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Case Report

Resolution of Diabetic Macular Edema after Metabolic Control of Glycated Hemoglobin. A Case Report

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Abstract

Objective: To report a case of diabetic macular edema that resolved following metabolic control of glycated hemoglobin (HbA1c).

Methods: Prospective case report.

Case Report: A 62-year old man with uncontrolled type 2 diabetes mellitus presented with progressively worsening bilateral visual acuity occurring for 3 months, predominantly in the left eye. Ophthalmologic examination revealed a thickening of the macular area and presence of hard exudates 500 µm within the fovea. Fluorescein angiography and Spectralis Optical Coherence Tomography (OCT) were performed on the retina to determine the type and magnitude of macular edema. Strict metabolic control and a follow-up appointment were suggested. Afterwards, the patient presented with improved visual acuity in the left eye, with HbA1c < 7.5% and with a decrease in macular thickness evidenced by OCT.

Conclusion: Strict metabolic control measured by an acceptable range of HbA1c values in patients with diabetes can be a determining factor of the treatment of diabetic macular edema.

Keywords: *Diabetic Macular Edema; Glycated Hemoglobin; Diabetic Retinopathy; Diabetes Mellitus; Macular Edema Treatment*

Abbreviations

VEGF: Vascular Endothelial Growth Factor; TNF: Tumor Necrosis Factor; ILs: Interleukins; ICAM-1: Intercellular Adhesion Molecule 1; OCT: Optical Coherence Tomography; FA: Fluorescence Angiography

Introduction

Diabetic retinopathy is the principal cause of blindness in people with advanced age in developed countries [1,2]. An important complication of diabetic retinopathy is macular edema, which is the primary cause of visual acuity loss in these patients and can present during any stage of retinopathy [3,4]. The prevalence of diabetic macular edema is 11.7% among patients with diabetic retinopathy [4].

Physiopathology

Hyperglycemia is an initial metabolic abnormality that can cause changes in retinal microvasculature and degenerative neuroretinopathy [1]. Hyperglycemia activates four major metabolic pathways: 1) polyol pathway, 2) advanced glycosylation end product pathway, 3) protein kinase C, and 4) hexosamine pathway [3]. These pathways induce intracellular disorders, including enzymatic degradation and mitochondrial dysfunction. The advanced glycosylation end products induce changes in the extracellular matrix, resulting in increased oxidative stress, the formation of reactive oxygen species, and the activation of the inflammatory cascade [1].

Oxidative stress and inflammation result in an increase of the production of growth factors and cytosines, such as Vascular Endothelial Growth Factor (VEGF), angiopoietins, Tumor Necrosis Factor (TNF), interleukins (ILs), and extracellular matrix metalloproteinases [3].

These events consequently lead to the loss of pericytes and endothelial cells and the destruction of the narrow junction, which provokes the rupture of the internal hematorretinal barrier, causing the extravasation of fluid, ions, and macromolecules to the extracellular area that clinically presents as macular edema [1,3,4].

Another consequent event of the initial vascular abnormalities is hypoxia induced by capillary obstruction caused by the presence of inflammatory markers such as Intercellular Adhesion Molecule 1 (ICAM-1) expressed in the endothelial surface. This causes an adhesion among the surrounding leukocytes and the endothelial cells aggravating the edema [1,3,4].

Neuroretinopathy also contributes to the pathogenesis of macular edema prior to the development of vascular changes. This neuroretinal degeneration happens as a result of neuronal apoptosis and the proliferation of glial cells caused by damage produced by free radicals, glycosylation end products, and inflammatory mediators. Glutamate and N-methyl-D-aspartate receptors accumulate and contribute to the breakdown of the internal blood-retinal barrier, by increased production of VEGF [1,3,4].

There is an increase in the thickness of the macular area and loss of the normal retinal architecture, which reduces visual function. With chronic macular edema, destruction and degradation of the photoreceptor layer occurs, further worsening the visual prognosis [1].

Diagnosis and Classification

Optical Coherence Tomography (OCT) and Fluorescence Angiography (FA) are the "gold standard" diagnostic tools for diabetic macular edema [4-6]. The use of these imaging tools allows for the classification of macular edema as focal or diffuse, and FA alone can additionally determine the presence of macular ischemia [4,5].

OCT provides a quantitative and qualitative diagnosis of diabetic macular edema, classifying it as: 1) spongy, 2) cystic, 3) serous detachment, or 4) vitreomacular traction [4,6]. It is also useful for follow-up and evaluating the type of treatment appropriate to each case.

Treatment

Diabetic macular edema treatment can be complicated, despite the diverse options available, which include laser photocoagulation, anti-VEGF therapy, corticosteroids, and pars plana vitrectomy. The selection of a treatment modality is determined by the classification of macular edema and its severity.

Macular laser photocoagulation

Laser photocoagulation has been the standard treatment for diabetic macular edema since the Early Treatment Diabetic Retinopathy Study. This therapy decreases vision loss. However, it has been demonstrated that it has limited capacity to restore vision [7].

Anti-VEGF therapy

Diverse studies have shown the efficacy of the use of antiangiogenics in the treatment of diabetic macular edema, resulting in improved visual acuity when compared to conventional laser photocoagulation therapy or compared to a placebo (RISE, RIDE, BOLT, VIVID, VISTA) [1,7].

A Cochrane meta-analysis analyzed 24 studies that compared the efficacy of ranibizumab, bevacizumab, and aflibercept without a placebo, laser, or other treatment comparator. The results indicated that there is high evidence that these three drugs prevented vision loss and at the same time improved visual acuity in patients with diabetic macular edema [8]. There exists a greater relative beneficial effect in the use of aflibercept vs ranibizumab and bevacizumab in patients with visual acuity less than 20/50 [1,8].

The T protocol of DRCR.net [9] compared the efficacy of ranibizumab, bevacizumab, and aflibercept for the treatment of diabetic macular edema, concluding that aflibercept should be considered the first line of treatment for diabetic macular edema, given that it results in a greater long-term improvement in visual acuity [1,7,8]. However, given its low cost-effectiveness, aflibercept is not a realistic option in low-income countries. It has also been reported that up to 50% of patients do not respond to antiangiogenic therapy, probably due to genetic variations in VEGF receptors [1].

Corticosteroids

In addition to partially inhibiting VEGF activity, corticosteroids inhibit leukostasis and stabilize the hematorretinal barrier [1]. Treatment options include dexamethasone and fluocinolone implants, among others. The serious side effects to using these drugs are the risks of significant ocular hypertension, increased incidence of cataract formation, and recurrence upon ending treatment [1,7].

In refractory macular edema, good results have been demonstrated in several studies (REEF, Ciulla., *et al,* Lim., *et al.*) with respect to the decrease of central macular thickness and the increase of visual acuity when switching therapies, whether it be to use another antiangiogenic, corticosteroid, or macular laser [7].

Metabolic control in diabetic macular edema

Four studies have demonstrated an association between diabetic retinopathy and glycemic control: 1) Diabetes Control and Complications Trial (DCCT), 2) UK Prospective Diabetes Study (UKPDS), 3) Action to Control Cardiovascular Risk in Diabetes (ACCORD), and 4) Action to Control Cardiovascular Risk in Diabetes Follow-On (ACCORDION). These studies showed that better control of glycated hemoglobin (HbA1c) levels can contribute to a reduced risk of diabetic retinopathy [4]. A relationship between the prevalence of diabetic macular edema and HbA1c levels greater or equal to 7.1% has also been reported [4].

Clinical Case Description

A 62-year old male patient with type 2 diabetes mellitus of a duration of 5 years, as well as controlled arterial hypertension, underwent an ophthalmic examination for gradual visual loss lasting in both eyes, but predominantly in the left eye, which had occurred during 3 months.

Systemic condition: Uncontrolled metabolism, with a glucose of 392 mg/dl, urea and creatinine within normal parameters, HbA1c of 10% (normal range of reference for acceptable control: 6.5 - 7.5), total cholesterol of 293 mg/dL (reference range less than 200), HDL cholesterol of 46 mg/dL (reference value: < 35 - 55), LDL cholesterol of 146 mg/dL (reference value: 65 - 130), VLDL cholesterol of 100 mg/dL (reference value: 6 - 30), and triglycerides of 503 mg/dL. Systemic treatment with glibenclamide and enalapril.

Ophthalmic examination

Initial examination of visual acuity in the right eye of 20/100, in the left eye 20/60. Refraction: right eye: +0.50 - 2.00 x 90° left eye: +0.75 - 1.50 x 60°.

Additional examination without alterations: Biomicroscopy of the anterior segment with bilateral cortical cataract. Intraocular pressure of 12 mmHg in both eyes. Indirect ophthalmoscope: right eye with presence of microaneurysms in the posterior pole and in the vascular arcades, as well as clotting hemorrhages, soft exudates, and flame hemorrhages in temporary arcades. Within the macular area, the presence of hard exudates within 500 µm of the fovea.

Left eye with microaneurysms, flame hemorrhages, a few soft exudates, and with a higher concentration of hard exudates within 500 µm of the fovea. The diagnosis was moderate, non-proliferative diabetic retinopathy with clinically significant macular edema in both eyes (Figure 1).

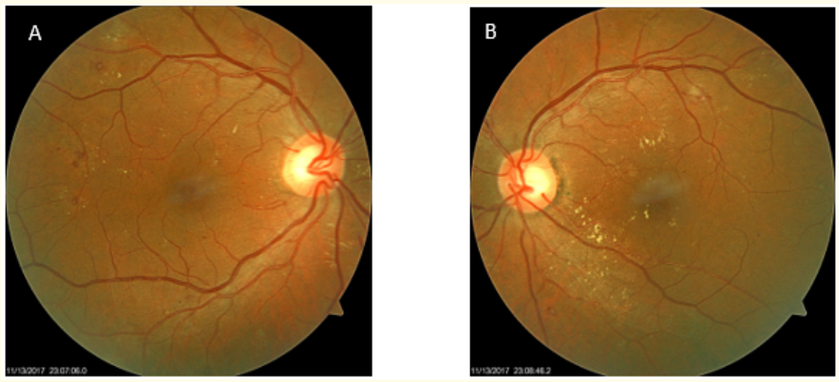

Figure 1: *Hard exudates are observed within the centered area measuring 500 µm, as well as multiple microaneurysms within the arcades. A: Right eye. B: Left eye.*

A fluorangiography study was done (Figure 2), which confirmed focalized macular edema in both eyes (various hyperfluorescent points within the disk diameter that appeared in early phases and increased in a focalized form until the assessment was completed), a foveal avascular zone of 500µm, and the lack of ischemia or neovessels.

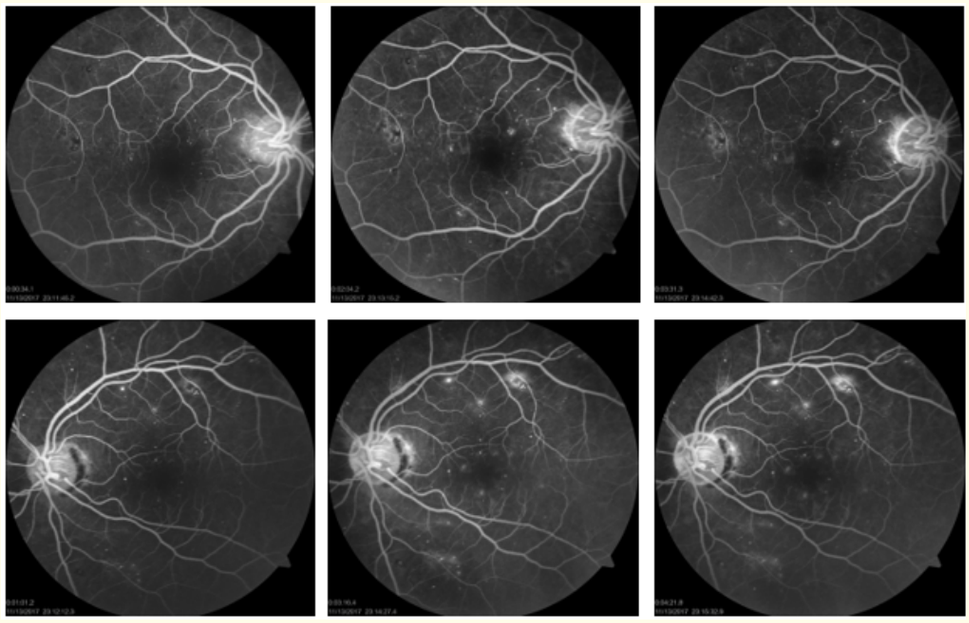

Figure 2: *Multiple hyperfluorescent points are observed that appear during early phases and increase in a focalized form until later phases of the study. A, B, C: Right eye fluorangiography. D, E, F: Left eye fluorangiography.*

OCT revealed an increase in central macular thickness of 300 µm in the right eye, with evidence of spongy macular edema.

Figure 3: right eye, macular volume of 9.55 mm^3, left eye with an increase in central macular thickness of 292 µm, as well as intraretinal cysts, macular volume of 9.94 mm^3.

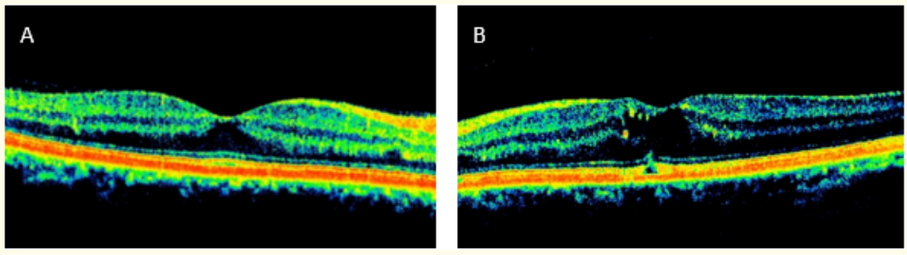

Figure 3: *A reduction in the reflectivity of the internal layers of the retina is observed, with some points of high reflectivity present in internal layers corresponding to hard exudates. Evidence of spongy macular edema. A: Right eye. B: Left eye. Images obtained with OCT Optovue.*

Metabolic control: It was decided to initiate strict metabolic control, reduction of glycemia and arterial hypertension, through diet and exercise. The patient agreed to comply with these indications and 3 months later lost 13 kg of weight. His systemic treatment with glibenclamide and enalapril was maintained without changes. His levels of central glucose dropped to 170 mg/dl and HbA1c to 7.5%.

Vision improvement: Visual acuity of 20/40 in both eyes, BCVA 20/30 with new refraction: right eye +1.75 = 2.00 x 75°, left eye +1.75 = 2.25 x 95°. Using OCT, a reduction in macular thickness was observed, as well as a reduction in macular volume and improvement in the reflectivity of the internal layers. Metabolic control alone, without the need for antiangiogenic therapy, resulted in these positive changes (Figure 4).

Discussion

This case demonstrates the impact of metabolic control on the treatment of diabetic macular edema. Previous studies found an association between low levels of HbA1c and a lower incidence of clinically significant macular edema [10].

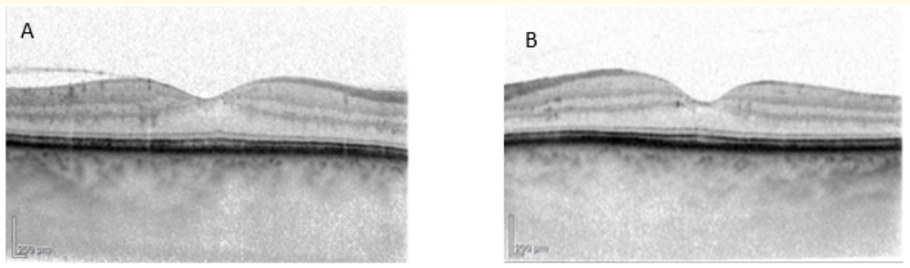

Figure 4: *A decrease of the macular thickness as well as restructured internal layers of the retina are observed. A: Right eye. B: Left eye. All images taken with OCT SD Heidelberg.*

Recent trials have had conflicting results: Macky and Mahgoub [10] evaluated the effect of metabolic control on the therapeutic response of clinically significant macular edema. They found that, beginning with follow-up, the patients with low levels of HbA1c demonstrated a better visual prognosis. Therefore, they recommended that metabolic control be done prior to initial treatment for clinically significant macular edema.

Peng and Tsai [11] investigated the relationship of metabolic control with the macular area thickness using OCT in patients with diabetes with and without macular edema. They found that high levels of HbA1c were associated with a greater thickness and larger macular volume in eyes without macular edema, but they did not find this association in patients who already had edema.

T-H Chou., *et al.* [2], found that, among patients older than 50 years with a shorter duration of diabetes, macular edema, and HbA1c levels greater than or equal to 8% had a statistically significant correlation with macular thickness measured by OCT.

Conclusions

We present an isolated case of clinically significant diabetic macular edema with surprising resolution solely by metabolic control and lifestyle changes, which demonstrate that metabolic control can be a determining factor in treatment of patients with diabetic macular edema, thereby reducing the risks incurred by conventional treatment (using laser, corticosteroids, and antiangiogenics), as well as reducing the cost of treatment. Randomized controlled trials are needed to better evaluate the effect of metabolic control on patients with diabetic macular edema and low levels of HbA1c.

Disclosure Statement

The authors have no financial or proprietary interest in the material presented herein. This paper has not been presented at any meeting or conference.

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