Review

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Posted Date: 10 July 2024

doi: 10.20944/preprints202407.0822.v1

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Macular Pigment Optical Density a Measurable Modifiable Clinical Biomarker

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Abstract: The macular pigment optical density (MPOD) signifies a vital component of macular well-being and high-resolution visual acuity. MPOD can serve as a reliable biomarker for assessing the retinal defense mechanisms against oxidative stress and the deleterious effects of excessive light exposure. Elevated MPOD levels offer robust protection against the onset and progression of age-related macular degeneration (AMD) a prevalent cause of vision impairment among the elderly population. MPOD's implications in diverse ocular conditions, including diabetic retinopathy and glaucoma, have been explored and indicate a real need for clinical measurement of MPOD. This review looks at the potential of MPOD as a modifiable biomarker influencing the progression and onset of these conditions, particularly in the context of oxidative stress and retinal ischemia. The integration of MPOD measurement into routine eye examinations presents an unparalleled opportunity for early disease detection, precise treatment planning, and longitudinal disease monitoring. Emerging technologies and longitudinal investigations promise to elucidate the dynamic nuances of MPOD in the context of age-related ocular diseases.

Keywords: MPOD; lutein; zeaxanthin; biomarker; glaucoma; diabetic retinopathy

1. Introduction

1.1. Structure:

The macular pigment, a yellowish deposit in the central retina, arises from the collective presence of carotenoid pigments strategically accumulated within the macular region [1]. These pigments exhibit distinct absorption spectra, aiding their identification and quantification [2]. Lutein, zeaxanthin, and meso-zeaxanthin compromise the macular pigment [2,3]. Lutein, a xanthophyll carotenoid, is known for its antioxidant abilities and light-filtering properties. Zeaxanthin, a close relative, exhibits similar characteristics and is particularly enriched in the central foveal region of the macula [4]. Meso-zeaxanthin, although structurally akin to zeaxanthin, is found in extremely lower quantities if any from dietary sources but is synthesized from lutein in the retina [1]. This interconversion of lutein to meso-zeaxanthin may be especially advantageous for diets that are dominated by lutein rich sources [1]. Notably however, this conversion is not shown in other locations particularly meso-zeaxanthin is starkly absent in brain [5]. Collectively, these pigments bolster ocular defense mechanisms by using reactive oxygen species and absorbing blue light, thereby protecting against oxidative stress and potential retinal damage [6].

1.2. Nutrition:

The journey of these pigments into the retina begins with dietary intake. Rich sources of lutein and zeaxanthin (L/Z) include leafy green vegetables such as spinach, kale, and collard greens, along with other vibrant fruits and vegetables [3]. However, meso-zeaxanthin's primary origin lies within

 doi:10.20944/preprints202407.0822.v1

the retina, where it is synthesized from lutein, as it is not commonly found in substantial quantities within typical diets [1]. The intricate interplay between dietary intake, transport, and metabolism influences the availability of these carotenoids for ocular uptake. Bioavailability studies reveal that factors such as food matrix, cooking methods, and individual genetics can affect the extent to which these carotenoids are absorbed and utilized by the body [7–10].

To better understand the effects of L/Z intake on the macular pigment density, it is important to know about the dietary sources of L/Z. In the past, nutritional analysis has reported L/Z as one value as analytical procedures had not permitted for the evaluation of them separately. Perry et al., have conducted testing to determine their individual quantities in food [11]. Given that L/Z accumulates in different regions of the retina and that they serve different functions it is important to assess their individual quantity [4,12,13]. As seen in Table 1, there is a stark difference in the foods that contain L/Z, with most foods containing lutein but not zeaxanthin. This in part explains why dietary intake in the standard American diet is lower in zeaxanthin and higher in lutein, despite there being a higher level of zeaxanthin in the central fovea thus emphasizing its importance in health maintenance of the eye.

Table 1. L/Z quantities in commonly consumed food.

Figure 100.	**Trans-Lutein (ug per 100g)**	**Trans-Zeaxanthin (ug per 100g)**	**L/Z Ratio**
Asparagus, cooked	991	0	-
Broccoli, cooked	772	0	-
Cucumber	361	0	-
Spinach, cooked	12,640	0	-
Spinach, raw	6,603	0	-
Tomato, raw	32	0	-
Lettuce, romaine	3,824	0	-
Lettuce, iceberg	171	12	14.3
Green beans, cooked from frozen	306	0	-
Kale, cooked	8,884	0	-
Pepper, orange	208	1,665	0.1
Pepper, green	173	0	-
Bread, white	15	0	-
Egg (yolk + white), cooked	237	216	1.1
Egg yolk, cooked	645	587	1.1
Pistachio, shelled	1405	0	-
Grapes, green	53	6	8.8
Cilantro	7703	0	-
Lima beans, cooked	155	0	-
Olive, green	79	0	-
Parsley, raw	4326	0	-
Squash, yellow, cooked	150	0	-
Zucchini, cooked with skin	1355	0	-

* Abbreviations: L/Z= Lutein/Zeaxanthin, ug= microgram; Data obtained from: [11].

The bioavailability of carotenoids has been shown to be significantly increased when consumed with foods containing fat [7,8]. Despite eggs having a lower L/Z content, their fat content allows them to significantly increase L/Z levels. A study by Goodrow et al. showed that consuming one egg per

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day over five weeks increased plasma levels of lutein by 26% and zeaxanthin by 38% [14]. It has also been shown that the bioavailability of carotenoids decreases due to competition for absorption when different carotenoids are consumed in the same meal [10,15]. Heat plays an interesting role as it has been shown to decrease carotenoid content but significantly increases carotenoid bioavailability [8]. Dietary fiber has been shown to have a negative effect on the absorption of carotenoids as seen in Riedl et al. with a 40-74% decrease in plasma levels of lutein when these carotenoids were consumed with water soluble fibers such as pectin, guar, and alginate [10].

2.1. Macular Pigment Optical Density (MPOD):

The carotenoids lutein, zeaxanthin and meso-zeaxanthin form the macular pigment. Macular pigment's optical density (MPOD) is an assessment of the strength of the presence of these carotenoids in an individual. This metric can be measured clinically, and it can be used as a clinical biomarker for ocular disease, ocular performance, and effects of systemic disease. If the macular pigment were to be used as a clinical biomarker it would be imperative to be able to obtain accurate and consistent measurements of a patients MPOD.

2.2. Measurement of MPOD:

There are several techniques to measure MPOD levels. These techniques can be split into psychophysical vs objective techniques, each with their pros and cons. Psychophysical techniques include methods like Heterochromatic Flicker Photometry (HFP) and Minimum Notion Photometry (MNP). These techniques gauge macular pigment density by exploiting visual perception phenomena in response to specific stimulus conditions. While psychophysical methods offer insights into pigment distribution, they may be affected by individual variations in visual perception. Objective techniques include methods such as Fundus Reflectometry (FR), Fundus Autofluorescence (FAF) and Resonance Raman Spectroscopy (RRS).

Heterochromatic Flicker Photometry (HFP) is the most widely used psychophysical method that relies on color sensitivity modulation. It involves presenting a flickering stimulus comprising two lights with different wavelengths. By varying the intensity of one light, the point at which the flicker disappears is indicative of the macular pigment's absorption [16,17]. Its advantages include directly measuring overall macular pigment density, non-invasiveness, and relative simplicity to perform, as demonstrated by a large body of research [17].

Fundus Reflectometry (FR) is an objective technique that measures the amount of light reflected from the fundus. Light that is reflected from a part of the retina is compared to light reflected from the fovea. Because the fovea absorbs certain wavelengths of light at different wavelengths compared to the retina, the difference in reflected light can be used to determine the MPOD [18,19]. Studies have compared the widely used technique of HFP to FR and found that there was a significant correlation between these techniques, indicating FR as an objective, accurate, and reliable measurement tool for MPOD [12,13,20].

Resonance Raman Spectroscopy (RRS) is a technique that leverages the resonance Raman scattering properties of the macular pigments to assess their concentrations [21]. Laser light of specific wavelengths is directed at the retina causing the pigments to resonate and emit scattered light with altered frequencies [22]. By measuring this altered light, the density of pigments can be quantified [22]. While resonance Raman spectroscopy offers excellent sensitivity to changes in pigment density and allows for precise spatial mapping of MPOD, its complexity and dependence on sensitive, specialized, expensive equipment can pose challenges.

Fundus Autofluorescence (FAF) capitalizes on the phenomenon of autofluorescence exhibited by macular pigments. Pigments, when exposed to specific wavelengths of light, emit light of a longer wavelength [23]. FAF captures this emitted light and uses it as a surrogate marker for macular pigment density [23]. This technique is non-invasive and can be integrated into routine clinical examinations. However, the accuracy of the measurement is limited by variations in autofluorescence across individuals and by factors like aging and retinal health [19]. Davey et al. examined the precision and inter-eye-correlation of MPOD, finding that measurements using HFP had excellent

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short-term repeatability, and that the MPOD value of one eye could predict the value of the fellow eye with 89% accuracy [24]. MPOD, however, was not correlated with ocular dominance [24].

3.1. MPOD in Ocular and Systemic Disease:

Understanding the intricate relationship between MPOD and various aspects of eye health is paramount for deciphering the potential impact of pigment density on ocular diseases and conditions. This section delves into the multifaceted connection between MPOD and ocular health exploring its protective role against AMD, its potential as a biomarker for AMD risk assessment and progression, and its influence on other ocular conditions such as diabetic retinopathy and glaucoma. Figure 1 illustrates how environmental and disease processes interact to increase or decrease MPOD, demonstrating how MPOD can be used as a clinical biomarker for many ocular and systemic conditions.

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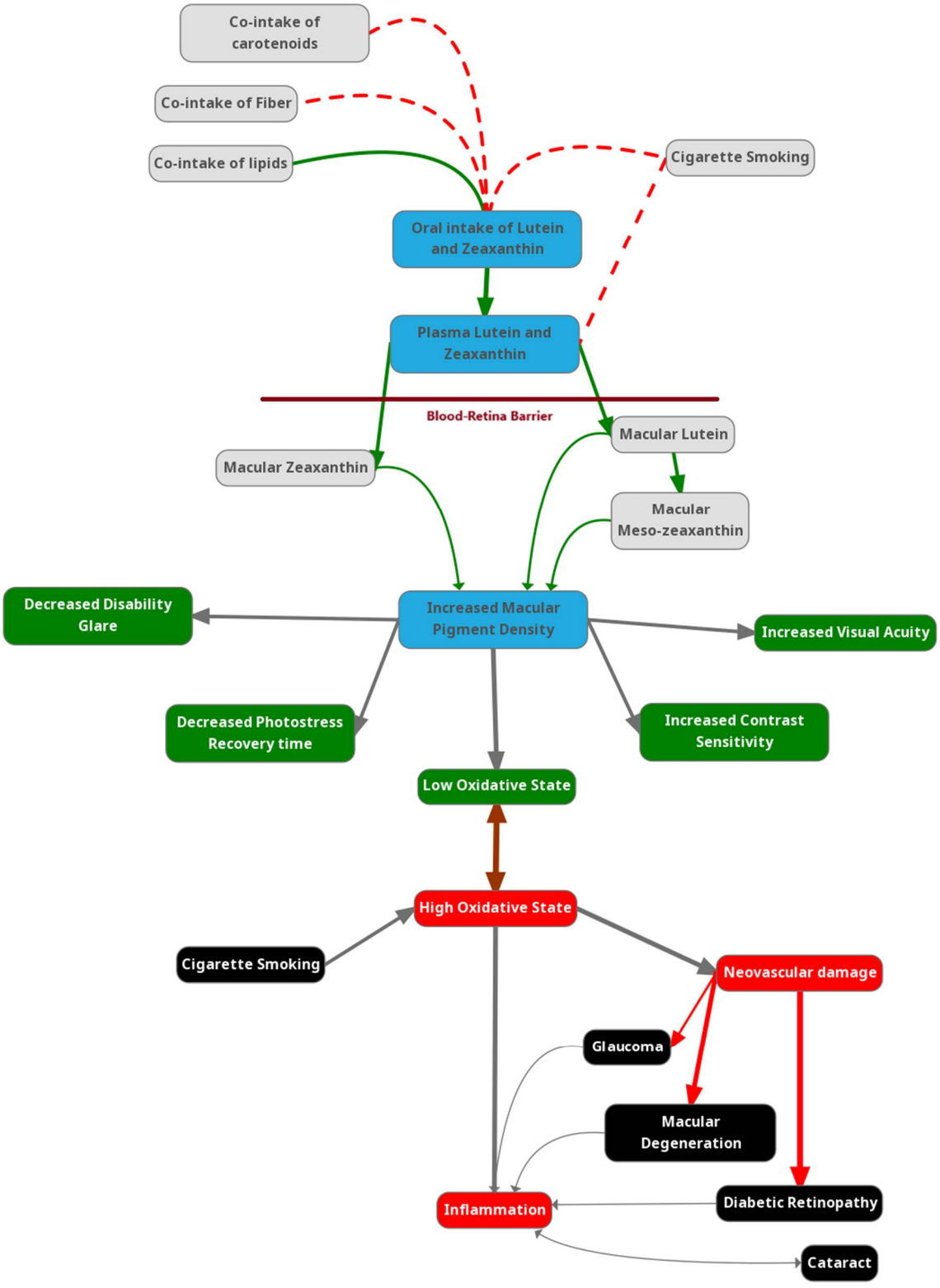

Figure 2. MPOD Model of Inflammation.

3.2. MPOD and Age-Related Macular Degeneration

Age-related macular degeneration (AMD), a leading cause of irreversible vision loss in older adults, underscores the importance of exploring potential protective factors [25]. Early signs of AMD are present in a quarter of the population older than 65, increasing the risk of developing late AMD

 doi:10.20944/preprints202407.0822.v1

[26]. Late AMD is the stage of AMD that affects vision and 7% of individuals over 75 years old will develop late AMD over the next 10 years of their life [26]. Modern medical interventions include anti-VEGF monoclonal antibodies and photodynamic therapy. These medical treatments present limitations in delaying and reversing the retinal changes seen in late AMD and are considered invasive by many patients, which can significantly affect patient compliance. No cure is currently present and this, along with the widespread prevalence of AMD, is why it is a leading cause of irreversible blindness [25]. MPOD emerges as a potential guardian against the onset and progression of AMD. Macular pigments, which encompass L/Z, exhibit powerful antioxidant properties that counteract the detrimental effects of oxidative stress and inflammation in the retina [6,27]. By scavenging free radicals and mitigating cellular damage, MPOD contributes to retinal health and reduces the risk of AMD development [6]. Higher MPOD levels are correlated with a decreased risk of both early and late-stage AMD, highlighting the potential of these pigments in preserving visual function [27,28].

The significance of MPOD transcends its protective role, extending to its potential as a biomarker for AMD risk assessment and progression. Lower MPOD levels have been associated with an increased likelihood of late AMD development, serving as an early indicator of susceptibility to the disease. Supplementation with lutein/zeaxanthin has been shown to increase MPOD and lower the progression of patients with wet AMD to the late stages of the disease [29]. It is important to note that people diagnosed with AMD have consistently been found to have lower MPOD [30–32]. Bone et al. examined donor eyes of individuals with and without AMD, finding lower concentrations of L/Z in individuals with AMD [33]. Monitoring MPOD over time may provide valuable insights into disease progression by aiding in identifying individuals who may be at higher risk of transitioning to advanced stages of AMD. Tsika et al. showed a significantly higher MPOD in the fellow eyes of patients with wet AMD, with no difference in the fellow eyes of patients with dry AMD [32]. Integrating MPOD measurements into routine clinical assessments can enhance AMD risk stratification, enabling proactive interventions and personalized management strategies. Table 2 below summarizes the findings of the randomized control trial and observational cross-sectional studies that have examined the relationship between MPOD and AMD, supporting the idea of using MPOD as a clinical biomarker of progression in AMD.

Table 2. Randomized control trial studies examining the relationship between MPOD and AMD.

Author (Year)	Study Design	Inclusion Criteria	Sample Size	Interventions	Duration	Relation between MPOD & AMD	MPOD Technique
Beatty study (2013) [34]	RCT	Adults ≥55 years with early or late-stage AMD.	433	Group 1: L and Z, Vitamin C, Vitamin E, Copper, Zinc. Group 2: Placebo.	Minimum 12 months, up to 36 months	Supplementation with L, Z, and antioxidants showed functional and morphologic benefits in early AMD. MPOD increased in the active group and decreased in the placebo group.	RS
LUTEGA study (2013) [35]	RCT	Adults 60-80 years with non-	172	Group 1: L, Z, Omega-3, antioxidants. Group 2: Placebo	12 months	Supplementation resulted in a considerable increase in MPOD and	FA

 doi:10.20944/preprints202407.0822.v1

		exudative AMD.				improvement/stabilization in BCVA. No difference in MPOD accumulation between dosages.	
CLEAR study (2013) [36]	RCT	Adults 50-80 years with early AMD.	72	Group 1: L (10 mg) Group 2: Placebo	12 months	Lutein supplementation increased MPOD and may have a mild beneficial effect on visual acuity. No change in MPOD found in the placebo group.	HFP
LAST study (2004) [37]	RCT	Adults 55-80 years with atrophic AMD.	90	Group 1: L (10 mg) Group 2: L (10 mg) with antioxidants Group 3: Placebo	12 months	Lutein alone or with antioxidants improved MPOD, glare recovery, and contrast sensitivity. No significant change in placebo group.	HFP
LUNA study (2007) [38]	RCT	Adults ≥55 years with or without AMD.	120	Group 1: L (6 mg) Group 2: Placebo	6 months	Lutein supplementation increased MPOD and improved visual function. No change in placebo group.	FA
ZVF study (2011) [39]	RCT	Early and moderate AMD retinopathy, symptoms of visual deficits.	60	Group 1: Z (8 mg) Group 2: Z (8 mg) + L (9 mg), Group 3: Placebo	12 months	MPOD increased in the intervention groups compared to the placebo group	HFP
Weigert (2011) [40]	RCT	Adults 50-90 years with AREDS stages 2, 3, and 4.	126	Group 1: L (20 mg for first 3 months, then 10 mg) Group 2: Placebo	6 months	Lutein significantly increased MPOD by 27.9%. No significant effect on macular function or visual acuity.	HFP

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Sabour-Pickett (2014) [41]	RCT	Adults 50-79 years with early AMD.	52	Group 1: L (20 mg) and Z (2 mg) Group 2: MZ (10 mg), L (10 mg), Z (2 mg) Group 3: MZ (17 mg), L (3 mg), Z (2 mg)	12 months	Statistically significant increase in MPOD was observed in Group 2 and Group 3. Improvements in letter contrast sensitivity were seen in all groups, with the best results in Group 3.	HFP
Huang (2015) [42]	RCT	Adults 50-79 years with early AMD.	112	Group 1: L (10 mg) Group 2: L (20 mg) Group 3: L (10 mg) and Z (10 mg)	2 years	All active treatment groups showed a significant increase in MPOD. The 20 mg lutein group was the most effective in increasing MPOD and contrast sensitivity at 3 cycles/degree for the first 48 weeks.	FA
Davey (2020) [43]	RCT	Adults 50-79 years with retinal drusen.	56	Group 1: Lumega-Z softgel Group 2: PreserVision AREDS2 softgel	6 months	Both groups demonstrated statistically significant improvements in contrast sensitivity function (CSF) in both eyes at six months.	HFP
Ma (2012) [44]	RCT	Ages 50-79, Early AMD.	108	Group 1: L (10 mg) Group 2: L (20 mg) Group 3: L (10 mg) plus Z (10 mg)	48 weeks	Significant increase in MPOD in the high-dose lutein and lutein plus zeaxanthin groups, with improvements in contrast sensitivity at certain spatial frequencies.	FA

*Abbreviations: RCT = Randomized Control Trial, AMD = Age-related Macular Degeneration, L = Lutein, Z = Zeaxanthin, MZ = Meso-zeaxanthin, BCVA = Best Corrected Visual Acuity, RS = Raman Spectroscopy, HFP = Heterochromatic flicker photometry, FA = Fundus Autofluorescence.

 doi:10.20944/preprints202407.0822.v1

3.3. Glaucoma

Glaucoma is the world's leading cause of irreversible blindness. Glaucoma is characterized by progressive degeneration of the optic nerve head, permanent damage to the retinal nerve fiber layer, and loss of retinal ganglion cells [45]. It results in vision loss that begins peripherally and moves centrally through the course of the disease [45]. In addition to elevated IOP, retinal ischemia, oxidative stress, and damage from ischemia-reperfusion, have been proposed as major factors causing retinal ganglion cell death [46]. It has been well established that increased macular pigment density aids in stopping the progression of AMD through potentially anti-oxidative effects [6]. This raises questions regarding the role of the macular pigment in mitigating the oxidative damage seen in glaucoma.

One study injected lutein into a transient ischemia model of high IOP in rats [47]. Rats injected with lutein showed significantly decreased levels of oxidative markers and decreased ischemia-induced retinal cell death compared to controls [47,48]. Research has demonstrated that administering lutein through intravitreal injections to rats suffering from ischemia-reperfusion injuries led to a significant reduction in oxidative markers, an increase in anti-oxidative markers, and a significant decrease in retinal ganglion cell death [49,50]. Müller cells fulfill a dual role by offering homeostatic and metabolic support to retinal neurons while also serving as key mediators of inflammation within the retina [51,52]. A Cross-sectional analysis assessed the MPOD of patients with glaucomatous eyes and found that MPOD was lower in eyes that had a thinner ganglion cell complex, a thinner retinal nerve fiber layer, and an increased cup-to-disc ratio, ultimately indicating a correlation between MPOD and glaucoma severity [53]. Studies have primarily focused on assessing the impact of MPOD and L/Z concentration in animal models, yielding promising results [47–50]. A recent review paper has suggested that carotenoid vitamin therapy provides synergic neuroprotective benefits and has the capacity to serve as adjunctive therapy in the management of glaucoma [54]. However, further research involving human subjects is essential to understand the mechanism and explore the potential anti-oxidative effects, particularly in the context of a high oxidation disease like glaucoma. Table 3 below summarizes the findings of the randomized control trial and observational cross-sectional studies that have examined the relationship between MPOD and glaucoma supporting the idea of using MPOD as a clinical biomarker of progression in glaucoma.

Table 3. Cross-sectional and randomized control trial studies examining the **relationship between MPOD and Glaucoma**

Author (Year)	Study Design	Inclusion Criteria	Sample Size	Intervention(s)	Duration	Relation between MPOD and Glaucoma	MPOD Technique
Fikret (2021) [55]	CS	Age not mentioned. Patients with POAG, PEX and controls.	79	None	N/A	Higher MPOD values in patients with PEX glaucoma; no significant differences in POAG compared to controls. There was no correlation between MPOD values and RNFL or GCL.	FR
Bruns (2020) [56]	CS	Adults 34-87 years; Patients with POAG	86	None	N/A	No significant difference in MPOD values between POAG patients and controls.	DWA

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		and controls.					
Loughman (2021) [57]	RCT	Adults >18 years. Patients with POAG and controls.	62	Group 1: L (10mg) + Z (2mg) + MZ (10mg). Group 2: Placebo.	18 months	Supplementation led to a significant increase in MPOD volume. No clinically meaningful changes were noted in glaucoma parameters.	DWA
Siah (2015) [53]	CS	Adults 36-84 years. Patients with POAG and controls.	88	None	N/A	Lower MPOD was observed in glaucomatous eyes compared to control. Worse glaucomatous parameters were observed in patients with lower MPOD.	HFP
Ji (2016) [58]	CS	Adults 20-76 years. Patients with POAG and controls.	82	None	N/A	MPOD was significantly lower in POAG patients compared to controls, and correlated positively with GCC thickness.	FR
Arnould (2022) [59]	CS	Adults >75 years. Patients with POAG and controls.	1153	None	N/A	No significant differences in MPOD were found between the POAG group and the control group.	DWA
Daga (2018) [60]	CS	Adults 20-76 years. Patients with POAG and controls.	107	None	N/A	No significant association was found between MPOD volume and glaucoma status.	DWA

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Lawler (2023) [61]	CS	Adults 55-81 years. Patients with POAG and controls.	379	None	N/A	MPOD was positively associated with GCC, GCL, among POAG and controls.	HFP
Igras (2013) [62]	CS	Adults 58-80 years. Patients with POAG and controls.	40	None	N/A	MPOD was significantly lower in POAG patients compared to controls.	HFP
Siah (2018) [63]	CS	Adults 36-84 years. Patients with POAG and controls.	88	None	N/A	MPOD was associated with improved glare-affected visual function and less central visual field loss in POAG patients.	HFP
Eraslan (2023) [64]	CS	Adults >55 years. Patients with POAG currently receiving topical medication and controls.	52	None	N/A	MPOD levels were higher in POAG patients compared to controls, suggesting a possible protective effect of topical therapies.	FR

*Abbreviations: RCT = Randomized Control Trial, CS = Cross-sectional, POAG = Primary open angle glaucoma, L = Lutein, Z = Zeaxanthin, MZ = Meso-zeaxanthin, BCVA = Best Corrected Visual Acuity, RS = Raman Spectroscopy, HFP = Heterochromatic flicker photometry, FR = Fundus Reflectance, DWA = Dual-wavelength autofluorescence. RNFL = retinal nerve fiber layer, GCL = Ganglion cell layer thickness, PEX = Pseudoexfoliative, GCC = Ganglion cell complex.

3.4. Systemic Disease

The assessment of MPOD could be used to gauge the risk of developing ocular and/or systemic disease. At the same time, maintenance or enhancement of MPOD could prevent the onset or advancement of associated co-morbidities. The theorized pathogenic mechanisms and metabolic co-

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morbidities to explain the lower MP levels reported in diabetes include a process of increased oxidative stress, inflammation, hyperglycemia, insulin resistance or deficiency, obesity, dyslipidemia, and vascular dysfunction/neovascularization [65,66]. In addition to possibly depleting potent antioxidants, such as macular carotenoids lutein, zeaxanthin, and meso-zeaxanthin that are pertinent for retinal protection, these factors may have related and/or independent relationships with MP that warrant further study [65,66]. A significant inverse correlation between MPOD and HbA1C was found and decreased MPOD is evident in type II diabetes with or without retinopathy [67]. Currently, there is robust evidence and early clinical trials supporting the use of carotenoid vitamin supplementation in diabetics with and without retinopathy. A trial on mice demonstrated promising effects on the prevention of diabetic retinopathy with MPOD-bolstering supplements; by reducing apoptosis of retinal ganglion cells, astaxanthin may prevent oxidative stress from causing retinal neurodegeneration [68]. Table 4 below summarizes the findings of the randomized control trial and observational cross-sectional studies that have examined the relationship between MPOD and diabetes, supporting the idea of using MPOD as a clinical biomarker of progression in diabetes and diabetic retinopathy.

Table 4. Cross-sectional and randomized control trial studies **examining the relationship between MPOD and Diabetes**

Author (Year)	Study Design	Inclusion Criteria	Sample Size	Intervention(s)	Duration	Relation between MPOD and DR	MPOD Technique
Lima (2010) [69]	CS	Adults 56-63; BCVA ≤20/40.	43	None	N/A	MPOD was lower in diabetic patients, with significant inverse correlation with HbA1C levels.	DWA
Scanlon (2019) [70]	CS	Adults 50+; BCVA ≤20/40.	2782	None	N/A	MPOD was found to be lower in individuals with T2D compared to healthy controls.	HFP
Bikbov (2015) [71]	CS	Adults 55-71; BCVA ≤20/40.	52	None	N/A	Significant reduction of MPOD in patients with diabetic macular edema compared to controls.	FR
Scanlon (2015) [72]	CS	Adults 36-73; BCVA ≤20/25.	150	None	N/A	MPOD was significantly lower in T2D compared to T1D and controls. Diabetes control was not associated with MPOD.	HFP
She (2016) [73]	CS	Adults over 55-71; BCVA ≤20/25.	401	None	N/A	No significant difference in MPOD levels among groups with or without early-stage non-proliferative DR	HFP

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Bikbov (2015) [74]	CS	Adults 54-69; BCVA ≤20/25.	31	None	N/A	Significant reduction of MPOD in DME patients, strong inverse correlation between retinal thickness and MPOD	FR
Chous (2016) [75]	RCT	Adults 43-69; BCVA ≥20/30; no or mild to moderate DR.	67	Group 1: Carotenoid supplement Group 2: placebo	6 months	Supplemented group showed significant improvements in visual functions which correlated with increased MPOD compared to placebo	HFP
Zagers (2005) [76]	CS	Adults 23-61; BCVA ≤20/32.	14	None	N/A	No significant difference in MPOD density between diabetic patients and healthy controls.	FR
Varghese (2019) [77]	CS	Adults 49-54 years.	150	None	N/A	MPOD was similar across diabetic patients with and without DR, suggesting no significant difference due to DR.	FR
Cennamo (2019) [78]	CS	Adults 31-38 years; T1D and controls.	59	None	N/A	MPOD and vessel density were both significantly lower in diabetic patients compared to controls. Moderate correlation between vessel density and MPOD.	FR

*Abbreviations: RCT = Randomized Control Trial, CS = Cross-sectional, DR = Diabetic retinopathy, L = Lutein, Z = Zeaxanthin, MZ = Meso-zeaxanthin, BCVA = Best Corrected Visual Acuity, T1D = Type 1 diabetic, T2D = Type 2 diabetic, HFP = Heterochromatic flicker photometry, DWA = Dual-wavelength autofluorescence, FR = Fundus Reflectance.

3.4.1. Diabetic Retinopathy

Retinopathy is a common ocular complication of uncontrolled type I and type II diabetes. People recently diagnosed with diabetes have been shown to have significantly lower L/Z plasma concentrations [79]. Studies have commonly examined the effects of carotenoids on the development of diabetes but there is limited research examining the effects of carotenoids on diabetic retinopathy. An animal study conducted by Kowluru et al., examined the effects of zeaxanthin supplementation on the retina in diabetic rats and results showed significant inhibition of diabetes-induced retinal oxidative damage [80]. A study conducted by Chous et al., showed that compared to placebo, subjects taking a xanthophyll multicomponent nutritional supplement demonstrated a 27% increase in MPOD

 doi:10.20944/preprints202407.0822.v1

after six months which correlated with an improvement in visual function, serum lipids and a decrease in peripheral neuropathy [81]. As discussed earlier, increased MPOD has been shown to mitigate oxidative processes in the retina, studies have shown that type II diabetes patients have lower levels of MPOD [70]. MPOD levels have also been correlated with HbA1C levels [67]. Evidence regarding MPODs effect on the treatment and development of diabetic retinopathy is limited. Early studies and animal models suggest a potential protective role of MPOD in the development of diabetic retinopathy [67,80,81]. Figure 2 provides conceptual framework for the processes leading to reduced macular pigment in diabetes, including oxidative stress and metabolic issues, and their impact on antioxidants. It highlights the relationship between MPOD and HbA1C, as well as the potential role of carotenoid supplementation in the prevention of retinopathy.

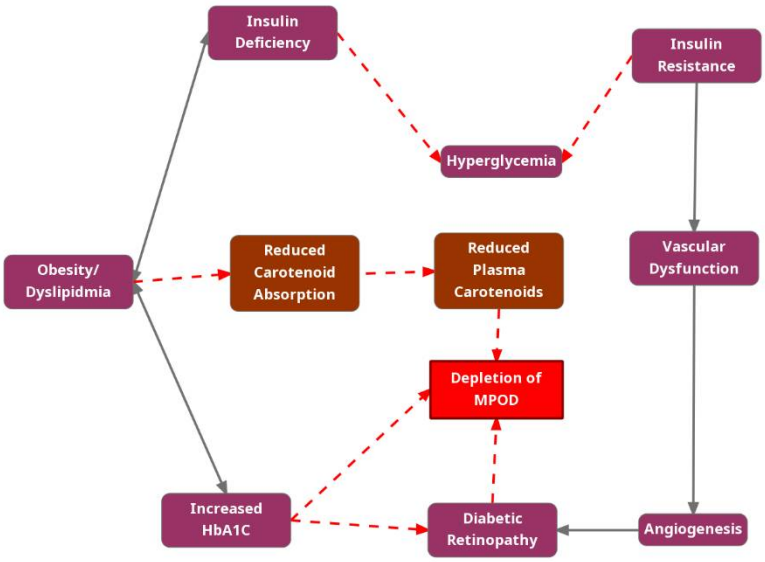

Figure 2. MPOD and Diabetic Retinopathy.

3.5. Visual Performance

MPOD's influence on visual performance resonates with its role as a natural optical filter. Higher pigment density corresponds to enhanced light absorption, which aids in optimizing contrast sensitivity – the ability to discern subtle differences in light and dark areas [82–85]. Studies have demonstrated a positive correlation between MPOD and contrast sensitivity, particularly in conditions of low light and reduced contrast [67,80,81]. This correlation underscores the potential of MPOD to fine-tune visual acuity, translating to improved day-to-day activities such as reading, driving, and recognizing facial expressions.

Glare, often experienced as visual discomfort caused by intense light sources, can significantly impede visual function. MPOD's protective role against glare becomes evident as the pigments selectively filter high-energy blue light, thus reducing glare's impact on visual perception [82,86].

Moreover, MPOD aids in hastening recovery from photostress – the temporary blinding effect experienced after exposure to bright light [82,86]. The pigments' capacity to absorb excess light and dissipate its energy contributes to quicker recovery times, enhancing visual comfort in challenging lighting conditions [82,86].

Increasing MPOD has been linked to a noteworthy enhancement in best corrected visual acuity (BCVA), as indicated by a study by Loughman et al., revealing a significant positive association (r=0.237) between MPOD levels and BCVA [84]. This finding suggests that interventions aimed at increasing MPOD levels could be promising in enhancing visual acuity, offering a potential avenue for improving the eyesight of individuals with less-than-optimal BCVA [87].

MPOD's beneficial effects on disability glare, photo stress recovery time, and contrast sensitivity are seen across diverse demographics, including certain professional athletes and individuals with low vision. A one year randomized, double-blind placebo-controlled trial in truck drivers showed

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that 20mg of daily lutein supplementation resulted in increased MPOD, contrast sensitivity, and decreased disability glare [88]. This underlines the potential commercial uses of increasing and measuring MPOD. There is evidence to support that MPOD can potentially be used as a clinical biomarker for ocular health in the setting of increased screen time and associated short-wavelength light exposure [89]. One study examined the effects of carotenoid supplementation versus placebo and found that carotenoid supplementation increased MPOD, which was also associated with improvements in headache frequency, eye strain, eye fatigue, and all measured visual performance variables [85]. Richer et al., conducted an RCT to assess the impact of increasing MPOD on night vision in elderly drivers [90]. They found that over a six-month period, participants who took a 14 mg Z + 7 mg L supplement experienced significant improvements in MPOD, glare recovery, contrast sensitivity, and preferred luminance, suggesting that carotenoid supplementation can enhance visual functions important for night driving [90]. In the realm of sports, where visual acuity and contrast sensitivity are paramount, higher MPOD levels could confer a competitive advantage. Improved contrast sensitivity could enhance an athlete's ability to discern critical visual cues, thereby refining their performance. Conversely, individuals with low vision may experience perceptual deficits due to compromised contrast sensitivity and glare discomfort. Modulating MPOD offers a potential avenue for ameliorating these challenges, enhancing the visual experiences of those with impaired vision, and improving visual performance in those in visually demanding fields. See Table 5 below for a summary.

Table 5. Cross-sectional and randomized control trial studies examining the **relationship between MPOD and Visual Function**

Author (Year)	Study Design	Demographic	Sample Size	Interventions	Duration	Relation between MPOD and Visual Function	MPOD Technique
Stringham (2011) [86]	CS	Adults 23-50; BCVA ≤20/25.	26	None	N/A	MPOD was associated with faster photo stress recovery, lower disability glare thresholds, and reduced visual discomfort.	HFP
Engles (2007) [91]	CS	Adults 18-40; BCVA ≤20/40.	80	None	N/A	No significant correlation found between MPOD and measures of visual acuity.	HFP
Tudosescu (2018) [92]	CS	Adults 18-65 years; BCVA ≤20/125.	83	None	N/A	No significant correlation between MPOD and blue-light exposure from computers, iris color, refractive errors, or glare sensibility was found.	HFP

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Patryas (2014) [93]	CS	Adults 18-68 years; BCVA ≤20/32.	33	None	N/A	MPOD was weakly associated with rod-mediated recovery, not with cone-mediated recovery.	HFP
Bovier (2014) [94]	RCT	Adults 18-32 years; BCVA ≤20/60.	92	Group 1: Z - 20mg Group 2: Mixed (Z - 26mg, L - 8mg, Omega-3 - 190mg) Group 3: Placebo	4 months	MPOD increased with supplementation and led to significant improvements in visual processing speed and motor reaction time.	HFP
Kvansakul – (2006) [95]	RCT	Adults 18-40 years; BCVA ≤20/60.	92	Group 1: L - 10mg Group 2: Z - 10mg Group 3: Combination (L - 10mg, Z - 10mg) Group 4: Placebo	12 months	Supplementation with L or Z increases MPOD improved contrast acuity thresholds at high mesopic levels, thus enhancing visual performance at low illumination.	HFP
Putnam (2015) [96]	CS	Adults 18-35 years; BCVA ≤20/25.	33	None	N/A	Increased MPOD correlates with reduced glare disability, significantly at higher spatial frequencies.	HFP
Stringham (2008) [97]	RCT	Adults 17-41 years.	40	Group 1: L - 10mg, Z - 2mg Group 2: Placebo	6 months	Supplementation led to increased MPOD, which significantly improved performance in glare disability and photostress recovery tasks.	HFP

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Stringham (2017) [98]	RCT	Adults 18–25 years.	59	Group 1: L - 6mg and Z - 6mg Group 2: L - 12mg and Z - 12mg Group 3: Placebo	12 months	Increases in MPOD led to improved contrast sensitivity	HFP
Nolan (2016) [99]	RCT	Adults with mean age of 21.5 years.	105	Group 1: L - 10 mg, Z - 2mg, and MZ - 10 mg Group 2: Placebo	12 months	MPOD increased with supplementation and was significantly correlated with improvements in contrast sensitivity in the active group compared to placebo.	DWA
Hammond (2014) [100]	RCT	Adults 20-40 years.	115	Group 1: L - 10mg, Z - 2mg. Group 2: Placebo	12 months	Supplementation increased MPOD significantly, improving chromatic contrast and photostress recovery time, but glare disability improvements were not statistically significant.	HFP
Hammond Jr (2013) [101]	CS	Adults 20-40 years.	150	None	N/A	MPOD density significantly correlated with positive outcomes in glare disability, photostress recovery time, and chromatic contrast thresholds.	HFP

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Stringham (2016) [102]	RCT	Adults 18-25 years, BCVA ≤20/20.	59	Group 1: L - 10mg + Z - 2mg. Group 2: L - 20mg + Z - 4mg. Group 3: Placebo	12 months	Supplementation led to significant increases in MPOD, which in turn resulted in improvements in photostress recovery, and disability glare.	HFP
Hammond Jr. (1998) [103]	CS	Adults 60-84 years; ≤20/32 visual acuity.	37	None	N/A	Higher MPOD was associated with preserved visual sensitivity in older ages.	HFP
Estévez-Santiago (2016) [104]	CS	Adults 20-35 and 45-65 years; BCVA ≤20/20.	108	None	N/A	Contrast threshold inversely correlated with MPOD, particularly in the older group.	HFP
Nolan (2011) [105]	RCT	Adults 18-41 years; BCVA ≤20/20.	121	Group 1: L - 12mg + Z - 1mg. Group 2: Placebo.	12 months	Statistically significant increase in MPOD in the active group was not generally associated with improvement in visual performance.	HFP
Loughman (2010) [106]	CS	Adults 18-41 years; BCVA ≤20/20.	142	None	N/A	MPOD was positively associated with BCVA and contrast sensitivity, while photostress recovery and glare sensitivity were unrelated to MPOD.	HFP

*Abbreviations: RCT = Randomized Control Trial, CS = Cross-sectional, L = Lutein, Z = Zeaxanthin, MZ = Meso-zeaxanthin, BCVA = Best Corrected Visual Acuity, HFP = Heterochromatic flicker photometry, DWA = Dual-wavelength autofluorescence.

3.7. MPOD and Cognitive Function

It has been well established that a higher level of serum and brain carotenoids are associated with improved cognitive function [107–110]. It is important to note that the carotenoids present in the macular pigment are also widely present in the brain [111]. One study investigated the relationship between MPOD and cognitive function in 4,453 adults aged >50 years and found that lower MPOD was associated with poorer performance on the Mini-Mental State Examination and on

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the Montreal Cognitive Assessment [109]. Lower MPOD was also associated with poorer prospective memory and slower reaction times [109]. As seen in Table 6, MPOD and cognitive function have been positively correlated across various mental processes in various age groups, strongly supporting the use of MPOD as a clinical biomarker for cognitive function.

Table 6. Cross-sectional and randomized control trial studies examining the relationship between MPOD and Cognitive Function.

Author (Year)	Study Design	Inclusion Criteria	Sample Size	Intervention(s)	Duration	Relation between MPOD and Cognitive Function	MPOD Technique
Khan (2018) [112]	CS	Adults 25-45 years with BMI ≥ 25 kg/m².	114	None	N/A	MPOD positively associated with IQ and fluid intelligence, but not with crystallized intelligence	HFP
Saint (2018) [113]	CS	Children 7-13 years.	51	None	N/A	MPOD positively associated with reasoning skills and executive mental processes	HFP
Renzi-Hammond (2017) [114]	RCT	Adults 18-30 years.	51	Group 1: L (10mg) + MZ (2mg). Group 2: Placebo	1 year	MPOD positively associated with improvements in spatial memory, reasoning ability, and complex attention tasks	HFP
Barnett (2018) [115]	CS	Preadolescent children 8-9 years.	56	None	N/A	MPOD positively associated with overall academic achievement, mathematics, and written language	HFP
Lindbergh (2018) [116]	RCT	Adults 64-86 years.	44	Group 1: L (10mg) + MZ (2mg). Group 2: Placebo	1 year	L and Z supplementation increased MPOD and was associated with enhanced signals in prefrontal regions, suggesting a potential mechanism for improved cognitive performance	HFP

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Kelly (2015) [117]	CS	Group 1: Adults 35-74 years with low MPOD, Group 2: Adults 35-74 years with early AMD.	226	None	N/A	MPOD positively associated with phonemic fluency, attention switching, visual and verbal memory, and learning	HFP and DWA
Power (2018) [118]	RCT	Adults 33-57 years with low MPOD.	91	Group 1: L (10mg) + MZ (10mg) + Z (2mg). Group 2: Placebo	12 months	Supplementation improved MPOD which positively associated with episodic memory and overall cognitive function	DWA
Ajana (2018) [119]	CS	Adults 75-93 years with low MPOD.	184	None	N/A	Higher MPOD significantly associated with better global cognitive performance, visual memory, and verbal fluency	DWA
Vishwanathan (2014) [120]	CS	Adults 75-80 years.	108	None	N/A	MPOD levels significantly positively associated with better global cognition, verbal learning and fluency, recall, processing speed, and perceptual speed	HFP
Renzi (2014) [121]	CS	Adults 65-83 years with mild cognitive impairment.	53	None	N/A	In unimpaired adults, higher MPOD was associated with better visuospatial and constructional abilities. In mildly impaired adults, higher MPOD was associated with better performance in multiple cognitive domains including memory, language, and attention	HFP

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Feeney (2013) [122]	CS	Adults 50+ years.	4453	None	N/A	Lower MPOD was associated with poorer performance on the MMSE and MoCA, prospective memory, and executive function	HFP
Stringham (2019) [123]	RCT	Adults 18-25 years.	59	Group 1: MZ (13 mg), Group 2: MZ (27 mg), Group 3: Placebo.	6 months	Supplementation improved cognitive performance in composite memory, verbal memory, sustained attention, psychomotor speed, and processing speed	HFP
Hassevoort (2017) [124]	CS	Children 7-10 years.	40	None	N/A	MPOD negatively associated with relational memory errors	HFP
Edwards (2019) [125]	CS	Adults 25-45 years with BMI ≥ 25 kg/m².	101	None	N/A	MPOD positively associated with improvements attentional resource allocation and information processing speed	HFP
Mewborn (2018) [126]	CS	Adults 64-77 years.	51	None	N/A	Higher MPOD positively associated with better neural efficiency in visual–spatial processing	HFP

*Abbreviations: RCT = Randomized Control Trial, AMD = Age-related Macular Degeneration, L = Lutein, Z = Zeaxanthin, MZ = Meso-zeaxanthin, BCVA = Best Corrected Visual Acuity, MMSE = Mini-mental state examination, MoCA = Montreal cognitive assessment, HFP = Heterochromatic flicker photometry, DWA = Dual-wavelength autofluorescence.

4. Discussion

MPOD assessment, once confined to research settings, is finding its stride as a pivotal component of routine eye examinations. Including MPOD measurement within these examinations provides clinicians with a comprehensive snapshot of a patient's macular health. This insight extends beyond mere pigment quantification, unveiling potential susceptibility to AMD and other ocular conditions. By integrating MPOD assessment into the standard ocular assessment paradigm, clinicians can gain a deeper understanding of an individual's visual health trajectory, enabling proactive interventions and tailored recommendations.

The potential of MPOD as a predictive marker revolutionizes the landscape of treatment planning. As our understanding of the relationship between pigment density and ocular health deepens, MPOD emerges as a prognostic tool that guides personalized interventions. For instance, individuals with lower MPOD values may benefit from proactive strategies aimed at enhancing pigment density to mitigate AMD risk. Furthermore, MPOD assessment can aid in identifying

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individuals likely to respond favorably to specific treatments, optimizing therapeutic outcomes, and minimizing potential side effects.

The longitudinal monitoring of disease progression and treatment efficacy is essential in ocular health management. MPOD's potential in this realm is significant, offering insights into the evolution of macular health over time. By tracking changes in MPOD, clinicians can gauge dietary inadequacies and disease progression in conditions such as AMD and assess the impact of interventions on pigment density. This enables timely adjustments to treatment and management plans, ensuring that patients receive the most effective care. Additionally, MPOD measurements provide an objective parameter for assessing treatment efficacy, supplementing traditional subjective measures of visual function.

Current clinically available technologies for measuring macular pigment optical density (MPOD) lack the ability to estimate lutein and zeaxanthin optical densities, limiting personalized carotenoid supplementation therapies. The introduction of new biomarkers like lutein and zeaxanthin optical densities through technologies such as the Macular Pigment Reflectometer (MPR) could revolutionize precision medicine by providing repeatable MPOD and carotenoid optical density measurements [12]. Unlike heterochromatic flicker photometers (HFP), the MPR objectively measures MPOD and individual lutein and zeaxanthin components, offering a faster and more precise method that addresses the limitations of current technologies. The MPR utilizes controlled light beams and internal spectrometers to quantify lutein and zeaxanthin optical densities, providing reliable measurements for personalized supplementation strategies [13]. The current market and consumers are not ready for prophylactic personalized vitamin and nutritional therapies; nor do we have clinically available devices that can objectively measure MPOD and its individual components. The cost is the major prohibiting factor in the implementation of such strategies. The current conditions further emphasize the importance, dominance, and need for HFP devices in the measurement of MPOD.

Integrating MPOD measurement into clinical applications is not merely an addition to the diagnostic toolkit; it's a paradigm shift that empowers clinicians to provide personalized, proactive, and precise ocular care. The ability to predict risk, tailor treatments, and monitor changes in pigment density imbues ocular health management with unprecedented depth. By harnessing MPOD's potential, clinicians are poised to elevate the standard of care, ensuring that patients receive interventions that are not only evidence-based but also finely tuned to their individual ocular profiles.

Advances in technology are poised to revolutionize how MPOD is measured and interpreted. Emerging techniques, such as adaptive optics imaging and multi-wavelength fundus autofluorescence, offer enhanced spatial resolution and the ability to quantify pigment distribution across the macula with unprecedented detail. These technologies enable researchers to unravel nuances in pigment density and distribution, potentially linking specific pigment patterns to ocular health outcomes. As these methods become more affordable and accessible, the precision and granularity of MPOD assessment are set to soar, enhancing our understanding of its role in visual health.

The trajectory of ocular and systemic health is a marathon rather than a sprint, necessitating long-term studies to unravel the intricacies of MPOD's relationship with well-being. Longitudinal investigations are key to deciphering the dynamic interplay between MPOD and age-related ocular diseases, tracking changes in pigment density as individuals age and potentially developing early predictive markers for disease onset. These studies also illuminate the temporal dynamics of MPOD alterations due to lifestyle changes, ethnicities [127], interventions, and genetic predispositions. As we venture into the future, long-term studies will anchor our understanding of MPOD's enduring influence on ocular health.

Author Contributions: Conceptualization, B.V. and P.G.D.; methodology, A.M., K.I., B.V.; data curation, A.M.; writing—original draft preparation, B.V., A.M., M.A., K.I. and P.G.D.; writing—review and editing, B.V., A.M., M.A. K.I., D.L.G and P.G.D. All authors have read and agreed to the published version of the manuscript.

 doi:10.20944/preprints202407.0822.v1

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.
Data Availability Statement: Dataset available on request from the authors.

Conflicts of Interest: Abdul Masri, none; Mohammed Armanazi, none; Keiko Inouye, none; Dennis L. Gierhart is the Chairman of EyePromise, manufacturer of various nutritional supplements and Zx Pro none of these products have been mentioned in the paper; Pinakin Davey is an Employee of EyePromise; Balamurali Vasudevan, none.

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