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Adaptive Optics Retinal Imaging – Clinical Opportunities and Challenges

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Abstract

The array of therapeutic options available to clinicians for treating retinal disease is expanding. With these advances comes the need for better understanding of the etiology of these diseases on a cellular level as well as improved non-invasive tools for identifying the best candidates for given therapies and monitoring the efficacy of those therapies. While spectral domain optical coherence tomography (SD-OCT) offers a widely available tool for clinicians to assay the living retina, it suffers from poor lateral resolution due to the eye's monochromatic aberrations. Adaptive optics (AO) is a technique to compensate for the eye's aberrations and provide nearly diffraction-limited resolution. The result is the ability to visualize the living retina with cellular resolution. While AO is unquestionably a powerful research tool, many clinicians remain undecided on the clinical potential of AO imaging – putting many at a crossroads with respect to adoption of this technology. This review will briefly summarize the current state of AO retinal imaging, discuss current as well as future clinical applications of AO retinal imaging, and finally provide some discussion of research needs to facilitate more widespread clinical use.

Keywords

retinal imaging; adaptive optics; retinal degeneration; photoreceptor

Introduction

The human retina is a uniquely accessible tissue, and is routinely imaged in clinical practice using a number of different modalities such as optical coherence tomography (OCT), ultrasound, scanning laser ophthalmoscopy (SLO), and conventional fundus imaging. The

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ability to directly visualize the living retina provides an implicit advantage in diagnosing and monitoring retinal disease, however it is becoming appreciated that by the time pathology is visible with these imaging tools, significant cellular damage has often already occurred. Adaptive optics (AO) enables correction of the eye's monochromatic aberrations,[1] and as a result provides nearly diffraction-limited imaging when combined with any one of the above imaging modalities. The improved resolution provides a more sensitive tool with which to study retinal disease. However, while the use of AO imaging in clinical research has increased, nearly all peer-reviewed studies on retinal disease have used custom-built AO imaging systems housed in research labs. These systems are expensive and complex, and as such, AO imaging has not been viewed as a clinically viable tool until quite recently, with at least four companies having developed AO prototypes at the time of this minireview (Boston Micromachines Corporation, Canon, Inc., Imagine Eyes, and Physical Sciences, Inc.). The availability of commercial systems, coupled with the mounting examples of clinical utility from research-grade systems has dramatically increased the interest in AO imaging among ophthalmologists and optometrists. With potential widespread clinical adoption of this technology on the horizon, we provide here an overview of the current state of AO retinal imaging, summarize recent clinical applications of AO retinal imaging and highlight possible future applications, and finally discuss challenges facing widespread clinical adoption. This invited minireview was prompted by the extensive amount of AO work presented at the ARVO 2012 Annual Meeting in Fort Lauderdale, Florida, USA; as such we have included many of these in the current review to capture the rapid growth of this research area.

Retinal Structures Visible With AO Imaging Tools

AO has been successfully integrated with the three major ophthalmic imaging technologies – fundus cameras,[1–4] SLO,[5–7] and OCT.[8–11] Each modality offers different advantages, and it remains uncertain whether one will prove to have more utility in the clinical arena than the others. Current imaging systems are able to resolve numerous structural aspects of the living human retina. Photoreceptors have been the primary target for many groups, with it now possible to resolve even the smallest photoreceptor cells in the retina – rods and foveal cones (Figure 1a,b).[12] Beyond the photoreceptors, there are reports on visualizing the retinal pigment epithelium (RPE) in the normal human retina using either reflectance in patients with retinal diseases,[13] or by taking advantage of the intrinsic autofluorescence of the RPE in the normal retina (Figure 1c),[14] though there are light safety issues to consider with the autofluorescence technique.[15, 16] As shown in Figure 1d, it is also possible to examine the retinal vasculature (including the smallest foveal capillaries) and to noninvasively measure blood velocity.[11, 17–22] The retinal nerve fiber layer (RNFL) and lamina cribrosa can also be visualized with AO imaging tools (Figure 2).[23–27] While the images shown in Figure 2 are derived from AOSLO instruments, many of these same structures have also been visualized with AO-OCT imaging systems.[9, 11] Although AO-OCT has not been applied to many clinical studies, it does offer some technical advantages over AOSLO that may make it a more desirable modality in the future, including much better axial resolution than AOSLO and increased sensitivity to weak reflections.

Clinical Applications of AO Retinal Imaging

As shown in Figure 3, the number of publications using AO retinal imaging in a clinical setting has increased dramatically in recent years. As such, an exhaustive survey of the clinical applications of AO imaging is beyond the scope of this minireview, so we highlight here four examples with high clinical relevance.

Inherited Retinal Degenerations

Inherited retinal degenerations affect about 1:2,000 – 1:7,000 people worldwide, and are characterized by progressive loss of vision.[28, 29] While there are currently no effective treatments by which the course of these disorders can be altered, a number of therapeutic options are under development (*e.g*., stem cells, gene therapy, neuroprotective drugs, retinal prosthesis).[30–32] The successful application of these approaches requires an improved understanding of the cellular pathogenesis of these degenerative diseases on an individualized basis – an ideal application for non-invasive AO imaging tools.

The first published application of AO to image human retinal pathology was in 2000, where images from a single patient with a cone–rod dystrophy were presented.[33] Not surprisingly, subsequent early clinical applications also focused on inherited retinal degenerations. This was due to the fact that photoreceptors, the primary cell type affected in these conditions, are easily visualized with AO-based imaging tools due to their strong waveguiding behavior. In fact, in eyes of good optical quality, it is possible to resolve cone photoreceptors without the use of AO.[34–36] Nevertheless, the ability to document and track longitudinally the integrity of the photoreceptor mosaic takes on vital importance as therapies for these conditions emerge. For example, in patients with retinitis pigmentosa (RP) receiving ciliary neurotrophic factor, AOSLO images revealed a relative preservation of cone structure despite an absence of significant functional improvement,[37] suggesting that AO-based imaging tools could provide sensitive anatomical outcome measures for clinical trials, providing more immediate feedback as to whether the therapeutic intervention has positively impacted retinal structure. It was suggested by Ratnam *et al*. at ARVO 2012 that structural changes in RP can be detected with AOSLO even prior to functional changes on standard clinical tests of vision.[38]

Another way that AO imaging may prove useful in treating inherited retinal degenerations is in the selection of patients for specific trials. In both dog and mouse models of achromatopsia (ACHM),[39–42] it was shown that cone function could be restored using a gene therapy approach. Translation of this specific approach to human trials requires that cone cells remain, else there are no cells whose function can be restored. AO imaging of patients with ACHM revealed a varying degree of retained cone structure,[43] and though it is unclear how this impacts calculation of the risk:benefit ratio, one could imagine that such detailed information about the degree of residual cone structure in these patients could help set expectations as to the anticipated degree of functional recovery.

In patients with ACHM, the remaining cones are sparse and have diminished reflectivity[43] (Figure 4). In patients with certain opsin mutations, we found that a subset of cones (presumably those expressing the mutant opsin) had similarly altered waveguiding[44] (Figure

4). Interestingly, we see a similar cone phenotype in patients with acute macular neuroretinopathy (AMN)[45] and closed-globe blunt ocular trauma (Figure 4). While the underlying structural defect is likely different in these cases, photoreceptor reflectivity appears to represent an optical biomarker of photoreceptor integrity, and might prove useful in examining photoreceptor integrity in other conditions. Similarly, rod and cone photoreceptors have been shown to vary in their intensity over time, and developing methods to reliably quantify this temporal variability may be useful in probing the health of individual photoreceptors.[46–49] Needed are further studies exploring the reflective behavior of photoreceptors in retinal degenerative diseases to better understand the physiological origin of the variability and thus its potential as a biomarker.

Glaucoma

Glaucoma is the leading cause of irreversible, preventable blindness worldwide, with some 11 million glaucoma sufferers worldwide being bilaterally blind from the disease.[50, 51] Primary open angle glaucoma (POAG) is a chronic disease characterized by progressive loss of retinal ganglion cells that leads to structural damage of the inner retinal layers, as shown by progressive local or diffuse thinning of the retinal nerve fiber layer (RNFL).[52] Axonal tissue loss in the RNFL has been reported to be one of the earliest detectable glaucomatous changes, preceding morphologic changes of the optic nerve head (ONH), as well as functional loss, as shown by progressive visual field (VF) defects. The temporal sequence of glaucomatous structural/functional damage suggests that micro-structural changes of the RNFL/ONH structures could allow for earlier detection of the disease.[53–55] As AO imaging tools can visualize both the RNFL and lamina cribrosa with high resolution,[23–27] we anticipate that application of AO imaging to glaucoma will increase in the coming years. Visualization of the RNFL is a particularly attractive target for AO-OCT, as it is possible to examine individual bundles of nerve fibers in cross section across the retina.[24]

Previous applications of AO imaging to glaucoma examined retinal structures other than the RNFL. In experimentally induced primate models of glaucoma, AO imaging has shown altered morphology of the lamina cribrosa in glaucomatous versus fellow control eyes.[56] Ivers *et al*. also demonstrated at ARVO 2012 the ability to examine the structure of the lamina cribrosa longitudinally in these models (Figure 5a,b),[57] providing a powerful tool with which to monitor structural changes in response to experimentally-induced increases in intraocular pressure or even in response to therapeutic intervention. In human patients with glaucoma, Choi *et al*. reported a loss in cone density along with expected thinning of the inner retina; dark areas in the cone mosaic were found at the same retinal locations with reduced visual sensitivity (measured via visual field testing).[58] Similar degradation of the photoreceptor mosaic has been reported histologically,[59, 60] but whether this represents an early or late feature of the disease remains unclear. While the involvement of the photoreceptors in the disease process remains controversial, AO-based imaging tools provide a direct means to resolve the issue. Finally, recent work using AOSLO revealed numerous reflective structures in the inner retina in patients with primary open angle glaucoma (Figure 5d–f).[61] It is unclear what the significance of these and other structures is, but they are nonetheless dynamic and are prevalent in glaucomatous eyes.[61] While analysis of lamina pore geometry is relatively straightforward,[25, 62, 63] the interpretation and

quantification of these unique hyperreflective structures is difficult and represents a major challenge facing the application of this technology to a heterogeneous disease like glaucoma.

Diabetic retinopathy

Diabetic retinopathy (DR) is a frequently occurring complication of diabetes mellitus (DM). According to the World Health Organization, DM is responsible for about 12% of new cases of blindness between the ages of 45 and 74 years in the developed world.[64, 65] DR can be classified as non-proliferative (NPDR) or proliferative (PDR), and NPDR is further graded as mild, moderate and severe according to the Early Treatment Diabetic Retinopathy Study (ETDRS) severity scale. DR consists of a microangiopathy that induces pathological changes of the vascular structures and the blood rheological properties as a consequence of chronic hyperglycemia.[66–68] Recently, DR has been postulated to be a multifactorial disease involving the retinal neuronal cells.[69–73] The neurodegenerative change consists of apoptosis of several populations, including photoreceptors, bipolar and ganglion cells. This functional and structural impairment of neural tissue has been theorized to participate in the generation of the earliest morphological alterations of the vascular structures.[69–71, 73, 74]

The earliest clinical pathological changes associated with DR occur to the microvascular structures. Fluorescein angiography (FA) is usually performed to assess the integrity of the blood retinal barrier as the amount of fluorescein leakage is related to the dysfunction of the retinal vascular endothelium, though it requires injection of a fluorescent dye that can lead to unintended systemic complications.[75] AOSLO imaging has recently demonstrated non-invasive images of the retinal microvascular damages in patients with DM without the need of contrast enhancing agents, by detecting microaneurysms, increased foveal avascular zone (FAZ) size and dropout of capillaries at the edge of the FAZ.[76–79] Tam *et al*. evaluated the parafoveal capillary network in 15 patients with type 2 diabetes and no retinopathy. They showed a higher tortuosity of the arterovenous channels (26% higher) in eyes of patients with diabetes and no DR than in healthy controls.[76] In a follow up study, longitudinal assessment of the capillaries near the FAZ showed microaneurysm formation and disappearance as well as the *de novo* formation of tiny capillary bends similar in appearance to intraretinal microvascular abnormalities.[77] Phan *et al*. showed, in both mild and moderate NPDR eyes, decreased capillary density and blood flow stasis.[78] Non-invasive assessment of the capillary network is also possible using AO-OCT[11, 80] or even high-speed SD-OCT without AO,[81] thus DR would be an ideal application for such imaging efforts.

Recently, cone photoreceptor involvement in DR has also been examined with AO imaging tools. Two studies at the 2012 ARVO meeting reported disruption of the cone photoreceptor mosaic in patients with type 1 diabetes,[82, 83] (and see Figure 6) though additional studies are required to understand how this involvement is related to the microvasculature aspects of the disease.

Age-related Macular Degeneration (AMD)

AMD is the leading cause of blindness in the elderly across the developed world. AMD is a multifactorial disease, involving ocular, systemic and genetic risk factors. Several patho-

biological pathways have been implicated in the pathogenesis of AMD, including senescence (with lipofuscin accumulation in the RPE), choroidal ischemia and oxidative damage.[84, 85] There are two clinical types of AMD, “dry” and “wet”. In the early asymptomatic stages of both types of AMD, which is asymptomatic, insoluble extracellular aggregates called *drusen* accumulate in the outer retina. The late stage of dry AMD, which is also known as *geographic atrophy* (GA), is characterized by scattered or confluent areas of degeneration of RPE cells and the overlying retinal photoreceptors, which rely on the RPE for trophic support. The other late stage form of AMD, the wet form (10–15%), is typified by *choroidal neo-vascularization* (CNV), wherein newly immature blood vessels grow toward the outer retina from the underlying choroid, often leaking fluid below or within the retina.[86, 87]

In the early stages of AMD, the ability to predict the rate of progression is currently limited. By monitoring drusen over time, *en face* and axial AO imaging tools could be used to monitor drusen progression and assess their direct effect on the overlying photoreceptor mosaic. For example, in a patient with early onset large colloid drusen, preservation of cones over the drusen was observed,[88] consistent with observations in a patient with basal laminar drusen.[89] In a study of early AMD with AO, Boretsky *et al.* identified several small drusen deposits that were not observed with wide field fundus imaging or SD-OCT in early AMD.[90] They also investigated large coalescent drusen and areas of GA in advanced stages of dry AMD, showing a significant decrease in visible photoreceptor density. A 30% decrease in cone counts was found (at 5–7 degrees eccentricity) in eyes with later stages in comparison with eyes with earlier stages of AMD progression. Two groups at the 2012 ARVO meeting demonstrated the capability of AO imaging to visualize disruptions to the photoreceptor mosaic even outside the clinically visible GA lesions and to track the progression of the GA lesions over time.[91, 92] Given the prevalence of AMD, it seems likely that this will be one of the more active growth areas in clinical AO imaging.

Where Do We Go From Here?

Recent years have seen an expanding interest in AO imaging for clinical applications, evident by the increasing number of presentations and publications utilizing this technology in clinical populations. As commercial prototypes become more widespread, it is worth highlighting a couple of areas of need to propel AO from a predominantly research “toy” to an invaluable tool in the clinical arsenal.

First, while there has been some work on characterizing the properties of normal photoreceptor mosaic, larger databases are desperately needed. Impeding construction of a reference database has been the lack of convergence on the methods used to quantify the mosaic. While density and spacing are commonly used, the way in which they are measured varies from group to group. Moreover, there are very few studies examining the reliability and repeatability of methods used to quantify the mosaic.[93, 94] Such data is critical to the utilization of any particular method for assessing departures from normality. In addition, metrics that characterize mosaic geometry hold promise for detecting more subtle changes to the mosaic,[82, 95] thus a reference database that incorporates multiple metrics is most desirable.

Second, as new structures become accessible (beyond photoreceptors), new analytical tools will be needed to describe these in quantitative terms, and will require the same validation studies as cone spacing or density does. Quantifying blood flow, determining capillary density, measuring RNFL bundles, measuring lamina cribrosa pore size, and assessing intrinsic RPE autofluorescence are all possible with existing AO technology and the reference/normative data for these assays are even more lacking than those for the cone mosaic. Resolving these issues requires putting this technology in the hands of more clinician scientists. The activation energy (cost and expertise) remains quite high to access AO technology; making it more widely available will help accelerate the maturation of the clinical applications of the technology. Commercialization of robust, easy-to-use devices is necessary to assist with expanding access. Moreover, there are multiple versions of AO retinal imaging tools (flood, SLO, & OCT) in use, and all have advantages and disadvantages. There have not been any systematic studies examining the same diseases with the various modalities, and as such the relative information provided by each modality is not clear, and would certainly vary on a disease-by-disease basis.

In summary, while there are certainly challenges to the clinical application of AO retinal imaging, the rapid growth in just the past couple of years suggests these can soon be overcome. Moreover, the current opportunities are many, with expansion of AO imaging into clinical trials among the most exciting. This could potentially enable targeting of treatments to specific patients or specific retinal areas, and allow for more sensitive evaluation of treatment response.[37] In addition, the numerous areas of specific need in a relatively small field have already spawned a number of collaborative relationships to resolve them. The AO community remains a uniquely collegial field, and for this reason, the future appears very bright for AO as a clinical tool.

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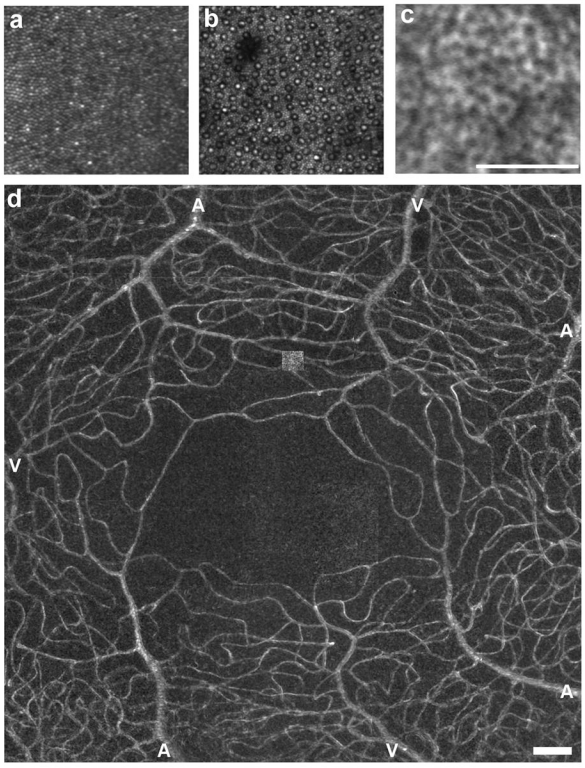

Figure 1.

Reflectance images of the photoreceptor mosaic (**a, b**). Panel **a** is an image of the parafoveal cone mosaic, with the foveal center at the lower right corner of the image; image courtesy of Jacque Duncan, MD, University of California San Francisco. Panel **b** is an image of the perifoveal rod and cone mosaic, with the rods being the smaller structures amongst the coarser cone mosaic.[48] Panel **c** is an autofluorescence image of the RPE mosaic taken at approximately 10 deg superior from a 26 year old male (550 nm excitation wavelength). Panel **d** is a standard error map showing the complete foveal microvascular network in a 35 year old male. Image courtesy of Stephen Burns and Toco Chui, Indiana University.[96] Arterioles and venules are labeled as “A” and “V”, respectively. Scale bars are 100 μm.

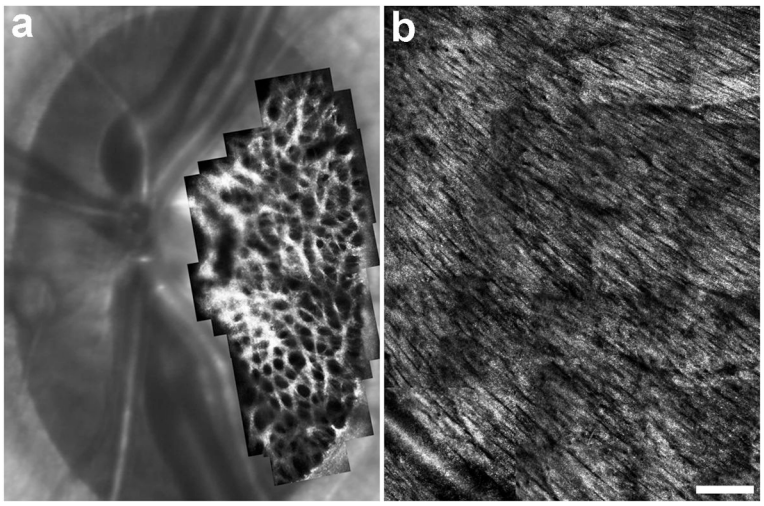

Figure 2.

Imaging the lamina cribrosa (**a**) and retinal nerve fiber layer (**b**). Image in (**a**) is a montage from a 5-year old normal rhesus macaque monkey, courtesy of Jason Porter, PhD and Kevin Ivers at the University of Houston College of Optometry. The image in (**b**) is a montage of the nerve fiber layer in a 62-year-old male with normal vision. Scale bar is 200 μm.

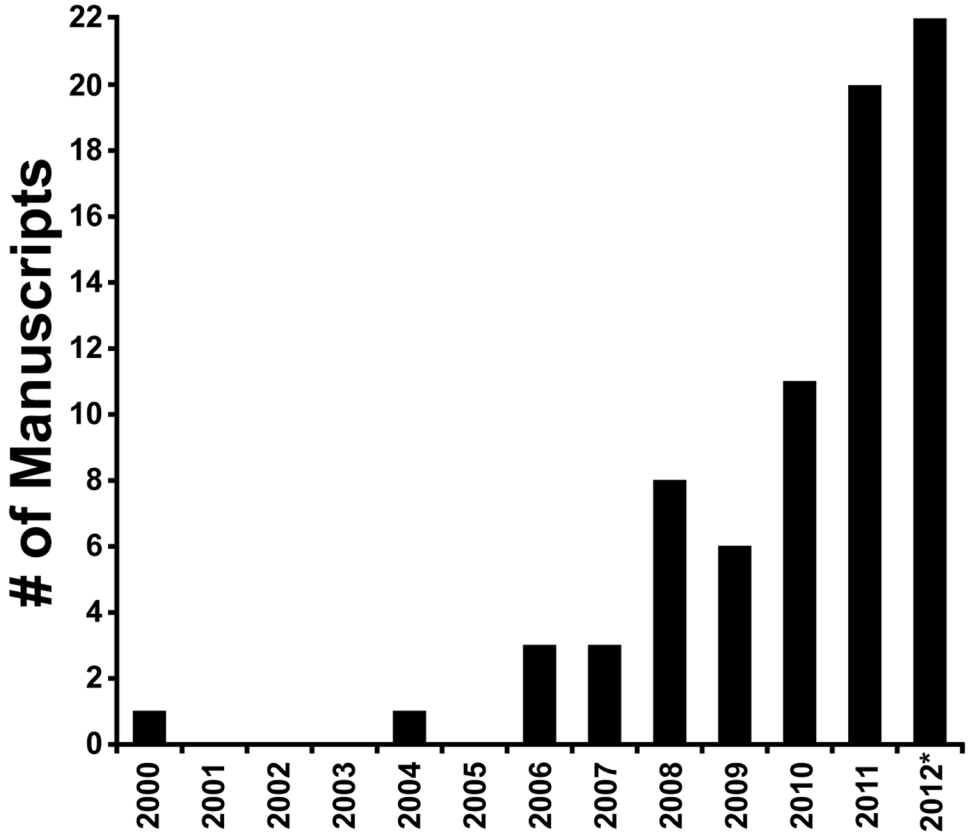

Figure 3.

Number of peer-reviewed manuscripts by year that have used adaptive optics systems to image the retina in one or more patients. A literature search (February 1, 2013) found 75 such papers.[9, 33, 37, 43–45, 49, 58, 62, 76, 77, 79, 88–90, 95, 97–155] *=2012 includes papers from the first few weeks of 2013. We did not include papers that only referenced normal subjects.

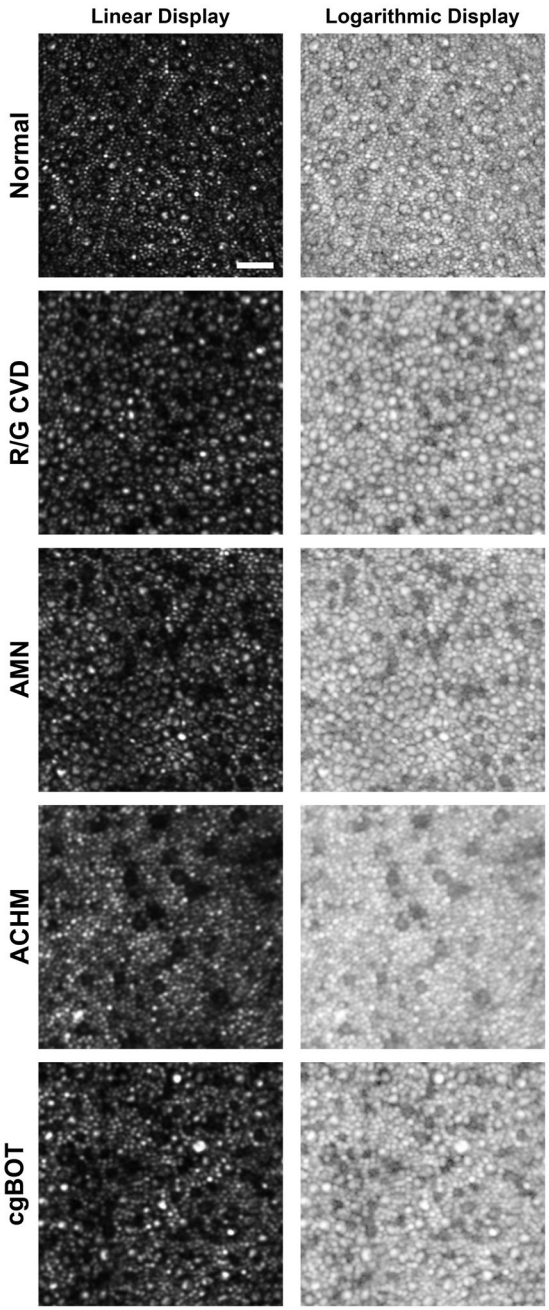

Figure 4.

Non-waveguiding cones in retinal disease. Shown are perifoveal images (linear and logarithmic display) of the photoreceptor mosaic for a subject with normal vision and 4 subjects with various retinal disorders. Normal cones at this eccentricity (~10 degrees from fixation) have a bright reflective center surrounded by a dark ring, where the extent of the dark area represents the inner segment diameter. Numerous cones devoid of the central reflective profile can be seen in a subject with red-green color blindness due to an LIAVA opsin mutation (R/G CVD),[44] a subject with acute macular neuroretinopathy (AMN),[45] a subject with achromatopsia (ACHM),[43] and a subject with vision loss as a result of closed-

globe blunt ocular trauma (cg-BOT). This altered reflectivity profile may indicate altered outer segment morphology. Scale bar is 20 μm.

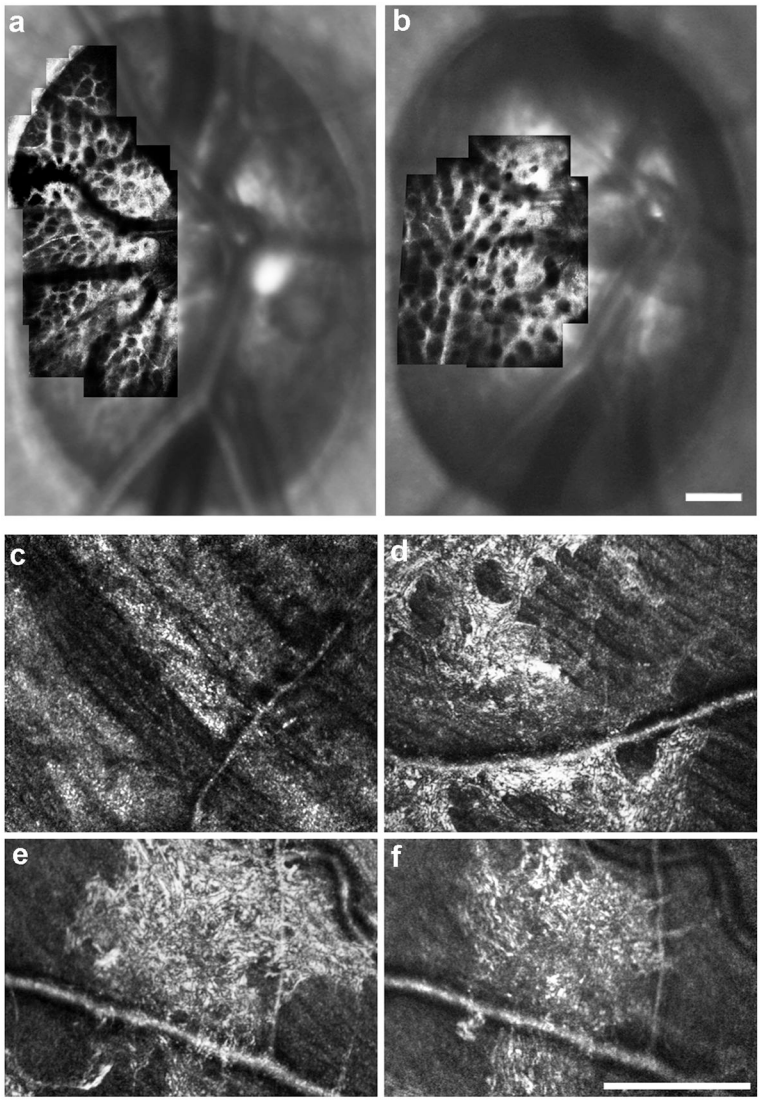

Figure 5.

AOSLO imaging in glaucoma. Panel (**a**) shows an image of the anterior lamina cribrosa surface from the eye of a normal rhesus macaque prior to induction of experimental glaucoma, and panel (**b**) shows the laminar surface of the same eye at an early stage of experimental glaucoma showing an alteration to laminar beam and pore geometry. Images courtesy of Jason Porter, PhD and Kevin Ivers at the University of Houston College of Optometry. In human patients with glaucoma, drastic changes in reflectivity and striation in the peripapillary NFL corresponding to what would be clinically described as arcuate defects can be seen (**c**). Panels (**d–f**) illustrate hyper-reflective structures residing near the RNFL.[61] These features were observed over areas of reduced visual sensitivity, and were not visible on SD-OCT or fundus photography. A four-month follow-up in one patient revealed significant changes in both the extent and appearance of the hyper-reflective patterns (**e, f**). Scale bars are 200 μm.

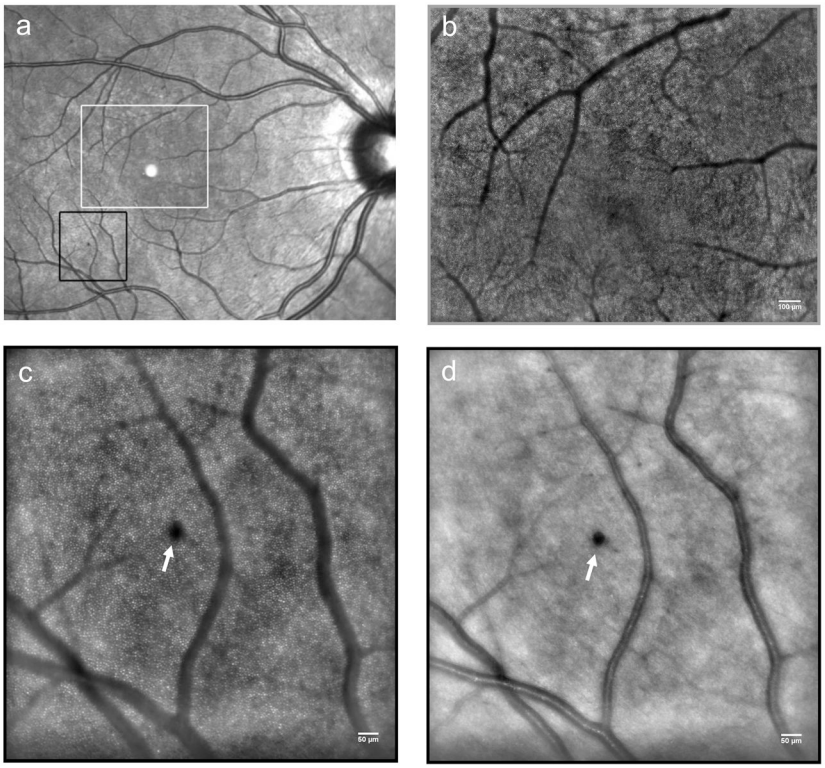

Figure 6.

Panel (**a**) shows a wide field fundus image from the left eye of a patient with NPDR. The white box indicates the area of the retina shown in panel (**b**) and the black box indicates the area of the retina displayed in panels (**c**) and (**d**). (**b**) Adaptive optics retinal imaging allows for a more detailed visualization of the capillary network around the FAZ. Scale bar is 100 μm. High-resolution images of the photoreceptor layer (**c**) and the overlying structures of the inner retina (**d**) can be acquired at exactly the same location with AO ophthalmoscopy. A micro-haemorrhage (white arrow) can be clearly focused on the retinal nerve fiber layer. The cone photoreceptors underlying the haemorrhage cannot be resolved (*masking effect*). (**c**) and (**d**) Scale bars represent 50 μm.