• Review Article •

Macular pigment optical density and measurement technology based on artificial intelligence: a narrative review

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Abstract

● Macular pigment (MP) is a crucial pigment in the macular region. It plays an important role in filtering blue light, and exhibits anti-inflammatory and antioxidant properties. Macular pigment optical density (MPOD) is a key indicator for assessing the density of MP in the macular area and is closely associated with eye diseases, including age-related macular degeneration, diabetic retinopathy, and glaucoma. This review aims to explore the clinical significance of MPOD and its research value in ophthalmology and other medical fields. It summarizes the current MPOD measurement techniques, categorizing them into two main types (*in vivo* and *in vitro*), and discusses their respective advantages and limitations. Additionally, given the advancements in artificial intelligence (AI) and deep-learning technologies that offer new opportunities for improving MPOD assessment, this review analyzes the significant potential and future prospects of AI-based fundus image analysis in MPOD measurement. The goal of AI-based analysis is to provide faster and more accurate detection methods, thereby promoting further research and new clinical applications of MPOD in the field of ophthalmology.

● **KEYWORDS:** macular pigment optical density; clinical application; measurement technology; artificial intelligence
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INTRODUCTION

The macular pigment (MP) is primarily concentrated in the macular region of the retina and is composed of three carotenoids, namely lutein, zeaxanthin, and meso-zeaxanthin[1-2]. The density of MP is typically represented by macular pigment optical density (MPOD)[2-3]. It has been demonstrated that MP plays a role in filtering blue light, reducing inflammation, and combating oxidative stress[1,4-8]. MPOD is closely associated with the onset and progression of several ocular diseases, including age-related macular degeneration (AMD), diabetic retinopathy (DR), and glaucoma, which highlights its broad research and clinical application value[3,9-10]. Methods for measuring MPOD can be categorized *in vivo* and *in vitro* techniques[10-11]. *In vitro* methods include microdensitometry and high-performance liquid chromatography (HPLC)[11]. *In vivo* methods can be further divided into subjective and objective techniques[11-12]. Subjective methods include heterochromatic flicker photometry (HFP), color matching, and minimum motion photometry, while objective methods encompass fundus reflectometry (FR), fundus autofluorescence (FAF), resonance Raman spectroscopy (RRS), and visual evoked potential (VEP) based on electrophysiology[3,13-15]. Among these techniques, HFP is regarded as the standard method for measuring MPOD due to its extensive clinical application and reliability[15]. However, all methods have advantages, disadvantages, and limitations, making it challenging for MPOD to fully realize its potential in the prevention and treatment of ocular diseases.

In recent years, with the rapid advancement in use of deep-learning algorithms for medical image analysis, artificial intelligence-based fundus image recognition technology has created new possibilities for MPOD measurement[16]. This approach not only promises to enhance measurement accuracy and efficiency, but also overcome certain limitations of traditional techniques. The present study investigates the relationship between MPOD and various ocular diseases, as

well as its value in ophthalmology and other medical research fields. Additionally, this study emphasizes the importance of MPOD measurement, evaluates the limitations of current techniques, and explores the potential of artificial intelligence-based fundus image MPOD measurement, with the hope of providing a faster and more accurate detection method for the clinical application and further development of MPOD research.

MPOD AND ITS APPLICATIONS

Macular Pigment and Macular Pigment Optical Density

The macula, located in the central optical region of the posterior pole of the retina, is a vital area for maintaining visual functions (*e.g.*, fine vision and color perception), and appears yellow due to its high concentration of MP[2]. As the primary functional component of the macular region, MP is concentrated in the Henle fiber layer, the inner nuclear layer of the retina, the axons of cone cells, and the outer segments of rod cells[4-6], and is mainly composed of three lutein-related carotenoids, namely lutein, zeaxanthin, and meso-zeaxanthin[1]. MP helps maintain the normal function and morphology of the macula and protect ocular health. Moreover, MP act as a blue-light filter by absorbing 40%-90% of high-energy short-wavelength blue light[5,7], reducing oxidative damage from blue light within the eye and thereby protecting the retina from photochemical damage[1]. MP also quenches singlet oxygen and related reactive oxygen species to reduce oxidative stress-induced damage to photoreceptor cells, thereby preserving healthy vision[4,6,8]. Additionally, it has been reported that MP can inhibit ocular inflammation by reducing inflammatory factors and regulating the expression of related genes[7]. Therefore, it has been suggested that supplementing with lutein, zeaxanthin, and other antioxidant blends may help improve eye health[17-18].

MP density is expressed as MPOD, which linearly correlates with the total amount of MP, *i.e.*, the product of its concentration, the length of the light transmission path, and the area[2,19]. MPOD is measured in optical density units, ranging from 0 to 1, with one optical density unit corresponding to approximately 0.025 nanograms of MP covering one square millimeter of retinal tissue[7,20]. In addition to MPOD, serum lutein levels, and dietary intake of lutein are also commonly used as indicators of MP levels. However, these indicators do not fully account for potential confounding factors in the processes of lutein digestion, absorption, and transport[1].

MPOD and Ocular Diseases Several clinical studies have demonstrated a correlation between MPOD and eye diseases, including AMD, DR, central serous chorioretinopathy (CSC), glaucoma, macular telangiectasia type 2 (MacTel-2), and myopia[3,9-10,21], suggesting that MPOD might serve as a biomarker for these conditions[3]. It has been confirmed that AMD patients have lower MPOD compared with healthy individuals, and low MPOD may be a risk factor for the development of AMD[22]. Because oxidative stress caused by prolonged light exposure is believed to be closely related to the etiology and pathogenesis of AMD[23], some researchers suggest that supplementing lutein and zeaxanthin may reduce oxidative stress and increase MPOD in AMD patients[24], thereby lowering the risk of developing AMD[23] and slowing its progression[7]. One study indicated that low MPOD could be a risk factor for the development of dry AMD; therefore, routine MPOD screening in individuals over 50 years of age may help identify those who need nutritional supplementation to prevent the further progression of dry AMD[25]. Additionally, a previous study has reported that combining MPOD with the length of the photoreceptor outer segment may serve as a biomarker for AMD[22], providing a potential screening method for individuals at high risk of AMD.

DR is the most common retinal vascular disease[26], and higher plasma lutein levels or higher MPOD are associated with a lower risk of DR[27]. A recent study of 150 participants has shown that the average MPOD values among three groups—healthy controls, diabetes patients without DR, and diabetes patients with mild to moderate DR—were the same. However, hemoglobin A1c levels negatively correlated with the maximum optical density of MPOD, suggesting that a decrease in MPOD might reflect oxidative stress in the retina among patients with diabetes. This suggests that MPOD measurements could be useful for monitoring macular health in diabetes and identifying early biomarkers of DR[13].

CSC is characterized by serous retinal detachment in the macular region, dysfunction of the retinal pigment epithelium, and thickening of the choroid, leading to symptoms such as blurred vision and central scotomas[28]. Several studies have shown that CSC patients have lower MPOD compared with healthy controls, suggesting that low MPOD might be a risk factor for CSC[10,29-30]. One study of 54 patients with acute CSC and 62 healthy controls showed that the maximum optical density and the mean optical density in CSC patients were lower than those in the control group[29], suggesting that MPOD could serve as a biomarker for early CSC screening.

Glaucoma causes optic nerve damage and is the leading cause of irreversible blindness worldwide[31]. Its main characteristics include the loss of retinal ganglion cells, thinning of the retinal nerve fiber layer, and deepening of optic disc cupping[32]. Glaucoma encompasses various subtypes, including primary and secondary glaucoma, with primary glaucoma further classified into open-angle and angle-closure types[31]. Low MPOD has been linked to primary open-angle glaucoma (POAG), where lower MPOD values are associated with more severe glaucoma[8,33-34]. In a study of 426 women, researchers

Table 1 Summary of the relationship between MPOD and ocular diseases

Eye disease	Correlation between disease and MPOD	MPOD as a biomarker
AMD	Low MPOD may be a risk factor for AMD. Supplementing lutein and zeaxanthin can increase MPOD and reduce AMD risk	Yes (combined with photoreceptor outer segment length)
DR	High plasma lutein or high MPOD is associated with a lower DR risk. Decreased MPOD may reflect retinal oxidative stress	Yes (as early biomarker)
CSC	MPOD is significantly lower in CSC patients than in controls. Low MPOD may be a risk factor for CSC	Yes (for early CSC screening)
Glaucoma	Primary open-angle glaucoma patients have lower MPOD, whereas pseudoexfoliation glaucoma patients have higher MPOD	Yes (as early retinal structural indicator of primary open-angle glaucoma)
MacTel-2	MPOD is significantly reduced, and correlates with retinal function. Abnormal spatial distribution of macular pigment is observed	Yes (to monitor disease progression in MacTel-2)
Myopia (high myopia)	MPOD negatively correlates with high myopia severity. Low MPOD may increase the risk of complications such as lacquer cracks	Possibly (related to myopic complications)

MPOD: Macular pigment optical density; AMD: Age-related macular degeneration; DR: Diabetic retinopathy; CSC: Central serous chorioretinopathy; MacTel-2: Macular telangiectasia type 2.

measured MPOD using customized HFP and found that the eyes of POAG patients had 25% lower MPOD than those of healthy individuals[33]. Another study of 379 participants reported that MPOD in POAG patients positively correlated with the thickness of certain retinal layers in the macular and peripapillary regions, while in non-POAG patients, MPOD positively correlated only with the thickness of certain retinal layers in the central macula[34]. These findings support the hypothesis that low MPOD could be a new risk factor for glaucoma and may serve as an indicator of retinal structural changes in early glaucoma. In contrast to POAG, a previous study has shown that patients with pseudoexfoliation glaucoma (PEX) have higher MPOD than healthy individuals[35]. Specifically, in the study of 25 patients with PEX and 20 normal individuals, MPOD measurements revealed that the mean and maximum MPOD values in PEX patients were significantly higher than those in the POAG and control groups, indicating the potential of MPOD as a biomarker for PEX. The above results indicate that MPOD levels vary among patients with different types of glaucoma.

MacTel-2 is a slowly progressive neurodegenerative macular disease characterized by decreased visual acuity, metamorphopsia, or difficulty reading. A reduction in MPOD can be observed in MacTel-2 patients due to the loss of lutein pigment in the macula[21,36]. A study of 31 healthy individuals and 22 MacTel-2 patients showed that MPOD values were lower in all macular regions of the MacTel-2 patients compared with the healthy controls, and the spatial distribution of MP in the MacTel-2 patients varied across regions[36]. In a separate study, Heeren *et al*[37] reported a correlation between MPOD and retinal function in MacTel-2 patients, suggesting that MP levels could serve as an auxiliary measure of disease progression in MacTel-2.

Other studies have linked MPOD to myopia. In a study of 54 patients with high myopia, MPOD was found to negatively correlate with the degree of high myopia, with MPOD decreasing as axial length increased and corrected visual acuity decreased[6]. Another observational study suggested that low MPOD might make individuals with myopia more prone to lacquer cracks, a complication of high myopia characterized by breaks in Bruch's membrane and the retinal pigment epithelium[38].

The relationship between MPOD and various ocular diseases was summarized in Table 1.

Other Applications of MPOD

The measurement of MPOD is critical in the clinical diagnosis and treatment of ophthalmological diseases. Furthermore, MPOD is widely used in scientific research in ophthalmology and other medical fields, demonstrating its practical value. Recent studies have shown the correlation between MPOD and visual function. In a study where 23 healthy participants were assessed for their visual quality of life using the National Eye Institute Visual Function Questionnaire-25 and their MPOD was measured using objective techniques, a trend of association between MPOD levels and eye discomfort, as well as difficulty in night driving was reported[2]. This suggests that MPOD may play a role in alleviating eye discomfort and improving visual quality. Thus, the use of MPOD measurements in clinical practice to assess the visual health of healthy individuals was recommended[2]. Furthermore, a meta-analysis of 22 studies revealed a clear relationship between MPOD and visual functions such as recovery from light stress, glare disability, and contrast sensitivity, with visual function improving as MPOD levels increased[39]. In addition, other studies have found a correlation between MPOD and cognitive health and retinal health, suggesting that MPOD could serve as a biomarker for cognitive health[40] and provide valuable information on changes in retinal health[41]. Specifically, Garcia-Romera *et al*[40] conducted a systematic review of 19 studies and found that individuals with higher MPOD levels

Table 2 Summary of application examples of MPOD

Authors	Research application	Findings
Wilson *et al*[2]	MPOD and visual function	MPOD levels associated with eye discomfort and difficulty in night driving; higher MPOD may improve visual quality of life.
Johnson *et al*[39]	MPOD and visual functions (Meta-analysis)	Positive correlation between MPOD and visual functions; higher MPOD improves visual function.
Garcia-Romera *et al*[40]	MPOD as a biomarker for cognitive health	Higher MPOD linked to better performance in cognitive tests; MPOD may serve as a biomarker for cognitive health.
Nagai *et al*[41]	MPOD and retinal health	MPOD levels may indicate retinal health changes, providing valuable insights into retinal conditions.
Rinaldi *et al*[19]	MPOD as a postoperative biomarker	MPOD increased during postoperative recovery after macular hole surgery, suggesting its potential as a biomarker for visual prognosis following surgery.
Al-Hassan *et al*[42]	MPOD and maternal nutrition	MPOD could serve as a noninvasive marker of maternal nutritional intake, potentially informing personalized nutrition during pregnancy and lactation.
Barnett *et al*[43]	MPOD and academic performance	Positive correlation between MPOD levels in children and academic performance, highlighting the role of carotenoids in diet.

MPOD: Macular pigment optical density.

performed better in cognitive tests, particularly in areas such as memory, attention, and reasoning abilities, suggesting that MPOD could also serve as a biomarker for cognitive health. Beyond its use as a health biomarker, some studies have proposed that MPOD could serve as a postoperative biomarker. Namely, Rinaldi *et al*[19] reported a case in which a large full-thickness macular hole was successfully closed using the inverted flap technique. The patient, who had experienced severe vision loss before the surgery, showed improvement in vision and retinal structure after the procedure, as evaluated through multimodal imaging, including MPOD measurement. Notably, MPOD increased during the postoperative recovery, indicating that MPOD may be a valuable biomarker for assessing visual prognosis following surgery[19]. Moreover, Al-Hassan *et al*[42] proposed that MPOD could serve as a noninvasive quantitative marker of maternal nutritional intake, helping to identify dietary factors that affect maternal nutrition during pregnancy and lactation, and providing opportunities for personalized nutritional advice in the future. Barnett *et al*[43] measured MPOD in 56 children aged 8 to 9y and assessed their academic performance. The authors found a positive association between MP and academic outcomes, such as mathematics and written language, highlighting the importance of nutrients such as lutein and carotenoids in the diet. Other application examples of MPOD were summarized in Table 2.

In summary, not only is MPOD an effective biomarker for various eye diseases and health conditions, but it also holds broad value in ophthalmological and other medical research fields. Therefore, precise and efficient measurement of MPOD is essential for early disease detection, individual health assessment, and related scientific research.

CURRENT MPOD MEASUREMENT METHODS AND THEIR LIMITATIONS

Classification of MPOD Measurement Methods Current methods for measuring MPOD can be classified into two categories, namely *in vivo* and *in vitro* measurements[10-11]. *In vitro* methods include microdensitometry and HPLC[11]. Although *in vitro* methods can provide the most accurate MPOD values and the most detailed spatial distribution of MP, they require retinal tissue samples, which makes them unsuitable for use in living subjects, thereby limiting their widespread application[11]. As a result, there are very few studies that assess the *in vitro* measurements of MPOD. *In vivo* methods are further divided into subjective and objective approaches[12]. Subjective methods, also known as psychophysical techniques, include HFP, color matching, and minimum motion photometry. Objective methods, also known as optical techniques, include FR, FAF, RRS, and VEP based on electrophysiology[3,13-15].

Subjective Methods HFP is currently the most widely used method for measuring MPOD in clinical practice[14], and it is considered the standard technique for MPOD measurement[15]. HFP requires the test subject to perform luminance matching between flickering green and blue lights to measure MPOD at one or more eccentricities[44-45]. Although this technique has the advantages of high repeatability and good reliability[46], it also has notable limitations. First, the method requires training for participants and demands that they strictly follow detailed instructions, maintain focus, and fixate their gaze for an extended period[47]. Such strict requirements can be challenging for some individuals. Additionally, the technique has high visual acuity requirements, so it is difficult to apply to groups with impaired vision, such as patients with AMD or older individuals with glaucoma[47]. Furthermore, HFP rarely provides information about the spatial distribution of MPOD[48] and cannot distinguish the specific amounts of all pigments that constitute the MP[49].

The color matching requires participants to perform a color matching task by observing and adjusting light sources at the fovea and perifoveal areas to make the colors and brightness

appear identical. MPOD is then calculated by comparing the matching light intensity ratios between these two areas[50]. The minimum motion photometry requires participants to compare light at the peak absorption wavelength of MP with light that is not absorbed by MP. The radiance of the longer wavelength light is adjusted until the motion of the grating appears to slow down. MPOD is then measured by calculating the log ratio of the radiance required for equiluminance at the foveal and parafoveal positions[51-52]. Although both methods have the advantages of being simple and precise, it is clear that these two methods require responses from participants and depend on their subjective perception, leading to limitations similar to those of HFP[11].

FR Measurement FR measures MPOD by emitting light at specific wavelengths onto the macular region of the retina and utilizing the absorption characteristics of different tissues and pigments[53-54]. For this reason, FR is also referred to as single-wavelength reflectometry[13], and is also known as macular pigment reflectometry[49]. Based on different methods for calculating MPOD, FR can be divided into two approaches, namely the macula-to-periphery comparison method and the spectral method[55]. The comparison method measures MPOD by comparing the light reflection intensity between the macular region and the peripheral retina[12], while the spectral method quantifies the absorption of MP by analyzing the reflected light spectrum to directly obtain MPOD[46,49]. Although FR offers advantages such as fast measurement speed, high repeatability of results, and the ability to provide more precise measurements of carotenoid optical density[46], it also has certain limitations. One study has indicated that the Visucam 200 device, which is based on FR, provides higher repeatability and reliability for MPOD measurements under dilated conditions compared with measurements under non-dilation conditions[9]. Although MPOD can be measured without pupil dilation, the consistency of results before and after dilation is poor due to the effects of pupil size and intraocular light reflection[9], making pupil dilation necessary for FR measurements. Additionally, the intensity of blue light required for FR can be too bright for awake children[12]. To address this issue, Morita *et al*[12] have proposed a method for measuring MPOD using blue laser scanning images through the macula-to-periphery comparison approach. Their research has shown that reflectometry based on confocal scanning laser ophthalmoscopy is a feasible method for MPOD measurement, is suitable for children and patients with various retinal diseases, and does not require special equipment or procedures, demonstrating good clinical potential. However, the study had a limited sample size and did not conduct subgroup analyses based on gender, race, age, axial length, or refractive error, which may limit the generalizability of the results and prevent large-scale clinical application[12].

FAF Measurement FAF measurement uses the autofluorescent properties of lipofuscin in retinal epithelial cells and the attenuation of this fluorescence caused by the presence of MP to detect MPOD[56]. Specifically, blue and green light are sequentially used to illuminate the retina, taking advantage of the fact that blue light is strongly absorbed by MP, while green light is weakly absorbed. By measuring changes in lipofuscin fluorescence, the absorption of MP can be inferred[53], thereby enabling the measurement of MPOD. For this reason, FAF is sometimes referred to as two-wavelength fundus autofluorescence[57-58]. FAF is a relatively stable and reliable method for measuring MPOD[59], and has been shown to be consistent with results obtained using HFP[53]. Even in the presence of severe retinal pathologies such as exudative AMD or diabetic macular edema, FAF shows high repeatability[60-61]. Additionally, it requires minimal participation from the subject and can provide detailed information on the spatial distribution of MPOD[47]. Loskutova *et al*[47] used FAF to measure MPOD, and found that the optical density unit was 0.26 at a retinal eccentricity of 0.51°, whereas at 8.98°, the optical density unit increased to 4.452. This indicates that the measurement results were inconsistent before and after pupil dilation, with MPOD values measured by FAF varying as a function of pupil dilation in the same eye[47]. Therefore, accurate results with this technique require pupil dilation[47]. According to Obana *et al*[56], cataracts affect MPOD measurements based on Spectralis-MP autofluorescence imaging. Namely, before cataract surgery, MPOD levels were underestimated due to lens opacities, and postoperatively, MPOD levels increased in all patients, suggesting that FAF cannot accurately measure MPOD in patients with cataract. Although Obana *et al*[62] proposed a deep learning-based correction method to improve the accuracy of MPOD measurements in patients with cataract, and achieved satisfactory measurements with high-quality autofluorescence images, the method still had limitations, such as poor correction performance on low-quality images and a lack of diverse training samples. Thus, their approach is difficult to apply in clinical studies. Additionally, the high cost of FAF-based equipment limits its large-scale commercialization and widespread use[63].

RRS and VEP Measurements RRS measures MPOD by using a 488 nm laser to illuminate the retina and then detecting the Raman intensity scattered back from the carbon-carbon double bonds in carotenoid molecules, which is used to calculate MPOD[64]. However, this method is susceptible to age-related ocular factors, such as cataracts, which can affect its accuracy[65]. VEP uses luminance stimuli, such as red-green or blue-green combinations, adjusting the color and intensity to achieve visual isoelectric conditions, and processes

Table 3 Summary of MPOD measurement methods

MPOD measurement classification	Measurement method	Advantages	Limitations
In vitro	Microdensitometry	Precise MPOD values and detailed MP spatial distribution	Requires retinal tissue samples, not applicable *in vivo*
	High-performance liquid chromatography		
In vivo subjective methods	Heterochromatic flicker photometry	Widely used, high repeatability and reliability	Requires training and high focus, difficult for patients with visual impairment, limited spatial data, no pigment differentiation
	Color matching	Simple and accurate	Depends on subjective perception
	Minimum motion photometry		
In vivo objective methods	Fundus reflectometry	Fast measurement, high repeatability, measures MP optical density	Requires pupil dilation for consistent results, high blue light intensity can be uncomfortable
	Fundus autofluorescence	Reliable, repeatable, minimal participant involvement, provides spatial MPOD data, works for retinal diseases	Affected by pupil dilation, inaccurate for cataracts, expensive
	Resonance Raman spectroscopy	Objective and noninvasive	Lack of large-scale clinical validation, high equipment cost, complex operation
	Visual evoked potentials		

MPOD: Macular pigment optical density; MP: Macular pigment.

the recorded electrical responses through Fourier analysis to assess neural activity at different retinal eccentricities, from which MPOD is calculated[66]. Although both methods provide objective and noninvasive measurement options, they lack large-scale clinical studies to fully validate their effectiveness and reliability for MPOD measurement. The methods are further limited by high equipment costs and operational complexity[11], which has resulted in fewer studies using these methods directly for MPOD measurement in recent years.

Summary of Current MPOD Measurement Techniques MPOD measurement techniques were summarized in Table 3. *In vitro* measurement methods, such as microdensitometry and HPLC, provide accurate data but are limited by the need for tissue samples. Among *in vivo* measurement methods, subjective techniques such as HFP are commonly used, but they rely on the subject's subjective responses, which limits their applicability. Although objective methods, such as FR and FAF, have improved in terms of measurement accuracy and stability, they face challenges such as the need for pupil dilation, limitations when applied to patients with specific eye diseases, and the complexity and high cost of the testing equipment. While recent studies have proposed improvements based on traditional MPOD measurement techniques, such as a deep learning-based correction method to enhance the accuracy of FAF in cataract patients and an improved FR method that utilizes blue laser scanning images to measure MPOD by comparing the macula and peripheral regions, these methods are still in the early stages of research and have not fully overcome the limitations of the existing technologies. Therefore, with the growing recognition of MPOD's importance in eye health, it is becoming increasingly important to develop a new measurement method. New methods should have the ability to accurately measure MPOD *in vivo* without the need for complex preparations like pupil dilation, while also simplifying operational procedures, reducing equipment costs, and being suitable for subjects with various vision conditions. Such advancements would improve the accessibility and practicality of MPOD measurements and could foster further research and clinical applications in related fields.

PROSPECTS FOR ARTIFICIAL INTELLIGENCE-BASED MPOD MEASUREMENT TECHNOLOGY

Advances in Artificial Intelligence for Medical Image Recognition In recent years, with the rapid development of artificial intelligence (AI) technology and the gradual maturation of deep-learning algorithms, deep learning-based image recognition technology has been the subject of extensive research in the field of medical image analysis. Deep learning in medical image analysis can be broadly categorized into four areas—classification, segmentation, detection, and registration—used to distinguish disease types, precisely extract lesions, locate lesions, and align multimodal images, respectively[67]. These technologies have demonstrated utility in areas such as cardiovascular disease diagnosis[68], retinal image screening[69], and histopathological analysis[70], greatly advancing research and clinical applications in these fields. For example, Ghorbani *et al*[71] utilized image recognition technology with a hybrid convolutional neural network model to analyze a large volume of echocardiography data. They employed data augmentation techniques to enhance the model's generalization ability and used sensitivity maps to interpret the model's prediction process. Their system was identified localized cardiac structures, accurately estimated cardiac functions such as left ventricular volume and ejection fraction, and predicted systemic features such as age, gender, weight, and height from cardiac images. The final evaluation

showed that the model exhibited excellent predictive performance and interpretability, providing new possibilities for the automated interpretation and risk assessment of cardiac imaging[71]. Similarly, Liu *et al*[72] proposed an AI-based method for spatially aware joint segmentation of the optic disc and cup in fundus images. By using a dilated convolutional neural network to extract spatial structural features and a pyramid filtering model to capture multiscale information, this method addressed the complex vascular layout and sparse optic cup boundary issues in optic nerve head images and improved segmentation accuracy. Their model performed well across multiple datasets and achieved improvements in the accuracy of glaucoma screening[72], which is a typical example of a segmentation task for extracting biomarkers from biomedical images. Thus, an MPOD measurement technique can be developed based on fundus images, utilizing image recognition algorithms to analyze these images and achieve automated MPOD measurement, while generating detailed eye health reports.

Advantages and Prospects of a New Method for Measuring MPOD Based on Fundus Images Pang *et al*[16] developed and applied for a utility patent titled "A Method and Device for Measuring Macular Pigment Density Based on Fundus Images". The patent utilizes deep learning-based image recognition technology. First, the neural network model is trained on a large amount of labeled data, enabling it to automatically extract and identify features in fundus images. With this neural network model, automatic segmentation of the macular and foveal regions can be achieved. Then, by measuring the distance and positional relationship between the macular region and the center of the fovea, the boundaries of these areas are further defined. After segmentation, the system extracts the color values of the blue and green channels from these regions, which reflect the area's reflection characteristics for specific wavelengths of light. Finally, the MPOD is calculated by determining the ratio of the blue-to-green channel color values and using a logarithmic relationship, followed by normalization to eliminate the impact of different imaging devices and conditions. This patent proposes a noninvasive, objective method for measuring MPOD. In contrast to traditional objective methods that measure MPOD by projecting light of specific wavelengths onto the retina and rely on precise optical instruments to detect the intensity of reflected light, the patented method eliminates the need for light sources and photodetection equipment by introducing AI technology, which uses neural network models to identify the macular and foveal regions in fundus images and calculates MPOD based on the color values from these regions. Therefore, this approach provides a novel technological pathway for MPOD measurement.

The patented MPOD measurement method has several advantages over traditional methods. First, compared with traditional subjective methods, which require patients to maintain prolonged visual fixation or perform complex visual target observations, the fundus image-based MPOD measurement process is short and requires minimal patient cooperation, reducing discomfort and fatigue, thereby increasing the acceptability of the measurement. This makes it particularly suitable for special populations such as the elderly and children, while still providing good noninvasive qualities and user-friendliness. Second, unlike objective methods that require complex optical equipment, the patented method only requires standard fundus images taken by a fundus camera to measure MPOD. With the rapid development of handheld fundus cameras and smartphone-based fundus imaging technologies, fundus cameras are becoming more portable and affordable, greatly reducing the cost of acquiring fundus images and facilitating the widespread adoption and application of fundus imaging technologies[73-74]. To account for performance differences across various fundus cameras, the patented method also incorporates deep learning-based image recognition technology to accurately segment target regions and normalize the final measurement results, reducing errors due to image quality and improving measurement accuracy and repeatability. Additionally, traditional objective methods are influenced by pupil size, but with advancements in fundus camera technology, modern cameras have made improvements in optical design and imaging methods, allowing high-quality fundus images to be captured without the need for pharmacological pupil dilation[75-76], greatly simplifying the MPOD measurement process and improving convenience.

Although the existing fundus image-based MPOD measurement methods have helped reduce costs and improve convenience, there is still room for further optimization and development. First, more advanced object detection algorithms could be introduced to optimize the detection and segmentation of the macular and foveal regions. You Only Look Once (YOLO) is one of the most commonly used object detection algorithms. It efficiently achieves multi-object detection by dividing the image into multiple grid cells and completing both object localization and classification through a single neural network forward pass, which offers the advantage of maintaining high detection speed while providing high detection accuracy[77-79]. The algorithm has been iterated rapidly, with each version, from YOLO-v1 released in 2015 to YOLO-v8 in 2023, introducing new improvements to further enhance detection accuracy, speed, and computational efficiency[77]. Based on YOLO, Sobek *et al*[80] developed a medical image object detection system called MedYOLO designed specifically for object detection

in medical imaging data. This system generates bounding boxes for different organs and structures to achieve fast and accurate multi-object detection in complex medical images, and has demonstrated excellent performance across various medical imaging datasets[80]. Region-CNN (R-CNN) is a class of object detection methods based on convolutional neural networks (CNN). It includes variants like Mask R-CNN, Fast R-CNN, and Faster R-CNN, that identify objects in images using a region proposal mechanism with selective search to generate candidate regions, extract features from each region, and perform classification and bounding box regression; these models have been used to analyze large-scale image datasets[81-83]. In addition to these two algorithms, others like SSD (Single Shot MultiBox Detector)[84] and RetinaNet[85] have also been applied in the medical research field. Second, the applicability of fundus image-based MPOD measurement methods for special cases requires further exploration and validation. For example, in patients with cataract, lens opacities cause blurred retinal imaging[86], posing major challenges for the accurate segmentation of the macular and foveal regions and the extraction of color values. To address these issues, AI technology can be used to automatically optimize fundus image quality and improve the model's applicability to various complex cases and enhance the accuracy and robustness of MPOD measurements. Additionally, multispectral imaging technology could be incorporated to capture more comprehensive spectral information. Lastly, to expand the application scenarios of this system, real-time retinal health information display functionality could be developed based on the existing technology. As mentioned earlier, MPOD is closely related to various eye diseases. Therefore, by using AI technology to generate eye health reports after real-time MPOD measurement, early screening for multiple eye diseases could be facilitated, improving diagnostic efficiency and accuracy.

As AI technology continues to advance in the medical field, MPOD measurement will increasingly integrate with AI. Fundus image-based MPOD measurement offers advantages over traditional methods and clearly points to the future direction of this technology. By optimizing object detection algorithms, improving applicability for special cases, incorporating multispectral imaging, and expanding application scenarios, the application of MPOD measurement technology can be further improved.

CONCLUSION

MPOD has been shown to be closely related to various eye diseases and serves as an effective biomarker for numerous ocular conditions and health statuses. Traditional MPOD measurement methods have useful applications as well as limitations. While recent studies have introduced improvements and optimizations to these methods, issues such as high equipment costs and complex procedures remain unresolved. New MPOD measurement methods based on fundus imaging combined with image recognition technology may overcome some of the shortcomings of traditional methods and show promise as the future direction for MPOD measurement. However, this technology still requires further optimization and expansion to better facilitate its widespread application in both clinical practice and research.

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REFERENCES

1 Hu W, Shankar P, Yao Y, *et al*. Effect of xanthophyll-rich food and supplement intake on visual outcomes in healthy adults and those with eye disease: a systematic review, meta-analysis, and meta-regression of randomized controlled trials. *Nutr Rev* 2023;82(1):34-46.

2 Wilson MR, Sandberg KA, Foutch BK. Macular pigment optical density and visual quality of life. *J Optom* 2021;14(1):92-99.

3 Masri A, Armanazi M, Inouye K, *et al*. Macular pigment optical density as a measurable modifiable clinical biomarker. *Nutrients* 2024;16(19):3273.

4 Li X, Holt RR, Keen CL, *et al*. Potential roles of dietary zeaxanthin and lutein in macular health and function. *Nutr Rev* 2023;81(6):670-683.

5 Eraslan N, Yilmaz M, Celikay O. Assessment of macular pigment optical density of primary open-angle glaucoma patients under topical medication. *Photodiagnosis Photodyn Ther* 2023;42:103585.

6 Zhang Y, Hao J, Cao K, *et al*. Macular pigment optical density responses to different levels of zeaxanthin in patients with high myopia. *Graefes Arch Clin Exp Ophthalmol* 2022;260(7):2329-2337.

7 Mares J. Lutein and zeaxanthin isomers in eye health and disease. *Annu Rev Nutr* 2016;36:571-602.

8 Bikbov MM, Gilmanshin TR, Zainullin RM, *et al*. Macular pigment optical density and its determinants in a Russian population: the ural eye and medical study. *Acta Ophthalmol* 2022;100(8): e1691-e1700.

9 Huang H, Guan C, Ng DS, *et al*. Macular pigment optical density measured by a single wavelength reflection photometry with and without mydriasis. *Curr Eye Res* 2019;44(3):324-328.

10 Polat Gultekin B, Sahli E. Macular pigment optical density in central serous chorioretinopathy. *Ther Adv Ophthalmol* 2021;13:2515841421997195.

11 Howells O, Eperjesi F, Bartlett H. Measuring macular pigment optical density *in vivo*: a review of techniques. *Graefes Arch Clin Exp Ophthalmol* 2011;249(3):315-347.

12 Morita H, Matsushita I, Fujino Y, *et al*. Measuring macular pigment optical density using reflective images of confocal scanning laser system. *Jpn J Ophthalmol* 2024;68(1):19-25.

13 Varghese M, Antony J. Assessment of macular pigment optical density using fundus reflectometry in diabetic patients. *Middle East Afr J Ophthalmol* 2019;26(1):2-6.

14 Christaras D, Ginis H, Pennos A, *et al*. Objective method for measuring the macular pigment optical density in the eye. *Biomed Opt Express* 2019;10(7):3572-3583.

15 Tsujinaka H, Saeki K, Obayashi K, *et al*. Positive association between macular pigment optical density and glomerular filtration rate: a cross-sectional study. *J Clin Med* 2023;12(16):5312.

16 Pang XQ, Xiong JH, Zhao X, *et al*. A method and device for measuring macular pigment density based on fundus images. China patent CN202010257198.7. 2020 Apr 3.

17 Hu W, Seah V, Huang V, *et al*. Effect of antioxidant supplementation on macular pigment optical density and visual functions: a systematic review and network meta-analysis of randomized controlled trials. *Adv Nutr* 2024;15(5):100216.

18 Lopresti AL, Smith SJ. The effects of lutein/zeaxanthin (Lute-gen®) on eye health, eye strain, sleep quality, and attention in high electronic screen users: a randomized, double-blind, placebo-controlled study. *Front Nutr* 2025;12:1522302.

19 Rinaldi M, Cennamo G, Passaro ML, *et al*. Changes in macular pigment optical density after full-thickness macular hole closure using inverted flap technique. *Photodiagnosis Photodyn Ther* 2024;45:103950.

20 Wilson LM, Tharmarajah S, Jia Y, *et al*. The effect of lutein/zeaxanthin intake on human macular pigment optical density: a systematic review and meta-analysis. *Adv Nutr* 2021;12(6):2244-2254.

21 Kedarisetti KC, Narayanan R, Stewart MW, *et al*. Macular telangiectasia type 2: a comprehensive review. *Clin Ophthalmol* 2022;16:3297-3309.

22 Nagai N, Minami S, Suzuki M, *et al*. Macular pigment optical density and photoreceptor outer segment length as predisease biomarkers for age-related macular degeneration. *J Clin Med* 2020;9(5):1347.

23 Sawa M, Shunto T, Nishiyama I, *et al*. Effects of lutein supplementation in Japanese patients with unilateral age-related macular degeneration: the Sakai lutein study. *Sci Rep* 2020;10(1):5958.

24 Ma L, Liu R, Du JH, *et al*. Lutein, zeaxanthin and meso-zeaxanthin supplementation associated with macular pigment optical density. *Nutrients* 2016;8(7):426.

25 Hong IH, Jung WH, Lee JH, *et al*. Macular pigment optical density in the Korean population: a cross sectional study. *J Korean Med Sci* 2020;35(5):e30.

26 Fung TH, Patel B, Wilmot EG, *et al*. Diabetic retinopathy for the non-ophthalmologist. *Clin Med* (*Lond*) 2022;22(2):112-116.

27 Li LH, Lee JC, Leung HH, *et al*. Lutein supplementation for eye diseases. *Nutrients* 2020;12(6):1721.

28 Fung AT, Yang Y, Kam AW. Central serous chorioretinopathy: a review. *Clin Exp Ophthalmol* 2023;51(3):243-270.

29 Ji Y, Gan Y, Su Y, *et al*. Investigation of serum and macular carotenoids in central serous chorioretinopathy. *Front Med* (*Lausanne*) 2022;9:805305.

30 Sasamoto Y, Gomi F, Sawa M, *et al*. Macular pigment optical density in central serous chorioretinopathy. *Invest Ophthalmol Vis Sci* 2010;51(10):5219-5225.

31 Jayaram H, Kolko M, Friedman DS, *et al*. Glaucoma: now and beyond. *Lancet* 2023;402(10414):1788-1801.

32 Schuster AK, Erb C, Hoffmann EM, *et al*. The diagnosis and treatment of glaucoma. *Dtsch Arztebl Int* 2020;117(13):225-234.

33 Liu Y, Lawler T, Liu Z, *et al*. Low macular pigment optical density is associated with manifest primary open-angle glaucoma in older women. *Curr Dev Nutr* 2024;8(6):103789.

34 Lawler T, Mares JA, Liu Z, *et al*. Association of macular pigment optical density with retinal layer thicknesses in eyes with and without manifest primary open-angle glaucoma. *BMJ Open Ophthalmol* 2023;8(1):e001331.

35 Zeki Fikret C, Ucgun NI. Macular pigment optical density change analysis in primary open-angle glaucoma and pseudoexfoliation glaucoma. *Int Ophthalmol* 2021;41(6):2235-2240.

36 Srinivasan R, Teussink MM, Sloan KR, *et al*. Distribution of macular pigments in macular telangiectasia type 2 and correlation with optical coherence tomography characteristics and visual acuity. *BMC Ophthalmol* 2022;22(1):264.

37 Heeren TFC, Tzaridis S, Bonelli R, *et al*. Dark-adapted two-color fundus-controlled perimetry in macular telangiectasia type 2. *Invest Ophthalmol Vis Sci* 2019;60(5):1760-1767.

38 Benoudis L, Ingrand P, Jeau J, *et al*. Relationships between macular pigment optical density and lacquer cracks in high myopia. *J Fr Ophtalmol* 2016;39(7):615-621.

39 Johnson EJ, Avendano EE, Mohn ES, *et al*. The association between macular pigment optical density and visual function outcomes: a systematic review and meta-analysis. *Eye (Lond)* 2021;35(6):1620-1628.

40 García-Romera MC, Silva-Viguera MC, López-Izquierdo I, *et al*. Effect of macular pigment carotenoids on cognitive functions: a systematic review. *Physiol Behav* 2022;254:113891.

41 Nagai N, Asato T, Minami S, *et al*. Correlation between macular pigment optical density and neural thickness and volume of the retina. *Nutrients* 2020;12(4):888.

42 Al-Hassan A, Vyas R, Zhang Y, *et al*. Assessment of maternal macular pigment optical density (MPOD) as a potential marker

for dietary carotenoid intake during lactation in humans. *Nutrients* 2021;14(1):182.

43 Barnett SM, Khan NA, Walk AM, *et al*. Macular pigment optical density is positively associated with academic performance among preadolescent children. *Nutr Neurosci* 2018;21(9):632-640.

44 Beirne RO, McConnell E. Investigation of the relationship between macular pigment levels and rod-mediated dark adaptation in intermediate age-related macular degeneration. *Clin Exp Optom* 2019;102(6):611-616.

45 Marta-C GR, Úrsula TP, Victor PG. Effect of Mediterranean diet and blue light exposition on macular pigment optical density values in a Spanish childhood population. *Heliyon* 2024;10(1):e23361.

46 Davey PG, Rosen RB, Gierhart DL. Macular pigment reflectometry: developing clinical protocols, comparison with heterochromatic flicker photometry and individual carotenoid levels. *Nutrients* 2021;13(8):2553.

47 Loskutova E, Butler JS, Hernandez Martinez G, *et al*. Macular pigment optical density fluctuation as a function of pupillary mydriasis: methodological considerations for dual-wavelength autofluorescence. *Curr Eye Res* 2021;46(4):532-538.

48 Bernstein PS, Li B, Vachali PP, *et al*. Lutein, zeaxanthin, and meso-zeaxanthin: the basic and clinical science underlying carotenoid-based nutritional interventions against ocular disease. *Prog Retin Eye Res* 2016;50:34-66.

49 Sanabria JC, Bass J, Spors F, *et al*. Measurement of carotenoids in perifovea using the macular pigment reflectometer. *J Vis Exp* 2020(155).

50 Davies NP, Morland AB. Color matching in diabetes: optical density of the crystalline lens and macular pigments. *Invest Ophthalmol Vis Sci* 2002;43(1):281-289.

51 Robson AG, Harding G, van Kuijk FJ, *et al*. Comparison of fundus autofluorescence and minimum-motion measurements of macular pigment distribution profiles derived from identical retinal areas. *Perception* 2005;34(8):1029-1034.

52 Robson AG, Holder GE, Moreland JD, *et al*. Chromatic VEP assessment of human macular pigment: comparison with minimum motion and minimum flicker profiles. *Vis Neurosci* 2006;23(2):275-283.

53 Obana A, Gellermann W, Gohto Y, *et al*. Reliability of a two-wavelength autofluorescence technique by Heidelberg Spectralis to measure macular pigment optical density in Asian subjects. *Exp Eye Res* 2018;168:100-106.

54 Wang C, Yu J, Pan M, *et al*. Macular pigment optical density of hyperopic anisometropic amblyopic patients measured by fundus reflectometry. *Front Med* (*Lausanne*) 2022;9:991423.

55 Dennison JL, Stack J, Beatty S, *et al*. Concordance of macular pigment measurements obtained using customized heterochromatic flicker photometry, dual-wavelength autofluorescence, and single-wavelength reflectance. *Exp Eye Res* 2013;116:190-198.

56 Obana A, Gohto Y, Sasano H, *et al*. Grade of cataract and its influence on measurement of macular pigment optical density using autofluorescence imaging. *Invest Ophthalmol Vis Sci* 2018;59(7):3011-3019.

57 Obana A, Nakazawa R, Noma S, *et al*. Macular pigment in eyes with macular hole formation and its change after surgery. *Transl Vis Sci Technol* 2020;9(11):28.

58 Müller S, Charbel Issa P, Heeren TFC, *et al*. Macular pigment distribution as prognostic marker for disease progression in macular telangiectasia type 2. *Am J Ophthalmol* 2018;194:163-169.

59 Loughman J, Loskutova E, Butler JS, *et al*. Macular pigment response to lutein, zeaxanthin, and meso-zeaxanthin supplementation in open-angle glaucoma: a randomized controlled trial. *Ophthalmol Sci* 2021;1(3):100039.

60 Green-Gomez M, Bernstein PS, Curcio CA, *et al*. Standardizing the assessment of macular pigment using a dual-wavelength autofluorescence technique. *Transl Vis Sci Technol* 2019;8(6):41.

61 Conrady CD, Bell JP, Besch BM, *et al*. Correlations between macular, skin, and serum carotenoids. *Invest Ophthalmol Vis Sci* 2017;58(9):3616-3627.

62 Obana A, Ote K, Gohto Y, *et al*. Deep learning-based correction of cataract-induced influence on macular pigment optical density measurement by autofluorescence spectroscopy. *PLoS One* 2024;19(2):e0298132.

63 Arunkumar R, Calvo CM, Conrady CD, *et al*. What do we know about the macular pigment in AMD: the past, the present, and the future. *Eye* (*Lond*) 2018;32(5):992-1004.

64 Tanito M, Obana A, Gohto Y, *et al*. Macular pigment density changes in Japanese individuals supplemented with lutein or zeaxanthin: quantification *via* resonance Raman spectrophotometry and autofluorescence imaging. *Jpn J Ophthalmol* 2012;56(5):488-496.

65 Obana A, Gohto Y, Tanito M, *et al*. Effect of age and other factors on macular pigment optical density measured with resonance Raman spectroscopy. *Graefes Arch Clin Exp Ophthalmol* 2014;252(11):1867.

66 Robson AG, Parry NR. Measurement of macular pigment optical density and distribution using the steady-state visual evoked potential. *Vis Neurosci* 2008;25(4):575-583.

67 Chen X, Wang X, Zhang K, *et al*. Recent advances and clinical applications of deep learning in medical image analysis. *Med Image Anal* 2022;79:102444.

68 Litjens G, Ciompi F, Wolterink JM, *et al*. State-of-the-art deep learning in cardiovascular image analysis. *JACC Cardiovasc Imaging* 2019;12(8 Pt 1):1549-1565.

69 Li T, Bo W, Hu C, *et al*. Applications of deep learning in fundus images: a review. *Med Image Anal* 2021;69:101971.

70 Srinidhi CL, Ciga O, Martel AL. Deep neural network models for computational histopathology: a survey. *Med Image Anal* 2021;67:101813.

71 Ghorbani A, Ouyang D, Abid A, *et al*. Deep learning interpretation of echocardiograms. *NPJ Digit Med* 2020;3:10.

72 Liu Q, Hong X, Li S, *et al*. A spatial-aware joint optic disc and cup segmentation method. *Neurocomputing* 2019;359:285-297.

73 Wintergerst MWM, Jansen LG, Holz FG, *et al*. Smartphone-based fundus imaging-where are we now. *Asia Pac J Ophthalmol* (*Phila*) 2020;9(4):308-314.

74 Naz H, Nijhawan R, Ahuja NJ. Clinical utility of handheld fundus and smartphone-based camera for monitoring diabetic retinal diseases: a review study. *Int Ophthalmol* 2024;44(1):41.

75 Jin K, Lu H, Su Z, *et al*. Telemedicine screening of retinal diseases with a handheld portable non-mydriatic fundus camera. *BMC Ophthalmol* 2017;17(1):89.

76 Lin TC, Chiang YH, Hsu CL, *et al*. Image quality and diagnostic accuracy of a handheld nonmydriatic fundus camera: Feasibility of a telemedical approach in screening retinal diseases. *J Chin Med Assoc* 2020;83(10):962-966.

77 Hussain M. YOLO-v1 to YOLO-v8, the rise of YOLO and its complementary nature toward digital manufacturing and industrial defect detection. *Machines* 2023;11(7):677.

78 Diwan T, Anirudh G, Tembhurne JV. Object detection using YOLO: challenges, architectural successors, datasets and applications. *Multimed Tools Appl* 2023;82(6):9243-9275.

79 Shao YH, Zhang D, Chu HY, *et al*. A review of YOLO object detection based on deep learning. *Journal of Electronics & Information Technology* 2022;44(10):3697-3708.

80 Sobek J, Medina Inojosa JR, Medina Inojosa BJ, *et al*. MedYOLO: a medical image object detection framework. *J Imaging Inform Med* 2024;37(6):3208-3216.

81 Girshick R. *Fast R-CNN*. 2015 IEEE International Conference on Computer Vision (ICCV). https://ieeexplore.ieee.org/document/7410526. Accessed on 7-13 Dec. 2015.

82 Ren S, He K, Girshick R, *et al*. Faster R-CNN: towards real-time object detection with region proposal networks. *IEEE Trans Pattern Anal Mach Intell* 2017;39(6):1137-1149.

83 He K, Gkioxari G, Dollár P, *et al*. Mask R-CNN. *IEEE Trans Pattern Anal Mach Intell* 2020;42(2):386-397.

84 Nagrath P, Jain R, Madan A, *et al*. SSDMNV2: a real time DNN-based face mask detection system using single shot multibox detector and MobileNetV2. *Sustain Cities Soc* 2021;66:102692.

85 Sirazitdinov I, Kholiavchenko M, Mustafaev T, *et al*. Deep neural network ensemble for pneumonia localization from a large-scale chest X-ray database. *Computers & Electrical Engineering* 2019;78:388-399.

86 Mitra A, Roy S, Roy S, *et al*. Enhancement and restoration of non-uniform illuminated Fundus Image of Retina obtained through thin layer of cataract. *Comput Methods Programs Biomed* 2018;156:169-178.