The ROYAL COLLEGE of OPHTHALMOLOGISTS

www.nature.com/eye

ARTICLE

Check for updates

Photobiomodulation-induced choriocapillaris perfusion enhancement and outer retinal remodelling in intermediate age-related macular degeneration: a promising therapeutic approach with short-term results

Pasquale Viggiano[1]✉, Giacomo Boscia[1], Arcangelo Clemente[1], Mariapia Laterza[1], Alba Chiara Termite[1], Maria Grazia Pignataro[1], Antonio Salvelli[1], Enrico Borrelli[2], Michele Reibaldi[2], Giuseppe Giannaccare[3], Giovanni Alessio[1] and Francesco Boscia[1]

PURPOSE: To evaluate the effects of photobiomodulation (PBM) on choriocapillaris (CC) perfusion and drusen volume in patients with intermediate age-related macular degeneration (AMD).

METHODS: In this retrospective pilot study, 30 patients receiving PBM therapy and 30 age-matched controls were analysed. Treatment consisted of 8 sessions over 4 weeks using the EYE-LIGHT® device. Best-corrected visual acuity (BCVA), low luminance visual acuity (LLVA), mean drusen volume (MDV), and CC flow deficit percentage (FD%) were evaluated at baseline and 2-month follow-up.

RESULTS: The PBM group showed significant improvements in BCVA (Δ +3.2 ± 1.4 letters, $p = 0.042$), reduction in drusen volume (Δ −0.003 ± 0.001 mm^3, $p = 0.028$), and decrease in choriocapillaris FD% (Δ −3.1 ± 1.4%, $p = 0.024$), while no significant changes were observed in the control group. Changes in choriocapillaris FD% correlated with BCVA improvement ($r = -0.54$, $p = 0.002$) and drusen volume reduction ($r = 0.35$, $p = 0.042$).

CONCLUSIONS: PBM therapy induces significant choriocapillaris remodelling in intermediate AMD, associated with functional improvement and drusen volume reduction. These findings suggest a potential therapeutic role of PBM in modulating choroidal perfusion in AMD.

Eye; https://doi.org/10.1038/s41433-025-03805-2

INTRODUCTION

Age-related macular degeneration (AMD) represents one of the leading causes of irreversible vision loss in developed countries, affecting approximately 196 million people worldwide [1]. The pathogenesis of AMD is complex and multifactorial, involving oxidative stress, inflammation, and mitochondrial dysfunction, which particularly affect the retinal pigment epithelium (RPE), photoreceptors, and choriocapillaris (CC) [2].

Intermediate AMD is characterized by the presence of drusen and/or pseudodrusen, which represent accumulations of extracellular material between the RPE and Bruch's membrane [3–5]. Recent evidence suggests that CC dysfunction may play a crucial role in drusen formation and AMD progression [6–8]. Indeed, areas of CC impairment have been documented in correspondence with drusen deposits, suggesting a potential relationship between these two features [8].

Currently, there are no approved treatments for intermediate AMD, with management largely limited to nutritional supplements based on the AREDS formula [2]. In this context, photobiomodulation (PBM) has emerged as a promising therapeutic approach [9]. PBM employs specific wavelengths of light to modulate cellular function, particularly targeting mitochondrial activity and inflammatory pathways [10]. Moreover, PBM may enhance CC perfusion through direct effects on endothelial cells, promoting vasodilation via nitric oxide pathways, and by reducing RPE-derived inflammatory factors that impair choroidal microcirculation [10, 11].

Recent studies have demonstrated that PBM can improve visual function in patients with AMD [11, 12]. However, the effects of PBM on CC perfusion and its relationship with drusen characteristics have not been thoroughly investigated. The advent of swept-source optical coherence tomography angiography (SS-OCTA) has enabled detailed evaluation of CC perfusion, providing new opportunities to assess treatment effects at the microvascular level [13, 14].

The aim of this study was to evaluate the effects of PBM in patients with intermediate AMD. Specifically, we investigated both functional (best-corrected visual acuity and low luminance visual acuity) and anatomical outcomes (drusen volume and CC perfusion). Furthermore, we aimed to investigate potential correlations between changes in these parameters following treatment.

[1]Department of Translational Biomedicine Neuroscience, University of Bari "Aldo Moro", Bari, Italy. [2]Department of Surgical Sciences, University of Turin, Turin, Italy. [3]Eye Clinic, Department of Surgical Sciences, University of Cagliari, Cagliari, Italy. ✉email: pasquale.viggiano90@gmail.com

Received: 12 January 2025 Revised: 31 March 2025 Accepted: 7 April 2025
Published online: 19 April 2025

METHODS

Study participants

This retrospective cohort study, conducted at the Medical Retina Service of the Department of Translational Biomedicine Neuroscience, University of Bari Aldo Moro, Italy, analysed data from consecutive patients with intermediate age-related macular degeneration between June 2024 and December 2024. Disease staging was performed according to the Ferris clinical classification [15], which defines intermediate AMD by the presence of large drusen (>125 µm) and/or pigmentary abnormalities. The treatment group included patients who received PBM therapy as part of their standard care, while the control group comprised patients who, during the same period, opted not to undergo PBM treatment despite it being offered as a therapeutic option. Control patients were matched for disease severity, baseline visual acuity (±5 ETDRS letters), and lens status. Reasons for declining PBM included scheduling conflicts (42%), cost considerations (31%), and preference for observation (27%). The study protocol was approved by the institutional review board of the University of Bari 'Aldo Moro' and adhered to the tenets of the Declaration of Helsinki. All patients provided written informed consent for the use of their clinical data and images for research purposes. All patient data were anonymized to ensure confidentiality.

Eligible subjects were aged 50 years or older with a diagnosis of intermediate AMD. We specifically included patients presenting with drusen and reticular pseudodrusen, as identified by multimodal imaging including spectral-domain OCT, infrared reflectance, and fundus autofluorescence. Best-corrected visual acuity (BCVA) at baseline ranged between 20/25 and 20/100 Snellen equivalent. Only patients who completed the full photobiomodulation treatment protocol and had swept-source OCTA and OCT volume scans of adequate quality at both baseline and 2-months follow-up were included in the analysis. In the treatment group, when both eyes were eligible for the study, the eye with more severe AMD manifestations (larger drusen volume and/or more extensive reticular pseudodrusen) was selected for treatment and analysis.

Patients were excluded if they presented any form of advanced AMD, including macular neovascularization or geographic atrophy, or had a history of other retinal diseases that could affect visual function. Additional exclusion criteria encompassed prior retinal treatment within 6 months of PBM therapy, significant media opacities affecting imaging quality, active or previous sensitivity to light therapy, history of epilepsy and ongoing treatment with AREDS2 formulation or other nutritional supplements for AMD.

Outcome measures

All patients underwent comprehensive functional and anatomical evaluation at baseline and at 2 months after completion of the PBM treatment protocol. For the control group, evaluations were performed at the same time intervals.

Functional outcomes

The functional evaluation included BCVA and low luminance visual acuity (LLVA). BCVA was measured using ETDRS charts at 4 meters distance, while LLVA was assessed using the same ETDRS charts with a 2.0 log unit neutral density filter placed in front of the patient's best correction. All measurements were performed by certified examiners under standardized lighting conditions.

Anatomical outcomes

All patients underwent multimodal imaging examination including enhanced depth imaging spectral-domain OCT (Heidelberg Spectralis OCT, Heidelberg Engineering, Germany) and SS-OCTA (PLEX Elite 9000, Carl Zeiss Meditec).

Mean Drusen volume (MDV). The structural OCT protocol included a 20 × 20 high-resolution (HR) horizontal dense volume scan (49 sections each) for drusen and reticular pseudodrusen volume quantification. All follow-up scans were obtained using the automatic real-time tracking system (ART) and reference function of the Heidelberg device to ensure acquisition at the same retinal location at follow up visit. Drusen volume quantification was performed using the automated Heidelberg Spectralis segmentation software within the standardized ETDRS grid (central 1 mm, inner 3 mm, and outer 6 mm rings) [16, 17]. The total drusen volume was calculated for each of the nine ETDRS subfields and the total 6 mm macular area [18]. The software identifies drusen as RPE elevations from the RPE floor and provides volumetric measurements [11, 18]. All automated segmentations were reviewed by two experienced graders (PV and GB) and manually corrected when necessary to ensure accurate measurements.

Choriocapillaris flow deficit percentage (FD%). Swept-source OCTA scans of the macular region were acquired using a 6 × 6-mm scanning protocol centered on the fovea. Only scans with signal strength index ≥8/10 and without significant artifacts were included in the analysis [19]. We excluded scans with motion artifacts, segmentation errors, and shadowing artifacts exceeding 10% of the analysed area. The CC was visualized as a 10-µm thick slab immediately beneath the RPE-Bruch's membrane complex. Quantitative analysis was performed using ImageJ software (version 2.0.0; National Institute of Health, Bethesda, MD). To optimize the accuracy of CC flow measurements in areas underlying drusen, we implemented a shadow compensation algorithm as described in previous studies [20]. Images were then binarized using the Phansalkar method with a 6-pixel radius, following established protocols [21]. The FD%, representing the percentage of flow deficits within the analysed area, was calculated using the "Analyze Particles" function (Fig. 1A).

Examiners performing quantitative analysis of imaging data were masked to treatment assignment. All segmentation and CC flow deficit quantifications were conducted by blinded graders (PV and EB) using standardized protocols.

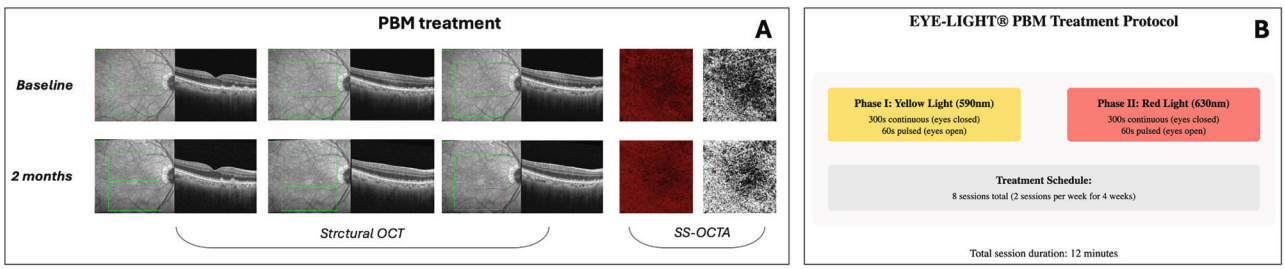

Fig. 1 Photobiomodulation (PBM) treatment in retinal diseases. A Multimodal imaging analysis of a representative case before and after photobiomodulation treatment. Multimodal imaging showing changes in retinal structure and choriocapillaris perfusion at baseline and 2-month follow-up after photobiomodulation (PBM) treatment. Left panels show infrared reflectance images with corresponding structural OCT B-scans obtained using the automatic real-time tracking system (ART) to ensure acquisition at the same retinal location. The green boxes on infrared images indicate the location of the corresponding B-scans. Structural OCT B-scans show reduction in drusen volume at 2-month follow-up. Right panels show swept-source OCTA (SS-OCTA) analysis of the choriocapillaris: the original flow signal (in red) and the binarized image showing flow deficits (in white). Flow deficit analysis was performed after shadow compensation and binarization using the Phansalkar method. The binarized images demonstrate decreased choriocapillaris flow deficit percentage (CC FD%) after PBM treatment. **B** EYE-LIGHT® Photobiomodulation Treatment Protocol. Schematic representation of the photobiomodulation (PBM) treatment protocol using the EYE-LIGHT® device. Each treatment session (12 min total) consists of two sequential phases: Phase I utilizes yellow light (590 nm wavelength) delivered first continuously for 300 s with eyes closed, followed by 60 s of pulsed delivery with eyes open. Phase II employs red light (630 nm wavelength) following the same pattern of 300 s continuous delivery with eyes closed and 60 s pulsed delivery with eyes open. The complete treatment course comprises 8 sessions administered over 4 weeks (2 sessions per week). No pupil dilation is required for the treatment.

Table 1. Baseline characteristics of study population.

Characteristic	PBM Group ($n = 30$)	Control Group ($n = 30$)	*P* value
Age, years	72.4 ± 7.8	71.8 ± 8.1	0.78
Female sex, n (%)	18 (60%)	17 (56.7%)	0.83
Hypertension, n (%)	16 (53.3%)	15 (50%)	0.80
Diabetes, n (%)	8 (26.7%)	7 (23.3%)	0.77
Family history of AMD, n (%)	12 (40%)	11 (36.7%)	0.79
Current/former smoker, n (%)	14 (46.7%)	13 (43.3%)	0.80
Early lens opacity, n (%)	18 (60%)	17 (56.7%)	0.79
BCVA, ETDRS letters	77.2 ± 6.1	76.8 ± 6.3	0.81
LLVA, ETDRS letters	59.8 ± 8.2	60.1 ± 8.4	0.89
Mean drusen volume, mm^3	0.021 ± 0.011	0.020 ± 0.010	0.72
CC FD%	54.2 ± 4.8	53.8 ± 4.9	0.75

Values are presented as mean ± standard deviation where applicable. *PBM* photobiomodulation, *AMD* age-related macular degeneration, *BCVA* best-corrected visual acuity, *ETDRS* Early Treatment Diabetic Retinopathy Study, *LLVA* low luminance visual acuity, *CC* choriocapillaris, *FD%* flow deficit percentage.

The intragrader and intergrader reproducibility for both MDV and CC FD% was assessed in a subset of 15 randomly selected eyes, showing excellent agreement (ICC > 0.90 for all measurements).

Treatment protocol

Photobiomodulation therapy was performed using the EYE-LIGHT® device (Espansione Group S.p.A., Bologna, Italy), which employs two wavelengths: 590 nm (yellow) at a power density of 50 mW/cm^2 and 630 nm (red) at 40 mW/cm^2, with a total energy delivery of 9.0 J/cm^2 per session and in both continuous and pulsed modes. Each treatment session lasted 12 min and consisted of two phases: in phase I, yellow light was delivered continuously with eyes closed for 300 s, followed by pulsed delivery with eyes open for 60 s; in phase II, red light was delivered continuously with eyes closed for 300 s, followed by pulsed delivery with eyes open for 60 s (Fig. 1B).

The treatment protocol consisted of 8 sessions, with two sessions per week over 4 weeks. No pupil dilation was required during the treatment. Treatment sessions were performed in a dedicated room under standardized conditions. Compliance and any adverse events were recorded at each visit.

Statistical analysis

Statistical analysis was performed using SPSS Statistics (version 27.0, IBM Corp., USA). The Shapiro-Wilk test was used to verify the normal distribution of continuous variables. Descriptive statistics were presented as mean ± standard deviation for continuous variables and as frequencies and percentages for categorical variables. For between-group comparisons at baseline, independent *t* test or Mann–Whitney U test were used for continuous variables according to their distribution. Changes in BCVA, LLVA, drusen volume, and CC FD% between baseline and 2-month follow-up were analysed using paired *t* test or Wilcoxon signed-rank test for within-group comparisons. The differences in these changes between treatment and control groups were evaluated using independent *t* test or Mann–Whitney U test. The relationships between anatomical and functional parameters were assessed using Pearson correlation. To account for potential confounding factors, multiple linear regression analysis was performed with changes in BCVA and LLVA as dependent variables. *P* values less than 0.05 were considered statistically significant.

RESULTS

Baseline characteristics

A total of 60 patients were included in this study: 30 patients in the PBM treatment group and 30 age-matched controls. The mean age was 72.4 ± 7.8 years in the treatment group and 71.8 ± 8.1 years in the control group ($p = 0.78$). The gender distribution was similar between groups, with 18 females (60%) in the treatment group and 17 females (56.7%) in the control group ($p = 0.83$). Medical history and systemic conditions were comparable between groups. In the treatment and control groups, respectively: hypertension was present in 16 (53.3%) and 15 (50%) patients ($p = 0.80$), diabetes in 8 (26.7%) and 7 (23.3%) patients ($p = 0.77$), and family history of AMD in 12 (40%) and 11 (36.7%) patients ($p = 0.79$). Current or former smokers represented 14 (46.7%) patients in the treatment group and 13 (43.3%) in the control group ($p = 0.80$). Early lens opacities were present in 18 (60%) and 17 (56.7%) patients in the treatment and control groups, respectively ($p = 0.79$). At baseline, there were no significant differences between groups in BCVA (77.2 ± 6.1 vs 76.8 ± 6.3 ETDRS letters, $p = 0.81$), LLVA (59.8 ± 8.2 vs 60.1 ± 8.4 ETDRS letters, $p = 0.89$), MDV (0.021 ± 0.011 vs 0.020 ± 0.010 mm^3, $p = 0.72$), or CC FD% (54.2 ± 4.8% vs 53.8 ± 4.9%, $p = 0.75$) (Table 1).

Safety and adverse events

During the study period, no treatment-related adverse events were reported in the PBM group. All patients completed the full treatment protocol with excellent compliance. None of the patients in either group developed macular neovascularization or atrophy during the 2-month follow-up period. No cases of photophobia, ocular discomfort, or other treatment-related side effects were reported throughout the study duration.

Treatment outcomes

Treatment group. At 2-month follow-up, the treatment group showed significant improvements in all parameters. BCVA improved from 77.2 ± 6.1 to 80.4 ± 5.8 ETDRS letters ($p = 0.038$) and LLVA increased from 59.8 ± 8.2 to 63.5 ± 7.9 letters ($p = 0.042$). MDV showed a significant reduction from 0.021 ± 0.011 to 0.018 ± 0.009 mm^3 ($p = 0.034$). CC FD% decreased from 54.2 ± 4.8% to 51.1 ± 4.2% ($p = 0.028$), indicating an improvement in CC perfusion (Table 2).

Control group. No significant changes were observed in the control group over the same period. BCVA changed from 76.8 ± 6.3 to 77.1 ± 6.4 letters ($p = 0.82$) and LLVA from 60.1 ± 8.4 to 59.8 ± 8.6 letters ($p = 0.91$). MDV showed minimal variation from 0.020 ± 0.010 to 0.021 ± 0.011 mm^3 ($p = 0.68$), while CC FD% remained stable (53.8 ± 4.9% to 54.1 ± 5.1%, $p = 0.75$) (Table 2).

Between-group comparison. The mean changes (Δ) between baseline and 2-month follow-up were significantly different between groups for all parameters. The treatment group showed greater improvements in BCVA (Δ +3.2 ± 1.4 vs +0.3 ± 1.1 letters,

Table 2. Functional and anatomical outcomes at baseline and 2-month follow-up.

	PBM Group ($n = 30$)			Control Group ($n = 30$)			
	Baseline	2 months	*P* value*	Baseline	2 months	*P* value*	Between-group P†
BCVA, ETDRS letters	77.2 ± 6.1	80.4 ± 5.8	0.038	76.8 ± 6.3	77.1 ± 6.4	0.82	0.042
LLVA, ETDRS letters	59.8 ± 8.2	63.5 ± 7.9	0.042	60.1 ± 8.4	59.8 ± 8.6	0.91	0.038
Mean drusen volume, mm^3	0.021 ± 0.011	0.018 ± 0.009	0.034	0.020 ± 0.010	0.021 ± 0.011	0.68	0.028
CC FD%	54.2 ± 4.8	51.1 ± 4.2	0.028	53.8 ± 4.9	54.1 ± 5.1	0.75	0.024

Values are presented as mean ± standard deviation. *PBM* = photobiomodulation; *BCVA* = best-corrected visual acuity; *ETDRS* Early Treatment Diabetic Retinopathy Study, *LLVA* low luminance visual acuity, *CC* choriocapillaris, *FD%* flow deficit percentage. **P* value for within-group comparison (baseline vs 2 months) †P value for between-group comparison of changes from baseline

$p = 0.042$) and LLVA (Δ +3.7 ± 1.6 vs -0.3 ± 1.2 letters, $p = 0.038$). MDV reduction was significantly larger in the treatment group (Δ -0.003 ± 0.001 vs +0.001 ± 0.001 mm^3, $p = 0.028$). The decrease in CC FD% was also significantly greater in the treatment group (Δ –3.1 ± 1.4% vs +0.3 ± 1.1%, $p = 0.024$) (Table 2).

Correlation analysis

In the treatment group, Pearson correlation analysis showed significant associations between anatomical and functional changes. Changes in CC FD% demonstrated a moderate negative correlation with BCVA improvement ($r = –0.54$, $p = 0.002$). Similarly, changes in MDV showed a moderate negative correlation with improvements in BCVA ($r = –0.48$, $p = 0.008$) (Table 3).

A weak but significant positive correlation was observed between changes in CC FD% and changes in MDV ($r = 0.35$, $p = 0.042$). Changes in both CC FD% and MDV showed no significant correlation with LLVA changes ($r = –0.22$, $p = 0.24$ and $r = –0.18$, $p = 0.33$, respectively) (Table 3).

Regression analysis

A stepwise multiple linear regression analysis was performed to identify factors associated with BCVA improvement. The model included changes in CC FD%, changes in drusen volume, baseline BCVA, and other potential confounding factors such as age, lens status, hypertension, smoking status, diabetes, and family history of AMD. The analysis revealed that changes in CC FD% (β = –0.41, $p = 0.005$), baseline BCVA (β = –0.35, $p = 0.015$), and changes in drusen volume (β = –0.28, $p = 0.045$) were independent predictors of BCVA improvement. The final model accounted for 51.3% of the variance in BCVA improvement ($R^2 = 0.513$). Other variables, including age ($p = 0.34$), lens status ($p = 0.28$), hypertension ($p = 0.41$), smoking status ($p = 0.38$), diabetes ($p = 0.45$), and family history of AMD ($p = 0.52$) did not significantly contribute to the model (Table 4).

DISCUSSION

In this retrospective study, we investigated the effects of photobiomodulation therapy on both functional and anatomical parameters in patients with intermediate AMD. Our results demonstrated a significant improvement in BCVA and a reduction in drusen volume following PBM treatment. Notably, we observed a significant improvement in CC perfusion, as evidenced by the reduction in FD%. The correlation between perfusion improvement and functional outcomes suggests a potential relationship between choroidal circulation and visual function in AMD patients undergoing PBM therapy.

Previous studies investigating PBM in AMD have primarily focused on functional outcomes and drusen characteristics. The LIGHTSITE III trial demonstrated significant improvements in BCVA after PBM treatment using the Valeda Light Delivery System, reporting a gain of approximately 4 ETDRS letters at 13 months [12]. Similarly, our study found a mean improvement of 3.2 ETDRS letters at 2 months, albeit using different treatment parameters and follow-up duration. Regarding drusen volume, our findings align with previous reports [11, 18] showing a significant reduction following PBM treatment, although the magnitude of change varies across studies.

The most notable finding of our study is the demonstration of improved CC perfusion following PBM treatment using SS-OCTA, a parameter not previously investigated in this context. This improvement in choroidal circulation may represent one of the mechanisms through which PBM exerts its therapeutic effect. The correlation between reduced FD% and improved visual acuity suggests that enhanced choroidal perfusion might play a role in the functional benefits observed with PBM therapy. While correlation between reduced CC FD% and improved BCVA does not establish causation, our regression analysis showed both CC FD% improvement and drusen reduction independently contributed to BCVA gains, suggesting parallel mechanisms.

Table 3. Correlation analysis in the treatment group.

	Δ *BCVA*	Δ *LLVA*	Δ *MDV*
Δ *CC FD%*	r = –0.54, p = 0.002	r = –0.22, p = 0.24	r = 0.35, p = 0.042
Δ *MDV*	r = –0.48, p = 0.008	r = –0.18, p = 0.33	–

Values are expressed as Pearson correlation coefficients (r) with corresponding *P* values. *Δ* change from baseline, *BCVA* best-corrected visual acuity, *LLVA* low luminance visual acuity, *MDV* mean drusen volume, *CC* choriocapillaris, *FD%* flow deficit percentage.

Table 4. Multiple linear regression analysis for factors associated with Δ *BCVA*.

Variable	Standardized β	*P* value
Δ CC FD%	–0.41	0.005
Baseline BCVA	–0.35	0.015
Δ MDV	–0.28	0.045
Age	–0.11	0.34
Lens status	–0.13	0.28
Hypertension	–0.09	0.41
Smoking status	–0.10	0.38
Diabetes	–0.08	0.45
Family history of AMD	–0.07	0.52

Values are expressed as standardized β coefficients from stepwise multiple linear regression analysis. Final model $R^2 = 0.513$. *Δ* change from baseline, *CC* choriocapillaris, *FD%* flow deficit percentage, *BCVA* best-corrected visual acuity, *MDV* mean drusen volume, *AMD* age-related macular degeneration.

The relationship between CC perfusion and visual function in AMD has been well documented in previous studies [22–24]. Kar et al. [22, 23]. demonstrated that CC FD% correlate with visual acuity in AMD patients, highlighting the crucial role of choroidal circulation in maintaining photoreceptor function. Indeed, the CC represents the primary source of oxygen and nutrients for the outer retina, and its impairment may lead to photoreceptor dysfunction [13, 25, 26]. Our findings of improved visual acuity following enhancement of CC perfusion are consistent with this pathophysiological model and suggest that PBM might act by optimizing choroidal blood flow and, consequently, outer retinal function.

The biological mechanisms underlying the improvement in CC perfusion after PBM therapy may be explained by different pathways [27]. The primary mechanism likely involves PBM's effect on mitochondrial function in the RPE. By enhancing mitochondrial ATP production in RPE cells [28], PBM may improve the metabolic activity of these cells, which, due to their anatomical contiguity with the CC, could lead to improved choroidal perfusion. However, the interpretation of improved CC perfusion should be considered with caution. While we employed shadow compensation algorithms and swept-source OCTA technology, the observed enhancement in CC flow signal might be partially attributed to the reduction in drusen volume, which could result in decreased shadowing effects on the underlying CC [20]. Thus, the improved visualization of CC flow might represent a combination of both actual perfusion enhancement and reduced artifacts from overlying drusen.

The clinical implications of our findings extend beyond the observed improvements in visual acuity. Several studies have demonstrated that CC impairment plays a crucial role in the progression from intermediate to neovascular AMD. Corvi et al. [29, 30]. showed that areas of CC FD are closely associated with the development of macular neovascularization, while Nassisi et al. [31]. demonstrated that regional CC ischemia may drive the development and enlargement of drusen through the upregulation of pro-angiogenic factors. Therefore, the improvement in CC perfusion observed after PBM therapy might represent a potential protective mechanism against disease progression, by reducing the ischemic drive that leads to neovascularization. The combination of enhanced CC perfusion and drusen volume reduction suggests that PBM might influence the underlying pathophysiology of AMD. The strong correlation between decreased FD% and improved BCVA supports the potential role of CC perfusion as a biomarker for treatment response. Moreover, the structural changes observed in our study, particularly the reduction in drusen volume, might indicate a potential effect on disease progression, although longer follow-up studies are needed to confirm this hypothesis.

Several limitations of our study should be acknowledged. First, its retrospective nature and the relatively small sample size may limit the generalizability of our findings, and the impossibility of patient masking potentially introducing placebo effects. Future research should implement randomized designs with sham treatments, longer follow-up periods (≥12 months), and standardized PBM protocols to establish optimal treatment parameters. Second, the follow-up period of two months, while sufficient to demonstrate short-term effects, does not allow us to assess the durability of the observed improvements or the long-term impact on disease progression. Third, while our shadow compensation algorithms minimize interference, we acknowledge that reduced FD% may partially reflect decreased optical shadowing from shrinking drusen rather than true perfusion enhancement. Future studies should employ multimodal approaches, including indocyanine green angiography and OCT-based flow quantification, to verify the biological nature of these perfusion changes. Finally, the lack of standardized protocols for PBM treatment in AMD makes it difficult to compare our results directly with other studies using different devices or treatment parameters.

In conclusion, our study demonstrates that PBM therapy in intermediate AMD leads to significant short-term improvements in both functional and anatomical parameters, with particular emphasis on enhanced CC perfusion and reduced drusen volume. The correlation between perfusion improvement and visual function suggests that CC flow might serve as a potential biomarker for treatment response. While these short-term results are promising, prospective randomized controlled trials with larger cohorts and longer follow-up periods are needed to evaluate the durability of these effects and their potential impact on disease progression.

SUMMARY

What was known before

- Photobiomodulation therapy can improve visual function in patients with intermediate age-related macular degeneration Choriocapillaris dysfunction plays a crucial role in drusen formation and AMD progression Previous studies on PBM mainly focused on functional outcomes and drusen characteristics The effects of PBM on choroidal perfusion remained largely unexplored.

What this study adds

- First demonstration of PBM-induced improvement in choriocapillaris perfusion using swept-source OCTA Evidence of

correlation between enhanced choroidal perfusion and visual function improvement following PBM treatment Documentation of concurrent structural changes in drusen volume and choriocapillaris flow deficits Identification of choriocapillaris flow as a potential biomarker for monitoring treatment response in AMD patients undergoing PBM therapy.

DATA AVAILABILITY

The datasets generated and analysed during the current study are not publicly available due to privacy concerns and regulations regarding patient data protection, but de-identified data are available from the corresponding author upon reasonable request and with appropriate institutional review board approval.

REFERENCES

1. Flaxman SR, Bourne RRA, Resnikoff S, Ackland P, Braithwaite T, Cicinelli MV, et al. Global causes of blindness and distance vision impairment 1990–2020: a systematic review and meta-analysis. Lancet Glob Health. 2017;5:e1221–34. Available at: https://pubmed.ncbi.nlm.nih.gov/29032195/ [Accessed March 12, 2021].
2. Milton RC, Clemons TE, Klien R, Seddon JM, Ferris FL. Risk factors for the incidence of advanced age-related macular degeneration in the age-related eye disease study (AREDS) AREDS report no. 19. Ophthalmology. 2005;112:533–9.e1. Available at: https://pubmed.ncbi.nlm.nih.gov/15808240/ [Accessed November 14, 2022].
3. Viggiano P, Toto L, Ferro G, Evangelista F, Porreca A, Mastropasqua R. Choroidal structural changes in different intermediate AMD patterns. Eur J Ophthalmol. 2021. Available at: [https://pubmed.ncbi.nlm.nih.gov/33506710/ Accessed March 25, 2021]
4. Voichanski S, Bousquet E, Abraham N, Santina A, Mafi M, Fossataro C, et al. En face optical coherence tomography illustrates the trizonal distribution of Drusen and subretinal drusenoid deposits in the macula. Am J Ophthalmol. 2024;261:187–98. Available at: https://pubmed.ncbi.nlm.nih.gov/38218515/ [Accessed October 14, 2024].
5. Curcio CA, Presley JB, Millican CL, Medeiros NE. Basal deposits and drusen in eyes with age-related maculopathy: Evidence for solid lipid particles. Exp Eye Res. 2005;80:761–75.
6. Byon I, Ji Y, Alagorie AR, Tiosano L, Sadda SR. Topographic assessment of choriocapillaris flow deficits in the intermediate age-related macular degeneration eyes with hyporeflective cores inside Drusen. Retina. 2021;41:393–401.
7. Clemens CR, Lauermann JL, Schmitz B, Eter N, Alten F. Longitudinal choriocapillaris changes in the presence of reticular pseudodrusen. Sci Rep. 2021; 11. Available at: https://pubmed.ncbi.nlm.nih.gov/34521974/ [Accessed April 8, 2023].
8. Borrelli E, Uji A, Sarraf D, Sadda SVR. Alterations in the choriocapillaris in intermediate age-related macular degeneration. Invest Ophthalmol Vis Sci. 2017;58:4792–8. Available at: https://pubmed.ncbi.nlm.nih.gov/28973325/ [Accessed April 20, 2023].
9. Rodriguez DA, Song A, Bhatnagar A, Weng CY. Photobiomodulation therapy for non-exudative age-related macular degeneration. Int Ophthalmol Clin. 2025;65:47–52. Available at: https://pubmed.ncbi.nlm.nih.gov/39710905/ [Accessed January 5, 2025].
10. Hamblin MR, Demidova TN Mechanisms of low level light therapy. https://doi.org/10.1117/12.646294. 2006; 6140: 614001. Available at: https://www.spiedigitallibrary.org/conference-proceedings-of-spie/6140/614001/Mechanisms-of-low-level-light-therapy/10.1117/12.646294.full [Accessed January 5, 2025].
11. Nassisi M, Mainetti C, Paparella GR, Belloni Baroni L, Milella P, Leone G, et al. Short-term efficacy of photobiomodulation in early and intermediate age-related macular degeneration: the PBM4AMD study. Eye (Lond). 2024; 38. Available at: https://pubmed.ncbi.nlm.nih.gov/39277630/ [Accessed January 5, 2025].
12. Boyer DS, Munk MR, Tedford SE, Croissant CL, Rückert R, Tedford CE. " LIGHTSITE III: 13-month efficacy and safety evaluation of multiwavelength photobiomodulation in nonexudative (Dry) age-related macular degeneration using the LumiThera valeda light delivery system ". Retina. 2024;44:e83–7. Available at: https://pubmed.ncbi.nlm.nih.gov/39312884/ [Accessed January 5, 2025].
13. Viggiano P, Costanzo E, Giannini D, Fragiotta S, De Geronimo D, Giorno P, et al. In vivo assessment of associations between photoreceptors structure and macular perfusion in type 1 diabetes. Br J Ophthalmol. 2022. Available at: https://pubmed.ncbi.nlm.nih.gov/36126103/ [Accessed April 8, 2023].
14. Mastropasqua R, Evangelista F, Amodei F, D'aloisio R, Pinto F, Doronzo E, et al. Optical coherence tomography angiography in macular neovascularization: a comparison between different octa devices. Transl Vis Sci Technol. 2020;9:1–7.
15. Ferris FL, Wilkinson CP, Bird A, Chakravarthy U, Chew E, Csaky K, et al. Clinical classification of age-related macular degeneration. Ophthalmology. 2013;120:844–51.
16. Viggiano P, Bisceglia G, Bacherini D, Chhablani J, Grassi MO, Boscia G, et al. Long-term visual outcomes and optical coherence tomography biomarkers in eyes with macular edema secondary to retinal vein occlusion following anti-vascular endothelial growth factor therapy. Retina. 2024;44:1572–9.
17. Viggiano P, Vujosevic S, Palumbo F, Grassi MO, Boscia G, Borrelli E, et al. Optical coherence tomography biomarkers indicating visual enhancement in diabetic macular edema resolved through anti-VEGF therapy: OCT biomarkers in resolved DME. Photodiagnosis Photodyn Ther. 2024; 46. Available at: https://pubmed.ncbi.nlm.nih.gov/38460657/ [Accessed May 27, 2024].
18. Borrelli E, Coco G, Pellegrini M, Mura M, Ciarmatori N, Scorcia V, et al. Safety, tolerability, and short-term efficacy of low-level light therapy for dry age-related macular degeneration. Ophthalmol Ther. 2024; 13. Available at: https://pubmed.ncbi.nlm.nih.gov/39271642/ [Accessed January 5, 2025].
19. Borrelli E, Toto L, Viggiano P, Evangelista F, Palmieri M, Mastropasqua R. Wide-field topographical analysis of the retinal perfusion and neuroretinal thickness in healthy eyes: a pilot study. Eye (Basingstoke). 2020.
20. Shi Y, Chu Z, Wang L, Zhang Q, Feuer W, de Sisternes L, et al. Validation of a compensation strategy used to detect choriocapillaris flow deficits under Drusen with swept source OCT angiography. Am J Ophthalmol. 2020;220:115–27. Available at: https://pubmed.ncbi.nlm.nih.gov/32621895/ [Accessed January 5, 2025].
21. Chu Z, Zhang Q, Gregori G, Rosenfeld PJ, Wang RK. Guidelines for imaging the choriocapillaris using OCT angiography. Am J Ophthalmol. 2021;222:92–101.
22. Kar D, Amjad M, Corradetti G, Swain TA, Clark ME, McGwin G, et al. Choriocapillaris impairment, visual function, and distance to fovea in aging and age-related macular degeneration: ALSTAR2 baseline. Invest Ophthalmol Vis Sci. 2024; 65. Available at: https://pubmed.ncbi.nlm.nih.gov/39042400/ [Accessed January 6, 2025].
23. Kar D, Corradetti G, Swain TA, Clark ME, McGwin G, Owsley C, et al. Choriocapillaris impairment is associated with delayed rod-mediated dark adaptation in age-related macular degeneration. Invest Ophthalmol Vis Sci. 2023; 64.
24. Lutty G, Grunwald J, Majji AB, Uyama M, Yoneya S. Changes in choriocapillaris and retinal pigment epithelium in age-related macular degeneration. Mol Vis. 1999;5:35.
25. Borrelli E, Palmieri M, Viggiano P, Ferro G, Mastropasqua R. PHOTORECEPTOR DAMAGE IN DIABETIC CHOROIDOPATHY. Retina. 2020;40:1062–9. Available at: https://pubmed.ncbi.nlm.nih.gov/30986798/ [Accessed October 6, 2020].
26. Borrelli E, Costanzo E, Parravano M, Viggiano P, Varano M, Giorno P, et al. Impact of bleaching on photoreceptors in different intermediate AMD phenotypes. Transl Vis Sci Technol. 2019;8:5–5.
27. Heinig N, Schumann U, Calzia D, Panfoli I, Ader M, Schmidt MHH, et al. Photobiomodulation mediates neuroprotection against blue light induced retinal photoreceptor degeneration. Int J Mol Sci. 2020;21:1–14.
28. Anon. Photobiomodulation with 670 nm light increased phagocytosis in human retinal pigment epithelial cells - PubMed. Available at: https://pubmed.ncbi.nlm.nih.gov/26321863/ [Accessed January 6, 2025].
29. Corvi F, Corradetti G, Tiosano L, McLaughlin JA, Lee TK, Sadda SR. Topography of choriocapillaris flow deficit predicts development of neovascularization or atrophy in age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol. 2021;259:2887–95. Available at: https://pubmed.ncbi.nlm.nih.gov/33900443/ [Accessed January 7, 2025].
30. Corvi F, Tiosano L, Corradetti G, Nittala MG, Lindenberg S, Alagorie AR, et al. Choriocapillaris flow deficits as a risk factor for progression of age-related macular degeneration. Retina. 2021;41:686–93.
31. Nassisi M, Tepelus T, Nittala MG, Sadda SR. Choriocapillaris flow impairment predicts the development and enlargement of drusen. Graefes Arch Clin Exp Ophthalmol. 2019;257:2079–85. Available at: https://pubmed.ncbi.nlm.nih.gov/31263948/ [Accessed January 7, 2025].

AUTHOR CONTRIBUTIONS

PV conceived the study, performed data analysis, and drafted the manuscript. GB and AC contributed to study design and critically revised the manuscript. MLT and ACT were involved in data collection and interpretation. MGP and AS provided expertise in image analysis and contributed to the interpretation of results. EB and MR contributed to patient recruitment and data collection. GG and GA provided statistical expertise and critical feedback. FB supervised the study, provided critical feedback, and helped shape the research and analysis. All authors reviewed and approved the final version of the manuscript.

FUNDING

PV is a consultant for: Abbvie, Bayer, Hofmann La Roche, Novartis and Zeiss. FB is a consultant for: Alcon, Abbvie, Bayer, Hofmann La Roche, Novartis and Zeiss. EB is a

consultant for: Abbvie, Bayer, Hofmann La Roche, Novartis and Zeiss. MR is a consultant for: Abbvie, Bayer, Hofmann La Roche, Novartis and Zeiss. Other authors: None

COMPETING INTERESTS

EB is a member of the Eye editorial board. The other authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Pasquale Viggiano.