining approval from the Institutional Review Board, study subjects were selected from consecutive patients who were seen at the University of California, Davis Eye Center from January 1, 2015 to April 1, 2016. Patients were identified from the electronic medical record system and included if they had a diagnosis of neovascular AMD, diabetic macular edema (DME), any type of retinal vein occlusion, central serous chorioretinopathy, choroidal neovascularization, or cystoid macular edema from any cause. Eyes were selected if they underwent EDI-OCT imaging and demonstrated fovea-involving macular fluid on a central

horizontal line scan. We excluded patients with high myopia (-6D), or other retinal or macular pathologies that are not among the inclusion criteria. If both eyes showed fluid, the eye with worse visual acuity was determined to be the study eye. If visual acuity was equal, the study eye was determined by birth month (right eye for even-number birth month; left eye for odd-number birth month). If EDI-OCT was obtained on multiple visits, the first visit showing retinal fluid was chosen for analysis. Patient charts were also reviewed for basic demographic data, retinal diagnosis, best corrected visual acuity, refractive error, intraocular pressure, and lens status. All steps of the study were conducted in accordance with the tenets of the Declaration of Helsinki.

EDI-OCT Imaging and Analysis

All imaging was performed by experienced ophthalmic photographers using the Spectralis OCT instrument (Heidelberg Engineering, Heidelberg, Germany), operating at 40,000 Hz. Nine mm line scans were obtained in EDI mode, with 1536 A-scans per B-scan and Automatic Real Time frame-averaging up to 100 B-scans to reduce noise. Fluid type was determined from EDI-OCT images by two experienced graders (SSW, VSV), with any discrepancies resolved by a senior grader (GY). Macular fluid was categorized as intraretinal, subretinal, or sub-retinal pigment epithelial (sub-RPE) fluid. Most eyes had predominantly one type of retinal fluid. Two eyes showing similar amounts of more than one fluid type were excluded from the analysis.

EDI-OCT images were analyzed using Duke Optical Coherence Tomography Retinal Analysis Program (DOCTRAP, v62.0), which was used for semi-automated segmentation of the internal limiting membrane and Bruch's membrane, while the choroidal-scleral junction (CSJ) was manually traced by the two graders. The CSJ was taken to be the outermost border of the choroidal stroma (Figure 1). The fovea was manually marked based on the widest separation between the inner segment-outer segment border (or ellipsoid zone) and the cone outer-segment tips (or interdigitation zone). In cases where this anatomy was obscured by pathology, the fovea was taken to be the smallest tapering point of the inner nuclear layer. CT measured at the fovea (subfoveal CT) and at 600 other points corresponding to individual A-scans averaged across the central 3 mm of the line scan (from 1.5 mm nasal to 1.5 mm temporal to the fovea; average CT) were calculated from mean measurements of the two graders to determine intergrader repeatability. One grader (VSV) performed a second discrete set of manual segmentations at least one month later to assess intragrader repeatability. The central macular thickness (CMT), measured between the internal limiting membrane and Bruch's membrane, was also measured by the DOCTRAP software.

Statistical Analysis

One-way analysis of variance was used to compare baseline CT between diagnoses and fluid type. Repeatability was evaluated using intraclass correlation coefficients (ICC) and coefficients of repeatability (CR). The ICC is a ratio of the variance between subjects over the total variance. It indicates the proportion of the total variation that is attributed to between-subject differences rather than measurement variation for an individual subject. The CR is the value under which repeated measurements of the same subject should fall with

95% probability, and represents the threshold for demonstrating true clinical change. Statistical analyses were performed using SPSS Statistics 24.0 (IBM, New York), and figures were generated with Microsoft software (Microsoft, Washington).

Results

Demographics and Ocular Characteristics

A total of 615 consecutive patient charts were reviewed, of which 491 were excluded, due to absence of macular fluid (n = 141), absence of EDI-OCT imaging (n = 269), presence of other pathologies (n = 62), or high myopia (n = 17). Two subjects were excluded for having equal amounts of more than one fluid type and two outliers were excluded due to significant pathology that precluded adequate automated segmentation of Bruch's membrane, leaving 124 eyes of 124 subjects for final analysis. The mean age of subjects was 65.9 ± 15.2 years and 71 subjects (57.3%) were male. Of the study eyes, 67 (54%) were left eyes and 57 (46%) were right eyes. Ninety eyes (72.6%) of the sample were phakic, and the remaining 34 eyes (27.4%) were pseudophakic. No high myopes or high hyperopes were included in the final sample. All eyes had fovea-involving macular fluid based on inclusion criteria. Among these, 60 eyes (48.4%) had DME, 32 eyes (25.8%) had neovascular AMD, and 32 eyes (25.8%) had macular fluid from other causes, including vitreomacular interface disease (9 eyes), retinal vein occlusion (8 eyes), inflammatory syndromes including post-cataract cystoid macular edema and idiopathic uveitides (8 eyes), central serous chorioretinopathy (4 eyes), idiopathic choroidal neovascularization (2 eyes) and optic nerve pit (1 eye). There were 101 scans with intraretinal fluid (IRF), 14 with subretinal fluid (SRF), and 9 with sub-retinal pigment epithelial fluid (sub-RPE fluid). Scans were also divided into tertiles according to CMT, subfoveal CT and average CT.

The mean (SD) CMT was 350.4 μm (136.9 μm). Mean (SD) subfoveal CT was 267.2 μm (100.4 μm) and mean average CT was 258.5 μm (96.2 μm). CMT was lower in eyes with DME than those with fluid from other causes (p = 0.004), but was not significantly different between fluid types (p = 0.088). Subfoveal CT and average CT were not statistically different between diagnoses (p = 0.100 and p = 0.073) or fluid type (p = 0.133 and p = 0.130) (Table 1).

Repeatability Based on Diagnosis and Fluid Type

Among all eyes, intergrader ICC (CR) were 0.95 (74.1 μm) for subfoveal CT and 0.96 (63.9 μm) for average CT (Table 2). Repeatability between different diagnoses was similar, with a narrow range of CR for subfoveal CT (69.3 to 77.9 μm) and average CT (62.0 to 77.9 μm). In contrast, repeatability measures were different between fluid types, with subretinal fluid showing the highest CR (123.7 μm for subfoveal CT and 127.1 μm for average CT) when compared to eyes with intraretinal or sub-RPE fluid (Table 2). Bland-Altman analyses of the 95% limits of agreement between graders demonstrated comparable lower and upper limits between diagnoses, but a significantly wider interval for subretinal fluid compared to other fluid types (Figure 2).

Intragrader repeatability was better than intergrader repeatability, showing higher ICC and lower CR values. There was a similar trend toward higher CR in eyes with subretinal fluid (Supplemental Table 1; Supplemental Material at AJO.com).

Repeatability Based on Retinal and Choroidal Thickness

Reproducibility of CT measurements also appeared to be affected by choroidal thickness. We found repeatability to be worse in eyes with a thicker choroid, with the lowest ICC and highest CR values measured in eyes falling within the highest CT tertile. However, repeatability measures did not vary significantly by retinal thickness based on CMT tertiles (Table 3). Similar trends were noted in the intragrader values (Supplemental Table 2; Supplemental Material at AJO.com).

Discussion

As our visualization of the choroid improves, our understanding of its impact on various retinal diseases increases. Studies have shown that CT may be increased in central serous chorioretinopathy or retinal vein occlusion,[3,28] or decreased in conditions like diabetic retinopathy and DME.[5,29–35] In some conditions, CT may predict clinical outcome or even be used to monitor treatment response. For instance, one study found that greater subfoveal CT may be correlated with better short-term visual and morphologic outcomes after anti-vascular endothelial growth factor (anti-VEGF) treatment for DME.[36] However, therapies for treating macular fluid, such as anti-VEGF or corticosteroid injections, may decrease CT also.[37–39] Hence, robust reliability studies are necessary to determine clinically significant changes in CT.

The repeatability of CT measurements has been well established in normal subjects, with reported ICC values of 0.89–0.99.[17–23,40,41] Overall, ICC values appear uniformly strong across many studies, including ours, but is susceptible to being artificially increased as the between-patient differences increase. Hence, CR values may be better indicators of test-retest repeatability. Using the posterior boundary of the choroid stroma, we had determined the intergrader CR value of 50.4 μm as the threshold for determining true clinical change in subfoveal CT in normal eyes.[16] Averaging CT across the central 3 mm in a horizontal line scan further improves the reliability with a CR value of 41.4 μm.[16] This is within the range of previously reported CR of 30.9 μm and 78.1 μm in normal eyes.[14,22]

In this study, we employed a similar semi-automated method for measuring CT in diseased eyes with retinal fluid, and found that a difference of 74.1 μm or 63.9 μm is necessary to determine true change in subfoveal and average CT, respectively. These higher CR values support our hypothesis that macular fluid reduces the reliability of CT measurements in diseased eyes compared with normal eyes. Interestingly, we noted that the repeatability of CT measurements is poorest in eyes with subretinal fluid, compared with other types of macular fluid. One possible explanation is that subretinal fluid often occurs as a contiguous collection that results in greater signal attenuation or "shadowing" of the underlying choroid, in contrast to the pockets of cystic spaces seen with intraretinal fluid. In addition, eyes with subretinal fluid tend to have thicker choroids, though this relationship was not significant in our cohort. Consistent with prior studies, we also found that a thicker choroid reduces

measurement repeatability,[14,15,19] so we cannot exclude the possibility that CT may exert a stronger influence on measurement precision, especially since retinal thickness did not appear to have an effect. We also cannot exclude the potential effect of other OCT features such as intraretinal hyperreflective foci or subretinal hyperreflective material which may warrant future research. Additional prospective studies to address intervisit reliability of CT measurements will also enhance our understanding.

Our study suggests that the retinal diagnosis or cause of macular fluid is not as strong of a factor in determining CT repeatability as the type of retinal fluid. We hypothesize that the accuracy of CT measurements is more dependent on anatomic factors that may affect light penetration and signal strength at the posterior boundary of the choroid, than the biological process underlying the retinal exudation. Prior reports in eyes with neovascular AMD demonstrated intergrader CR values of 30–36 μm, which were comparable to other reports from normal eyes,[15,22,26] but lower compared to our prior study. Those results may have been confounded by eyes with a thinner choroid, which tends to occur in advanced AMD. In eyes with diabetic retinopathy, the intergrader CR for CT measurements was reported to be 41.5 μm.[24] However, none of those studies specified the presence of retinal fluid on the OCT scans analyzed, which may contribute to the lower CR values in those reports.

Our study is limited by its retrospective nature, with unequal distribution of eyes with various retinal pathologies and fluid types. We also did not assess measurement repeatability at specific locations that may correlate with the location and area of macular fluid. Thus, macular fluid outside the central foveal region, for example, may account for average CT appearing less reproducible than subfoveal CT in some subgroup of eyes in our study such as those with DME or SRF. EDI-OCT as an imaging modality also has limitations. Measurement repeatability is compromised when the choroidal-scleral junction is obscured. In comparison, swept source OCT employs a longer wavelength of light that penetrates deeper and allows greater depth of visualization. CT measurements using swept source OCT are highly repeatable, but tend to be slightly thicker compared to spectral domain OCT.[23,27]

In conclusion, the repeatability of CT measurements using EDI-OCT is reduced by the presence of macular fluid, particularly in eyes with greater choroidal thickness and in the presence of subretinal fluid. Clinicians and researchers should account for these characteristics when obtaining repeated CT measurements and following eyes over time. Future investigation with prospective studies is warranted to further elucidate these findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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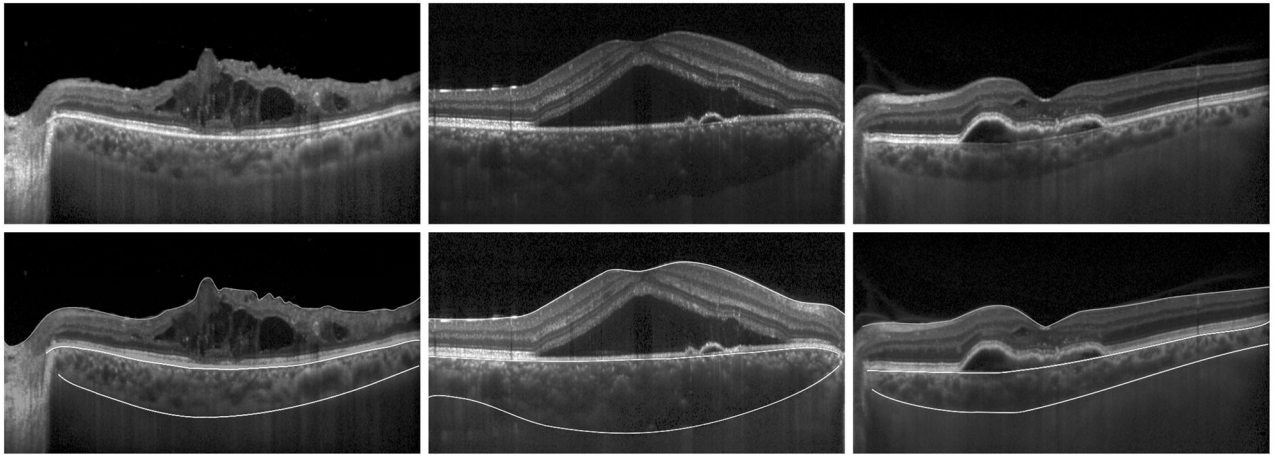
FIGURE 1.
Enhanced-depth imaging optical coherence tomography (EDI-OCT) images of eyes with macular fluid using semi-automated segmentation. Scans are shown before (top) and after (bottom) segmentation, including eyes with intraretinal fluid (left), subretinal fluid (center), and sub-retinal pigment epithelial (sub-RPE) fluid (right). Segmentation lines delineate the internal limiting membrane (top line), Bruch's membrane (middle line), and choroidal-scleral junction (bottom line).
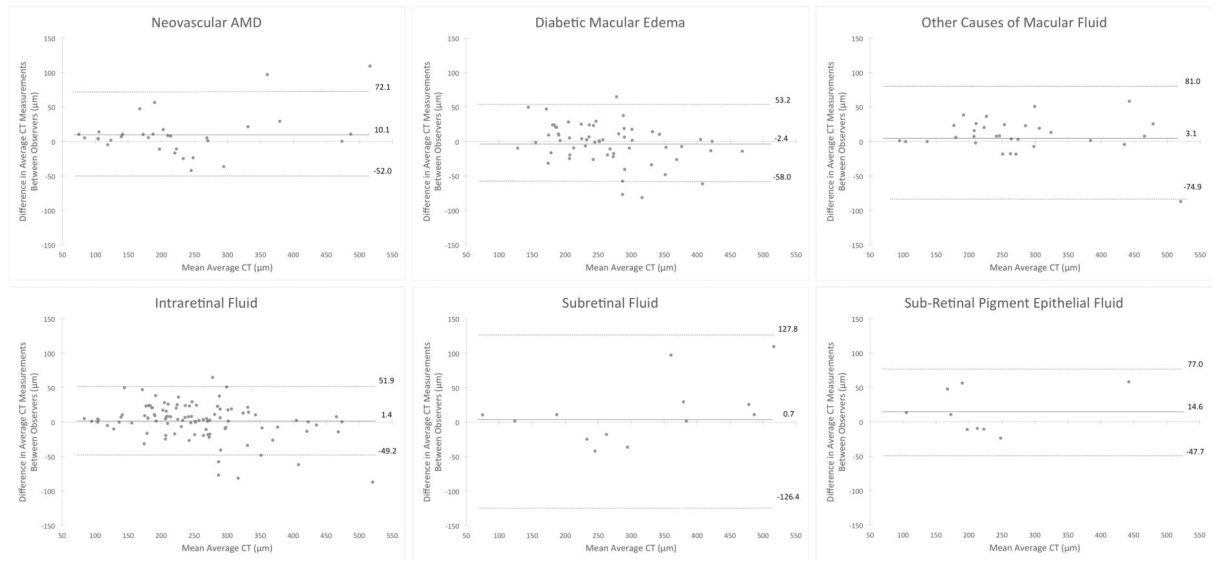
FIGURE 2.

Bland-Altman plots of intergrader agreement for measuring choroidal thickness in eyes with macular fluid. Plots are shown by diagnosis (top) and fluid type (bottom). Solid lines represent the mean difference, while dashed lines show the 95% limits of agreement.

Table 1

Retinal and Choroidal Thickness based on Diagnosis and Fluid Type in Eyes with Macular Fluid

	Mean CMT (SD) (μm)		Mean Subfoveal CT (SD) (μm)		Mean Average CT (SD) (μm)	
Diagnosis						
AMD	355.8	(130.9)	236.7	(133.0)	228.0	(124.0)
DME	314.6	(121.7)	268.2	(74.9)	261.5	(72.3)
Other	412.1	(150.5)	289.5	(109.6)	279.2	(103.8)
Fluid						
Intraretinal	338.6	(139.2)	264.0	(99.4)	256.8	(94.3)
Subretinal	422.9	(134.3)	345.8	(160.3)	329.5	(152.2)
Sub-RPE	369.7	(73.9)	225.3	(106.0)	214.2	(104.9)
Total	**350.4**	**(136.9)**	**267.2**	**(100.4)**	**258.5**	**(96.2)**

[a]CMT = central macular thickness; CT = choroidal thickness; SD = standard deviation; AMD = age-related macular degeneration; DME = diabetic macular edema

Table 2

Intergrader Repeatability of Choroidal Thickness based on Diagnosis and Fluid Type in Eyes with Macular Fluid

	Subfoveal CT		Average CT	
	ICC	CR (μm)	ICC	CR (μm)
Diagnosis				
AMD	0.97	77.9	0.98	62.0
DME	0.95	69.3	0.97	72.2
Other	0.97	76.9	0.97	77.9
Fluid				
Intraretinal	0.97	63.3	0.98	50.6
Subretinal	0.96	123.7	0.95	127.1
Sub-RPE	0.94	86.8	0.97	62.4
Total	**0.95**	**74.1**	**0.96**	**63.9**

[a]CT = choroidal thickness; ICC = intraclass correlation coefficient; CR = coefficient of repeatability; AMD = age-related macular degeneration; DME = diabetic macular edema

Table 3

Intergrader Repeatability of Choroidal Thickness According to Thickness Tertiles in Eyes with Macular Fluid

	Subfoveal CT		Average CT	
	ICC	CR (μm)	ICC	CR (μm)
CMT Range (μm)				
Lower (166–348)	0.97	68.1	0.98	54.7
Middle (349–531)	0.94	82.5	0.94	75.3
Upper (532–714)	0.98	67.9	0.98	67.3
Subfoveal / Average CT Range (μm)				
Lower (81–242 / 79–242)	0.93	48.9	0.95	38.8
Middle (243–404 / 243–407)	0.81	85.3	0.85	73.1
Upper (405–565 / 408–571)	0.79	100.4	0.65	107.7

[a]CT = choroidal thickness; CMT = central macular thickness; ICC = intraclass correlation coefficient; CR = coefficient of repeatability