A STUDY OF THERAPEUTIC EFFECTS OF 670 NM IRRADIATION IN DIFFERENT TYPES OF DIABETIC MACULAR EDEMA

Ramin S.[1], **Ahadi M.**[1], **Ebrahimi A.**[2]
[1]Student Research Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Basir Eye clinic, Tehran, Iran

Abstract

The purpose of this study was to investigate the therapeutic effects of 670 nm irradiation in patients with diabetic macular edema. In several studies, positive effects of red/near-infrared irradiation showed in a range of ocular diseases such as macular degeneration, macular edema, and retinitis pigmentosa. This study was conducted on forty five eyes of 26 diabetic patients with macular edema between the ages of 51 and 80. Measurement of visual acuity and slit lamp examination, funduscopy, and optical coherence tomography were performed in all subjects. None of the patients had proliferative retinopathy. We used a portable LED device (Warp 10, Quantum Devices) for treatment. Patients held this device at a distance of 3 cm from their eyes for 240 seconds for three months. Full ophthalmic examinations were repeated 1, 2, and 3 months after treatment. After 3 months, the mean visual acuity improved from 0.44 ± 0.38 log MAR to 0.27 ± 0.24 log MAR and vision increased by 1.52 ± 1.16 lines post treatment ($p<0.001$). The mean central macula thickness decreased from 381.49 ± 144.40 μm to 359.72 ± 128.84 μm ($p=0.050$). In patients with mild and moderate nonproliferative diabetic retinopathy, the mean central retinal thickness decreased 52.06 ± 67.78 μm and 39.27 ± 44.69 μm, respectively, but patients with severe type showed an increase of 34.93 ± 65.65 μm in the mean central retinal thickness ($p<0.001$). Also, the severity of macular edema had no effect on final outcomes ($p>0.05$). Photobiomodulation can positively affect diabetic macular edema, especially in patients with mild to moderate diabetic retinopathy.

Keywords: diabetic macular edema, photobiomodulation, diabetic retinopathy.

For citations: Ramin S., Ahadi M., Ebrahimi A. A study of therapeutic effects of 670 nm irradiation in different types of diabetic macular edema, *Biomedical Photonics*, 2020, vol. 9, no. 4, pp. 15–22. doi: 10.24931/2413–9432–2020–9–4–15–22.

Contacts: Ramin S., dr.shahrokhramin46@gmail.com, Ahadi M., sepid01@yahoo.com

ИЗУЧЕНИЕ ТЕРАПЕВТИЧЕСКИХ ЭФФЕКТОВ ИЗЛУЧЕНИЯ С ДЛИНОЙ ВОЛНЫ 670 НМ ПРИ РАЗЛИЧНЫХ ТИПАХ ДИАБЕТИЧЕСКОГО МАКУЛЯРНОГО ОТЕКА

Ramin S.[1], **Ahadi M.**[1], **Ebrahimi A.**[2]
[1]Университет медицинских наук Шахида Бехешти, Тегеран, Иран
[2]Офтальмологический центр Басир, Тегеран, Иран

Резюме

Целью данной исследовательской работы являлось изучение терапевтических эффектов излучения с длиной волны 670 нм у пациентов с диабетическим макулярным отеком. Ряд предыдущих исследований свидетельствует о положительном эффекте красного / инфракрасного излучения при некоторых заболеваниях глаз, таких как макулодистрофия (дегенерация желтого пятна), макулярный отек и пигментный ретинит. Наше исследование было проведено на 45 глазах у 26 больных сахарным диабетом в возрасте от 51 до 80 лет с макулярным отеком. Всем пациентам были проведены определение остроты зрения, осмотр глаз щелевой лампой, фундоскопия и оптическая когерентная томография. Ни у одного из пациентов не было пролиферативной ретинопатии. Для лечения нами был применен портативный светодиодный прибор (Warp 10, Quantum devices). Пациенты держали светодиод на расстоянии 3 см от глаза в течение 240 сек в течение 3 мес. Все офтальмологические исследования были повторены через 1, 2 и 3 мес после проведения лечебной процедуры. Через 3 мес средняя острота зрения улучшилась с показателем логарифма минимального угла разрешения 0,44 ± 0,38 до 0,27 ± 0,24, что показало увеличение показателя остроты зрения на 1,52 ± 1,16 после лечения ($p<0,001$). Средняя центральная толщина сетчатки в области макулы уменьшилась с 381,49 ± 144,40 мкм до 359,72 ± 128,84 мкм ($p=0,050$). У пациентов с легкой и умеренной непролиферативной диабетической ретинопатией средняя толщина сетчатки уменьшилась до 52,06 ± 67,78 и 52,06 ± 67,78 мкм, соответственно, а у пациентов с тяжелой ретинопатией наблюдалось увеличение на 34,93 ± 65,65 мкм ($p<0,001$). Помимо

того, степень макулярного отека не повлияла на окончательный результат лечения (p>0,05). Фотобиомодуляция была эффективной при диабетическом макулярном отеке, в частности, у пациентов с легкой и умеренной диабетической ретинопатией.

Ключевые слова: диабетический макулярный отек, фотобиомодуляция, диабетическая ретинопатия.

Для цитирования: Ramin S., Ahadi M., Ebrahimi A. A study of therapeutic effects of 670 nm irradiation in different types of diabetic macular edema // Biomedical Photonics. – 2020 – T.9, № 4. – C. 15-22. pp. 15–22. doi: 10.24931/2413–9432–2020–9–4–15–22.

Контакты: Ramin S., dr.shahrokhramin46@gmail.com, Ahadi M., sepid01@yahoo.com

Introduction

According to International Diabetes Federation (IDF) reports, the global prevalence of diabetes among adults over 18 was 8.4% in 2017. The number of patients is expected to increase to 693 million by 2045 [1]. Visual impairment due to diabetes is a major global health problem in the world. Diabetic macular edema (DME) and diabetic retinopathy are the main causes of visual impairment in these patients affecting their activities and lives [2–3]. Chronic hyperglycemia causes the generation of advanced glycation endproducts (AGEs), activation of protein kinase C, upregulation of vascular endothelial growth factor (VEGF), vascular endothelial dysfunction, and increased vascular permeability and chronic inflammation [4–5]. Treatment modalities include laser photocoagulation and anti-vascular endothelial growth factor (VEGF) drugs with aggressive control of glycemia. Although these methods have been effective against macular edema, they have disadvantages such as decreased vision in some patients, a need for repeated injections, and high costs [6–8].

Several studies demonstrated the therapeutic effects of red to near-infrared light (NIR) (630–1000 nm) by using low-level lasers or light-emitting diode (LED) arrays. Light photons can penetrate into living tissues, and the absorbed energy creates photochemical changes within cellular structures that define photobiomodulation (PBM) therapy. Photobiomodulation therapy affects endogenous chromophores in the body and improves the biological functions of cells without heating or damage [9–12]. In the injured optic nerve, this approach has shown the potential to reduce inflammation and alleviate degeneration. Following photo-irradiation of nervous cells, cytochrome oxidase production is increased, and the activity of the cytochrome oxidase inhibitors is reduced [13]. In another study, NIR irradiation of the optic nerve following an injury in a transcranial manner reduced oxidative stress. Reduced oxidative stress by NIR light improved function in the CNS post traumatic injury in vivo [14]. Photobiomodulation has shown positive effects in the treatment of strokes and myocardial infarction, and stem cell proliferation [15]. The first study of photobiomodulation efficacy in the treatment of dry age-related macular degeneration (AMD) was conducted by Merry et al. They demonstrated improvements of functional and anatomical outcomes in their subjects with PBM therapy [16]. PBM effects on diabetic macular edema was studied by Tang in a pilot study. Daily photobiomodulation caused a significant reduction in focal retinal thickening and improved vision in treated eyes. He reported PBM as an effective and non-invasive method to treat diabetic macular edema lesions. [17]. In previous studies, PBM was reported as a safe method without side effects [9–10, 17].

According to this evidence, photobiomodulation might have positive effects in diabetic macular edema. Therefore, the present study is designed to evaluate whether 670 nm irradiation has therapeutic effect in diabetic macular edema, focusing on different types of edema and several stages of nonproliferative diabetic retinopathy.

Materials and Methods

This study was conducted on 26 diabetic patients in Abhar, Iran, in 2019. Our study followed the tenets of the Declaration of Helsinki and was approved by the Human Ethics Committee of Shahid Beheshti University of Medical Sciences (IR. SBMU. RETECH. REC. 1398.558). After approval by the human ethics committee of the University, diabetic patients were recruited from an eye clinic. All patients had diabetic macular edema and associated decreased visual acuity. Only patients who did not wish to receive the standard treatment or had not responded to current modalities participated in this study. In our patients, visual acuity measurement with ETDRS chart, slit lamp examination, funduscopy, and optical coherence tomography were performed. According to the International Clinical Diabetic Macular Edema Disease Severity Scale [18], diagnosis of diabetic macular edema was approved on the basis of clinical findings and optical coherence tomography (OCT SD) data. Exclusion criteria were a history of systemic or topical anti-inflammatory drugs usage, intravitreal injections of steroids and anti-VEGF, focal laser therapy within 1 year, and evidence of proliferative diabetic retinopathy. The treatment method was described to all patients, and the consent form was received from them. Photobiomodulation therapy was applied using a portable LED device Warp 10 (Quantum Devices).

This device emits red light at a wavelength of 670 nm with 25 J/cm^2 energy in 3 cm distance to an eye. The duration of treatment was three months, and it was carried out at home. Our patients would keep this device at a distance of 3 cm from their eyes for 240s three times a week in the first month. In the following month, they performed photobiomodulation two times a week, and in the last month, they continued it weekly. After three months, all examinations were repeated, and changes in ocular findings were considered as the final outcomes.

Statistical analysis of results was performed by SPSS software version 18. After the assessment of normality of data distribution with the Shapiro-Wilk test, we used Student's, Wilcoxon, and Kruskal-Wallis tests for statistical analysis of results.

Results

Twenty six patients (11 male and 15 female) with a mean age of 63.44 ± 7.51 (range 51–80) years participated in this study. During this study, routine treatment of diabetes, including drugs and diet, were not changed in all patients. Mean FBS in the first and final examinations were 200.11 ± 54.68 and 193.35 ± 61.25, respectively. The mean spherical equivalent was 0.68 ± 0.89 diopter (D) with range –2.0 to +3.25 D. Photobiomodulation was performed in both eyes of 19 subjects and did in one eye of 7 patients. Eighteen eyes had mild nonproliferative diabetic retinopathy (NPDR), 13 eyes had moderate nonproliferative diabetic retinopathy, and 14 eyes were in a stage of severe NPDR. In terms of severity of disease, DME in 8 eyes was mild, in 15 eyes was moderate, and in 22 eyes was severe. According to morphology of edema, 8 patients had simple edema, and 26 patients had cystoid type, and 11 of them had neuroretinal detachment.

Initially, the mean visual acuity of patients was 0.44 ± 0.38 log MAR that improved to 0.29 ± 0.25 log MAR, 0.26 ± 0.28 log MAR, and 0.27 ± 0.24 log MAR after one, two, and three months, respectively ($p < 0.001$). The mean visual acuity in patients increased 1.52 ± 1.16 lines after 3 months. While visual acuity improved in 67% of subjects (between 1–2 lines in 19 eyes (42%) and more than 2 lines in 11 eyes (25%)), no positive effects were observed in 33% of eyes (no change in visual acuity in 9 eyes (20%), and decreased visual acuity in 6 eyes (13%)). The mean central retinal thickness was 381.49 ± 144.40 μm primarily and decreased to 359.72 ± 128.84 μm after 3 months (p=0.050) (figures 1–3). At baseline, the mean retinal thickness in 3 mm central circle was 404.16± 91.15 μm that decreased to 390.24 ± 97.87 μm after treatment (p=0.004) and the mean retinal thickness in 6 mm central circle was 367.54 ± 76.37 μm primarily that decreased to 356.31± 83.03 μm finally (p=0.002). The mean retinal thickness decreased 20.47± 72.20 μm (range: from 275 μm decrease to 121 μm increase in thickness), 14.01 ± 40.13 μm (range: from 130 μm decrease to 118 μm increase in thickness), and 11.21 ± 39.22 μm (range: from 155 μm decrease to 136 μm increase in thickness) in the central, 3 mm circle, and 6 mm circle respectively (Table 1).

According to changes of the retinal thickness, patients were divided in three groups: stable, decrease, and increase. Nine eyes (20%) had no change in the central retinal thickness (±10.00 μm changes in the retinal thickness). Twenty five eyes (56%) showed reduction of the central retinal thickness (from 10 to 50 μm decrease of the mean retinal thickness in 14 eyes (31%) and from 50 to 275 μm decrease of the mean retinal thickness in 11 eyes (25%)). Also, the central retinal thickness increased in 11 eyes (24%) (from 10 to 50 μm increase of mean retinal thickness in 6 eyes (13%) and from 50 to 121 μm increase of mean retinal thickness in 5 eyes (11%)).

The severity of macular edema had no effect on final outcomes (p>0.05). Central retinal thickness decreased 12.25 ± 45.01 μm, 17.15 ± 33.30 μm, and 25.41± 95.17 μm in mild, moderate, and severe macular edema respectively (Table 2). The morphology of macular edema had significant effect on central retinal thickness (p=0.01). The mean central retinal thickness decreased 19.50 ± 26.36 μm and 41.23 ± 70.84 μm in simple and cystoid macular edema, respectively, but it increased 28.09 ± 72.71 μm in neuroretinal detachment macular edema (Table 3).

Furthermore, the rate of central retinal thickness changes depended on the severity of diabetic retinopathy. In patients with mild and moderate NPDR, the mean central retinal thickness decreased 52.06 ± 67.78 μm and 39.27 ± 44.69 μm, respectively, but patients with severe NPDR showed the rate of 34.93 ± 65.65 μm increase in the mean central retinal thickness (p<0.001). Fourteen eyes (78%) with mild NPDR and 8 eyes (61%) with moderate NPDR showed a reduction of macular thickness between 10 to 273 μm. Of the total 14 eyes with severe NPDR, 3 eyes (21%) had 10 to 135 μm decrease of central retinal thickness, and 10 eyes (70%) had 10 to 121 μm increase of central retinal thickness. Eight patients (15 eyes) had a history of previous anti-VEGF injection, and their results showed no difference from other patients (p>0.05). Finally, our subjects showed no adverse events such as blurred vision, inflammation, or increased intraocular pressure after photobiomodulation.

Discussion

Evidence is growing that photobiomodulation has beneficial effects in a variety of diseases, including wound healing, rheumatoid arthritis, cerebral degeneration, Alzheimer's disease, and retinal degeneration [19,20]. In several studies, therapeutic effects of PBM were investigated in the field of ocular diseases such as age-related macular degeneration (AMD), diabetic macular edema, and retinitis pigmentosa [17, 21–23]. Albarracin et al. showed protective effect of NIR light in

Table 1
Results of photobiomodulation at baseline and during the study
Таблица 1
Результаты фотобиомодуляции до и во время исследования

Results Результаты	Baseline Исходный уровень	3th month 3-й месяц	p
Best Corrected Visual Acuity Наилучшая скорректированная острота зрения	0.44 ± 0.38 Log MAR	0.27 ± 0.24 Log MAR	<0.001
Mean central macular thickness Толщина макулы в центре	381.49 ± 144.40 μm	359.72 ± 128.84 μm	0.050
Mean minimum central macular thickness Минимальная толщина макулы в центре	332.60 ± 117.37 μm	309.17 ± 113.09 μm	0.005
Mean maximum central macular thickness Максимальная толщина макулы в центре	461.51 ± 130.01 μm	438.26 ± 125.92 μm	0.087
Mean 3 mm central macular thickness Толщина макулы в 3 мм от центра	404.16 ± 91.15 μm	390.24 ± 97.87 μm	0.004
Mean 6 mm central macular thickness Толщина макулы в 6 мм от центра	367.54 ± 76.37 μm	356.32 ± 83.04 μm	0.002

Table 2
Results of photobiomodulation according to Macular Edema Severity
Таблица 2
Результаты фотобиомодуляции в соответствии со степенью тяжести отека желтого пятна

Macular Edema Макулярный отек	Visual acuity improvement (line) Улучшение остроты зрения	Retinal thickness changes in the center (μm) Изменения толщины сетчатки в центре (мкм)	Retinal thickness changes 3 mm from the center (μm) Изменения толщины сетчатки в 3 мм от центра (мкм)	Retinal thickness changes 3 mm from the center (μm) Изменения толщины сетчатки в 6 мм от центра (мкм)
Mild Edema **Слабый отек** **n=8 eyes**	2.07 ± 0.98	−12.25 ± 45.01	−5.38 ± 5.71	−12.25 ± 10.21
Moderate Edema **Умеренный отек** **n=15 eyes**	1.50 ± 104	−17.15 ± 33.30	−12.77 ± 29.44	−15.54 ± 22.80
Severe Edema **Сильный отек** **n=22 eyes**	1.32 ± 1.27	−25.41 ± 95.17	−18.15 ± 52.73	−8.00 ± 53.36
p	0.339	0.952	0.616	0.503

Table 3
Results of photobiomodulation according to macular edema morphology
Таблица 3
Результаты фотобиомодуляции в соответствии с морфологией отека желтого пятна

Macular Edema Макулярный отек	Visual acuity improvement (line) Улучшение остроты зрения	Retinal thickness changes in the center (μm) Изменения толщины сетчатки в центре (мкм)	Retinal thickness changes 3 mm from the center (μm) Изменения толщины сетчатки в 3 мм от центра (мкм)	Retinal thickness changes 3 mm from the center (μm) Изменения толщины сетчатки в 6 мм от центра (мкм)
Simple Edema **Простой отек** **n=8 eyes**	1.75 ± 1.10	−19.50 ± 26.36	−7.50 ± 4.81	−12.17 ± 7.63
Cystoid Edema **Цистоидный отек** **n=26 eyes**	1.88 ± 0.89	−41.23 ± 70.84	−24.86 ± 37.41	−24.71 ± 35.88
Neuroretinal detachment **Нейроретинальная отслойка** **n=11 eyes**	0.49 ± 1.24	+28.09 ± 72.71	+6.36 ± 49.46	18.73 ± 41.69
p	0.010	0.014	0.028	0.001

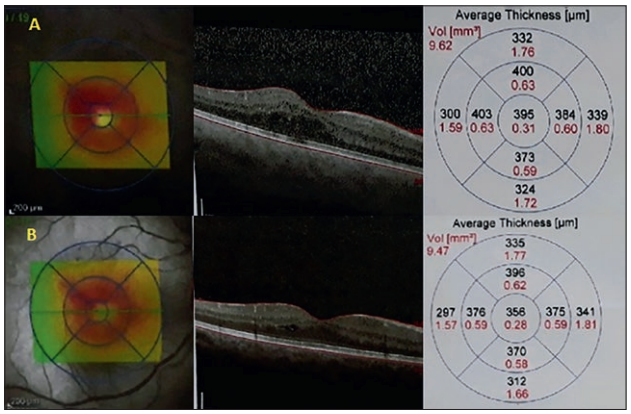

Fig. 1. A: Pre Photobiomodulation OCT of a patient with BCVA: 0.22 Log MAR. B: Post photobiomodulation OCT of same patient with BCVA: 0.05 Log MAR after three months.
Рис. 1. A: Оптическая когерентная томография перед фотобиомодуляцией пациента с наилучшей коррегируемой остротой зрения: логарифм минимального угла разрешения 0,22; B: Оптическая когерентная томография после фотобиомодуляции пациента с наилучшей коррегируемой остротой зрения: через 3 мес логарифм минимального угла разрешения 0,05

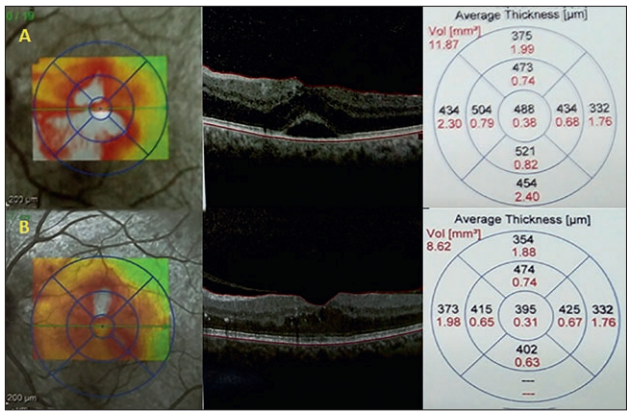

Fig.2. A: Pre photobiomodulation OCT of another patient with BCVA: 0.80 Log MAR. B: Post photobiomodulation OCT of same patient with BCVA: 0.30 Log MAR after 3 months.
Рис. 2. A: Оптическая когерентная томография перед фотобиомодуляцией другого пациента с наилучшей коррегируемой остротой зрения: логарифм минимального угла разрешения 0,80; B: Оптическая когерентная томография после фотобиомодуляции пациента с наилучшей коррегируемой остротой зрения: через 3 мес логарифм минимального угла разрешения 0,30

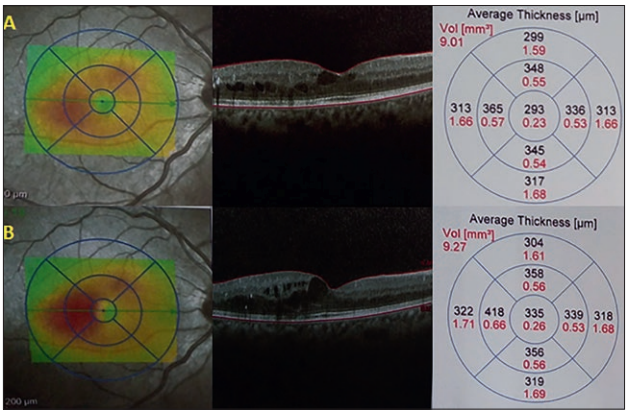

Fig. 3. A: Pre photobiomodulation OCT of another patient with BCVA: 0.20 Log MAR. B: Post photobiomodulation OCT of same patient with BCVA: 0.25 Log MAR after 3 months.
Рис. 3. A: Оптическая когерентная томография перед фотобиомодуляцией пациента с наилучшей коррегируемой остротой зрения: логарифм минимального угла разрешения 0,20; B: Оптическая когерентная томография после фотобиомодуляции пациента с наилучшей коррегируемой остротой зрения: через 3 мес логарифм минимального угла разрешения 0,25

the albino rat retina from light-induced photoreceptor degeneration. This protective effect appears to involve a reduction of cell death and inflammation [21]. Ivandic and Ivandic evaluated therapeutic effects of photobiomodulation in 203 patients with AMD. Visual acuity improved in 97% of the subjects [22]. Merry et al. studied the efficacy of PBM in 42 eyes with dry AMD. PBM resulted in a significant improvement in mean BCVA and contrast sensitivity. Although drusen volume decreased, overall central retinal thickness and retinal volume remained stable. They reported these results were related to anti-inflammatory, anti-oxidative, neuroprotective, and anti-apoptotic properties of PBM [23]. Tang et al., in another study, demonstrated the efficacy of PBM in four eyes of 4 diabetic patients as increased visual acuity and 20% reduction in macular thickness in all treated eyes [17]. In agreement with previous works, our results showed the beneficial effects of photobiomodulation. In 67% of subjects, vision improved, and visual acuity increased more than 1.50 lines after treatment. Improvement of vision occurred for two months and then remained stable for the third month. Positive effects of PBM were observed in all three types of mild, moderate, and severe types of macular edema. In our study, the rate of improvement was related to the morphology of edema. Cystoid form of edema showed a better response to PBM associated with decreased honeycomb spaces. Macular thickening after PBM decreased to approach near normal architecture, and retinal layers were more regularly arranged. Interestingly, the amount of therapeutic effects of PBM on macular edema was dependent on diabetic retinopathy severity. In patients with mild to moderate nonproliferative diabetic retinopathy, macular edema decreased after photobiomodulation. However, in the majority of patients with severe nonproliferative diabetic retinopathy (70%), photobiomodulation could not arrest or regress macular thickening.

Direct and indirect mechanisms of biological effects by PBM are still under investigation. Previous studies demonstrated beneficial effects of PBM on the activity of cytochrome oxidase, activation of light-gated ion channels, stem cell proliferation, and anti-inflammatory actions [24]. Activity and expression of cytochrome oxidase in retinas of diabetic rats was not affected by

PBM. Although, some studies showed increased cytochrome oxidase activity in retinal pigment epithelium [19, 25]. The beneficial effects of PBM on stem cells have been investigated in several studies [19, 24, 26]. Proliferation of mesenchymal stem cells and cellular viability was enhanced by multiple exposures to 630-nm LEDs [26]. In diabetic mice treated with PBM, the number of c-Kit$^+$ cells in the circulation increased, which was related to a significant effect of photobiomodulation on stem cells [19]. However, the lack of accumulation of c-Kit$^+$ cells within the neural retina or retinal vasculature demonstrated no positive effect of PBM on stem cells in the retina in diabetes [19, 24, 27]. Several studies showed that photobiomodulation inhibited the oxidative stress and inflammation development in the diabetic retina, as well as upregulating survival pathways [25, 28]. The pathogenesis of diabetic retinopathy is related to oxidative stress (upregulation of reactive oxygen species (ROS)) and inflammatory changes (increased pro-inflammatory cytokines and nitric oxide) in the retina [29]. Oxidative stress-induced damage of mitochondrial DNA leads to impaired transcription of electron transport chain proteins, which compromises electron transport chain function and further intensifies ROS production [30]. Also, leukocyte adhesion and endothelial cell death cause the structural and functional abnormalities related to diabetic retinopathy [24, 31]. Heo et al. assessed the anti-oxidative effect LED of 660 nm in hippocampal cell line and the activation of cAMP response element. Photobiomodulation therapy inhibited apoptosis of hippocampal cells induced by oxidative stress and increased neurotrophic factor expression [32]. de Oliveira et al. studied oxidative stress markers following low-intensity laser therapy on rats subjected to a high-intensity resistive exercise session. They stated that LLLT prior to resistive exercise reduced the oxidative stress markers and increased the antioxidant capacity [33]. In another study, Saliba et al. assessed the protective effects of far-red light exposure against retinal oxidative stress and inflammation in diabetic mice. PBM improved diabetes-induced changes in superoxide generation, leukostasis, expression of ICAM-1 (intercellular adhesion molecule-1). Also, in assessments, PBM enhanced both inner and outer retinal uptake of manganese, and ion channel function secondary to inhibition of the oxidative stress [34]. Finally, some studies showed an indirect effect of photobiomodulation. Because of the deep penetration of far-red light into tissues, beneficial effects of PBM via systemic mediators in kidney and heart of diabetic animals and skin wounds have been seen [34–36]. This effect of PBM in diabetic macular edema has not yet been investigated, but due to the close proximity of the eyes, there may be an indirect effect of photobiomodulation that needs further evaluation. In addition, our findings indicated that the severity of diabetic retinopathy influenced on therapeutic effects of PBM. In the severe stage of diabetic retinopathy, vascular abnormalities result in retinal ischemia, with a release of proangiogenic factors and enhanced expression of VEGF [37]. It has been recently revealed that half of the patients with severe nonproliferative diabetic retinopathy have small preretinal neovascularization not seen on clinical examination or OCT [38]. It seems to be essential to use anti-VEGF drugs in severe cases.

The limitation of this study is that we had no control group. Moreover, we could not assess vascular changes after PBM using OCTA. We suggest further studies with more patients and long-term follow-up and combined other therapies.

Conclusion

According to our results, PBM can positively affect diabetic macular edema, especially in patients with mild to moderate diabetic retinopathy. Three months of PBM improves the visual function of diabetic patients and reduces macular edema by anti-oxidative stress and anti-inflammatory actions. Also, this method is a non-invasive and inexpensive method administered at home.

Acknowledgment

This study is related to the project with number IR. SBMU. RETECH. REC.1398.558 from Student Research Committee, Shahid Beheshti University of Medical Sciences, Tehran, Iran. We also appreciate the "Student Research Committee" and "Research & Technology Chancellor" in Shahid Beheshti University of Medical Sciences for their financial support of this study.

REFERENCES

1. Cho NH, Shaw JE, Karuranga S, et al. Malanda B. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res Clin Pract,* 2018, Vol. 138, pp. 271–281.
2. Varma R, Bressler NM, Doan QV, et al. Prevalence of and risk factors for diabetic macular edema in the United States. *JAMA Ophthalmol,* 2014, Vol.132 (11), pp. 1334–1340.
3. Ding J, Wong TY. Current epidemiology of diabetic retinopathy and diabetic macular edema. *Curr Diab Rep*, 2012, Vol. 12 (4), pp. 346–354.
4. Sayin N, Kara N, Pekel G. Ocular complications of diabetes mellitus. *World J Diabetes*, 2015, Vol. 6 (1), pp. 92–108.

ЛИТЕРАТУРА

1. Cho NH, Shaw JE, Karuranga S, Huang Y. et al. Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045//Diabetes Res Clin Pract. – 2018. – Vol. 138. – P. 271–281.
2. Varma R, Bressler NM, Doan QV, et al. Prevalence of and risk factors for diabetic macular edema in the United States//JAMA Ophthalmol. –2014. – Vol. 132 (11). – P. 1334–1340.
3. Ding J, Wong TY. Current epidemiology of diabetic retinopathy and diabetic macular edema//Curr Diab Rep. – 2012. – Vol.12 (4). – P.346–354.
4. Sayin N, Kara N, Pekel G. Ocular complications of diabetes mellitus//World J Diabetes. – 2015. – Vol. 6 (1). – P. 92–108.

5. Pedro Romero-Aroca. Managing diabetic macular edema: The leading cause of diabetes blindness. *World J Diabetes*, 2011, Vol. 2 (6), pp. 98–104.
6. Wenick AS, Bressler MN. Diabetic Macular Edema: Current and emerging therapies. *Middle East Afr J Ophthalmol*, 2012, Vol. 19, pp. 4–12.
7. Tarr JM, Kaul K, Chopra M, et al. Pathophysiology of Diabetic Retinopathy. *ISRN Ophthalmol,* 2013, pp. 343560.
8. Chan WC, Tsai SH, Wu AC, et al. Current Treatments of Diabetic Macular Edema. *International Journal of Gerontology*, 2011, Vol. 5 (4), pp.183–188.
9. Rojas JC, Gonzalez-Lima F. Low-level light therapy of the eye and brain. *Eye Brain,* 2011, Vol. 3. pp. 49–67.
10. Houreld NN. Shedding light on a new treatment for diabetic wound healing: a review on phototherapy. *Scientific World Journal*, 2014, pp. 398412.
11. Anders JJ, Lanzafame RJ, Arany PR. Low-Level Light/Laser Therapy Versus Photobiomodulation Therapy. *Photomed Laser Surg,* 2015, Vol. 33 (4), pp.183–184.
12. Freitas LF, Hamblin MR. Proposed Mechanisms of Photobiomodulation or Low-Level Light Therapy. *IEEE J Sel Top Quantum Electron*, 2016, Vol. 22 (3), pp.7000417.
13. Eells JT, Wong-Riley MT, VerHoeve J, et al. Mitochondrial signal transduction in accelerated wound and retinal healing by near-infrared light therapy. *Mitochondrion,* 2004, Vol. 4 (5–6), pp. 559–567.
14. Fitzgerald M1, Bartlett CA, Payne SC, et al. Near Infrared Light Reduces Oxidative Stress and Preserves function in CNS Tissue Vulnerable to Secondary Degeneration following Partial Transection of the Optic Nerve. *J Neurotrauma,* 2010, Vol. 27 (11), pp. 2107–2119.
15. Karu T. Mitochondrial mechanisms of photobiomodulation in context of new data about multiple roles of ATP. *Photomed Laser Sur,*. 2010, Vol. 28 (2), pp.159–160.
16. Merry GF, Munk MR, Dotson RS, et al. Photobiomodulation reduces drusen volume and improves visual acuity and contrast sensitivity in dry age-related macular degeneration. *Acta Ophthalmologica*, 2017, Vol. 95, pp. 270–277.
17. Tang J, Herda AA, Kern TS. Photobiomodulation in the treatment of patients with non-center-involving diabetic macular oedema. *Br J Ophthalmol,* 2014, Vol. 98, pp. 1013–1015.
18. Panozzo G1, Parolini B, Gusson E, et al. Diabetic macular edema: an OCT-based classification. *Semin Ophthalmol*, 2004, Vol. 19 (1–2), pp. 13–20.
19. Cheng Y, Du Y, Liu H, et al. Photobiomodulation Inhibits Long-term Structural and Functional Lesions of Diabetic Retinopathy. *Diabete,* 2018, Vol. 67 (2), pp. 291–298.
20. Zomorrodi, R., Loheswaran, G., Pushparaj, A. et al. Pulsed Near Infrared Transcranial and Intranasal Photobiomodulation Significantly Modulates Neural Oscillations: a pilot exploratory study. *Sci Rep 9,* 2019, 6309. https://doi.org/10.1038/s41598–019–42693-x.
21. Albarracin R, Eells J, Valter K. Photobiomodulation protects the retina from light-induced photoreceptor degeneration. *Invest Ophthalmol Vis Sc,* 2011, Vol. 52, pp. 3582–3592.
22. Ivandic BT, Ivandic T. Low-level laser therapy improves vision in patients with age-related macular degeneration. *Photomed Laser Surg,* 2008, Vol. 26 (3), pp. 241–245.
23. Merry GF, Munk MR, Dotson RS, et al. Photobiomodulation reduces drusen volume and improves visual acuity and contrast sensitivity in dry age-related macular degeneration. *Acta Ophthalmol,* 2017, Vol. 95 (4), pp. 270–277.
24. Hamblin MR. Mechanisms and Mitochondrial Redox Signaling in Photobiomodulation. *Photochem Photobiol,* 2018, Vol. 94 (2), pp. 199–212.
25. Tang J, Du Y, Lee CA, et al. Low-intensity far-red light inhibits early lesions that contribute to diabetic retinopathy: in vivo

5. Pedro Romero-Aroca. Managing diabetic macular edema: The leading cause of diabetes blindness//World J Diabetes 2011. – Vol. 2 (6). – P. 98–104.
6. Wenick AS, Bressler MN. Diabetic Macular Edema: Current and emerging therapies//Middle East Afr J Ophthalmol. – 2012. – Vol. 19. – P. 4–12.
7. Tarr JM, Kaul K, Chopra M, et al. Pathophysiology of Diabetic Retinopathy//ISRN Ophthalmol. – 2013. – Vol. 2013. – P. 343560.
8. Chan WC, Tsai SH, Wu AC, et al. Current Treatments of Diabetic Macular Edema//International Journal of Gerontology. – 2011. – Vol. 5 (4). – P. 183–188.
9. Rojas JC, Gonzalez-Lima F. Low-level light therapy of the eye and brain//Eye Brain. –2011. – Vol. 3. – P. 49–67.
10. Houreld NN. Shedding light on a new treatment for diabetic wound healing: a review on phototherapy//Scientific World Journal. – 2014. – P. 398412.
11. Anders JJ, Lanzafame RJ, Arany PR. Low-Level Light/Laser Therapy Versus Photobiomodulation Therapy//Photomed Laser Surg. – 2015. – Vol. 33 (4). – P.183–184.
12. Freitas LF, Hamblin MR. Proposed Mechanisms of Photobiomodulation or Low-Level Light Therapy//IEEE J Sel Top Quantum Electron. – 2016. – Vol. 22 (3). –P. 7000417.
13. Eells JT, Wong-Riley MT, VerHoeve J, et al. Whelan HT. Mitochondrial signal transduction in accelerated wound and retinal healing by near-infrared light therapy//Mitochondrion. – 2004. – Vol. 4 (5–6). – P. 559–567.
14. Fitzgerald M1, Bartlett CA, Payne SC, et al. Near Infrared Light Reduces Oxidative Stress and Preserves function in CNS Tissue Vulnerable to Secondary Degeneration following Partial Transection of the Optic Nerve//J Neurotrauma. – 2010. – Vol. 27 (11). – P. 2107–2119.
15. Karu T. Mitochondrial mechanisms of photobiomodulation in context of new data about multiple roles of ATP//Photomed Laser Surg. – 2010. – Vol. 28 (2). –P. 159–160.
16. Merry GF, Munk MR, Dotson RS, et al. Photobiomodulation reduces drusen volume and improves visual acuity and contrast sensitivity in dry age-related macular degeneration//Acta Ophthalmologica. – 2017. – Vol. 95. – P. 270–277.
17. Tang J, Herda AA, Kern TS. Photobiomodulation in the treatment of patients with non-center-involving diabetic macular oedema//Br J Ophthalmol. – 2014. – Vol. 98. – P. 1013–1015.
18. Panozzo G1, Parolini B, Gusson E, et al. Diabetic macular edema: an OCT-based classification//Semin Ophthalmol. – 2004. – Vol. 19 (1–2). – P. 13–20.
19. Cheng Y, Du Y, Liu H, et al. Photobiomodulation Inhibits Long-term Structural and Functional Lesions of Diabetic Retinopathy//Diabetes. – 2018. – Vol. 67 (2). – P. 291–298.
20. Zomorrodi, R., Loheswaran, G., Pushparaj, A. et al. Pulsed Near Infrared Transcranial and Intranasal Photobiomodulation Significantly Modulates Neural Oscillations: a pilot exploratory study//Sci Rep. – 2019. – Vol. 9. – P. 6309. https://doi.org/10.1038/s41598–019–42693-x.
21. Albarracin R, Eells J, Valter K. Photobiomodulation protects the retina from light-induced photoreceptor degeneration//Invest Ophthalmol Vis Sci. – 2011. – Vol. 52. – P. 3582–3592.
22. Ivandic BT, Ivandic T. Low-level laser therapy improves vision in patients with age-related macular degeneration//Photomed Laser Surg. – 2008. – Vol. 26 (3). – P. 241–245.
23. Merry GF, Munk MR, Dotson RS, et al. Photobiomodulation reduces drusen volume and improves visual acuity and contrast sensitivity in dry age-related macular degeneration//Acta Ophthalmol. – 2017. – Vol. 95 (4). – P. 270–277.
24. Hamblin MR. Mechanisms and Mitochondrial Redox Signaling in Photobiomodulation//Photochem Photobiol. – 2018. – Vol. 94 (2). – P. 199–212.
25. Tang J, Du Y, Lee CA, et al. Low-intensity far-red light inhibits early lesions that contribute to diabetic retinopathy: in vivo

and in vitro. *Invest Ophthalmol Vis Sci*, 2013, Vol. 54, pp. 3681–3690.
26. Li WT, Leu YC, Wu JL. Red-light light-emitting diode irradiation increases the proliferation and osteogenic differentiation of rat bone marrow mesenchymal stem cells. *Photomed Laser Surg*, 2010, Vol. 28 (1), pp.157–165.
27. Li G, Veenstra AA, Talahalli RR, et al. Marrow-derived cells regulate the development of early diabetic retinopathy and tactile allodynia in mice. *Diabetes*, 2012, Vol. 61, pp. 3294–3303.
28. de Oliveira HA, Antonio EL, Arsa G, Santana ET, et al. Photobiomodulation Leads to Reduced Oxidative Stress in Rats Submitted to High-Intensity Resistive Exercise. *Oxid Med Cell Longev,* 2018, pp. 5763256.
29. Roy S, Kern TS, Song B, Stuebe C. Mechanistic Insights into Pathological Changes in the Diabetic Retina: Implications for Targeting Diabetic Retinopathy. *Am J Pathol*, 2017, Vol. 187 (1), pp. 9–19.
30. Madsen-Bouterse S. A., Zhong Q., Mohammad G., et al. Oxidative damage of mitochondrial DNA in diabetes and its protection by manganese superoxide dismutase. *Free Radic Res*, 2010, Vol. 44, pp.313–321.
31. Joussen A. M., Murata T., Tsujikawa A., et al. Leukocyte-mediated endothelial cell injury and death in the diabetic retina. *Am J Pathol,* 2001, Vol. 158, pp. 147–152.
32. Heo JC, Park JA, Kim DK, Lee JH. Photobiomodulation (660 nm) therapy reduces oxidative stress and induces BDNF expression in the hippocampus. *Sci Rep*, 2019, Vol. 9 (1), pp. 10114.
33. de Oliveira HA, Antonio EL, Arsa G, et al. Photobiomodulation Leads to Reduced Oxidative Stress in Rats Submitted to High-Intensity Resistive Exercise. *Oxid Med Cell Longev*, 2018, pp. 5763256.
34. Saliba A, Du Y, Liu H, et al. Photobiomodulation Mitigates Diabetes-Induced Retinopathy by Direct and Indirect Mechanisms: Evidence from Intervention Studies in Pigmented Mice. *PLOS One,* 2015, Vol. 10 (10), pp. 0139003.
35. Schindl A, Heinze G, Schindl M, et al. Systemic effects of low-inten-sity laser irradiation on skin microcirculation in patients with diabetic microangiopathy. *Microvasc Res*, 2002, Vol. 64 (2), pp. 240–246.
36. Lim J, Ali ZM, Sanders RA, et al. Effects of low-level light ther-apy on hepatic antioxidant defense in acute and chronic diabetic rats. *J Biochem Mol Toxicol*, 2009, Vol. 23 (1), pp. 1–8.
37. Semeraro F, Cancarini A, dell'Omo R, et al. Diabetic Retinopathy: Vascular and Inflammatory Disease. *J Diabetes Res,* 2015, Vol. 7, pp. 582060. doi: 10.1155/2015/582060
38. You QS, Guo Y, Wang J, et al. Detection of clinically unsuspected retinal neovascularization with wide-field OCT angiography. *Retina*, 2019.

and in vitro//Invest Ophthalmol Vis Sci. – 2013. – Vol. 54. – P. 3681–3690.
26. Li WT, Leu YC, Wu JL. Red-light light-emitting diode irradiation increases the proliferation and osteogenic differentiation of rat bone marrow mesenchymal stem cells//Photomed Laser Surg. – 2010. – Vol. 28 (1). – P. 157–165.
27. Li G, Veenstra AA, Talahalli RR, et al. Marrow-derived cells regulate the development of early diabetic retinopathy and tactile allodynia in mice//Diabetes. – 2012. – Vol. 61. – P. 3294–3303.
28. de Oliveira HA, Antonio EL, Arsa G, Santana ET, et al. Photobiomodulation Leads to Reduced Oxidative Stress in Rats Submitted to High-Intensity Resistive Exercise//Oxid Med Cell Longev. – 2018. – P. 5763256.
29. Roy S, Kern TS, Song B, Stuebe C. Mechanistic Insights into Pathological Changes in the Diabetic Retina: Implications for Targeting Diabetic Retinopathy//Am J Pathol. – 2017. – Vol.187 (1). – P. 9–19.
30. Madsen-Bouterse S. A., Zhong Q., Mohammad G., et al. Oxidative damage of mitochondrial DNA in diabetes and its protection by manganese superoxide dismutase//Free Radic Res. – 2010. – Vol. 44. – P. 313–321.
31. Joussen A. M., Murata T., Tsujikawa A., et al. Leukocyte-mediated endothelial cell injury and death in the diabetic retina//Am J Pathol. – 2001. – Vol. 158. – P.147–152.
32. Heo JC, Park JA, Kim DK, Lee JH. Photobiomodulation (660 nm) therapy reduces oxidative stress and induces BDNF expression in the hippocampus//Sci Rep. – 2019. – Vol. 9 (1). – P. 10114.
33. de Oliveira HA, Antonio EL, Arsa G, et al. Photobiomodulation Leads to Reduced Oxidative Stress in Rats Submitted to High-Intensity Resistive Exercise//Oxid Med Cell Longev. – 2018. – P. 5763256.
34. Saliba A, Du Y, Liu H, et al. Photobiomodulation Mitigates Diabetes-Induced Retinopathy by Direct and Indirect Mechanisms: Evidence from Intervention Studies in Pigmented Mice//PLOS One. – 2015. – Vol. 10 (10). – P. 0139003.
35. Schindl A, Heinze G, Schindl M, et al. Systemic effects of low-inten-sity laser irradiation on skin microcirculation in patients with diabetic microangiopathy//Microvasc Res. – 2002. – Vol. 64 (2). – P. 240–246.
36. Lim J, Ali ZM, Sanders RA, et al. Effects of low-level light ther-apy on hepatic antioxidant defense in acute and chronic diabetic rats//J Biochem Mol Toxicol. – 2009. – Vol. 23 (1). – P.1–8.
37. Semeraro F, Cancarini A, dell'Omo R, et al. Diabetic Retinopathy: Vascular and Inflammatory Disease//J Diabetes Res. – 2015. – vol. 7. – P. 582060. doi: 10.1155/2015/582060
38. You QS, Guo Y, Wang J, Wei X, et al. Detection of clinically unsuspected retinal neovascularization with wide-field OCT angiography//Retina. – 2019.