Scientific Research Publishing

Open Journal of Ophthalmology, 2020, 10, 307-322
https://www.scirp.org/journal/ojoph
ISSN Online: 2165-7416
ISSN Print: 2165-7408

Efficacy of Alzer® and Diamel, Nutritional Supplements, in the Prevention of Severe Diabetic Macular Edema

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How to cite this paper: Rodríguez, J.E.M., Muñoz, M.E.P., Rode, E.C., Piño, L.R.R., Sainz, R.B., Calero, T.G., Puig, M.L., Anta, J.L., Santiesteban, R.P., Álvarez, Y.M. and Navares, E.S. (2020) Efficacy of Alzer® and Diamel, Nutritional Supplements, in the Prevention of Severe Diabetic Macular Edema. *Open Journal of Ophthalmology*, **10**, 307-322.
https://doi.org/10.4236/ojoph.2020.104034

Received: August 12, 2020
Accepted: November 9, 2020
Published: November 12, 2020

Abstract

Introduction: Macular edema is the main cause of low vision in diabetic patients. Laser photocoagulation continues to be the treatment of choice in conjunction with the use of steroids and anti-angiogenics, but these treatments include possible ocular complications. The nutritional supplement Alzer (whose primary active ingredient is *Ginkgo biloba*, a powerful antioxidant that acts on vascular factors and oxidative damage, which are two of the mechanisms implicated in the pathogenesis of diabetic macular edema), which has been used on other non-diabetic macular conditions, along with the Diamel nutritional supplement has been shown to be effective on glycemic control and could represent a treatment alternative for mild to moderate macular edema by reducing the thickness of the macular retina and preventing the progression of other more advanced clinical presentations that are harder to treat. **Objective:** Identify the effect of Alzer along with Diamel in reduction of the thickness of the macular retina among patients with mild to moderate diabetic macular edema. **Materials and Methods:** A phase II double-blind clinical trial was conducted in 64 patients with non-severe diabetic macular edema over the course of non-proliferative diabetic retinopathy, who attended the ophthalmology service of the Institute of Endocrinology of Havana from January 2016 to December 2016. The treatment was randomly assigned to two groups: one received Alzer plus Diamel (n = 32) and

the other group received Alzer placebo + Diamel placebo (n = 32). All patients were given an initial clinical evaluation, blood testing and ophthalmological evaluation at the start of treatment and after one year of follow-up. **Results:** There was a clinical improvement in the macular thickness upon the conclusion of the study in the patients treated with Alzer and Diamel. This decrease in thickness was statistically significant in the left eye. There was no decrease in visual acuity one year after treatment. Adverse events were mild and uncommon. **Conclusions:** Severe macular edema did not evolve in the Alzer and Diamel group. The clinical, but not statistically significant, success obtained in the experimental group proves the protocol hypothesis regarding the efficacy of the product being researched. The positive results in this small sample lead to the suggestion of performing larger-scale studies (Phase III). The clinical trial was registered in Clinical Trials.gov Identifier: NCT03533478.

Keywords

Alzer, Diamel, Ginkgo Biloba, Macular Edema, Macular Thickness, Nutritional Supplement

1. Introduction

Diabetes mellitus (DM) threatens become an epidemic due to its rapid increase worldwide [1]. It is projected that 642 million of people will have diabetes mellitus by 2040 [2]. This is why prevention, acting upon modifiable risk factors and appropriate, timely treatments are increasingly necessary in order to avoid the early appearance of complications.

Diabetic macular edema (DME) is considered to be the primary cause of visual deficit in patients with diabetes [3] and is defined as the thickening of the retina due to the accumulation of liquid in the outer plexiform and inner nuclear layers resulting from an electrolytic imbalance that occurs as a consequence of prolonged hyperglycemia. It entails an increase in the thickness of the retina in the macular area, affecting central vision [4] and can present itself during any stage of diabetic retinopathy (DR) and is associated with a longer evolution period [5].

The pathogenesis of DME is comprised of multiple factors: mechanisms implicated in its development include damage to the blood-retina barrier, the secretion from the retina into the vitreous humour of factors that trigger an increase in vascular permeability, such as vascular endothelial growth factor (VEGF) and its capacity to increase vascular endothelial permeability, with additional angiogenic and neuroprotective functions [6]. This also includes interleukin 6 (IL-6) and angiotensin II (AG II) as well as hypoxia, alterations to the retinal blood flow [7], and vitreomacular traction [8]. There are various factors that facilitate and accelerate the development and aggravation of DME, including the type of

diabetes, the period of evolution of diabetes, elevated glucose levels [9], lipid disorders, arterial hypertension [10] [11] and prior ocular surgeries [12].

Some studies report a higher incidence rate of DME in patients with type 1 DM (13.6%) after 10 years of evolution relative to 12.6% of patients with type 2 DM [13]. Likewise, the presence of elevated HbA1c levels is associated with a greater incidence of DME for both type 1 and type 2 DM patients [14]. All these prior studies have been reviewed by the Diabetes Control and Complications Trial (DCCT) in type 1 DM patients, where it was demonstrated the glycemic control is one of the most important factors in the development of macular edema. The DCCT demonstrated that strict glycemic control over a prolonged period reduced the incidence rate of DME. Nevertheless, the DCCT also proved that strict control imposed suddenly on patients with diabetes could trigger the appearance of DME [15]. In addition, blood lipid control seemed to be important in patients with macular edema. The presence of hard exudates in the macula is a factor of a poor prognosis and the severity of these exudates is predictive of low vision associated with subretinal fibrosis [16] [17].

There are different ways to classify DME in accordance with the behavior of the hard exudates and its relationship to the macula and fovea, and the thickness of the macular retina. The American Academy of Ophthalmology classifies DME into three groups: *Mild macular edema*: mild retinal thickening or hard exudates in the posterior pole, but distant from the centre of the macula; m*oderate macular edema*: retinal thickening or hard exudates near the centre of the macula but without affecting it; s*evere macular edema*: retinal thickening or hard exudates affecting the centre of the macula [18].

DME is evaluated clinically using contact lenses that allow the affected areas to be identified by comparing them with non-thickened retina. Identification can become difficult if the difference in thickness is not evident, but a quantitative method of measurement would overcome this limitation. This is the case with optical coherence tomography (OCT): an infrared light is projected through the pupil and then the vitreous humour, retina and choroid. The coherence of the rays of light in the retina generates an interference pattern that is quantified by the instrument [19]. OCT can measure retinal thickness and quantify information about DME objectively and in a reproducible manner that cannot be obtained through qualitative methods. Rapid macular mapping tests combine topographical thickness maps of three concentric circles at 1, 3 and 6 mm divided into 9 zones. This test additionally determines the central foveal thickness and the macular volume [20]. In healthy patients, average central foveal thicknesses of 153 (SD ± 15), 170 (SD ± 18), 174 microns (SD ± 18) have been reported; in patients with macular edema, the reported average is 307 microns (SD ± 136) [21]. OCT is useful for detecting mild retinal thickening (between 201 and 300 microns), which is difficult to evaluate clinically [22].

Currently, the OCT is the most accurate method to determine macular thickness and document changes in it. Considering that the normal macular thickness

is around 150 microns, we used the STRATUS OCT-3000 from Carl Zeiss, and we applied the rapid macular thickness acquisition protocol and the macular volume-thickness analysis protocol. The retinal thickness was measured, the single eye retinal mapping strategy divides the macula into nine fields and determines the thickness of the central macular retina (microns) and the macular volume (mm^3).

The rapid macular test measures the thickness of the macular retina in microns and the macular volume in cubic millimeters. We evaluated the mean macular thickness at the beginning and its modification one year after starting the treatment with respect to the initial measurement.

DME treatment constitutes a major challenge for modern ophthalmology. Essential requirements include optimization of medical treatment of diabetes by improvement in the control of the glycemic index and the associated risk factors. The focal laser and mesh are used in thickened areas that do not compromise the centre of the macula. For more severe edema, more effective medicines are used in conjunction with this test, such as intravitreal steroids and anti-angiogenics [23]. Included among intravitreal anti-angiogenics are Bevacizumab, which is a humanized monoclonal antibody directed against all of the biologically active isoforms of VEGF; Ranibizumab, which is the Fab fragment of the anti-VEGF antibody, a monoclonal antibody directed against VEGF-A; and Aflibercept, which is a fusion protein that blocks the effects of VEGF and acts as a competitive receptor to inhibit placental growth factors. These anti-angiogenics can be used alone or in conjunction with laser treatment or surgery according to the type of DME present. The Diabetic Clinical Research Network's Protocol T demonstrated that these medications improve the vision of patients with diabetic macular edema, but the relative effect depends upon the initial visual acuity [24]. Intravitreal steroids are also effective in the treatment of DME, but can induce cataracts and/or ocular hypertension. Intravitreal injection of corticoids such as triamcinolone and extended release intravitreal implants such as dexamethasone and fluocinolone can help patients who are non-responsive to injections of anti-angiogenics as well as in pseudophakic eyes, where they can be utilized as the first line of treatment [25]. Finally, it must be taken into consideration that cases of vitreomacular traction or epiretinal membrane require a vitrectomy [26]. Nowadays, MicroPulse lasers have become part of the first line of treatment for DME due to the advantage of being a less-invasive procedure that stimulates the retinal pigment epithelium without causing lesions or burning the fovea. They have the effect of a photostimulating laser with the same efficacy as a continuous wavelength laser. In addition, they are highly useful for patients who reject intravitreal therapy or who are in the initial stages, which can be controlled without the need for injections. Typically, MicroPulse laser therapy has better results in patients with appropriate glycemic control and a central macular thickness (CMT) of less than 400 pm. Therefore, it is recommended in this type of patients, but the high cost prevents its use in countries with limited resources

[27] [28].

Currently, DME treatment continues to cause controversy and the search for new alternatives is oriented towards the etiology of DME, but there is a consensus regarding the importance of prevention and early diagnosis.

Meanwhile, the ingredients in ALZER®, a nutritional supplement based on antioxidants and vitamins specifically chosen to strengthen the organic processes related to the nervous system [29], include: Acetyl-L-carnitine, which reduces age-related damage to mitochondrial functioning; dry lettuce extract, indicated for relaxing the nervous system; and *Gingko biloba* extract, a known antioxidant attributed with properties of improving the circulatory system and memory and concentration capacities. It is thought that Alzer works with several potential mechanisms of action, such as increasing blood flow, antagonizing the platelet activating factor and prevention of membrane damage caused by free radicals, keeping in mind that vascular factors and oxidative damage are two mechanisms implied in the pathogenesis of macular edema. It has been used in age-related macular degeneration. **Table 1** summarizes chemical ingredients of Alzer®.

In a placebo-controlled 6-month double-blind study of 20 persons with macular degeneration, the use of *Ginkgo* at a dose of 160 mg per day resulted in improved visual acuity [30]. A double-blind study of 99 patients with macular degeneration compared *Ginkgo biloba* extract at doses of 240 mg per day and 60 mg per day; the results showed that vision improved in both groups, but at a greater level in the group with the higher dose. In both studies the treatment was for six months. They reported some positive effects of *Ginkgo biloba* on vision; however, the results could not be summarized. No side effects or information on the quality of life of persons with age-related macular degeneration were reported [31].

Another component of Alzer is lipoic acid, which acts as an antioxidant and could have an anti-angiogenic effect and have beneficial and protective effects against DR [32].

No studies on experiments using Alzer as a DME treatment have been reported, but this study has been based on the mechanism of action on the macula that has in fact been reported in other non-diabetic macular pathologies.

Diamel has been recognized as a nutritional supplement. It is comprised of oligoelements, amino acids, vitamins, lettuce extract and cranberry extract, which are activated through a molecular magnetization process. It is specially designed to stimulate pancreatic β-cell functioning and act on the digestive apparatus. Using these natural ingredients that act as biocatalysts, along with antioxidants and lettuce extract, it can decrease the absorption of gastrointestinal glucose. It acts at a pancreatic, gastrointestinal, renal and intracellular level, where diabetes causes great oxidative stress, which gives rise to the formation of free radicals which are responsible, in large part, for cellular damage. Therefore, it can be used advantageously for improving glycemic control and preventing complications. **Table 2** displays chemical composition of Diamel.

Table 1. Chemical composition of Alzer (500 mg).

Glucose flavones	180 mg	Guar gum	67.2 mg
Carnitine	20.5 mg	Parabensodium methyl	0.3 mg
Lipoic acid	18 mg	Ginkgo biloba	180 mg
Lettuce extract	214.5 mg		

Table 2. Chemical composition of Diamel (600 mg).

Arginine	35.5 mg	Glycine	7.1 mg
Ascorbic acid	10 mg	Ornithine	17.7 mg
Zinc sulfate	6 mg	Calcium pantothenate	1 mg
Folic acid	33 μg	Cranberry extract	345 mg
Fumaric acid	35.5 mg	Lettuce extract	152 mg
L-Carnitine	35.5 mg	L-Cysteine	14.4 mg
Methyl parabensodium	0.33 mg	Pyridoxal	0.3 mg
Cyanocobalamin	0.16 μg		

The first controlled clinical study of the Diamel supplement proved its efficacy in improving metabolic control and beta-cell functioning for at least six months after treatment in patients with type 2 DM. In the group with Diamel, a decrease in the daily dose of hypoglycemic agents and elevated levels of insulin secretion were observed in comparison with the control group six months after treatment [33]. Other studies performed on subjects with metabolic syndrome have demonstrated that Diamel reduces average glycemic levels by 16% ($p < 0.05$) [34].

This study would be the first to use the combination of these two nutritional supplements in the prevention of the progression of macular edema to more advanced and difficult-to-treat forms, it represents another therapeutic weapon, depending on prevention. Thus, we aimed to evaluate the efficacy and safety of Alzer in combination with Diamel in patients with mild or moderate macular edema.

2. Materials and Method

A phase II monocentric randomized double-blind (subject-researcher) controlled (experimental vs. control group) study was conducted on type 2 diabetic patients from 18 to 65 years old, who were consecutively seen at the ophthalmology service of the Institute of Endocrinology of Havana, Cuba from January 2016 to December 2016. After study enrollment, all patients were followed up for 1 year. Subjects were included in the study if they fulfilled the following criteria: had a diagnosis of mild to moderate diabetic macular edema during the course of non-proliferative diabetic retinopathy without laser treatment criteria in any

of the eyes studied, hemoglobin levels glycosylated (HbA1c) below 8%, treated with insulin or combined oral hypoglycemic drugs. This study was registered at *Clinical Trials.gov* with the following identifier*: NCT*03533478. All patients gave written informed consent. The medical ethical committees of the participating hospital approved the study protocol. The study was conducted in accordance with the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) dated 17 July 1996 and in accordance with the Declaration of Helsinki (revised version of Hong Kong, 1989).

2.1. Clinical Trial Design

Patient population: Patients with light and moderate macular edema were consecutively seen in our service and fulfilled the selection criteria. A total of 64 patients with mild and moderate diabetic macular edema were included and randomly assigned to receive Alzer and Diamel (n = 32) or placebo (n = 32). Randomization was conducted by allocation into blocks of 4. It was performed by a health worker experienced in randomization techniques who was not involved in the evaluation or treatment of the participants. The physicians, study coordinators, and patients were blinded to the randomization scheme. The patients, investigators, and study coordinators were blinded as to the treatment administered. Catalysis Laboratories S.L., Spain provided Diamel, Alzer and placebo. There was no difference in appearance, smell or flavor between Alzer, Diamel and placebo. A simple randomization was used in an allocation ratio of 1:1, the sequences were generated using a random number generator.

2.2. Clinical Evaluation and Blood Testing

In order to diagnose mild to moderate diabetic macular edema, the visual acuity of the patients was tested with optical correction, biomicroscopy of the posterior pole, retinography and optical coherence tomography. Patients were evaluated at the start of treatment and one year later, although there were quarterly checks of glycemic levels, glycosylated haemoglobin, cholesterol and triglycerides. The differences between the effects of the treatments on the metabolic, biochemical and clinical indicators during the follow-up period per data pair from the two groups were evaluated using the Wilcoxon signed-rank test to compare changes between the start and end of treatment (12 months).

3. Results

Seventy-four type 2 diabetic patients being treated with insulin with mild to moderate diabetic macular edema were evaluated. Of these, 10 were excluded because they did not comply with the inclusion criteria (did not volunteer to participate in the study, HbA1c percentage statistics did not meet the guidelines for inclusion, or opacity due to cataracts prevented the correct ophthalmological examination as proposed in the study). Sixty-four patients remained, 32 of which were assigned to the experimental Alzer and Diamel group and 32 of

which to the placebo group. The average age of the patients included in the study was 56, with a 5.3 standard deviation value. No significant differences were observed between the study groups in terms of this variable's distribution. In both groups, females predominated, the disease evolution period was focused between 10 and 20 years. Most patients received a nutritional assessment that placed them in the overweight and obese categories, but in neither case were there significant variations in the groups (Table 3).

During the study, 15 patients abandoned treatment and did not take part in the second or third consultation, 8 from the placebo group and 7 from the study group. The Alzer and Diamel group was comprised of 25 patients and the Placebo group of 24 (Figure 1).

The resulting sample was also distributed homogeneously among the groups, as no significant differences were found between them in terms of gender, mean age, evolution period and nutritional assessment. For these variables, the p in the resulting groups were 0.187, 0.469, 0.898 and 0.278, respectively.

No statistical differences were found between the groups studied in the initial clinical and biochemical characteristics of those being treated (Table 4). After 12 months, none of the clinical or biochemical parameters showed a difference between the study groups (Table 5).

When analyzing macular thickness at 12 months relative to the start of the study, a decrease can be observed in the group assigned Alzer and Diamel for the year of treatment. This decrease was significant in the left eye (LE) ($p = 0.016$). Although there was no statistically significant difference in the right eye (RE), there was a decrease in the macular thickness, which did not occur in either eye in the group that received the placebo (Table 6).

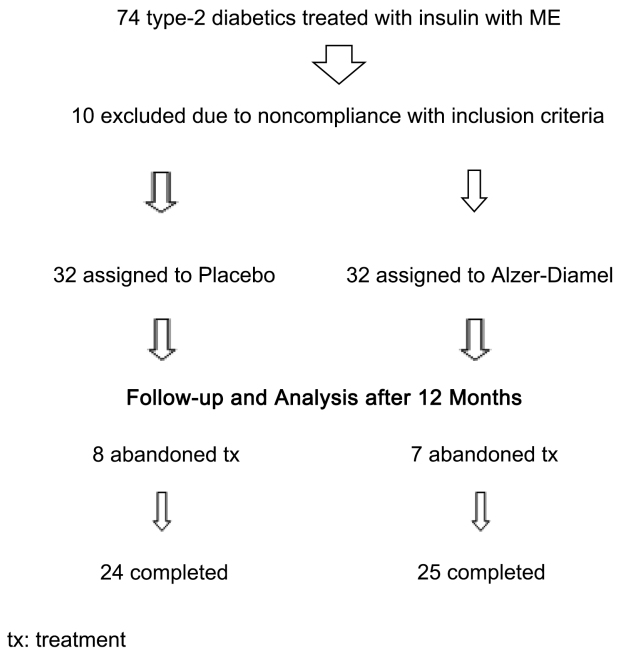

Figure 1. Distribution of participants through the study.

Table 3. Initial clinical characteristics of persons with type 2 diabetes treated with insulin with mild to moderate macular edema who received Alzer-Diamel or Placebo.

Characteristics	Alzer & Diamel (n = 32)	Placebo (n = 32)	Total	P
Sex				
Male	15 (46.9)	13 (40.6)	28 (43.8)	0.64
Female	17 (53.1)	19 (59.4)	36 (56.3)	
Age (years), Mean (SD)	56.0 (5.3)	56.1 (6.9)	56.0 (6.1)	0.93
Evolution period in years				
< 10	4 (12.5)	6 (19.4)	10 (15.9)	0.51
10 - 20	23 (71.9)	19 (58.0)	42 (65.1)	
> 20	5 (15.6)	7 (22.6)	12 (19.0)	
Nutritional information				
Normal weight	5 (15.6)	4 (12.5)	9 (14.6)	0.43
Overweight	10 (31.2)	15 (46.8)	25 (39.1)	
Obese	17 (53.1)	13 (40.6)	30 (46.9)	

Abbreviations: SD, standard deviation.

Table 4. Initial clinical and biochemical characteristics of persons with type 2 diabetes treated with insulin with mild to moderate macular edema who received Alzer-Diamel or Placebo.

Variables	Alzer & Diamel (n = 32)	Placebo (n = 32)	P-Value
	Average ± SD	Average ± SD	
Weight (kg)	81.83 ± 17.33	78.98 ± 12.33	0.448
Height (cm)	163.56 ± 11.65	164.38 ± 10.62	0.772
BMI (kg/m^2)	30.54 ± 5.28	29.28 ± 4.31	0.300
SBP (mmHg)	127.66 ± 11.98	130.47 ± 14.39	0.399
DBP (mmHg)	75.63 ± 9.65	75.31 ± 8.13	0.889
HbA1c (%)	7.39 ± 0.84	7.53 ± 0.72	0.465
Cholesterol (mmol/L)	4.89 ± 1.17	5.36 ± 1.12	0.106
Triglycerides (mmol/L)	1.59 ± 0.89	1.75 ± 0.91	0.479

Abbreviations: BMI: Body Mass Index; HbA1c: Glycosylated Hemoglobin; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

Table 5. Evolution of clinical and biochemical measurements in persons with type 2 diabetes treated with insulin with macular edema who received Alzer-Diamel or Placebo.

Variables	Per-protocol	Alzer & Diamel	Placebo	P-Value
		n = 25	n = 24	
		Average ± SD	Average ± SD	
Weight (kg)	Start	85.10 ± 16.68	77.02 ± 12.63	0.156
	12 months	87.14 ± 17.84	78.99 ± 13.29[a]	0.303
BMI (kg/m^2)	Start	30.70 ± 5.07	29.19 ± 4.93	0.322
	12 months	31.45 ± 5.56	30.01 ± 5.62[b]	0.490
SBP (mmHg)	Start	127.40 ± 12.51	131.46 ± 14.41	0.457
	12 months	129.80 ± 9.63	128.75 ± 9.81	0.717
DBP (mmHg)	Start	76.40 ± 9.74	73.54 ± 7.59	0.275
	12 months	76.40 ± 6.04	76.25 ± 6.95	0.837
HbA1c (%)	Start	7.49 ± 0.67	7.49 ± 0.81	0.511
	12 months	7.62 ± 1.41	8.10 ± 1.86	0.522
Cholesterol (mmol/L)	Start	4.67 ± 1.22	5.57 ± 1.17	0.013
	12 months	5.18 ± 1.08	5.61 ± 1.01	0.107
Triglycerides (mmol/L)	Start	1.56 ± 0.93	1.74 ± 0.76	0.161
	12 months	1.70 ± 1.04	1.82 ± 0.82	0.332

Abbreviations: BMI: Body Mass Index; HbA1c: Glycosylated Hemoglobin; SBP: Systolic blood pressure; DBP: Diastolic blood pressure. [a]p = 0.022; [b]p = 0.015 for comparisons between end-of-treatment vs baseline according to Wilcoxon signed-rank test.

Table 6. Macular thickness and visual acuity at start of treatment and after one year.

Macular Thickness	Duration	Alzer-Diamel Average ± SEM n = 25	Placebo Average ± SEM n = 24	P-Value
MT LE	Start	189.28 ± 10.26	181.48 ± 13.20	0.331
	12 months	178.94 ± 8.74	199.52 ± 13.30	0.291
	Change	**−10.33 ± 11.99**	18.05 ± 8.94	**0.016**
MT RE	Start	184.06 ± 11.76	184.65 ± 14.16	0.610
	12 months	171.81 ± 10.47	210.63 ± 14.96	0.066
	Change	−13.07 ± 12.64	15.45 ± 13.26	0.463
VA LE	Start	0.95 ± 0.03	0.93 ± 0.03	0.300
	12 months	0.94 ± 0.04	0.092 ± 0.03	0.153
	Change	−0.008 ± 0.03	−0.013 ± 0.016	0.988
VA RE	Start	0.97 ± 0.03	0.95 ± 0.04	0.532
	12 months	0.97 ± 0.02	0.95 ± 0.04	0.966
	Change	−0.004 ± 0.015	−0.008 ± 0.006	0.333

Abbreviations: MT: Macular thickness VA: Visual acuity RE: Right eye LE: Left eye.

With regards to visual acuity, almost all patients had good vision, given that the macular edema was mild to moderate with little visual compromise due to this condition. Upon comparison of the initial statistics relative to one year of treatment, almost no difference was observed (Table 6).

In general, therapy with Alzer-Diamel was well-tolerated. Adverse effects (gastritis, nausea and vitreous bleeding) were generally minimal and equally common among patients from both groups during the period of treatment. In this study, only four patients presented with mild to moderate adverse events: two in the Alzer-Diamel group (one with gastritis and another with nausea). These two patients abandoned treatment, and when combined with the five who abandoned treatment voluntarily, the Alzer and Diamel group was left with 25 patients from the 32 included at the start. In the placebo group, two patients also presented with adverse events (one with nausea and another with vitreous bleeding). Only one abandoned treatment, and in the case of vitreous bleeding, which was not related to the product in question, the patient stayed in the study; however, seven patients abandoned treatment voluntarily and the group was left with 24 patients from the initial 32.

With respect to the primary efficacy measure, it can be seen that the success rate was greater than the failure rate, therefore proving the hypothesis proposed at the start of the study which proposed a 50% reduction in macular thickness with respect to the base value in 25% or more of all cases under study (Table 7). Figure 2 displays the clinical improvement of lesions can be observed upon comparing retinography at one year of treatment against the retinography performed at the time of inclusion of the patient in the study.

4. Discussion

Normal retinas are an ideal organ for elevated production of free oxygen radicals due to their composition, which is high in polyunsaturated fatty acids, the perfect substrata for lipid peroxidation. Their high consumption of oxygen, the highest of all organs in the human body, and their exposure to radiation create an environment that favours oxidative damage. Current recommendations for a varied diet rich in natural antioxidants along with strict glycemic control as the most effective strategy against oxidation motivated the researchers to use these nutritional supplements with proven antioxidant benefits on diabetic macular edema [35].

Table 7. Success of treatment. Primary efficacy measure.

Primary Efficacy	Alzer-Diamel Group		Placebo Group		Total		P-Value
	No	%	No	%	No	%	
Success	*16*	*64*	*12*	*50*	*28*	*57.14*	0.322
Failure	9	36	12	50	21	42.86	
Total	25	100	24	100	49	100	

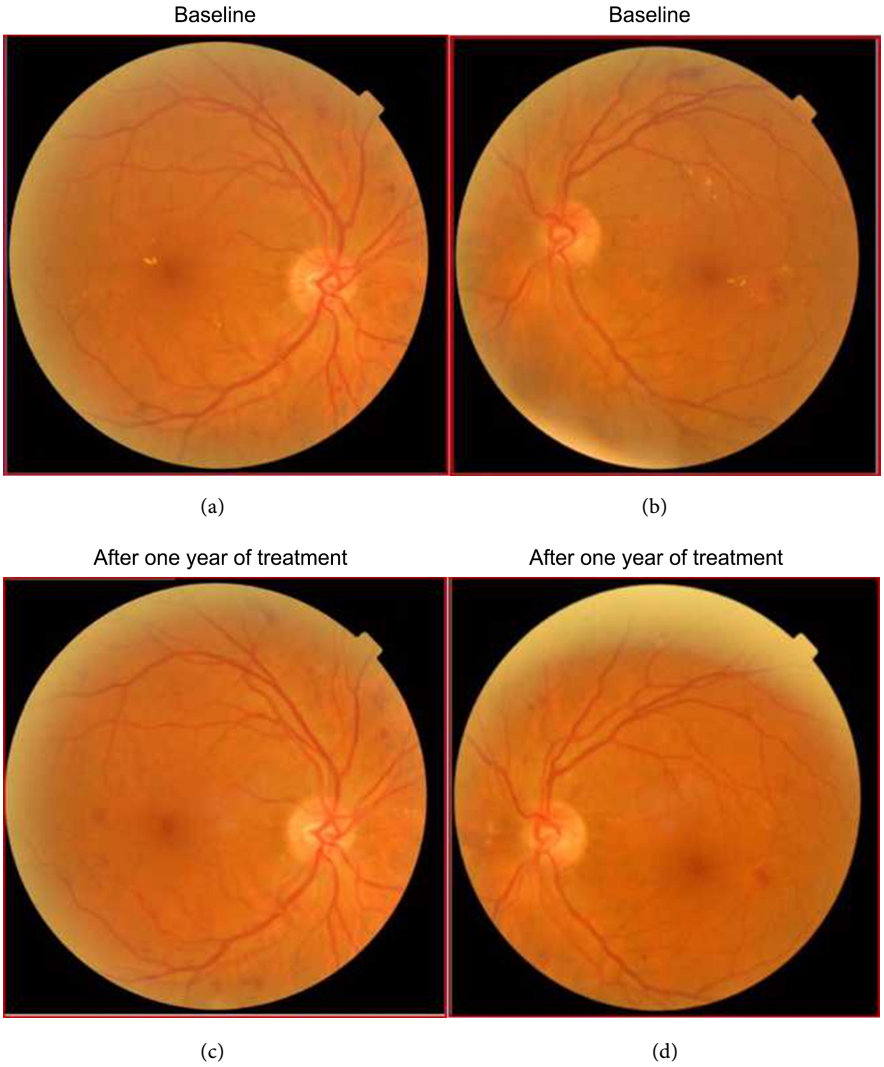

Figure 2. Clinical improvement of lesions after 1 year of treatment. In **Figure 2**, imaging panel A and B represent baseline evaluations whereas panel C and D represent end-of-study assessments. The clinical improvement of lesions was assessed by retinography.

At inclusion, the patients in this study had HbA1c percentages under 8%, and in this respect no significant difference was found after one year of treatment. Therefore, the patient glycemic control was considered to be adequate for both groups throughout the study. After one year, none of the studied clinical and biochemical parameters showed a variation between the experimental and control groups.

Currently, DME without central compromise may be allowed to progress until a central compromise is observed, or a focal laser can be considered for leaking microaneurysms if the thickening is threatening the fovea. No treatment can be applied to lesions closer than 300 to 500 microns from the centre of the macula. In DME with central compromise and good visual acuity (better than 20/30), three treatment options are evaluated: careful follow-up with an anti-VEGF

treatment, but only if DME is worsening; anti-VEGF intravitreal injections; or laser photocoagulation with an anti-VEGF, if necessary [36].

In addition, the Diabetic Retinopathy Clinical Research Network (DRCR.net) reported another randomized clinical trial to evaluate three treatment strategies for 702 eyes in patients with diabetic macular edema and good visual acuity, who were assigned randomly to three treatment groups: intravitreal injection of aflibercept (2.0 mg) (n = 226), photocoagulation laser (n = 240) or observation (n = 236), with a 2-year follow-up period. These 3 treatment strategies (anti-VEGF therapy, laser, or observation) produced no difference in vision loss risk at 24 months and showed no impairment to visual function while awaiting the start of anti-VEGF therapy. In fact, 74% of the laser group and 64% of the observation group did not need aflibercept injections over those 2 years. This strategy of holding back treatment with aflibercept unless visual acuity decreases could mean savings on medical care costs, as anti-VEGF therapies are expensive [37].

Patients were included in this study that had mild to moderate macular edema, the majority with 20/20 vision, a macular thickness under 300 microns and who were not going to be treated with lasers nor anti-angiogenics, just with the administration of Alzer and Diamel nutritional supplements in comparison with a placebo group. In this small controlled double-blind randomized phase II study of type 2 diabetic patients treated with insulin with a diagnosis of mild to moderate diabetic macular edema, Alzer-Diamel was found to decrease macular thickness in both eyes, but only significantly in the left eye. This is the first known study in humans to evaluate the effect of daily ingestion of Alzer-Diamel on the reduction of macular thickness in adults with type 2 diabetes with macular edema. Various articles have described the beneficial effect of the Ginkgo biloba component in Alzer on macular degeneration [30] [31].

The small sample of this study is our main limitation. However, our positive results on the reduction of macular thickness along with the excellent safety profile of Alzer and Diamel during administration might be attractive to further design a large phase III trial exploring the efficacy of Alzer and Diamel in the wide spectrum of severity of macular edema along with other standard therapies.

5. Conclusion

The patients included in the Alzer and Diamel experimental group did not progress to severe macular edema. Despite the p-value only being significant in the LE, the positive results obtained from this small sample invite the proposal of larger-scale studies (phase III). The clinical, but not statistically significant, success from treatment obtained in the Alzer and Diamel group proves the protocol hypothesis regarding the efficacy of the product being researched. Visual acuity was not affected from the start of treatment to one year later. Almost all patients maintained the good level of vision that they had when included in the study. There were few adverse events which were of mild to moderate severity and only three patients abandoned the study due to this reason.

Funding

This study was supported in part by a grant from Catalysis Laboratories, Spain. They provided the Diamel and Alzer for the study protocol. The supporting sources had no role in the study design, collection of data, interpretation of data, writing of the manuscript or submission for publication.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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