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DIABETIC RETINOPATHY UPDATE

Predicting visual outcomes for macular disease using optical coherence tomography

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Abstract In recent years, the management of macular disease has undergone radical changes, in part because of new therapeutic approaches, but also due to the introduction of a new imaging modality – optical coherence tomography (OCT). The application of OCT imaging has clarified many aspects of chorioretinal disease pathophysiology and elucidated many hitherto unrecognized disease characteristics. From an early stage in its development, OCT has also been revolutionary in attempting to extract clinically useful measurements from image data in an automated fashion. As a

Abbreviations: ETDRS, Early Treatment Diabetic Retinopathy Study; MPS, Macular Photocoagulation Study; AMD, age-related macular degeneration; OCT, optical coherence tomography; logMAR, logarithm of the minimum angle of resolution; RPE, retinal pigment epithelium; CNV, choroidal neovascularization; ELM, external limiting membrane; IS–OS, inner segment–outer segment; PED, pigment epithelium detachment; CME, cystoid macular edema; ERM, epiretinal membrane; DME, diabetic macular edema; CRVO, central retinal vein occlusion; BRVO, branch retinal vein occlusion; CSC, central serous chorioretinopathy; GA, geographic atrophy.

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result, OCT-derived measurements of retinal thickness have been rapidly embraced in clinical and research settings. However, as knowledge of OCT image analysis has developed, it has become increasingly clear that even accurate measurements of retinal thickness may fail to predict visual outcomes for many diseases. As a result, the focus of much current clinical imaging research is on the identification of other OCT-derived anatomic biomarkers predictive of visual outcomes – such biomarkers could serve as surrogate endpoints in clinical trials and provide prognostic information in clinical practice. In this review, we begin by highlighting the importance of accurate visual function assessment and describing the fundamentals of OCT image evaluation, before describing the current state-of-the-art with regard to predicting visual outcomes, for a variety of macular diseases, using OCT.

Contents

1. Introduction

The advent of fundus fluorescein angiography in the 1960s heralded a revolution in our understanding of macular diseases, with the insights afforded by such imaging providing the basis for the development and application of many new therapeutic approaches (Keane and Sadda, 2010). At the same time, advances in color photography led to the acquisition of fundus images with enhanced resolution, stereopsis, and field of view, allowing medical retina specialists to segregate the retinal from the choroidal circulations and to isolate anatomic compartments within the fundus (Yannuzzi et al., 2004). Thus, fluorescein angiography and stereoscopic color fundus photography came to form the fundamental basis for the care of patients with macular disease and were quickly incorporated into related clinical trials. In these trials, photographic and angiographic derived parameters were adopted as anatomic endpoints, with the information providing helping to optimize many new therapeutic approaches (Fine, 2005). For example, in the Early Treatment Diabetic Retinopathy Study (ETDRS) color photography was used to define a subset of patients with diabetic maculopathy who were likely to benefit from laser photocoagulation (Early Treatment Diabetic Retinopathy Study Research Group, 1985); and in the Macular Photocoagulation Study (MPS) the importance of recognizing "classic" and "occult" patterns of fluorescein leakage was identified in patients receiving treatment for neovascular age-related macular degeneration (AMD) (Macular Photocoagulation Study Group, 1996).

More recently, evaluation of macular disease has undergone a further revolution, with the introduction of a wholly new imaging modality – optical coherence tomography (OCT) (Keane and Sadda, 2008). OCT is analogous to ultrasonography, but utilizes light waves instead of sound waves, thus providing cross-sectional images of the retina with unprecedented detail and resolution, and in a non-invasive manner (Drexler and Fujimoto, 2008; Schuman et al., 2004). The application of this imaging modality by medical retina specialists has clarified many aspects of chorioretinal disease pathophys-

iology and elucidated many hitherto unrecognized disease characteristics (Keane and Sadda, 2010). From an early stage in its development, OCT has also been revolutionary in attempting to extract clinically useful measurements from image data in an automated fashion (Hee et al., 1995a,b). As a result, OCT-derived measurements of retinal thickness have been rapidly embraced in clinical and research settings (Hee et al., 1998; Brown and Regillo, 2007; Keane et al., 2009a; Keane and Sadda, 2009).

In clinical imaging research, much of the focus has been on the identification of novel OCT-derived anatomic biomarkers for use in clinical trials and subsequently in clinical practice (Ahlers et al., 2008a,b; Keane et al., 2008a,b; Kiss et al., 2009). In clinical trials, such biomarkers may provide valuable information regarding therapeutic mechanisms of action, pharmacodynamics, and pharmacokinetics (Keane et al., 2008b). They may be of most value, however, when they can serve as surrogate endpoints – endpoints that are reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit (Csaky et al., 2008; Duivenvoorden et al., 2009). If, and when, these criteria are fulfilled, OCT-derived morphologic parameters could be employed to increase the accuracy, reduce the costs, and potentially shorten the duration of clinical trials (Csaky et al., 2008; Lloyd et al., 2008). Similarly, in clinical practice, such parameters could extend the application of OCT imaging beyond simple diagnosis and toward prognosis. With the rapid evolution of new treatments for macular disease (Zarbin and Rosenfeld, 2010), such prognostic information may be crucial for the clinician in choosing the appropriate type and level of treatment, as well as for appropriate counseling of patients. Therefore, the importance of predicting visual outcomes for macular disease using OCT imaging is clear. Unfortunately however, many studies using OCT-derived measurements of retinal thickness have failed to find consistent correlations with visual outcomes (Moutray et al., 2008; Spaide et al., 2006). These failures may be related, at least in part, to the significant errors that are known to occur in automated retinal thickness measurements for many macular diseases (Sadda et al., 2006; Keane et al., 2009b). As our knowledge of OCT image analysis has grown, however, it has become progressively clear that even accurate measurements of retinal thickness may fail to predict visual outcomes, and that further progress may be dependent on the discovery of other, more novel, OCT-derived morphologic parameters (Keane et al., 2008a). It is also increasingly clear that prediction of visual outcomes will be dependent on accurate assessment of visual function – an area where significant advances have also been made (Keane et al., 2010a).

In this review, we begin by highlighting the importance of accurate visual function assessment and describing the fundamentals of OCT image evaluation, before describing the current state-of-the-art with regard to predicting visual outcomes, for a variety of macular diseases, using OCT imaging.

2. Visual function

2.1. Visual acuity

Visual acuity is a measure of the spatial resolving ability of the visual system under conditions of high contrast (Neelam et al., 2009). Both in clinical practice and in clinical research, distance visual acuity is the most frequently used test of visual function (Holladay, 2004). In clinical practice, distance visual acuity is most commonly assessed using Snellen optotype test charts, first introduced by Herbert Snellen in 1862 (an optotype is a standardized symbol for testing vision and can be a specially shaped letter, number, or geometric symbol). Snellen visual acuities express the angular size of an optotype as a fraction, with the numerator specifying the test distance, and the denominator specifying the line read. However, the limitations of Snellen test charts are well established, and include an unequal legibility of letters, unequal spacing between letters and rows, and an unequal progression of difficulty between lines (Neelam et al., 2009; Hogg and Chakravarthy, 2006). These flaws result in many clinical problems, such as inaccurate measurement of visual acuity in children with amblyopia as a result of crowding phenomena, and limited assessment of visual acuity in patients with low vision in disorders such as advanced AMD (Falkenstein et al., 2007). Furthermore, the test–retest variability using Snellen charts has proven low, and many statistical analyses are not possible using visual acuities expressed as Snellen fractions (Lovie-Kitchin, 1988).

The limitations of Snellen visual acuity charts led to the development of "logMAR" (logarithm of the minimum angle of resolution) charts by Bailey and Lovie (1976). The major advantages of these charts include the regular geometric progression of letter size and spacing (following a logarithmic scale in steps of 0.1 log units), the equal number of letters in each row (five), and the comparable legibility of the five Sloan optotypes used. As a result, the logMAR charts used for the ETDRS study have emerged as the test-of-choice for measuring distance visual acuity in vision research. Despite their superiority, logMAR charts have not replaced Snellen charts in clinical practice. It is perhaps not surprising, then, that many retrospective clinical studies have failed to predict visual outcomes using OCT-derived parameters (Moutray et al., 2008).

2.2. Reading speed and contrast sensitivity

Distance visual acuity is largely a function of foveal integrity, i.e. it measures the central 1–2° of visual field (although extrafoveal fixation may sometimes occur in patients with macular disease) (Moutray et al., 2008). Therefore, the assessment of other visual parameters, such as contrast sensitivity and reading speed, may better reflect macular integrity as a whole, and thus provide stronger correlations with OCT-derived morphologic parameters (Keane et al., 2010a).

As distance visual acuity is measured in conditions of high contrast, some patients with macular disease may have near-normal distance visual acuity measurements, yet have significantly decreased contrast sensitivities (Arditi, 2005; Monés and Rubin, 2005; Patel et al., 2009a). This distinction is of functional importance – contrast sensitivity has been closely linked with both orientation and mobility and thus may provide valuable additional information regarding functional status in patients with macular disease (Arditi, 2005). In most clinical trials, contrast sensitivity is measured using Pelli-Robinson charts and such measurements have been also found to be highly predictive of reading performance (Neelam et al., 2009). Word reading is a complex process that requires a variety of component processes, such as letter and word resolution, stability of retinal images, saccadic accuracy, and accurate

cognitive processing (Neelam et al., 2009). While reading speed cannot be determined accurately in illiterate patients, and is often impaired due to non-visual factors (Elliott et al., 2001), it is minimally affected by media opacities such as cataract (Elliott et al., 2000), and is strongly associated with vision-related quality of life (Hazel et al., 2000). Thus, as new treatments continue to emerge for previously intractable macular disorders, assessment of both contrast sensitivity and reading ability may attain a position of increased importance for medical retina specialists in clinical settings and as a secondary endpoint in clinical trials (Csaky et al., 2008).

2.3. Microperimetry

While distance visual acuity is the most widely used measure of visual function in macular disease, an alternative approach is to measure paracentral retinal sensitivity using perimetry (Rohrschneider et al., 2008). So-called ''microperimetry'' allows direct, real-time evaluation of retinal fixation and macular sensitivity, and thus accurate comparison of fundus characteristics versus function in macular disease (Midena et al., 2007, 2010). Currently, the most commonly used microperimeter is the MP1 microperimeter (Nidek Technology, Gamagori, Japan) – this device allows the examiner to conduct automated static perimetry, while the use of a built-in infrared camera allows the instrument to track the patient's eye movements and present the stimuli at exact, predefined, retinal foci (Midena et al., 2010; Weingessel et al., 2009). Recent studies have overlaid microperimetric sensitivity maps with dense OCT raster scan datasets through the registration of color fundus photographs obtained with both devices – such an approach has allowed a systematic correlation between OCT-derived morphologic parameters and functional alterations in disorders such as diabetic maculopathy (Deák et al., 2010b). In addition, microperimetry is increasingly being incorporated into clinical trials, however, advances in image registration, eye tracker technology, and testing strategies, are still required to reduce the test–retest variability of these devices (Chen et al., 2009).

3. Optical coherence tomography

OCT, first described by Huang et al. (1991), allows high-resolution tomographic (cross-sectional) images of the neurosensory retina to be obtained in a non-invasive manner (Keane and Sadda, 2008). Commercially available OCT systems are now capable of obtaining retinal images with an axial resolution of approximately 3–8 μm, and a transverse resolution of approximately 14–20 μm (Kiernan et al., 2010).

3.1. Qualitative analysis of OCT images in ''Normal'' eyes

Light waves traveling through tissue can be reflected, scattered, or absorbed at each tissue interface – as a result, the multilayered structure of the retina is particularly amenable to assessment using OCT (Schuman et al., 2004). However, care must be taken when making assumptions about the correlation between OCT images and retinal histological sections – the strength of backscattered light is related to its angle of incidence on the area of interest. Therefore, structures running obliquely in the retina, such as Henle fiber layer, are often not well visualized on standard OCT images (Lujan et al., 2010; Otani et al., 2010).

On OCT false-color B-scans, highly reflective tissue is reddish-white in color, while hyporeflective tissue is blue-black in color (Schuman et al., 2004; Brar et al., 2009b). On most OCT scans, the first hyperreflective layer detected is the internal limiting membrane (ILM) at the vitreoretinal interface. In a subset of the population, the posterior hyaloid may be seen as a thin hyperreflective layer above the ILM. Within the retina, the ganglion cell layer and both the inner and outer plexiform layers are seen as hyperreflective layers while the inner and outer nuclear layers are hyporeflective. Recent studies have also shown that, by varying the measurement beam, two aspects of the outer plexiform layer may be alternately seen: (1) a thin hyperreflective layer corresponding to the photoreceptor synapses, and (2) a thicker hyperreflective layer corresponding to photoreceptor axonal extensions (Henle fiber layer) enveloped by the outer cytoplasm of Muller cells (Lujan et al., 2010; Otani et al., 2010).

Correlation of OCT images with the microstructure of the outer retina is less well defined than that of the inner retina (Srinivasan et al., 2008; Gloesmann et al., 2003). The first continuous hyperreflective line typically seen in the outer retina is believed to correspond to the junction of the inner and outer segments of the photoreceptors (IS–OS junction). A faint, less continuous hyperreflective line may be present above this line and is thought to represent the external limiting membrane (ELM). Beneath the IS–OS junction, the interdigitations of the photoreceptor outer segments and apical microvilli of the RPE may be visible with high-resolution OCT systems. Finally, a wide, hyperreflective line corresponding to the RPE–Bruch membrane–choriocapillaris complex lies at the outermost extent of these tissue layers. With newer OCT devices, using specific scanning protocols, visualization of choroidal structure, and the choroidal–scleral junction, is also possible (Spaide et al., 2008).

3.2. Quantitative OCT image analysis

The high axial resolution offered by OCT is well suited to the objective, accurate measurement of retinal thickness (Hee et al., 1995b). Stratus OCT (Carl Zeiss Meditec, Dublin, CA), the first widely adopted commercial OCT system, uses image processing techniques to automatically detect the inner and outer retinal boundaries on OCT B-scans (segmentation) and thus provides measurements of retinal thickness (Schuman et al., 2004). Using these techniques, it is possible to measure retinal thickness at multiple locations and to construct retinal thickness maps corresponding to the ETDRS subfields (Hee et al., 1998). Caution is required, however, as errors in automated measurements are known to occur, and these errors are often severe in macular disorders with complex morphology such as neovascular AMD (Sadda et al., 2006; Patel et al., 2009b). Newer OCT systems offer considerably improved image acquisition speed, as well as improved sensitivity and axial resolution. These changes have facilitated improved accuracy in retinal segmentation; however, further improvements in image processing algorithms are still required before segmentation errors can be eliminated entirely, particularly for disorders such as neovascular AMD (Keane et al., 2009b; Krebs et al., 2009).

4. Neovascular age-related macular degeneration

AMD is the leading cause of irreversible visual loss in elderly populations in the developed world, the majority of which is attributable to the neovascular form of this disorder (Klein et al., 2011). Currently, severe visual loss can be prevented in most patients with neovascular AMD through the use of anti-angiogenic agents such as ranibizumab or bevacizumab (Lucentis and Avastin, respectively, Genentech, South San Francisco, CA) (Tufail et al., 2010; Rosenfeld et al., 2006; Brown et al., 2006). However, these therapies typically only result in significant visual improvement for about one-third of those treated. Furthermore, at presentation many patients have advanced disease that ultimately proves refractory to therapy (Rosenfeld et al., 2010). Anti-angiogenic therapy is also costly and requires frequent intraocular injections over extended time periods (Smiddy, 2009). Prediction of visual outcomes from OCT images, and identification of those patients likely to respond to these and other treatments, thus represents a significant and unmet clinical need.

The complex morphology of neovascular AMD presents a number of unique challenges for the prediction of visual outcomes from OCT. In neovascular AMD, abnormal blood vessels develop from the choroidal circulation, pass anteriorly, and proliferate in the subretinal pigment epithelium (RPE) or subretinal space (Grossniklaus and Green, 2004). The resulting hemorrhage, fluid exudation, and ultimately fibrosis, of these vessels typically results in severe visual loss, particularly if left untreated. The prototypical feature of neovascular AMD – choroidal neovascularization (CNV) – thus results in a wide range of alterations in chorioretinal morphology, with intraretinal, subretinal, and sub-RPE components of differing sizes and locations relative to the fovea. CNV occurs in many disorders other than neovascular AMD, albeit less commonly (e.g. pathologic myopia, trauma, and miscellaneous ocular inflammatory disorders) (Grossniklaus and Green, 2004). While some variation is likely, the insights provided by the characterization of neovascular AMD using OCT may also be useful for the management of patients with CNV of other etiologies.

4.1. Neurosensory retina

Invasion and proliferation of the CNV lesion results in significant degradation and remodeling of the retinal extracellular space, as well as the incursion of cellular components such as fibroblasts (Grossniklaus and Green, 2004). The resultant disruption of the ELM–photoreceptor complex in the outer retina often leads to accumulation of fluid in the neurosensory retina (Gass, 1997). Thus, thickening of the neurosensory retina is a common feature in patients with neovascular AMD (Keane et al., 2008b, 2009c). Despite this, many studies have failed to find a significant correlation between increases in retinal thickness and decreases in visual function (Moutray et al., 2008; Spaide et al., 2006). This failure may be related, at least in part, to the frequency inaccuracy of automated retinal boundary segmentation in patients with neovascular AMD (Keane et al., 2009a; Patel et al., 2009b). In an effort to reduce these errors, manual segmentation of OCT images can be performed; studies using this approach have successfully demonstrated significant correlations between retinal thickness and visual function (Keane et al., 2008a, 2009c). In subjects enrolled in the Avastin (Bevacizumab) for Choroidal Neovascularization (ABC) Trial, prior to treatment, increased retinal thickness at the foveal center was significantly associated with decreased visual function – approximately 20% of the variation in ETDRS visual acuity seen in these patients could be explained by thickening of the neurosensory retina (Keane et al., 2010a).

Many studies have also failed to detect a significant correlation between reductions in retinal thickness as a result of treatment and associated improvements in visual acuity (Spaide et al., 2006). However, there is evidence, from the PrONTO study, to suggest that reduction in retinal thickness at 1 month following initiation of ranibizumab therapy may show a modest correlation with longer-term visual outcomes (i.e. visual acuity at 12 and 24 months post-treatment initiation) (Fung et al., 2007; Lalwani et al., 2009). Stronger longitudinal correlations have again been found using manual segmentation of OCT images; one such study, while failing to detect associations between reduced retinal thickness and improved visual acuity, has demonstrated that ''regression'' of initial anatomic improvements over time may be associated with longer-term visual loss (Keane et al., 2009c). Such findings may have implications for OCT-derived dosing regimens where increased intraretinal fluid acts as a trigger for retreatment – the fluctuations in retinal thickness that can occur in such regimes may have an adverse effect on the ultimate visual outcome (Mitchell et al., 2010).

Failure to detect a stronger correlation between thickness of the neurosensory retina and visual outcomes may be related to the heterogeneous structural characteristics of this disorder – retinal thickening is often less marked in lesions where CNV growth is contained entirely beneath the RPE (type 1 CNV) (Keane et al., 2008a; Liakopoulos et al., 2008). Moreover, choroidal neovascular exudation may result in varying patterns of intraretinal fluid collection on OCT. Initially, intraretinal fluid may be seen as diffuse retinal thickening beginning in the outer nuclear and outer plexiform layers; subsequently, with more severe exudation, cystoid spaces may form. These spaces may be seen on OCT as round or oval hyporeflective areas, with larger spaces often containing tissue septa and involving all layers of the retina (Ting et al., 2002). In disorders such as diabetic maculopathy (see later), the presence of cystoid macular edema (CME) is often associated with more severely reduced visual acuity than diffuse retinal thickening alone (Keane and Sadda, 2009). In addition, it has been suggested that, in neovascular AMD, the presence of cystoid changes may mask the presence of retinal neuronal cell loss (Kashani et al., 2009). To account for these possibilities, quantification of cystoid spaces is possible using manual segmentation of OCT images. However, using this approach, Kashani et al. failed to detect a significant relationship between cystoid space volume and visual acuity and failed to improve the strength of retinal thickness–visual acuity correlation through adjustment for intraretinal cystoid space thickness (Kashani et al., 2009).

A number of other features associated with intraretinal fluid exudation have been described in patients with neovascular AMD. In some patients with chronic exudation, irreparable structural changes may occur and, as a result, cystoid spaces may persist even in the absence of leakage; such changes are often described as ''cystoid macular degeneration'' (Iida et al., 2003). Furthermore, when monitoring patients following treatment for neovascular AMD, the recurrence of intraretinal

fluid must be differentiated from that of "outer retinal tubulation" – a recently described OCT finding (Zweifel et al., 2009). Outer retinal tubulations are branching tubular structures that appear as round or ovoid hyporeflective spaces with hyperreflective borders in the outer nuclear layer (commonly overlying areas of pigment epithelium detachment (PED) or subretinal fibrosis). They are most commonly seen in patients with neovascular AMD, but may also be seen in other disorders. Outer retinal tubulations may represent a rearrangement of photoreceptors in response to injury – their association with visual outcomes has yet to be examined.

Failure to detect a strong correlation between thickness of the neurosensory retina, and visual outcomes, may also be related to the disease state at examination – more advanced lesions may be associated with substantial photoreceptor degeneration, thus complicating any analyses (Kim et al., 2002a). Furthermore, in some patients, geographic atrophy (GA) – and thus reduced retinal thickness – may predate the occurrence of CNV (Kim et al., 2002b; Sunness, 1999, 2006). In an attempt to address this, Kashani et al. evaluated the relationship between visual acuity and the thickness and volume of the outer nuclear layer in patients with neovascular AMD (Kashani et al., 2009). In this study, outer nuclear layer volume was correlated with visual acuity, although the strength of the association remained modest. Photoreceptor degeneration is also believed to be visible on OCT images as disruption of the thin hyperreflective lines in the outer retina that are thought to represent the ELM and photoreceptor IS–OS junctions (Hayashi et al., 2009; Oishi et al., 2010; Sayanagi et al., 2009). In patients with neovascular AMD, the ELM and IS–OS junction are often seen to be intact on OCT images in those patients who have responded well to therapy – the role of these parameters as prognostic indicators in neovascular AMD remains less clear.

4.2. Pigment epithelium detachment

Growth of the choroidal neovascular membrane in the sub-RPE space produces an elevated lesion visible on clinical examination, termed a fibrovascular PED; this growth is often accompanied by variable amounts of fluid leakage or frank hemorrhage (when either of these predominate the lesion is often described as a serous or hemorrhagic PED) (Macular Photocoagulation Study Group, 1991). On OCT examination, PEDs appear as broad elevations of the RPE band relative to Bruch membrane (Coscas et al., 2007). Using quantitative subanalysis, it is possible to quantify the thickness and volume of PEDs in patients with neovascular AMD (Joeres et al., 2007a,b). However, to date, no consistent correlation has been found between PED measurements and visual function (Keane et al., 2008a, 2010a). This lack of correlation is perhaps not surprising as the presence of CNV beneath the RPE may not always result in disruption of photoreceptor–RPE interactions (it is also in line with experience from clinical practice, where it is relatively common to see large fibrovascular PEDs that prove refractory to treatment but where adequate visual function is maintained) (Gass, 1997). The failure to find a significant correlation may also be related to the relative inability of conventional OCT devices to visualize the areas underneath the highly reflective RPE and thus to characterize PED subtypes. Recent studies have utilized "enhanced depth" spectral domain OCT imaging to aid visualization of the sub-RPE space and have shown that many fibrovascular PEDs appear to be filled with solid layers of material of medium reflectivity, separated by hyporeflective clefts (Spaide et al., 2008; Spaide, 2009). Prototype OCT devices utilizing longer wavelength light sources to aid light penetration have also allowed improved visualization of choroidal structure (Yasuno et al., 2009). Further studies will be required to accurately characterize OCT-derived images of choroidal structure and subsequently to determine their prognostic significance, if any.

4.3. Subretinal hyperreflective material

In many cases of neovascular AMD, vessels from the choroidal neovascular complex may pass directly into the subretinal space after their initial penetration of Bruch membrane (Grossniklaus and Green, 2004; Green and Enger, 1993; Green et al., 1985). In these initial growth phases, the CNV membrane is often highly vascular and appears on OCT as an amorphous lesion of medium- to high-reflectivity above the RPE (Liakopoulos et al., 2008; Joeres et al., 2007b). As the CNV lesion becomes less active over time, the vascular component typically regresses, while the fibrous component increases, resulting in disciform scar formation that appears on OCT as a well demarcated highly hyperreflective lesion. A number of studies have demonstrated that the total volume of subretinal tissue present correlates with visual parameters such as distance acuity, reading ability, and contrast sensitivity (Keane et al., 2008a, 2010a; Kashani et al., 2009). For example, in the ABC trial, approximately 24% of the variation in contrast sensitivity at the baseline could be accounted for by increases in the total volume of subretinal tissue (Keane et al., 2010a). Since the positioning of the fibrovascular tissue in the subretinal space may disrupt communication between the photoreceptors and the RPE, a deleterious effect on contrast sensitivity is not surprising (Gass, 1997).

4.4. Subretinal fluid

As the choroidal neovascular membrane grows, it is often accompanied by profuse leakage from its immature blood vessels (Grossniklaus and Green, 2004). Consequently, pockets of fluid commonly accumulate between the neurosensory retina and the RPE, and these areas may be seen on OCT as hyporeflective spaces (Joeres et al., 2007b). When fluid exudation is serous in nature, subretinal fluid pockets are seen on OCT as homogenous hyporeflective spaces; when the exudate contains fibrin or red blood cells, the area of subretinal fluid may by sparsely hyperreflective (Keane et al., 2010b). Spectral domain OCT allows enhanced visualization of the subretinal space and assessment of the optical density of subretinal fluid compartments may have value for the differentiation of macular disorders associated with subretinal accumulation (Ahlers et al., 2009b). Weak correlations have been reported between increased volumes of subretinal fluid and decreased contrast sensitivity, although evidence for its association with other visual parameters in neovascular AMD is lacking (Keane et al., 2010a).

4.5. Vitreomacular interface abnormalities

Retinal imaging with OCT allows detailed evaluation of the vitreomacular interface (Mirza et al., 2007). On OCT,

vitreomacular traction may be seen when a thickened, taut, posterior hyaloid causes deformation of the inner retinal surface, which may often be accompanied by CME (Koizumi et al., 2008). Epiretinal membranes (ERMs) are often seen on OCT as hyperreflective bands anterior to the inner retinal surface, with distortion of the underlying anatomy (Legarreta et al., 2008). A number of authors have recently suggested that vitreomacular interface abnormalities may play a role in the pathogenesis of CNV (Lee et al., 2009; Mojana et al., 2008; Krebs et al., 2007; Nomura et al., 2010; Robison et al., 2009). Further study is required to confirm this theory and to determine whether it has any prognostic implications.

5. Retinal vascular disease

Although histopathologic reports suggest that the features of retinal vascular disease may vary according to its underlying etiology (e.g. intraretinal cyst location and extent; serous retinal detachment frequency and severity) (Traustason et al., 2009; Fine and Brucker, 1981), the lessons learnt from characterization of diabetic maculopathy using OCT may also be important for the management of other diseases where the tomographic features have been less well-defined (Keane and Sadda, 2009).

5.1. Diabetic maculopathy

On OCT, diabetic macular edema (DME) is generally seen as an area of retinal thickening that is often accompanied by loss of the foveal depression. Approximately 90% of patients with DME show evidence of sponge-like retinal thickening associated with decreased optical backscattering on OCT – this thickening may be localized to the outer nuclear layer, or extend diffusely to involve the entire retina (Kim et al., 2009; Otani et al., 1999). Sponge-like retinal thickening is often seen in association with both CME and serous retinal detachment, however, it may also occur in isolation, particularly in patients with mild-moderate nonproliferative diabetic retinopathy, and in this context is associated with less severe visual loss (Alkuraya et al., 2005). Approximately 50% of patients with DME demonstrate evidence of round or oval hyporeflective areas on OCT consistent with intraretinal cystoid spaces (Otani et al., 1999; Kim et al., 2006). On FA, leakage into cystoid spaces may result in a ''petalloid'' or ''honeycomb'' appearance. On OCT, petalloid hyperfluorescence is associated with cystoid space formation in the radially arranged outer plexiform layer of Henle, while honeycomb hyperfluorescence correlates with cystoid space in the vertically arranged inner nuclear layer (Otani and Kishi, 2007). Detection of CME on OCT is associated with a more severe reduction in visual acuity and a poorer response to treatment than OCTs displaying sponge-like retinal thickening alone (Brasil et al., 2007). Using microperimetry, Deák et al. have demonstrated that outer nuclear layer cysts – in particular those >220 μm in size – have greater negative effects on retinal sensitivity than inner nuclear layer cysts (Deák et al., 2010b).

Approximately 15–30% of patients with DME demonstrate evidence of serous retinal detachment on OCT (Catier et al., 2005; Ozdemir et al., 2005a,b; Gaucher et al., 2008). Serous retinal detachment occurs when fluid accumulation leads to separation of the neurosensory retina and the RPE, and is seen on OCT as a hyporeflective space. The presence of a serous retinal detachment may represent a specific feature of a severe stage of DME (Kim et al., 2006; Alkuraya et al., 2009), although this feature may occur even when the central retinal thickness above the detachment is within the normal range (Gaucher et al., 2008). Furthermore, serous retinal detachment may resolve despite worsening of DME, and the presence of this feature on OCT does not appear indicative of a poor prognosis (Gaucher et al., 2008; Ozdemir et al., 2005b).

In areas of long-standing edema, lipid and protein may precipitate in the outer retina, forming hard exudates that appear as focal areas of hyperreflectivity with posterior shadowing (Otani and Kishi, 2001; Bolz et al., 2009). In some cases these foci can be located on OCT before they can be seen on either biomicroscopy, color photography, or infrared imaging and may thus constitute a marker for early subclinical blood–retinal-barrier breakdown in DME (Bolz et al., 2009). In more advanced cases, these foci may become confluent forming hyperreflective plaques in the outer plexiform and outer nuclear layers and resulting in decreased retinal sensitivity (Deák et al., 2010a,b; Ota et al., 2010a).

Abnormalities of the vitreomacular interface are also commonly seen in DME (Gaucher et al., 2005; Ghazi et al., 2007). On OCT, the posterior hyaloid may be seen as a thin hyperreflective membrane with a broad or focal adhesion to the retinal surface. In patients with DME, this membrane often appears thickened and taut, exerting obvious traction on the retina and resulting in a characteristic peaked appearance. ERMs also commonly form in patients with DME and may be clearly seen on OCT. Identification of these features is important as surgical intervention may lead to significantly improved visual outcomes (Otani and Kishi, 2000; Patel et al., 2006; Thomas et al., 2005). Thus, evaluation of the vitreomacular interface should always be performed in patients with DME, particularly when retinal thickening is present on clinical examination but fluorescein angiography discloses no significant leakage or ischemia.

Ischemic changes are commonly seen in patients with diabetic maculopathy and may have a negative impact on visual function, as well as on response to treatment, in patients with DME (in a minority of patients, visually significant ischemic maculopathy may also occur in the absence of DME) (Bresnick et al., 1984; Conrath et al., 2005). In general, the features and natural history of diabetic ischemic maculopathy remain poorly understood – a finding reflected in the relative paucity of related OCT studies. Recently however, studies using spectral domain OCT have shown that macular ischemia is associated with disorganization and loss of inner retinal layers, as well as reductions in retinal sensitivity (Yeung et al., 2009; Byeon et al., 2009). Other evidence suggests that eyes with cystoid spaces at the foveal center on OCT may have larger foveal avascular zones on fluorescein angiography (Murakami et al., 2010). As anti-angiogenic therapies are introduced for the treatment of DME, further research is necessary to more completely characterize the OCT features of diabetic macular ischemia and thus determine their prognostic significance.

Numerous studies have used a quantitative approach when examining the correlation between visual acuity and OCT-derived features in patients with DME (Hee et al., 1995b, 1998; Otani et al., 1999; Catier et al., 2005; Goebel and Kretzchmar-Gross, 2002; Massin et al., 2003). Initial studies

found evidence of a strong correlation between increased retinal thickness and decreased visual acuity, although many involved small sample sizes and lacked best-corrected ETDRS visual acuities. The evidence from more recent studies is less clear, with the most comprehensive data to date suggesting a modest correlation between OCT-measured foveal center point thickness and visual acuity ($r = 0.52$), and a modest correlation between changes in retinal thickening and visual acuity after laser treatment for DME ($r = 0.44$) (Network et al., 2007). The strength of the observed correlations may be treatment-dependent – in a recent randomized controlled trial assessing the efficacy of intravitreal triamcinolone, no statistically significant correlation was detected between changes in retinal thickness and visual acuity in treated patients (Larsson et al., 2005). The visual significance of OCT-derived parameters other than retinal thickness/volume has also been assessed. Alasil et al. demonstrated a significant correlation between visual acuity and photoreceptor outer segment thickening and volume, but no association of vision with subretinal fluid volume (Alasil et al., 2010).

5.2. Retinal vein occlusion

Both central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO) are common causes of macular edema (Johnson, 2009). In these disorders, acute extravasation of fluid into the extracellular space of the retina results from increased hydrostatic pressure in retinal veins distal to their point of occlusion. In addition, growth factors released in response to hypoxia may lead to breakdown of the inner blood–retinal barrier, increasing fluid extravasation. Macular edema in retinal vein occlusion appears similar to that in DME, although in BRVO the observed changes on OCT are usually restricted to either the superior or inferior aspects of the macula (Spaide et al., 2003). In addition, serous detachment of the retina is more commonly seen in retinal vein occlusions than from other etiologies, although the presence of serous macular detachments does not appear to be associated with worse visual outcomes (Catier et al., 2005). A number of studies have evaluated the correlation between OCT-derived retinal thickness parameters and visual acuity, but have only identified moderate correlations (Scott et al., 2009). More recently, studies have shown that the integrity of the ELM, and photoreceptor IS–OS junction, appears to correlate with visual acuity in both forms of retinal vein occlusion (Ota et al., 2007, 2008a,b, 2010b; Yamaike et al., 2008).

5.3. Uveitic syndromes

Macular edema typically develops in patients with intermediate and posterior uveitis, but may also be seen in cases of isolated anterior uveitis, and is a common cause of visual loss (Gallagher et al., 2007; Tran et al., 2008; Iannetti et al., 2008). Many of the edematous changes seen on OCT in DME may also be seen in chronic uveitis and similar OCT–visual acuity correlations have typically been described (Tran et al., 2008; Roesel et al., 2009).

6. Central serous chorioretinopathy

Central serous chorioretinopathy (CSC) is a common macular disorder characterized by serous detachment of the neurosensory retina and/or the RPE (Wang et al., 2008). CSC occurs most commonly in young and middle-aged males and is often only associated with modest reduction in visual function. CSC is believed to occur as a result of choroidal hyperpermeability, although the integrity of the RPE may play a role in determining the exact disease phenotype (Spitznas, 1986). On fluorescein angiography in CSC, leakage of dye may be seen at the level of the RPE, followed by pooling of the dye in the sub-RPE and/or subretinal space. In some patients with CSC, particularly Asians and older age groups, multiple sites of prolonged or recurrent leakage may affect one or both eyes leading to widespread abnormalities of the RPE – a condition termed "chronic CSC" (Iida et al., 2003).

On OCT, the characteristic feature of CSC is the presence of subretinal fluid distributed in a disciform pattern (i.e. serous retinal detachment), accompanied by one or more discrete areas of PED (Iida et al., 2000; Montero and Ruiz-Moreno, 2005). Typically, the subretinal fluid is homogeneously hyporeflective, reflecting its serous nature, although subretinal fibrinous deposits are sometimes present (Wang et al., 2005). In CSC, PEDs are usually small, well demarcated, and lack any evidence of the RPE hypertrophy or hyperplasia that can occur in PEDs associated with other macular disorders (Cho et al., 2010; Ooto et al., 2010). PEDs in CSC are also usually dome-shaped and homogenously hyporeflective, with clear visibility of the Bruch membrane/choriocapillaris complex. In Asian populations, multiple larger PEDs are often seen and, in some cases, focal defects in the RPE, associated with overlying hyperreflective fibrinous exudation, may be evident (Fujimoto et al., 2008). When such fibrinous exudation is severe it may result in the formation of fibrinous bands that extend between the RPE and the neurosensory retina, and lead to sagging/dipping of the retina over leakage sites in areas of serous detachment.

When patients with CSC are examined using OCT, changes in the overlying neurosensory retina can also be observed (Ahlers et al., 2009a). Hyperreflective deposits are often seen adherent to the undersurface of the retina in areas of serous detachment – these deposits may represent fragments of photoreceptor outer segments that have been incompletely phagocytosed due to separation from the RPE. In most patients with CSC, the ELM appears intact on OCT, but the IS–OS junction and outer plexiform layers show diffusely increased hyperreflectivity (Ahlers et al., 2009a; Matsumoto et al., 2008). These changes may represent structural changes in the neurosensory retina, although recent studies suggest that they more likely reflect changes in the OCT signal from changes in the orientation of vertically oriented retinal microstructures (see above) (Lujan et al., 2010; Otani et al., 2010). More recently, "enhanced depth imaging" OCT has been used to evaluate choroidal thickness in patients with CSC – these studies have demonstrated that the choroidal thickness is significantly greater in patients with CSC than in normal eyes, and that treatment with photodynamic therapy leads to reductions in this parameter (Imamura et al., 2009; Maruko et al., 2010).

Considerable efforts have been made to predict visual outcomes using OCT in patients with CSC – particularly as the disease affects a relatively young population, often with "type A" personalities, for whom duration of symptoms and ultimate visual prognosis is a major concern (Yannuzzi, 1987). Matsumoto et al. have demonstrated that thickness of the outer nuclear layer is positively correlated with visual acuity in patients with resolved CSC; they also reported that eyes with thinner outer

nuclear layers and reduced visual acuity were more likely to manifest discontinuities of their IS–OS junctions when examined with OCT (Matsumoto et al., 2009). The importance of both IS–OS junction and ELM integrity has been confirmed in other reports, many of which have also detected a relationship between initial foveal thickness and final visual outcome (Ojima et al., 2007; Piccolino et al., 2005; Aggio et al., 2010; Shinojima et al., 2010). In the near future, advances in OCT technology will allow enhanced visualization of both choroidal and RPE structure; such advances may allow the clinician to better predict the course of the disease, including time to symptom resolution and the likelihood of recurrent or chronic disease (Keane and Sadda, 2010).

7. Non-neovascular age-related macular degeneration

The clinical hallmark of AMD is the deposition of acellular, polymorphous material, termed drusen, between the RPE and Bruch membrane (Jager et al., 2008). In early AMD, drusen are often accompanied by focal retinal pigmentary abnormalities; as AMD progresses, alterations in the RPE often accumulate, resulting in the loss of large areas of RPE and outer retina, a phenomenon termed GA (Sunness et al., 2007).

With current commercial OCT systems, small and intermediate size drusen may be clearly seen as discrete areas of RPE elevation with variable reflectivity, reflecting the variable composition of the underlying material (Gorczynska et al., 2009; Khanifar et al., 2008). In larger drusen, or drusenoid PED, greater elevation of the RPE may be seen, often dome-shaped, with a hypo- or medium-reflective material separating the RPE from the underlying Bruch membrane (Roquet et al., 2004; Spaide and Curcio, 2010). Larger drusen may often become confluent, resulting in a large lateral dimension, but no single broad-domed lesion. On OCT, drusen are often accompanied by changes in the overlying neurosensory retina – these may be seen as disruption of the IS–OS junction and ELM, as well as significant thinning of the outer nuclear layer (Schuman et al., 2009). These findings are consistent with previous histopathologic studies demonstrating photoreceptor loss in patients with drusen (Curcio et al., 1996).

In GA, confluent areas of RPE atrophy are accompanied by loss of the overlying photoreceptors and varying degrees of choriocapillaris loss seen on fluorescein angiography (Gass, 1997; Sunness, 1999). On OCT, GA appears as areas of sharply demarcated choroidal hyperreflectivity due to loss of the overlying RPE (atrophy from causes other than AMD – e.g. from confluent laser photocoagulation – may have a similar appearance) (Wolf-Schnurrbusch et al., 2008). Associated retinal atrophy is seen as thinning or loss of the outer nuclear layer and the absence of ELM and IS–OS junctions (Fleckenstein et al., 2008). On OCT, islands of preserved outer retina may sometime be identified in areas of GA, as can regressing drusenoid materials, seen as hyperreflective plaques at the level of the RPE. GA may also be associated with the presence of small cyst-like spaces in the inner nuclear layer, in the absence of macular edema (Cohen et al., 2010).

Assessment of visual prognosis in patients with GA is dependent on knowledge of GA size, location, and rates of progression (Sunness et al., 2007). For the latter, fundus autofluorescence findings in the junctional zone surrounding GA have proven useful in highlighting those cases likely to progress rapidly (Holz et al., 2007). Evaluation of the junctional zones around GA, using OCT, has shown that the ELM and IS–OS junctions may be seen to taper off, and the outer plexiform later can be seen to approach toward Bruch membrane (suggesting that photoreceptor loss often extends beyond the margins of GA lesions) (Bearelly et al., 2009). OCT studies have also demonstrated a variety of dynamic changes in the junctional zone, including pigment migration and alterations in drusen height (Fleckenstein et al., 2010). GA assessment using OCT may thus provide insight into disease pathogenesis, but its potential benefits for prediction of visual outcomes remain to be determined (Schütze et al., 2010; Yehoshua et al., 2010a,b; Brar et al., 2009a; Lujan et al., 2009).

8. Conclusion

Following its release in 2002, Stratus OCT (Carl Zeiss Meditec, Dublin, CA) became the first OCT system to become ubiquitous among retina specialists worldwide and led to significant advances in the diagnosis and management of disorders such as diabetic retinopathy and neovascular AMD. More recently, the next generation of commercial OCT systems – spectral domain OCT – has provided significant increases in image acquisition speed, resolution, and sensitivity. While use of spectral domain OCT technology has led to the identification of many new structural features of macular disease, much work remains to correlate these findings with visual function and, thus, to predict visual outcomes. The rate of ongoing change in OCT hardware is also rapid, with new commercial systems expected to allow enhanced visualization of the choroid as well direct, non-invasive measurements of macular blood flow, and greatly increased speeds. Although our current ability to predict visual outcomes using OCT remains somewhat limited, such advances should ultimately allow clinicians a comprehensive understanding of visual prognosis in macular disease, with all the attendant benefits for their patients.

Disclosure

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