



Diabetic choroidopathy: a review of the current literature

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Abstract Diabetic retinopathy is an increasingly prevalent disease, and a leading contributor to the burden of all-cause blindness worldwide. In addition to retinal changes, choroidal abnormalities are common in patients with diabetes. The first studies concerning this vascular structure were based on histologic, indocyanine angiography and laser Doppler flowmetry techniques, but the development of new optical coherence tomography (OCT) technologies and imaging software for enhanced depth imaging (EDI)-OCT in recent years has made it possible to provide more detailed images of the choroidal anatomy and topography.

In diabetic patients, several choroidal changes have been described in the literature throughout the years; the recent focus is choroidal thickness, which is significantly different from that in healthy patients. However, understanding choroidal manifestations of diabetic eye disease remains a real challenge, and this gap is hindering efforts towards better defining

choroidal evaluation as a predictive factor for disease evolution and treatment response.

This review aims to summarize the recent literature concerning changes in choroidal structure in diabetic patients, the relationship to diabetic retinal disease progression, and finally, the current and potential application of the measurement of variations in choroidal thickness for patient management.

Keywords Diabetic choroidopathy · Diabetic retinopathy · Enhanced depth imaging · Optical coherence tomography

Diabetic choroidopathy

Diabetic retinopathy (DR) is a leading cause of visual impairment and blindness, affecting almost 35 % of all diabetic patients worldwide [1]. The main retinal insults are vascular and neural, with vessel occlusion and leakage, leukostasis, and alteration of the blood–retinal barrier as a result of dysfunctional tight junctions, causing increased vascular permeability, generation of free radicals, mitochondrial dysfunction, and neuronal swelling and apoptosis [2]. The visual impairment is attributed primarily to retinal damage, but evidence from histologic, angiographic and laser Doppler flowmetry studies suggests the simultaneous presence of diabetic choroidopathy (DC). The choroid is an important vascular tissue, responsible for the blood supply to the outer layers of the retina, including the retinal pigmented epithelium (RPE) and photoreceptors, and is the only source of metabolic exchange for the avascular fovea [3]. The choroidal abnormalities in diabetic eyes include microaneurysms, dilatation and obstruction of the choriocapillaris, vascular remodelling with increased vascular tortuosity, vascular dropout, areas of vascular non-perfusion and choroidal neovascularization.

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Until recently, evaluation of the choroid was typically performed using indocyanine green angiography (ICGA) or laser Doppler flowmetry. These techniques, however, are only able to show vascular abnormalities and are not able to provide any information concerning anatomic and structural features of the choroid.

With the recent development of spectral domain optical coherence tomography (SD-OCT) and enhanced depth imaging (EDI)-OCT software, a more detailed evaluation of the choroid became possible. The classical OCT devices were unhelpful, as the RPE blocked the signal from the choroid. By moving the peak of the sensitivity curve to the sclera, maximizing sensitivity and detail, SD-OCT—and EDI-OCT software in particular—provide a better view of the choroidal cross-sectional structure, thickness and choroidal–scleral interface [4]. This technique launched a new era in choroidal evaluation and encouraged further research on possible clinical applications for choroidal thickness (CT) measurement. Nowadays, the role of CT as a predictive factor of diabetic eye disease is almost nonexistent. Nevertheless, a recent study reported that CT may be useful for predicting short-term outcomes of anti-vascular endothelial growth factor (VEGF) treatment in patients with diabetic macular edema (DME), as greater baseline CT was significantly associated with better visual and anatomic outcomes after intravitreal anti-VEGF injections [5]. Research is ongoing in efforts to better understand and to identify other possible roles for choroidal changes that are seen, albeit inconsistently, in diabetic patients.

The aim of this review is to summarize recent literature regarding the use of the newer OCT technology for evaluation of the choroid in diabetic patients, particularly CT and its relation to the severity of DR.

Imaging the choroid

Histologic studies of diabetic patients have revealed many changes consistent with vascular anomalies: atrophy and loss of the choriocapillaris endothelium, capillary narrowing and dropout, laminar deposits, tortuous and beaded vessels, and choroidal neovascularization [6, 7]. In more advanced cases, even larger vessels have shown onion-skin changes and aneurysmal formation [8]. They were also found to be present in diabetic patients without clinical DR, possibly clarifying the unexplained loss of visual acuity in diabetic eyes without clinical evidence of DR [6, 9].

Studies using fluorescein angiography and ICGA have shown several filling abnormalities in diabetic eyes. Reports of patients with mild non-proliferative diabetic

retinopathy (mNPDR) have described a characteristic “salt-and-pepper” pattern caused by selective filling of the choriocapillaris, in contrast to the normal ground-glass appearance [10]. Several other abnormalities have been observed later in the disease course, notably hypofluorescent spots and both small and large hyperfluorescent spots. These abnormal patterns are well correlated with the severity of DR, HbA1c levels and poor diabetes control [11–13].

An increased resistance index is seen when laser Doppler flowmetry is used to access choroidal blood flow beneath the fovea, possibly resulting from the progressive reduction of choroidal blood flow and volume in patients with diabetes, even in eyes with clinically undetected DR [14, 15]. This suggests that choroidopathy might trigger the development of retinopathy due to retinal tissue hypoxia and overexpression of VEGF, contributing to further retinal damage and macular edema. Reduced blood flow in the central ophthalmic artery and vein was also found in diabetic patients, with a steeper decrease in patients with proliferative diabetic retinopathy (PDR) [16]. Inconsistencies remain among published studies with regard to choroidal blood flow measurements in diabetic patients, as CT has been reported to be reduced (as stated above), unchanged (particularly in the early stages of diabetic disease) and even increased (mNPDR or untreated PDR) [17].

Recent developments in SD-OCT and EDI-OCT software have allowed CT to be studied in many conditions. Studies in normal eyes have revealed variations in CT with age (decrease of 15.6 μm with each decade of life), axial length (AL; -17 to -58.2 μm per millimeter of AL) [18], and even time of day, with diurnal variation in CT that can be as great as 67 μm [3, 19, 20]. In addition, the thickness of the central choroid seems to increase with progressive nasal and temporal thinning, a pattern that is characteristic of all diabetic patients regardless of DR grade [3, 21, 22]. Another OCT technology, swept-source (SS)-OCT, uses a different light source and detection method, and offers the advantages of higher imaging speed and accuracy, which are important in analyzing the choroid [23–27]. Lastly, the recent development of OCT angiography enables non-invasive visualization of vascular structures based on the motion of erythrocytes within the retinal and choroidal vasculature. Given the importance of documenting choriocapillaris and choroidal vasculature *in vivo*, this technique will have a role in the investigation of the choroid in both physiological and pathological conditions [28, 29].

The advent of these technologies has facilitated a large number of studies focused on the structure of the choroid in diabetic patients, and recent results show a relevant association between DR and CT.

Diabetic choroidopathy: optical coherence tomography

Decreased choroidal thickness

Many authors have found that decreased CT is associated with diabetes [21, 22, 30–33], and some have suggested that this might well relate to the instigated retinal insult—since the choroid is the major source of oxygen and nutrition to the outer layers of the retina and RPE, disturbances in this structure may lead to increased susceptibility to retinal tissue hypoxia and ischemia seen in diabetes mellitus. Comparisons of CT among diabetic patients with mNPDR, DME and PDR has revealed a trend towards significant choroidal thinning in eyes with DR (Table 1).

Querques et al. [34] and Esmaelpour et al. [30] reported a significant decrease in CT among diabetic patients without clinical evidence of retinopathy, suggesting that decreased choroidal blood flow may be the primary event. These results are consistent with the findings of vascular studies of the choroid [15, 35]. Esmaelpour, who used thickness maps of 36°x36° instead of single-point measurements, reported choroidal thinning in an NDR group, particularly in the subfoveal ($p=0.001$) and inferior regions ($p=0.05$). Furthermore, the authors extended the thickness maps to the retina and reported perimacular thinning, possibly caused by atrophy of the nerve fiber layer, not visible with slit lamp examination. However, in the presence of macular lesions (M1 and M2), there was no apparent choroidal thinning directly below the lesions [30].

Increased choroidal thickness

Some data, however, disagree with the findings above, suggesting that rather than thinning, the choroid may become thicker in eyes with DR [32, 33, 36]. Kim et al., for example, found significant choroidal thickening in eyes with DR, increasing as the disease progressed in severity from severe NPDR (sNPDR; $p<0.05$) to untreated PDR ($p<0.01$) [36]. These inconsistencies were justified by the authors as possible differences in patient profiles and study limitations (see below; Table 1). The study by Kase et al. somewhat agrees with these findings, as their results show a non-significant trend towards increased choroidal layer thickness with increasing DR severity [37]. However, DR patients in that study were subdivided into an under-treatment group receiving anti-diabetic drugs and a no-treatment group, and only the no-treatment group showed a significant change in CT, decreasing in the mNPDR stage ($p<0.05$) and increasing posteriorly in the sNPDR and PDR groups ($p<0.05$). Furthermore, DME patients were not considered separately. These results suggest that a chronic hyperglycemia may be a factor in further deterioration of damaged choroidal microvasculature.

It is still unclear whether the choroidal changes are primary or independent of the retinopathy. Some authors contend that primary choroidal angiopathy is present before the onset of DR, while others believe these to be unrelated events [32, 33, 36], with choroidopathy occurring only in more severe grades of DR [21, 22, 24] or worsening with increasing DR severity [36, 37].

A recent study by Ferreira et al., which evaluated CT among diabetic patients without DR, showed a significant increase in CT at 1500 μm superior to the fovea ($p=0.021$). None of the other 12 location comparisons were statically significant ($p>0.05$; Fig. 1) [38]. These changes in CT may well represent early pre-clinical changes in diabetic patients, but the reason for the inconsistencies in the location and direction of CT changes remains unknown.

Ferrara et al., who included 76 eyes in their recent study using SS-OCT (22 eyes of 22 patients with DM but without DR, 20 eyes of patients with NPDR, 15 eyes with PDR, and 26 eyes of healthy age-matched controls), detected vascular remodelling in all DM patients corresponding to irregular, tortuous and beaded choroidal vessels with focal dilation and narrowing. Small vessel loss in the topography of previous retinal photocoagulation was another relevant observation by the authors [39].

Choroidal thickness and diabetic macular edema

Uncertainties also exist concerning the connection between the evolution of CT and increasing severity of diabetic retinopathy. Some studies have found a correlation with increasing DR severity [22], while others have found no correlation between CT and grade of DR [21, 32, 40]. Thus the exact relationship between CT and the severity of DR remains largely unknown, and although some authors have cautiously suggested choroidal thinning in areas with documented retinal thickening (Querques et al. 2012; data not shown) [34], no significant correlation between retinal and CT has been found [21, 24, 33]. The exception is patients with macular edema (with a thicker retina), who have clinically significant subfoveal choroidal thinning compared to healthy eyes, but have a tendency towards a thicker choroid when compared to other grades of the disease, NPDR and PDR. While very few authors have compared subgroups of diabetic patients given the small samples in each group, Kim et al. reported significant choroidal thickening in DME patients versus non-DME patients ($p<0.05$). Furthermore, among DME patients, CT appeared to be greater in the serous retinal detachment-type (SRD-type) group than patients with cystoid-type macular edema ($p<0.05$). These results are in agreement with other observations of a tendency towards a thicker choroid in patients with DME, although the difference was not significant [21, 22, 30–32]. Some authors, however, have cautiously reported a thinner choroid in the presence of clinically significant macular edema (CSME) [34, 35, 41], explaining this pattern as an artefact induced by macular

Table 1 Clinical studies comparing subfoveal choroidal thickness in eyes with different grades of diabetic disease

| Study | Number of patients | Method | Groups | SCT | <i>p</i> value | Valuable points/limitations |
|------------------------|--------------------|-------------------|-----------|---------------|------------------|---|
| Esmaeelpour [30], 2011 | 42 | High-speed 3D-OCT | Control | 327 ± 74 | <i>p</i> < 0.001 | No relationship between macular lesions and choroidal thinning Previous treatments (PRP or anti-VEGF) were not mentioned. |
| | | | NDR | 214 ± 55 | <i>p</i> < 0.001 | |
| | | | M1 | 208 ± 49 | <i>p</i> < 0.001 | |
| | | | M2 | 205 ± 54 | <i>p</i> < 0.001 | |
| | | | CSME | 211 ± 76 | | |
| Esmaeelpour [31], 2012 | 33 | High-speed 3D-OCT | Control | 388 ± 109 | <i>p</i> < 0.001 | |
| | | | NDR | 291 ± 64 | <i>p</i> < 0.001 | |
| Querques [34], 2012 | 63 | EDI-OCT | Control | 309.8 ± 58.5 | <i>p</i> < 0.001 | PRP and anti-VEGF-treated patients were excluded. |
| | | | NDR | 238.4 ± 47.9 | <i>p</i> < 0.001 | |
| | | | NPDR | 207.0 ± 55.9 | <i>p</i> < 0.001 | |
| | | | NPDR/CSME | 190.8 ± 58.5 | | |
| Regatieri [21], 2012 | 49 | HD-OCT | Control | 232.3 ± 15.2 | NS | All DME patients had received PRP more than 6 months earlier; untreated PDR patients were not included. Cirrus HD-OCT was less accurate in identifying small and focal lesions on the choriocapillaris. |
| | | | mNPDR | 222.0 ± 21.6 | <i>p</i> < 0.001 | |
| | | | PDR | 162.7 ± 7.0 | <i>p</i> < 0.001 | |
| | | | NPDR/DME | 169.5 ± 14.7 | | |
| Vujosevic [33], 2012 | 102 | SD-OCT | Control | 329.5 ± 65.2 | NS | Patients previously treated with PRP or anti-VEGF drugs were excluded. Data on DME patients was not shown. |
| | | | NDR | 280.6 ± 65.2 | <i>p</i> < 0.05 | |
| | | | NPDR | 279.4 ± 81.6 | <i>p</i> < 0.05 | |
| | | | PDR | 230.5 ± 25.8 | | |
| Kim [36], 2013 | 235 | EDI-OCT | Control | 276.0 ± 58.1 | — | Patients with previous PRP treatments were considered separately, and eyes previously treated with anti-VEGF were excluded. Patients with and without DME were compared, disregarding the grade of DR, and groups with milder retinopathy (NDR, mild NPDR) typically had patients without DME, as opposed to patients with more severe DR that had a greater number of DME patients. |
| | | | NDR | 262.3 ± 68.4 | <i>p</i> < 0.01* | |
| | | | mNPDR | 244.6 ± 77.0 | <i>p</i> < 0.01* | |
| | | | sNPDR | 291.1 ± 107.7 | <i>p</i> < 0.05* | |
| | | | PDR | 363.6 ± 74.9 | — | |
| Lee [32], 2013 | 203 | EDI-OCT | Control | 228.5 ± 38.9 | NS | DME patients revealed no significant differences in CT compared to PDR and sNPDR patients without DME, but a slight trend towards a thicker choroid. There was no reference to whether PDR patients received PRP or anti-VEGF treatment. |
| | | | NDR | 219.1 ± 47.8 | <i>p</i> = 0.05 | |
| | | | mNPDR | 158.9 ± 56.3 | <i>p</i> < 0.001 | |
| | | | sNPDR | 161.2 ± 38.5 | <i>p</i> < 0.001 | |
| | | | PDR | 157.4 ± 45.7 | <i>p</i> < 0.001 | |
| | | | DME | 164.1 ± 63.0 | | |

Table 1 (continued)

| Study | Number of patients | Method | Groups | SCT | <i>p</i> value | Valuable points/limitations |
|---------------------|--------------------|---------|--------------|--------------|-----------------|--|
| Xu [40], 2013 | 246 | SD-OCT | Control | 250 ± 103 | <i>P</i> = 0.02 | Comparisons to diabetic patients ignored the presence or absence of DR and its grade. There were few patients with DR (23) among the 246 diabetic patients. |
| | | | DM | 266 ± 108 | NS | |
| | | | NDR | 251 ± 104 | | |
| | | | DR | 249 ± 86 | | |
| Adhi [24], 2013 | 33 | SD-OCT | Control | 276.4 | NS** | Anti-VEGF-treated DME patients (57 %) were not studied separately. All eyes with PDR and DME had received PRP, and time between PRP and CT measurement was ignored. Blood pressure and HbA1c values were ignored; groups were not matched for axial length. Subgroups of DR were small. |
| | | | NPDR | 252.9 | <i>p</i> < 0.05 | |
| | | | PDR | 209.6 | <i>p</i> < 0.05 | |
| | | | DME | 211.6 | | |
| Ünsal [22], 2014 | 151 | EDI-OCT | Control | 259.1 ± 13.1 | NS | All PDR patients had already received PRP treatment, and time between PRP and CT measurement was not considered. Axial length, which affects CT values, was not evaluated. |
| | | | mNPDR | 235.4 ± 84.5 | <i>p</i> < 0.01 | |
| | | | PDR | 203.8 ± 47.6 | <i>p</i> < 0.01 | |
| | | | NPDR/ DME | 206.8 ± 45.4 | | |
| Kase [37], 2015 | 86 | SD-OCT | Control | 272 ± 72 | NS | None of the diabetic patients received any PRP or anti-VEGF treatment. Subdivided DR patients into groups receiving oral anti-diabetic drugs and those without therapy; only patients in the no-treatment group experienced significant differences in CT with increasing severity of DR. DME patients were not considered separately. |
| | | | NDR | 255 ± 68 | NS | |
| | | | mNPDR | 253 ± 81 | NS | |
| | | | sNPDR | 309 ± 80 | NS | |
| | | | PDR | 287 ± 71 | NS | |
| | | | DME | 276 ± 71 | | |
| Ferreira [38], 2015 | 125 | EDI-OCT | Control | 240.6 ± 7.92 | <i>p</i> < 0.05 | 125 diabetic patients without DR, CT thicker at 1500 μm superior to the fovea |
| | | | NDR | 267.9 ± 6.16 | | |

SCT subfoveal choroidal thickness, NS not significant, NA not available, NDR no diabetic retinopathy, M1 microaneurysms within 1 disc-diameter of the fovea, M2 exudates within 1 disc-diameter of the fovea, CSME clinically significant macular edema, DM diabetes mellitus, DME diabetic macular edema, NPDR non-proliferative diabetic retinopathy, mNPDR mild to moderate NPDR, sNPDR severe NPDR, PDR proliferative diabetic retinopathy, PRP pan-retinal laser photocoagulation

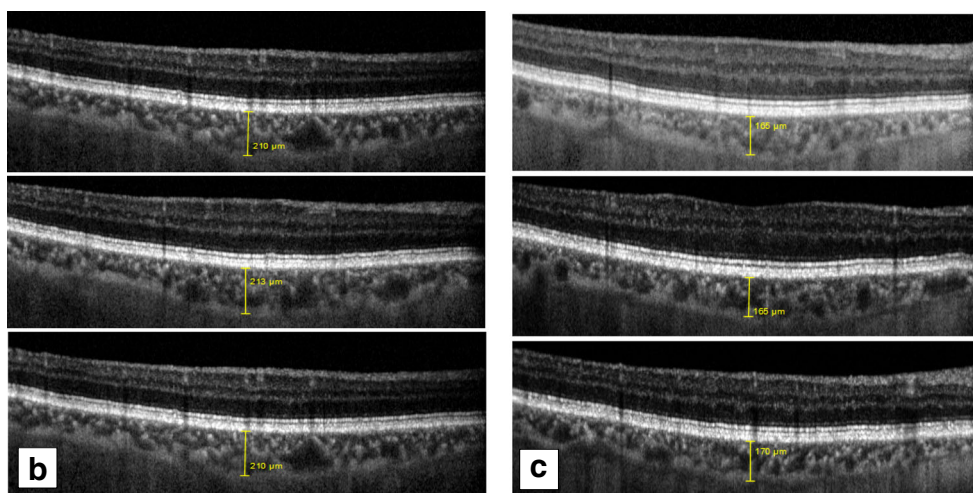
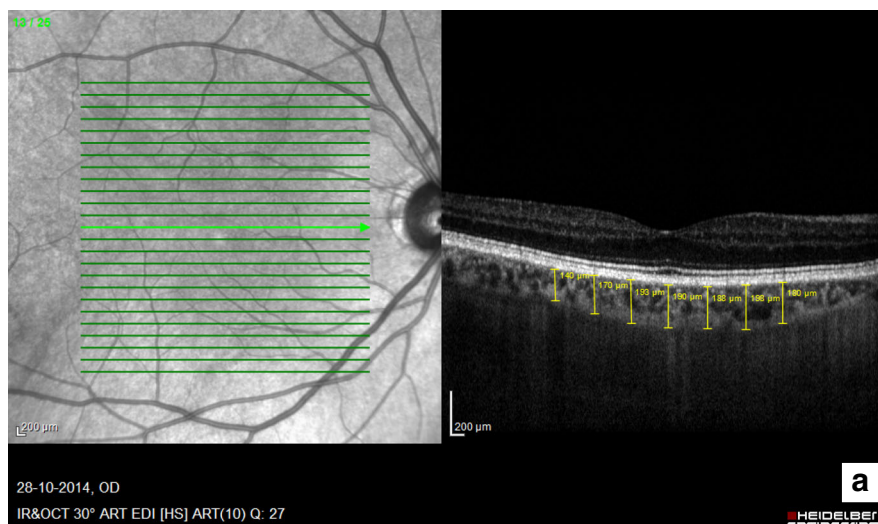
*Compared with the PDR group

** Significant in other peripheral regions (see text)

edema, inhibiting the signal transduction and reflection from the choroid due to increased ocular opacity. In

contrast, a study by Gerendas et al. reported that this CT thinning was consistent among 142 eyes with DME, and that

Fig. 1 Measurements of choroidal thickness at 13 locations—subfoveal area (a) and at 500- μm intervals from the fovea to 1500 μm nasal (a), 1500 μm temporal (a), 1500 μm superior (b) and 1500 μm inferior (c)—in diabetic patients without DR



fellow eyes without macular edema were equally affected, suggesting a systemic pathophysiologic mechanism [41].

Choroidal thickness after treatment for diabetic retinopathy

The results discussed above should be interpreted with caution, however, as most patients included in PDR groups were not treatment-naïve, and had already undergone pan-retinal laser photocoagulation (PRP) or anti-VEGF treatment. In addition, the time between treatment and measurement of CT was seldom mentioned. There is evidence that PRP may induce long-term thinning of the choroid (possibly by downregulation of VEGF [36]), but in the short term (1 week), it may be responsible for choroidal swelling, probably due to a shifting of blood vessels from the peripheral retina to the foveal area [42, 43]. Zhu et al. found significant thickening of the subfoveal choroid 1 and 3 months after PRP, versus a significant decrease in CT in the area subjected to photocoagulation. In the latter, although scar formation may limit a local

inflammatory reaction, choroidal inflammation could induce vasodilation of untreated areas, leading to an early increase in CT [42]. Moreover, the effect of anti-VEGF drugs on CT is still not well understood, although some studies have reported choroidal thinning, at least in the first 6 months [44, 45]. Lee et al. investigated changes in CT after intravitreal bevacizumab injection, PRP or both for the treatment of DR, and reported a decrease in CT after all treatments, suggesting that both methods reduced choroidal vascular permeability [46].

Other common limitations were a lack of consideration for local variables influencing CT—particularly age, time of day, and axial length/refractive error—as well as systemic conditions that appear to alter the choroidal structure (see the “Other factors” section below). Some studies suggested the influence of other variables on the visibility of the choroidal–scleral interface (CSI) in OCT images and, consequently, CT measurements. Notably, the study by Gupta et al. suggested that a well-defined CSI was present in only 60 % of subjects. The variables believed to be responsible for this CSI measurement

inaccuracy include axial length, age, diabetes, retinal thickness and ocular opacities [47], which may thus help to explain differences in results and findings among the clinical studies cited in this review.

Others factors influencing choroidal thickness

In addition to local ocular factors, systemic conditions can influence CT. Control of blood hemoglobin A1c (HbA1c) appears to be directly correlated with CT, as patients with lower baseline HbA1c have shown a significant increase in CT after strict blood sugar control; however, no correlation was found between these choroidal changes and fasting or average blood glucose [48].

In contrast, a significant correlation was found between CT changes and systemic blood pressure control (systolic, diastolic and mean arterial blood pressure) after 2 weeks of hospitalization [49].

Hypertension is a known factor affecting the choroid [49–51], and a recent study by Akay et al. found a significant decrease in CT among patients with high blood pressure ($p < 0.001$), from 1000 μm nasally to 1500 μm temporally, although there was no significant correlation between blood pressure levels and duration of disease [51].

Hypercholesterolemia, on the other hand, was recently found to cause a focal increase in CT, as reported by Wong et al. The study showed increased CT in the subfoveal 1000- μm nasal and 1000- μm superior areas, and is well supported by animal models demonstrating atherosclerotic changes in the choroid in the presence of high levels of serum cholesterol [52]. Low triglyceride levels also appear to be related to a thicker choroid, but the mechanism remains unknown [53].

All of these systemic imbalances are prone to atherosclerotic changes, and frequently coexist in diabetic patients; thus they warrant further consideration in future studies. However, the complexity of their interactions makes it difficult to contemplate them as isolated variables, and so additional basic studies in experimental models are needed.

Conclusion

Although it is clear that choroidal changes are present in patients with in diabetes, it remains unclear whether these changes are predictive, modulatory, causative or independent factors for DR, and the results from clinical studies remain inconsistent.

The majority of clinical findings supported by histology, laser Doppler flowmetry and indocyanine green angiography suggest choroidal thinning after the onset of diabetes in the absence of clinical evidence of DR, which may account for the visual defects reported by these patients. However, slightly contradictory results, suggesting early thinning with later thickening, or completely opposite results showing choroidal

thickening or the appearance of CT abnormalities in secondary stages of DR, have also been obtained.

Differences in methods of choroidal evaluation may account for these conflicting results, as vascular abnormalities are most commonly found in media-peripheral regions, and OCT exams tend to focus on the central macular/foveal region. In addition, CT appears to be influenced by many factors other than the severity of DR. A prior anti-VEGF or laser (PRP) treatment was recently shown to have modulatory effects on choroidal vessels; hence, the CT and time between treatment and measurement should not be disregarded when designing clinical studies. The presence of DME may also interfere with the measurement of CT, or may even influence choriocapillaris function, as well as other local and systemic factors.

Lastly, although the pattern of diabetic choroidopathy-related changes in CT is still not well understood, it may have a predictive role for diabetic eye disease in the future. Studies in age-related macular degeneration (AMD) have shown that CT correlates with best-corrected visual acuity (BCVA), and is helpful for predicting non-exudative disease and progression of geographic atrophy as well as treatment response and visual outcome in exudative AMD [54, 55]. Rayess et al. similarly described a possible role for CT as a predictor of visual and treatment outcome in patients with DME, as patients with thicker CT had anatomic and functional responses [5].

In conclusion, with the advent of the latest OCT technologies, diabetic choroidopathy has become a highly studied clinical entity garnering great interest among researchers. Nonetheless, the relationship between DC and DR, and even the role of DC in diabetic eye disease, remains unknown, and further investigation is warranted.

Compliance with ethical standards

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