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REVIEW

Choroidal binarization analysis: clinical application

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Abstract

Introduction Image processing of optical coherence tomography scans through binarization techniques represent a non-invasive way to separately asses and measure choroidal components, in vivo. In this review, we systematically search the scientific literature regarding binarization studies published so far.

Methods A systematic research was conducted at PubMed database, including English literature articles for all of the following terms in various combinations: binarization, choroid/al, enhanced depth spectral domain/swept source optic coherence tomography, and latest publications up to November 2018 were reviewed.

Results Thirty-seven articles were included and analyzed regarding studied disease, binarization method, studied variables, and outcomes. Most of the studies have focused on the more common retinal pathologies, such as age-related macular degeneration, central serous chorioretinopathy and diabetic retinopathy but binarization techniques have also been applied to the study of choroidal characteristics in ocular inflammatory diseases, corneal dystrophies and in postsurgical follow-up. Advantages and disadvantages of binarization techniques are also discussed.

Conclusion Binarization of choroidal images seems to represent a promising approach to study choroid subcomponents in an increasingly detailed manner.

Keywords Choroid · Choroidal imaging · Binarization · Optic coherence tomography

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Introduction

The choroid is a cardinal structure within the eye globe, with important functions in outer retinal vascular supply, thermoregulation and possibly in the regulation of scleral growth [1]. It is a vascular layer of the eye composed of blood vessels embedded in a stromal matrix. It contains connective tissue and

cellular elements such as fibroblasts, leukocytes, non-vascular smooth muscle cells, neurons and melanocytes. It has one of the highest blood flow rates in the body [1, 2] and is highly important for the integrity of the retinal pigment epithelium (RPE) and the retina altogether [3, 4]. Its role in the pathogenesis of various ocular diseases has been vastly studied and it has been implicated in age-related macular degeneration (AMD), central serous chorioretinopathy (CSC), polypoidal choroidal vasculopathy (PCV) and pathologic myopia [5–10]. For this reason, choroidal imaging techniques are on demand. A major advance in choroidal imaging was introduced by Spaide et al. [11], with the advent of enhanced depth imaging in spectral domain optical coherence tomography (EDI SD-OCT). Through repositioning of the OCT closer to the eye in order to bring the choroid closer to the zero delay line, it allowed for a noninvasive, more detailed visualization of the choroid in comparison with conventional SD-OCT. This novel advances have allowed in vivo imaging of the choroidal components which had only been studied in histological or electron microscopy sections from postmortem samples [12–14]. One major advantage from EDI-choroidal enhancing imaging technology has been the more accurate measure of the choroidal thickness (CT). However, integrating data of such a complex tissue as the choroid-based solely on its thickness are intuitively an under-use of the output of commercially available imaging devices. Choroidal binarization includes a more complex analysis of the raw data, captured in vivo, adding more functionally relatable parameters, such as the status of individual choroidal components. The rationale behind this review is to provide a thorough investigation on what is already published regarding this quantitative measurement of choroidal vascular and stromal elements.

Image binarization technique

Sonoda et al. [15] proposed a reproducible, repeatable, quantitative way to measure vascular luminal and stromal components through image binarization, resorting to the open-access software ImageJ. Image binarization consists in converting gray-scale images into black-and-white binaries, through a process involving, image thresholding. The original image binarization method starts with the selection of a region of interest (ROI) of an EDI SD-OCT scan, which is limited by the hyperreflective RPE line internally and the choroid–scleral border externally. This is accomplished through the polygonal tool of the open-access software ImageJ. The vascular lumen of three vessels with more than 100 μm is selected through the oval tool in order to determine average reflectivity. Average brightness is set at a minimum value to minimize OCT image noise. Furthermore, the image is converted to 8 bits and submitted to autolocal thresholding (Niblack method). In order to select the luminal area, the image is again converted into RGB (red, green, blue) and the color threshold tool is applied for the selection of dark pixels. The luminal area (LA) is calculated from the sum of dark pixel areas, and the interstitial or stromal area (SA) results from the subtraction of LA from the total selected choroidal area (TCA) of the ROI. Agrawal et al. proposed a modified method which involves binarization prior to the selection of the ROI in order to increase the accuracy of choroid border determination. Furthermore, the concept of the choroidal vascularity index (CVI) was introduced, which corresponds to the ratio between choroidal luminal area to total choroidal area. Various thresholding techniques have been described, including Otsu's, Bernse's and Niblack's autolocal thresholding [16, 17]. The majority of binarization studies use Niblack's autolocal thresholding, allegedly due to its capacity to consider the mean and standard deviation of all pixels in the ROI with an increased resolution and demarcation of different choroidal areas [18, 19]. Binarization procedures have also been applied to *en face* swept source (SS) OCT images, with CVI being replaced by other parameters such as choroidal vascular area or density (CVA or CVD = VA/whole choroidal area) and choroidal vascular volume (CVV: CVD × CT) [20–23].

Sonoda et al. [24] recently developed a software called *EyeGround* to perform binarization in a simpler, faster and increasingly automatic manner, with

automatic detection of the RPE–choroid border. Despite its advantages, the inter-method agreement for all measurements, with and without *EyeGround,* was high (ICC 0.990–0.916).

Vupparaboina et al. proposed a fully automated method, without resorting to ImageJ, involving image median filtering, adaptive histogram equalization, exponential enhancement and binarization through Otsu's bimodal histogram-based thresholding. Choroidal borders were determined by locating the RPE, through a gradient-based Canny edge operator, and the choroid outer border (COB) through a structural similarity index, Hessian matrix analysis and tensor voting. The authors claim that this method is more accurate compared to the conventional *ImageJ*-based approach [25]. Mahajan et al. [26] proposed another automated approach to choroidal binarization involving denoising, segmentation (through population thresholding) and contour detection (through boundary sensitive, intensity sensitive and vessel enhancement and detection). Recently Uppugunduri et al. suggested an interesting way to detect the boundary between Haller's and Sattler's layer, in an increasingly objective manner. The proposed method involves binarization and choroidal segmentation according to cross-sectional vessel LA [27].

Normal choroid

Sonoda et al. performed a study on 180 healthy eyes and correlated vascular and stromal areas with ocular and systemic findings. In a multivariate analysis, axial length and age significantly and negatively correlated with LA, SA and TCA, with age showing the strongest correlation [28]. Agrawal et al. adapted the imaging segmentation technique proposed by Sonoda et al. [15, 28] and introduced the concept of the choroidal vascularity index (CVI), resulting from the ratio between the LA and TCA. This group of investigators analyzed the subfoveal CVI of 345 healthy subjects through EDI SD-OCT, and correlated ocular and systemic findings with subfoveal choroidal thickness (SFCT) and CVI in a multivariate regression analysis [18]. Age, axial length, higher IOP, LA and systolic blood pressure correlated with CT, as had been shown in previous studies [29, 30] but not with CVI, while the only parameter that was found to be correlated with CVI was the SFCT. Two other studies reported an association between CT and age but not between CVI and any other factors [31, 32]. Fujiwara et al. studied the large choroidal vessel layer in *en face* SS-OCT scans (5×5 mm^2) of 163 eyes of normal volunteers. Evaluated parameters were age, gender, refractive error, axial length and SFCT. The only parameters that were significantly correlated with vascular density were age (negative correlation) in patients 30 years or older and SFCT (positive correlation). Medrano et al. found a correlation between TCA, LA, vascular density and age, but not SA [33].

Choroid in ocular pathology

Since binarization techniques have been applied to the choroidal layer, numerous studies have been conducted on patients with established retinal and choroidal diseases. See Table 1 for a detailed description of methods and results. Although promising, the majority of studies are still limited by small sample sizes and retrospective study designs.

Age-related macular disease (AMD) and polypoidal choroidal vasculopathy (PCV)

Sonoda et al. [15] compared the SFCT, TCA, SA and LA between eyes with exudative AMD, prior and after photodynamic therapy (PDT) and concluded that all parameters decreased significantly. Interestingly, there was no difference between AMD eyes at baseline and fellow eyes. Koh et al. compared AMD eyes to

Table 1 Summarization of characteristics and most important findings of studies involving choroidal image binarization

References	*N*	Binarization details (thresholding method; used software; OCT scan type; binarized area; binarization technique according to first publishing authors)	Study details (design, variables)	Results
Sonoda et al. [28]	Healthy eyes (180)	Niblack autolocal thresholding; ImageJ; EDI SD-OCT; 7500 μm. Technique: Sonoda	Prospective. TCA, LA, SA, SA/LA	TCA ($\bar{x}$ = 1.84 mm^2); LA ($\bar{x}$ = 1.21 mm^2); SA ($\bar{x}$ = 0.63 mm^2). TCA, LA and SA negatively correlated with age ($r = -0.70$ to -0.739) and axial length ($r = -0.350$ to -0.426). LA/SA ratio negatively correlated with axial length ($r = -0.531$, $p < 0.01$), age ($r = -0.389$, $p < 0.01$) and sex ($r = -0.153$, $p = 0.04$)
Agrawal et al. [18]	Healthy eyes (345)	Niblack autolocal thresholding; ImageJ; EDI SD-OCT; N/S; Technique: Agrawal	N/S. TCA, LA, SA, CVI, LA/SA, SFCT	TCA ($\bar{x}$ = 0.74 mm^2); LA ($\bar{x}$ = 0.49 mm^2); SA ($\bar{x}$ = 0.25 mm^2); CVI (65.61%); LA/SA (1.92); SFCT ($\bar{x}$ = 241.34 μm)
Medrano et al. [33]	Healthy eyes (136)	Otsu autolocal thresholding; SS-OCT, 1500 μm; Technique: Vupparaboina	Cross-sectional. CT, SFCT, TCA, LA, SA, %VA (comparable to CVI)	Negative correlation between age, TCA ($r = -0.396$; $p < 0.001$), LA ($r = -0.664$; $p < 0.001$) and CVI ($r = -0.653$; $p < 0.001$), but not SA ($p = 0.712$)
Sonoda et al. [15]	Exudative AMD prior and after PDT (15); fellow eyes (15); healthy control group (20)	Niblack autolocal thresholding; ImageJ; EDI SD-OCT; 1500 μm. Technique: Sonoda	Retrospective. SFCT, TCA, LA, SA, LA/CA	*Healthy eyes* TCA ($\bar{x}$ = 675,526 μm^2), LA ($\bar{x}$ = 445,562 μm^2); SA ($\bar{x}$ = 229,964 μm^2), LA/CA (65.4%) *Comparison between exudative AMD before and after 6 mo of PDT* Reduction in SFCT (278.8/217.5 μm, $p = 0.01$), TCA (629,578/500,778 μm^2), SA (215,134/181,905 μm^2, $p < 0.01$) and LA (414,443/318,872 μm^2, $p < 0.01$). No significant differences between AMD at baseline and fellow eyes, in any parameter

Table 1 continued

References	*N*	Binarization details (thresholding method; used software; OCT scan type; binarized area; binarization technique according to first publishing authors)	Study details (design, variables)	Results
Koh et al. [34]	AMD [63; dry (36) and exudative (27)]; fellow eyes (35); healthy controls (30)	Niblack autolocal thresholding; ImageJ; EDI SD-OCT; N/S; Technique: Agrawal	Retrospective. SFCT, CVI	CVI: Lower in all AMD eyes (64.04%) and fellow eyes (64.66%) compared to healthy controls (66.07%), with $p < 0.001$ and $p = 0.007$, respectively. No difference between all AMD eyes and fellow eyes ($p = 0.21$) and between exudative and dry eyes ($p = 0.29$). SFCT: No significant difference between groups
Bakthavatsalam et al. [32]	PVC (44); t-AMD (29); healthy controls (72)	Niblack autolocal thresholding; ImageJ software, SS-OCT, 1500. Technique: Agrawal	Cross-sectional. SFCT, TCA, LA, CVI	SFCT higher in PCV than AMD (214.23/172.74 μm; $p = 0.03$), LA higher in PCV than t-AMD (0.23/0.19 mm^2; $p < 0.05$); *CVI* No difference between PCV and t-AMD ($p = 0.10$); lower in PCV and t-AMD compared to controls (64.94/68.53%; $p = 0.01$ and 68.53/62.54%; < 0.01, respectively); lower in t-AMD compared to fellow eyes (62.54/65.70%; $p = 0.02$). Age was related to a lower SFCT but not CVI ($p < 0.01$ and $p = 0.07$, respectively)
Wei et al. [31]	Treatment-naive t-AMD (20); PVC (22); fellow eyes (42)	Niblack autolocal thresholding; ImageJ; EDI SD-OCT; "entire length of foveal scan". Technique: Agrawal	Prospective. SFCT, TCA, LA, SA, CVI	LA (2.19/2.49; $p < 0.01$) and CVI (60.14/62.75%; $p < 0.01$) were lower in t-AMD + PCV eyes compared to fellow eyes, without a significant difference in TCA and CT. There was no significant difference in TCA, LA, SA and CVI between t-AMD and PVC eye subgroups. CT ($\beta = -3.87$; $p < 0.0001$) but not CVI ($p = 0.19$) was significantly correlated with age

Table 1 continued

References	*N*	Binarization details (thresholding method; used software; OCT scan type; binarized area; binarization technique according to first publishing authors)	Study details (design, variables)	Results
Ng et al. [48]	Exudative maculopathy with (38) and without (35) pachyvessels	Niblack autolocal thresholding; ImageJ; SS-OCT, 1500 µm. Technique: Agrawal	Retrospective. SFCT, CVI	52.1% of eyes had pachyvessels, of which 64.3% had polypoidal lesions. The presence of pachyvessels correlated with age (69.1/73.7; OR = 0.95, $p = 0.04$), SFCT (225.8/157.3 µm; OR = 1.08, $p < 0.01$), CVI (65.4/58.3%; OR = 1.12, $p = 0.01$) and polypoidal lesions (64.3/37.5%; OR = 1.24, $p = 0.01$) in a univariate regression, whereas only CVI maintained correlation (OR = 1.24, $p = 0.04$) with a multivariate regression model. High agreement of SFCT and CVI in fellow eyes ($r = 0.73$ and 0.85, respectively)
Daizumoto et al. [47]	PCV before (40) and after 3 and 12 mo of as needed anti-VEGF injection (40); healthy controls (38)	Niblack autolocal thresholding; ImageJ; EDI SD-OCT; 1500 µm; N/S. Technique: Sonoda	Retrospective. The choroid was segmented according to vessel diameter into inner and outer choroid. CCT, whole choroid LA, SA and CA; inner CA, LA, SA; outer CA, LA, SA; PI (outer LA/outer SA)/(inner LA/inner SA)	*In PCV eyes,* CCT decreased from baseline to 3 and 12 mo (all, $p < 0.05$). Whole choroid LA and SA decreased at 3 and 12 mo ($p < 0.005$). Inner SA decreased ($p < 0.001$) and outer layer LA decreased ($p < 0.001$) at 3 and 12 mo. Decrease in PI between baseline and 3 and 12 mo ($p < 0.001$, $p = 0.011$); higher baseline PI in eyes without dry maculas at 12 mo ($p = 0.003$). Correlation between baseline PI and decreased CCT and BCVA improvement at 12 mo ($p = 0.024$, $p = 0.002$). Increased PI fluctuation with recurrences ($p < 0.001$). *PCV eyes versus controls* PI higher in PVC eyes at baseline, 3 and 12 mo compared to fellow eyes and controls ($p < 0.005$)

Table 1 continued

References	*N*	Binarization details (thresholding method; used software; OCT scan type; binarized area; binarization technique according to first publishing authors)	Study details (design, variables)	Results
Gupta et al. [49]	t-AMD (78), PCV [78; CT $\geq$ 275 (39) $<$ 275 μm (39) and $<$ 200 μm (21)]	Niblack autolocal thresholding; ImageJ; EDI SD-OCT; 1500 μm and 6000 μm. Technique: N/S	Data from a prospective study. CT, SFCT, LA	Higher CT (263.62/224.33 μm; $p = 0.004$), SFCT (288.54/243.47 μm; $p = 0.002$), subfoveal LA (0.177/0.1486 mm^2; $p = 0.003$) and macular LA (0.639/0.554 mm^2; $p = 0.013$) in PVC eyes compared to t-AMD, respectively. After age adjustment, these differences were lost except for nasal CT ($p < 0.029$). In PCV eyes with CA $\geq$ 257 μm, all parameters were significantly higher than t-AMD and remained significant after adjusting for age ($p < 0.001$). In PCV with CT $<$ 200 μm, mean CT, SFCT, subfoveal and macular LA were lower in comparison with t-AMD ($p < 0.001$), which remained after age adjustment
Ting et al. [50]	Treatment-naive t-AMD (55) and PCV (63)	Niblack autolocal thresholding; ImageJ; EDI SD-OCT; N/S. Technique: Agrawal	Prospective. 12 mo of treatment with anti-VEGF (PRN) or PDT. Patients were stratified into tertiles (upper, mid and lower tertile), according to CVI at baseline. SFCT, TCA, LA, SA, CVI	Decrease in SFCT between baseline and 3, 6 and 12 mo for AMD and PCV ($p < 0.001$). Decrease in TCA, LA, SA in AMD and PCV between baseline and follow-up ($p < 0.001$). CVI changes for AMD and PCV were not significant between baseline and follow-up; however, eyes in the highest CVI tertile exhibited a decrease in CVI at 12 mo (65.3/62.4%; $p < 0.001$). No statistically significant difference between t-AMD and PCV for whole CT parameters (CVI, TCA, LA, SA). No difference in CVI before and after treatment in PCV eyes submitted to monotherapy or combined therapy with PDT. SFCT decreased in both groups ($p = 0.04$ and $p < 0.0001$, respectively)

Table 1 continued

References	*N*	Binarization details (thresholding method; used software; OCT scan type; binarized area; binarization technique according to first publishing authors)	Study details (design, variables)	Results
Masuda et al. [51]	RPD eyes (20); healthy controls (35)	Niblack autolocal thresholding; ImageJ software, EDI SD-OCT, 1500 μm. Technique: Sonoda	Cross-sectional. TCA, SA, LA, LA ratio	TCA (193,370/273,951 μm^2, $p = 0.001$), LA (127,505/183,152 μm^2, $p = 0.001$), SA (65,865/90,763 μm^2, $p = 0.003$) decreased in RPD eyes compared to controls. No significant difference in LA ratio
Zheng et al. [22]	Dry AMD without RPD (25); dry AMD with RPD (25)	N/S; SS-OCT, *en face* 12 × 12 mm; Technique: N/S.	Data from a prospective study. Choroidal division into inner and outer subfields (superonasal, superotemporal, inferonasal and inferotemporal). CT, CVD	CT was higher in AMD without RPD compared to AMD with RPD in all, except the outer inferotemporal subfield ($p = < 0.001–0.023$). CVD was higher in AMD without RPD in the central ($p < 0.001$), inner superonasal ($p < 0.002$), outer superonasal subfields ($p < 0.01$) and in overall CVD (0.55/0.45; $p < 0.001$) compared to AMD with RPD
Agrawal et al. [56]	CSC eyes (78): acute CSC (32), resolved CSC (19); fellow eyes without history of CSC (27); healthy control group (30)	Niblack autolocal thresholding; ImageJ; EDI SD-OCT; 1500 μm; N/S. Technique: Agrawal	Retrospective. SFCT, TCA, LA, SA, CVI	*SFCT* Higher in active CSC compared to fellow eyes and controls (474.6/401.6/278.5 μm; $p < 0.0001$), higher in fellow eyes compared to resolved CSC and controls (401.6/374.6/278.5 μm; $p < 0.0001$); *LA* Higher in active CSC compared to other groups (1.12/0.84/0.83/0.98 mm^2; p = N/S). *CVI* Higher in active CSC compared to fellow eyes and healthy controls (70.54/67.42/65.18%; $p < 0.0001$), higher in fellow eyes compared to resolved CSC and controls (67.45/65.44/65.18%; $p < 0.0001$). No statistically significant difference in SA between groups

Table 1 continued

References	*N*	Binarization details (thresholding method; used software; OCT scan type; binarized area; binarization technique according to first publishing authors)	Study details (design, variables)	Results
Sonoda et al. [57]	CSC eyes (40), fellow eyes (40), control eyes (40)	Niblack autolocal thresholding; ImageJ; EDI SD-OCT; 7500 μm. Technique: Sonoda	Retrospective. TCA, total choroidal hyporeflective area (HypoA), total choroidal hyperreflective area (HyperA). Segmentation into inner and outer choroid through modified Branchini method	TCA (702,101/580,833/442,877 μm^2), whole hypoA (520,020/428,276/301,696 μm^2) and whole hyperA (182,081/152,557/141,181 μm^2) all larger in CSC compared to fellow eyes and controls ($p < 0.01$). TCA and whole HypoA but not HyperA larger in fellow eyes than controls ($p < 0.01$). Inner choroid: HyperA but not HypoA larger in CSC than in fellow eyes and controls ($p < 0.01$). Outer choroid: HypoA but not HyperA higher in CSC than in fellow eyes and controls ($p < 0.01$). Parameters of the inner choroid were not different between fellow eyes and controls. Outer choroid HypoA but not HyperA larger in fellow eyes than controls ($p < 0.01$). 87.5% of CSC eyes, 20% of fellow eyes, 15% of controls had an CSC index > 1

Table 1 continued

References	*N*	Binarization details (thresholding method; used software; OCT scan type; binarized area; binarization technique according to first publishing authors)	Study details (design, variables)	Results
Kinoshita et al. [59]	Chronic active CSC before (29) and after 3 mo of hPDT (29), fellow eyes (24)	Niblack autolocal thresholding; ImageJ software, EDI SD-OCT, 1500 μm; N/S. Technique: Sonoda	Retrospective. CT; TCA; total choroidal hyporeflective area, and in the inner and outer choroid; total choroidal hyperreflective area, and in inner and outer choroid; ratio of hyporeflective area to TCA; CSC index defined as: [(Outer hyporeflective area/outer hyperreflective area)/(inner hyporeflective area/inner hyperreflective area)]	Total CT (408.5/310.9 μm; $p < 0.001$), TCA (6.14/4.72 × 10^5 μm^2; $p < 0.0001$), total hyporeflective area (4.41/3.24 × 10^5 μm^2; $p < 0.001$) and total hyperreflective area (1.73/1.49 × 10^5 μm^2; $p = 0.025$) higher at baseline in CSC eyes compared to fellow eyes. Total hyporeflective area to TCA ratio of CSC eyes at baseline was higher than fellow eyes (70.8/67.1%, $p = 0.020$). CT (408.5/354.9 μm; $p = 0.001$), total TCA (6.14/5.36 × 10^5 μm^2; $p = 0.001$), total hyporeflective area (4.41/3.71 × 10^5 μm^2; $p = 0.003$) and hyporeflective to TCA ratio (70.8/67.9%, $p = 0.009$) were all higher at baseline and three mo of follow-up. Inner choroid: hyperreflective but not hyporeflective area higher in CSC eyes at baseline compared to fellow eyes and after 3 mo of hPDT ($p < 0.001$, $p = 0.002$). Outer layer: Hyporeflective but not hyperreflective areas higher in CSC eyes at baseline compared to fellow eyes and after 3 mo of hPDT ($p < 0.001$, $p = 0.001$). The CSC index was higher in CSC at baseline (2.36) compared to fellow eyes (1.24; $p < 0.001$) and after 3 mo of hPDT (1.72; $p < 0.002$)

Table 1 continued

References	*N*	Binarization details (thresholding method; used software; OCT scan type; binarized area; binarization technique according to first publishing authors)	Study details (design, variables)	Results
Kuroda et al. [20]	CSC eyes (40): classic (21), diffuse retinal pigment epitheliopathy (DRPE) (13) and multifocal posterior pigment epitheliopathy (MPPE) (6); fellow eyes (28); healthy controls (26)	Otsu automatic thresholding; ImageJ software, SS-OCT, *en face* 3×3 mm^2 and 6×6 mm^2 with inner and outer choroid automatic segmentation at 2.6 µm; Technique: N/S	Prospective. SFCT, %VA	%VA higher in CSC compared to controls at inner choroid (3×3 mm^2: 53.4/52.2%, $p = 0.028$; 6×6 mm^2: 54.0/51.9; $p < 0.001$) and outer choroid (3×3 mm^2: 66.9/54.9%, $p < 0.001$; 6×6 mm^2: 64.8/53.8, $p < 0.001$) levels. Fellow eyes had higher outer choroid %VA than controls in the 3×3 mm^2 (62.1/54.9%; $p < 0.001$) and 6×6 mm^2 regions (61.0/53.8%; $p < 0.001$) and inner choroid 6×6 mm^2 region (53.4/51.9%, $p = 0.006$), but not the inner 3×3 mm^2 region. CSC eyes had higher outer choroid %VA than fellow eyes (3×3 mm^2: 65.5/62.1%, $p = 0.12$; 6×6 mm^2: 63.2/61.0%; $p = 0.03$), but not at the inner choroid level. MPPE subtype had higher inner %VA (55.8%) compared to classic (53.1%; $p = 0.038$) and DRPE (52.9%; $p = 0.042$). SFCT was larger in CSC and fellow eyes compared to controls (all, $p < 0.001$) and between CSC and fellow eyes ($p = 0.005$). No significant change in any parameter between active and resolved CSC

Table 1 continued

References	*N*	Binarization details (thresholding method; used software; OCT scan type; binarized area; binarization technique according to first publishing authors)	Study details (design, variables)	Results
Wang et al. [21]	Diabetics (143), No DR (27), NPDR (47), NPDR + DME (51), PDR (18); healthy controls (64)	Otsu automatic thresholding; ImageJ; SS-OCT; en face 12 × 9 mm^2 and 6 × 6 mm^2 with inner and outer choroid automatic segmentation at 2,6 μm; Technique: N/S	Prospective. CVD, CVV	Overall mean CVD was smaller in NPDR (0.22/0.23; $\beta = -0.01$, $p = 0.041$), NPDR + DME (0.22/0.23; $\beta = -0.02$, $p = 0.009$) and PDR (0.20/0.23; $\beta = -0.02$, $p = 0.005$) compared to controls. Mean macular CVD was smaller in NPDR + DME (0.28/0.31; $\beta = -0.03$, $p = 0.023$) and PDR (0.26/0.31; $\beta = -0.04$, $p = 0.011$) compared to controls. Macular CVV was lower in PDR (0.020/0.025; $\beta = -0.007$, $p = 0.011$) compared to controls (results stem from a multivariate linear regression analysis)

Table 1 continued

References	*N*	Binarization details (thresholding method; used software; OCT scan type; binarized area; binarization technique according to first publishing authors)	Study details (design, variables)	Results
Kim et al. [71]	No DR (30); Mild/Moderate NPDR (41); Severe NPDR (40); PDR (8) PRP-treated (35), CSME (31); Healthy controls (45)	Niblack autolocal thresholding; ImageJ; SS-OCT; 1500; automatic CT determination. Technique: Agrawal	Retrospective. SFCT, CVI	SFCT: In comparison with healthy controls (320.00 μm), values were lower in no DR (258,13 μm, $p = 0.005$), PDR (258.75 μm; $p = 0.043$) and PRP (276.29 μm, $p = 0.017$). In comparison with no DR, values were higher in mild/moderate NPDR (310.22 μm, $p = 0.009$) and severe NPDR (304.53 μm, $p = 0.018$). CVI: Lower in all diabetic patients in general compared to controls ($p < 0.001$). Lower in PDR (63.48%) than controls (69.08%, $p < 0.001$), no DR (67.07%, $p = 0.029$) and mild/moderate NPDR (66.28%; $p = 0.015$). The PRP group had lower values than no DR (65.38/67.07%; $p = 0.04$) but not in comparison with other DR groups. In a multivariate analysis, the variables that correlated with CVI were SFCT ($p = 0.003$) and a thinner central retina ($p = 0.024$), but not demographic characteristics or systemic factors

Table 1 continued

References	*N*	Binarization details (thresholding method; used software; OCT scan type; binarized area; binarization technique according to first publishing authors)	Study details (design, variables)	Results
Tan et al. [70]	DM with or without DR (38), healthy controls (38)	Niblack autolocal thresholding; ImageJ software, EDI SD-OCT, 1500 μm. Technique: Sonoda	Prospective. TCA, LA, SA, CVI	No statistically significant difference in TCA, LA and SA between healthy controls and diabetics altogether. CVI lower in DM patients compared to controls (65.10/67.20%; $p < 0.0001$). TCA (0.75/0.97 mm^2; $p = 0.026$), LA (0.49/0.62 mm^2; $p = 0.036$), SA (0.26/0.34 mm^2; $p = 0.01$) were increased in diabetics with DR compared to no DR, whereas CVI was decreased (65.30/64.20%; $p = 0.035$). CVI correlated with the presence of DM ($p < 0.0001$) but not with age, gender or AL
Agrawal et al. [78]	VKH eyes (16), control eyes (12)	Niblack autolocal thresholding; ImageJ; EDI SD-OCT; 1500 μm. Technique: Agrawal	Retrospective. CT and CVI at baseline and at follow-up (6–12 mo). CT, CVI	In the VKH eyes: CT and CVI decreased between baseline and follow-up (359.23/282.62 μm; $p < 0.0001$) and (70.03/66.94%; $p < 0.0001$), respectively. Higher CT (359.23/274.09 μm; $p = 0.003$) and CVI (70.03/64.63%; $p < 0.0001$) in VKH compared to control eyes
Jaisankar et al. [79]	VKH(12); healthy controls (8)	Niblack autolocal thresholding; ImageJ; SS-OCT; "entire length of scan''. Technique: modified Sonoda	Prospective, interventional. CT, SFCT,TCA, LA, SA, CVI	Overall CT decreased after treatment (261.07/217.08 μm; $p < 0.0001$). CVI decreased (67.97/66.12%; $p = 0.02$) and choroidal stromal index increased after treatment (32.03/33.8%; $p = 0.02$). No significant change in TCA, LA and SA

Table 1 continued

References	*N*	Binarization details (thresholding method; used software; OCT scan type; binarized area; binarization technique according to first publishing authors)	Study details (design, variables)	Results
Liu et al. [80]	Chronic VKH with anterior segment recurrence (40, 28 complete and 12 incomplete); Healthy controls (40)	Niblack autolocal thresholding; ImageJ; EDI SD-OCT; 1500 μm. Technique: modified Sonoda	N/S. CT, TCA, LA, SA, CVI	CT: thinner in quiescent eyes compared to controls ($p = 0.03$), with a significant increase in anterior acute recurrence ($p = 0.025$). TCA (1.37/1.84 mm^2; $p < 0.0001$), LA (0.99/1.28 mm^2; $p < 0.0001$), SA (0.38/0.56 mm^2; $p < 0.0001$) lower in quiescent stage compared to controls. CVI higher in quiescent VKH than in controls (0.75/0.70; $p < 0.0001$). CVI decrease during and acute attack (0.75/0.72; $p = 0.019$), and increase in resolution (0.72/0.75; $p = 0.01$)
Kawano et al. [81]	Acute, treatment-naive VKH (32)	Niblack autolocal thresholding; ImageJ; EDI SD-OCT; 7500 μm; N/S. Technique: Sonoda	Retrospective. At baseline, 1 week and 1 month of follow-up. CT, TCA, LA, SA, CVI	CT (678.8/363.3 μm, $p < 0.01$), TCA (472/242 $\times$ 10^4 μm; $p < 0.01$), LA (285/163 $\times$ 10^4 μm; $p < 0.01$), SA (188/80 $\times$ 10^4 μm; $p < 0.01$) reduced between baseline and 1 week but not between 1 week and 1 month of treatment. CVI: Increased between baseline and 1 week of treatment (0.6/0.67, $p < 0.01$), but not between 1 week and 1 month. Increased percent reduction of SA (56.5%) compared to LA (42.5%) between baseline, 1 week and 1 month of treatment ($p < 0.01$)
Onal et al. [82]	Behçet uveitis (28); healthy controls (28)	Otsu's thresholding; MATLAB; EDI SD-OCT; 1500 μm	Prospective. SA/LA (designated as choroidal stromal-to-choroidal lumen ratio), SFCT	SA/LA, was lower in Behçet compared to controls (0.413/0.351; $p = 0.003$); SFCT was lower in Behçet compared to controls (352.750/263.500 μm, $p < 0.001$)

Table 1 continued

References	*N*	Binarization details (thresholding method; used software; OCT scan type; binarized area; binarization technique according to first publishing authors)	Study details (design, variables)	Results
Agrawal et al. [19]	Panuveitis (19); fellow eyes (19)	Niblack autolocal thresholding; ImageJ; EDI SD-OCT; 1500 μm. Technique: Agrawal	Retrospective. CT, SFCA, LA, SA, CVI at baseline and at 3 mo of follow-up versus control group	In the panuveitis group: reduction in LA (0.6/0.5 mm^2; $p = 0.01$), CVI (74.1/69.4%; $p < 0.001$) and LA/SA ratio (3.00/2.3%; $p < 0.005$) but not CT ($p = 0.06$) between baseline and 3 mo. The control group did not show a significant change in CVI or any other parameter. Statistical difference between groups in LA ($r^2 = 0.14$; $p = 0.02$) and CVI ($r^2 = 0.52$; $p < 0.001$)
Agrawal et al. [83]	Active tubercular multifocal serpiginoid choroiditis (T-MSC) (18); healthy controls (30)	Niblack autolocal thresholding; ImageJ; EDI SD-OCT; "entire length of scan". Technique: Agrawal	Prospective. At active and healed stages T-MSC. CT, TCA, LA, SA, CVI.	CT (329.33/313.44 μm; $p < 0.001$); TCA (9.81/8.63 × 10^4 pixels; $p > 0.04$); LA (6.43/5.56 × 10^4 pixels; $p > 0.03$) and CVI (65.46/63.77%; $p < 0.05$) decreased between active and healed stages of T-MSC, respectively. CT (329.33/278.90 μm, $p < 0.001$); TCA (9.81/6.50 × 10^4 pixels; $p < 0.001$), LA (6.43/3.90 × 10^4 pixels; $p < 0.001$), SA (3.38/2.6 × 10^4 pixels; $p < 0.001$) were larger and CVI (65.46/66.90%; $p = 0.01$) was smaller in T-MSC eyes compared to controls
Alshareef et al. [90]	Myopia (AL 25–27.5 mm) (30), emmetropic (AL 23.5–24.5 mm) controls (30)	Niblack autolocal thresholding; ImageJ; EDI SD-OCT; 1500 μm. Technique: Vupparaboina	Retrospective. CT, TCA, LA, SA, LA/SA, CVI	Mean CT (181.1/300.3 μm, $p < 0.001$), TCA (1.38/1.83 mm^2; $p < 0.0001$) and SA (0.95/1.33 mm^2; $p < 0.0001$) were significantly lower in myopic eyes, which did not reflect significantly on CVI differences (25.46/30.25%; $p = 0.07$)

Table 1 continued

References	*N*	Binarization details (thresholding method; used software; OCT scan type; binarized area; binarization technique according to first publishing authors)	Study details (design, variables)	Results
Gupta et al. [89]	High myopia (≤ -6D) (515); emmetropic controls (88)	Niblack autolocal thresholding; ImageJ; EDI SD-OCT; 1500 μm and 6000 μm. Technique: N/S	Cross-sectional. CT, SFCT, LA, SA	Mean CT (257.19/371.33 μm, $p < 0.001$) lower in myopic eyes. Subfoveal TCA (0.416/0.608 mm^2) LA (0.236/0.314 mm^2) and SA (0.179/0.293 mm^2) were lower; CVI was higher (0.575/0.520 mm^2) in myopic eyes (all $p < 0.001$). Macular TCA (1.543/2.228 mm^2), LA (0.851/1.156 mm^2) and SA (0.692/1.071 mm^2) were lower, CVI (0.554/0.522) was higher in myopic eyes (all $p < 0.001$)
Ng et al. [91]	Myopic CNV (20), fellow eyes (20)	Niblack autolocal thresholding; ImageJ software, EDI SD-OCT, "entire length of scan". Technique: Agrawal	Prospective. SFCT, CVI	No change in CVI (59.44/58.59/59.25% at baseline, 6 mo and 12 mo, respectively; $p > 0.635$) before and after treatment and between CNV eyes and fellow eyes (59.44/59.03%; $p = 0.96$). SFCT decreased in CNV eyes between baseline and 12 mo of follow-up (69.20/54.75 μm; $p < 0.017$), but there was no difference between CNV at baseline and fellow eyes
Ratra et al. [92]	Stargardt eyes (78); healthy controls (50)	Niblack autolocal thresholding; ImageJ; SS-OCT; "entire length of scan". Technique: Agrawal	Retrospective. SFCT, CVI	CVI lower in Stargardt eyes compared do controls (62.51/65.45%; $p < 0.001$). VA correlated negatively with CVI ($r = -0.75$; $p < 0.001$) and positively with SFCT ($r = 0.21$; $p = 0.035$). No significant difference in SFCT between groups

Table 1 continued

References	*N*	Binarization details (thresholding method; used software; OCT scan type; binarized area; binarization technique according to first publishing authors)	Study details (design, variables)	Results
Hirashima et al. [95]	Bietti crystalline dystrophy (9), retinitis pigmentosa with EYS mutation (16), healthy controls (16)	Otsu automatic thresholding; ImageJ software; SS-OCT; *en face* 3×3 mm^2 with inner and outer choroid automatic segmentation at 2,6 µm; Technique: N/S	SFCT, ratio of SF inner against total thickness, outer CVA	Lower SFCT (102.9 vs. 208.5/237.8 µm), SFICT/SFTCT ratio (22.8 vs. 36.2/34.4%), outer CVA (43.34 vs. 53.73/52.80%) in BCG compared to EYS-RP and healthy controls (all, $p < 0.001$)

AMD age-related macular degeneration (*t* typical), *AL* axial length, *CCT* central choroidal thickness, *CNV* choroidal neovascularization, *CVD* Choroidal vascular density, *CVI* Choroidal vascular index, *CVV* Choroidal vascular volume, *CSC* central serous chorioretinopathy, *CSME* Central significant macular edema, *CT* choroidal thickness, *DM* diabetes mellitus, *DME* diabetic macular edema, *DR* diabetic retinopathy (*NPDR* non-proliferative, *PDR* proliferative types), *DRPE* diffuse retinal pigment epitheliopathy, *EDI SD-OCT* enhanced depth spectral domain optic coherence tomography, *HyperA* hyperreflective areas, *HypoA* hyporeflective areas, *IOP* intraocular pressure, *LA* luminal area, *mo* months, *MSC* multifocal serpiginous choroiditis (*t* tubercular), *MTX* methotrexate, *MPPE* multifocal posterior pigment epitheliopathy, *OR* odds ratio, *PCV* polypoidal choroidal vasculopathy, *PDT* photodynamic therapy (*h* half-fluence), *PRN* pro-re-nata intravitreal injection regimen, *PRP* panretinal photocoagulation, *PI* pachychoroid index, *RPD* reticular pseudodrusen, *SA* stromal area, *SALA* stromal-to-luminal area ratio, *SFCT* subfoveal choroidal thickness, *SS-OCT* swept source optic coherence tomography, *VA* visual acuity, *VEGF* vascular endothelial growth factor, *VKH* Voght–Koyanagi–Harada disease, *TCA* total choroidal area, *%VA* vascular area percentage

fellow eyes and healthy controls and further stratified AMD into dry and exudative subgroups. CVI was significantly lower in AMD eyes altogether, as well as in fellow eyes, compared to controls [34]. There was no statistical difference in CVI between AMD subtypes or between AMD eyes and fellow eyes. SFCT was not statistically different in any group. These findings point toward a possible subclinical disease in fellow eyes, unveiled through the measurement of the CVI but not CT.

Controversy still exists around the etiology of PCV, as to whether it is a distinct entity or a subtype of exudative AMD. Although both disease entities share common features, risk factors, prognosis and treatment response vary between them [35–38]. Recently, the choroid has been pointed out as one of the main differences, with findings of a thinner CT in typical AMD (t-AMD) and an increased CT in PCV [6, 9, 39]. Nevertheless, CT has been reported to vary in t-AMD [40, 41]. The pachychoroid configuration has recently been described and can be found in various retinal diseases including CSC, PCV and retinal pigment epitheliopathy [42–45]. It refers to the grouped characteristics of an increased CT; choroidal pachyvessels (dilated outer choroidal vessels with a club-shaped posterior termination); an attenuated or thinned choriocapillaris; reduced fundus tessellation overlying an area of thickened choroid and choroidal hyperpermeability on indocyanine green angiography (ICGA). Notwithstanding, a pachychoroidal configuration is not necessarily synonymous with a thickened choroid [46]. Choroidal image binarization is a promising technique to quantify different choroidal elements in the pachychoroid spectrum. Wei et al. [31] compared SFCT, TCA, LA, SA and CVI in eyes with typical AMD (t-AMD), PCV and fellow eyes. LA and CVI were significantly decreased in diseased eyes. In a subgroup analysis between t-AMD eyes and PCV, the authors did not find significant differences in choroidal parameters.

Daizumoto et al. [47] measured the LA and SA of the inner and outer choroid separately and calculated the pachychoroid index (PI), before and after intravitreal anti-VEGF injection (aflibercept), defined as follows:

$$\text{PI index} = (\text{luminal area of outer choroid/stromal area of outer choroid}) / (\text{luminal area of inner choroid/stromal area of inner choroid}).$$

Measurements for the whole choroid (CT, LA and SA) decreased at 3 and 12 months. Outer choroid LA but not SA, and inner choroid SA but not LA were significantly decreased at 3 and 12 months, which lead to a total reduction in the PI after treatment. The authors also found that patients who had a higher PI at baseline presented significantly lower proportions of dry maculas at 12 months. The PI increased significantly with disease recurrence and decreased with treatment. The PI was significantly higher in PCV eyes compared to fellow eyes and controls. The authors suggest that these findings may be attributed to a reduction in stromal exudation at the inner choroid and a decreased vascular dilation at the outer choroid, after successful treatment.

Bakthavatsalam et al. compared the SFCT and CVI between PCV, t-AMD and healthy controls and found that SFCT and LA were lower in t-AMD compared to PCV. CVI was lower in PCV and t-AMD compared to controls but there was no difference between PCV and t-AMD eyes. AMD eyes had a lower CVI compared to fellow eyes [32]. Ng et al. measured SFCT, TCA and CVI, as well as the prevalence of pachyvessels, in previously treated exudative maculopathy eyes. 52% of patients had pachyvessels of which 64.3% had polypoidal lesions. The presence of pachyvessels correlated significantly with younger patient age, an increased SFCT, increased CVI and the presence of polypoidal lesions in a univariate analysis, but only the correlation with CVI remained in a multivariate regression model [48].

Gupta et al. [49] compared t-AMD and PCV eyes, and further stratified PCV into subgroups, according to choroidal thickness. When comparing PCV eyes altogether with t-AMD eyes, mean CT, SFCT, LA in the central 1500 μm and 6000 μm were significantly higher in the former, but significance was lost after adjustment for age. After stratification, the group with thicker choroids (≥ 257 μm) showed increased differences compared to t-AMD, which remained after age adjustment, whereas the group with thinner choroids (< 200 μm) showed statistically significant lower values of CT, SFCT and LA in the subfoveal 6000 μm and 1500 μm areas, before and after age adjustment. The authors suggest that there may be two categories of PCV, one that falls within the pachychoroid spectrum, or typical PCV, and one that falls within the AMD spectrum, which may be considered polypoidal CNV. These findings could have important treatment implications, with binarization techniques representing a promising tool to aid in the sub classification of PCV. Another study by Ting et al. [50] evaluated treatment-naïve t-AMD and PCV eyes prospectively: at baseline, 3, 6 and 12 months after initiation of treatment with anti-VEGF or photodynamic therapy (PDT). SFCT, TCA, LA and SA decreased significantly at all measurement points in both t-AMD and PCV eyes. Additionally, eyes were stratified according to the CVI into tertiles. While all tertiles exhibited lower LA and SFCT at 12 months, only the highest tertile exhibited a significant decrease in CVI.

Zheng et al. [22] evaluated *en face* SS-OCT images of non-exudative AMD eyes with and without reticular pseudodrusen (RPD). Furthermore, the submacular choroid was divided into inner and outer sectors centered on the fovea. Results show that CT decreased in RPD eyes in almost every choroidal subfield, whereas the decrease in CVD was limited to the central and superonasal subfields. Regarding these results, there may be an underlying choroidal disease in RPD eyes and CVD may be a more specific marker than CT, which was decreased in an indiscriminate manner. The downside of this study is that the binarization protocol was different than previously

described and its description lacks detail. Masuda et al. [51] compared TCA, LA and SA between eyes with RPD and healthy controls which were significantly decreased in the former.

Central serous chorioretinopathy (CSC)

CSC is characteristically associated with serous retinal detachments, with or without RPE detachments, and fluorescein angiography (FA) findings of single or multiple leakage patterns at the RPE level with pooling into the subretinal space [5, 52–55]. The pathophysiology has been linked to choroidal hyperpermeability, delayed filling and vascular congestion. It has been hypothesized to fall into the pachychoroid spectrum of chorioretinopathies [42, 44, 45], and therefore studying isolate choroidal components is of paramount interest.

Agrawal et al. [56] studied the SFCT, TCA, LA, SA and CVI in acute CSC, resolved CSC, fellow eyes without CSC history and healthy age-matched controls. Eyes with acute CSC showed significantly higher CVI and SFCT compared to fellow eyes and controls. There was also a higher LA between acute CSC and all other groups, without a significant change in SA. This leads to the assumption that SFCT could be increased at the expense of LA in acute CSC. Interestingly, fellow eyes had higher SFCT and CVI compared to resolved CSC and healthy controls.

In order to understand the choroidal changes subjacent to CSC, Sonoda et al. [57] studied the choroidal inner and outer layers separately, introducing the concept of the CSC index. Posterior to image binarization, the authors segmented the choroid into an inner layer composed of small- and medium-sized hyporeflective spaces and an outer layer formed by large hyporeflective spaces, through a modified Branchini method [58]. Hyporeflective/hyperreflective areas and hyporeflective to TCA ratio correspond to LA, SA and CVI in other studies, respectively. The index was calculated through the following formula:

$$\begin{aligned}\text{CSC index} = {} & (\text{hyporeflective area of outer choroid/hyperreflective area of outer choroid}) \\ & /(\text{hyporeflective area of inner choroid/hyperreflective area of inner choroid}).\end{aligned}$$

Findings were compared between CSC eyes, fellow eyes and age-matched healthy controls. TCA, total hyperreflective areas and total hyporeflective areas were all significantly increased in CSC compared to fellow eyes and controls. Interestingly, the authors noticed that inner and outer choroid characteristics varied, with inner choroid hyperreflective areas and outer choroid hyporeflective areas being increased in CSC eyes compared to fellow eyes and controls. TCA and total hyporeflective areas were increased in fellow eyes compared to controls but only at the expense of an outer choroid hyporeflective area increase. Consequently, there was a higher CSC index in CSC eyes and, to a lesser degree, fellow eyes in comparison with controls. These findings may give further clues toward CSC pathophysiology and forme fruste CSC properties, possibly involving inner choroid stromal swelling and outer choroid vessel dilation. However, the authors warn about cautious interpretations of outer choroid measurements due to a worse signal-to-noise ratio compared to superficial layers. Kinoshita et al. [59] performed a study on segmented inner and outer choroid components in CSC eyes in comparison with fellow eyes, and after 3 months of half-fluence photodynamic therapy (hPDT). Whole choroid TCA, whole choroid hyporeflective and hyperreflective areas, as well as the hyporeflective to TCA ratio were significantly higher in CSC eyes at baseline compared to fellow eyes. After choroidal segmentation, there were differences among the inner and outer choroid. The inner choroid hyperreflective but not hyporeflective areas were higher in CSC eyes compared to fellow eyes and after treatment, whereas outer choroid hyporeflective but not hyperreflective areas were higher in CSC eyes compared to fellow eyes and after treatment. These findings result in a higher CSC index in active chronic CSC eyes at baseline compared to fellow eyes and after treatment with hPDT.

Kuroda et al. [20] studied the choroidal vasculature in CSC eyes, fellow eyes and healthy controls and further subclassified CSC into classic CSC, diffuse

retinal pigment epitheliopathy (DRPE) and multifocal posterior pigment epitheliopathy (MPPE). Additionally, the authors segmented the choroid into an inner and outer layer and applied the binarization technique to *en face* images of central macular 3×3 mm^2 and 6×6 mm^2 regions. CSC eyes showed a higher CVA in comparison with healthy controls in both regions, and at the inner and outer choroidal level. Fellow eyes showed increased CVA compared to healthy controls in all layers, except for the 3×3 mm^2 inner choroid. When it comes to CSC subgroup analysis, there was only a statistically significant difference in the MPPE subtype, with a higher inner CVA in the 3×3 mm^2 region.

Diabetes mellitus (DM)

With DM being a disease primarily affecting the vascular component, studying individual choroidal elements is of high importance. CT studies in diabetic patients with or without diabetic retinopathy (DR) have been vastly performed, with conflicting results [60–69].

Tan et al. [70] studied choroidal compartments through binarization in diabetic patients with and without DR. Results showed that only CVI, but not TCA, LA and SA, was significantly reduced in diabetic patients, regardless of DR, in comparison with healthy controls. TCA, LA and SA were increased and CVI was decreased in diabetics with DR compared to no DR. These findings suggest that there is a disproportional decreased LA in comparison with SA, leading to a decreased vascularity index.

Kim et al. [71] performed a larger study and also stratified patients according to DR stage. The authors compared CVI between healthy controls, diabetic patients without DR, and different stages of DR (mild/moderate non-proliferative diabetic retinopathy (NPDR), severe NPDR, proliferative (PDR), panretinal photocoagulation (PRP)-treated patients). There was a significant reduction in CVI between healthy controls and diabetic patients altogether, with or without DR. Between groups, there were lower CVI values in PDR eyes compared to controls, eyes without DR and mild-to-moderate DR as well as between PRP-treated eyes and eyes without DR. A multivariate regression showed that CVI was related to SFCT and central retinal thickness but not to demographic or systemic characteristics.

Wang et al. [21] studied eyes in a diabetic population stratified according to DR severity (no DR, NPDR, NDPR + DME, PDR) and compared results to healthy controls through binarization of *en face* SS-OCT images. Univariate and multivariate regression analyses showed that there was a significant correlation between increasing DR severity and decreased whole CVD values, and which were lower compared to controls.

Intraocular inflammation

Vogt–Koyanagi–Harada (VKH) is a condition with ocular and systemic manifestations, characterized by an autoimmune response against melanocytes. It presents as a bilateral granulomatous panuveitis, which also affects the choroidal layer [72–74]. Choroidal changes have been previously described in OCT studies of VKH patients [75–77].

Agrawal et al. [78] published results regarding patients with VKH disease and compared CT and CVI during active inflammation at baseline, at 6 and 12 months of follow-up and with a healthy control group. Both parameters were significantly higher at baseline than follow-up, and also between VKH eyes and controls. The baseline EDI SD-OCT used for binarization had to be deferred for 2 weeks after the acute phase, since image acquisition at presentation was difficult to acquire due to marked choroid thickening and serous detachments. Regarding these results, the authors hypothesize that there may be an increased vascular component in VKH eyes compared to normal eyes. Further studies are needed to reinforce the accuracy of CVI as a parameter for disease activity and progression.

Jaisankar et al. studied CT, SFCT, TCA, LA, SA and CVI in patients with active VKH with either first or recurrent episodes, before and after systemic immunomodulatory treatment. Mean overall CT and CVI decreased significantly after treatment [79].

A third study was performed by Liu et al. [80] on chronic VKH eyes, eyes with acute anterior segment reactivations and healthy controls. Overall CT was thinner in quiescent eyes compared to controls, with significant increases with recurrence. TCA, LA and SA were all smaller in the quiescent stage compared to controls. Surprisingly, the CVI decreased during recurrent inflammation in comparison with the quiescent stage and again increased with recovery. The

authors hypothesize that these findings may be correlated with stromal edema during active inflammation. Kawano et al. [81] obtained similar findings, with an increased CVI between baseline and 1 week of treatment, although this study was limited by difficulties with image quality due to the increased CT in the acute phase.

Agrawal et al. [19] studied eyes with panuveitis and evaluated CT, TCA, LA, SA and CVI at baseline and after 3 months compared to a control group. There was a significant reduction in LA, LA/SA ratio and CVI but not CT in the panuveitis group between baseline and follow-up, which could not be verified for the control group. CVI may be a good follow-up tool and biomarker of disease activity in these patients. Onal et al. [82] studied eyes with Behçet and evaluated the central SFCT and choroidal stromal-to-vascular lumen ratio (which relates to SA/LA ratio). There was a significant decrease in Behçet eyes in both parameters in comparison with healthy controls.

Agrawal et al. [83] conducted a prospective study on patients with serpiginous choroiditis measuring TCA, LA, SA and CVI at baseline and at the healed stage and compared results with a group of healthy controls. The results show that TCA, LA and SA were all increased in SC patients, but the CVI was decreased in comparison with controls. These findings suggest that although there is an increased choroidal area, there is a proportional decrease in the vascular component. Also, there was a decrease in TCA, LA and CVI between the active and healed phase, possibly indicative of choroidal atrophy. An important limitation in this study was the posterior shadowing artifact resultant from RPE proliferation of SC lesions, which could be erroneously interpreted as luminal areas.

Myopia

The typical anteroposterior globe elongation and stretching of compartments in eyes with high myopia not only affect the retina and Bruch membrane but also the choroidal layer, leading to the well-known changes of lacquer cracks, chorioretinal atrophy and choroidal neovascularization [84–86]. A reduction in CT has been previously described [7, 87, 88].

Choroidal binarization studies have been conducted to evaluate choroidal components in myopic eyes. Gupta et al. [89] studied 515 eyes with high myopia (defined as a SE $\geq$ -6D) and compared findings to emmetropic controls. CT, TCA, LA and SA were all significantly reduced in myopic eyes in subfoveal (1500 μm) and macular (6000 μm) regions, but CVI was increased in myopic eyes, thus pointing toward a more accentuated difference in stromal compared to vascular components. Alshareef et al. [90] determined CT, TCA, SA, LA and CVI in myopic eyes (axial length: 25–27.5 mm, without ocular complications) and emmetropic eyes. There was a significant reduction in CT, TCA, and SA, albeit without a reduction in CVI. LA was not significantly different between groups. The authors suggest that these findings could indicate a pathogenic reduction in stromal components rather than a vascularity reduction in myopic eyes.

Ng et al. [91] evaluated choroidal characteristics before and after treatment of myopic CNV with intravitreal anti-VEGF. Patients were evaluated at baseline; 6 months and 12 months of follow-up and results were compared with fellow eyes. SFCT decreased significantly between baseline and 12 months of follow-up. This reduction was not accompanied by a significant change in CVI. CVI was not significantly different between CNV and fellow eyes. These findings may suggest that there is a concomitant reduction in LA and SA with anti-VEGF treatment; however, this study lacked a healthy control group.

Chorioretinal dystrophies

Stargardt disease

Ratra et al. [92] studied choroidal characteristics in Stargardt disease, based on previously described losses in the choroidal circulation on histopathological studies, particularly affecting the choriocapillaris [93, 94]. Results showed that CVI was significantly reduced in Stargardt eyes compared to controls, but not SFCT. CVI may be a more sensitive biomarker than SFCT for evaluating choroidal changes in this disease.

Bietti crystalline dystrophy (CYP4V2 mutation) and retinitis pigmentosa (EYS mutation)

Hirashima et al. studied the SFCT and outer CVA in *en face* SS-OCT scans of Bietti crystalline dystrophy (BCD) and retinitis pigmentosa (EYS-RP). The SFCT was significantly lower in the BCG group compared to

controls and EYS-RP group. There was also a decreased inner against total choroidal thickness ratio, and outer CVA in BCG compared to the other groups [95].

Discussion

Binarization of OCT images is a promising way to study the choroidal circulation and its architecture. Previous optic and electron microscopy studies have brought some insight into the understanding of different choroidal component properties, but they do not correspond directly to in situ findings. There are artifacts subjacent to tissue fixation and vascular diameter changes associated with tissue processing which alter the natural structure. Other major advantages are a low coefficient of variability and less variation with systemic and ocular characteristics, such as axial length and blood pressure in comparison with the more vastly studied CT [18, 71]. Another important aspect is that the technique has shown to be highly reproducible, with a high interobserver correspondence (ICC 0.81–0.99) [15, 32, 56, 96]. Important insights into frequent ocular pathologies have been made. When it comes to AMD, the evaluation of separate choroidal sub-components showed results not measurable through CT. Findings support a decreased vascular percentage, but not CT, in AMD and fellow eyes in comparison with controls [34]. It has also shown to be a promising tool in the subclassification of PCV subtypes [48, 49] Subclinical OCT changes measured in CSC and PCV through binarization studies could not have been depicted solely through CT measurements. The possibility to analyze luminal and stromal components separately and the calculation of vascular indexes is advantageous when it comes to these chorioretinal diseases and may bring major advances in the understanding of their pathophysiology. The evaluation of outer and inner choroidal parameters separately showed a proportional increase in outer choroid vascular and in inner choroid stromal components in PCV, whereas the inverse was verified after treatment [47]. In active CSC, increased inner choroid stromal components and increased outer choroid luminal areas point toward inner choroid exudation and an outer choroid vascularity increase. Another interesting finding was observed in fellow eyes without a previous history of CSC, which also showed increased vascularity in the outer choroid [57]. Choroidal binarization studies in diabetic retinopathy revealed a tendency for a decreased choroidal vascularity [21, 71], even in the presence of an increased choroidal area [70]. Conflicting results were seen in VKH, with some studies indicating CVI increases [78, 79], and others decreases in the acute phase [80, 81]. In myopia, results favored a normal or increased choroidal vascularity despite a reduction in choroidal thickness [89, 90].

Disadvantages associated with image binarization techniques include no concrete evidence that the hyporeflective areas represented vascular and hyperreflective areas represented stromal areas. Spaide and Ryan [97] recently reported that fluid may be captured as a hyporeflective area in CSC eyes and confounded as luminal areas. Furthermore, thresholding techniques do not guarantee that there is not an underestimation or overestimation of hyporeflective and hyperreflective areas [18]. Also, the caption of a tangential cut of a vessel may lead to the overestimation of stromal areas [15]. Binarization procedures have important limitations when it comes to the segmentation process, delimitation of the choroidal boundaries and image brightness adjustments, which are, in part, performed by the observer. Some studies have measured inner and outer choroid parameters separately, but the border between the two is difficult to delineate. Additionally, the outer segment may have a lower resolution demanding a cautious selection of OCT scans. Notwithstanding, general reported intraobserver (ICC 0.87–0.99) and interobserver reproducibilities (ICC 0.81–0.98) of choroidal binarization procedures are high [15, 18, 56, 96]. It still remains to be confirmed whether the subfoveal CVI is representative of the whole choroidal vascularity. Agrawal et al. conducted a study to compare mean CVI between foveal, central macular and total macular CVI and to evaluate the intraclass correlation coefficient (ICC) between these measurements. There was a high correlation (ICC > 0.9) and no significant variance between groups, suggesting that foveal choroidal scans are representative of total macular CVI [96]; however, this might not be the case in focal disease processes. It is also important to keep in mind that OCT is a static imaging study, and thus, an increased CVI and vascular area cannot distinguish between an increase in vascular flow or stasis as in ICGA [78]. Additionally, the majority of studies do not take

diurnal variation of choroidal blood flow into consideration.

In conclusion, binarization of choroidal EDI OCT or SS-OCT scans is a very promising technique particularly for the study of chorioretinal vasculopathies and their pathophysiology, since it allows for the consideration of vascular and stromal components separately. Various recent binarization studies have been published concerning choroidal alterations in AMD, PCV, CSC, DM, myopia, inflammatory diseases, among others. Although there are still some limitations to the binarization technique that need to be improved, it allows for a more detailed depiction of the choroidal architecture than what is solely obtained through CT measurements.

Methods of literature search

A PubMed and Medline literature search was performed for all of the following terms in various combinations: binarization, choroid/al, enhanced depth spectral domain/swept source optic coherence tomography. All articles in English language were reviewed and included in this study.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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