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Short-term effects of intravitreal bevacizumab in contrast sensitivity of patients with diabetic macular edema and optimizing glycemic control

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ABSTRACT

Aims: To analyze contrast sensitivity of intravitreal bevacizumab injections with optimizing glycemic control versus optimizing glycemic control (in combination with sham injections) in eyes with Diabetic Macular Edema (DME).

Design: Prospective, interventional, masked, randomized controlled trial.

Methods: Forty-one eyes of 34 patients with type 2 diabetes mellitus and DME with glycated hemoglobin (HbA1c) < 11% received either intravitreal bevacizumab injection (Group 1) or sham injection (Group 2) at 0 and 6 weeks along with optimizing glycemic control. Mean change in best-corrected visual acuity (BCVA), contrast sensitivity (CS), optical coherence tomography (OCT)-measured by central macular thickness (CMT) were compared and correlated at baseline, 2, 6 and 12 weeks.

Results: The study showed a mean CS improved in group 1 from 1.14 ± 0.36 logCS to 1.32 ± 0.24 logCS and also in group 2 from 1.11 ± 0.29 logCS to 1.18 ± 0.29 logCS at 12 weeks ($P = 0.12$). CS and CMT promptly decreased in group 1 compared to group 2 at 2 weeks (ΔCS = 0.15 ± 0.25 vs. 0.03 ± 0.15 logCS; $P = 0.04$; ΔCMT = 116 ± 115 vs. 17 ± 71 μm; $P = 0.01$). There was a mean reduction of approximately 0.5% in HbA1c levels in both groups at 12 weeks ($P = 0.002$).

Conclusion: The use of bevacizumab in combination with optimizing glycemic control results in earlier improvement of contrast sensitivity in type 2 diabetes patients with DME. However, the optimizing glycemic control itself has shown also to be effective at 12 weeks.

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1. Introduction

Diabetic Macular Edema (DME) is defined as the accumulation of fluid in the extra- cellular spaces in the neurosensory retina and is the major cause of low visual acuity in patients with DR. After 15 years of diagnosis of diabetes, the prevalence of macular edema is about 20% in patients with type 1 and 18% in type 2 diabetes [1,2].

Several systemic strategies have been described for the treatment of DME including exercise, smoking cessation, reduction in body mass index, better blood pressure control and improved blood sugar control. In The United Kingdom Prospective Diabetes Study (UKPDS), type 2 diabetes patients under intensive blood glucose control were less likely to need retinal laser photocoagulation for DR or DME [3]. Moreover, systemic factors such as poor glycemic control may contribute to the recurrence of DME [4]. In the United States population aged 40 years or older with DME, the mean of HbA1c levels was 8.4% (68 mmol/l) [5].

Among ophthalmic strategies, nowadays anti-vascular endothelial growth factor (Anti-VEGF) therapy is the gold standard for the treatment of DME. Vascular endothelial growth factor (VEGF) induces neovascularization and increases vascular permeability in human eyes, causing DME and worsening central vision [6]. VEGF levels are directly related to the growth and the permeability of neovasculature [7,8].

Several retrospective and prospective studies have reported favorable effects of intravitreal bevacizumab, an anti-VEGF antibody, in the management of DME [9–13]. The effects of anti-VEGF enable it to be used in the vitreous for the same indication as corticosteroids, but without the associated side effects such as ocular hypertension and cataractogenesis [14]. Initial studies of bevacizumab have demonstrated its action on macular edema by observing central macular thickness (CMT) measured on optical coherence tomography (OCT) [15].

There is ample evidence that the contrast sensitivity (CS) may be affected in DME, even before changes in visual acuity [16]. To date, the subjective functional evaluation in the treatment of DME in studies with intravitreal bevacizumab has been performed with visual acuity-measured by ETDRS (logMAR) [10–14].

CS is a frequent complication of DME. As a result, patients may have a serious impact on life quality and their functional abilities [17–19]. CS tests characterize aspects of visual function that are not well captured by the visual acuity [20]. They are substantially associated with reading performance [21], face recognition [22], abilities to walk and drive [23,24] and tasks of daily life [25].

The combination of systemic and local treatments, involving optimized metabolic control with control of HbA1c levels and anti-VEGF therapy may be the ideal way to maintain the visual acuity and contrast sensitivity stable. Retrospective review demonstrated that patients with better glycemic control might have a better response to anti-VEGF therapy [26].

2. Research design and methods

The protocol of the study adhered to the provisions of the Declaration of Helsinki. The study was conducted at Hospital das Clínicas, University of São Paulo, São Paulo, Brazil from February 2010 to December 2012 and was approved by the Local Ethics Committee (CAPPesq - 0875-08). Informed consent was obtained from all the patients before enrollment. The study is registered at www.clinicaltrials.gov under the identifier NCT02308644.

2.1. *Participants eligibility*

The following criteria were used to guide patient enrollment.

– Inclusion Criteria

(1) Minimum age 18 years old; (2) Patients with type 2 diabetes mellitus; (3) Presence of macular edema with CMT $\geq$ 250 μm measured by OCT; (4) Best-corrected visual acuity (BCVA) between 20/40 (<70 Early Treatment Diabetic Retinopathy Study (ETDRS) letters)) and 20/200 (>31 ETDRS letters); (5) Women not pregnant; (6) Ability to adhere to the study protocol.

– Exclusion Criteria

(1) Treatment for DME within the prior 3 months; (2) Vitreoretinal traction within 1 disc diameter (DD) of the fovea, confirmed on clinical exam or by OCT; (3) Atrophy or fibrosis surrounding the fovea; (4) Any level of cataract (lens opacity); (5) Vitreous hemorrhage or other vitreous opacity; (6) Eye disease not related to diabetic retinopathy that may impair central vision such as Age-Related Macular Degeneration, chorioretinitis scar and epiretinal membrane; (7) Intraocular surgery within 3 months before randomization; (8) Aphakia; (9) Any thromboembolic event within 6 months before randomization, unstable angina, or evidence of active ischemia on electrocardiogram (ECG) at time of screening; (10) BCVA better than 20/40 (>70 letters ETDRS); (11) Hemoglobin A1c (HbA_{1c}) > 11% (97 mmol/l); (12) Uncontrolled blood-pressure (systolic and diastolic blood-pressure >170 and >100 mmHg, respectively); (13) Chronic kidney disease defined by Modification of Diet in Renal Disease (MDRD) study group criteria [27]; (14) Debilitating systemic disorder that precludes the patient's admission to the study, as per the clinical judgment of the investigator.

2.2. *Study protocol*

Medical and ophthalmic history was recorded and ophthalmologic examination was performed, including BCVA using ETDRS visual acuity (VA) charts, contrast sensitivity (CS) using Pelli-Robson Charts [28], intraocular pressure using Goldmann applanation tonometry, anterior segment biomicroscopic examination and dilated fundus examination with 78 diopters lens.

All subjects had Fundus pictures, Fundus Fluorescence Angiography (FFA), and OCT imaging. Retinal thickness was measured using a 6 mm circular grid centered on the point of fixation. The mean thickness of the 1-mm circle centered on the fovea (CMT) was recorded and used for statistical analysis. Diabetic retinopathy was graded as one of the following levels: 35 = mild nonproliferative diabetic retinopathy (NPDR), 43 = moderate NPDR, 47 = moderately severe NPDR, 53 = severe NPDR, and 65 = moderate (non-high risk) proliferative diabetic retinopathy.

Laboratorial Methods: HbA1c (normal range 4–6%) was determined in whole blood using ion-exchange high-performance liquid chromatography (HPLC). Other biochemical analyses were carried out using commercial kits, as part of the routine assessment.

Eligible eyes were allocated to 1 of 2 study groups: Group 1, eyes receiving IVB injection at baseline or within a week of randomization and week 6 and Group 2, eyes receiving sham injection (simulated injections) at baseline or within a week of randomization and at week 6. Both groups underwent metabolic control optimization as measured by serum HbA1c level. Patients whose both eyes had been randomized were allocated to different groups. Indication for rescue therapy with modified ETDRS macular laser therapy (MLT) consisted as loss of more than 15 ETDRS letters in BCVA at 2 consecutive visits [2]. All patients had their blood pressure (BP), HbA1c, and other laboratory data such as urea, creatinine, cholesterol and triglycerides recorded at screening and at week 12.

2.3. Randomization and masking

Patients were randomized into 2 groups by means of an in-house computerized randomization program by an assigned biostatistician. Patients were stratified by HbA1c and retinopathy fundus grade (ETDRS) following which random allocation sequence was performed.

Ophthalmologists administering injections were not masked to the treatment groups. Patients, technicians/nursing staff performing testing and medical physicians optimizing glycemic control were masked to the treatments.

2.4. Follow-up visits

All patients underwent follow-up with a diabetes specialist, following which oral diabetic drugs were adjusted or insulin therapy initiated to achieve a mean target of HbA1C 7.5% (7.0–7.9%) [29]. Medications for treatment of hypertension and dyslipidemia were titrated as secondary targets as proposed by the American Diabetes Association.

Subjects were subsequently evaluated at weeks 2, 6 and 12. After baseline Group1 patients received 1 further IVB injection while Group 2 patients received 1 further sham injection at the 6th week visit.

2.5. Surgical/Injection technique

Intravitreal injection of Bevacizumab (Avastin, Genentech Inc., South San Francisco, CA, EUA) was performed in a designated intravitreal treatment room, under sterile conditions. Topical anesthesia with tetracaine and topical antisepsis with povidone-iodine 5% was applied into the conjunctival sac and onto the lid margins, followed by placement of a drape and insertion of a lid speculum. The site of injection was marked in the infratemporal quadrant, 3.5–4 mm from the limbus. Intravitreal injection of 0.05 ml (1.25 mg) of Bevacizumab with 30.5 Gauge needle was performed followed by compression of the injection site with a sterile swab, after needle removal, to prevent reflux. After each injection, topical antibiotic eye drops of ofloxacin 4 times per day was instilled for 5 days. Patency of fundus retinal circulation was determined by indirect ophthalmoscopy. Possible complications were recorded and treated. In group 2, a sham injection was simulated with an injection syringe and an atraumatic cannula using the same procedures described above.

2.6. Outcome measures

The primary outcome measure of the trial was a comparison of the mean change in ETDRS BCVA, CS and CMT at 12 weeks; mean change in ETDRS BCVA, CS and CMT at 2 weeks; the proportion of patients who gained $\geq$ 11 and $\geq$ 6 ETDRS letters (improvement); the proportion of patients who lost $\leq$ 1 ETDRS letters (worsening) at 12 weeks.

The secondary outcome measures included mean change of HbA1c at 12 weeks; the correlation between mean change in CMT vs. HbA1c levels in group 1 at 12 weeks; the correlation between BCVA vs. CS at baseline.

Safety outcome measures included ocular side effects and systemic side effects. Serious Ocular Adverse Events were defined as loss of more than 15 ETDRS letters, vitreous hemorrhage, endophthalmitis and retinal detachment. Serious Systemic Adverse Events included thromboembolic events and myocardial ischemia events.

2.7. Sample size

Sample size was based on a pilot study that reported a mean gain of CMT 115 μm for IVB group and 12 μm for Sham group at two weeks [30] Therefore, to have 80% power to detect a difference of 103 μm in the mean CMT (the difference between the mean of the 2 groups – 115 vs. 12) of the two groups as significant (at the 2-sided 5% level), with an assumed common standard deviation of 112, the sample size required in each group was 20 eyes. Twenty-two eyes per treatment group were required if one assumed a 10% dropout rate.

2.8. Statistical analysis

Descriptive statistics have been shown as mean, standard deviation, median, interquartile range [IQR] and percentages. Median was used to stratify the percentage of gain. All randomized subjects were included in the efficacy analyses. Analysis of variance (ANOVA) with repeated measures was used to assess whether any observed differences between the 2 groups at 12 weeks were statistically significant. The sphericity assumption was evaluated by Mauchly's test and when violated, the degrees of freedom were corrected using Huynh-Feldt's Epsilon. The main effects and / or significant interactions were analyzed by multiple comparisons with Bonferroni correction. The effect size was calculated by eta

square (η2). Independent t tests were used to compare Δ BCVA, Δ CS and Δ CMT between both groups. To compare correlations Pearson's correlation test (quantitative variables) and Chi-Square Test (qualitative variables) were used. Statistical analyses were performed with SPSS 21.0 (IBM Corp., Armonk, NY) with the level of statistical significance set at $P < 0.05$.

3. Results

3.1. Baseline characteristics of the study groups

Forty-one eyes of 34 patients were enrolled. The baseline characteristics of each treatment group are summarized in Table 1. The mean age of the patients was 61.8 ± 9.0 years (range 45–77 years), with 21 females (51%) subjects. Twenty eyes were randomized to the group 1, and twenty-one eyes were randomized to group 2. There were no differences observed at baseline between treatments arms, including demographic characteristics, age, duration of DM, BP and HbA1c ($P > 0.05$).

The associations of metformin and sulfonylurea (n = 11) and metformin and NPH insulin (n = 10) were more often medications used for diabetes treatment during study protocol, followed by metformin, sulfonylurea and insulin NPH (n = 6). Four patients were under sole insulin therapy (NPH insulin or NPH associated with regular insulin), while the rest of them was taking either metformin or gliptine or sulfonylurea. Just one patient was taking NPH insulin and gliptine. Oral diabetic drugs or insulin were adjusted at week 2, 6 and 12 to achieve a mean target of HbA1c 7.5% (7.0–7.9%).

There were no clinically significant differences detected in the ETDRS retinopathy severity level at baseline between treatment arms ($P = 0.59$) (Table 1). There were no eyes with high-risk proliferative diabetic retinopathy due to inclusion and exclusion criteria. Two patients in each group at baseline had persistent inactive new vessels elsewhere despite previous panretinal photocoagulation. At 12 weeks, these vessels had resolved in one patient in the IVB group (level 65 to level 47), whereas the sham group patient remained in the same severity level (level 65).

3.2. Primary outcome measures

The primary efficacy outcomes are summarized in Table 2. Contrast sensitivity had a meaningful gain from baseline to week 2 in group 1 compared to group 2 (log0.15 ± 0.25 vs. log0.03 ± 0.15, respectively; $P = 0.04$). Significant main effect for the measure factor ($F3,117 = 7.407$; $P < 0.001$; $\eta 2 = 0.16$) was observed for CS with improvement in both groups: baseline: log1.12 ± 0.33 vs. week 2: log1.21 ± 0.26 vs. week 6: log1.24 ± 0.28 vs. week 12: log1.25 ± 0.26. The difference between both arms was not significant with respect to CS at baseline and 12 weeks (Table 2).

There was no significant difference between the treatment groups regarding BCVA at baseline and 12 weeks. However, group 1 obtained meaningful improvement of letters from baseline to 2 weeks and 12 weeks compared to group 2 (Table 2). There was no significant difference between treatment groups regarding the proportion of eyes which gained or lost vision at 12 weeks (Table 2).

Both groups showed improvement of CMT (baseline: 541.8 ± 173.8 vs. week 2: 475.2 ± 141.7 vs. week 6: 461.8 ± 146.5 vs.

Table 1 – Baseline characteristics.

	Group 1	Group 2*
No. of eyes	20	21
Male n (%)	9 (45%)	11 (52%)
Mean age ± SD (years)	62.9 ± 9.1	60.8 ± 9
Ethnicity n (%)		
White	16 (80%)	18 (85%)
Afro-Brazilian (black)	3 (15%)	2 (10%)
Asian	1 (5%)	1 (5%)
Mean duration of DM ± SD (years)	16,9 ± 7,8	16,6 ± 7,1
Mean HbA1c ± SD (%)	8.10 ± 1.27 (range 5.9–11)	8.39 ± 1.30 (range 5.8–10.6)
Mean systolic BP ± SD (mmHg)	144 ± 14	142 ± 16
Mean diastolic BP ± SD (mmHg)	81 ± 8	79 ± 10
Mean GFR-MDRD (ml/min/1.73 m^2)	80.9	82.1
Mean serum urea ± SD (mg/dl)	45 ± 17	49 ± 19
Mean serum cholesterol ± SD (mg/dl)	183 ± 48	189 ± 49
Retinopathy Severity Level n (%)		
Mild NPDR	9.5	10
Moderate NPDR	14.3	20
Moderately Severe NPDR	47.6	35
Severe NPDR	19	25
Moderate (non-high risk) PDR	9.5	10

BP: Blood Pressure.
GFR-MDRD: Glomerular Filtration Rate – Modification of Diet in Renal Disease.
NPDR: Non-Proliferative Diabetic Retinopathy.
* There were no significant difference between both groups - $P \geq 0.05$.

Table 2 – Outcome measures in the two treatment groups.

	Group 1	Group 2	P Value
Baseline mean HbA1c (%)	8.18 ± 1.27	8.39 ± 1.30	0.60
3-month mean HbA1c (%)	7.72 ± 1.20	7.83 ± 1.38	0.79
Δ HbA1c at 3 months (%)	0.46 ± 0.10	0.46 ± 0.11	0.84
Baseline mean ETDRS BCVA (letters)	24.6 ± 11.2	22.8 ± 10.7	0.59
3-month mean ETDRS BCVA (letters)	33.5 ± 13.6	27.0 ± 12.8	0.12
Δ ETDRS BCVA at 3 months (letters)	8.9 ± 7.6	4.2 ± 5.6	0.03*
Median and [IQR] of change in ETDRS BCVA (letters)	6.5 [4–14.7]	5.0 [0–8.5]	0.09
% of patients gaining ≥ 11 ETDRS letters	40.0 (8/20)	14.3 (3/21)	0.08
% of patients gaining ≥ 6 ETDRS letters	55.0 (11/20)	47.6 (10/21)	0.76
% of patients losing ≤ 1or 0 ETDRS letters	5.0 (1/20)	23.8 (5/21)	0.18
Baseline mean CMT (μm)	533 ± 128 range 374–930	550 ± 207 range 310–1031	0.75
3-month mean CMT (μm)	441 ± 126	481 ± 184	0.42
Δ CMT at 3 months (μm)	91 ± 184 range − 658–165	69 ± 152 range − 454–154	0.72
Baseline mean CS (log units)	1.14 ± 0.36	1.11 ± 0.29	0.71
3-month mean CS (log units)	1.32 ± 0.24	1.18 ± 0.29	0.10
Δ CS (log units) at 3 months	0.18 ± 0.24	0.07 ± 0.20	0.12
Δ ETDRS BCVA at 2 weeks	7.6 ± 6.2	1.6 ± 4.0	0.01*
Δ CMT at 2 weeks (μm)	116 ± 155 range − 613–61	17 ± 71 range − 218–115	0.01*
Δ CS (log units) at 2 weeks	0.15 ± 0.25	0.03 ± 0.15	0.04*

ETDRS: Early Treatment Diabetic Retinopathy Study.
BCVA: Best Corrected Visual Acuity.
CMT: Central Macular Thickness.
CS: Contrast Sensitivity.
* P value < 0.05.

week 12: 461.8 ± 158.8 μm; P = 0.001). However, in group 1, the CMT obtained a significant decrease from baseline to week 2 compared to group 2 (P = 0.01) (Table 2). Patients showed no significant difference between the two treatment groups regarding CMT at baseline and 12 weeks (Table 2).

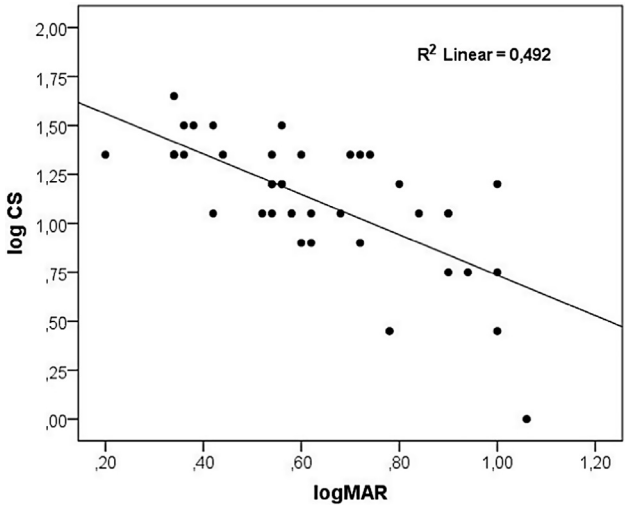

Fig. 1 – Relationship between in patients with diabetic macular edema between Contrast Sensitivity (LogCS) and Visual Acuity (LogMAR - ETDRS) (r = −0.70; P < 0.001; n = 41).

3.3. *Secondary outcome measures*

Patients had a mean reduction of HbA1c levels of 0.46 ± 0.91% and 0.56 ± 1.07% in groups 1 and 2, respectively (Table 2). There was no statistically significant difference between the 2 treatment groups regarding HbA1c at baseline and 12 weeks (P > 0.05) (Table 2). A significant main effect for the measure factor (F1,39 = 10.532; P = 0.002; η2 = 0.21) was observed, demonstrating that both groups had a decrease in HbA1c levels at 12 weeks (8.28 ± 1.29 vs. 7.78 ± 1.29; P = 0.002) (Table 2).

The correlation between CS vs. BCVA at baseline was negative and statistically significant (r = −0.70; P < 0.001; n = 41) (Fig. 1). Intraclass correlation coefficient between CS vs. BCVA was −0.68 (CI 95%: −1.05 to 0.33; P = 1.00), showing no concordance between both methods. No correlation was found between HbA1c levels vs. morphologic response of DME measured by CMT (r = −0.20; P = 0.39; n = 20) in the group 1.

3.4. *Adverse events*

There was 1 serious adverse event; a patient in sham group suffered a mild cerebral vascular accident 2 weeks after his second sham injection. The patient was at high risk for cerebral vascular accident because of preexisting cardiovascular disease, and the event was judged to be unrelated to this study. There were no serious ocular events. Ocular and Systemic Adverse events are shown in Table 3.

Table 3 – Adverse Events (AEs) and serious AEs.

AEs and Serious AEs	Group 1	Group 2
Ocular AEs, No.		
Red eye after injection, including subconjunctival hemorrhage	12	8
Floaters after injection	2	0
Corneal epithelial defect	1	1
Transient increased IOP $\geq$ 30 mmHg	2	0
Subtotal	**22**	**3**
Nonocular AEs, No.		
Gastroenteritis	2	1
Vomiting after FFA	2	1
Fall	1	2
Headaches, dizziness, tiredness	1	2
Urinary tract infection	1	1
Subtotal	**7**	**7**
Nonocular serious AEs, No.		
Stroke	0	1
Active myocardial ischemia	0	0
Uncontrolled hypertension	0	0
Hospitalizations for transient complications of diabetes	3	2
Subtotal	**3**	**2**
Total	**32**	**12**

IOP: Intraocular pressure.
FFA: Fundus Fluorescein Angiography.

4. Discussion

The results of this randomized, masked, sham-controlled clinical trial has demonstrated the great efficacy of optimizing glycemic control (OGC) along with bevacizumab injections in patients with DME up till 12 weeks. The endpoint of this study was successfully met; there was improvement in visual function including contrast sensitivity in both groups at week 12, but with significant improvement in the group treated with bevacizumab and OGC.

Bevacizumab compared with other anti-VEGF agents to treat DME has proven to be very effective and is more cost-effective than other anti-VEGF agents [31]. Evaluating the morphological and functional data at 2 weeks in this study allows us to compare the peak of intravitreal bevacizumab's action compared to sham [15]. We demonstrated a corresponding higher improvement in CS (Table 2) and BCVA (Table 2). It was accompanied with a corresponding significant difference between the mean CMT levels at week 2 showing the rapid morphological improvement of DME (Table 2). In addition, the outcomes were significantly better at 12 weeks, indicating that the short term rapid improvement and sustained respite from edema in group 1 may lead to better visual outcomes than slow resolution of DME due to improved glycemic control alone in group 2 (Table 2).

There were no systemic safety concerns associated with repeated IVB identified in this study, and no serious ocular adverse events (Table 3). We excluded patients with poorly controlled diabetes (HbA1c > 11% [97 mmol/mol]) and hypertension, or evidence of either recent stroke or cardiac ischemia. The two treatment groups were well balanced in terms of demographics and baseline characteristics including retinopathy grading (Table 1) allowing for a well-matched control and robust analysis.

Several studies have shown the large effectiveness of anti-VEGF therapy on DME [10–15], however, they have not explored other types of visual function as well as contrast sensitivity for example. The contrast sensitivity had significant correlation between visual acuity at baseline (Fig. 1), showing good accuracy to visual impairment diagnosis on DME. Rubin et al. [32] showed differences between reduced visual acuity and contrast sensitivity. They were independently associated with overall vision disability score. Visual acuity was associated with difficulty in tasks requiring good resolution and adaptation to changing light conditions, whereas contrast sensitivity was associated with difficulty in tasks requiring 'distance judgments, night driving, and mobility. Sokol et al. [16] found changes in contrast sensitivity on DME even before visual acuity changes in eyes without background retinopathy. Our results provide evidence that contrast sensitivity should be used in visual function tests on DME characterizing a better evaluation and follow-up these patients. Low contrast sensitivity has been associated with disability [33] and poor life quality [19].

Control of the metabolic abnormalities of diabetes has a major effect on the development of diabetic microvascular complications. [34] The epidemiological analysis of UKPDS data suggests that a 0.5% decrement in HbA1c might equate to a 11.5% reduction in risk for diabetes-related complications and a 1% reduction in mean HbA1c may reduce the risk for microvascular disease by 37% [35,36]. The management of the disease makes adherence to treatment difficult, and up to 73% of type 2 diabetes patients have poor glycemic control with serum HbA1c levels above 7% (53 mmol/mol) in Brazil [37,38]. Rajendram et al. [39] showed a greater improvement of VA in patients with persistent macular edema that received bevacizumab compared to macular laser treatment (MLT). In their study, patients treated with bevacizumab had a mean gain of 8.6 letters compared to loss of 0.5 letters for MLT, with serum HbA1c levels worsening by about 0.4% from baseline to 12 months in both groups. In our study, a combined approach was most beneficial, both groups improved on average 0.5% in serum HbA1c levels, and even with sham injection, the group 2 achieves significant outcomes at 12 weeks (Fig. 2). This suggests that improving HbA1c levels by optimizing glycemic control under endocrinology professional assistance in combination with bevacizumab injections may lead to better outcomes for DME treatment.

Type 2 diabetes management was based on the lower risk of serious adverse effects associated with intensive glycemic control (targeting glycated hemoglobin level of <6.0% [42 mmol/mol]). It has been shown that glucose variability is associated with increased mortality in the intensive care unit [40]. Similarly, the lowest glycemic fluctuation in a short-term period has been shown to be less damaging to retinal microvasculature [41]. We can demonstrate that 0.5% HbA1c decrease should create an impact at 12-weeks end point outcomes on DME patients.

Potential limitations, as with all clinical trials, existed in this study but there are factors that are worth mentioning

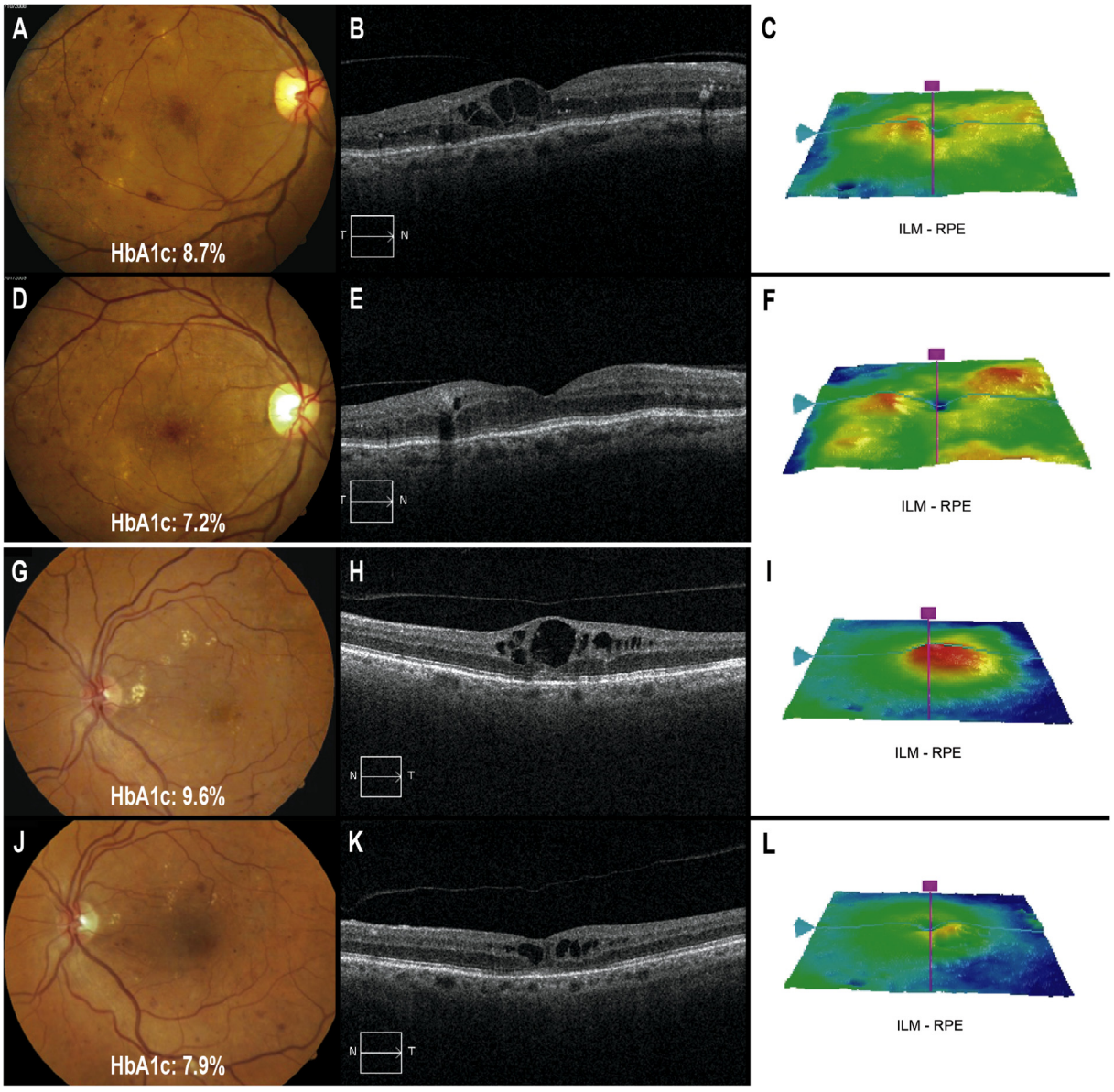

Fig. 2 – The patient on bevacizumab group showed substantial macular edema before injections at baseline (central macular thickness, CMT = 385 μm). As observed from the images the macular edema and glycated hemoglobin (HbA1c) significantly decreased from baseline (A–C) to week 12 (D–F), reducing CMT to 286 μm. The decrease in CMT was also paralleled by an increase in best-corrected visual acuity (BCVA) and contrast sensitivity (CS), from 59 to 77 letters and from log1.20 to log0.90, respectively, from baseline to week 12. The sham case also showed substantial macular edema at baseline (CMT = 450 μm; BCVA = 56 letters and CS = log1.35; G–I). The edema and HbA1c level also improved over the 12-week study period, decreasing the CMT to 314 μm while BCVA increased from 56 to 65 letters and CS improved from log1.35 to log1.05 (J–L).

even though the number of patients included in our study is not so large. Furthermore, patients were not evaluated for the improvement of contrast sensitivity in performing a task of everyday life [25]. This could be important in differentiating the benefits of contrast sensitivity enhancement. Studies indicate the importance of physical activity levels on lowering HbA1c in patients with type 2 diabetes. Physical activity could play an important role in assisting to manage type 2 diabetes patients, thereby helping to decrease the HbA1c levels and stabilize the DME in diabetic retinopathy [42]. Perhaps, adding physical exercise to the treatment regimen would have led to improved outcomes.

In conclusion, the results of this study further highlight the importance of combining two therapies, systemic treatment and ocular treatment, for the contrast sensitivity fast improvement of patients with DME. It is important to remember that Diabetes Mellitus is a chronic systemic disorder, so a better glycemic control in combination with anti-VEGF therapy may set a greater standard for treatment of DME.

Disclosure

The authors have no financial/conflicting interests to disclose.

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Authors' contributions

A.A.L.M. wrote the manuscript and researched data; L.M.V., R. C.P. and D.A.F. researched data; M.S.Q. wrote the manuscript and researched data; M.T.B., S.L.G.P. and W.Y.T. reviewed/edited the manuscript.; M.F.A, R.S. and F.M.D. contributed to the discussion and reviewed/edited the manuscript.

All authors have no relevant conflict of interest to disclose.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.02.002.

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