Original Article

Evaluation of Choroidal Layer Thickness in Central Serous Chorioretinopathy

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Abstract

Purpose: To evaluate medium and large choroidal vessel layer thickness (MCVT and LCVT, respectively) in eyes with acute and chronic central serous chorioretinopathy (CSC) in comparison with age-matched controls.

Methods: The study included 96 eyes of 96 patients with CSC, including 53 eyes with acute CSC, 43 eyes with chronic CSC, and 30 eyes of 30 age-matched normal subjects. Manual measurements of subfoveal choroidal thickness (SFCT), MCVT, and LCVT at subfoveal and 750 μm nasal and temporal to the fovea locations were made on enhanced depth imaging optical coherence tomography (EDI-OCT) of the macula in all subjects using ImageJ software (National Institutes of Health, Bethesda, MD, USA).

Results: SFCT in acute CSC was significantly larger than that in healthy eyes ($P = 0.0001$). SFCT in acute CSC did not differ significantly from that in chronic CSC eyes. Subfoveal LCVT and MCVT in acute CSC eyes were greater than those in healthy eyes ($P = 0.02$ and $P = 0.03$, respectively). Mean SFCT and MCVT in chronic CSC eyes were significantly larger than those in control eyes ($P = 0.01$ and $P = 0.04$, respectively). No significant difference in LCVT was observed between chronic and control eyes.

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Conclusion: Choroidal vasculature is altered in both acute and chronic CSC. SFCT, MCVT, and LCVT are higher in eyes with acute CSC. The thickening of medium choroidal vessels is still detectable in chronic CSC compared to control eyes.

Keywords: Central Serous Chorioretinopathy; Choroid; Optical Coherence Tomography

INTRODUCTION

Central serous chorioretinopathy (CSC) is characterized by serous detachment of the neurosensory retina at the macula.[1] CSC has been associated with middle age, male sex, pregnancy, steroid use, and obstructive sleep apnea.[2] Fundus fluorescein angiography (FFA) and indocyanine angiography (ICGA) are used in the assessment of CSC.[3] In acute CSC, FFA shows focal leakage from the retinal pigment epithelium (RPE), whereas ICGA identifies decreased filling of the choriocapillaris in the early phase and hyperfluorescence in the middle phase associated with choroidal vascular hyperpermeability. Choroidal thickness analysis using optical coherence tomography (OCT) suggests that choroidal thickness in eyes with CSC is larger than that in age-matched control eyes and fellow eyes.[4,5] Enhanced depth imaging (EDI)-OCT has enabled further characterization of choroidal changes because of improved resolution of OCT imaging of deeper structures.[6] EDI-OCT reveals alterations within the choroidal layers and features of RPE disturbance.[7]

The visualization of choroidal vessels has allowed analysis of choroidal vessel layer thickness and has demonstrated that vascular layers are altered in disease processes.[8,9] Previous studies have suggested that choroidal vessel diameter appears to change in CSC and alterations in vascular permeability may be associated with the detachment of the neurosensory retina.[10] However, understanding how choroidal vessels are altered in CSC could help determine the pathogenesis of CSC and suggest possible new treatment approaches.

Although dilation of vessels has been suggested to persist in chronic disease, whether this change occurs in all choroidal vascular layers and whether it is persistently altered compared with control eyes remains unclear.[11] EDI-OCT of choroidal vascular layers may be crucial to our understanding of the remodeling of choroidal tissue in persistent CSC and this characterization may be helpful in determining the length of disease activity. Treatment decisions with photodynamic therapy (PDT) and the analysis of the efficacy of new therapies in CSC require a clear assessment of disease activity.

The aim of this study was to investigate how EDI-OCT-derived measurements of choroidal thickness, large and medium choroidal vessel layers, and retinal thickness differ in eyes with acute and chronic CSC, compared with age-matched controls.

METHODS

Retrospective analysis of EDI-OCT scans was performed in patients with CSC. Written informed consent was obtained from all patients. Approval was obtained from the institutional review board or ethics committee of each center and the study adhered to the tenets set forth in the Declaration of Helsinki.

Study Population

Spectral domain EDI-OCT images of patients with CSC in JPEG format and with identical resolutions were collected from retina clinics at various centers in India (Giridhar Eye Institute, Kochi, Kerala, India; Banker's Retina Clinic and Laser Centre, Ahmedabad, Gujarat, India; and L V Prasad Eye Institute, Hyderabad, Telangana, India), the United States (Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, MD, USA), and the Netherlands (Leiden University Medical Center, Leiden, the Netherlands) and were sent to L V Prasad Eye Institute. Healthy patients were recruited from the aforementioned clinics. This study included treatment naïve eyes with acute and chronic CSC and age-matched healthy control eyes recruited through the database of each center. Acute CSC was defined as the presence of subfoveal subretinal fluid on SD-OCT with a history of symptoms <3 months without evidence of chronicity on clinical examination, fluorescein angiography, or fundus autofluorescence. Chronic CSC was defined as subretinal fluid in the foveal region persisting for ≥3 months, with or without serous pigment epithelial detachment on OCT, and widespread RPE changes in the macular region associated with leaks and/or pigment epithelial detachment on FFA.[12,13] The exclusion criteria included a history of any treatment for CSC, a history of active or previous choroidal neovascular membrane, media opacity preventing examination of the fundus, previous ocular surgery (other than cataract surgery), myopia more than -3 dioptres spherical equivalent and any other significant ocular comorbidity causing vision loss.

SD-OCT Imaging Protocol

All subjects underwent EDI-OCT imaging of the macula (6-mm horizontal line scan centered on the fovea) using Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany). High-quality images with a signal strength of more than 15 dB were included. Best corrected visual acuity, medical history, and previous ocular treatment were ascertained from patient records.

Manual OCT Thickness Measurements

All manual measurements were performed twice using callipers on the ImageJ software (a publicly available image processing program (National Institutes of Health, Bethesda, MD, USA) by two observers. Figure 1 shows OCT images of the measured parameters. Choroidal thickness was measured at the fovea (SFCT), 750 μm temporal to the fovea and 750 μm nasal to the fovea. Choroidal thickness was defined as the vertical distance between the hyperreflective lines of the Bruch's membrane and the chorio–scleral interface.

Large choroidal vessels were identified on EDI-OCT images as vessels with a diameter >100 μm, as previously defined by Branchini et al.[14] The large choroidal vessel layer was measured as the perpendicular distance from the innermost aspect of the large choroidal vessel layer to the chorio–scleral interface (at the fovea and at or close to loci 750 μm nasal and temporal to the fovea). The medium choroidal vessel layer (inclusive of the choriocapillaris) thickness was defined as the difference between choroidal thickness and the large choroidal vessel layer thickness.

Central macular thickness was measured manually as the retinal thickness at the fovea between the RPE and internal limiting membrane. Neurosensory detachment was visualized in patients with CSC and the height of subretinal fluid at the fovea was measured manually as the perpendicular distance between the RPE and the outermost part of the neurosensory retina.

Statistical Analysis

All statistical analyses were performed using GraphPad Prism V7 (GraphPad Software, San Diego, CA, USA). The mean (± standard deviation; SD) thickness of all layers was calculated. One-way ANOVA with *post hoc* Tukey's test were used to assess the differences among eyes with acute CSC, eyes with chronic CSC, and age-matched controls for each of the EDI-OCT-derived thickness parameters. Generalized estimating equations were used to analyze the differences among the groups.

RESULTS

Patient Characteristics

A total of 96 eyes of 96 patients with CSC were included, of which 53 eyes had acute CSC and 43 had chronic CSC. Mean (± SD) age of the study subjects was 45.5 ± 8.5 years. These 96 patients comprised 81 male and 15 female patients. Thirty eyes of 30 age-matched subjects were included. The mean (± SD) age of the normal subjects was 44.8 ± 9.4 years (5 males and 25 females).

Patient demographics (age, sex, laterality, visual acuity), duration of symptoms, treatment history, and comorbidities are summarized in Table 1. No significant difference in age or laterality was observed among the subgroups.

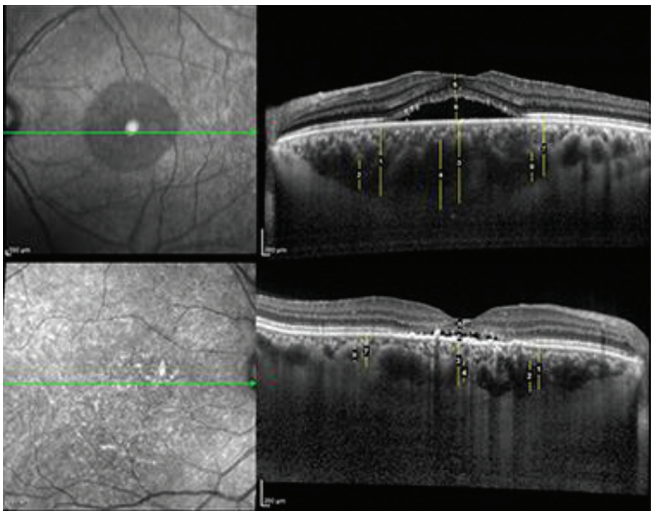

Figure 1. Retinal, choroidal and choroidal vessel thickness measurements derived from manual enhanced-depth imaging optical coherence tomography. Measurements of retinal thickness, choroidal thickness, and large choroidal vessel thickness (LCVT) in eyes with acute (top) and chronic (bottom) central serous retinopathy. Yellow lines show manual measurements (one nasal choroidal thickness, two nasal LCVT, three subfoveal choroidal thickness, four subfoveal LCVT, five retinal thickness, six neurosensory detachment, seven temporal choroidal thickness, and eight temporal LCVT measurements). Choroidal thickness and LCVT were measured in the same loci (subfoveal, temporal, and nasal).

Analysis of Choroidal Thickness and Vessel Layer Measurements

EDI-OCT-derived thickness measurements for all layers and subgroups are shown in Table 2. The inter-observer repeatability for measurements in this study was 0.92–0.99.

Choroidal thickness: Mean (± SD) SFCT in eyes with acute and chronic CSC was 360.5 ± 94.7 μm and 338.4 ± 86.0 μm, respectively, whereas it was 277.8 ± 46.8 μm in control eyes. Mean SFCT in eyes with acute CSC was significantly greater than that in control eyes (P = 0.0001), but not compared to eyes with chronic CSC [Figure 2a]. Mean SFCT in eyes with chronic CSC was significantly greater than in control eyes (P = 0.01). Mean choroidal thickness measurements 750 μm nasal to the fovea in eyes with both acute and chronic CSC were greater than in control eyes (P = 0.006 and P = 0.008, respectively; Figure 2b). There was no significant difference in mean choroidal thickness measurements 750 μm temporal to the fovea between eyes in any of the subgroups [Figure 2c].

Large choroidal vessel thickness: Mean (± SD) subfoveal large choroidal vessel thickness in eyes with acute and

chronic CSC was 167.5 ± 55.0 μm and 148.7 ± 44.3 μm, respectively, whereas it was 133.0 ± 43.0 μm in control eyes. Mean (± SD) subfoveal large choroidal vessel thickness in eyes with acute CSC was greater than that in control eyes ($P = 0.02$), but did not differ significantly from that in chronic CSC eyes [Figure 2d]. There was no significant difference in large choroidal vessel thickness between chronic and control eyes. There was no significant difference in the large choroidal vessel thickness measurements temporal and nasal to the fovea between any of the subgroups [Figure 2e and f].

Table 1. Demographics, lens status, and comorbidities of patients

	Acute	Chronic	Normal	*P*
No of eyes	53	43	30	
Age, years (mean±SD)	42.7±8.4	48.9±7.3	44.8±9.4	0.32
Gender (*n*, %)				
Male	42 (79.2)	39 (90.7)	5 (16.7)	0.03
Female	11 (20.8	4 (9.3)	25 (83.3)	
Laterality (*n*, %)				
Left	34 (64.2)	20 (46.5)	16 (53.3)	0.68
Right	19 (35.8)	23 (53.5)	14 (46.7)	
Visual acuity, Log MAR (mean±SD)	0.22±0.2	0.54±0.4	0±0	0.02
Lens status (*n*, %)				
Phakic	53 (100)	39 (90.7)	30 (100)	0.84
Pseudophakic	0 (0)	4 (9.3)	0 (0)	
Symptom duration (mean months±SD)	1.2±2.3	11.9±19.3	0±0	0.04
Previous steroid exposure (*n*, %)	4 (7.5)	7 (16.3)	1 (3.3)	0.52
Comorbidities (*n*, %)				
Hypertension	4 (7.5)	9 (20.9)	0 (0)	0.44
Diabetes mellitus	2 (3.8)	1 (2.3)	1 (3.3)	

Log MAR, logarithm minimum angle of resolution; SD, standard deviation; n, number

Medium choroidal vessel thickness: Mean (± SD) subfoveal medium choroidal vessel thickness in eyes with acute and chronic CSC was 192.9 ± 85.7 μm and 191.5 ± 76.4 μm, respectively, whereas mean (± SD) subfoveal medium choroidal vessel thickness in control eyes was 144.7 ± 73.6 μm. Subfoveal medium choroidal vessel thickness in both acute and chronic CSC eyes was significantly greater than that in control eyes ($P = 0.03$ and $P = 0.04$, respectively) [Figure 2g]. Nasal medium choroidal vessel thickness in acute CSC eyes was significantly greater than that in control eyes ($P = 0.003$), but this difference was not observed in eyes with chronic CSC [Figure 2h]. Temporal medium choroidal vessel thickness in eyes with acute and chronic CSC did not differ significantly from that in control eyes [Figure 2i].

Analysis of Macular Thickness and Degree of Neurosensory Detachment

Mean (± SD) macular thickness at the fovea in eyes with acute and chronic CSC was 331.3 ± 155.8 μm and 265.7 ± 136.7 μm, respectively, whereas in control eyes it was 223.4 ± 45.2 μm. Macular thickness in eyes with acute CSC was significantly greater than that in eyes with chronic CSC ($P < 0.05$) as well as control eyes ($P = 0.0009$) [Figure 3]. Macular thickness in chronic CSC eyes did not differ significantly from that in control eyes. No significant difference in mean neurosensory detachment thickness was observed between acute and chronic CSC eyes.

DISCUSSION

EDI-OCT has enabled non-invasive *in vivo* investigation of choroidal thickness in eyes with CSC. In acute CSC, choroidal thickness appears to be larger than in control eyes, as suggested by previous studies of CSC.[15-17]

Table 2. Optical coherence tomography-derived thickness parameters of the patients

	Acute	Chronic	Normal
Choroidal thickness			
mean±SD, (μm)	360.5±94.7	338.4±86.9	277.7±46.8
Subfoveal	314.7±86.1	314.6±77.9	257.2±66.6
750 μm nasal to fovea	305.3±88.8	305.8±81.2	280.2±11.5
750 μm temporal to fovea			
Large vessel thickness, mean±SD (μm)			
Subfoveal	167.5±55.0	148.7±44.3	133.0±43.0
750 μm nasal to fovea	156.5±62.0	149.2±44.3	138.1±35.1
750 μm temporal to fovea	144.0±49.5	131.9±44.8	134.9±46.4
Medium vessel thickness, mean±SD (μm)			
Subfoveal	192.9±85.7	191.5±76.4	144.7±43.6
750 μm nasal to fovea	172.0±79.5	160.7±66.4	119.1±52.1
750 μm temporal to fovea	153.7±77.2	173.9±61.8	145.4±65.4
Macular thickness, mean±SD (μm)	331.3±155.8	265.7±136.7	223.4±45.2
Neurosensory detachment, mean±SD (μm)	186.1±156.1	131.2±133.6	0

SD, standard deviation

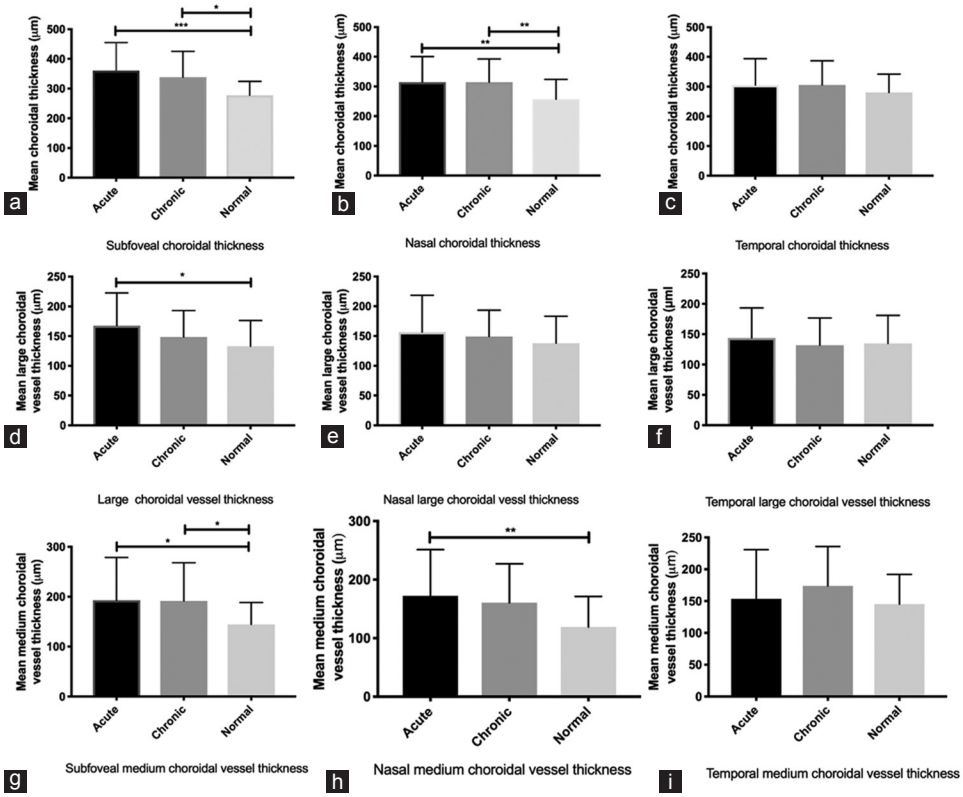

Figure 2. Optical coherence tomography-derived measurements of choroidal thickness and large and medium vessel thickness. Measurements of choroidal thickness performed at the fovea and loci 750 µm nasal and temporal to the fovea (a, b and c, respectively), as well as large vessel choroidal thickness (d, e and f, respectively) and medium vessel choroidal thickness (g, h and i, respectively). Eyes with acute (black) and chronic central serous retinopathy (dark grey) and controls (light grey) are included for all layers and measurement locations. Statistical analysis of subgroup thickness measurements (generalized estimating equation, one-way analysis of variance, post-hoc Tukey's test * $P < 0.05$, ** $P < 0.001$, *** $P < 0.0001$).

This was accompanied by an increase in the thickness of both large and medium choroidal vessel layers in eyes with acute CSC in this study. The mechanism of choroidal thickening warrants further investigation. It has been suggested that non-vascular smooth muscles cells may stretch out, causing enlargement of vessels and development of edema by extravasation through the vessel walls, thus altering choroidal thickness.[18,19] Choroidal thickening has also been suggested to be associated with sympathetic stimulation, focally increased hydrostatic pressure of the choroid, and even mineralocorticoid receptor overaction altering choroidal vessel dilatation.[20,21]

In this study, analysis of eyes with chronic CSC suggested an increase in subfoveal and nasal choroidal thickness compared with age-matched control eyes. However, the pattern of choroidal vessel layer thickness in the acute phase did not appear to be maintained in the chronic phase. In particular, medium vessel thickness but not large vessel choroidal thickness appeared to remain larger in chronic CSC eyes compared with control eyes. Some studies have suggested relative attenuation of inner choroidal layers in CSC eyes.[11,22] This may therefore reflect variation in chronicity of the disease between our patients and those of previous studies.

Significant enlargement of choroidal thickness and large vessel layers in acute CSC eyes appears to be replicated at the nasal locus (measured 750 µm nasal to the fovea) but not in the temporal locus. OCT analysis of topographic changes in choroidal thickness in CSC eyes has also revealed variation in choroidal thickness enlargement.[16,23] Clinicians should be aware that the choroidal thickness changes seen in CSC eyes are not necessarily diffuse and CSC may be a multifocal disease process. Therefore, ensuring that choroidal thickness is assessed at the same retinal locus is imperative when assessing disease activity and progression in CSC using this parameter.

Analysis of the progression of CSC has an important role particularly when considering photodynamic therapy. Determination of the choroidal vessel layers involved could be crucial in PDT settings because higher light doses have been associated with the closure of deeper choroidal vascular tissue compared to lower light doses that only affect the choriocapillaris, according to electron microscopy studies.[17] The apparent persistence in increased choroidal thickness reported after PDT

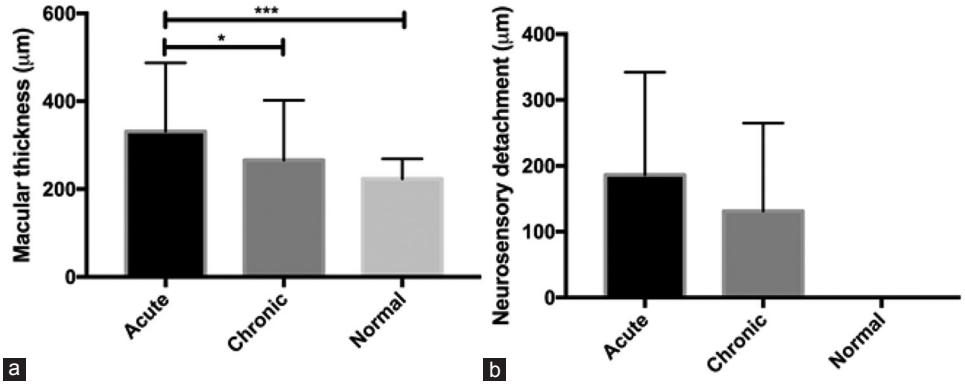

Figure 3. Optical coherence tomography-derived measurements of macular thickness and neurosensory detachment. Enhanced-depth imaging manual measurements at the fovea of the macular layer (a) and neurosensory detachment (b). Graphs show thicknesses in the subgroups included in the study: eyes with acute and chronic central serous retinopathy and age-matched control eyes. Statistical analysis of each thickness measurement between the subgroups (generalized estimating equation, one-way analysis of variance, post-hoc Tukey's test * $P < 0.05$, ** $P < 0.001$, *** $P < 0.0001$).

may be a reflection of inadequate PDT or alteration in choroidal vasculature after treatment.[23] Accurate evaluation of disease chronicity will be important to help characterize treatment response to new PDT strategies. Large choroidal vessel thickness alteration may be useful to determine disease chronicity and distinguish these patients during recruitment in clinical trials of new treatments for CSC.

Increased choroidal thickness and dilated outer choroidal vessels have also been demonstrated in several pachychoroid spectrum conditions, including CSC, pachychoroid neovasculopathy, and pachychoroid pigment epitheliopathy.[24,25] Further evaluation of alterations in choroidal vascular layers in pachychoroid spectrum disorders would help in evaluating the role of the choroidal vasculature in the development of these conditions in both acute and chronic disease. Evaluating whether subjects with exogenous steroid use have different choroidal thickness measurements would also be of interest.

Strengths of this study include the investigation of multiple layers, including choroidal vessel layers in both acute and chronic phases. Analysis at multiple retinal loci allowed investigation of whether these changes are part of a diffuse response at the posterior pole in CSC eyes. Limitations of this study include its retrospective multi-center nature, inclusion of different ethnic populations, and only two observers performing measurements. However, the individuals involved in data collection at the various study sites did not perform data analysis. Diurnal variation in choroidal thickness may have affected our measurements. Considering the complex arrangement of choroidal vessels, B scans may not be the ideal approach to assess the diameter of choroidal vessels; structural en-face images may provide a more accurate measurement Different gender ratio between the controls and patients with CSC may have affected the conclusions drawn in this study. Our methodology included the choriocapillaris in the medium choroidal vessel layer thickness; alterations in choriocapillaris thickness may therefore have affected our measurements.

In summary, we report an increase in the thickness of both the medium and large choroidal vessel layers in eyes with acute CSC. Choroid is thicker than normal in chronic CSC, and thickness of subfoveal medium choroidal vessel layer was larger than in control eyes, however, thickness of subfoveal large choroidal vessel layer was not different from control eyes. These choroidal changes in CSC could be useful in determining the chronicity of CSC and developing possible structural end points in clinical trials of CSC treatments.

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Conflicts of Interest

There are no conflicts of interest.

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