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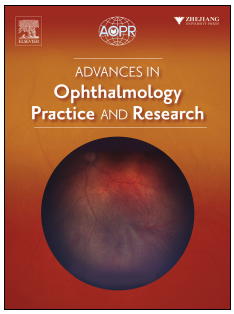

A preliminary observation on rod cell photobiomodulation in treating diabetic macular edema

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Advances in Ophthalmology Practice and Research

Title of the manuscript

A preliminary observation on rod cell photobiomodulation in treating diabetic macular edema

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Study Approval

This study followed the Declaration of Helsinki and was approved by the Ethics Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine (approval number: 2016013). All patients participating in this study were fully informed and signed an informed consent form.

Author Contributions

The authors confirm contribution to the paper as follows: Conception and design of study: SK, WB; Data collection: SK; Analysis and interpretation of results: SK, WB, JM; Drafting the manuscript: SK, WB, JM; All authors reviewed the results and approved the final version of the manuscript.

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Editorship Disclosure

Abbreviations

Diabetic macular edema (DME)

photobiomodulation (PBM)

Diabetic retinopathy (DR)

vascular endothelial growth factor (VEGF)

Early Treatment Diabetic Retinopathy Study (ETDRS)

Fundus fluorescence angiography （FFA）

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Abstract

Objective To evaluate the safety and effectiveness of photobiomodulation (PBM) in the treatment of diabetic macular edema (DME). **Methods:** It was a single-center, self-controlled prospective study. The clinical records of 12 diabetic retinopathy patients (5 males and 7 females, 20 eyes in total) who were treated with PBM for DME at the Second Affiliated Hospital, Zhejiang University School of Medicine, were analyzed. The mean age was 56（26-68）years. All the participants received PBM treatment during darkness at night in no less than 5 days per week and no less than 8 hours per day. In the baseline check and follow-up checks (1, 2, 6, 10, and 12 months after the start of treatment), the best-corrected visual acuity, the thickness of the retina in the macula, and the changes of the fundus lesions were observed. Wilcoxon signed rank test was used to compare the results before and after treatment. P <0.05 was considered statistically significant.

Results: No fundus complication was observed during follow-up checks. In baseline and 12-month follow-up checks, the best-corrected visual acuity was 71.75±12.47 and 79.50±10.85, maximal retinal thickness in macular area was 390.95±77.12 μm and 354.13±55.03 μm, average retinal thickness in macular area was 334.25±36.45 μm and 314.31±33.28 μm, foveal thickness was 287.00±46.79 μm and 265.63±67.14 μm. The best-corrected visual acuity, average retinal thickness in macular area results in consecutive follow-up results except that in the 1st month showed significant difference compared with baseline results. There were

significant difference between every follow-up visit and baseline results of maximal retinal thickness in macular area (P <0.05). All follow-up results of foveal thickness were not significantly different (P >0.05) from the baseline result, except that in the 6th month (P =0.049). Obvious improvement could be observed in retinal fundus fluorescein angiography images.

Conclusions: PBM is a safe and effective treatment of DME, which deserves further investigation.

Key Words: dark adaptation, diabetic macular edema, diabetic retinopathy, photobiomodulation, rod cells

Introduction

Diabetic retinopathy (DR) is the commonest disease that can lead to vision loss or blindness among working-age people. According to data from the World Health Organization (WHO), DR accounts for 2.5% of the 37 million blindness cases in the world. Diabetic macular edema (DME) is the accumulation of intraretinal and subretinal fluid in the macular area [1]. DME can occur at any stage of DR. With the aggravation of DR, the incidence of DME gradually increases, which is one of the main reasons for the vision loss in DR patients. Recent development in optical coherence tomography (OCT) technology provides a reliable observation of DME-related features, including central retinal thickness[2], central subfield thickness [3], and outer retinal hyperreflective deposits, for early diagnosis of DME and the evaluation of treatment efficacy [4].

Currently, treatment of DME and its clinical intervention mainly rely on laser, anti-vascular endothelial growth factor injection and surgical treatment to delay the disease development. Some new treatments including corticosteroids [5] and intravitreal dexamethasone implant [2] have also shown efficacy in relieving DME. However, these treatments are invasive and expensive. There is an urgent need for non-invasive and low-cost treatments of DME [6].

In recent years, based on the theoretical analysis and experimental results that rod cells consume more energy and oxygen in the dark than in the light, photobiomodulation (PBM) is proposed as a potential treatment of DR. PBM can relieve retinal anoxia caused by high oxygen demands of rods during dark adaptation which promotes the formation of DME in patients with DR [7 8]. Proposed mechanisms of PBM in relieving DME include enhanced photoreceptor mitochondrial function, counteracting inflammation, and enhanced supporting cell function [9]. Clinical observations have shown that PBM can reduce the thickness of retinal edema and increase visual acuity in patients with DME [10]. Compared with current mainstream

treatments (e.g., injection of anti-VEGF drugs, laser photocoagulation, vitrectomy surgery), PBM may provide an alternative with a non-invasive and low-cost treatment of DMR to improve the current standard of care. However, there are limited existing clnical human studies on the treatment efficacy of PBM for DME, where the conclusions are inconsistent [11 12]. This study aimed to preliminarily evaluate the treatment efficacy of PBM as a therapy of DME in Chinese population.

Materials and methods

1. Subjects

This study is a single-center, self-controlled prospective study. Data were collected from 20 eyes of 12 patients with DR and DME who met the inclusion criteria. They were admitted to the Second Affiliated Hospital of Zhejiang University School of Medicine from April 2016 to April 2019. There were 5 males and 7 females. The average age was 56.0±17.7 years.

The DR diagnostic procedure was identical for all the patients in this study. We used commercially available OCT (RTVue-XR; Optovue, Inc., Freemont, CA) device in clinical practice where the extracted features were quantitative. The OCT device with a light source centered on 840 nm and a bandwidth of 50 nm could operate with two consecutive 304 raster B-scans (each B-scan containing 304 A-scans). The A-scan rate was 70,000 scans per second with motion correction minimized artifacts arising from microsaccades and fixation changes. Ultra-wield-filed scanning laser ophthalmoscopy (OPTOS Daytona, P200) and fundus fluorescein angiography (HEIDELBERG HRA2) were mandatory in the process of detecting DR.

Inclusion criteria: patients over 18 years with diabetes mellitus (type 1 or type 2) and mild to moderate non-proliferative DR (NPDR); the best corrected visual acuity of the study eye is better than 55 letters of ETDRS (Snellen VA 6/24); mild or moderate DME: thickening or hard exudation of the retina in the posterior pole away from the center of the macula or close to the macula but not involving the center of the macula; OCT shows that the thickness of the fovea involved is less than 400 μm; previous macular photocoagulation, vitreous cavity hormones for at least 6 months and anti-VEGF treatment for at least 3 months; the refractive interstitium is transparent and the fundus image is clear.

Exclusion criteria: patients with severe non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) ; visual acuity less than 55 ETDRS letters; patients with severe DME where the thickness of involved fovea is greater than 400 μm on OCT; previous macular photocoagulation, vitreous cavity corticosteroids and anti- VEGF treatment for at least 3 months; the refractive interstitium is opacity

and the fundus image is unclear; macular edema caused by other reasons.

This study followed the Declaration of Helsinki and was approved by the Ethics Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine. All patients participating in this study were fully informed and signed an informed consent form.

2. Light-emitting device for PBM treatment

The light-emitting device delivers phototherapy to a user’s retina through closed eyelids. It is a patented product (Patent No: CN206508107U). It consists of a light-emitting body, a protective eye shield, and a charger. When worn, the light-emitting body is inserted into the fabric mask (i.e., eye shield) which was placed over the patient’s eyes and attached using an adjustable Velcro strap. The fabric mask is made of nylon, polyurethane and polyester. These materials are non-toxic and are commonly used in a wide variety of skin-contacting apparel. The protective goggles protect the luminous body and optimizes comfort for users. Different patients used different goggles which were identically designed.

The light-emitting body, which is the core component of the device, contains two Light Emitting Diodes (LEDs). The LEDs are powered by rechargeable batteries which power the device without the need for an external power source when it is worn. The time slots and duration when the device is worn was logged for compliance analysis.The light-emitting body is made from medical grade low-density polyethylene, which has been tested and passed the relevant physiochemical and in vivo biological reactivity tests. The device emits low-brightness green light. The illuminance is not higher than 15lux, and the working current of the light source is 10 mA, which meets the photoelectric biological safety standards and regulations.

3. Treatment and follow up monitoring methods

The study eye (at least one eye) is slightly light-adapted to DME patients during night sleep. Light-emitting devices emit low-brightness visible light of specific wavelengths, allowing patients to undergo light-adaptation therapy in dark conditions at night for no less than 5 days a week and more than 8 hours per day.

The baseline examination included: ETDRS best corrected vision, fundus color photographs and ultra-wield-filed scanning laser ophthalmoscopy to check the severity of DR and DME, OCT scan to detect the thickness of the retina in the macular area, fluorescein angiography to evaluate the stage of DR, eye slit lamp examination, intraocular pressure, blood pressure, blood sugar, glycosylated hemoglobin, and Pittsburgh Insomnia Rating Score to assess the quality of sleep. The patients were followed up in 1, 2, 4, 6, and 12 months after starting the treatment. During each follow-up, the best corrected visual acuity, the thickness of

the retina in the macular area and the changes of the fundus lesions were examined. If the edema is greater than 400 μm, the rescue mode of management for these patients in DME is anti-VEGF or grid laser. If the disease progresses to PDR, the rescue mode of management for these patients is panretinal photocongulation or vitrectomy surgery. The PBM treatment mode was identical for all the included eyes. For patients where one of the eye needed conventional treatment, these patients were not excluded.

4. Statistical analysis

In this pilot study, we performed longitudinal observation of the treatment efficacy. For each subject, the comparison was made between the baseline and follow-up data. Statistical analysis was performed using SPSS 23.0 statistical software. Levene's test for homogeneity of variance and Shapiro-Wilk test for normal distribution were performed on the distributions of baseline and follow-up visual acuity and thickness of macular area. Paired comparisons were performed between the baseline and follow-up results. Paired t test was used if the homogeneity of variance and normality were satisfied, otherwise the Wilcoxon signed rank test was used. Statistically significance was defined as *P* value less than 0.05.

Results

1. Subjects and eyes

The number of patients at baseline, after 1, 2, 4, 6, and 12 months of treatment were 12, 12, 12, 12, 11, and 10, respectively. The corresponding number of eyes were 20, 20, 20, 20, 18, and 16.

2. Best corrected visual acuity

The comprehensive best corrected visual acuity (mean ± standard deviation[SD]) of the patients at baseline, after 1, 2, 4, 6, and 12 months of treatment were: 71.75± 12.47, 73.74±13.87, 74.65±12.98, 75.84±12.03, 77.24±11.67, and 79.50±10.85. All the results satisfied the homogeneity of variance ($p>0.05$ in Levene's test) but not normality ($P<0.05$ in Shapiro-Wilk test) except for the 4-month follow-up ($P=0.064$). According to the results of Wilcoxon test, compared with the baseline, the follow-up results were significantly different ($P<0.05$) except the 1-month follow-up ($P=0.11$).

3. Maximum thickness of the retina in the macular area

The maximum retinal thickness (mean ± SD, unit: μm) in the macular area of the patients at baseline, after 1, 2, 4, 6, and 12 months of treatment were 390.95±77.12, 381.47±70.27, 373.85±61.25, 361.68±59.99, 352.00±50.83, and 354.13±55.03. All results met the homogeneity of variance ($P>0.05$ in Levene's test) but not normality ($P<0.05$ in Shapiro-Wilk test). According to the results of Wilcoxon's test, compared with the baseline, the follow-up results were significantly different ($P<0.05$ for all).

4. Average thickness of the retina in the macular area

The average retinal thickness (mean ± SD, unit: μm) of the macular area of the patients at baseline, after 1, 2, 4, 6, and 12 months of treatment were 334.25±36.45, 331.32±37.78, 328.50±35.26, 324.77±44.31, 316.24±30.93, and 314.31±33.28. All results meet the homogeneity of variance (P >0.05 in Levene's test) but not normality (P <0.05 in Shapiro-Wilk test). According to the results of Wilcoxon test, compared with the baseline, the follow-up results were significantly different (p<0.05) except the 1-month follow-up (P =0.06).

5. Thickness of retinal fovea

The thickness of retinal fovea (mean ± SD, unit: μm) of the patients' at baseline, after 1, 2, 4, 6, and 12 months of treatment were: 287.00±46.79, 289.63±65.29, 285.35±52.93, 279.68±66.39, 272.18±57.56, and 265.63±67.14. All results met the homogeneity of variance (p>0.05 in Levene's test) but not normality (P <0.05 in Shapiro-Wilk test). According to the results of Wilcoxon test, there was no statistically significant difference in between the baseline and follow-up results (P >0.05) except for the 6-month follow-up (P =0.049).

6. A typical case

A 33-year old male had type 2 diabetes of 5 years with moderate NPDR in both eyes and DME in the left eye which was included in this study. The best corrected visual acuity was 82 letters in the ETDRS chart. The maximum and average thicknesses of the retina in the macular area were 346μm and 323.5μm, respectively. The thickness of the fovea was 252μm. FFA angiography showed microaneurysms, telangiectasia and leakage, with fluorescence obscured by bleeding, macular area fluorescence accumulates in the later stage. The patient was treated using the retinal photo-adaptation device for 12 months. The 12-month follow-up showed the best corrected visual acuity of 84 letters in the ETDRS chart. The follow-up maximum and average thicknesses of the retina in the macular area were 315μm and 288.2μm, respectively. The follow-up thickness of the fovea was 227μm. As shown in Figure 1, the follow-up FFA imaging showed significant improvement in microaneurysms of the macular area and the leakage of telangiectasia.

7. Summary of therapeutic effectiveness

Table 1 shows that after 12 months of treatment, 87.5% of patients had improved visual acuity, and more than 60% of patients had reduced retinal thickness. With the treatment for 2-12 months, the best corrected visual acuity, the maximum and average thicknesses of retina in the macular area were all significantly different from the baseline results (P<0.05 for all). Table 2 shows that, with the treatments for 1-12 months, the medians of changes in best corrected visual acuity were all positive, and the medians of changes in maximum and average thicknesses of the retina in the macular area, as well as the thickness of

the fovea were all negative, indicating the consistency in therapeutic effectiveness.

Discussion

With economic growth and changes in lifestyle, the number of diabetic patients has been increasing rapidly. In 2010, in China there were 13.16 million DR patients over 45 years old, where the prevalence of DR in diabetic patients was 18.45% [13]. The incidence of diabetes in adults in China is higher than global average, with estimated prevalence of 11.6% in adults [14]. The number of patients with diabetes is as high as 114 million, which is the largest in the world, accounting for more than 1/4 of world adult diabetes patients. With the extending course of diabetic patients, the prevalence and blindness rate of DR are increasing. The timely treatment of DR is of great significance for improving the quality of life of diabetic patients, avoiding blindness and labor loss, and reducing the consumption of economy and medical resources. The treatment of DR currently mainly relies on laser, drugs, and surgery to decelerate the course of the disease. However, the existing treatment methods are invasive and expensive, which brings a heavy burden to patients and society.

Studies have shown that hypoxia generated by dark adaptation promotes the development of DR [7]. The main hypothesis is that the rod cells on the outer retina are depolarized to the maximum in the dark, and continuously release a large amount of neurotransmitter glutamate, which increases the consumption of energy and oxygen. Hypoxia and hyperglycemia accumulate over time and affect intracellular and extracellular functions through oxidative stress, free radicals, and inflammation. In Müller cells, this process promotes the expression of glial fibrillary acidic protein that can be observed in the early stages of diabetes and the production of vascular endothelial growth factor (VEGF). Once hypoxia is formed, a cascading effect occurs, which promotes the production of VEGF and causes related changes in DR microangiopathy, and these changes in turn exacerbate the underlying hypoxia. With the progression of diabetes, pathological changes in retinal capillaries can appear due to the hypoxia of retina aggravated by long-term nightly dark adaptation [8 10]. In early stage of DR, visual acuity is still normal. However, visual function can be abnormal during dark adaptation due to the low oxygen partial pressure in retina. Arden et al. did a series of studies to confirm the hypothesis that dark adaptation exacerbates DR and induces DME [7 10 15 16].

Since the primary cause of retinal hypoxia during dark adaptation is the demand of rod cells for oxygen, it is speculated that reducing the rod’s dark current can alleviate the development of DR. Tang et al. studied the effect of PBM of far-red and near-infrared lights near the wavelength of 670nm on streptozotocin-induced DR mice [17]. They found that, although the use of 670nm, 6 J/cm^2 PBM treatment did not change the

cytochrome oxidase activity in the retina or in cultured retinal cells, it inhibited the superoxide production and leukocyte stasis caused by diabetes and the expression of ICAM-1, which effectively reduced the death of retinal glial cells. In cultured retinal cells (including ganglion cells, photoreceptors, Müller cells, and pigment epithelial cells) exposure to 30-mM glucose, PBM can inhibit the production of superoxide, the expression of inflammatory markers, and cell death. The author therefore concludes that PBM can be used as a low-cost therapy in the treatment of DR. Based on animal experiment and clinical test on human subjects with DME, Shen et al. found that PBM enhanced the photoreceptor mitochondrial membrane potential and protected Müller cells and photoreceptors [18]. Therefore, PBM results in anatomical improvement of DME , that can be used as a safe and non-invasive treatment.

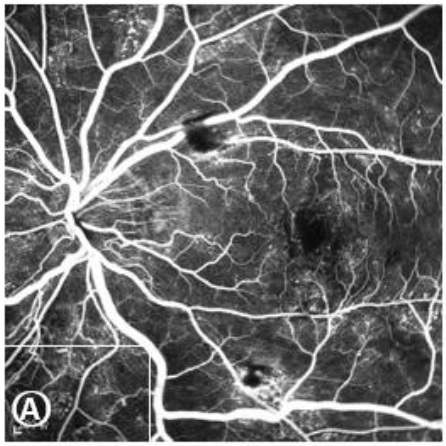
In 2011, Arden et al. completed a 6-month study of PBM on 34 patients with DME. The thickness of the retinal edema of the study eye decreased with visual acuity increased, which was statistically different from that of the control eye. Thus, the authors proposed that sleep in the presence of weak light can delay the progression of diabetic macular edema [10]. In 2018, Cook et al. invented a contact lens that reduces the metabolic intensity of rod cells in the dark at night based on the clinical research on the PBM of DR. Their device got the FDA safety certification with the efficacy initially verified in animal experiments, while further clinical trials are needed [19].

With the knowledge from the abovementioned experiments and clinical research, we developed a bespoke retinal light adaptation device and optimised the key specification for Chinese population: wavelength, uniformity, illuminance, dose control, etc. Short-term PBM is common in published studies, in which the patients with DME are exposed to high-intensity PBM for 0-10 minutes as a daily dose and the length of treatment varies from 2 weeks to 36 weeks, where 4-10 weeks are the most common [9 20]. In our study, we adopted the long-term, low-intensity PBM treatment. The treatment lasted for one year. The light intensity and dose of PBM are similar as those of an earlier clinical trial where the treatment lasted for two years [11 12]. In addition, there is currently a lack of standardized design of PBM devices. The designs include hand-hold LED units, fixed LED devices for large-area light exposure, and novel low-power contact lens, where the light wavelength, power, and distance to the eyes are different [9 21]. All these factors may affect the treatment length required. Some devices are for general PBM instead of ophthalmologic treatment [22]. For long-term PBM treatment and light exposure during sleep, the safety and user comfort are significant considerations in designing the PBM device. Our PMB device met the requirement of photoelectric biological safety standards, passed the medical device safety registration test. Most importantly, it was

specifically designed to treat DME in Chinese population. The results showed no adverse events or sleep disorders. This therapy has the advantages of non-invasiveness, low cost and easy operation.

We observed the curative effect of DME treated by PBM in Chinese adults with diabetes. The results were consistent with those of Arden's research. By observing the changes in the patient’s fundus, retinal thickness and best corrected visual acuity, after 12 months of treatment, 87.5% of patients have improved vision, and more than 60% of patients have reduced retinal thickness. With the treatment of 2-12 months, the best-corrected visual acuity, the maximum thickness of the retina in the macular area, and the average thickness of the retina in the macular area were consistently significantly different from those before treatment (P<0.05). From 1 -12 months after the start of treatment, the median change in best corrected visual acuity was greater than zero, while the median change in maximum retinal thickness in the macular area, average retinal thickness in the macular area, and foveal thickness were all less than zero, which reflects the consistency of curative effect. Between April 2014 and June 2015, 308 patients with non-foveal involvement with DME participated in a phase three multi-center clinical trial CLEOPATRA on the treatment of PBM in the United Kingdom [11 12]. The results showed that compared with the baseline, the macular edema of non-foveal involvement was degraded to a certain extent, but there was no significant difference compared with the control group. Our results are consistent with published studies on the safety of the therapy, but not on the therapeutic effectiveness. In the CLEOPATRA study, subjects in CLEOPATRA were at too early stages of macular edema, and the patients had poor compliance, which affected the observation of efficacy to a certain extent. In our study, the enrolled patients were strictly classified regarding the DME condition and visual acuity, so that the curative effect can be displayed more clearly. As far as we know, this is the first observational study on the efficacy of PBM in treating DME in Chinese population. Based on a bespoke treatment device, our results preliminarily validated the safety and efficacy of PBM in treating DME, which paved the way for future large-scale clinical validation for different types of DR as well as in different populations.

This study has certain limitations, the sample size is small, and there is no randomized control. Considering the large number of DR and the rapid growth in China, large-scale multi-center randomized control studies are necessary to further validate our conclusion.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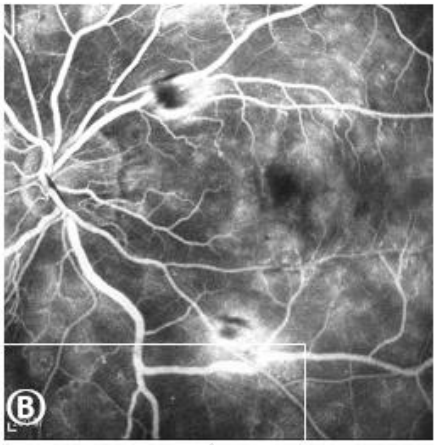
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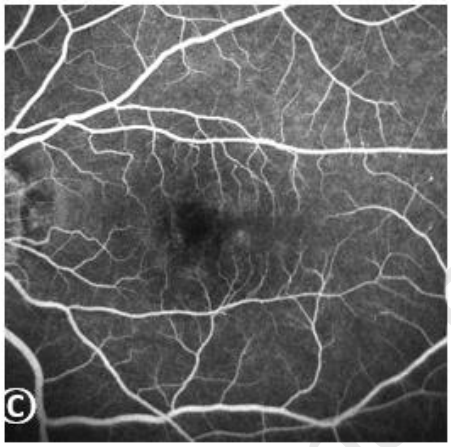
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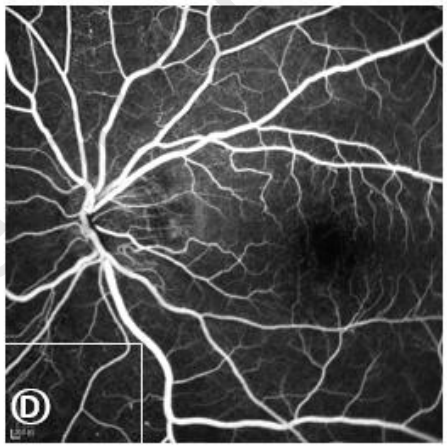
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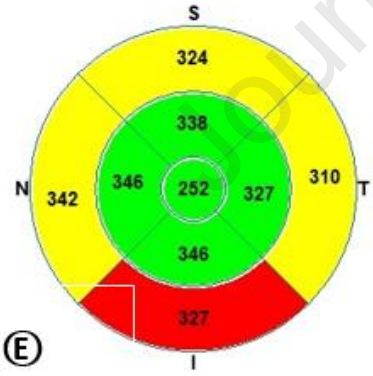
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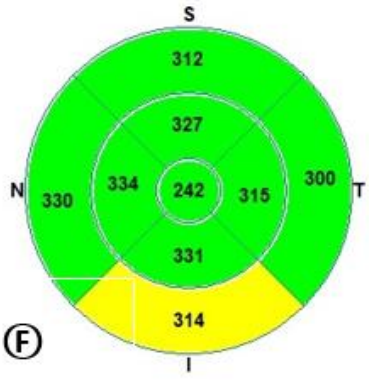
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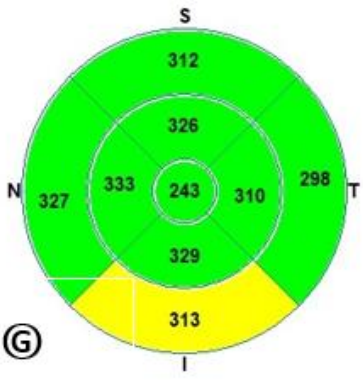
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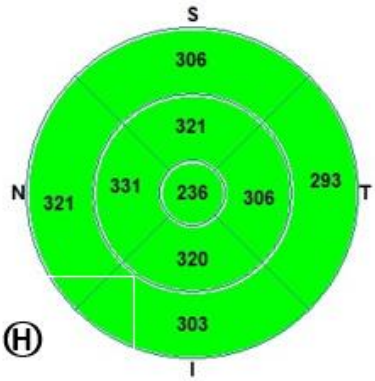
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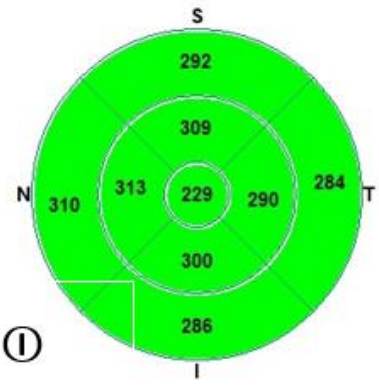
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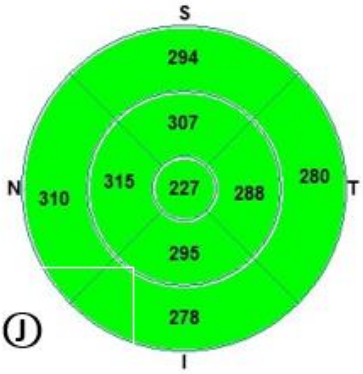
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Figure 1. A 33 year old male with type 2 diabetes. A: early retinal FFA telangiectasia before PBM treatment. B: late-stage macular area fluorescence accumulation. C: early retinal FFA telangiectasia relieved significantly after PBM treatment of 12 months. D: Relief in late-stage macular area fluorescence accumulation. E: macular area ETDRS retinal thickness topography before PBM treatment. F: retinal thickness after one-month treatment. G: retinal thickness after two-month treatment. H: retinal thickness after four-month treatment. I: retinal thickness after six-month treatment. J: retinal thickness after 12-month treatment which is significantly lower than the baseline result.

Table 1. The improvement of patients' visual acuity and retinal thickness after treatment. Values are expressed as medians (interquartile range). An asterisk (*) represents a significant difference from the initial value before treatment ($P<0.05$).

Treatment time (month)	0 (baseline)	1	2	4	6	12	Ratio of effectively treated eyes
Best corrected vision (number of letters)	**74.00 (64.25, 81.50)**	**79.00 (56.00, 84.00)**	**78.50 (66.25, 85.00)***	**81.00 (67.00, 84.00)***	**83.00 (64.00, 85.00)***	**82.50 (75.25, 87.75)***	87.5%
Maximum thickness of the retina in the macular area (μm)	**352.50 (335.75, 431.75)**	**349.00 (333.00, 399.00) ***	**349.50 (333.00, 383.50) ***	**335.00 (327.00, 371.00) ***	**337.00 (320.00, 381.00) ***	**338.00 (315.50, 377.25) ***	81.25%
Average thickness of the retina in the macular area (μm)	**320.50 (310.25, 359.25)**	**318.00 (304.00, 350.00)**	**315.00 (306.00, 352.50) ***	**309.00 (302.00, 343.00) ***	**308.00 (295.50, 337.00) ***	**311.00 (291.75, 326.00) ***	75%
Foveal thickness (μm)	**268.50 (247.50, 324.25)**	**267.00 (248.00, 304.00)**	**263.00 (247.75, 311.50)**	**253.00 (242.00, 303.00)**	**248.00 (236.00, 303.50) ***	**260.00 (229.25, 277.50)**	62.5%

Table 2. Changes in patients' visual acuity and retinal thickness of patients between follow-up and background results. Values are expressed as medians (interquartile range).

Treatment time (month)	1	2	4	6	12
Best corrected vision (number of letters)	**2.00 (1.00, 4.00)**	**3.50 (-0.75, 5.75)**	**3.00 (0.00, 6.00)**	**5.00（1.00,8.50）**	**4.00 (2.25, 7.25)**
Maximum thickness of the retina in the macular area (μm)	**-6.00 (-34.00, 5.00)**	**-5.00(-37.25, -1.25)**	**-8.00 (-40.00, 1.00)**	**-21.00(-55.00, -3.00)**	**-17.00(-60.00, -1.50)**
Average thickness of the retina in the macular area (μm)	**-4.00 (-11.00, 0.00)**	**-4.00(-13.00, -1.25)**	**-5.00 (-19.00, 0.00)**	**-10.0(-28.50, -1.50)**	**-10.5 (-29.00, 0.00)**
Foveal thickness (μm)	**-5.00 (-18.00, 2.00)**	**-4.50 (-16.50, 1.75)**	**-8.00 (-19.00, 0.00)**	**-9.00 (-30.50, 0.00)**	**-8.50 (-30.00, 3.50)**

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Conflict of Interest

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