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Vitrectomy results for diffuse diabetic macular edema with and without inner limiting membrane removal

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PURPOSE. *To determine whether vitrectomy for diffuse diabetic macular edema with and without internal limiting membrane (ILM) peeling is equally effective in reducing edema.*
METHODS. *The authors retrospectively analyzed the surgical outcomes in 73 eyes of 52 patients with diffuse diabetic macular edema. Eighteen eyes (Group A) underwent three-port pars plana vitrectomy with posterior hyaloid membrane (PHM) removal, while 55 eyes (Group B) had pars plana vitrectomy with additional ILM peeling after PHM removal.*
RESULTS. *Intraoperatively, the posterior hyaloid was found to be attached to the macula in all eyes. In Group A, macular edema resolved completely in 8 eyes (44.4%) with improvement of visual acuity (VA). In Group B, VA improved in 38 eyes (69.1%) with complete resolution of edema. The results of this study indicated that vitrectomy effectively reduced macular edema but eyes with ILM peeling (Group B) presented better results than those without ILM peeling. Another important factor related to the outcome seems to be the level of glycosylated hemoglobin (HbA1c).*
CONCLUSIONS. *In eyes with diffuse diabetic macular edema vitrectomy seems to be effective, but additional ILM peeling presented better results. (Eur J Ophthalmol 2004; 14: 137-43)*

KEY WORDS. *Diabetic macular edema, Vitrectomy, Posterior hyaloid removal, Internal limiting membrane removal*

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INTRODUCTION

Macular edema secondary to diabetic retinopathy is a major cause for visual loss in diabetics. It has been predicted that 42% of individuals with type I diabetes will develop macular edema during their lifetime, so diabetic macular edema is an important public health problem and a major cause for suffering, disability, and lost productivity (1). The Early Treatment Diabetic Retinopathy Study has shown that laser photocoagulation is beneficial in the treatment of clinically significant diabetic macular edema by reducing the risk of moderate visual loss by 50%. However, only 3% of the patients in the study had improvement of three or more lines of vision (2). The edema may sometimes become very severe and cause diffuse thickening of the retina, with excessive confluent hard exudates reducing vision tremendously. Laser treatment has little ability to improve such severe edema (3).

The absence of a fully successful treatment has resulted in the search for alternative therapies. Vitrectomy has been described as a powerful tool by many

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investigators in the treatment of diabetic macular edema (3-7). Gandorfer et al reported that vitrectomy with additional inner limiting membrane (ILM) peeling leads to expedited resolution of diffuse diabetic macular edema and improvement of visual acuity (VA) (8).

The purpose of our study was to determine whether vitrectomy with and without ILM peeling is equally effective in reducing the macular edema in diabetic patients. In the course of this study we were able to obtain specimens of ILM for electron microscopy analysis.

MATERIALS AND METHODS

The present study was a retrospective series of 52 consecutive diabetic patients (73 eyes) with diffuse diabetic macular edema. All patients underwent pars plana vitrectomy in the University Eye Clinic of Ioannina from January 2000 to December 2002.

Twenty-five patients were men and 27 were women. Fifteen patients had non-insulin dependent diabetes mellitus while 37 had insulin-dependent diabetes. All patients had complete ophthalmologic examinations, including best-corrected Snellen VA, intraocular pressure measurement, biomicroscopic examination of the anterior and posterior segment, and stereoscopic biomicroscopy of the vitreous and the vitreomacular interface. Fluorescein angiography (FA) and fundus photography were routine procedures performed before every operation in all patients. FA delineated deep and diffuse retinal leakage in the macular region in all patients. Eyes with detached posterior hyaloid (diagnosed by three mirror contact lens examination) and ischemic macular edema (established by FA) were excluded from the study. All patients had regular control of preexisting hyperglycemia or hypertension by internists.

The subjects were divided into two groups: Group A (15 patients, 18 eyes) and Group B (37 patients, 55 eyes). Patients in Group A had a standard three-port pars plana vitrectomy. After core vitrectomy had been performed, the remaining cortical vitreous was aspirated with a flexible tipped cannula or a vitreous cutter to create posterior hyaloid detachment. After confirming the presence of a sheet-like posterior hyaloid membrane (PHM), the remaining vitreous was removed. For Group B, the same procedure was followed but after PHM removal, ILM was peeled using a diamond-dusted silicone cannula and a special intraocular forceps. Indocyanine green (ICG) (2.5 mg/ml) was used to facilitate the procedure.

Previous focal laser photocoagulation was performed in nine eyes (four in Group A and five in Group B) 4 to 6 months before the operation, without any improvement of the edema. Mild nucleus sclerosis of the crystalline lens was present in five eyes preoperatively (two in Group A and three in Group B). Two of them had cataract surgery with intraocular lens implantation (one in Group A and one in Group B). The main characteristics of the two groups compared preoperatively are presented in Table I. Patients in Group A (aged 65.06 ± 5.30 years) presented high blood pressure controlled with medications in 66.7%, while glycosylated hemoglobin (HbA1c) was 7.65 ± 0.90. VA preoperatively was equal to or less than 1/20 in 7 eyes (38.9%) and more than 1/20 in 11 eyes (61.1%). Patients in Group B (aged 63.75 ± 6.58 years) presented high blood pressure in 81.8%, while HbA1c was 8.18 ± 0.98. Preoperative VA was equal to or less than 1/20 in 27 out of 56 eyes (49.5%). Seven out of 18 eyes (38.9%) in Group A and 16 eyes (29.9%) in Group B presented cystoids formation or posterior hyaloid thickening while 11 eyes (61.1%) in Group A and 39 (70.9%) in Group B had diffuse diabetic macular edema.

The ILM specimens obtained during vitrectomy were fixed in a solution of 25% glutaraldehyde (in 0.08 M phosphate buffer pH 7.4) for 2 hours and then washed in 0.02 M phosphate buffer, postfixed in 0.5 M phosphate-buffered osmium tetroxide for 1 hour subsequently. The section was stained in 0.55 uranyl acetate, dehydrated, and embedded in epoxy resin. Ultrathin sections were stained with uranyl acetate and lead citrate. The specimens were viewed on a transmission electron microscope at 80 KV (JEOL, JEM, 100 CX II). Intraoperative recordings included evidence of thickening of the posterior hyaloid, presence of firm vitreous attachment, and presence of an epiretinal membrane. The following postoperative data were recorded 6 months after the operation: best-corrected VA; resolution, improvement, or worsening of macular edema (established by FA); and postoperative complications.

Statistical analysis

Comparisons between the two groups were conducted using the χ^2 test for categorical parameters and the t-test for continuous parameters. Logistic regression

analysis was applied using the changes in VA and macular edema after surgery as dependent parameters (improvement vs stability or worsening). The change in VA after surgery with respect to preoperative values was evaluated using the McNemar test.

RESULTS

Intraoperatively, the PHM was found attached to the macula in all eyes. After surgery, in Group A, macular edema resolved completely in 8 eyes (44.4%). VA improved in those 8 eyes (44%). Biomicroscopically, we noticed decrease of retinal thickness and significant decrease of macular edema in fluoroangiography. In 3 eyes (16.6%), VA dropped without resolution of macular edema. The change in VA with respect to the preoperative values was not statistically significant.

In Group B, VA improved in 38 eyes (69.1 %) with complete resolution of edema. In 15 eyes (26.7%) VA remained stable with partial or complete resolution of macular edema. In 2 eyes (3.6%) VA was worsening despite resolution of edema. Finally, macular edema (established by FA) resolved in 43 eyes (78.2%). The change in VA with respect to the preoperative values was marginally significant (p=0.08).

Both groups differ at a statistically significant level as concerning the glycosylated hemoglobin levels before surgery. Postoperative complications were noted in some cases. In one patient of Group A mild iris neovascularization was observed (3 months after vitrectomy), which regressed after panretinal photocoagulation. Two eyes in Group B had mild progression of nuclear sclerosis that did not affect vision. A peripheral retinal break was detected in two eyes (one in Group A and one in Group B) near the sclerotomy sites after vitrectomy, successfully treated with laser photocoagulation and exo-cryopexy. No epiretinal membrane formation was observed during the postoperative period.

Table II shows the results of logistic regression analysis. Glycosylated hemoglobin and type of surgery present an independent statistically significant association with VA improvement and edema resolution. Ultrastructural analysis (transmission electron microscopy) showed the presence of ILM in specimens removed from the area of diffuse macular edema during vitrectomy. Vitreous surface of ILM is smooth where-

TABLE I - MAIN CHARACTERISTICS OF THE TWO GROUPS COMPARED

Characteristics	Group A	Group B
Number of eyes	18	55
Sex, n (%)		
Male	8 (44.4)	30 (54.5)
Female	10 (55.6)	25 (45.5)
Type of diabetes, n (%)		
Type I	7 (38.9)	19 (34.5)
Type II	11 (61.1)	36 (65.5)
Hypertension, n (%)	12 (66.7)	45 (81.8)
Vision, HM–CF: 1/10, n (%)	7 (38.9)	27 (49.1)
Diffuse edema, n (%)	11 (61.1)	39 (70.9)
Age, yr, mean (SD)	65.06 (5.30)	63.75 (6.58)
HbA1c, mean (SD)*	7.65 (0.90)	8.18 (0.98)

*Difference significant at p<0.05, HM = Hand movements; CF = Count fingers

TABLE II - LOGISTIC REGRESSION ANALYSIS: DEPENDENT VARIABLES: VISUAL ACUITY IMPROVEMENT AND MACULAR EDEMA RESOLUTION (adjusted for age)

Independent variables	Odds ratio (95% CI)	Odds ratio (95% CI)
Sex (women vs men)	1.81 (0.56-5.91)	1.01 (0.31-3.32)
Type of diabetes (II vs I)	1.94 (0.56-6.56)	1.91 (0.55-6.67)
Hypertension (no/yes)	1.33 (0.31-5.61)	1.00 (0.24-4.28)
HbA1c (<7.5 vs >7.5)	24.04 (2.56-225.78)*	11.69 (1.30-105.22)†
Vision before surgery (>1/10 vs <1/10)	2.60 (0.79-8.55)	1.46 (0.44-4.80)
Edema before surgery (diffuse vs nondiffuse)	2.05 (0.53-7.99)	1.28 (0.33-5.00)
Surgery (Group B vs Group A)	3.67 (0.98-13.70)†	4.78 (1.31-17.40)†

*p<0.01, †p<0.05

as retinal surface is irregular (Fig. 1). In almost all of our specimens many irregular shaped vacuoles were observed containing electron-dense concentric masses of lamellae (lamellas lipid figures) (arrowhead, Fig. 1). The inner portion of ILM, which is formed by vitreous fibrils, is indicated between arrows in Figure 2. Fibrous astrocytes were observed very rarely, laying at the vitreal surface of the ILM (Fig. 3). Some specimens were lost during preparation.

Figure 4a presents a fundus photograph of a patient with severe macular edema and confluent exudates preoperatively while Figure 4b shows the apparent improvement of the same patient 8 months after vitrectomy. Figure 5a presents FA of a patient who demonstrated cystoid macular edema that resolved after vitrectomy, as shown in Figure 5b.

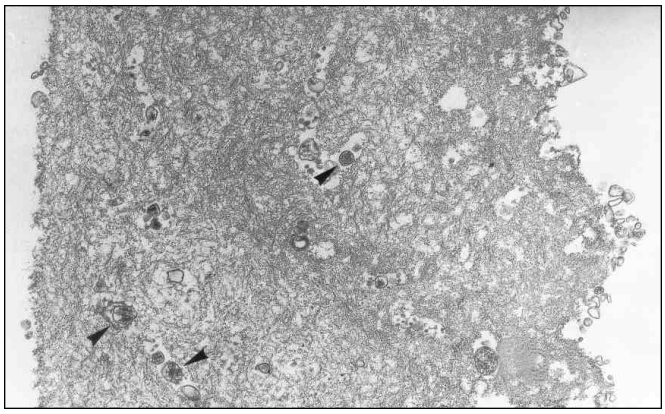

Fig. 1 - *Electron microscopic findings of a part of the inner limiting membrane (ILM) removed from the area of diffuse diabetic macular edema. Vitreous surface of the ILM is smooth whereas retinal surface is irregular. Many irregular shaped vacuoles containing electron dense concentric lamellar masses are obvious (arrowheads) (original magnification x 5,300).*

DISCUSSION

Macular edema secondary to diabetic retinopathy is a major cause for visual loss in diabetics. Once macular edema is present, laser photocoagulation may be beneficial, but some authors have observed and reported patients with diabetic macular edema who do not respond to laser treatment (5, 9). Vitrectomy for diffuse diabetic macular edema has recently been reported to be an effective approach for the management of some patients with diabetic macular edema (3-10). The pathogenesis of diabetic macular edema is multifactorial: the duration of diabetes, insulin use, high blood pressure, cardiac and renal failure, obesity, proteinuria, high glycosylated hemoglobin, and panretinal photocoagulation are implicated (11, 12). Current evidence suggests that the vitreous could be implicated in the development or exacerbation of diabetic macular edema through several mechanisms. Vitreous attachment over the macular region may exert traction producing a shallow macular detachment. By removing these tractional forces by vitrectomy, spontaneous macular reattachment may occur, according to Lewis (1). Kaiser et al confirm this hypothesis using optical tomography (9). Hikichi et al demonstrated that vitreomacular separation might promote the spontaneous resolution of diabetic macular edema (13). Nasralah et al showed that diabetic eyes with macular edema have a lower rate of PVD than those without edema (14). The major mechanism of the improvement

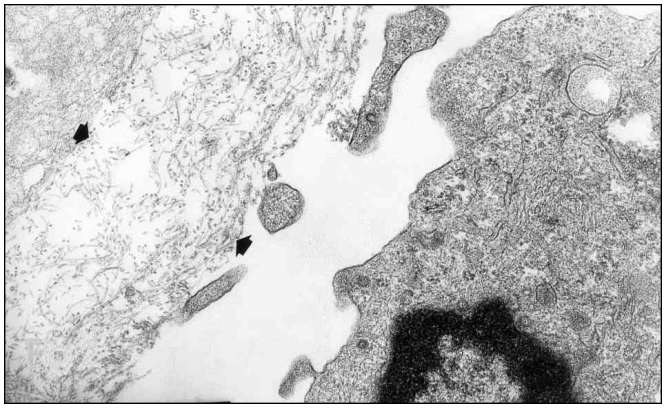

Fig. 2 - *The inner part of vitreous surface of inner limiting membrane is indicated between arrows (original magnification x 13,000).*

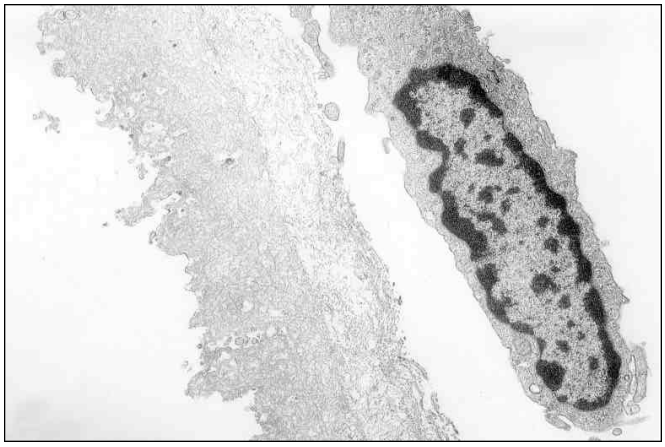

Fig. 3 - *A fibrous astrocyte covering the vitreous surface of the inner limiting membrane (original magnification x 4000).*

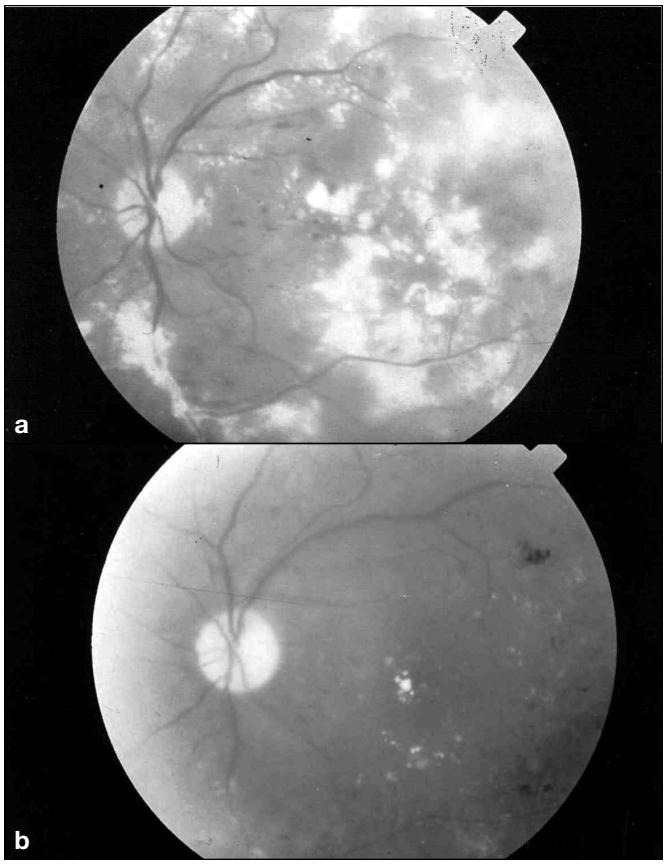

Fig. 4 - a) *Preoperative fundus photograph of a patient with severe macular edema and confluent exudates.* **b)** *Fundus photograph of the same patient 8 months after vitrectomy shows resolution of hard exudates.*

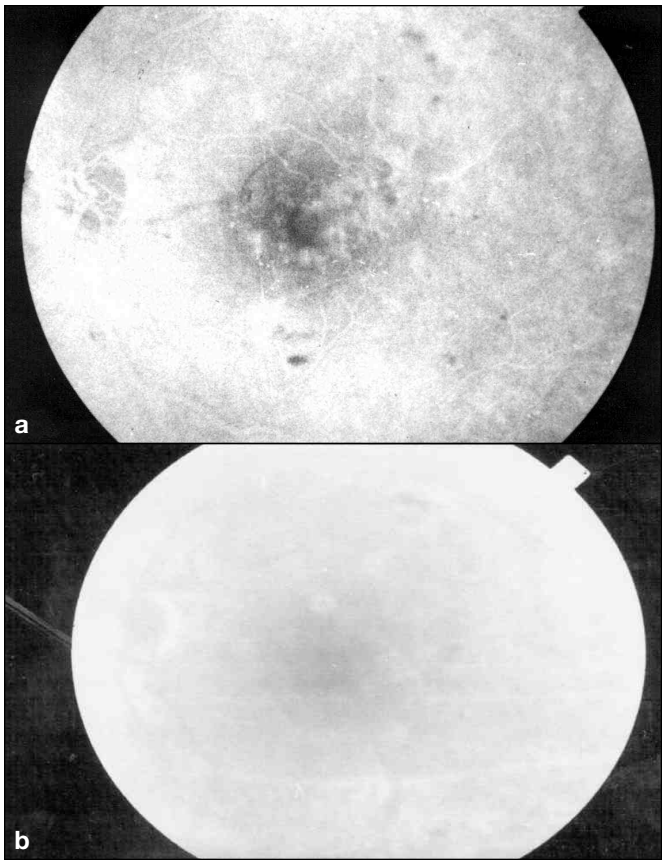

Fig. 5 - a) *Preoperative late phase fluorescein angiogram of another patient demonstrates cystoid macular edema.* **b)** *late phase fluorescein angiogram of the same patient 6 months after vitrectomy shows resolution of cystoid macular edema.*

as well is thought to be the relief of vitreomacular traction by vitrectomy.

In macular hole surgery a number of vitreoretinal surgeons have reported better success rates with peeling of the ILM. It has been hypothesized that removal of the ILM may mobilize the retina by reducing tangential traction. Although this theory is unproven, tangential traction may also play a role in the formation and progression of diffuse macular edema associated with advanced vitreoretinal interface disease. Therefore, some authors investigate further the impact of peeling of the ILM in eyes with otherwise refractory diffuse diabetic macular edema. The reported results were very good, but the study was not controlled (8).

The results of this study indicated that vitrectomy effectively reduced macular edema, but eyes with ILM peeling (Group B) presented better results compared with eyes that had vitrectomy without ILM peeling (Group A). The improvement of VA presented a significant trend only in Group B.

The ILM is known to play an important role as a scaffold for proliferating astrocytes (15, 16). According to Gandorfer et al removal of ILM may result in almost complete release of tractional forces and may also inhibit the reproliferation of fibrous astrocytes on the retinal surface (8). In addition to ILM, in our specimens fibrous astrocytes were observed very rarely lying on the vitreal side of the ILM. Gandorfer et al identified also (by electron microscopy) fibrous astrocytes in some specimens of ILM removed from the area of diffuse diabetic macular edema, lying on the vitreal side of the ILM. This uncommon finding could be due to the tissue preparation procedure for electron microscopy analysis or it could be related to the

use of ICG. Li et al observed a fragment of neural retina in addition to ILM in one ERM, and some glial elements on the apparent retinal side of the ILM in macular pucker and macular hole specimens (17). ICG has been shown to be helpful in staining ILM and thus facilitating its removal (18-20). Although it has been used in humans for many years and shown to be nontoxic, there is growing evidence that this might not entirely be the case. The presence of glial and/or neural components on the retinal side of the ILM would suggest retina damage. However, these have been observed as well in membranes removed without the aid of dye (17). Although the use of ICG in vitreoretinal surgery seems to be controversial, its long-term safety requires further in-depth study.

Research over the past few decades has provided ample evidence that hyperglycemia is one of the main forces driving the onset and progression of diabetic retinopathy. According to our study level of glycosylated hemoglobin seems to be an important factor related to the outcome.

Although no intraoperative complications occurred in our patients we noticed some postoperative complications. Peeling of ILM did not increase this incidence beyond the complication rates of other reports (8).

In conclusion, our study indicates that vitrectomy facilitates absorption of macular edema especially when ILM is peeled; VA improvement presented a significant trend only in Group B. Therefore, a randomized controlled prospective trial is necessary to define clearly the role of vitrectomy and ILM peeling in diffuse diabetic macular edema.

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