Section A-Research paper

Role of Hyperbaric Oxygen Therapy in Diabetic Macular Edema

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Abstract

Objective: The aim of this work is to evaluate the effect of Hyperbaric oxygen (HBO) therapy in diabetic macular edema (DME).
Patients and Methods: In this study we selected 100 eyes of 50 patients having bilateral DME. Patients did not receive intravitreal injections or laser before the study. They had exposed to HBO according to the treatment protocol. Evaluation was done by measuring the macular thickness using Optical Coherent Tomography (OCT) and best corrected visual acuity (BCVA).
Results: The LogMAR BCVA was improved from 0.96 ± 0.28 at baseline to 0.65 ± 0.27, 0.63 ± 0.19, 0.58 ± 0.25, 0.61 ± 0.21 and 0.62 ± 0.23 at 1, 2, 3, 6 and 12, respectively, with change of 0.31 (32.3%), 33 (34.4%), 0.38 (39.6%), 0.35 (36.5) and 0.34 (35.4%), at 1, 2, 3, 6 and 12, respectively, from the baseline. They all showed statistically significant difference in comparison to baseline. The CMT was decreased from 439.2 ± 144.5 µm at baseline to 375.6 ± 132.2 µm, 332.5 ± 129.7 µm, 289.4 ± 131.4 µm, 238.7 ± 142.5 µm and 273.8 ± 145.1 µm at 1, 2, 3, 6 and 12, respectively, with change of 63.6 µm (14.5%), 106.7 µm (24.3%), 149.8 µm (34.1%), 200.5 µm (45.7% and 165.4 µm (37.7%), at 1, 2, 3, 6 and 12, respectively, from the baseline. They all showed statistically significant difference in comparison to baseline.
Conclusion: HBO is proved in this study that it was safe and effective in treatment of DME. However, more researches were recommended with extensive details to explore its efficacy especially in long-term follow-up periods.

Keywords: Hyperbaric oxygen, diabetic macular edema, cystoid macular edema.

Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by persistent hyperglycemia due to insulin secretion or action malfunction. On a global scale, DM has been listed as one of the main contributors to vision loss and the only cause of blindness, showing a global increasing trend in age-standardized prevalence between the years 1990 and 2020 **[1]**. The single leading cause of visual dysfunction in the diabetic population is clinically significant diabetic macular edema (DME), followed by diabetic vitreous hemorrhage and tractional retinal detachment **[2]**.

The pathogenesis of DME is poorly understood. Extensive research in the field of laser, medical and surgical therapy has cumulated over the years. One hypothesis of development of DME is that retinal hypoxia contributes to release of vascular endothelial growth factor (VEGF) and potentially other mediators that are capable of causing leakage **[3]**. One way to begin to explore this hypothesis is to decrease retinal

hypoxia in patients with DME and determine whether reduction of DME occurs with improvement of visual acuity and retinal thickness **[4]**.

Hyperbaric oxygen (HBO) therapy is defined by undersea and hyperbaric medical society (UHMS) as a treatment in which a patient breathes 100% oxygen intermittently at atmospheric pressure that is greater than that found in the air at sea level (one atmospheric absolute (ATA)) and it should be at least 1.4 ATA or higher **[5]**. The efficacy of HBO is based on a reduction in volume of gas-filled spaces and an elevation of the partial pressure of oxygen (PO_2) resulting in hyper-oxygenation of perfused tissues that has a beneficial biochemical, cellular, and physiological effects that result in effective oxygen consumption at the tissue level **[6]**. This modality of treatment is used generally in ischemic diseases to increase oxygen supply to ischemic tissue, and in inflammatory diseases as the high oxygen perfusion can increase the healing process **[7]**.

HBO therapy was reported to be useful in the treatment of diabetic retinopathy; an experimental study demonstrated that HBO therapy ameliorated the blood--retinal barrier breakdown. Hence, it can prevent and treat persistent macular edema due to blood--retinal barrier breakdown in patients with diabetes **[6]**. However, the effects of HBO therapy in treating this common ophthalmic disorder have not been extensively studied **[8]**. So, the aim of this study is to determine the efficacy of HBO therapy as primary treatment modality of clinically significant macular edema (CSME) in diabetic patients as regards changes in central macular thickness and visual outcome and to evaluate safety of its use.

Patients and Methods

This prospective clinical trial conducted between January 2021 and June 2023 at the Airforce Specialized Hospital, Egypt. The study protocol was done, which was adhered to the tenets of the Declaration of Helsinki, and written informed consent was obtained from all participants before participation.

It involved 100 eyes of 50 selected patients with bilateral clinically significant cystoid ME agreed to be enrolled in the study and provided informed consent.

All included patients were eligible for HBO with age more than 50 years. Patients had intact clear cornea and intact anterior chamber with CMT above 240 µm by OCT. However, patients with elevated intraocular pressure (IOP), corneal diseases (e.g., pterygium, ulcer, opacity, dystrophy, … etc), symblepharon or conjunctival scar, previous trauma or surgery, posterior segment diseases such as vitreo macular traction or dense sub-foveal hard exudates by biomicroscopy or OCT, Fluorescein leakage, Previous pan-retinal photocoagulation in the previous 3 months were excluded.

Patients with history of previous treatment of DME, any ocular pathology rather than diabetic retinopathy, ocular surgeries and absolute or relative contraindications of HBO therapy (HBOT). e.g., untreated pneumothorax, asthma, chronic obstructive airway disease, upper respiratory tract infection, fever pacemaker use, claustrophobia, seizures, and pregnancy, were also excluded from study.

Methodology:

History and clinical ophthalmic examination including uncorrected and corrected visual acuity, refraction, anterior chamber (AC) examination by slit-lamp biomicroscopy, IOP measurement, and fundus examination by indirect +28 & +90 ophthalmoscopy.

Fundus fluorescein angiography (FFA) was conducted using Topcon (TRC-50LX retinal camera, Tokyo, Japan), central macular thickness (CMT) was measured using OCT (OCT- I , Zeiss - Carl Humphrey system, Dublin) using six linear scans accurately centered on fixation and processed as a retinal map.

Haux Oxystar 800 Cylindrical multiplace compression hyperbaric chamber was used for administration of therapy. More than one patient was received HBO therapy in a single chamber at the same time. Before treatment, the patients were instructed about the procedure. Each patient was undergoing cardiopulmonary clinical examination by internist with electrocardiogram, chest x-ray examinations and pulmonary function tests. Smokers were instructed to stop smoking during therapy. The patients were instructed to wear cotton only cloths, remove jewelries, accessories, and unnecessary prosthetic devices such as hearing aids and any foreign objects.

The course of HBO was 40 sessions in total, five sessions per week. The overall time of each session was 90 minutes. The profile of treatment in each session was divided into three phases; compression, treatment, and decompression as follow: Over the first 15 minutes; the pressure was increased gradually from normal atmospheric pressure till reaching 2.4 ATA i.e., the patient was exposed to compression. The patient here would feel the change in pressure in ears as fullness. To equalize the pressure, they would be instructed by the chamber staff how to blow air into the space behind the eardrum by holding the nose and attempting to blow through it, or simply swallowing (chewing gums), so air could be allowed to enter the middle ear cavity via the eustachian tube.

Following this phase; the patient breathed continuously 100% oxygen at this high pressure (2.4 ATA) through mask for the next 60 minutes. This was followed by the third phase of decreasing the pressure gradually over the last 15 minutes reaching normal atmospheric pressure i.e., patient decompression. Regulation of pressures was controlled digitally with monitoring of the patients using video graphed supervision outside the chamber and a trained nursing staff inside.

At follow-up period, patients were examined clinically, by FFA and OCT after four weeks, eight weeks, 12 weeks, 20 weeks, and 32 weeks from the beginning of therapy. Main outcome measures were changes in CMT, decreased leakage on FFA, visual outcome, occurrence of side effects and need for re-treatment.

Statistical analysis

Statistical analyses were performed using SPSS v23 statistical software (SPSS, Inc, Chicago, Illinois). Descriptive statistics (means correlation standard deviations) were calculated for quantitative variables. Two-sided Chi-square, student-t and ANOVA test were used as appropriate for parametric data, and Mann-Whitney U and Kruskal Wallis tests were employed for non-parametric variables. The significance level was calculated and $P \leq 0.05$ was considered statistically significant, while $P > 0.05$ was considered statistically non-significant.

Results

This study involved 100 eyes of 50 patients with bilateral DME. They were 16 males (32%) and 34 females (68%) with age ranged from 54 to 72 years with mean ± SD of 62.1 ± 12.1 years. The mean intraocular pressure (IOP) was 15.27 ± 4.35 mmHg and range of 11 to 19 mmHg. The mean LogMAR UCVA was 0.98 ± 0.31 and the BCVA was 0.96 ± 0.28, while the CMT was ranged between 252.7 to 637.4 with average of 439.2 ± 144.5 (table 1).

The LogMAR BCVA was improved from 0.96 ± 0.28 at baseline to 0.65 ± 0.27, 0.63 ± 0.19, 0.58 ± 0.25, 0.61 ± 0.21 and 0.62 ± 0.23 at 1, 2, 3, 6 and 12, respectively, with change of 0.31 (32.3%), 33 (34.4%), 0.38 (39.6%), 0.35 (36.5) and 0.34 (35.4%), at 1, 2, 3, 6 and 12, respectively, from the baseline. They all showed statistically significant difference in comparison to baseline (table 2 and fig. 1).

The CMT was decreased from 439.2 ± 144.5 µm at baseline to 375.6 ± 132.2 µm, 332.5 ± 129.7 µm, 289.4 ± 131.4 µm, 238.7 ± 142.5 µm and 273.8 ± 145.1 µm at 1, 2, 3, 6 and 12, respectively, with change

of 63.6 µm (14.5%), 106.7 µm (24.3%), 149.8 µm (34.1%), 200.5 µm (45.7% and 165.4 µm (37.7%), at 1, 2, 3, 6 and 12, respectively, from the baseline. They all showed statistically significant difference in comparison to baseline (table 3 and fig. 2).

Discussion

This clinical trial aimed to determine the benefits of HBOT in treatment of DME eyes. Patients enrolled in the trial were received a "HBO treatment" according to the mentioned protocol. Treatment of diabetes and diabetic controls was achieved according to the type of diabetes by professional medical physicians. The Gold standard treatment of diabetic retinopathy is by laser photocoagulation, however, a question posed by the Early Treatment Diabetic Retinopathy Study (ETDRS) was whether photocoagulation was effective in the treatment of DME **[9]**. When patients with DME, defined initially as thickening of the retina within one disc diameter of the center of the macula, were treated with focal laser, there was no significant VA benefit **[10]**.

HBO therapy was reported to be useful in the treatment of ocular vascular diseases **[11]**. Vasoconstriction of the retinal vessels is probably a direct response to the interaction between free oxygen radicals and nitric oxide, together with the autoregulation in this treatment. After 10 minutes of HBO treatment, vasoconstriction occurs significantly **[5]**. On the other hand, the increased nitric oxide and free oxygen are used promptly after the treatment and therefore, rapid vasodilatation occurs after ending of hyperbaric oxidation **[12]**. Despite vasoconstriction of retinal vessels during HBO therapy, oxygen saturation rises up to 23% and retina is not damaged **[13]**.

Over a year, this study evaluated visual acuities and CMT in 100 eyes with DME. The study found a significant improvement of visual acuities and decrease CMT during the follow-up period (12 months).

In agreement with our results, Said **[8]** found a highly significant improvement of visual acuity and CMT after 32 weeks of HBOT. Similar results obtained by previous studies **[14-16]**. The reduction of edema was explained by vasoconstriction that produced by HBOT and the increased nitric oxide and free oxygen are released and used promptly after the treatment and therefore, rapid vasodilatation occurs after ending of hyperbaric oxidation **[12]**. Despite vasoconstriction of retinal vessels during HBO therapy, oxygen saturation rises up to 23% and retina is not damaged **[13]**. In addition, the downregulation of VEGF, reduction of vascular permeability with amelioration of the blood retinal barrier and hyper oxygenation of macula and retina to reverse diabetic retinopathy and DME **[8]**.

We observed that the improvement of visual acuity and CMT were gradually increased in the first 3 months of therapy, while they start to decline in little degrees at 6 and 12 months (figs 1 & 2). The same was reported by Said **[8]** as they found a highly significant improvement of CMT and BCVA over 20 weeks of start of HBO therapy. Increased CMT than the previous reading was encountered at 32 weeks of follow up in four eyes (21%), this indicates that HBO therapy have to be undertaken on long-term basis to provide sustained benefit. No intraocular or systemic side effects were noted in any patient such as intraocular pressure changes and reversible myopia. The angiographic findings didn't always correlate with increase in function.

Our data were in line with that of Ogura et al. **[17]** that used HBO for treatment of DME in 22 eyes of 11 patients with DME were treated at 2.0 ATA for one hour twice a day for two weeks and then once a day for the third week. Visual acuity improved by two lines or more in 15 eyes (68%) after HBO therapy. The improvement in vision diminished overtime but at the end of follow up was still better than pre-treatment. Averous et al. **[14]** reported resolution of DME in one patient following high altitude

exercise due to enhanced tissue oxygenation. Consequently, after the recurrence of macular oedema HBO therapy had a beneficial effect, which was reproducible over a three-year period.

HBO relieved the oxygen deficit and might have induced a long-lasting regeneration of retinal cell metabolism. This would explain improved BCVA extending beyond the time of mere hyper oxygenation. Restoration of vascular tight junctions induced by HBO may explain angiographic edema reduction in some patients **[8]**.

The current study was also consistent with the results of previous reports **[11, 14-18]**. Pfoff and Thom **[18]** conducted a preliminary study of five patients treated with HBO with an intensive regimen of 1.5 hours two times per day for seven days and two hours per day for an additional 14 days. Visual acuity improved within 14 days in all patients compared to controls (follow up of three months).

Our study did not differentiate between recent and late onset diabetic retinopathy. Previous study by Jansen and Nielsen **[15]** used HBO treatment in two patients with chronic diabetic cystoid macular edema refractory to other modalities. Visual acuity improved significantly from 0.2 to 1.0 with normal reading vision and no metamorphobsia, FFA and OCT showed marked reduction of cystoid edema as early as two days after beginning of therapy. These improvements have been long standing (8 months).

Regarding the same point of respond of chronic edema to HBO therapy; Krott and his colleagues **[11]** used additional HBO in 5 patients with persistent macular edema of vascular origin (3 eyes had diabetic retinopathy and 2 eyes had vein occlusion) and peripheral retinal ischemia after failure of other therapies. Follow up schedule was every three months for 15 months. Each patient received 10.0-30.0 HBO treatments (median 15). The mean increase in BCVA was 3.5 (2.0 - 4.0) lines after therapy. Retinal photocoagulation was performed in six eyes. DME showed no morphologic change. They concluded that visual acuity with macular edema of vascular origin seemed to improve with HBO and a randomized clinical trial was needed to further assess beneficial influences of HBO Therapy as a first line treatment and its application before extended retinal ischemia had developed.

Conclusion:

HBO is proved in this study that it was safe and effective in treatment of DME. However, more researches were recommended with extensive details to explore its efficacy especially in long-term follow-up periods.

References:

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Table (1): Characteristics of the studied populations at baseline.

Item	Males		Females		Total	
	No.	%	No.	%	No.	%
Gender	16	32.0	34	68.0	50	100
	Min	Max	Mean	± SD		
Age (years)	54	72	62.1	12.1		
IOP (mmHg)	11	19	15.27	4.35		
UCVA (LogMAR)	0.78	0.99	0.98	0.31		
BCVA (LogMAR)	0.76	0.98	0.96	0.28		
CMT	252.7	637.4	439.2	144.5		

IOP: intraocular pressure, UCVA: uncorrected visual acuity, BCVA: best corrected visual acuity, CMT: central macular thickness.

Table (2): Change in best corrected visual acuities of CME patients after treatment with HBO.

Follow-up period	Best corrected visual acuity (LogMAR)				P (one way ANOVA)
	Mean	± SD	Change	%	
Before treatment	0.96	0.28	*Reference value*		
1 month post-treatment	0.65	0.27	0.31	32.3	0.012*
2 months post-treatment	0.63	0.19	0.33	34.4	0.011*
3 months post-treatment	0.58	0.25	0.38	39.6	0.006*
6 months post-treatment	0.61	0.21	0.35	36.5	0.009*
12 months post-treatment	0.62	0.23	0.34	35.4	0.009*

* P <0.05: significant. CME: cystoid macular edema, HBO: hyperbaric oxygen.

Table (3): Change in CMT of CME patients after treatment with HBO.

Follow-up period	Central macular thickness (µm)				P (one way ANOVA)
	Mean	± SD	Reduction	%	
Before treatment	439.2	144.5	*Reference value*		
1 month post-treatment	375.6	132.2	63.6	14.5	0.037*
2 months post-treatment	332.5	129.7	106.7	24.3	0.021*
3 months post-treatment	289.4	131.4	149.8	34.1	0.010*
6 months post-treatment	238.7	142.5	200.5	45.7	0.000*
12 months post-treatment	273.8	145.1	165.4	37.7	0.001*

* P <0.05: significant. CMT: central macular thickness, CME: cystoid macular edema, HBO: hyperbaric oxygen.

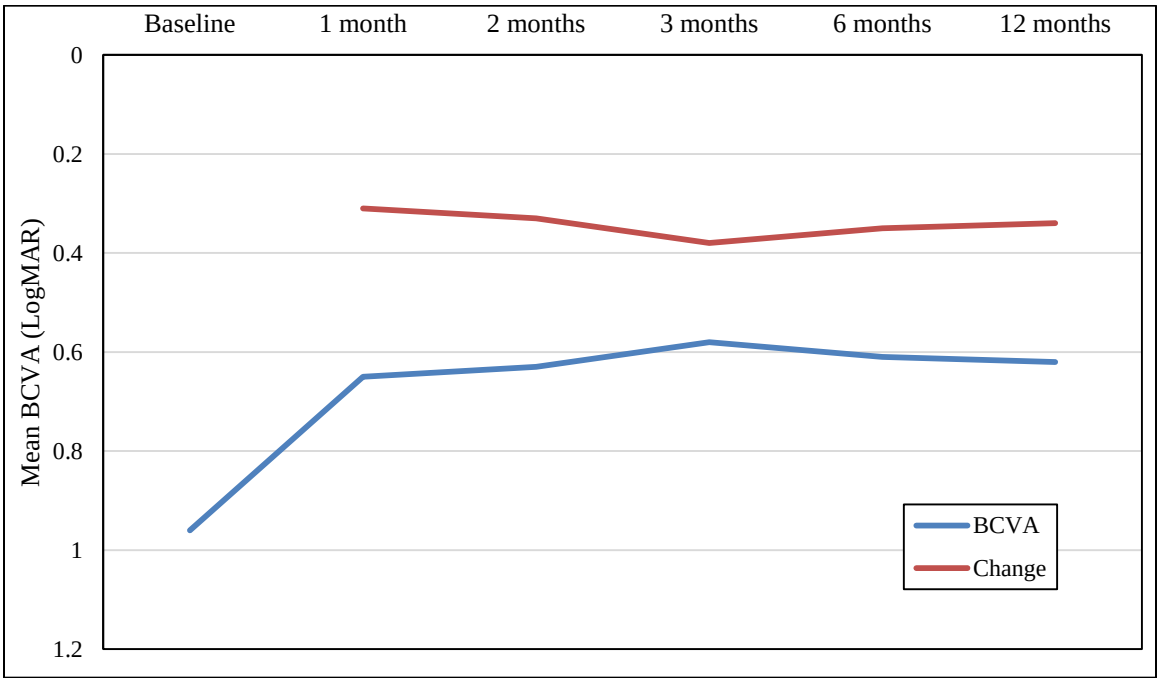

Fig. (1): Mean best corrected visual acuity (BCVA) of the studied cases and their changes during the study period.

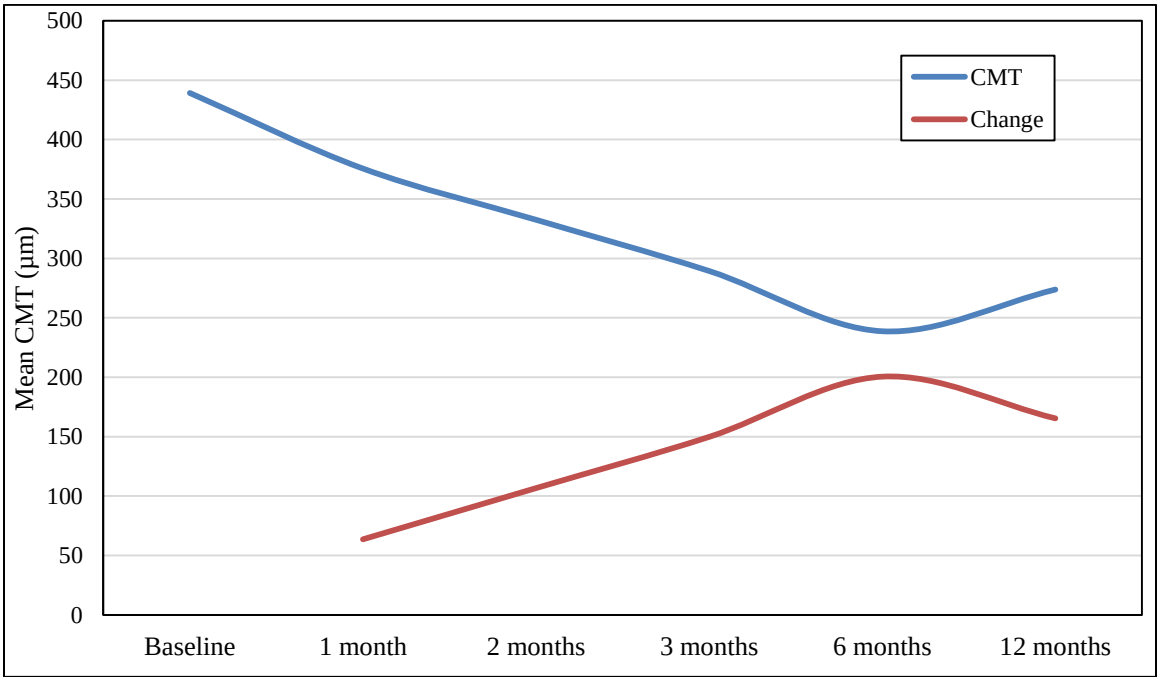

Fig. (2): Mean central macular thickness (CNT) of the studied cases and their changes during the study period.

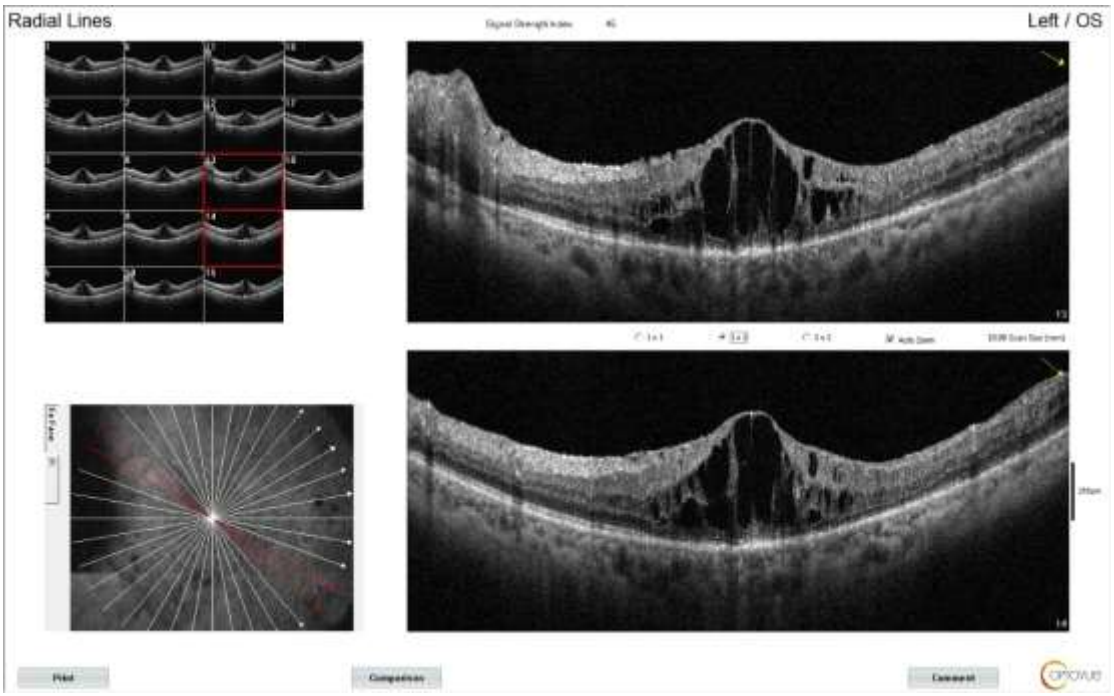

Fig. (3): OCT showing macular thickness before HBO.

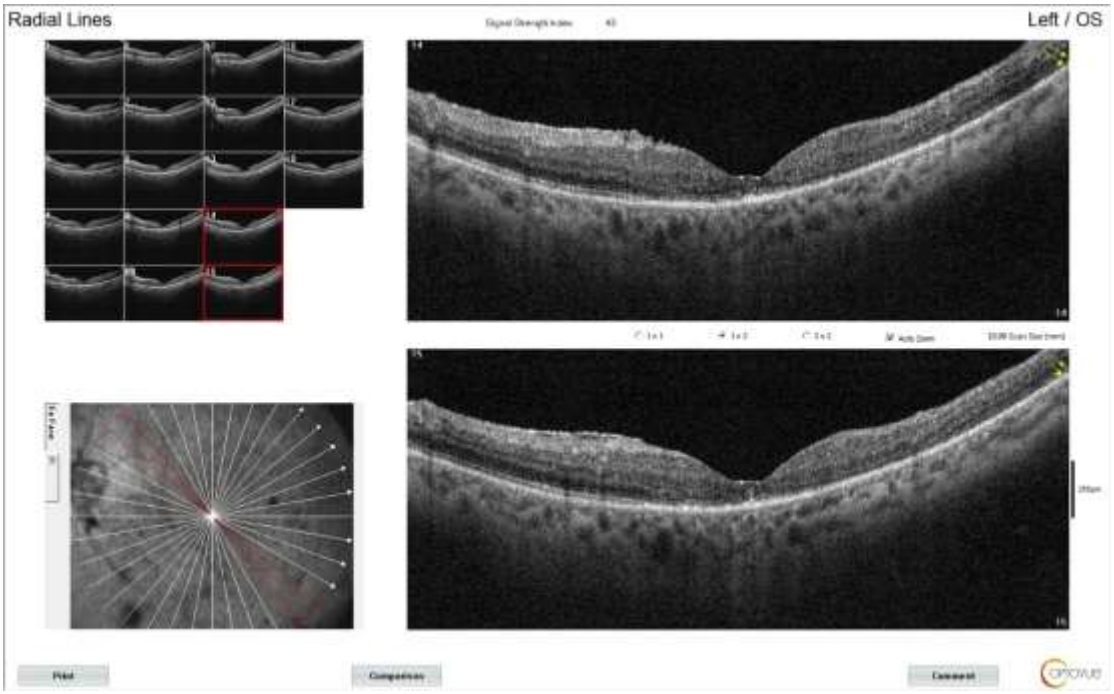

Fig. (4): The same case after 6 months of HBO administration.

Fig. (5): The Control; Panel from outside.

Fig. (6): Breathing of 100% oxygen under compression.

Fig. (7): Compression phase