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Clinical Application of Adaptive Optics Imaging in Diagnosis, Management, and Monitoring of Ophthalmological Diseases: A Narrative Review

Authors' Contribution:
Study Design A
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Literature Search F
Funds Collection G

BDEF 1 Alina Szewczuk
DEF 2 Anna Zaleska-Żmijewska
DE 3 Jacek Dziedziak
DEF 2 Jacek P. Szaflik

1 Department of Ophthalmology, Public Ophthalmic Clinical Hospital (SPKSO), Warsaw, Poland
2 Department of Ophthalmology, Public Ophthalmic Clinical Hospital (SPKSO), Medical University of Warsaw, Warsaw, Poland
3 Department of Experimental and Clinical Physiology, Center for Preclinical Research, Medical University of Warsaw, Warsaw, Poland

Corresponding Author: Alina Szewczuk, e-mail: alinaszewczuk16@gmail.com
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Visualization of the retinal structure is crucial for understanding the pathophysiology of ophthalmic diseases, as well as for monitoring their course and treatment effects. Until recently, evaluation of the retina at the cellular level was only possible using histological methods, because the available retinal imaging technology had insufficient resolution due to aberrations caused by the optics of the eye. Adaptive optics (AO) technology improved the resolution of optical systems to 2 µm by correcting optical wave-front aberrations, thereby revolutionizing methods for studying eye structures in vivo. Within 25 years of its first application in ophthalmology, AO has been integrated into almost all existing retinal imaging devices, such as the fundus camera (FC), scanning laser ophthalmoscopy (SLO), and optical coherence tomography (OCT). Numerous studies have evaluated individual retinal structures, such as photoreceptors, blood vessels, nerve fibers, ganglion cells, lamina cribrosa, and trabeculum. AO technology has been applied in imaging structures in healthy eyes and in various ocular diseases. This article aims to review the roles of AO imaging in the diagnosis, management, and monitoring of age-related macular degeneration (AMD), diabetic retinopathy (DR), glaucoma, hypertensive retinopathy (HR), central serous chorioretinopathy (CSCR), and inherited retinal diseases (IRDs).

Keywords: Glaucoma • Hypertensive Retinopathy • Photoreceptor Cells, Vertebrate • Retinal Diseases

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Background

Retinal imaging is crucial for understanding physiological and pathological processes in the eye and monitoring disease progression and treatment effects. Until recently, evaluation of single retinal cells was only possible using histological techniques because the available retinal imaging techniques (such as scanning laser ophthalmoscopy [SLO] and optical coherence tomography [OCT]) had insufficient resolution to image structures at the cellular level, mainly due to aberrations caused by the optics of the eye. Generally, optical aberrations can be divided into 2 main groups: chromatic and monochromatic aberrations [1]. Differences in the refractive index of the eye structures for various wavelengths cause chromatic aberrations. It is possible to compensate for them using a single-wavelength light source [2]. Monochromatic aberrations are wavelength-independent and are caused by optical imperfections of eye structures, such as the tear film, cornea, and lens [1,2]. Monochromatic aberrations are classified into low-order and high-order aberrations [2]. The first can be corrected with spherical or cylindrical lenses, while high-order aberrations, also termed optical wave-front aberrations, cause parallel rays of light entering the eye to focus on different parts of the retina, greatly reducing lateral resolution and worsening the retinal image quality [1,2]. Adaptive optics (AO) technology has enhanced the performance of optical systems by correcting optical wave-front aberrations and has revolutionized methods of examining eye structures in vivo. Since its first use by Liang 20 years ago, AO technology has been applied to imaging structures in healthy eyes and various ocular diseases, allowing a better understanding of the etiology of ophthalmic diseases and accurate monitoring of their progression. This article aims to review the role of AO imaging in the diagnosis, management, and monitoring of age-related macular degeneration (AMD), diabetic retinopathy (DR), glaucoma, hypertensive retinopathy (HR), central serous chorioretinopathy (CSCR), and inherited retinal diseases (IRDs).

Methods of Adaptive Optical Imaging

AO was first used in astronomical telescopes to remove optical wave-front aberrations caused by atmospheric turbulence. This technology has improved the quality of images of distant astronomical objects. The history of the use of AO in ophthalmology is more than 20 years old – it was first used in 1997 by Liang to obtain high-quality retinal images [3]. The AO system consists of 3 basic elements – a wave-front sensor, a wave-front corrector, and a control system – which are used to identify the eye's optical aberrations and then correct them [4]. A wave-front sensor measures the aberrations of the eye. There are many different wave-front sensors, but the Shack-Hartmann sensor (SHS) is the most commonly used type. It consists of lenslets, aiming to sample a local portion of the incident wave-front and focus collimated light onto an area detector [5]. A wave-front corrector compensates for the aberrations measured by the SHS. The most commonly used type of wave-front corrector is the deformable mirror, which works by changing the shape of the surface [4,5]. A series of electric actuators connected to the mirror deform its surface to modify the light beam and thus effectively remove optical distortion in real-time [2,4]. The control system aims to connect the first 2 elements: a wave-front sensor and a wave-front corrector [2].

AO alone does not create an image, so the AO system must be integrated into existing retinal imaging devices such as fundus cameras (FC), SLO, and OCT. The first device integrated with AO to visualize the photoreceptor mosaic was FC-AO-FC [3]. The AO-FC is also the first commercially available system – rtx1 (Imagine Eyes, Orsay, France). The rtx1 camera is characterized by high lateral resolution (1.6 microns) and fast image acquisition time (4 s), during which 40 individual images are taken [6]. Due to the short capture time, AO-FC images are minimally disturbed by eye movements [1,2]. Another advantage of AO-FC is its lower cost and better availability than AO-OCT and AO-SLO. Disadvantages of AO-FC include low axial image resolution and reduced contrast compared to other devices [1,2]. The advantage of AO-OCT is the high axial resolution (about 5 µm) compared to AO-FC (about 300 µm) and AO-SLO (about 100 µm), which enables 3D visualization of retinal structures [7]. In AO-SLO, the collimated laser light beam uses only the central 1 mm of the pupil aperture to image the eye's structures, while the scattered light is back-focused on the focal point, resulting in increasing contrast and axial resolution [8]. The main advantages of AOSLO are its confocal configuration, allowing it to generate images of planes at different retinal depths, and its ability to integrate fluorescence and AF imaging with AO-SLO imaging [9]. Of particular interest is multimodal AO imaging; for example, the integration of OCT with the AO-SLO system to create an AO-SLO-OCT [10]. As mentioned above, AO enables non-invasive imaging of the retina at the microscopic level in vivo, allowing the analysis of individual structures such as photoreceptors (**Figure 1**), blood vessels (**Figure 2**), nerve fibers, ganglion cells, and the lamina cribrosa. The AO technique can improve lateral resolution to 2 µm providing information about the retinal structure that cannot be obtained with currently available in vivo methods [2]. The main photoreceptors parameters examined by AO imaging are cone density, spacing, reflectivity, and regularity [11,12]. For density estimation, the number of cones is divided by its area. In the case of cone spacing, the distances between adjacent cells are measured. As the cones are usually organized in a hexagonal lattice pattern, cone regularity is defined as the frequency of cones with exactly 6 adjacent cells. Reflectivity is defined as the mean intensity of the pixels

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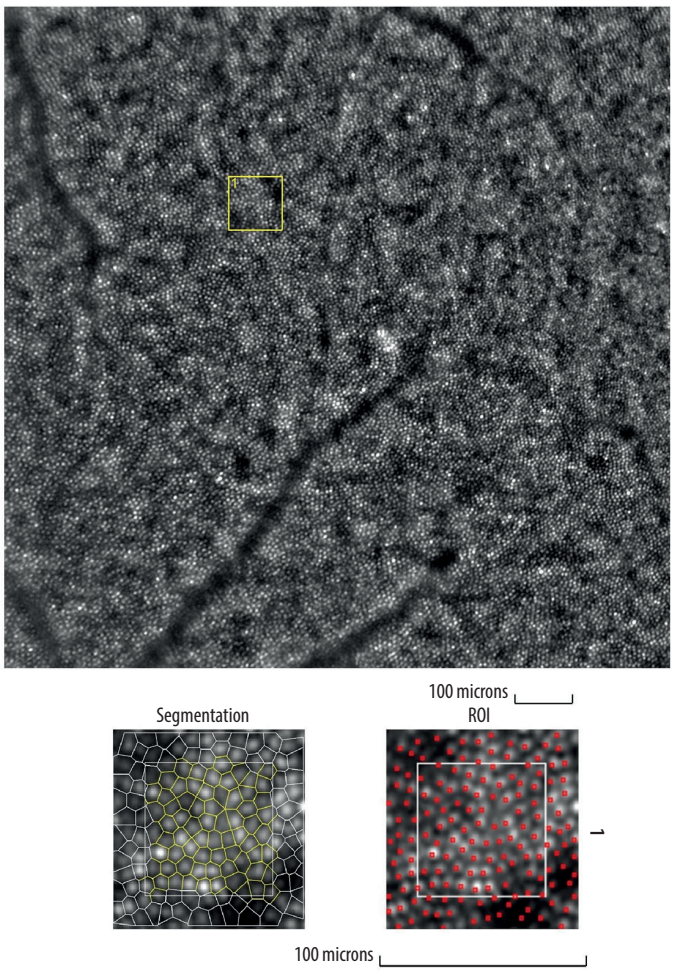

Figure 1. Image of normal cone mosaic. Image of normal cone mosaic in a healthy volunteer obtained with adaptive optics camera 4°×4° degree square (Rtx-1, Imagine Eyes, Orsay, France). The analysis was performed at superior 2° from the fovea (**top**). The region of interest (ROI) (yellow square in the top image) was used for automated cone segmentation (**bottom left**) and detection (**bottom right**) using dedicated software. Red squares correspond to automatically identified cones (**bottom right**). *The image is from the author's collection.*

corresponding to the cones [2]. To assess vascular morphology, the following parameters are measured: total vessel diameter (TD), lumen diameter (LD), and wall thickness (WT). Additional parameters are the wall-to-lumen ratio (WLR), defined as the ratio of the vessel WT to the LD, and the wall cross-sectional area (WCSA), describing the relationship between LD and TD [13]. The parameters used to assess lamina cribrosa (LC) include pore number, pore density and area, and pore ovality index [14]. In addition, using AO-OCT, it is possible to assess 3D LC parameters such as connective tissue volume fraction [15].

Diabetic Retinopathy

DR is a complication of diabetes mellitus (DM) and is the fifth leading cause of blindness worldwide [16]. DR consists of microangiopathy and neurodegenerative changes in retinal cells [17]. Assessing photoreceptors and vessels in diabetic patients is one of the main directions in AO imaging (**Figure 3**), although AO retinal imaging in patients with DM can be difficult due to diabetic complications such as difficulties with mydriasis, cataract, and vitreous hemorrhage [18]. Lombardo et al, using AO-FC, found a loss of cones in DM eyes compared with controls and decreased cones numbers in patients with glucose intolerance, high glycohemoglobin level, and signs of DR [19]. In other research, Lammer et al, using AOSLO, found that reduced regularity of the cone mosaic is correlated with increasing severity of DR and DME [20]. Cristescu et al, using AO-FC, showed similar results, demonstrating photoreceptor loss in DM 1 patients compared to the control group [21]. In contrast, Tan et al, using AO-FC, found that photoreceptors did not differ from the control group [22]. Cone parameters and retinal vessels were assessed by Zaleska-Zmijewska et al with the AO-FC in the course of DM. A significantly lower density of cones was observed in DR compared to the control group, as well as a decrease in density and regularity of cones as the severity of DR increased. Moreover, the artery walls were significantly thicker in the DR group compared to the control group [18]. In another study, Datlinger et al analyzed the density and morphology of photoreceptors in ischemic versus nonischemic

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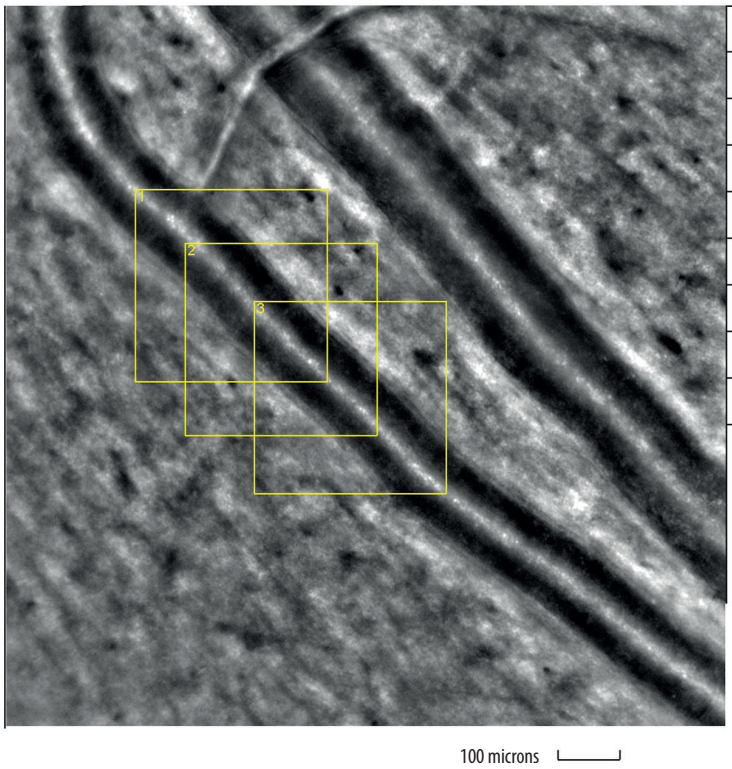

	ROI 1	ROI 2	ROI 3
Lumen diam	110.0	112.5	107.3
Total diam	131.3	134.2	129.6
Wall#1	10.7	12.2	11.9
Wall#2	10.7	9.5	10.5
WCSA	4038.77	4204.61	4151.18
WLR	0.19	0.19	0.21
X	13.75N°	13.47N°	13.09N°
Y	6.25°	5.95°	5.62°

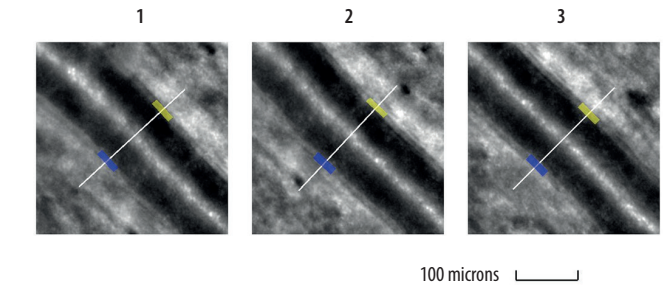

Figure 2. Image of normal retinal arteriole and venule. Evaluation of retinal arteriolar morphology in a healthy volunteer with adaptive optics camera 4°×4° degree square (Rtx-1, Imagine Eyes, Orsay, France) and measurement of morphological parameters using AOdetect software (**top**). The parameters calculated from the 3 selected regions of interest, for each time landmark (100 µm width and height each) (**bottom**). *The image is from the author's collection.*

retinal areas in the patients with DR. It was found that the areas affected by capillary non-perfusion showed severe changes in cone morphology and density compared to areas with intact capillary perfusion, and these structural changes were associated with a severe reduction in retinal sensitivity [23]. Lombardo et al found that average capillary LD in parafoveal areas was significantly narrower in eyes with nonproliferative DR (NPDR) than in the control group [24]. Ueno et al assessed the retinal vessels' morphological parameters using AO-FC and retinal blood flow using laser speckle flowgraphy (LSFG) in patients with DM 2. The WLR was significantly higher in the proliferative DR (PDR) group than in all other groups. Furthermore, the retinal blood flow was correlated with WLR and was significantly lower in the PDR group than in the other groups [25]. Cristescu et al confirmed previous results. They assessed changes in the retinal microcirculation in patients with DM 1 and DM 2. The WLR in the eyes of diabetic patients in both groups was higher compared to the control group and there were no substantial differences between the DM1 and DM2 groups [26]. In another study, Palochak et al, using AO-SLO, showed that retinal blood flow and velocity in diabetic patients without DR were significantly higher than in the control group, and these parameters were significantly reduced in eyes with NPDR compared to the controls. The trends were

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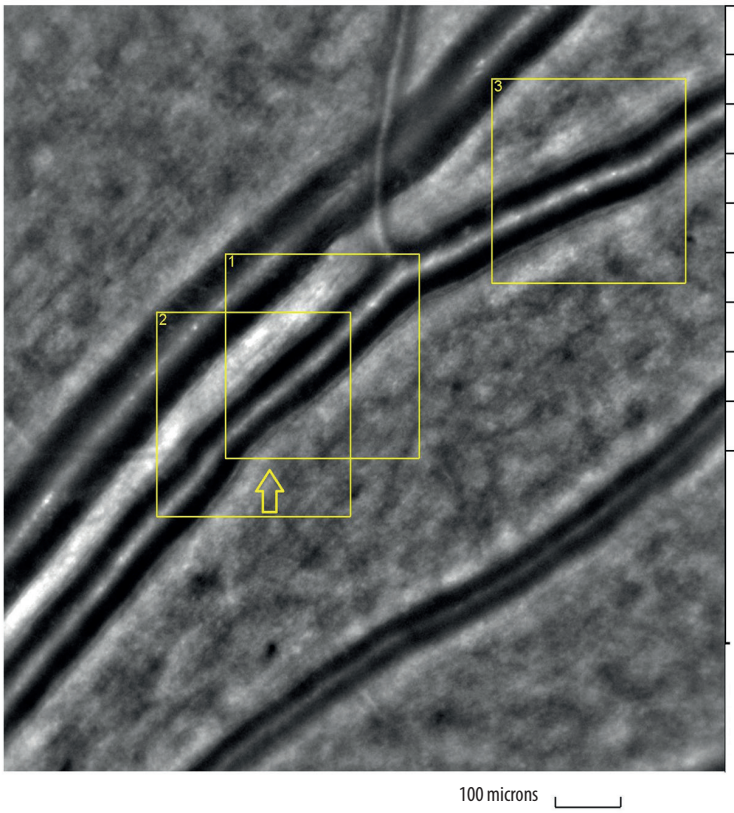

	ROI 1	ROI 2	ROI 3
Lumen diam	75.6	65.8	79.1
Total diam	99.7	90.0	102.1
Wall#1	14.0	11.5	10.2
Wall#2	10.1	12.7	12.9
WCSA	3325.40	2961.93	3281.60
WLR	0.32	0.37	0.29
X	9.92N°	10.29N°	8.45N°
Y	9.97°	9.66°	10.88°

Figure 3. Image of retinal vessels in a patient with diabetes mellitus type 2. Evaluation of retinal arteriolar morphology in a patient with diabetes mellitus type 2 with adaptive optics camera 4°×4° degree square (Rtx-1, Imagine Eyes, Orsay, France) and measurement of morphological parameters using AOdetect software. Retinal artery with focal luminal narrowing (yellow arrow) and increased wall-to-lumen ratio (WLR 0,33; 0,37; 0,29) (**top**). The parameters calculated from the 3 selected regions of interest, for each time landmark (100 µm width and height each) (**bottom**). The image is from the author's collection

similar for vessel density measured with OCTA. The researchers suggested that increased retinal blood flow and velocity can cause endothelial damage during the early stages of diabetes, resulting in reduced retinal blood flow later [27]. Using AOSLO, Tam et al assessed the characteristics of arteriovenous (AV) channels in DM2 patients without DR. The mean tortuosity of AV channels was 26% greater in DM2 patients compared to the control group, and it was suggested that the increased tortuosity of the AV channel in DM may result from a gradual loss of key capillary segments [28].

Age-Related Macular Degeneration

AMD is the leading cause of vision loss worldwide in people aged 60 years and older [29]. In this context, the benefits of

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identifying patients at increased risk of disease progression early is invaluable. By using AO, progression in drusen size can be determined, and its impact on the underlying retinal layers can be assessed [30]. Drusen is usually visible as poorly demarcated hyper-reflective patches and are therefore a challenge for AO imaging [30]. Rossi et al found that the contrast of drusen can be increased by capturing images from different gaze positions and combining them into a composite image using statistical operations [31]. The differences in reflectance between the drusen and reticular pseudodrusen can be assessed using AO [32]. Furthermore, the studies with the use of AO demonstrated the dynamism of drusen and pseudodrusen, showing new and regressive changes over time [33]. The researchers demonstrated an undisturbed photoreceptor mosaic for early drusen with normal regularity and cone density [34]. Boretsky et al, using AO-SLO, found increasing disruption of photoreceptors across the macula in direct relation to the progression of AMD [35]. Geographical atrophy (GA) has also been examined using AO. Changes in cone density in atrophic and adjacent regions with numerous hyporeflective clumps were revealed by Gocho using adaptive optics near-infrared reflectance (AO NIR) fundus imaging. These clumps may represent melanin-containing cells and are possible biomarkers of retinal pigment epithelium (RPE) damage [36]. Querques et al also examined AO features of functional photoreceptors of foveal sparing in eyes with GA. En-face AO images showed foveal sparing as well-demarcated regions of reduced reflectivity with fewer hyporeflective clumps compared to GA regions. [37]. Finally, AO has been used in clinical trials to assess the success of stem cell therapy in patients with exudative AMD and polypoidal choroidal vasculopathy (PCV) [38]. It should be noted that investigating wet AMD is still technically difficult due to the lack of retinal transparency [39].

Glaucoma

Glaucoma is the leading cause of irreversible blindness worldwide and is characterized by progressive dysfunction and loss of retinal ganglion cells (RGC) and their axons. Many studies have shown the use of AO in glaucoma [40-50]. In their study using AO-SLO, Takayama et al examined pathological changes in the retinal nerve fiber layer (RNFL) in eyes with glaucoma, finding a decrease in the width of the nerve fiber bundles in both clinically normal and abnormal regions of the retina. These abnormalities were correlated with the loss of visual field [40]. Hasegawa et al demonstrated the expansion of individual retinal nerve fiber (RNF) bundle narrowing in eyes with glaucoma [41]. Chen et al used AO to compare the pattern of RNF bundles in retinal regions with normal (WN) and abnormal (AB) RNFL thickness on OCT images [42]. A few studies have investigated the effects of glaucoma on photoreceptors, but the results are contradictory. Choi et al demonstrated structural changes in cone photoreceptors at the retinal locations with reduced visual sensitivity with AO images. In these locations, AO-FC en-face images showed dark areas in the cone mosaic, while AO-OCT showed shortening of the cone outer segments (OS) [43]. Structural changes in the cone mosaic have also been shown in patients with optic neuropathies and glaucoma-like VF defects [44], but Hasegawa et al found no difference in either density or spatial organization of cones in glaucomatous eyes [45]. Several studies have assessed the morphology of lamina cribrosa in glaucoma eyes. In rhesus monkeys, Vilupuru et al demonstrated greater area and elongation of LC pores in the eye with experimental glaucoma than in its healthy fellow [46]. These findings were confirmed by Akagi et al, showing significantly larger pore areas in glaucomatous eyes than in normal ones, which was significantly correlated with higher IOP [47]. Zwillinger, in turn, revealed elongated LC pores not only in primary open-angle glaucoma (POAG) eyes, but also in healthy eyes of POAG relatives [48]. Another application of AO was presented by King et al by combining AOSLO with a gonioscopic lens for trabecular meshwork imaging [49]. Finally, morphological analysis of the peripapillary microcirculation in glaucoma was assessed using AO-FC by Hugo et al, who found narrowing of the arterial LD without any change in the WT, which may suggest that the vasospastic mechanism is associated with POAG [50].

Hypertensive Retinopathy

HR is the most common ophthalmologic complication of hypertension [51]. Recently, OCT and angio OCT have also been frequently used to evaluate vasculature in patients with HR. With AO it became possible to assess vascular remodelling in HR at the microscopic level (**Figure 4**). Metha et al, using AO-FC, observed a significant increase in retinal arteriolar WLR and WCSA in a hypertensive group compared to the control group, and they suggested that AO enables distinguishing between 2 types of vessel wall remodelling in HR: eutrophic and hypertrophic [52]. Rosenbaum et al found that lowering blood pressure increased arterial LD without changes in WT, while chronic antihypertensive treatment led to normalization of remodelling [53]. The correlation of WLR with hypertension and microvascular abnormalities has been confirmed by other studies [54-57]. Gallo et al investigated whether retinal arteriolar WLR and LD parameters can distinguish hypertensive from healthy subjects [58], and they also assessed vascular parameters in people with masked arterial hypertension (MAH), finding that AO analysis could help diagnose hypertension, particularly in cases of MAH [58]. In addition, a case report presenting the application of AO-SLO in a patient with malignant hypertension has been published [59].

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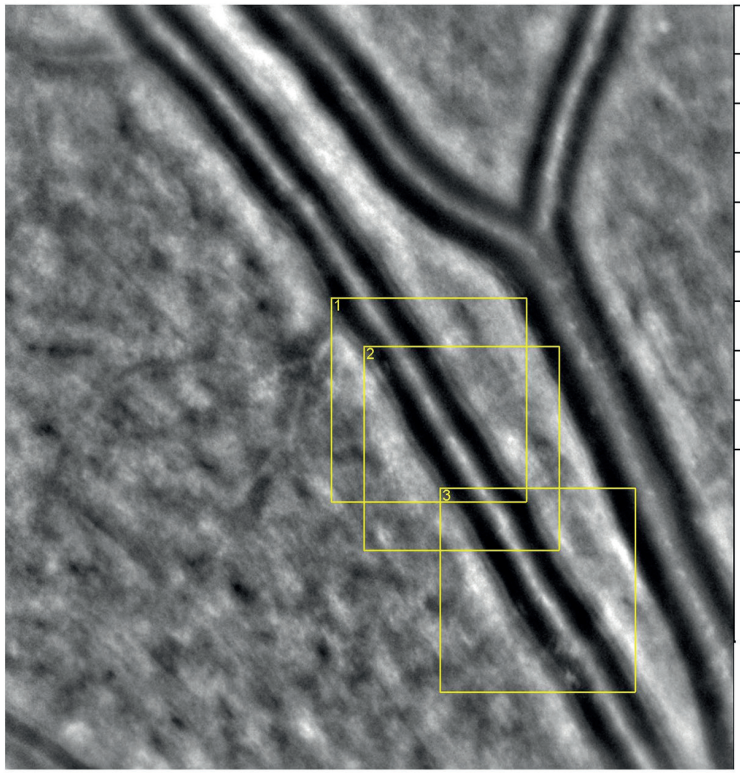

	ROI 1	ROI 2	ROI 3
Lumen diam	77.2	84.1	84.2
Total diam	101.4	112.0	111.4
Wall#1	11.5	13.6	12.9
Wall#2	12.7	14.3	14.4
WCSA	3397.38	4295.46	4188.26
WLR	0.31	0.33	0.32
X	12.64N°	12.81N°	13.23N°
Y	9.43°	9.18°	8.44°

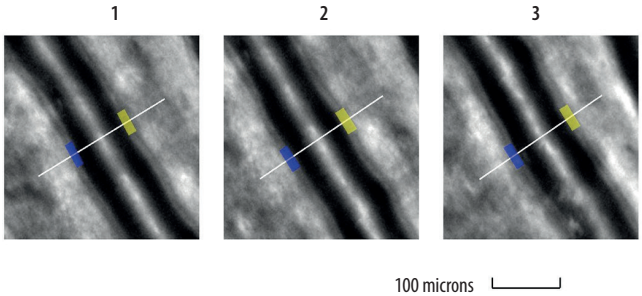

Figure 4. Image of retinal vessels in a patient with hypertensive retinopathy. Evaluation of retinal arteriolar morphology in a patient with hypertensive retinopathy with adaptive optics camera 4°×4° degree square (Rtx-1, Imagine Eyes, Orsay, France) and measurement of morphological parameters using AOdetect software. Retinal artery with increased wall-to-lumen ratio (WLR 0,31; 0,33; 0,32) (**top**). The parameters calculated from the 3 selected regions of interest, for each time landmark (100 µm width and height each) (**bottom**). *The image is from the author's collection.*

Central Serous Chorioretinopathy

CSCR is a common type of maculopathy, with multiple causes, including hyperperfusion and hyperpermeability of the choroid vasculature [60]. Ochinciuci et al, using AO-FC, showed that photoreceptor density was significantly reduced in eyes with CSCR compared to healthy eyes [60]. Ooto et al, using AO-SLO, revealed abnormal cone mosaic and reduced cone density in eyes with resolved CSCR, and these abnormalities were correlated with decreased VA [61]. Meirelles et al, using AO, showed changes in the photoreceptors mosaic in the eye after CSCR resolution, suggesting that resolved CSCR may cause photoreceptor changes, even after clinical recovery [62]. Gerardy et al examined cone mosaic in the asymptomatic fellow eye in patients with unilateral CSCR, showing reduced cone density in the fovea, suggesting that photoreceptors may be affected

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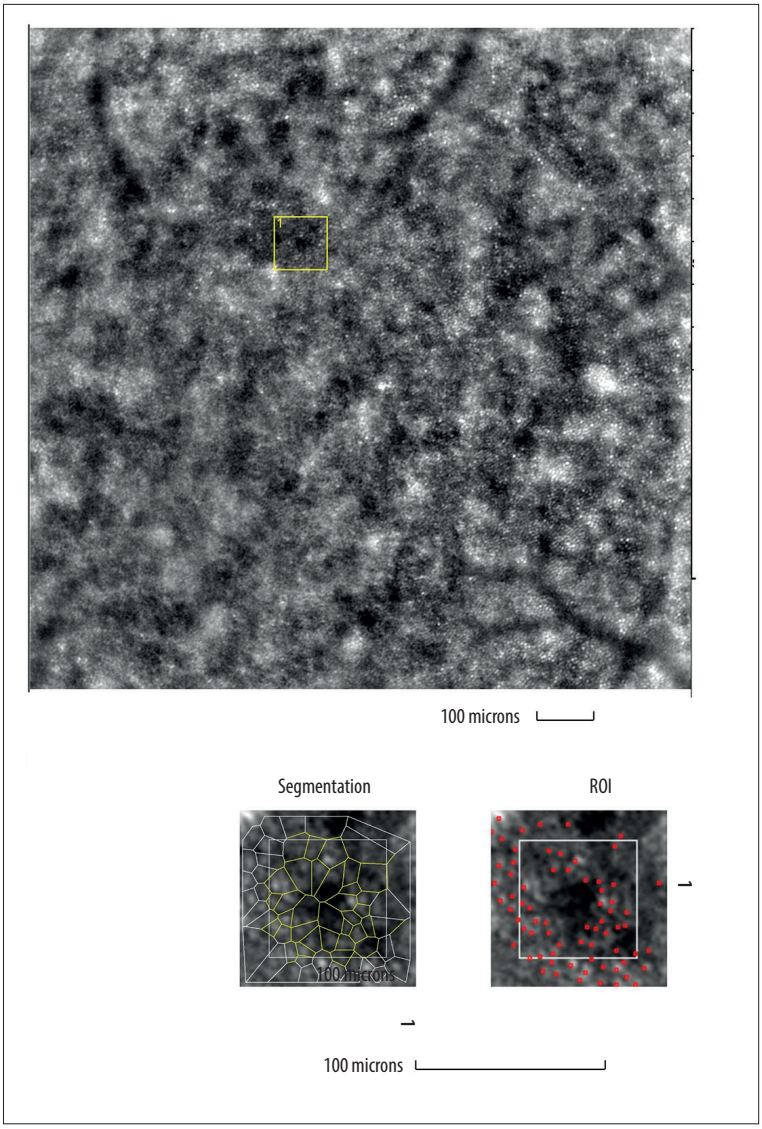

Figure 5. Image of cone mosaic in a patient with cone-rod dystrophy. Image of cone mosaic in a patient with cone-rod dystrophy obtained with adaptive optics camera 4°×4° degree square (Rtx-1, Imagine Eyes, Orsay, France). The analysis was performed at superior 2° from the fovea. Empty spaces at the photoreceptor level and a disrupted mosaic of photoreceptors are demonstrated (**top**). The region of interest (ROI) (yellow square in the top image) was used for automated cone segmentation (**bottom right**) and detection (**bottom left**) using dedicated software. Red squares correspond to automatically identified cones (**bottom right**). Low density of the cones and the defect in the cones is demonstrated (**bottom**). *The image is from the author's collection.*

independently of the development of CSCR [63]. Vienola et al, using AO-SLO, revealed hyperautofluorescent punctate patches in patients with CSCR, which may correspond to the accumulation of fluorophores within macrophages from RPE and photoreceptors during the active stage of the disease [64].

Inflammatory Diseases

Retinal vasculitis is characterized by inflammation of the retinal vessels [65]. Inflammatory changes in the retinal vessels can be assessed by AF, indocyanine angiography, and angio OCT [66]. In vivo visualization of inflammatory changes in the vessels using AO can be a valuable diagnostic tool. AO technology enabled visualization of vessel sheeting in patients with confirmed autoimmune diseases and made it possible to monitor changes over time, such as the decrease and resolution of sheathings. The AO findings were correlated with the results of fundus photography and AF [66]. These findings were confirmed by Errera et al in a study using AO in patients with retinal vasculitis in the course of Lyme disease and presumed tuberculosis [67]. They observed increased vein diameter and thinning of the perivenous sheathing during treatment on subsequent follow-ups [68]. In addition to vascular changes in inflammatory diseases, abnormalities in the outer retina and RPE also occur [69]. Biggee et al demonstrated alterations of the parafoveal cone mosaic in eyes with posterior uveitis. In addition, after starting therapy, AO showed an improvement in cone density in the parafoveal region [69]. Photoreceptor abnormalities were also confirmed by other studies, such as those evaluating photoreceptor mosaic in idiopathic multifocal choroiditis [70], acute posterior placental syphilitic chorioretinopathy (ASPPC) [71], Behçet's disease (BD) [72], and white dot syndrome [73].

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Table 1. Examples of using AO in IRDs.

IRDs	Research findings using AO
Macular dystrophies	
Stargardt disease	Enlarged cone and rod spacing in retinal regions that appear normally in conventional images, suggesting that photoreceptor loss precedes clinically detectable disease [77] The cone mosaic parameters in AO-SLO images correspond to retinal structure in OCT images and visual function in microperimetry, demonstrating a valuable structure-function correlation [78]
Best vitelliform macular dystrophy	Photoreceptor morphology within vitelliform lesions can range from normal appearing mosaic to significant disruption depending on the disease stage [79]
X-linked retinoschisis	The increased cone spacing and abnormal packing in the macula but almost normal cone morphology outside the central foveal schisis [80]
Stationary retinal dystrophies	
Congenital stationary night blindness	AO-SLO demonstrated normal rod and cone mosaic topography, suggesting that the disease is caused by functional defects in retinal neurotransmission rather than morphological abnormalities of photoreceptors [81]
Blue cone monochromacy (X-linked)	Using AO-SLO, decreased density and impaired mosaic of cones in asymptomatic female carriers have been demonstrated [82] The degree of disruption in cone structure in affected men varies widely, which may depend on the type of mutation [83]
Achromatopsia	Empty spaces at the photoreceptor level in the fovea were demonstrated. The mosaic of photoreceptors was significantly disrupted compared to the control group, although in very different degrees depending on age and mutation type [84,85]
Progressive retinal dystrophies	
Retinitis Pigmentosa	Decreased cone density even in the retinal regions with unaffected the ellipsoid zone/the interdigitation zone (EZ/IZ) in OCT and preserved visual sensitivity [86]
Cone-Rod dystrophies (**Figure 5**)	Large areas without cones in atrophic regions. Regions that appeared relatively lesion-free on clinical examination contained abnormally large cones, resulting in reduced cone density [87]
Choroideremia	Relatively intact central retina with normal or reduced cone density and sudden loss of cones at the border of RPE atrophy. No RPE cells were seen in areas of cones' loss [88]

AO – adaptive optics; IRDs – inherited retinal diseases; AO-SLO – adaptive optics scanning laser ophthalmoscopy; RPE – retinal pigment epithelium.

Inherited Retinal Diseases (IRD)

IRD is a group of clinically and genetically heterogeneous conditions characterized by retinal dysfunction that can be stationary or progressive and even lead to visual loss [74]. AO imaging is an important tool in studying the pathogenesis and progression of IRD, allowing high-resolution characterization of the retinal cellular structure (**Figure 5**) such as phenotyping of hereditary retinal diseases and correlation of the findings with specific genetic mutations, which are essential for better selection of patients for new therapies (including stem cells and gene modification therapies) and better control of treatment outcomes [75,76]. Examples of studies in which IRD were assessed using AO are shown in **Table 1**.

Other Pathologies

AO technology has found application in many other ophthalmic diseases [89-103]. Examples of diseases studied with AO are shown in **Table 2**.

Future Developments

Despite the numerous studies using AO described in this article, AO technology is not yet widely used in clinical practice. For widespread use of AO in everyday practice, it is necessary to standardize measurement parameters, terminology, and proper validation of AO devices. The development of normative databases is also crucial to popularize AO in clinical

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Table 2. Examples of diseases studied with AO.

Ophthalmological disease	Research findings using AO
Retinal vein occlusion	Parafoveal aggregated erythrocyte velocity (AEV) assessed by the AO-SLO method in eyes with macular edema caused by retinal vein occlusion is significantly reduced compared to the control group [89] The microvascular density of fellow eyes was significantly higher than that of the affected eyes and significantly lower than that of the control group, reflecting subclinical pathology [90]
Macular Hole	Disruption of photoreceptor mosaic corresponding to regions of ellipsoid zone disruption on OCT was shown in all patients after successful MH closure [91] On AO-OCT images, scattered hyper-reflective dots were shown on the surface of the peeled retina in all patients after vitrectomy with internal limiting membrane peeling and gas tamponade, suggesting possible Müller cell reactive gliosis [92]
Choroidal melanoma	Photoreceptor alterations were shown in the retina lying above the choroidal lesion and in the adjacent retina [93]
Melanoma associated retinopathy	Reduced cone density was shown despite fundus examination being within normal limits [94]
Cancer Associated Retinopathy	Abnormal cone structure and reduced cone density were demonstrated using AO-SLO compared to the control group. These findings correspond to post-mortem findings on histopathological examination [95]
Solar retinopathy	The cone density in the fovea was decreased in all patients with solar retinopathy compared to the controls [96] Alterations in the foveal cone mosaic correspond to changes in reflectivity on en-face OCT image and reduced retinal sensitivity in microperimetry [97]
Laser Pointer Maculopathy	There was a loss of inner and outer segments of the cones, an increase in the Voronoi domain area, and a decrease in the regularity of the cone mosaic in the fovea [98]
Pseudoxanthoma Elasticum-related retinopathy	A cone mosaic of decreased density was demonstrated within the angioid streaks compared to adjacent areas of the retina. Three types of angioid streaks were identified: “crack,” “band,” and “hypopigmented” [99]
Retinal detachment	AO-OCT images showed a cone mosaic of severe irregularity and reduced density in eyes after gas-assisted vitrectomy for macular detachment compared to healthy eyes. After 56 weeks, although there has been significant improvement in parameters, structural impairment was still present [100]
Endophthalmitis	A decreased foveal cone density in the eye with resolving endophthalmitis was demonstrated compared to the fellow eye, despite near-normal vision and no structural changes in OCT [101]
Hydroxychloroquine induced maculopathy	Gradual loss of cones was observed as the accumulation dose of hydroxychloroquine increased without clinical evidence of maculopathy [102] The study showed a disturbed cone mosaic with a loss of cones correlating with visual field defects [103]

AO – adaptive optics; AO-OCT adaptive optics optical coherence tomography; AO-SLO – adaptive optics scanning laser ophthalmoscopy; OCT – optical coherence tomography.

ophthalmology [104]. The large size of AO equipment, as well as its high cost and difficulties in operation, cause many inconveniences in clinical applications. The development of AO hardware and software in the future may overcome these problems [105-107]. The most important directions for the development of AO are the miniaturization of AO hardware, lowering production costs, and developing user-friendly software, which will contribute to better AO availability. Further improvements in the resolution of AO imaging, as well as the combination of different methods and the development of multimodal AO systems, will improve imaging and analysis of eye structures [108]. Finally, artificial intelligence is expected to play an increasingly important role in analyzing images and interpreting results obtained with AO [109].

Conclusions

AO technology offers the possibility to assess lesions at a microscopic level, previously only available on post-mortem

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histological examination. This enables early disease detection at clinically asymptomatic stages and provides more effective monitoring of disease progression and treatment outcomes. In addition, AO provides the opportunity to improve our understanding of the pathogenesis of ophthalmic diseases.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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