Scanning Laser Ophthalmoscope in the Management of Age-related Macular Degeneration

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Abstract

Recent advances in retinal imaging have improved the evaluation and prognostication of age-related macular degeneration. The development and modification of the scanning laser ophthalmoscope (SLO) has played a pivotal role in our understanding of the disease. SLO has led to improved methods of visualising characteristics of the disease, such as drusen and alterations in autofluorescence, and also provided a platform for the quantification of structural and functional changes occurring as a result of the disease process. This article provides a review of the current literature on the impact and clinical utility of SLO devices for infrared viewing, fundus autofluorescence, microperimetry, and as integraded multimodal imaging systems such as optical coherence tomography and SLO.

Keywords

Age-related macular degeneration, scanning laser ophthalmoscope, autofluorescence, spectral-domain optical coherence tomography, microperimetry

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Age-related macular degeneration (AMD) is the most common cause of irreversible central vision loss and legal blindness in developed countries.[1–3] AMD represents a chronic disease with various phenotypic manifestations, disease stages and rates of progression over time. Severe vision loss results from choroidal neovascularisation (CNV), pigment epithelial detachment, or geographic atrophy (GA) of the retinal pigment epithelium (RPE).[4] While CNV is the most common cause of vision loss, GA is responsible for approximately 20 % of severe visual impairment in AMD.[5–8] The chronic nature of the disease, limited treatment options, and the ageing population are all factors suggesting that the prevalence of AMD will increase with time unless effective interventions are developed.

Retinal imaging plays a critical role in the detection and management of disease because it can reveal lesions difficult to visualise by funduscopic examination. Colour fundus photography is the standard imaging modality used for assessment and documentation of AMD. Fluorescein angiography provides additional functional information on vascular involvement, which is important in the detection of CNV and other complications of advanced disease that involve disturbance of the blood–retinal barrier. The scanning laser ophthalmoscope (SLO) adds the ability to test and image the retina in a point-by-point fashion, which enhances the evaluation of structural and functional changes in the disease process of exudative and non-exudative AMD.

The SLO was originally developed by Pomeranzeff and Webb to provide high-contrast images of the retina at illumination levels 1/1,000 of those required for indirect ophthalmoscopy.[9] The SLO scans a low energy laser beam (or other coherent illumination source such as the superluminescent diode) across the fundus and reconstructs images from reflected light, creating images with a higher level of contrast compared with fundus photography.[10,11] The technology of the sweeping illumination source provides a platform from which additional testing such as fluorescein angiography, manual and automated perimetry, and reflectometry of cone pigment densities can be accomplished.[10,12–15] Additional modifications of the device lead to the confocal SLO (cSLO), which uses light from a single plane for image reconstruction. By rejecting the returning scattered light, the cSLO provides improved contrast and complete retinal images (40°) without dilation of the pupil.[11,16] Pupil dilation is not necessary but it is often done in practice to obtain higher quality images. Currently there are three modalities that use the cSLO technology in the detection and management of AMD: fundus autofluorescence (FAF), optical coherence tomography (OCT)/SLO, and microperimetry (MP). Modification of the aperture and light source has also generated the indirect, infrared (IR) and retro-mode SLO devices that provide additional methods for the assessment of subretinal disease. The aim of this article is to review recent findings in AMD research that relate to the application of these devices for early detection and monitoring of progression of disease, or response to therapeutic interventions.

Indirect, Infrared and Retro-mode Scanning Laser Ophthalmoscope

Drusen are a hallmark of early AMD. The term describes the deposition of extracellular material between the RPE monolayer and inner aspects of Bruch's membrane.[17,18] The precise mechanisms of the biogenesis of drusen are unknown, but incomplete disassembly of photoreceptor outer segments by the RPE cells is thought to play an important role. Several modifications have been made to the SLO in attempts to better visualise the structural and functional changes associated with AMD, including changes in the RPE, Bruch's membrane and the deposition of drusen. These modifications have led to the development of IR, indirect and retro-mode SLO devices.

IR imaging was introduced for better visualisation of deep and subretinal structures. Initial studies reported that IR images with SLO revealed details of the fundus poorly delineated by the fundus camera.[19–21] IR SLO has the additional advantage of being able to obtain images even in the presence of mild cataract or haemorrhage.[29] IR imaging provides a non-invasive *in vivo* method for revealing subtle changes in the RPE/Bruch membrane complex and may be helpful for detecting early CNV, preclinical drusen and subretinal deposits.[22]

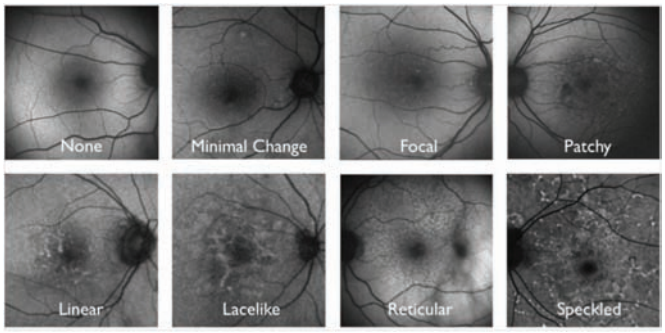
The improved capabilities of the cSLO, as previously mentioned, was achieved by modifying the aperture of the direct SLO to allow only the light reflected from the fundus to be detected, reducing the influence of scattered light and improving image quality.[11,16] In contrast to the confocal approach, it was determined that by blocking light reflected from the fundus with a central stop on the aperture, only laterally scattered light is detected.[23] This was the concept that led to the indirect SLO, which was designed to detect light scattered by lesions on the retina. Drusen are a prominent source of light scatter and are easily detected with indirect SLO.[23] In addition to providing enhanced imaging of macular drusen, in some patients indirect SLO has provided earlier visualisation of elevations due to CNV.[22]

Retro-mode imaging is another modification that integrates the concepts of confocal and indirect SLO. The aperture with retro-mode imaging is smaller than the indirect SLO, but deviates from the concept of the cSLO in that the aperture is placed laterally, so light reflected directly back from the fundus is blocked. This modification allows only the laterally scattered light from a single direction to pass through. Analysis of these images produces a pseudo-3D appearance to drusen, consistent with the capabilities of indirect IR SLO imaging.[24] Retro-mode SLO has been found to capture images consistent with the appearance of drusen on OCT imaging and can detect significantly more deposits than colour fundus photography.[24] This technique may also have the capability to detect subtle changes in drusen occurring over a short period of time. Alterations to the aperture and wavelength of the SLO generated the indirect, direct, IR and retro-mode SLO devices that all individually provide better methods for detecting subretinal changes occurring in patients with AMD.

Autofluorescence

With the advent of cSLO it became possible to visualise intrinsic FAF and its spatial distribution *in vivo*.[25–29] cSLO FAF provides a tool for the evaluation of the RPE in normal ageing and in retinal disease.[30] RPE lipofuscin (LF) granules contain fluorophores believed to be responsible for fundus autofluorescence.[31] LF granules typically accumulate gradually with age, but various monogeneic macular and retinal dystrophies manifest excessive accumulations of LF within the RPE cells.[27,32–35] One of the main autofluorescent components of LF is A2E,[36] a potentially cytotoxic compound capable of lysosomal disruption.[18,37–40] Another theory suggests that elevated LF levels may act as a trigger for the complement system, exposing the macula to chronic inflammation. Zhou and colleagues recently demonstrated a link between LF and complement activation, inflammation, oxidative damage and drusen using an *in vitro* assay.[41] Despite emerging controversial views regarding the effects of LF accumulation, there is some consensus that the disturbance of LF is implicated in AMD disease manifestations.

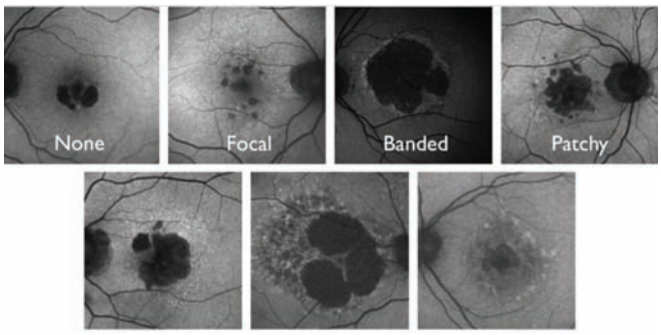
Figure 1: Examples of the Eight Different Fundus Autofluorescence Patterns Seen in Patients with Age-related Macular Degeneration



Recent studies demonstrate FAF changes in early and advanced AMD.[26,28,30,32,34,35,42,43] Early manifestations of AMD include focal hypo- and hyperpigmentation at the level of the RPE and drusen with extracellular material accumulating in the inner aspect of Bruch's membrane.[17,44] The alterations of FAF intensities in early AMD include focal areas of increased FAF intensity and drusen. Hard and soft drusen generally do not alter the FAF signal. There is, in fact, strong evidence supporting the conclusion that changes in FAF signal are not associated with funduscopically or angiographicaly visible drusen.[29,43,45–51] Hence, visible drusen on fundus photographs and alterations on FAF imaging are two independent measures of disease stage, activity and progression. FAF imaging provides metabolic assessment beyond colour fundus photography and allows for the characterisation of progressive changes in the RPE.[52,53]

The fundus autofluorescence in age-related macular degeneration (FAM) study group, representing the efforts of an international workshop on FAF phenotyping, introduced a classification system in 2005 for FAF patterns seen in early AMD.[52] The stated purpose of this classification system was to facilitate comparison between studies, to aid in identifying prognostic determinants based on FAF imaging, and to identify genetic factors contributing to AMD. The system defines eight distinct FAF phenotypes: the normal FAF pattern, a minimal change pattern, a focal increase pattern, a patchy pattern, a linear pattern, a lacelike pattern, a reticular pattern, and a speckled pattern (see *Figure 1*). Using this classification system in their longitudinal study, a clearer relationship between disease progression and FAF patterns was demonstrated. Of 125 eyes with early AMD, two developed GA and nine advanced to exudative AMD. Both eyes with GA had a focal FAF pattern at baseline. Six of the nine patients with exudative AMD had a patchy phenotype at baseline. There were 35 eyes with a patchy FAF pattern at baseline, and six progressed to exudative AMD over the course of the study (mean follow up was 18 months, with a range of 12–36 months). These initial findings suggest

Figure 2: The Five Categories of Abnormal Fundus Autofluorescence Patterns



Fundus autofluorescence (FAF) patterns in the junctional zone of patients with atrophic age-related macular degeneration, including three of the five subtypes in the diffuse category.

that baseline focal and patchy FAF phenotypes may be high-risk indicators for progression.[52]

The reticular pattern has recently attracted more interest as FAF and IR have become more commonly used in the imaging of patients with AMD. This pattern has been defined as a regular network of uniform round or oval irregularities of decreased FAF signal surrounded by mildly increased intensities (see *Figure 1*).[54] It is commonly seen in patients with reticular drusen, often referred to as reticular pseudo-drusen. These pseudo-drusen are a new, distinctive morphologic feature observed in AMD that is best seen with red-free, IR, FAF and indocyanine green angiography ICGA images.[55–57] Klein and colleagues defined them as ill-defined networks of broad, interlacing ribbons.[58] The combination of reticular drusen and a reticular FAF pattern has been associated with an increased risk of progression to advanced AMD. Smith and colleagues reported that 74 % of patients with the reticular drusen and a reticular FAF pattern had advanced AMD.[59] Prior studies reported lower percentages.[56,60–62] The recent discovery of the strong association between reticular disease and AMD progression is attributed to increased utilisation of autofluorescence and IR imaging in the management of AMD, as these patterns were difficult to visualise with colour fundus photography.[59]

A similar classification system was developed for FAF phenotypes seen in atrophic AMD. The classic FAF pattern in patients with GA consists of a marked decrease in FAF signal in the region of atrophy, coinciding with RPE cell loss.[63,64] Areas of GA gradually enlarge over time, possibly resulting from accumulation of excessive LF in RPE cells in the surrounding 'junctional zones'.[28,65–69] LF accumulation in the junctional zone becomes apparent with abnormal increases in FAF intensities. Functional impairment in the junctional zone, suggesting the extension of the disease process, has also been measured using fine matrix mapping and MP in patients with abnormal patterns of FAF in this zone.[70,71] These structural and functional alterations in the junctional zone appear consistent with the progression rate of GA. The FAF patterns identified were defined in an attempt to explain the large variability in rates of GA enlargement among patients that cannot be explained by baseline atrophy or any other risk factor (smoking, lens status, or family history).[68,69,72] The five junctional zone FAF patterns identified, include no change, focal, banded, patchy and diffuse patterns. The diffuse pattern, in turn, is separated into five different subtypes (see *Figure 2*).

The results reveal a significant correlation between GA expansion rates and specific FAF phenotype at baseline.[18] Two phenotypes showed significantly higher rates of expansion. These were the banded and diffuse FAF patterns. Slower progression rates were found in patients with either the focal pattern or no change in FAF signal. There was also variation seen within the diffuse subtypes. The 'diffuse trickling' subtype showed the fastest rate of expansion, which was twice as fast as other diffuse or banded FAF patterns.[72]

Further evidence relating to the significance of FAF patterns in early and atrophic AMD are necessary, but evidence from one of the largest longitudinal studies to date has contributed confirming evidence linking focal and patchy FAF in early AMD as a risk factor for progression to advanced disease. For patients with advanced AMD, the diffuse and banded FAF patterns in the junctional zone of GA appear to be precursors to expansion.[18,52,72] Newer studies investigating the association between reticular drusen, reticular FAF pattern, and advanced AMD indicate that reticular macular disease is another important risk factor for disease progression.[59]

Optical Coherence Tomography/Scanning Laser Ophthalmoscope

OCT is another commonly used non-invasive imaging technique in which retinal structures are visualised in cross section. The technology of OCT has become an essential clinical tool in the detection and management of retinal disease because it provides clinically relevant images that correlate well with histology.[73–75] The earlier devices such as the Stratus OCT (Carl Zeiss Meditec, Dublin, California) and the SLO/OCT (Ophthalmic Technologies, Inc., Toronto, Canada) used a technique referred to as time-domain OCT (TD-OCT), which acquired depth information by looking at the change in interference pattern as the reference arm of the interferometer moved mechanically over time. This produced 2D cross-sectional images consisting of 512 A-lines with an axial resolution of 10 µm.[76]

More recently, spectral-domain OCT (SD-OCT) has become the dominant technology. SD-OCT acquires depth information using the same interferometer configuration but replaces the single detector of the time domain system with a spectrophotometer that can detect multiple depths simultaneously. This results in SD-OCT devices with increased imaging speeds (34.1 µs per A-line), generating more than 100 high-resolution scans in the time required to capture less than 10 TD-OCT scans, providing 150-fold improvement in sensitivity with axial resolutions as small as 2 µm.[76–81] A major reason for the newly emphasised role of OCT in AMD lies in the ability of SD-OCT to detect even the finest drusen as they begin to appear beneath the RPE.[78] Other important features of the disease, such as RPE atrophy, intraretinal fluid, pigment epithelial detachments and neovascular membranes, can also be detected with this generation of OCT.[78,82]

The Spectral OCT/SLO (OPKO-OTI, Miami, Florida) was the first device to integrate simultaneous high-resolution cross-sectional OCT imaging of the retinal layers (SD-OCT) with SLO fundus imaging of the retina. This device uses a single superluminescent diode light source to simultaneously obtain SLO and OCT images. The one-to-one correspondence of the real-time SLO with the high-resolution SD-OCT provides better visualisation and precise localisation of small, discrete lesions. This makes OCT/SLO ideal for longitudinal analysis of individual lesions because it ensures an accurate assessment of changes. Subsequent to the introduction of the OPKO-OTI OCT/SLO,

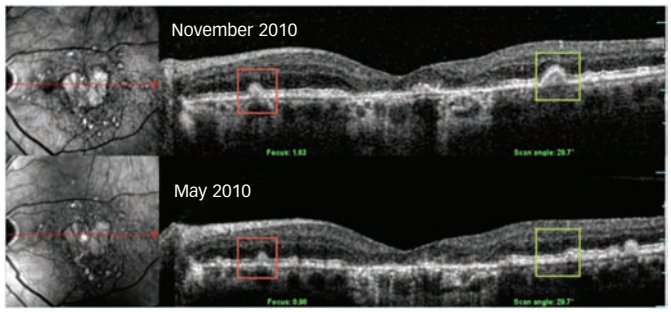
seven other manufacturers including Heidelberg Engineering (Germany; Spectralis), Zeiss (Hertfordshire, UK; Cirrus), Optivue (Oregon, Ohio; RT-Vue), Topcon (Tokyo, Japan; 3D OCT), Canon/Optipol (Tokyo, Japan; Copernicus), Nidek (Aichi, Japan; Retinascan) and Bioptigen (Research Triangle Park, North Carolina; SD-OCT) introduced their version of combined SD-OCT and SLO. Each manufacturer has developed its own set of features aimed at fulfilling their unique interpretation of clinical needs. Spectralis has emphasised tracking to obtain point-to-point registration along with averaging for improved image appearance. Cirrus has emphasised fixation independent centration, multilayered C-scan images (developed after the original OTI OCT/SLO C-scans) and seamless anterior segment imaging. Topcon has focused its efforts on the 3D OCT scan combined with colour fundus images. Optivue pioneered a low-cost system with anterior and posterior segment capabilities along with tracking and glaucoma management tools. Optipol offers higher speed and high-resolution scanning with Doppler blood flow analysis. Retinascan offers automatic segmentation analysis of the retina into six distinct layers. Bioptigen offers a portable handheld device for paediatric and veterinarian applications along with Doppler capabilities. The range of innovations in design among these competitors has provided a windfall of imaging options for the clinician and has helped advance diagnostic capabilities of the basic SLO and OCT combination and improve longitudinal tracking of slowly progressive disease.[83]

Longitudinal studies have found many associations between drusen and disease progression in AMD. Small, hard drusen are considered an early sign of AMD,[60] and large numbers of hard and soft drusen have been shown to progress to GA.[64,84,85] The disappearance of drusen has also been observed, and is associated with the absence of apparent progression of AMD.[86,87] Multiple studies have noted this finding, suggesting that up to 34 % of drusen can disappear over a five-year follow up.[86,88] The OCT/SLO provides the resolution and precise localisation required for quantitative and qualitative analysis of macular drusen.

Quantitative analysis of drusen suggests that greater drusen diameter and area may be associated with a significant risk of progression to advance AMD[8,89,90] and increased drusen load has been correlated with advanced stages of AMD.[31,64,85,91,92] Originally drusen were quantified using stereo viewing and manual segmentation. This mechanism had a relatively high specificity and sensitivity but inter-observer agreement was low and the process was time consuming.[93] The Columbia group assessed these problems and generated a semi-automatic mechanism for quantifying drusen on CFP by using automated background levelling and thresholding.[93] The automated drusen method offers an efficient method for drusen segmentation and maintains a similar sensitivity and specificity as the stereo viewing method.[93,94] This quantification strategy was also applied to OCT, using an SD-OCT to generate a volume scan with summed-voxel projection of a series of B-scans for drusen analysis and quantification. The results showed that drusen area determined with SD-OCT was similar to that determined with CFP and SD-OCT had increased sensitivity in patients with greater total drusen burden.[95] Integrating this method into an OCT/SLO system could offer the advantage of tracking precise changes in drusen load over time.

Another study used SD-OCT to quantify macular drusen to demonstrate that drusen volume strongly correlates with the standard Age-related eye disease study (AREDS) grading scale. They suggest that the addition of SD-OCT quantified macular drusen load to the AREDS grading system could increase the correlation between AREDS score and the incidence of CNV. Increasing the predictability of the AREDS system could better identify individuals at higher risk for progression, who require more intense and frequent monitoring to detect CNV earlier to limit visual loss.[96] In addition to monitoring drusen load to predict disease progression, several studies have attempted drusen reduction as a means of preventing vision loss.[97–99] However, before accurate correlations can be made between changes in drusen load and disease state, a reliable mechanism for quantifying drusen must be established.

Figure 3: An Example Demonstrating the Ability of OCT/SLO to Visualise Changes in the Retinal Layers Using High-resolution Spectral Domain-Optical Coherence Tomography



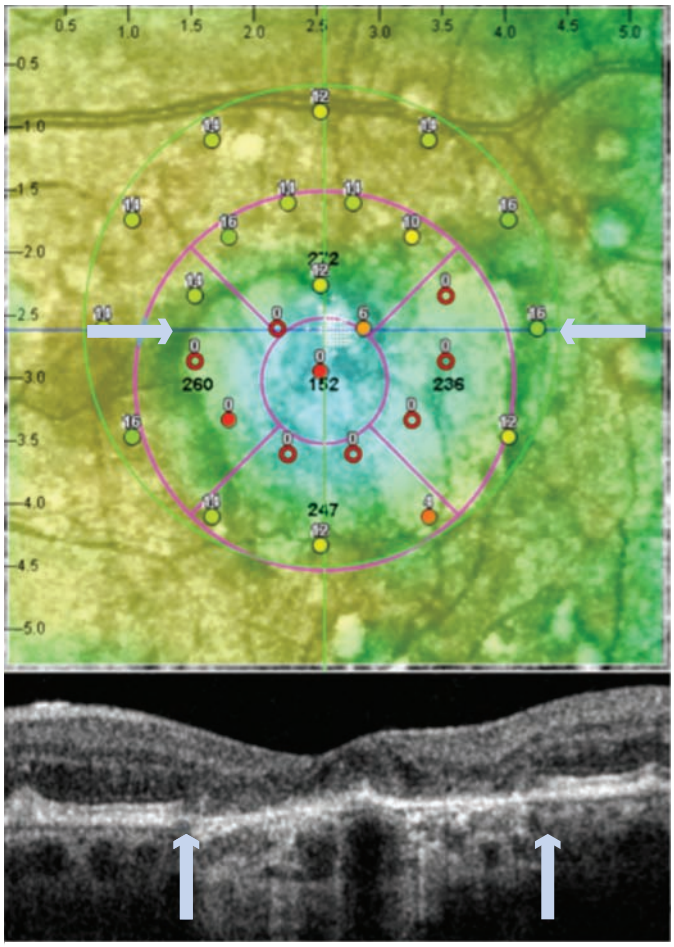
Combining the SD-OCT and SLO images, the lesions are precisely localised for serial analysis. Here drusen regression (green box) was visible in a patient with age-related macular degeneration treated with Copaxone. OCT = optical coherence tomography; SD = spectral domain; SLO = scanning laser ophthalmoscope.

Qualitative analysis of drusen is also possible with the advent of OCT/SLO. Several recent publications have focused on defining morphologic OCT characteristics observed in dry AMD.[81,100–103] Khanifar and colleagues described 17 different patterns based on drusen shape, internal reflectivity, homogeneity and the presence of foci over drusen.[102] The purpose, similar to the FAF classifications previously mentioned, is to determine what characteristics of drusen are associated with disease progression, to understand the pathophysiologic mechanisms relating to drusen accumulation and disappearance, and to investigate treatment response.

Landa and colleagues analysed the morphological changes of drusen in patients with AMD undergoing Copaxone (Teva Pharmaceuticals) treatment for elimination of drusen.[104] They demonstrated that a convex drusen shape and low or medium internal reflectivity were the drusen characteristics most responsive to Copaxone treatment. Convex drusen typically appear as hard drusen on SD-OCT. The variation in treatment response is consistent with the idea that while hard and soft drusen may be of common origin, they differ in their appearance, natural history, impact on progression to advanced AMD, and response to treatment.[105] The stability and regression of various drusen over the course of treatment is demonstrated in *Figure 3*.

The natural history of macular drusen and its relation to disease progression remains controversial. Further analysis of both qualitative and quantitative analysis of drusen changes with OCT/SLO is critical in understanding the pathophysiology of drusen, its role in progression, and in the assessment of treatment options for patients with AMD.

Figure 4: Microperimetry with Optical Coherence Tomography/Scanning Laser Ophthalmoscope



This technique allows direct correlation of retinal sensitivity changes with the precisely localised retinal lesions, a disruption within retinal layers, or changes in retinal thickness.

Microperimetry

MP is a novel technique of fundus-based perimetry that allows the clinician to evaluate macular function quantitatively while simultaneously tracking the location and stability of retinal fixation.[106] The Rodenstock SLO (RcSLO, Rodenstock, Düsseldorf, Germany) was the first fundus-based perimeter.[107,108] It used an IR image to perform manual perimetry. Initial reports found decreased retinal sensitivity in regions of large drusen with clearly defined borders. No change was noted over areas of soft drusen, nor was any correlation found between drusen size and severity of sensitivity loss.[109] Vujosevic and colleagues used this device to demonstrate a decrease in retinal sensitivity in patients with increased FAF signal in the junctional zone surrounding GA.[110] This suggested that LF accumulation in RPE cells surrounding areas of GA resulted in a functional deficit.[71] This supports a previously mentioned observation that the accumulation of LF in the junctional zone precedes the expansion of GA.[65]

With the introduction of the MP-1 (Nidek Technologies, Gamagori, Japan), MP was automated and designed to test identical points on the retina during baseline and follow-up testing. During the examination it also compensates for eye movements and functions independent of fixation location and stability; an essential feature for any test intended for patients with macular disease.[15] The MP-1 uses video fundus camera to capture real-time fundus imaging during perimetry and captures a colour fundus image at the end of the test phase, on which the results are presented. The MP-1 allowed testing of a greater retinal field than the Rodenstock SLO, but the quality of the non-SLO IR images were limited. This prevents analysis of retinal sensitivity in association with small features of macular disease such as drusen and other retinal pathologic abnormalities.

Studies with the MP-1 revealed macular function loss in early and intermediate AMD before significant visual impairment or changes in fixation are established.[111] The detection of macular dysfunction even in the absence of significant visual loss can be attributed to the degeneration of the RPE cells and photoreceptors.[14,112] Decreased macular sensitivity was demonstrated over large drusen, pigment abnormalities, and areas of increased FAF signal in patients with AMD.[113] These findings advise the use of FAF and MP in combination for monitoring AMD progression. Longitudinal analysis with MP-1 proposed a sequence of events in the functional deterioration of vision in patients with AMD. Initially, patients experience a mild decrease in central retinal sensitivity and visual acuity, followed by progressive fixation instability and ultimately the development of an absolute central scotoma with total eccentric fixation.[106,111]

Another form of manual perimetry is blue-on-yellow perimetry. This technique uses the SLO to simultaneously perform fundus imaging with invisible light while testing with a different laser source.[114] By using a yellow background it suppresses the response of most cones, isolating the response of only the short-wavelength sensitive (SWS) cones.[10,115–121] The selective loss of the SWS mechanism occurs in glaucoma, diabetes, AMD and other macular diseases.[112,119,121,122] It is proposed that the SWS pathway lacks the redundancy that other pathways possess, allowing disease of the inner retina or photoreceptor/RPE complex to cause loss of function.[123] Remky and Elsner found that in the early stages of AMD, patients had decreased macular sensitivity in the SWS pathway despite good visual acuity. These patients exhibited a diffuse loss of the short-wave sensitivity and a localised loss over areas of drusen, confluent material, atrophic patches, and hyperpigmentation.[123]

A more integrated version of MP was developed using the Spectral OCT/SLO. MP was incorporated into the system allowing real-time observation of the fundus and analysis of the neurosensory retina while testing retinal sensitivity.[124] The OCT/SLO-MP device scans a region of the fundus that is designated by the operator by directing the patient's fixation. The system automatically tracks fundus localisation using retinal vessel alignment to ensure accurate stimuli placement for the duration of the test and in subsequent scans.

Traditionally, colour fundus photographs were the gold standard for the assessment of macular degeneration, but the ability to view retinal abnormalities in a third dimension using SD-OCT provides a more comprehensive picture of retinal abnormalities.[96,102,125] Prior to this, MP was capable only of characterising the function of features and regions of the visible fundus. With the advent of SD-OCT/SLO it has become possible to simultaneously analyse retinal structures both *en face* and in cross section (see *Figure 4*). MP can now correlate changes in retinal function with precise retinal lesion, such as transformations within retinal layers, small RPE defects, and underlying structures such as drusen.[126]

Landa and colleagues reported that, in AMD, points of decreased retinal sensitivity showed a strong inverse correlation with the

amount of disruption in the underlying inner-segment outer-segment (IS-OS) layer.[127] The relationship between the IS-OS layer and retinal sensitivity has been reported in a variety of diseases.[128–132] Landa and colleagues demonstrated that retinal sensitivity was more influenced by IS-OS status than was best-corrected visual acuity (BCVA) in patients with AMD, suggesting that MP may be a more sensitive method than BCVA for following retinal function.[127] They also demonstrated that patients with 90–100 % disruption of the IS-OS layer often showed no indication of retinal function loss based on BCVA, maintaining visual acuities of 20/40 or better. However, mean MP values began to decline as the percentage of IS-OS disruption approached 60–70 %. Since integrity of the IS-OS layer has been identified as an important predictor of macular function in patients with AMD and correlates with decreased average retinal sensitivity, MP may be a better tool for detecting early progression of disease and response to therapy than conventional imaging and measures of acuity.

OCT/SLO MP is also able to detect a decrease in mean retinal sensitivity over areas of small drusen. This correlates with histological changes seen in the photoreceptor layer over larger drusen, such as the reduction of the outer nuclear layer and changes in the synaptic cytoarchitecture.[128] *In vivo* imaging studies also showed a thinning of the photoreceptor layer over drusen.[103] A multivariate analysis of factors including drusen height, volume, diameter, and IS-OS status found that IS-OS junction integrity was the strongest predictor of retinal sensitivity. If the extent of IS-OS junction integrity is known, individual drusen measurements do not give additional predictive information about retinal sensitivity.[133]

Using higher-quality images compared with the original Rodenstock SLO, the investigation of retinal sensitivity in the junctional zone of patients with atrophic AMD using OCT/SLO MP was repeated.[96] Similar to the original report, findings of variable but definite reduction in retinal sensitivity was noted in patients with increased FAF intensity in the junctional zone. RPE cell damage in the regions characterised by increased FAF was also confirmed by SD-OCT imaging.[126] The capability of MP to map transitions of retinal function along the borders of atrophic regions may prove useful in characterising phenotypes and evaluating future therapies.

Routine vision tests such as BCVA with Early treatment diabetic retinopathy study (ETDRS) charts may not adequately portray local macular dysfunction because results can appear normal despite the obvious macular disease. BCVA gives an indication of foveal function, but does not reflect the overall visual landscape and fine spatially distributed testing. MP surveys the wider area of extrafoveal retinal sensitivity, and when supplemented with OCT/SLO imaging, the relationship between functional and structural changes becomes clearer. As new therapeutic options become available, OCT/SLO MP may become a critical tool for measuring visual function, as its ability to measure focal retinal function is likely to be essential in determining the response to treatment.[133]

Conclusions

The SLO represents a significant advance in retinal imaging, which has enabled clinicians to better characterise the microstructural and functional changes characteristic of AMD. FAF has made a critical impact on the classification of early AMD and atrophic AMD and in determining risk factors for disease progression. The use of the combined OCT/SLO for the ultrastructural analysis and classification of drusen has already been incorporated into a clinical trial with Copaxone.[104,134] As previously mentioned with FAF, changes in drusen and abnormal FAF intensities are typically unrelated, and the combined utilisation of FAF and OCT/SLO is likely to become the gold standard in the management of AMD. The role of quantitative and qualitative analysis of drusen with the OCT/SLO has yet to be determined, but will likely influence the initial staging of disease and monitoring for the onset of advanced AMD. OCT/SLO MP is a sensitive method for analysing changes in retinal function that uses the OCT/SLO to examine structural disruptions related to decline in retinal sensitivity. The future of SLO imaging is the Adaptive Optics SLO, capable of imaging the rods and cones *in vivo*.[135] Current efforts to quantitatively and qualitatively describe drusen could be integrated with a quantitative analysis of photoreceptors in regions with drusen to reveal the intimate relationship between the presence of drusen, the loss of photoreceptors, and the resulting changes in retinal sensitivity measured with MP. ■

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