Review

Recent Advances on Imaging for Late-Stage Age-Related Macular Degeneration

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Abstract: Age-related macular degeneration (AMD) is a leading cause of blindness worldwide. In late-stage AMD, geographic atrophy (GA) of dry AMD or choroidal neovascularization (CNV) of neovascular AMD results in macular atrophy (MA), leading to significant visual loss. Despite the development of innovative therapies, there are currently no established effective treatments for MA. As a result, early detection of MA is critical in identifying later central macular involvement throughout time. Accurate and early diagnosis is achieved through a combination of clinical examination and imaging techniques. Our review of the literature depicted advances in retinal imaging to identify biomarkers of progression and risk factors for late AMD. Imaging methods like fundus autofluorescence (FAF), near-infrared reflectance (NIR), widefield imaging, optical coherence tomography (OCT), multicolor confocal scanning laser ophthalmoscopy (cSLO), and optical coherence tomography angiography (OCTA) can be used to detect and monitor the progression of retinal atrophy. Multifocal electroretinogram (ERG) and microperimetry are methods for quantifying visual function to map disease progression. The evolving diverse imaging modalities optimize detection of pathology anatomy and measurement of visual function; they may also contribute to the understanding of the underlying mechanistic pathways, particularly the underlying MA changes in late AMD.

Keywords: age-related macular degeneration; confocal scanning laser ophthalmoscope; fundus autofluorescence; macular atrophy; microperimetry; multifocal electroretinogram; optical coherence tomography angiography; optical coherence tomography

1. Introduction

Age-related macular degeneration (AMD) has been recognized as one of the leading causes of vision impairment and blindness worldwide in the elderly[1]. In a meta-analysis of individuals aged 45-85 years old, the pooled global prevalence of early, late, and any stage of AMD was 8.01%, 0.37%, and 8.69%, respectively. The number of individuals globally with AMD is projected to increase from 196 million in 2020 to 288 million in 2040[2] . Studies have suggested geographical or ethnic differences in different stages of AMD prevalence[3–6] .The prevalence rates of early (11.2% vs 6.8% vs 7.1%) and any stages of AMD (12.3% vs 7.4% vs 7.5%) were higher in Europeans compared to

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Asians and Africans. In the late stage of AMD, significant visual impairment is due to dry AMD with geographic macular atrophy (MA) or wet AMD with choroidal neovascularization (CNV). Of the nearly 12 million people considered legally blind from late AMD, with similar rates from overall geographic atrophy (GA) and neovascular AMD (nAMD), Europeans had a higher prevalence of GA (1.11%) than Africans (0.14%), Asians (0.21%), and Hispanics (0.16%)[2,5]. The increasing use of anti-vascular endothelial growth factor (VEGF) therapies has substantially altered the prognosis of nAMD, improved vision, and reduced the risk of severe vision loss[7] . In contrast, MA is the morphological end stage manifestation of a degenerative disease process which manifests as vision loss as the lesion enlarges and involves the foveal center[8] . Due to its chronic nature and progressive increase in vision loss, AMD, and specifically MA, will continue to be a global public health concern with substantial socioeconomic and healthcare consequences.

MA, an anatomic endpoint of AMD is characterized by the permanent degradation of the retinal pigment epithelium (RPE) and overlying photoreceptors. In wet nAMD, choroidal neovascularization penetrates the neural retina, leading to the leakage of fluid, lipid, blood and resulting in retinal fibrosis. While in GA, in the setting of dry AMD, the retinal pigment epithelium, choriocapillaris, and photoreceptors are progressively atrophied[9] . nAMD was essentially incurable two decades ago; however, treatments based on the suppression of VEGF have significantly prevented vision loss or improved vision[10–12] . A cohort study reported that 50% of the nAMD eyes in 647 patients had visual acuity of 20/40 or better in the 5 years following anti-VEGF treatment, confirming anti-VEGF therapy as a major long-term therapeutic advance for nAMD[13] . However, studies found that MA developed in nAMD despite intensive anti-VEGF therapy. In the CATT study, 18.3% and 38% of patients developed MA within 2 years and 5 years of initiating anti-VEGF treatment, respectively[14,15] . In the Seven Year Observational Update of Macular Degeneration study (SEVEN-UP) reporting on patients post MARINA/ANCHOR and HORIZON Trials, nearly all (98%) of eyes treated for nAMD over 7 years developed MA[16] .Furthermore, the HARBOR Study found 29.4% (229/778) of eyes had newly developed MA at 24 months after anti-VEGF injection [17] . What factors induce or aggravate MA progression in nAMD remains unknown[18] . Besides the natural progression of underlying or impending atrophy as GA in dry AMD, different hypotheses have implicated CNV-induced photoreceptor injury and anti-VEGF therapy in nAMD as causes of MA[19,20] . In fact, VEGF appears to be critical for the survival and maintenance of non-vascular tissues such as RPE and choriocapillaris integrity; therefore, its suppression could result in the development or progression of MA. In contrast a recent study showed anti-VEGF treatment regimen or injection frequency was not correlated to progression of existing MA or incidence of new MA in eyes with nAMD over 4 years[21] . In addition, the Alternative Treatments to Inhibit Vascular Endothelial Growth Factor in Patients with Age-Related Choroidal Neovascularization (IVAN) and RIVAL studies found no difference in incidence of MA among different anti-VEGF therapies[22,23] . A prospective cohort study, the Age-Related Eye Disease Study (AREDS), reported that the incident rate of MA in untreated nAMD was approximately one-third of eyes within 5 years and one-half by 8 years[24] . This further confirmed that natural progression to MA is the final common pathway in both nAMD and dry AMD disease progression.

In late-stage AMD, MA is present in areas previously occupied by drusenoid pigment epithelial detachments (PED) and is characterized by confluent loss of the RPE[25] . It has been proposed that MA development could depend on the underlying MA phenotype, in which type 3 (RAP) lesions may have a greater risk of the development and progression of atrophy, whereas type 1 lesions are associated with a lower risk of MA progression[26,27] . MA is also associated with reticular pseudodrusen (RPD), located subretinally as yellowish-white net-like patterns, which is a risk factor for progression to the late stage of AMD in both dry and wet AMD patients[28,29] . Currently, there are no standard and effective treatments for MA despite emerging innovative therapies. While new treatment modalities are being investigated that will improve the clinical course of AMD, implementing early detection and preventative techniques can help delay or halt disease progression. Hence, it is important to detect incident MA at the first appearance to identify subsequent progression to central macular involvement over time. Different imaging modalities are evolving for identifying

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disease progression and prognostic factors and may also contribute to the understanding of the pathogenetic pathways specifically the underlying macular changes in late AMD. A summary of these methods is provided below.

2. Assessment using Imaging

2.1. Fluorescein Angiography & Indocyanine green angiography

Angiography is an intravenous dye-based imaging technique to study the circulation of the choroid and retina where, once dye is administered, a time-based sequence of fundus images is digitally recorded. Fluorescein angiography utilizes sodium fluorescein dye to illuminate the retina at a peak wavelength of 490 nm (blue) and then photographically record the excited fluorescent 530 nm (green) light that is emitted[30] . Indocyanine Green (ICG) angiography utilizes ICG, a molecule that is 98% protein bound, and therefore remains in the fenestrated choriocapillaris longer and leaks less relative to fluorescein dye. It is sometimes more useful than fluorescein dye to study choroidal diseases such as nAMD[31]

As imaging technologies evolve, their diagnostic and monitoring applications for AMD and MA have expanded. The course of MA in late AMD is characterized by the development of atrophic areas that enlarge continuously over time with cell death of the RPE, the outer neurosensory retina, and the choriocapillaris[32] . In fundus fluorescein angiography (FA), atrophic patches appear as well-defined, hyperfluorescent areas because of enhanced visualization of the normal choroidal fluorescence caused by the loss of RPE cells (window defect), which would normally diminish the transmission of fluorescein fluorescence. Compared to fundus photography, this demarcated hyperfluorescent signal provides a sharper contrast between the atrophic and the surrounding non-atrophic areas. However, other pathologic findings in dry or wet AMD, such as drusen, pigmentary changes, fibrotic tissue, or neovascularization, may also result in an increased fluorescence signal or progressive dye leakage and therefore obscure the boundary demarcation of atrophy[33,34] .In indocyanine green angiography (ICG-A), atrophic patches appear as discrete hypofluorescent areas with loss of background fluorescence owing to small and medium vessel choriocapillaris atrophy[35] .However, the large, deep choroidal vessels may still be visible and interfere with the outline of the area of atrophy and cause more difficulty in exact and reliable delineation. While ICG-A is useful in the differential diagnosis of polypoidal choroidal vasculopathy (PCV), chronic central serous chorioretinopathy (CSC), and retinal angiomatous proliferation (RAP), which are often misdiagnosed as nAMD[36] , ICG-A has a negligible role for the identification of atrophy in AMD. In addition, both ICG-A and FA are invasive procedures that carry the risk of local infiltration, extravasation at the injection site, as well as the risk of an allergic reaction, which can be rare but severe and life-threatening, to the intravenously administered dye[37] . FA is therefore recommended for the detection, classification, and quantification of NV but not atrophic changes; ICG-A can be used to distinguish other disease entities that cause atrophy[38].

2.2. Fundus Autofluorescence

Fundus autofluorescence (FAF) is a non-invasive method, that provides rapid, noninvasive, high-contrast retinal images that are particularly useful for detecting atrophic areas, especially for better atrophic lesion boundary discrimination compared with color fundus photography[39,40] . FAF utilizes the fluorescent properties of lipofuscin, a byproduct of lysosomal breakdown of photoreceptor outer segments within the RPE cell. When excited by an appropriate light source, the bisretinoid components of lipofuscin absorb blue light with a peak excitation wavelength of approximately 470 nm and emit yellow-green light with a peak wavelength of 600 nm. A detector is then used to record the emissions signals as they are emitted. An FAF image, then, is a density map of lipofuscin where the brighter “hyperflourscent” areas represent areas of increased lipofuscin density and darker “hypflouresent” areas represent areas of decreased lipofuscin density[41,42]

One of the hallmarks of early and intermediate AMD is macular drusen[43], which form with RPE aging. Drusen are composed of lipofuscin containing dense lipids, carbohydrates, zinc, and

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proteins, including apolipoprotein B and E, as well as components of the complement system[44]. Recent grading systems, including the Age-Related Eye Disease Study (AREDS) and the Beckman Initiative for Macular Research Classification Committee, have classified drusen based on drusen type and size to associate drusen regression with or without RPE atrophy in NV or GA of late AMD[45–47]

A recent study classified drusen-associated atrophy stages based on FAF and histological findings in eyes with late AMD[48] . In stage 2, the earliest stage with detectable findings, FAF exhibited uniform hyperautofluorescence, indicating photoreceptor photopigment loss, whereas hypoautofluorescence in stages 3 and 4 corresponded to varying degrees of RPE atrophy. The FAF appearance is initially hyperfluorescent (stage 2), followed by a hypoautofluorescent center surrounded by hyperautofluorescent borders when associated with focal areas of RPE atrophy (stage 3), and hypoautofluorescent lesions with complete RPE loss (stage 4)[48] . As the disease progresses through stages, the proportion of lipid within the drusen decreases relative to the proportion of calcification, with 80% of the drusen being refractile at the advanced stage 4. The refractile drusen appear as yellowish-white, glistening lesions and are associated with an increased risk of developing late AMD; however, they are undetectable on FAF alone[49]

Of note, it was reported that cuticular drusen are strongly associated with late AMD[50] .Eyes with the cuticular drusen can develop NV or acquired vitelliform lesions (AVL)[51] which may regress to GA or RPE atrophy[52] . In longitudinal studies, GA developed in 19.0% of eyes with cuticular drusen over a mean follow-up period of 40±18months, whereas GA developed in 28.4% and NV in 12.5% over a 5-year follow-up period[53] . The cuticular drusen apex is steep and is where the atrophic RPE is located. FAF is an effective method to detect cuticular drusen with the display of numerous hypo-autofluorescences corresponding to the apex of the cuticle drusen with hyperautofluorescent rims. However, some FAF imaging cameras with different excitation wavelengths may not visualize these drusen[54]

Studies showed that reticular pseudodrusen (subretinal dursenoid deposits) are highly associated with late AMD, such as GA, Type 3 macular NV, and drusenoid PED[55–57] .Soft drusen are located beneath the RPE whereas reticular pseudodrusen are found on the surface of RPE[58] . Studies classify reticular pseudodrusen into 3 types[59,60] in which the ribbon/reticular type is likely to progress to advanced AMD, including GA and Type 3 macular NV[61–63] . Similar to cuticular drusen, eyes with the reticular pseudodrusen can develop NV or regress to GA or outer retina atrophy with focal photoreceptors loss and choroidal thinning[64] .FAF may demonstrate a reticular pattern in eyes with reticular pseudodrusen; however, studies indicate that FAF is not the most specific method for detecting reticular pseudodrusen[65]

Assessing the risk of late AMD depends on stratifying the types of drusenoid deposits and RPE abnormalities; and requires correctly evaluating imaging characteristics. The high-contrast differentiation of atrophic versus nonatrophic areas by FAF is a reliable image quantification of lesion area[66] . Currently, conventional blue light excitation with excitation wavelength of 488 nm is the most popularly used mode for FAF imaging. However, macular pigment blocks blue light, resulting in a relatively diminished signal intensity at the fovea, which appears as a zone of hypofluorescence[67] .Therefore, blue-light FAF may result in an overestimation of atrophic patch size and be mistaken for central atrophy involvement. The relative hypofluorescence of the fovea could mask an atrophic area, making it challenging to identify central minimal atrophic changes or adjacent paracentral atrophic margins[68] . The quality of blue FAF signal may also be affected by pupil size or media opacity such as cataracts or vitreous opacity. FAF imaging systems include confocal scanning laser ophthalmoscopy (cSLO) systems and flash fundus camera-based systems. cSLO has FAF imaging with two excitation wavelengths (488 nm and 514 nm), while fundus camera autofluorescence relies on excitation wavelengths in the green to orange range (510-610 nm). One study reported that green-light FAF images (514 nm) are superior to blue autofutofluorescence (488 nm) for the evaluation of small central GA lesion size[67] . Although the measurement of the atrophic lesions size in current clinical studies depends mainly on blue-light FAF, green-light FAF appears to

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be a more accurate, and a potentially important evaluation tool for central MA progression in future studies.

In certain phenotypic variants of GA, the loss of contrast between intact and atrophic RPE can have an altered FAF appearance, which differs from the markedly hypo-autofluorescent images in other forms of GA[69] . In eyes with hemorrhagic nAMD or late nAMD with MA, the FAF signal may be reduced, and it is difficult to distinguish between atrophy and areas of fibrosis using FAF alone[60] . Recently, blue-light FAF has been utilized in conjunction with near-infrared reflectance (NIR), which is unaffected by luteal pigment and enhances foveal evaluation. NIR is characterized by a long excitation wavelength (820 nm diode laser) [70] that avoids the absorption of a shorter wavelength of light (480 nm) by melanin and lipofuscin granules at the RPE level, thereby allowing visualization of the retina and choroid[71,72] .Specifically, NIR reveals sub-RPE lesions effectively. Refractile drusen, for instance, are highly reflective, seen as glistening dots using NIR that are undetectable using FAF[73] . Studies have reported that NIR has a very high sensitivity for detecting reticular pseudodrusen[74–77] .However, systematic validation studies for NIR alone in the detection of atrophic AMD are still lacking. Hence, FAF combined with other diagnostic modalities such as NIR may improve visibility of the obscured atrophic demarcated areas compared to when using FAF alone. Furthermore, widefield imaging devices can be used for the acquisition of FAF and both FA and ICG-A. Widefield imaging with a field of view that exceeds100 degrees and extends up to 150 degrees enables visualization of larger areas of the retina. Widefield imaging can monitor peripheral abnormalities to provide a more complete understanding of AMD[78]

2.3. Optical Coherence Tomography

OCT is a noninvasive imaging modality that utilizes transversely scanned short coherence length light with interferometry to generate 2 dimensional and 3 dimensional cross-sectional maps of the retina and choroid with micrometer level resolution [79] . While FAF is valuable for quantifying RPE loss in MA, it does not discern non-RPE layer changes[68] .The classic definition of atrophy has been revised to incorporate changes in the outer retinal layers based on optical coherence tomography (OCT) findings[69] . A classification system and criteria for OCT-defined atrophy associated with AMD has been proposed by The International Classification of Atrophy Meetings (CAM). According to the CAM study group, the OCT finding of atrophy undergoes an evolution of 4 different stages[80] : (1) incomplete outer retinal atrophy, (2) complete outer retinal atrophy, (3) incomplete RPE and outer retinal atrophy (iRORA), and (4) complete RPE and outer retinal atrophy (cRORA). Of note is that these terms apply to atrophy in both non-neovascular (dry) and neovascular (wet) forms of AMD[69] .The correlation between FAF changes and the four distinct atrophy categories is currently unknown. The severity to which hypoautofluorescence in FAF correlates with a single category of OCT-defined atrophy requires further investigation.

It is crucial that high resolution 3-dimensional OCT help identify the early phase of the atrophic process prior to lesion detection in 2-dimensional FAF [69–73] The high axial resolution of Fourier-domain OCT devices, including spectral-domain OCT (SD-OCT) and swept-source OCT (SS-OCT), allows for the study of atrophy to quantify specific retinal layer loss. The wide application of SD-OCT has revolutionized the diagnosis and management of nAMD as it can provide assessment of risk and treatment prognosis, including the need for repeated anti-VEGF injections and other therapeutic intervention[81] . Currently OCT has evolved into an effective imaging modality for evaluating early AMD changes. High-resolution OCT detects the presence of drusen and pigmentary changes in the early stages of AMD[82–84], but SD-OCT provides important information regarding changes in retinal layers such as the outer plexiform layer (OPL), inner nuclear layer (INL), external limiting membrane (ELM), and ellipsoid zone (EZ). Unlike previously reported non-unique risk factors for the development of atrophy, such as hyperreflective foci and drusen characteristics including heterogeneous internal reflectivity and maximum drusen height and choroidal thickness beneath the drusen[85,86] , SD-OCT may detect unique early features such as the subsidence of the OPL and INL and a hyporeflective wedge-shaped band within the limits of the OPL, that represent significant risk and are present prior to development of drusen-associated atrophy[87] . In addition, SD-OCT can

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detect early morphological changes before conventional diagnostic instruments can. For instance, in one study, SD-OCT showed that 2.9% of eyes with drusen-associated atrophy were already present in patients classified as having intermediate AMD on color fundus photography[47,87] . In another study, the pathological SD-OCT features occurred approximately one year prior to the development of definitive drusen-associated atrophy[87] .This may enable treatment to be considered at an earlier time point in order to halt the progression of atrophy[88–90] ,before late atrophic changes are detectable by conventional diagnostic methods.

A consensus was reached on the descriptions of imaging characteristics associated with atrophy or atrophy progression risk in eyes with AMD[80] .These OCT features at risk for atrophy include intraretinal hyperreflective foci, extracellular deposits (soft drusen, drusen with hyporeflective cores, cuticular drusen, drusenoid PED, and subretinal drusenoid deposits), hyperreflective crystalline deposits in the sub-RPE basal lamina (BL) space and acquired vitelliform lesions[74,91–97] .As drusen regress, the overlying retinal layers progress to atrophy that can be detected by OCT imaging. Outer retinal atrophy features included INL and OPL subsidence, ELM descent, a hyporeflective wedge-shaped band within the Henle fiber layer, often accompanied by RPE disturbance and increased signal hypertransmission into the choroid, and ELM and EZ disruption[98–101] .For iRORA to be present, three OCT features, including photoreceptor degeneration, RPE attenuation or disruption, and increased signal transmission into the choroid, are required to be present[102] . However, a minimum size limit for iRORA was not proposed. The study further reported that iRORA will progress and develop into cRORA over a variable time period ranging from months to years[102] . A model was then developed to estimate future potential atrophy growth regions and identify predictive biomarkers. The most predictive SD-OCT biomarkers were thickness loss of bands, reflectivity of bands, thickness of reticular pseudodrusen, GA projection image, increased minimum retinal intensity map, and GA eccentricity, based on quantitative characteristics of GA[103]

The anatomical correlations of the individual bands identified by an SD-OCT line scan are well established[104] .The distance interval between scans must be small enough to avoid missing pathologic characteristics such as drusen, reticular pseudodrusen, and pigment migration into the inner retina. Scanning with a spacing of 125–250 μm is suggested for the detection of reticular pseudodrusen, which indicate rapid atrophy progression, and the volume rendering of outer retinal tubulations[105,106] .However, a less density scan is typically preferred in longitudinal, large-scale clinical trials as a trade-off to achieve shorter acquisition time[107] . New advances in OCT imaging include SS-OCT, which offers faster scanning rates and a larger scan area[108] , and enhanced depth OCT (ED-OCT), which employs enhanced depth imaging acquisition techniques to enable greater tissue penetration in the axial direction and the visualization of more choroidal details[109] . Currently, detection of relevant clinical findings involves a volume scan by SD-OCT, or SS-OCT, but can be facilitated by screening with ED-OCT imaging to better detect the choroidal hyper transmission signal.

2.4. Multicolor Confocal Scanning Laser Ophthalmoscopy

Recently, MultiColor imaging has been developed for SD-OCT[110] . MultiColor images consist of a composite image by using the cSLO to capture three simultaneous laser wavelengths: blue reflectance (486 nm), green reflectance (518 nm) and infrared reflectance (815 nm)[111] . Hence, these various wavelengths of light penetrate and reveal the details of different retinal layers. Blue reflectance with the shortest wavelength reaches the vitreoretinal interface and inner retina, whereas infrared reflectance penetrates the deepest to detect structures in the outer retina and choroid. One study reported that both SD-OCT and MultiColor OCT detected smaller atrophic AMD size than blue-light FAF, which may represent an overestimation of the size of atrophic regions and foveal involvement[112] . However, retinal structures become less distinct due to chromatic aberration caused by the three lasers with slightly different focal planes. In addition, their optical reflection properties could hinder the distinction between subtle hemorrhages and pigmentary lesions. To date, only a few studies using this imaging are available[112–114] .Due to the limitations of current

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knowledge, the application of multicolor imaging for atrophic and nAMD should be optional, as its utility has yet to be demonstrated.

2.5. Optical Coherence Tomography Angiography

Imaging capable of providing appropriate visibility of the choriocapillaris and choroid has improved our understanding of atrophic and nAMD. While FA allows visualization of the retinal vasculature but not the choriocapillaris, ICG-A has not been widely utilized for choriocapillaris visualization in AMD due to its lack of depth resolution and inability to differentiate between choriocapillary blood flow and that of deeper choroidal vasculature [115–117] . In contrast, optical coherence tomography angiography (OCTA) allows depth-resolved imaging of the retinal, choriocapillarial, and choroidal vasculatures. OCTA generates three-dimensional images of vasculature but without dye injection. Repeated imaging of stationary tissue with OCTA produces a series of identical B-scans; when there is motion due to blood flow, the repeated B-scans will alter, and the changes can be quantified[118–121] .Unlike dye-based angiography, such as FA or ICG-A, which is time-consuming and has a limited imaging window after injection, OCTA is quick and can be administered at any time during each patient visit. Recent OCTA studies demonstrated choriocapillaris loss across a spectrum of AMD phenotypes, including soft drusen, reticular pseudodrusen[122–125] ,and CNV[126] .OCTA also allows for the evaluation of choroidal layers within and around atrophic lesions. Some studies found that the area surrounding the GA margin has greater choriocapillaris flow loss than the area of RPE atrophy or GA[127] , indicating that choriocapillaris degeneration may occur prior to the development of GA and may be a prognostic factor for atrophic progression[128–131] .However, there are conflicting findings that choriocapillaris loss was linearly related to or less than RPE loss in GA[132] , leading to the conclusion that the RPE appeared to be the primary target in GA[133,134] .In the GA region, it may be difficult to distinguish choriocapillaris flow impairment from atrophy due to OCTA's lower limit limitation in detecting slow blood flow. Increasing the interscan time can increase the sensitivity of OCTA to slow flows, but it also increases eye motion artifact noise[135] . Hence, both the sensitivity to slow flow and the potential artifacts must be considered when interpreting OCTA data[132] .In addition, OCTA limitations include acquisition time and field when used with conventional OCT. Therefore, dense, high-quality SD OCT or SS-OCT scans are required to obtain reliable OCTA results. The Consensus on Atrophy (CAM) study group recommended OCTA may be optionally included in studies on non-neovascular and neovascular AMD for exploratory purposes[38] .

3. Assessment through Visual Function

The progression of AMD to advanced stages invariably involves the foveal region, which develops dense and irreversible scotomas, resulting in retinal function impairment and irreversible vision loss. Currently, the progression of visual impairment and the estimation of ultimate residual visual function are determined by measuring visual acuity. Standard visual acuity tests, such as best corrected visual acuity (BCVA), do not fully capture the functional impact of atrophic AMD because lesions frequently spare the foveal center in the early stage, causing standard vision charts to falsely indicate that vision is unaffected[136] .Other tests such as dark adaptation, flicker threshold, and photostress recovery time, are more sensitive than BCVA in detecting early functional loss in AMD[137–139] ;however, they are time consuming and therefore limited their clinical use. Hence, there is a need for a clinical method that is both reliable and practical for assessing visual function across the macula.

3.1. Multifocal Electroretinogram (ERG) for mapping progression

Ophthalmic electrophysiology can be used to measure the function of the choroid, RPE, and photoreceptor layer [140] ; It can be a reliable method for mapping disease progression and quantifying not only retinal but also visual function. Multifocal ERG (mfERG) is based on an M-sequence stimulation technique that allows simultaneous measurements of multiple retinal

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responses at different locations. Retinal stimulation is conducted by an array of 61 or 103 hexagonal elements that map retinal function within the central 30–50 degrees to include the blind spot[141–143] . Accurate results require good patient fixation, suggesting mfERG may be more appropriate for assessing retinal function in patients with preserved central vision. Multiple studies have reported the efficacy of the mfERG in assessing AMD[144–155] .Studies evaluating the function of photoreceptors in AMD have revealed that rods are affected before cones, with rod-mediated scotopic sensitivity mfERG increasing latency in early AMD [145,156] .When comparing mfERG in AMD to normal controls, studies revealed reduced N1 and P1(bipolar cells) amplitudes and implicit latencies in AMD in both rod- and cone-mediated mfERGs, indicating that both rod and cone function are impaired in age-related maculopathy (ARM)[144,145,156,157] .Reduced photoreceptor inner segment ellipsoids (ISe), which are related to visual function, were observed in early AMD and significantly correlated with a delay in mfERG P1 implicit time[158] .ARM progression with drusen regression and increasing RPE changes has also been linked to a delay in mfERG implicit time[159] .Over time, mfERG became more delayed with reduced response density[144,149,159] .Some anti-VEGF injection of nAMD studies demonstrated a positive correlation between significant improvement of mfERG central zone amplitude and functional improvement of the macula, as measured by visual acuity and contrast sensitivity, along with decreased central foveal thickness[160–164] .This suggests that mfERG responses may be used to predict improvement in macular function and anatomical changes in AMD after treatment. ERG can detect the functional abnormalities observed in AMD, such as the early loss of rod photoreceptors and the loss of central and paracentral perimetric sensitivities, while they appear to improve after anti-VEGF therapy. The accuracy of mfERG in detecting photoreceptor degeneration and macular function disturbances may be beneficial in the early diagnosis and progression of AMD.

3.2. Microperimetry for retinal sensitivity for severity of degeneration

Microperimetry is an automated perimetry system with eye tracking that measures differential light sensitivity (DLS), which is the minimum luminance of a white-spot stimulus that can be perceived on a white superimposed background of uniform luminance. Mean sensitivity (MS) quantifies the average DLS across all stimulus locations. It is a non-invasive technique to map retinal sensitivity spatially. Researchers discovered that reductions in retinal sensitivity occur rapidly and precede visual acuity changes in AMD[165–167] .Localized decreases in retinal sensitivity have been reported in GA precursor lesions[168] ,in which the deterioration of visual function can occur months to years before the patient experiences visual problems[169] .Microperimetric sensitivity has also been associated with drusen volume, reticular pseudodrusen and extent of pigmentary changes[170] .In eyes affected by GA, microperimetry detects an increasing number of scotomatous points and a dropping of MS over time, which correlates anatomically with an increase in atrophic size [171] and a reduction of the inner segment–outer segment junctional layer of photoreceptors to indicate disease progression[172,173] .Eyes with atrophic AMD were found to have decreased sensitivity in all retinal regions, including those at the GA margin or outside atrophic lesions, indicating that patients with GA have a more extensive functional deficit than those with mild/intermediate AMD[174] .Currently, anatomic assessment of AMD via multimodal fundus imaging is commonly used to diagnose and monitor the disease; however, both mfERG and microperimetry can identify dysfunction in patients with AMD and quantify late-stage progression by measuring local functional deficits in the retina.

4. Ongoing trends in management and research

In this review, we attempt to correlate relevant diagnostic tools to corresponding features of dry AMD and findings that emerge prior to the formation of MA, based on consensus definitions.

With increasing life expectancy and an aging global population, late AMD poses a considerable and expanding threat to society, and the resulting visual impairment represents an enormous resource burden. The causes of AMD are multifactorial and include aging, genetic or high oxidative stress[175] .

In the late stage of AMD, significant visual impairment is due to CNV in wet AMD and GA in dry AMD. The visual outcomes of patients with late nAMD have improved due to the development of anti-VEGF medication[176–179] . Novel therapeutic techniques such as gene therapy using recombinant adeno-associated virus vectors delivering VEGF-inhibitory compounds and subsequent expression for long-term nAMD control are emerging[180,181] . However a staggering percentage of nAMD patients stabilized by anti-VEGF treatment still go onto to develop MA: more than 98 percent at 7 years in some studies[182] .New treatments for GA in dry AMD include complement pathway C3 and C5 inhbitors[183–186] .In all of these efforts, the ability to uitilize advances in imaging modalities to detect and document disease findings remains a critical stepping stone to future therapies.

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