SURGICAL TREATMENT
OF DIABETIC MACULAR EDEMA

DOCTORAL THESIS

Prague 2006          Tarek Aboutable, M.D.
Surgical Treatment of Diabetic Macular Edema

DOCTORAL THESIS
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February 2006
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ACKNOWLEDGEMENTS

I thank my wonderful parents, my family and my kind wife, who have supported and helped me all my life and especially during my doctoral study.

Thanks to Assoc. Prof. Bohdana Kalvodová, M.D., CSc, thesis advisor and the head of the Department of Ophthalmology, General Faculty Hospital and 1st Faculty of Medicine, Charles University in Prague.

Thanks to Assoc. Prof. Jaroslava Dušková M.D., CSc, from the Department of Pathology, 1st Faculty of Medicine, Charles University, for the histopathological analysis, and to Eng. Jakub Hrkal from the Institute of Health Information and Statistics of the Czech Republic, for statistical analysis, and to all my teachers and professors for all what they have taught me during my study.

I would like also to thank all consultants of the vitreoretinal service at Moorfields Eye Hospital and King’s College Hospital for their freely sharing of surgical expertise during my stay in London.
1. INTRODUCTION

1.1. BACKGROUND

Diabetes mellitus (DM) is a group of chronic metabolic disorders characterized by the body’s inability to effectively metabolize glucose due to relative endogenous insulin deficiency, or resistance or both. DM is usually irreversible and, although patients can have a reasonably normal life-style, its late complications result in reduced life expectancy and considerable uptake of health resources. The main types of DM are:

1. Type 1 DM, which develops most frequently between 10 and 20 years of age, patients need to use insulin, although elderly patients can also be insulin dependent.

2. Type 2 DM, which develops most frequently between the age of 50 and 70 years, patients may be in a diet, use oral antidiabetic tablets and/or insulin. Although type 1 and type 2 represent two distinct diseases from the epidemiological point of view, clinical distinction may sometimes be. The two disease processes should, in clinical terms, be visualized as opposite ends of a continuous spectrum (Gale and Anderson 1995).

Macrovascular disease leads to an increased prevalence of coronary artery disease, peripheral vascular disease and stroke, while microvascular damage results in diabetic retinopathy (DR), neuropathy and contributes to nephropathy (Gale and Anderson 1995). DR is the most common complication of DM (Hamilton et al. 1996). DM is common and affects about 7% of the population of the Czech Republic. At the end of 2004 approximately 712079 people were diagnosed with DM in the Czech Republic (Graf 1). About 111937 people are using insulin. Among these diabetic individuals, about 7% have type 1 DM, 92% have type 2 DM, and 1% have secondary DM. Approximately 84077 people (about 12% of the diabetic population) were diagnosed with DR, 18644 from them with proliferative DR (PDR) and 2364 are blinds (Graf 2).
Graf 1. Patients with diabetes mellitus in the Czech Republic

Graf 2. Patients with diabetic retinopathy in the Czech Republic

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The prevalence of DR is higher in type 1 DM (40%) than in type 2 DM (20%) (Kanski 1999). DR is the most common of the retinal vascular diseases associated with disruption of the blood-retinal barrier and macular edema. The classification of DR is generally on the severity of intraretinal microvascular changes and the presence or absence of neovascularization (American Academy of Ophthalmology-AAO 2006). DR is classified as nonproliferative (NPDR) when there are intraretinal microvascular changes like microvascular occlusion, intraretinal arteriovenous shunts, telangiectases, and microaneurysms. This early stage of DR precedes the proliferative (PDR) phase, in which new vessels or fibrous tissue, or both, form on the retina. The microvascular changes are associated with increased vascular permeability with intraretinal haemorrhages, lipid exudation, and retinal edema. The breakdown of endothelial tight junctions and loss of the blood-retinal barrier can be associated with both NPDR and PDR (AAO 2006). This excessive vascular permeability, resulting in the leakage of fluid and plasma constituents, such as lipoproteins into the retina, leads to thickening of the retina. Involvement of the macula by edema and/or lipid exudates is termed as diabetic macular edema (DME). When the centre of the fovea is involved, there is a higher risk of visual loss. DME is a common complication of DM. DME involving one or both eyes has been shown to occur in approximately 29% of diabetic patients with duration of disease of 20 years or more (Klein et al. 1984). Despite considerable recent advances in therapy, DR and DME remains the leading cause of blindness for those 20 through 74 years old (Klein et al. 1992, Eye Diseases Prevalence Research Group 2004). Although vision loss due to proliferative changes is more common in patients with type 1 DM, vision loss in patients with type 2 DM is more commonly due to DME (Wormald et al. 2004). The increasing number of individuals with diabetes worldwide suggests that DR and DME will continue to be major
contributors to vision loss and associated functional impairment in the working-age population of most developed countries.

1.2. APPLIED ANATOMY

The vitreous is a clear fluid-like substance composed of greater than 99% water (Peyman and Schulman 1994). The viscosity and rigidity of the vitreous are the result of a mixture of type II collagen with hyaluronic acid, glycoproteins and proteoglycans to form a delicate fibrillar meshwork (Sebag 1987, Swann 1987). The volume of the vitreous is approximately 4.0 ml (Tolentino et al. 1976), which represents 70-80% of the volume of the eye (Peyman and Schulman 1994, Reeser and Aaberg TM 1979). The outer, denser portion of the vitreous body is termed cortical vitreous and measures approximately 100 um in thickness. The anterior hyaloid is fixed to the posterior peripheral lens surface. The condensed posterior cortical vitreous forms the posterior hyaloid (vitreous) membrane, which merges with and is indistinguishable from the internal limiting membrane (ILM) (Peyman et al. 1994).

The ciliary body is composed of two parts: the pars plicata and the pars plana. The pars plicata extends from the iris root posteriorly approximately 2.5 mm and contains 70-80 ciliary processes that secrete aqueous humor. The pars plana is 3 mm in width nasally and 4.5 mm temporally. The posterior portion of the pars plana meets ora serrata (the junction of the retina and ciliary body) and is overlapped by the vitreous base more in the temporal side. Sclerotomies for vitrectomy surgery are performed within the pars plana (pars plana vitrectomy) and safest when placed 4.0 mm posterior to the limbus in phakic eyes and 3.5 mm posterior to the limbus in aphakic or pseudophakic eyes (Gross et al. 1989).

The retina extends from the ora serrata to the edge of the optic disc and is composed of 10 layers (Williams and Warwick 1980, El-Refaey 1990):

1. The ILM is in contact with the vitreous and made by ends of Müller fibres.
2. The nerve fibre layer is made by the axons of the ganglion cells. The fibres continue to form the optic nerve.

3. The ganglion cell layer.

4. The inner plexiform layer is made by the synapses between the bipolar cells and the ganglion cells.

5. The inner nuclear layer contains the bipolar cells, the cells of Muller’s fibres, bipolar and amacrine cells.

6. The outer plexiform layer is made by the synapses between the nuclei of the rods and cones and the bipolar cells.

7. The outer nuclear layer is formed by the nuclei of the rods and cones.

8. The external limiting membrane is made by the ends of the Müller fibres.

9. The rods and cones are the visual receptors. The rods are thin and responsible for vision in the dark (scotopic vision). They are mostly placed in the retinal periphery. Cones are thicker and concerned with day vision (photopic vision). They are mostly placed in the posterior part of the retina.

10. The pigment epithelium is the outermost layer and is in contact with Brush’s layer, which separates the pigment epithelium from the choriocapillaris. Retinal pigment epithelium serves two important functions in maintaining the integrity of the subretinal space: (a) it is part of the outer blood-retinal barrier and (b) it actively pumps ions and water out of the subretinal space.

Macula is an oval area at the posterior pole measuring about 5 mm in diameter.

Histologically, it is the region of the retina containing xanthophylls pigment and more than one layer of ganglion cells. The fovea is a central circular area 1.5 mm in diameter. It is centred 3.4 mm temporal to the optic disc margin (Sigelman et al. 1988). The center of the fovea is the foveola, measuring 350 µm in diameter. It is the thinnest part of the retina and
consists only of cones and their nuclei. Foveola appears in profile as a depression because of the absence of inner retinal layers. Foveal avascular zone is located inside the fovea but outside the foveola. It exact diameter is variable and its location can be determined with accuracy only by fluorescein angiography. The inner layers of the retina are supplied by branches of the central retinal artery (a branch of the ophthalmic artery). The outer layers of the retina and the fovea are avascular and receive nutrition by diffusion from the choriocapillaris. The central retinal vein ends in the cavernous sinus. The inner blood-retinal barrier is composed of the tight junctions of the retinal capillary endothelial cells. The outer blood-retinal barrier consists of tight junctional complexes, which are located between adjacent retinal pigment epithelium cells.

1.3. DIABETIC MACULAR EDEMA

DME is generally the most common cause of visual impairment in diabetic patients (Klein et al. 1984; Moss et al. 1988). DME remains a major cause of severe visual handicap and a serious public health problem. Clarke et al. reviewed blind registration data and found that 72% of all registrations were due to visual loss from DME (Clark et al. 1994). The overall incidence and prevalence of DME increase with longer duration of DM and greater severity level of DR (Klein et al. 1989). DME within 1 disk diameter of the fovea was found to be present in about 9% of the diabetic population (Klein et al.1984). Hikichi and associated (Hikichi et al. 1997) reported that the incidence of DME rises with increasing severity of retinopathy: 3% of patients with mild NPDR, 38% of patients with moderate to severe NPDR, and 71% of patients with PDR have DME. Various factors have been shown to exacerbate DME, such as fluid retention caused by cardiovascular or renal disease, uncontrolled hypertension, pregnancy, and panretinal photocoagulation (Bresnick 1986). In the Wisconsin Epidemiological Study of Diabetic Retinopathy (a large population-based study), the incidence of DME over a period of 10 years was 20.1% in patients with type
1 DM, 25.4% in patients with type 2 DM who required insulin and 13.9% in patients with type 2 DM who did not require insulin (Klein et al. 1995). Of patients who develop macular edema, more than half will experience a loss of 2 or more lines of best-corrected visual acuity after 2 years of follow-up (Ferris et al. 1984).

1. 3. 1 CLINICAL FEATURES

DME can be subdivided into focal and diffuse types, although many eyes show features of both (Takagi et al. 1999):

- Focal DME is characterized by well-defined areas of leakage from microaneurysms and hard exudate rings surrounding the foci of the edema.

- Diffuse DME is widespread and poorly demarked leakage caused by more generalised disruption of the inner blood-retina, in which not only microaneurysms but also retinal capillaries and arterioles leak diffusely. If DME is severe and prolonged cysts form at the fovea and in the perifoveal neuroretina. Cystoid DME (CME) is a frequent feature but other signs of DR may be absent.

The Early Treatment Diabetic Retinopathy investigators (ETDRS 1985) classified DME by its severity. It was defined as clinically significant DME (CSME) if one or more of the following features were present:

- Retinal edema within 500 µm of the centre of the fovea.
- Hard exudates within 500 µm of the center of the fovea, if associated with adjacent retinal thickening (which may be outside the 500 µm limit)
- Retinal edema that is one disc area (1500 µm) or larger, any part of which is within one disc diameter of the center of the fovea.

The International Clinical Diabetic Macular Edema Disease Severity Scale includes two major levels: absent and present (Ciulla et al. 2003). If DME present, it is divided into:
- Mild (some retinal thickening or hard exudates in the posterior pole, but distant from the center of the macula)
- Moderate (retinal thickening or hard exudates approaching the macula but not the center)
- Sever (retinal thickening or hard exudates involving the center of the macula).

In a recent optical coherent tomography (OCT) study Otani and Kishi (Otani and Kishi 1999) indicated that DME has three patterns: sponge-like retinal swelling, CME, and serous retinal detachment.

**Basic definitions**

- **Ischaemic maculopathy** is characterised clinically by the presence of reduced visual acuity in association with a relatively normal appearance of the macula although miroanaursms, retinal haemorrhages and hard exudates may be seen elsewhere. It is exact extent can only be delineated by fluorescein angiography but there does not appear to be a direct correlation between the level of visual acuity and the severity of ischemia (Kanski 1999).
- **Mixed maculopathy** is characterised by a combination of diffuse DME and ischaemia.
- **Retinal capillary Microaneurysms** ([Fig. 1](#)) are located in the inner nuclear layer of the retina and are the first clinically detectable lesions of DR. They appear as small round dots, usually temporal to the macula. The precise mechanism for the formation of microaneurysms is unknown. Possible mechanisms include release of a vasoproliferative factor with endothelial cell proliferation, weakness of the capillary wall (from loss of pericytes), abnormalities of the adjacent retina, and increased intraluminal pressure (Cogan et al. 1961, Frank et al. 1989).
- **Hard exudates** ([Fig. 1](#)) are composed of lipid deposits that presumably accumulate in association with lipoprotein leakage caused by breakdown of endothelial tight junctions in
microaneurysms or retinal capillaries and deposit in the outer plexiform layer (Murata et al. 1992). However, during surgical removal of foveal hard exudates, they also were found in the subretinal space (Takagi et al. 1999). They have a yellow waxy appearance with relatively distinct margins. They are arranged in clumps and/or rings. The centres of rings of hard exudates usually contain microaneurysms. Hard exudates are generally seen in the posterior pole, often at the border of the edematous and nonedematous parts of the retina, and usually cause significant visual loss when deposited in the foveal region. The extent of these lipid deposits in the retina is associated with the degree to which serum lipids are elevated (Chew et al. 1996, Klein et al. 1991).

Figure 1. Retinal capillary microaneurysms, retinal hemorrhagia and hard exudates in a patient with CSME

1.3.2 EVALUATION

The mean symptom of the DME (if the fovea is involved) is impairment of central vision. Extensive hard exudates in the fovea give the patients the feeling that something
is obstructing central vision (positive scotoma). The other symptoms, which may occur in DME, are metamorphopsia (an alteration in image shape); micropsia or macropsia. Clinical evaluation of patients with suspected DME begins with careful history that includes details of previous ocular surgery, review of symptoms, past medical history, family history, and medications. Best-corrected visual acuity is measured at distance and near; visual field testing may be useful. The anterior segment is performed with the slit-lamp and then fundus examination is performed. Biomicroscopic slit-lamp examination with a fundus contact lens (clinical gold standard) is essential in demonstrating even mild CME and also identifying contributing DR. Biomicroscopy with the 78 and 90 diopter lenses, while not as sensitive, is also useful in the diagnosis of DME. CME can be examined using the technique of light scattering (Fig. 2). Focusing the slit beam on the retina at the edge of the suspected area of CME retroilluminates and clearly defined the cystic spaces. Fundus photography can be individually used to document the progression of DME (especially with hard exudates) or efficacy of the treatment.

**Figure 2.** Careful ophthalmoscopic examination clearly defined the cystic spaces in patients with CME.
Fluorescein angiography is an important diagnostic tool and a good guide for laser photocoagulation of DME. It helps to determine the type and location of intended laser photocoagulation for DME. The advantage of fluorescein angiography is its ability to detect macular ischaemia denoted by nonperfusion of the retinal capillaries and to detect DME as evidenced by fluorescein leakage from the capillaries. After obtaining informed consent, sodium fluorescein (normally excluded from the retina by the blood-retina barrier) is injected intravenously. Sequential passage of the fluorescein through the retinal and choroidal circulations can be demonstrated by rapid-sequence fundus photography. This technique uses an exciting wavelength of blue light and filters that block all but the green emission wavelength of the dye. If the blood-retinal barrier is not intact there is no detectable leakage of fluorescein into the retina. In patients with CME, early views of the dye transiting through the eye may identify leakage sites, with late dye accumulation in honeycomb-like (flower-petal pattern, Fig. 3) parafoveal cystic spaces (Jaffe et al. 1981).

Although vascular leakage as demonstrated by fluorescein angiography is important in the evaluation of CME, visual loss may more correlate with the degree of macular thickening than with the amount of macular leakage seen on fluorescein angiography (Olk 1986). Fluorescein angiography is very helpful but an invasive method and therefore is not recommended for routine use in all patients with DME.

**Figure 3.** Fluorescein angiogram of chronic CME showing the typical flower-petal pattern
Ultrasound is a painless, non-invasive, dynamic examination that can be performed in the clinic, at the patient’s bedside, or in the operating room. Imagining of the eye is facilitated by the use of high frequency sound (8-10 MHZ). The basis of the system is the piezoelectric material that is located near the tip of the transducer (probe) that is placed directly on the eye or on the eyelid. As sound travels through the structures of the eye, reflected signals are returned to the probe, mechanical energy is converted to electrical energy, and signals or echoes are displayed on the screen. A-scan provides a one-dimensional image of spikes or deflections along a baseline and gives some information about the lesion’s character and its size. B-scan allows for two-dimensional imaging by using both the vertical and the horizontal dimensions of the screen to indicate configuration and location. B-scan images consist of a series of dots and lines and are most useful in documenting the topographic features of the eye structures, as well as the shape, contour, and distribution of normal and abnormal structure that may be present. Combined use of A-scan and B-scan is known as standardized echography. Echography is a useful diagnostic adjunct if media opacities preclude good fundus visualization is, or as a supplement to ophthalmoscopy. Echography may identify or document DME and very useful in evaluating the vitreomacular traction and status of the posterior vitreous membrane (Dibernardo et al. 1998) (Fig. 4).

**Figure 4.** DME in a patient with attached posterior hyaloid without echographic evident vitreomacular traction.
Objective and quantitative measurement of retinal thickening, which was not possible in the past, is recently available by modern technologies. OCT is a non-invasive, new technique, which projects a pair of near-infrared beams from a diode through the pupil of the eye and then through the vitreous, retina, and choroid. The structures of the eye disrupt the coherence of the two beams, producing an interference pattern detected by measuring system of the instrument and dependent on the optical reflectance and anatomical thickness of the retinal structures (Huang et al. 1991). In the most commonly used protocol, the instrument produces a series of six radially oriented scans at equal intervals around a circumference of 360 degrees. The scans pass through the fixation point of the patient’s eye (the center of the fovea). Each scan makes multiple measurements of retinal thickness. The images produced appear to be good approximations of the cross-sectional anatomy of the retina. The distance between the laser intersections with the anterior and the posterior surface of the retina yields a measurement of retinal thickness and visualized of the cysts in CME. OCT is useful in documenting anatomic features of the vitreous and retina, especially at the vitreoretinal interface. Measurements of mean retinal thickness along these radii are plotted along with a pseudocolor map of retinal thickness that enhances the visual interpretability of the images. OCT can therefore be used for the evaluation and follow-up of patients with DME (Rivellese et al. 2000). Because the method requires the projection of the light onto the retina, it is subject to error in the presence of interfering opacities such as cataracts, corneal opacities, or vitreous haemorrhage. Massin and associates noticed that day-to-day variation in the same patient appears to be small (Massin et al. 2001). An advance version of OCT, involving a different optical system and a titanium-aluminum oxide laser, provides even more striking images, which display the cellular anatomy of the retinal layers in nearly the detail of a histology section (Drexler et al. 2001).
Otani and Kishi (Otani and Kishi 1999) reported, in their OCT study, three patterns of DME: sponge-like retinal swelling (Fig. 5), CME, and serous retinal detachment (Fig. 6).

**Figure 5.** DME, sponge-like retinal swelling

**Figure 6.** CME and serous retinal detachment

1.3.3 PATHOGENESIS

DME is a non-specific pathologic response to the disruption of the blood-retinal barrier (Dick et al. 2002). The blood-retinal barrier, in combination with active and passive transport systems, restricts the free movement of plasma constituents into the retina and plays an important role in the maintenance of homeostasis within the neurosensory retina. The extracellular space of the retina normally accounts for only a small proportion of its total volume, this stat dependent on an intact blood-retinal barrier and on the active transport of electrolytes and larger molecules across the retinal pigment epithelium from retina to the choroid. With disruption of the either the inner or the outer blood-retinal barrier, unrestricted entry of plasma constituents, including plasma proteins and water,
causes a significant expansion in the extracellular space of the retina (Dick et al. 2002). This results in accumulation of fluid in the macular area and increase in the thickness of the parafoveal retina. Increased fluid accumulation in cystic spaces, located in the outer plexiform and inner nuclear layers of the parafoveal retina, leads to perform CME. The predisposition of the macula to develop CME is poorly understood. Histopathologic studies of the etiology of CME have been inconclusive. Study by Gass support the concept that primary change leading to CME is an increase in extracellular fluid in retina (Gass 1987). Fine et al. and Wolter, however, hypothesize a primary role of intracellular swelling and degeneration of Müller cells; speculate that the cystoid spaces in CME may represent swollen Müller cells without expansion of the extracellular space (Fine et al. 1981, Wolter 1981). The relative importance of increased extracellular fluid versus swelling of the Müller cells in the development of CME still remains uncertain. Tso (Tso 1980, Tso 1982) notes a localized loss of photoreceptors in eyes with CME and suggested that degeneration of the retinal pigment epithelium may be associated as well. The exact pathophysiologic mechanisms responsible for the disruption of the blood-retinal barrier in DME remain uncertain and is likely multifactorial. But this disruption is known to be associated with a number of factors associated with DM. Chronic hyperglycaemia results in disruption of the blood-retinal barrier via the aldose reductase pathway with production of the sugar alcohols and Glycation of the proteins (Frank 1984). The relatively selective loss of pericytes from the retinal capillaries is a characteristic lesion that occurs early in DR and DME (Kuwabara et al. 1963). Normal pericytes are thought to have a contractile function that helps to regulate capillary blood flow, a theory based on the observation that pericytes contain copious smooth-muscle actin and have multiple processes that are wrapped around the capillary endothelium. The loss of pericytes is followed by the loss of capillary endothelial cells. Apoptosis, or programmed cell death, is thought to account for the
disappearance of both types of cells (Mizutani 1996). Since neurons in the retina have high metabolic requirements, the hypoxia that results from extensive retinal capillary cell death is probable stimulus for the increased expression of molecules that enhance the breakdown of the blood-retinal barrier (Henkind 1978, Patz 1982). Several polypeptide growth factors such as vascular endothelial growth factor (VEGF) have possible relevance to the pathogenesis of DR and DME. The VEGFs are a family of peptides produced from a single gene by alternative splicing, VEGF isoforms are specifically mitogenic for vascular endothelial cells and also increase permeability at blood-tissue barriers- hence the original name, vascular permeability factor. VEGF is essential for the formation of the fetal vascular system (Carmeleit et al.1996). Normally, VEGF expression decreases substantially after birth, but some cells constitutively secrete picomolar amounts, cells in the neural retina secrete 15 to 20 pg per milligram of protein, and cells in the combined choroid and retinal pigment epithelium secrete 50 pg per milligram of protein (Kim et al. 2000). VEGF expression is enhanced by hypoxia (Shweiki et al. 1992, Aiello et al. 1995). Reduced retinal blood flow and accompanying hypoxia may be present even before the early signs of DR/DME, such as loss of capillary pericytes and endothelial cells, are identified, and these changes are likely to be accompanied by increase in the synthesis and secretion of VEGF (Ishii et al. 1996, Lutty et al.1996, Amin et al. 1997). Indeed, increased VEGF protein has been demonstrated by immunocytochemical analysis of nonvascular cells in the eyes of persons with DM even in the absence of retinopathy, supporting the hypothesis that DR begins as a disease of retinal neurons and glia and only later involves the retinal vasculature (Lutty et al.1996, Amin et al. 1997). In vitro experimentation has shown that VEGF appears to induce endothelial fenestrations, which are thought to increase vascular permeability (Esser et al. 1998). Exogenous VEGF injected into the vitreous of the eyes of monkeys causes neovascularization of the iris (Tolentino et al.
1996) or retina (Tolentino et al. 2002). The possible role of the posterior hyaloid membrane in the pathogenesis of DME has become increasingly recognised (Schepens et al. 1984). Nasrallah and associates (Nasrallah et al. 1988) observed that eyes with DME had a significantly higher incidence of an attached posterior vitreous than eyes without DME. Although it is unclear how the posterior hyaloid contributes to the development of DME, condensation and contraction of the premacular hyaloid membrane causes tangential vitreomacular traction, which may increase the permeability of the retinal vasculature. Tangential traction may also induce or exacerbate an existing breakdown of the outer blood-retinal barrier (Pendergast et al. 2000). Idiopathic epiretinal proliferative membranes are characterized by a contractile fibrocellular tissue layer covering the inner retinal surface. Contraction of the epiretinal membrane results in tangential traction on the inner retina that puckering the macula. Tractional distortion of the superficial retinal vasculature may lead to disruption of the inner blood-retinal barrier. In the vitreoretinal traction syndrome, persistent traction is exerted on the inner retinal surface by the adherent posterior hyaloid following a partial or incomplete posterior vitreous detachment. Localized vitreoretinal traction on the macula results in retinal vascular leakage and CME (Dick et al. 2002).

1.3.4 SURGICAL TREATMENT

Although in rare cases the edema may resolve spontaneously (Yamaguchi et al. 2003), treatment is highly recommended to avoid irreparable visual loss.

Laser photocoagulation is used to treat both DR and DME. The goal of the macular laser photocoagulation is to limit vascular leakage. The treatment recommendation of DME is based on the results of the ETDRS (ETDRS 1985, ETDRS 1987, ETDRS 1995). ETDRS is a major randomized clinical trial, which provide clinically important information to guide the treatment of DME. The ETDRS used two types of treatment form
DME, focal and grid. Focal refers to the direct treatment of all leaking microaneurysms in the edematous retina between 500 to 3000 microns from the center of the macula. Individual microaneurysms are treated with a spot size of 50 to 100 microns and an exposure time of 0.1 second. The power is set initially quite low and slowly increased to obtain either whitening or darkening of the microaneurysms with minimal power. The grid treatment is used for areas of diffuse leakage located more than 500 μm from the centre of the fovea and 500 μm from the temporal margin of the optic disc. The spot size is 50-200 μm and the exposure time 0.10 seconds. The grid is composed of light intensity burns, producing a grid of equally spaced burns more than one burn width apart. Focal laser photocoagulation reduced the risk of the moderate visual loss for all eyes with DME by 50% (Graf 3). The patient should be informed that the main aim of treatment is to preserve the current visual level and only 15% of eyes may improve. Regarding the functional results, grid-pattern laser photocoagulation in diffuse macular edema showed limited efficacy in several studies (Bresnick 1983, McDonald et al. 1985, Olk 1986, Lee et al. 1991). The effect of focal laser photocoagulation for DME was evaluated in eyes with a board range of baseline edema severity, visual acuity levels, and various baseline fluorescein angiographic characteristics (ETDRS 1995). Although these analyses were performed in eyes with mild and moderated NPDR only, the most important factor to consider in deciding whether to treat DME remains involvement the centre of the fovea. Because in some cases it may take up to 4 months for the edema to resolve, retreatment should not be considered prematurely. Treatment of eyes with focal DME was associated with better results than treatment of those with diffuse DME. Poor prognosis was documented in eyes with extensive macular capillary non-perfusion (ischemic maculopathy), CME and hard exudates located in the fovea. For patients with leakage arising close to the center of macula, it is preferable to observe closely rather than treat
early because of the increased risk of damage from direct treatment and possible subsequent migration of treatment scars. Patients can notice the scotomas related to the laser burns. One of the reported adverse effects of focal laser photocoagulation is development of choroidal neovascularization and subsequent subretinal fibrosis (Lewis et al. 1990, Han et al. 1992). In the ETDRS 9 of 109 eyes with subretinal fibrosis associated with DME could be directly attributed to focal photocoagulation. The strongest risk factor for the developing of subretinal fibrosis was the presence of severe hard exudates in the macula, which is associated with elevated lipid levels (Klein et al. 1991). The failure of laser photocoagulation in substantial subgroup of patients has prompted interest in other treatment methods, including surgical treatment with pars plana vitrectomy, removal of ILM and intravitreal application of corticosteroids.

![Graph](image)

**Graf 3.** Results of the ETDRS (ETDRS 1985, ETDRS 1987). Comparison of percentages of eyes that experienced visual loss of three or more lines (moderate visual loss) to eyes with CSME with center involvement. The control eyes were randomised to deferral of photocoagulation, and the treated eyes were of assigned to immediate focal
photocoagulation for DME. There was more than a 50% reduction in the rates of moderate visual loss in the treated eyes with focal photocoagulation.

Since the pilot study of Lewis in 1992 (Lewis et al. 1992), which have shown that vitrectomy with removal of the posterior hyaloid may be beneficial in eyes with diffuse DME associated with a thickened, taut premacular posterior hyaloid, there has been an interest in vitreous surgery as a potential treatment for DME. Many investigators have reported that vitrectomy is beneficial for DME, especially for eyes with DME and a thickened, taut posterior hyaloid. The favourable results were reported in such cases after vitrectomy and detachment of posterior hyaloid (Harbour et al. 1996; Pendergast 1998; Ikeda et al. 1999; Pendergast et al. 2000; Gandorfer et al. 2000; Yamamoto et al. 2001; Sato et al. 2002; Kalvodová et al. 2002, Yamamoto et al. 2003, Aboutable et al. 2005). Macular edema was hypothesized to exacerbate by tangential traction of the thickened and still attached posterior hyaloid membrane, causing a very shallow macular detachment similar to that observed in patients with macular holes (Lewis et al. 1992; Harbour et al. 1996; Pendergast 1998; Pendergast et al. 2000). Others have found that even among patients whose DME is not accompanied by visible evidence of posterior hyaloid thickening or traction some respond to vitrectomy with resolved DME and improved vision (Tachi et al. 1996, Otani et al. 2000, Ikeda et al. 2000; La Heij et al. 2001, Yamamoto et al. 2001). Most of the previous studies were retrospective and not controlled. Otani and Kishi (Otani and Kishi 2002) compared in a controlled study 7 eyes that underwent vitrectomy with untreated fellow eyes and found also vitrectomy to be beneficial for DME. First study in the Czech Republic about vitrectomy for DME documented by the OCT was published in 2002. Kalvodová et al. (Kalvodová et al. 2002) reported on positive effect of vitrectomy in resolving DME and improving of the visual acuity.
Although Takagi and associates (Takagi et al. 1997) found a positive effect of additional removing of massive foveal hard exudates allows replacing serous retinal detachment in low-vision patients with DME, Takaya and associates (Takaya et al. 2004) reported that visual improvement could not be obtained for a long period after removing submacular hard exudates in most of the patients, suggesting that diabetic maculopathy should be treated before massive exudate deposits appear in the macula. To date there are neither long-term reports, nor controlled, prospective, randomized, double masked, multicenter studies with large number of patients to give clear evidence about the benefits of vitrectomy for DME and to establish the best surgical technique. If vitrectomy is proved to be beneficial for DME, it could have a major impact on the quality of life of numerous diabetic patients.

In a pilot study, Gandorfer and associates reported on resolution of DME after surgical removal of ILM of 12 eyes (Gandorfer et al. 2000), in this study, however, a thickened posterior hyaloid membrane was removed in the same session in 10 of the 12 eyes, and therefore no useful conclusions on the effectiveness of ILM peeling alone can be drawn from this study. ILM peeling could be sometimes a traumatic procedure, Wolf and associates (Wolf et al. 2004) reported that ILM peeling resulted in minor, but demonstrable, damage of the adjacent retina and concluded that ILM peeling should be performed with caution. Currently, the value of ILM peeling is one of the most debated aspects of DME surgery. Although some investigators provided ILM peeling generally in cases with DME (Avci et al. 2004, Kuhn et al. 2004), others only in eyes that showed visible epimacular proliferation and cellophane maculopathy (La Heij 2001, Aboutable et al. 2005). Some reported on resolution of DME and improvement of visual acuity (VA) (Dillinger et al. 2004, Kuhn et al. 2004), others found that the ILM peeling accelerates the absorption of edema in more sever diabetic cases, without any improvement of VA.
In a recent retrospective study DME resolved and VA improved in eyes after vitrectomy without ILM peeling in 44, 4% and in 69, 1% of eyes that underwent vitrectomy with ILM peeling (Stefaniotou et al. 2004). Previous studies about ILM peeling for DME were not controlled and no firm conclusions can be drawn, whether ILM peeling for DME should be indicated generally as a standard surgical procedure or selectively in eyes with visible epimacular proliferation and cellophane maculopathy.

Corticosteroids have been known to reduce intraocular inflammation and tightened the capillary walls and depending on their concentration, to suppress proliferation of cells. Steroids have been used for treatment for many ocular diseases, applied topically as drops, given systematically or injected into the subconjunctival or sub-Tenon space. Often, the intraocular concentration of steroids was not high enough to achieve a therapeutic level, or the systemic side effects were too pronounced for a prolonged treatment. To avoid this limitation of the ocular steroid therapy some investigators started to inject steroids into the vitreous (Machemer et al. 1979). Some investigators used soluble cortisone; which is washed out of the eye within approximately 24 hours after a single intravitreal injection (Schindler et al. 1982, Scholes et al. 1985). Machemer propagated the use of triamcinolone acetonide (TA), which as a crystalline steroid has a considerably longer absorption time than an injection of soluble cortisone (Beer et al. 2003). Following the pioneers in the intravitreal use of TA, intravitreal triamcinolone (IVT) has increasingly been applied in recent studies for treatment of various intraocular edematous and neovascular proliferative diseases. Within last four years, IVT has increasingly used as a treatment option for DME. The eye makes out about 0.01% of the body volume. Assuming an equal distribution of TA through out the body, an intravitreal injection of 4 mg is equal to an intragluteal injection of 40 g, and an intravitreal injection of 25 mg TA is equal of a quarter of kilogram injected intragluteally (Jonas et al. 2005). IVT allows extremely high concentrations of steroid at its
site of acquired action, and simultaneously decreases or avoid systemic side effects. Some recent studies have suggested that IVT may be helpful in improving the visual acuity and reducing DME. (Jonas and Söfker 2001, Martidis et al. 2002, Chieh et al. 2003, Massin et al. 2004, Degenring et al. 2004). TA might be applied (1) into the vitreous body as an intravitreal injection, (2) as a subtenon injection, (3) or into the vitreous cavity at the end of vitrectomy.

Recently, many investigators have reported that vitreous samples from patients with DME contain elevated VEGF levels (Funatsu et al. 2002, Funatsu et al. 2002, Brooks et al. 2004). Experiments in animals have suggested a central role for the 165 isoform of VEGF specifically in the pathogenesis of DME (Tolentino et al. 1996, Qaum et al. 2001, Ishida et al. 2003). Increased retinal VEGF164 (the rodent equivalent to primate VEGF165) levels in this model coincide temporally with breakdown of the blood-retinal barrier (Qaum et al. 2001, Ishida et al. 2003). When VEGF164 bioactivity is selectively blocked using pegaptanib sodium injection (Macugen, Eyetech Pharmaceuticals, Inc., New York, NY), the blood-retinal barrier is re-established in animals with induced diabetes (Ishida et al. 2003). Other investigators found that VEGF165 injected into nonhuman primate eyes results in a rapid breakdown of the blood-retina barrier (Tolentino et al. 1996, Tolentino et al. 2002) accompanied by formation of retinal microaneurysms, increased vascular leakage and development of DME (Tolentino et al. 2002). In the light of these studies, one can suggest that VEGF165 inhibition may have the potential to reverse DME.

Macugen Diabetic Retinopathy Study Group (Macugen Diabetic Retinopathy Study Group 2005) evaluated in a double-masked, randomise, multicenter, dose-ranging, controlled trial, the safety and efficacy of intravitreal injection of pegaptanib sodium (pegaptanib) in the treatment of DME. They confirmed the absence of any safety issues that would preclude the use of pegaptanib and found that subjects assigned to pegaptanib had better visual
acuity outcomes, were more likely to show reduction in central retinal thickness, and were
deemed less likely to need additional therapy with photocoagulation at 36 weeks follow-up.

2. STUDY PURPOSE

The mean aim of this study is to determine the effectiveness of vitrectomy as a treatment option for DME, the possible role of additional ILM peeling during vitrectomy and to investigate safety and efficacy of IVT as an adjunctive treatment injected at the end of vitrectomy. The study includes 4 study groups:

- **First study (vitrectomy study):** The purpose of this study is to evaluate anatomic and functional results of vitrectomy for DME refractory to laser treatment in eyes with different states of posterior vitreous membrane and different duration of the edema. To report intraoperative and postoperative complications.

- **Second study (ILM peeling study):** The aim of this controlled study is to evaluate the effect of the ILM peeling during vitrectomy in eyes with DME without evident epimacular proliferation or cellophane maculopathy, unresponsive to laser photocoagulation. To determine whether ILM peeling improves anatomical and functional outcomes and whether is always essential in DME surgery.

- **Third study (triamcinolone study):** The purpose of this ongoing study is to determine whether injection of IVT at the end of vitrectomy is safe and effective in treating DME refractory to prior laser photocoagulation.

- **Fourth study (histopathological study):** The aim of this study is to describe the histopathological features of the ILM intentionally removed during vitrectomy for DME and to compare them with those peeled during vitrectomy for idiopathic macular hole (nondiabetic).
3. METHODS

3.1 STUDY GROUPS AND DESIGN

All surgeries were performed at the Department of Ophthalmology, General Faculty Hospital and 1st Faculty of Medicine, Charles University of Prague between 2001 and 2006. All patients received full information regarding all available treatment options and all of them gave their informed consent prior to the surgery. All studies were performed in a prospective design and included the following numbers of eyes:

- First study (vitrectomy study): This study includes 72 eyes (61 patients). All surgeries were performed between June 2001 and December 2003.

- Second study (ILM peeling study): In this controlled study, ten patients (20 eyes) with similar degree and duration of DME in both eyes underwent bilateral vitrectomy with and without ILM peeling to determine the role of ILM peeling in DME surgery. All patients were operated between April 2003 and January 2005.

- Third study (triamcinolone study): This ongoing study started in January 2005. At the end of July 2005 the study included 32 eyes (32 patients).

- Forth study (histopathological study): This comparative, interventional case series, using transmission electron microscopy study includes 6 samples of ILM obtained from 6 eyes (6 patients) during vitrectomy performed between September 2005 and January 2006. The histopathological analysis was performed by Assoc. Prof. Jaroslava Dušková M.D., CSs. at the Department of Pathology, the 1st Faculty of Medicine and Charles University of Prague.

All patients from the first and the second studies were followed up for at least 6 months after surgery. Patients from the third study were followed up at least 4 months.
3.2 INCLUSION AND EXCLUSION CRITERIA

3.2.1. The first and the third studies (the vitrectomy study and the triamcinolone study)

Inclusion criteria:

(1) Clinically significant diffuse DME with cystoid changes.
(2) Refractory to prior macular laser photocoagulation.

Excluded were eyes with:

(1) Ophthalmic disorders associated with macular edema, such as uveitis and branch or central retinal vein occlusion.
(2) Fibrovascular proliferation with tractional and/or rhegmatogenous retinal detachment and/or macular distortion.
(3) Dense media opacity such as cataract or vitreous hemorrhage.
(4) History of previous vitrectomy.

3.2.2. The second study (the ILM peeling study)

Inclusion criteria for this study were as follows:

(1) Patients with clinically detectable bilateral DME with similar degree and duration of DME in both eyes (visual disparity between the both eyes was less than 3 lines).
(2) Refractory to laser photocoagulation.
(3) No evident epimacular proliferation or cellophane maculopathy.
(4) Posterior hyaloid attachment without evident vitreomacular traction.
3.2. 3. The fourth study (histopathological study)

Excluded were eyes with:

(1) Ophthalmic disorders associated with macular edema, such as uveitis and branch or central retinal vein occlusion.

(2) Dens media opacity such as cataract or vitreous hemorrhage.

(3) Fibrovascular proliferation with tractional retinal detachment and/or macular distortion.

Inclusion criteria:

Eyes with refractory diffuse DME or idiopathic macular hole that underwent vitrectomy with ILM peeling, in which removed ILM were >2 disc diameters (PD).

Excluded were eyes in which the peeled ILM were < 2 PD in diameter or were destroyed during fixation, therefore their excellent histopathological analysis were not possible.

3.3 PREOPERATIVE COLLECTION DATA

The following preoperative data were recorded for each patient from any of the 4 studies:

- Age, gender, type and duration of diabetes, glycaemia, HbA1c in most patients, history of arterial hypertension and/or nephropathy.

- Severity of diabetic retinopathy, pervious ocular surgery, history of focal, grid and panretinal laser photocoagulation.
The duration of DME was defined as the interval between the time at which the patient was first seen in our clinic with DME and the time of operation. According to the duration of DME all eyes from the first study were divided into two groups, eyes with duration of DME shorter than 6 months and eyes with duration of DME longer than 6 months.

- Best-corrected Snellen visual acuity (BCVA), visual acuity for near and intraocular pressure by applanation tonometer.
- Careful examination of the anterior segment by the slit-lamp biomicroscopy to evaluate the absence or presence of neovascularization of the iris, lens status and to determine whether the view will be adequate to perform the precise surgical procedures that are required.
- The diagnosis of DME was made by careful ophthalmoscopy. Biomicroscopic examination of the posterior pole, with contact and noncontact (90 diopters or 78 diopters) fundus lenses, was performed to verify the presence of DME, to evaluate the vitreoretinal interface relationships and to check for any preretinal membranes. To determine the stat of the posterior hyaloid membrane, such as attachment or detachment of the posterior hyaloid and whether the still-attached posterior hyaloid was thickened. A careful fundus examination is imperative to differentiate the thickened, taut glistening, premacular posterior hyaloid from fibrovascular proliferation or an epiretinal membrane. Epiretinal membranes usually caused straightening of nearby retinal vessels. Also examination of the retinal periphery was performed to determine the presence of retinal pathology that may require treatment during vitrectomy.

- Fluorescein angiography and was performed in most cases to determine the retinal leakage and the capillary perfusion.

- Stratus OCT, Carl Zeiss 2. and 3. versions were used.
Standardized sonography was performed as a routine examination for all patients to document the status of the posterior hyaloid membrane and the presence of any vitreoretinal traction on the macula.

3.4 SURGICAL TECHNIQUES

All operations in the first study were performed by two surgeons (BK, TA), in the second study by one surgeon (TA), in the third study by three surgeons (BK, TA, JD)*. All surgeries were performed under local anaesthesia by using 5 ml Bubivacaine 0.5% injected into the retrobulbar space. Our vitrectomy technique consisted of a standard three-port vitrectomy. Our usual vitrectomy settings are 600-800 cuts per minute and suction levels of 200-250 mmHg. Intraoperatively, special attention was paid to the vitreoretinal interface: whether the posterior hyaloid membrane was attached or partially or complete detached, whether it was abnormally thickened, whether there was an epiretinal membrane, and whether there was a cellophane-type glistening with or without wrinkling of the inner retinal surface at the level of the ILM. In eyes with posterior hyaloid attachment the posterior hyaloid was detached from the posterior pole by using high suction power with the vitrectomy instrument at the optic disk until detachment was created, as evident by a Weiss ring. Further separation of the hyaloid towards the peripheral retina was achieved with the vitrectomy instrument, using a combination of suction and cutting. In some case with strongly attached posterior hyaloid membrane, especially in younger patients, we detached the posterior hyaloid membrane from the edge of the optic nerve disc using a retinal spatula. Sixty one (61) eyes from the first study underwent vitrectomy without ILM peeling and 11 eyes that showed an epimacular proliferation and a cellophane maculopathy, underwent vitrectomy with ILM.

*BK: Assoc. Prof. Bohdana Kalvodová M.D., CSc, TA: Tarek Aboutable M.D., JD: Jan Dvořák M.D.
Ten eyes from the second study underwent vitrectomy without ILM peeling and 10 eyes underwent vitrectomy with ILM peeling. Eyes that underwent vitrectomy with ILM peeling in the second study were selected at random. ILM was stained with about 0, 3 ml of Trypan-blue 0.2% (Membrane Blue, D.O.R.C. International, Zuidland, The Netherlands) injected in the front of the macula in a liquid-filled eye. The dye was removed in 60 s. Afterwards the ILM was incised and peeled within the temporal vascular arcade using forceps. Intraoperative focal laser photocoagulation for PDR was necessary in 30 eyes from the first group; eight eyes from the second study with PDR also received focal laser photocoagulation. No grid or focal macular laser therapy was applied intraoperatively. Endotamponade with 20% sulphur hexafluoride was used in one complicated eye from the first study, in one complicated eye from the second study and in 2 eyes from the fourth study. We carefully checked with scleral indentation the retinal periphery for iatrogenic tears. At the end of surgery, subconjunctival injections of dexamethasone (2 mg) and gentamycin (4 mg) were administered. Postoperatively, eyes were treated with gentamycin 3 mg drops for 1 week, dexamethasone 1 mg drops and atropine 1% drops for approximately 1 month.

In the third study (triamcinolone study) we injected 4 mg (0.1 ml x 40 mg) of TA into the eye at the end of vitrectomy with removal of the posterior hyaloid. The following method was routinely used to isolate TA particles and to remove preservatives and suspending agents in the vehicle (benzyl alcohol, carboxymethylcellulose) from its commercially available suspension (Fig. 7) before intravitreal application as previously described in detail (Jonas and Sofker 2001, Jonas et al. 2001, Jonas et al. 2003):

- The contents of a Triam vial (40 mg TA suspended in 1.0 ml vehicle) were loaded into a syringe with a three-port valve (Fig. 8) and passed through a millipore filter (pore size 5
µm; Sterifix Pury, B Braun Melsungen AG, Carl-Braun-Strasse 1, 34212 Melsungen, Germany).

- The filter was then backflushed with Ringer’s solution to yield a vehicle-poor suspension of TA in the initial syringe.
- This filtration and backflush procedure was repeated four times.
- The staff of the operating theatre before the intravitreallly application routinely performed the filtration procedure.

Figure 7. TRIAM INJEKT® 40 mg

Figure 8. Three-port valve used in the filtration process of TA

3.5 POSTOPERATIVE COLLECTION DATA

Postoperatively collected data included:

- BCVA and intraocular pressure by applanation tonometer.
- Careful examination of the anterior segment by the slit-lamp biomicroscopy to evaluate the absence or presence of neovascularization of the iris and lens status.
- Absorption, presence or recurrence of macular edema detected by careful biomicroscopic examination of the posterior pole with contact and noncontact fundus lenses performed 1 week, 1, 3 and 6 months after surgery.
• Length of follow-up period.
• Any postoperative complications.

• Postoperatively controlled OCT was performed 6 months after surgery in most cases of the first study, in all cases of the second study and in a few cases of the third study. The status of DME after surgery in the third study was largely based on slit-lamp ophthalmoscopy.

Wilcoxon Rank Sum Test and Wilcoxon Signed Rank Test were used for statistical analysis in the second study.

3.6 HISTOPATHOLOGIC EXAMINATION

Morphometric Evaluation of the ILM in the LUCIA G5 (Laboratory Universal Computer Image Analysis) Image Analysis System.

1) 2.5% glutaraldehyde fixed surgically peeled ILM and was embedded into artificial resin (Durcupan- Epon).

2) Semithin sections were stained with toluidine blue and ILM identified.

3) Ultrathin sections were contrasted with uranyl acetate and lead citrate.

4) ILM was photographed with the Jeol 100SX transmission electron microscope under the standard enlargement 5000x with a 1µm scale.

5) In the LUCIA G5 (Laboratory Imaging, Prague) the digitalized images were loaded, superimposed with a square grid of 500 px (= 3.25 µm). Any hit of the grid on a membrane was a place for the transversal ILM thickness measurement. The ILM of any patient with sufficient length of the membrane provided was measured on 10 photographs providing thus 40-50 dimensions for subsequent arithmetic mean +SD evaluation.

6) MS Excel predefined table served the final Arithmetic Mean ± SD evaluation.
4. RESULTS

4.1. FIRST STUDY

Seventy two consecutive eyes of 61 patients were included in the study, 26 (42, 6%) were females and 35 (57, 4%) were males. The right eye was operated on in 55%. Thirty (41, 7%) eyes with PDR were treated by panretinal laser photocoagulation and 42 (58, 3%) with NPDR received focal laser therapy.

According to the status of the posterior vitreous membrane examined by careful biomicroscopic examination and sonography all eyes were divided into 3 groups:
- Group A: 21 (29, 2%) eyes with attached and taut premacular posterior hyaloid with evident vitreomacular traction (Fig. 9, 10, 11, 13).
- Group B: 36 (50%) eyes with attached posterior hyaloid in the macular region, but without thickening and without traction on the macula (Fig. 12)
- Group C: 15 (20, 8%) eyes with posterior vitreous detachment.

Figure 9. I, II, III:

Patient (from group A) with attached, taut and thickened posterior hyaloid causing tangential vitreomacular traction

- 37 -
**Figure 10.** CME with partial detachment of the posterior hyaloid causing anterioposterior vitreomacular traction

**Figure 11.** (I, II)

Tangential vitreomacular traction by thickened premacular posterior hyaloid membrane detected even by echography

**Figure 12.** Attached posterior hyaloid in the macular region, without thickening, and without traction on the macula
Forty four eyes with duration of DME shorter than 6 months (15 eyes from group A, 20 eyes from group B, 9 eyes from group C) and 28 eyes with duration of DME longer than 6 months (6 eyes from group A, 16 eyes from group B, 6 eyes from group C). Cystoid changes were observed as diagnosed by biomicroscopic examination and confirmed by fluorescein angiography and/or OCT in all eyes. The median duration of the macular edema was approximately 9.0 months (range 2-32 months) at the time of vitrectomy. The preoperative visual acuities ranged from 0.02 to 0.4 (median 0.2, mean 0.25). ILM peeling was performed in 11 eyes from group C.

**Table 1.** Anatomic results

<table>
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<th>DME</th>
<th>Group A (n =21)</th>
<th>Group B (n =36)</th>
<th>Group C (n =15)</th>
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<tr>
<td>Resolved</td>
<td>20(95%)</td>
<td>21(58%)</td>
<td>3(20%)</td>
</tr>
<tr>
<td>Decreased</td>
<td>1(5%)</td>
<td>14(39%)</td>
<td>10(66%)</td>
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<tr>
<td>Unchanged</td>
<td>–</td>
<td>1(3%)</td>
<td>1(7%)</td>
</tr>
<tr>
<td>Increased</td>
<td>–</td>
<td>–</td>
<td>1(7%)</td>
</tr>
<tr>
<td>Recurrence</td>
<td>–</td>
<td>–</td>
<td>–</td>
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**Table 2.** Functional results

<table>
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<th>BCVA</th>
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<th>Group B (n =36)</th>
<th>Group C (n =15)</th>
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</thead>
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<tr>
<td>Increased [≥ 2 lines]</td>
<td>19(90%)</td>
<td>23(64%)</td>
<td>3(20%)</td>
</tr>
<tr>
<td>Unchanged</td>
<td>2(10%)</td>
<td>11(30%)</td>
<td>9(60%)</td>
</tr>
<tr>
<td>Deteriorated</td>
<td>–</td>
<td>2(6%)</td>
<td>3(20%)</td>
</tr>
</tbody>
</table>
Edema resolved completely 44 eyes (61%), decreased in 25 eyes (35%), the final visual acuity improved by 2 or more lines in 45 eyes (63%), remained unchanged in 22 eyes (31%), exacerbated after surgery in 5 eyes (7%), due to residual cystoid macular edema, massive macular hard exudates, and iatrogenic macular hole. Among eyes with visual acuity improvement by 2 or more lines (total 45 eyes) 37 eyes had duration of DME shorter than six months (15 eyes from group A, 19 eyes from group B, 3 eyes from group C) and 8 eyes had duration of DME longer than 6 months (4 eyes from group A, 4 eyes from group B). The average follow-up time was 14 months (range 6 - 27 months).

**Figure 13.**

A. Preoperative vitreomacular traction by the adherent posterior hyaloid following a partial posterior vitreous detachment results in retinal vascular leakage (B) in a patient with preoperative BCVA 0.1

C. 2 months after vitrectomy the BCVA was 0.8
Complications during surgery included:

- Peripheral retinal tear formation in one eye (1, 4%), could be treated by endolaser photocoagulation.
- Postoperatively easy vitreous haemorrhage was found in two eyes (2, 8%) and was resolved within 1 week.
- Cataract formation observed in two eyes (2, 8%).

We noticed that peeled ILM were thickened and showed great adherence to the retina, therefore theirs peeling was usually more difficult than in eyes with macular hole and takes more time because of its tendency to tear, specially in eyes with larger cysts. Among 11 eyes, that underwent ILM peeling, cyst rupture with formation of macular hole was documented in one eye (9%) with large cystoid spaces composed of thin inner retinal layer (Fig. 14). Required a fluid-gas (20% sulphur hexafluoride) exchange and the patient was asked to remain in a face- down position until gas absorption (14 days), then the iatrogenic macular hole was closed. Neither epiretinal membrane nor recurrence of the macular edema was documented.

**Figure 14.**

A. Preoperative large cystoid spaces composed of thin inner retinal layer

B. Postoperative decrease in the macular thickness and closure of the iatrogenic macular hole
4.2. SECOND STUDY

Ten patients (6 men and 4 women; 20 consecutive eyes), aged 45 to 62 years (average 56) made up the study population (Tab.3). The median duration of the edema was approximately 12.0 months (range 6-21 months) at the time of the surgery. The average follow-up time was 13.6 months (range 6 - 21 months). As diagnosed by biomicroscopic examination, sonography and OCT the posterior hyaloid was found to be attached in all eyes, but no taut, rigid membrane was found in any eye. OCT showed retinal swelling in all 20 eyes. An area of low reflectivity was mainly located in the outer retina. In addition to retinal swelling, cystoid spaces were observed in 18 of 20 eyes, and a serous retinal detachment in two eyes.
Table 3. Patient data

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<th>Patient Number</th>
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<th>Lens Status</th>
<th>Optical Coherence Tomographic Findings</th>
<th>Duration of Follow-up (Months)</th>
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<td>IOL</td>
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<td>M</td>
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<td>IOL</td>
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<td>Phakic</td>
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Eight (40%) eyes with proliferative diabetic retinopathy were treated preoperatively by panretinal laser photocoagulation and 12 (60%) eyes with non-proliferative diabetic retinopathy received focal laser therapy. All eyes were treated unsuccessfully preoperatively by focal macular laser; no grid laser was performed because of its limited beneficial effect in the treatment of diffuse or cystoid type of DME. Baseline BCVA and foveal thickness ranged, respectively, from 0.4 to 0.05 (mean 0.18) and 430 to 840 µm (mean 618) in eyes that underwent ILM peeling, 0.5 to 0.05 (mean 0.16) and 390 to 910 µm (mean 623 µm) in eyes without ILM peeling. There were no significant differences between the both groups in baseline BCVA (P = 0.4691, Wilcoxon Rank Sum Test) or foveal thickness (P = 0.8204, Wilcoxon Rank Sum Test). At six-months follow-up, mean BCVA improved significantly in both groups, from 0.18 to 0.33 (P = 0.0427, Wilcoxon Signed Rank Test) in eyes that underwent ILM peeling (Fig. 15) and from 0.16 to 0.25 (P = 0.0482, Wilcoxon Signed Rank Test) in eyes without ILM peeling. Mean foveal thickness decreased significantly from 618 to 265 (P = 0.0050) in eyes with ILM peeling and from 623 to 311 (P = 0.0050) in eyes without ILM peeling. Visual acuity improved by two or more lines in five eyes (50%) of each group (Tab.4). There were no significant differences in the improvement of BCVA and decreasing of foveal thickness between the both groups (Wilcoxon Rank Sum Test, P = 0.9083, P = 0.2720, respectively).
Figure 15. 1 week after vitrectomy with ILM peeling: The foveal thickness decreased from 560 µm to 220 µm; most cystoid spaces disappeared (note the cystoid spaces inside the circle before the surgery); the foveal depression was observed (note the circle after surgery); and the BCVA improved by 4 Snellen lines.
<table>
<thead>
<tr>
<th>No.</th>
<th>Macular Edema</th>
<th>Visual Acuity</th>
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<td>Eyes without ILM peeling</td>
</tr>
<tr>
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<td>Resolved</td>
<td>Resolved</td>
</tr>
<tr>
<td>2</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>3</td>
<td>Resolved</td>
<td>Resolved</td>
</tr>
<tr>
<td>4</td>
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<td>Decreased</td>
</tr>
<tr>
<td>5</td>
<td>Resolved</td>
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</tr>
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<td>7</td>
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<tr>
<td>8</td>
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</table>
Complications during surgery included peripheral retinal tear formation in one eye (5%) could be treated with laser photocoagulation and cyst broke during peeling ILM in one eye (5%) with formation of macular hole in a case with large cystoid spaces composed of thin inner retinal layer. Required a fluid-gas (20% sulphur hexafluoride) exchange and the patient was asked to remain in a face- down position until gas absorption. We noticed that peeled ILM were thickened and showed great adherence to the retina, therefore theirs peeling was usually more difficult than in eyes with macular hole and takes more time because of its tendency to tear, specially in cystoid macular edema with bigger cysts. Neither epiretinal membrane nor recurrence of the macular edema was found during the follow-up period.

4.3. THIRD STUDY

Thirty tow consecutive eyes of 32 patients with median age 59.54 years were included in the study. Eight (15 %) eyes with PDR were treated preoperatively by panretinal laser photocoagulation and 24 (75%) with NPDR received focal laser therapy. The mean baseline foveal thickness was 497.4 µm. The baseline BCVA ranged from 0.08 to 0.63 (mean 0.212). The mean follow-up time was 5.5 months (range 4 - 7 months). BCVA improved by ≥ 2 lines in 8 eyes (25%), stabilized in 20 eyes (62.5 %) and deteriorated in 4 eyes (12.5%). The foveal thickness decreased postoperatively in 23 eyes (71.8%) (Fig 16). Early postoperative complications included:

- Elevation of the intraocular pressure (< 35 mm Hg) in 7 eyes (21. 87%), all eyes could be treated by using local antiglaucoma medication within 1 month postoperatively.

- Retinal detachment in one eye required additional peripheral vitrectomy with fluid-gas (16 % C3F8) exchange.
Acute bacterial endophthalmitis (Staphylococcus epidermidis) in one eye required additional vitrectomy with intravitreal application of antibiotics and injection of silicon oil. During the follow-up period cataract formation was reported in 2 eyes.

Figure 16. A. Before surgery B. 1 week after vitrectomy and application of 4 mg of triamcinolone acetonide

4.4. FORTH STUDY

Four eyes with DME (DME group) and 2 eyes with idiopathic macular hole (MH group) were studied (Tab 5.) The DME group consisted of three men and one woman, with a mean age of 58.5 years (ranging from 52 to 65 years). The mean period from the diagnosis of DME to the surgery was 7.5 months. All eyes in the DME group were refractory to laser photocoagulation therapy performed at least 3 months before the surgery. The MH group consisted of one man and one woman with a mean age of 53 years. The both eyes were classified as stage 3 MH (Gass 1995). The mean period from detection of MH to ILM peeling was 3 months. In the ultrastructural examination, all surgical specimens were demonstrated to be ILM tissues. Transmission electron microscopy revealed ILM in the
both groups as a membrane with a smooth inner surface and an irregular undulating outer surface. The ILM in the both groups were composed of homogeneous electron-dense meshwork and these ultrastructural findings of the ILM correspond in shape to the lamina dense of basement membrane. The mean thickness (Tab. 6) of the peeled ILM was 3.77 µm (SD 0.71) in the DME group and 3.58 µm (SD 1.74) in the MH group. A few cellular elements seem to be macrophages were observed only on the vitreous side of ILM in the both groups. No structural or morphological differences of the specimens were observed between the two groups.

<table>
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<tr>
<th>Patient number</th>
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<th>Surgical diagnosis</th>
<th>Duration of DME or MH (months)</th>
<th>Mean Thickness of ILM in micrometers</th>
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Table 6. Evaluation of the mean thickness (+ SD) of the ILM (MS Excel predefined table served the final Arithmetic Mean+ SD evaluation).

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<th>ILM6</th>
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</tbody>
</table>
Figure 17. ILM removed from patient with DME, ILM thickness is 4.11 µm (SD 1.18).
Normal thickness of the ILM is about 0.5 µm (Williams and Warwick 1980).
**Figure 18.** ILM removed from patient with MH, ILM thickness is 4.4 µm (SD 1.8).

Normal thickness of the ILM 0.5 µm (Williams and Warwick 1980)
Many systemic abnormalities may affect macular thickness (Bresnick 1986, Stratton et al. 2001); therefore the treatment of DME includes medical control of these systemic abnormalities. Patients should achieve excellent glycemic control, normalize blood pressure, improve cardiac and renal status, and reduce serum lipids.

The ETDRS has shown that focal laser photocoagulation of leaking circumscribed retinal areas in eyes with focal DME is therapeutically useful to improve visual outcome (ETDRS 1985). Laser treatment is still take a place in many clinics as the first choice of treatment for DME as it is safety and less invasive that other surgical options. In eyes with diffuse DME, however laser treatment cannot be focused on localized retinal leakage spots since the entire macula is involved. Diffuse DME is, therefore, much less responsive to macular laser coagulation than focal DME (Olk 1986, Lee et Olk 1991). Laser photocoagulation therapy is beneficial in reducing the risk of moderate visual loss by 50% for patients with clinical significant DME at 3 years (ETDRS 1985). Laser therapy, however, is much less effective in improving the visual acuity. In the ETDRS, which excluded eyes with less than 20/200 presenting visual acuity, the improvement rate was below 3%, and 12% eyes had significant visual loss at 3 years (ETDRS 1985, ETDRS 1995). Furthermore, 24% of immediately treated eyes had thickening involving the center of the macula at 36 months. This suggests a distinct subgroup of eyes exist with DME resistant to conventional laser therapy. Recommendation for grid laser photocoagulation treatment covering the whole macular region with a fine net of small laser coagulation spots has been controversial since no large randomized prospective studies providing the efficacy of this treatment have been published (McDonald and Schutz 1985, Olk 1986, Lee and Olk 1991, Degenring et al. 2004). Lee and Olk showed limited benefit of modified grid laser photocoagulation for DME, with 60.9% of eyes unchanged and 24.6% of eyes worse
in 3 years (Lee and Olk 1991). Several reports showed no statistically benefit from laser treatment versus natural history, or the early effects of grid laser disappeared by the end of the 3rd year (Blankenship 1979, Park et al. 1997, Hykin et al. 1998). All eyes with DME in our studies were treated preoperatively with macular laser photocoagulation, with no marked resolution of macular edema or improvement of the BCVA.

The mechanisms of the effect of vitrectomy for DME have not been well understood. Since 1990, several authors have reported favourable anatomical and satisfactory functional results in-patients with DME undergoing vitrectomy combined with removal of the posterior hyaloid and premacular hyaloid –associated traction forces. To date, it is not clear whether traction primary causes DME or whether vitreous changes caused by DR have led to a secondary phenomenon of macular traction with exacerbation of DME (Lewis et al. 1992). Current evidence suggested that the vitreous could be implicated in the development or exacerbation of DME through several mechanical and physiologic mechanisms, all of which stem from the increased retinal vascular permeability caused by VEGF. This breakdown of the blood-retinal barrier could lead to a high concentration of intravitreal serum-derived chemoattractants, providing a stimulus for cellular migration into the attached premacular posterior hyaloid. Cellular contraction could lead to tangential traction and the development or exacerbation of DME and/or the development of a shallow macular detachment (Jumber et al. 2000). Sebag and associates (Sebag et al. 1984, Sebag et al. 1992, Sebag 1996) have found enzyme-mediated vitreous cross-linking and nonenzymatic glycation in the diabetic vitreous, and they have suggested that the abnormal cross-linking might affect the collagen structure and destabilize the attached vitreous gel, including macular traction. In addition to this mechanical effect, the cellular component in the attached posterior hyaloid could produce growth factors capable of inducing vasopermeability (Jumber et al. 2000). Another possible explanation for the vitreous
involvement in DME is that the breakdown of the blood-retinal barrier results in the presence of growth factors in the vitreous cavity, which in the presence of an abnormal attached premacular posterior hyaloid, could concentrate in the macular region and induce or exacerbate the DME. Based on these findings, vitrectomy with separation and removal of the attached posterior hyaloid and vitreous gel theoretically could benefit these patients. Other investigators have reported that vitrectomy may be useful, even in the absence of obvious posterior hyaloid anomalies (Tachi et al. 1996, Ikeda et al. 1999, Ikeda et al. 2000, La Heij et al. 2001, Otani et al. 2000, Yamamoto et al. 2001, Aboutable et al. 2005) and even when the posterior hyaloid was detached from the posterior pole (Ikeda et al. 2000). Several explanations have been suggested for postvitrectomy improvement of DME in the absence of vitreomacular traction. The vitreous may act as a potential reservoir of inflammatory substances or growth factors such as vascular endothelial growth factor, which promotes vascular permeability (Aiello 1997), and its removal by vitrectomy may improve DME. Another possible explanation is that vitrectomy may improve oxygenation of the retina (Stefansson et al. 1990). The results of our first study (the vitrectomy study) support the effectiveness of vitrectomy in resolving DME as first reported by Lewis et al. in 1992 and later studies by others (Tab. 7). We found that vitrectomy may be effective also in eyes without clinical evidence of traction by a thickened posterior hyaloid membrane and eyes with posterior hyaloid detachment. We found that vitrectomy may help in reducing the DME in majority of eyes. This however, is not always associated with VA improvement. Vitrectomy for DME seems to be more effective than traditional management of observation or further therapy by laser photocoagulation. In this study better outcomes were achieved in eyes with evident vitreomacular traction and with short duration of the edema. In agreement with earlier study by Harbour et al. (Harbour et al. 1996) we found that a shorter time interval from initial diagnosis of macular oedema to
vitrectomy may be associated with a better visual outcome. This discrepancy between anatomic and functional results may relate to irreversible destructive changes of the macula due to long-standing DME on the retinal layers (Gass 1987). This may suggest that early surgical intervention may improve the chances of visual recovery when performed before the occurrence of severe visual loss, therefore optimal timing of the surgery seems to be important. These surgical results have made us considerably reduce the use of laser photocoagulation for DME and decide for earlier intervention in selective cases. One has to keep in mind that the exact duration of DME is some times difficult to establish; therefore cooperation between the referring ophthalmologists and referral clinics is important to establish the onset of the visual deterioration.

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of eyes</th>
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<th>Follow-up (months)</th>
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<td>6(60)</td>
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<td>19(86)</td>
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<td>10(47)</td>
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<td>10(100)</td>
<td>6(60)</td>
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<td>69(96)</td>
<td>45(63)</td>
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The primary results of our first study were presented at the X. Annual Meeting of the Czech Society of Ophthalmology in Hradec Králové (2003), and the final results were
presented at the 102nd Annual Meeting of the German Society of Ophthalmology in Berlin (September 2004) and have been published in Klin Monatsbl Augenheilkd. 2005 Aug; 222(8): 643-8.

The innermost layer of the retina, the ILM, is composed in part of type IV collagen and its normal thickness is about 0.5 µm (Williams and Warwick 1980). This transparent structure rests on a bed of Müller cell footplates that in turn form a contiguous montage, separating the ILM from the nerve fibre layer (Williams and Warwick 1980, Kuhn 2002). The ILM received virtually no clinical attention until vitrectomy removal of epimacular proliferation became routine in the 1980s and ILM fragments were often identified in surgical specimens. The controversial issue of intentional ILM peeling first emerged in the early 1990s, following Gass’ theory of macular hole pathogenesis (Gass 1988) and coinciding with the advent of MH surgery (Kelly et al. 1991). In 1990, Morris et al. reported the first cases of intentional ILM removal (Morris et al. 1990). In patients with Terson’s syndrome and sub-ILM macular haemorrhage, they removed both the blood and the detached ILM. The patients in this pilot study were followed-up for 8 years and the authors documented that, 83% of eyes reached ≥20/25 vision without clinically visible surface re/proliferation (Morris et al 1997). Based on this experience, they suggested that ILM removal be considered for all forms of traction maculopathy (Morris et al. 1994). First study about the possible role of ILM peeling for DME reported resolution of the DME after surgery in 12 eyes. In this study however, a thickened posterior hyaloid membrane was removal in the same session in 10 of the 12 eyes (Gandorfer et al. 2000), and therefore no useful conclusion on the effectiveness of ILM peeling alone can be drawn from this study. ILM peeling has been reported incidentally in 75% of epiretinal membrane specimens studied by transmission electron microscopy (Smiddy et al. 1989). ILM peeling in MH surgery did not seem to affect visual acuity adversely, despite the fact that Müller cell
footplates must sustain some degree of injury with ILM removal (Smiddy et al. 2001). However, Sivalingam an associates, in their clinicopathologic (light microscopy) correlative study, did find a poorer visual prognosis in cases with large scrolls of ILM in the specimen (Sivalingam et al. 1990). Objective, quantitative studies of retinal function after ILM removal have not been performed. How additional ILM peeling may reduce DME is unclear. The discussed mechanisms are complete releasing of the tractional forces on the macula and inhabitation of reproliferation of fibrous astrocyts (Gandorfer et al. 2000, Radetzky et al. 2004) by removing the template (the ILM) on which the glial tissue proliferates and contracts. Histopathologic studies in MH surgery have supported the supposition that redirection of glial proliferation is the mechanism by which macular hole closure is effected (Funta et al. 1992, Madreperla et al. 1994, Rosa et al. 1996). Indeed, because ILM is composed of the footplates of Müller cell, we suggest that shearing the cells may injure the cells and thus represent the specific stimulus for glial proliferation, which may play a role in reducing the macular edema and causing resynapses between the bipolar cells and the ganglion cells in the inner plexiform layer. In agreement with Avci and associated (Avci et al. 2004) in our histopathologic study there was no significant difference in the structure or the thickness of the ILM peeled from patients with DME and thus peeled from patients with MH. But ILM from the both groups were significantly thickened than the normal ILM. However, Tano (Tano 2000) has reported that ILM taken from DME cases were indeed almost twice as thick as the ILM taken from MH cases; therefore it was suggested that abnormally thickened ILM might play a role as a diffusion barrier for the vitreous cytokines such as vascular endothelial growth factor and others leading to capillary permeability disturbance (Connolly 1991, Collins et al. 1993, Miller et al. 1994, Hofman et al. 2001). It was suggested that ILM peeling dose not influence the pathophysiological changes such as growth factor expression or altered fluid dynamics but
it is much more likely that ILM peeling merely reduces the diffusion barrier towards the vitreous and thus is more efficient in patients with preexisting interface alterations. The improvement after surgery is just as likely to be attributable to the vitrectomy as to the ILM peeling (Radetzky et al. 2004). To date little has been published on ILM peeling for DME. Some investigators provided ILM peeling generally in cases with DME (Gandorfer et al. 2000, Avci et al. 2004, Dillinger et al. 2004, Kuhn et al. 2004), others only in eyes that showed visible epimacular proliferation and cellophane maculopathy (La Heij et al. 2001, Aboutable et al. 2005). Some investigators reported on resolution of macular edema and improvement of VA (Avci et al. 2004, Dillinger et al. 2004, Kuhn et al. 2004), others found that the ILM peeling accelerates the absorption of edema in more severe diabetic cases, without any improvement of VA (Kumagai et al. 2002). In a recent retrospective study DME resolved and VA improved in eyes after vitrectomy without ILM peeling in 44, 4% and in 69, 1% of eyes that underwent vitrectomy with ILM peeling (Stefaniotou et al.).

Previous studies about ILM peeling for DME were not controlled and no firm conclusions can be drawn, whether ILM peeling for DME should be indicated generally as a standard surgical procedure or selectively in eyes with visible epimacular proliferation and cellophane maculopathy.

Our second study (the ILM peeling study) is certainly limited by the small number of patients included. However, this is the first controlled study of ILM peeling for DME without evident epimacular proliferation or cellophane maculopathy. Systemic conditions such as glycaemia, blood pressure and nephropathy differ in each case and may affect the surgery results. Because we used in the second study the fellow eyes as controls it was not necessary to consider the difference of individual systemic condition. The findings of the current study demonstrated that in eyes with persistent DME without evident epimacular proliferation vitrectomy without ILM peeling was as effective in reducing the foveal
thickness and improving the visual acuity as vitrectomy with ILM peeling. There were no significant differences in the improvement of BCVA and decreasing of foveal thickness between the both groups, a finding not reported before. We conclude that peeling of the ILM is not essential for anatomic and visual success in DME surgery. Our results of the second study were presented at the 15th Congress of the European Society of Ophthalmology and 103rd Annual Meeting of the German Society of Ophthalmology in September 2005 in Berlin, at the 5th Meeting of the Czech Vitreoretinal Society in November 2005 in Prague, and accepted for publication in Klin Monatsbl Augenheilkd.

Shortly after the presentation of our results in Berlin, Yamamoto and associates (Yamamoto et al. 2005) published the results of their prospective, controlled study about ILM peeling for DME and concluded that ILM need not to be removed to treat eyes with ILM. Yamamoto’s results support the findings of our pilot controlled study.

In MH surgery, ILM peeling has been proven to be a feasible and safe procedure that provides favourable anatomical and functional results (Brooks 2000). ILM peeling in eyes with DME, compared to eyes with macular hole was more difficult; ILM was more adherent to the retina especially in eyes with larger cysts. Cyst rupture during ILM peeling with formation of iatrogenic macular hole is a serious complication, which should be included in the list of the complications of ILM peeling in eyes with fragile edematous retina; therefore maximal attention should be paid for ILM peeling in these conditions.

The intraoperative application of dye provides a stark contrast between the unstained retina and the stained ILM. Therefore, indocyanine green (ICG) or trypan blue staining facilitates and accelerates ILM peeling. However, the potential toxic effect of ICG dye applied directly to the vitreous cavity is controversial. While some authors reported morphological and functional damage of the retina in rat eyes (Enaida et al. 2002) or visual field defects (Haritoglou et al. 2003) after intravitreous ICG staining. Recently, concerns
have been raised about the possible cytotoxic and phototoxic effects of ICG to the retinal pigment epithelial cells (Engelbrecht et al. 2002). Other investigators found no negative impact of ICG on retinal function in macular hole surgery (Weinberger et al. 2001). It was suggested that the toxicity is may related to the concentration and duration of tissue contact of the ICG dye (Enaida et al. 2002, Gandorfer et al. 2001, Sippy et al. 2001). Therefore it is necessary for all surgeons to remain carefully the risks and benefits of the dye. From our point of view, we suggest that ICG should be carefully used until it has been shown that its intraoperative application is really safe and leads to comparable good results as those achieved by ILM peeling with another dyes.

The choice of the anaesthesia for DME surgery is based on many factors such as the renal and cardiac status of the patient, the patient’s preference and the anaesthesiologist’s skill. Although general anaesthesia offers improved airway management, patient comfort and control of eye and head movements, we prefer performing this surgery under local anaesthesia with monitored care by an anaesthesiologist. The benefits of this approach are decreased cardiovascular morbidity; reduce recovery time and shorter operating times. We found it important to ask the anaesthesiologist to keep the patient ‘light’. This usually prevents the patient from awakening with a jolt, which is often seen with deeper forms of anaesthesia. This also makes the surgeon fell more comfortable and safe during performing fine surgical techniques like ILM peeling.

Several complications have been reported after vitrectomy with or without ILM peeling. These complications included:

- The appearance of a dissociated optic nerve fiber layer characterized by numerous arcuate striae within the posterior pole described by Tadayoni et al. (Tadayoni et al. 2001), the retina along the course of optic nerve fibers was slightly darker than the surrounding retina on blue-filter photographs. They reported that this appearance was detected in 43%
of eyes that had undergone epiretinal membrane peeling and was also observed after ILM peeling during macular hole surgery. Although the pathogenesis of this phenomenon is not known, they suggested that it could be due to permanent damage to the Müller cells.

- Intraoperative retinal tears and postoperative rhegmatogenous retinal detachment (Tachi et al. 1996, Gandorfer et al. 2000, Lewis et al.1992). This complication has been documented in one case from our third study. Creating of posterior vitreous detachment can be associated with peripheral retinal tears; therefore we found controlling the retinal periphery by scleral indentation at the end of vitrectomy very important. Using the exocryocoagulation or endolaser photocoagulation the iatrogenic tears can be successfully treated.
- Neovascular glaucoma (Tachi et al. 1996).
- Macular ischemia (Harbour et al. 1996).
- A lamellar macular hole associated with vitrectomy and removal of an epiretinal membrane without ILM peeling (Yamamoto et al. 2003).
- A cyst rupture with an iatrogenic macular hole associated with ILM peeling was documented in a case with large cystoid spaces (Yoon et al. 2003). This serious complication has been reported also in our first and second studies in two cases with large cystoid spaces composed of thin inner retinal layer. Required a fluid-gas (20% sulphur hexafluoride) exchange and the patient was asked to remain in a face- down position until gas absorption. We found that the performing of the ILM peeling in such cases include a high risk of cyst rupture, therefore ILM peeling showed be indicated very carefully. Generaly, in all eyes with cystoid DME extreme caution should be paid during ILM peeling to avoid cyst rupture and iatrogenic macular hole.
• Pendergast et al. observed postoperative epiretinal formation after removal of posterior hyaloid without ILM peeling for DME in 6 of 59 eyes (Pendergast et al. 2000); also Tachi (Tachi et al. 1996) reported this postoperatively complication in 6 from 58 eyes. This complication was not observed in the study by Gandorfer et al. (Gandorfer et al. 2000) after additional ILM peeling.
• Pendergast et al. reported recurrence of DME after ILM peeling in 3 of 55 eyes (Pendergast et al. 2000). In our first and second studies neither epiretinal membrane nor recurrence of the DME was reported during the follow-up period.

TA is a corticosteroid suspension that has been used locally as a periocular injection for the treatment of cystoid macular edema secondary to uveitis or as a result of intraocular surgery (Stern et al. 1981, Suckling et al. 1988). Intravitreal corticosteroids have also been tried experimentally in the prevention or treatment of proliferative vitreoretinopathy (Tano et al. 1980, Jonas et al. 2000), retinal neovascularization (Antoszyk et al. 1993, Danis et al. 1996), and choroidal neovascularization (Challa et al. 1998, Danis et al. 2000). After injection of IVT, the drug is delivered rapidly to its site of action with maximal bioavailability. Animal studies have shown that the intravitreally injected suspension maintains a depot lasting 21 to 41 days (Schindler et al. 1982, Scholes et al. 1985). In addition, TA has vitreous half-life of 1.6 days compared with 2.5 hours for dexamethasone, a glucocorticoid (Scholes et al. 1985). The mechanism of corticosteroid action on this complication of diabetic microangiopathy remains unclear. It is not specific to diabetic microangiopathy, because IVT is also effective for macular edema secondary to uveitis, venous occlusion, and cataract surgery (Antcliff et al. 2001, Greenberg et al. 2002, Jonas et al. 2002, Benhamou et al. 2003). Wilson and associates (Wilson et al. 1992) reported that TA has been shown experimentally to reduce breakdown of blood-retinal barrier. The role of corticosteroids in the treatment of macular edema might be based primarily on their
inhibition of the biosynthetic pathways of leukotrienes and prostaglandins, the inflammatory mediators implicated in the pathogenesis of CSME (Hood et al. 1999). Corticosteroids inhibit the expression of inflammatory adhesion molecules and contribute to stabilization of the blood-retinal barrier (Penfold et al. 2000, Osaki et al. 2002). Corticosteroids inhibit expression of VEGF gene in human vascular smooth muscle cells (Nauck et al. 1998). Corticosteroids have also been shown to abolish the induction of VEGF by platelet-derived growth factor and platelet-activating factor in a time- and dose-dependent manner (Nauck et al. 1997). Antonetti and associates (Antonetti et al. 2002) suggested that corticosteroids might reduce retinal capillary permeability by increasing the activity and/or density of the tight junctions in the retinal capillary endothelium. Fisher and associates (Fisher et al. 2001) also suggested that corticosteroids might inhibit the metabolic pathway of VEGF, but this has never been documented in the eye. Jonas and associates (Jonas et al. 2005) suspect that the crystals of TA due to their weight may lead to a posterior vitreous detachment if the vitreous was not already detached prior to the injection. The advantage of a posterior vitreous detachment in patients with DR may be a reduction of DME as achieved by pars plana vitrectomy.

Recent studies have suggested that IVT injection may be effective in reducing the DME and improving the BCVA (Degenring et al. 2004, Jonas et al. 2001, Jonas et al. 2003, Martidis et al. 2002, Massin et al. 2004) Interestingly, TA has not been found in clinically significant concentrations in serum shortly after intravitreal injections of about 20 mg TA, suggesting that major systemic side-effects may not be very probable (Degenring and Jonas 2004). It agrees with clinically observations that the metabolic control of patients with DM is not markedly influenced by the intraocular application of the steroid. TA as a treatment option for DME can be given in many forms: IVT injection, subtenon injection, and in combination with vitrectomy as an adjunctive procedure as in our third study.
In a prospective, noncomparative, interventional case series, Martidis and associates (Martidis et al. 2001) treated 16 eyes with injection of 4 mg of IVT for refractory DME. They found a mean improvement in BCVA of 2.4, 2.4, and 1.3 Snellen lines at the 1-, 3-, and 6-month follow-up intervals, respectively. The central macular thickness as measured by OCT decreased by 55%, 57.5%, and 38%, respectively, over these same intervals from an initial pretreatment mean of 540.3µm. Intraocular pressure elevation of >21 mmHg was noted in 36% of eyes. Retreatment was required in 37.5% of eyes after 6 months.

Jonas and associates (Jonas et al. 2000, Jonas et al. 2003) studied 26 eyes injected with 25 mg of IVT for diffuse DME. They showed that mean visual acuity improved significantly during the follow-up and 81% of eyes with a follow-up of ≥ 1 month had improved visual acuity. BCVA did not change significantly in their control group. Intraocular pressure increased significantly and then decreased significantly at the 5-months follow-up.

Chieh and associates (Chieh et al. 2005) studied in a retrospective, interventional, clinical case series 210 eyes who received an injection of 4 mg IVT for diffuse DME. They found that IVT was effective in improving BCVA in 39%, 41%, and 43% of patients at 1, 3, and 6 months, respectively. Although the number of eyes improving by 2 lines of Snellen vision acuity increased from 3 to 6 months, the median BCVA decreased from 3 to 6 months. Complications included culture-negative sterile endophthalmitis in six cases and cataract formation in five eyes. Repeated IVT injection was performed on 19% of eyes to address recurrent DME. Mean retreatment period was 5.3 months, suggesting that the duration of the IVT effect was from about 3 to 6 months.

Massin and associates (Massin el a. 2004) included in their comparative study 15 consecutive patients with bilateral DME unresponsive to laser photocoagulation therapy. All patients received a unilateral intravitreal injection of about 4 mg TA. They detected a significant reduction in macular thickness and slight, however not statistically significant,
increase in BCVA in the injected eyes compared with the contralateral eyes without IVT injection. In this study the duration of a reduction of the macular thickness as measured by OCT was less than 6 months. At the end of the fellow-up, visual acuity measurements returned to the baseline values with no significant difference between baseline values and the measurements obtained at the end of the fellow-up. In 6 of the 12 injected eyes, intraocular pressure exceeded 25 mmHg, and was controlled by topical medication.

In a recent, comparative study by Jonas and associates (Jonas et al. 2005) 25 consecutive patients with bilateral DME were injected with unilateral intravitreal injection of 20 mg TA. BCVA increased significantly in 92% of the injected eyes and remained unchanged in the contralateral eyes at any of the re-examinations during follow-up. In an intra-individual inter-eye comparison, gain in BCVA was significantly higher in the injected eyes, for the measurements obtained up to 4 months after baseline. In the injected eyes, from a peak in BCVA at about 2 to 6 months after the injection, BCVA decreased significantly towards the end of the follow-up, at which, BCVA was still higher, however not significantly higher, than at baseline. In the contralateral eyes, BCVA at the end of the follow-up was lower; however not significantly lower than at baseline. The increase in BCVA was most marked for the first 3-6 months after IVT injection and was observed for a period of about 6 to 9 months. Avci and associates (Avci et al. 2006) studied in a recent prospective, interventional consecutive case series study consisted of 59 eyes with chronic DME, which received a 4 mg IVT injection. All patients completed at least 6 months follow up. The mean BCVA improved significantly at the third postinjection month. However, the macular oedema reached the pretreatment level in 29 (49%) of the eyes at 6 months and 15 of 21 eyes (71%) at 9 months after injection.

In the light of the previous studies, IVT injection seems to be effective in reducing the DME and improving the BCVA in some cases, however the effect might be short term and
the reinjection might be required in many cases, and furthermore the IVT injection is not risk free procedure. In our study we did not apply the TA in an injection form; we applied it at the end of vitrectomy as an adjuvant potential treatment hopefully reaching the positive effect of both, the vitrectomy and the steroid.

The factors, which may influence change in BCVA after IVT injection as a treatment for DME, were studied by Jonas and associates (Jonas et al. 2005). They concluded that improvement of BCVA after the injection of IVT was significantly and negatively correlated with an increase degree of macular ischemia, higher preoperative BCVA, and grid laser treatment of the macula prior to inclusion into the study. Improvement in BCVA was significantly and positively correlated with an increase in intraocular pressure. Change in BCVA after the IVT injection was statistically independent of age, gender, and pseudophakia. The increase of BCVA was more pronounced in eyes in which a macular grid laser treatment had not been performed prior to inclusion into the study than in eyes with preceding macular grid laser coagulation. Spandau and associates (Spandau et. al 2005) studied in a recent randomized prospective study the dosage dependency of IVT injection as a treatment for DME. They found that maximal increase in BCVA was significantly correlated with the dosage of IVT injection. Additionally, the duration of the effect of IVT injection increased significantly with the dosage of IVT injection. Increased in intraocular pressure during follow-up was statistically not significantly associated with the dosage used. They concluded that treatment response may last longer and be more pronounced with a dosage of 13 mg TA than in lower doses of 5 mg or 2 mg. TA induced increase in intraocular pressure may not be markedly associated with the dosage used.

When we started our third study, at the beginning of 2005, most of the available studies used dosage of 4 mg of TA and we also preferred to use this dosage suggesting that 4 mg may hopefully carry out less side effects and potential complications than higher dosage.
Khairallah and associates (Khairallah et al. 2005) evaluated in a prospective, noncomparative recent study the efficacy of IVT injection as a primary treatment for DME with massive macular hard exudates involving the fovea without previous laser treatment. They reported that BCVA improved significantly at examinations performed 7 days, 1 month, 3 months, and 6 months after the injection. Foveal hard exudates resolved completely in 50% and partially in 50% of the injected eyes. They concluded that IVT injection appears to be beneficial for reducing massive hard exudates and improving BCVA in patients with DME. The absorption of the hard exudates was not studied systematically in our third study; however, our clinical observation is in agreement with the previous study. We noticed that IVT helps in resolving hard exudates in some cases.

Also Ciardella and associates (Ciardella et al. 2004) found that IVT is effective in improving BCVA, reducing macular thickness, and inducing reabsorption of hard exudates.

Recently growing evidence is indicating the usefulness of the transscleral pathway in delivering drugs to the retina (Geroski and Edelhauser 2001). Routine use of TA injected into the sub-tenon’s capsule for treatment of various inflammatory eye diseases (Helm and Holland 1995, Lafranco et al. 1999, Zamir et al. 2002) encourages additional research to also clarify its potential for the treatment of DME. This approach is less invasive and may allow feasible route for delivering therapeutic quantities of TA to the retina. In our department we don’t have yet experience with this type of application of TA; however for our interest we review the recent studies about it. In a recent, prospective, double-masked, randomized controlled trial, Cardillo and associates (Cardillo et al. 2005) investigate the therapeutic response and ocular tolerance of a single intravitreal injection of 4-mg TA in comparison with a single posterior sub-tenon injection of 40-mg TA for the treatment of diffuse DME. They found that both intravitreal and sub-tenon injections of TA result in a
significant but transit improvements in central macular thickness. The mean central macular thickness in eyes with intravitreal injection was significantly thinner than in the sub-tenon injected eyes at 1 month and 3 months after the TA injection. The mean BCVA in the intravitreally injected eyes was significantly better than in the sub-Tenon’s- injected eyes at 3 months after injection. Intraocular pressure did not show any significant difference between the 2 forms of TA delivery at any follow-up visit, and no eyes had >25 mmHg. Conversely, Inoue and associates (Inoue et al. 2004) have recently demonstrated that the sub-tenon route of TA administration is not feasible to achieve IVT therapeutic levels. The accurate placement of corticosteroids in the sub-tenon’s space, in direct proximity to the macula, may influence both the effectiveness and the side effects of the drug (Freeman et al. 1987, Mueller et al. 1998). In a recent double-masked, placebo-controlled trial, Entezari and associates (Entezari et al. 2005) evaluated the effect of posterior sub-tenon injection of TA in patients with diffuse DME. Treated eyes received 40 mg posterior sub-tenon injection of TA and the placebo group received subconjunctival injection of a placebo. The injections were repeated after 2 months in both groups. They found that no statistically significant differences in the macular thickness, in the amount of hard exudates, in the size foveal avascular zone, or in the leakage severity in the angiograms were detected between the eyes injected with TA and those injected with placebo. They concluded that two injections of posterior sub-tenon TA had no therapeutic effect on refractory DME.

In the light of the previous studies, TA injected into the sub-tenon’s capsule for treatment DME of is less invasive that IVT and may allow feasible route for delivering therapeutic quantities of TA to the retina; however the potential positive effect have not been evidently proven yet. Jonas and associates (Jonas et al. 2001) studied in a prospective study the clinical outcome and complications of TA as an adjunctive procedure in patients
undergoing pars plana vitrectomy for treatment of complicated PDR. They suggested that IVT injection (15 to 20 mg) with most of the vehicle removed seems to be well tolerated by eyes undergoing vitrectomy for PDR. They documented a pseudohypopyon consisting of TA crystals in the inferior anterior chamber angle detected in one patient and resolved spontaneously within 4 days. Again Jonas and associates in more recent study (Jonas et al. 2003) reported their results about IVT as an additional tool in vitrectomy for PDR. They found that eyes that underwent vitrectomy with application of IVT compared with the nonrandomized controlled group without IVT did not show a higher than usual rate of postoperative complications.

Although, the safety of IVT has been supported by results of prior animal studies and some human trials (McCuen et al. 1981, Hida et al. 1986, Kivilcim et al. 2000, Young et al. 2001), many side-effects and complications related to the therapy have been reported. The potential complications of IVT may be injection related or from the effect of corticosteroid suspension. One of the most common side-effects of IVT is the steroid-induced elevation of intraocular pressure (Wingate and Beaumont 1999, Martidis et al. 2002, Bakri and Beer 2003, Jonas et al. 2003, Janet et al. 2003, Jonas et al. 2003, Jonas et al.2004, Spandau et al. 2005). Diagnosis of DM or presence of CSME did not influence the reaction of intraocular pressure after the injection (Jonas et al. 2005). It may agree with previous randomized clinical trials in which DM was not a major risk factor for glaucoma (Palmberg 2001).

Jonas and associates (Jonas et al. 2004) reported that IVT injection of approximately 20 mg of TA can increase intraocular pressure beyond 21 mmHg in up to 40% of patients, and that in most patients, the TA-induced rise in intraocular pressure can be treated topically, except approximately 1% of patients who must undergo filtering surgery. Many of these eyes showed ophthalmoscopically visible TA crystals in the vitreous for a similar period as the increase in intraocular pressure lasted. They suggested that when the TA have resolved,
intraocular pressure may return to its baseline level, and that the TA induced increase in intraocular pressure is reversible. It agrees with previous studies on reaction of intraocular pressure after topical application of corticosteroids (Becker et al. 1966). Patients who received a second IVT injection of 20 to 25 mg showed a similar reaction of intraocular pressure as after the first injection (Jonas et al. 2004). It suggested that if after a first injection, intraocular pressure remained in the normal range, it may also remain in the normal range after the second injection. Previous comparing studies using different dosages of IVT injection may suggest that the higher the dosage is, the longer is the duration of secondary ocular hypertension (Wingate and Beaumont 1999, Bakri and Beer 2003, Jonas et al. 2003, Jonas et al. 2004). The figures of the frequency of secondary ocular hypertension may not directly be correlated with the dosage injected (Spandau et al. 2005). In our third study we documented elevation of the intraocular pressure (< 35 mm Hg) in 7 eyes (21.87%); all eyes could be treated by using local antiglaucoma medication.

Infectious, sterile and pseudo endophthalmitis after IVT injection have been reported in many recent trials (Benz et al. 2003, Jonas et al. 2003, Sakamoto et al. 2004, Moshfeghi et al. 2004, Moshfeghi et al. 2005, Kreissig et al. 2006). Kreissig and associates (Kreissig et al. 2006) studied, in a prospective interventional study included 645 eyes, treated with approximately 20 mg intravitreal TA, the IVT complication of infectious and sterile endophthalmitis. After removal of the vehicle the IVT injections were performed under sterile conditions. A total of 97 eyes received a second TA injection, 13 a third, 1 a fourth, 2 a fifth, and 1 a sixth injection. In the 1st week after 759 TA injections, 758 resulted in no hypopyon or Tyndall phenomenon >2+, but in one eye a pseudoendophthalmitis with hypopyon was present. Anterior chamber lavage demonstrated TA crystals, and the culture was negative. In the 2nd week, one patient developed infectious endophthalmitis after a fall had caused ocular perforation. In a multicenter study, Sakamoto and associates
(Sakamoto et al. 2004) evaluate the incidence of acute endophthalmitis after TA assisted pars plana vitrectomy. Of total 1,886 cases only one case showed acute endophthalmitis due to Staphylococcus epidermidis (0.053%) and concluded that intraoperative use of TA during vitrectomy is not a high risk factor for acute endophthalmitis. Yamashita and associates (Yamashita et al. 2004) reported a case of weak endophthalmitis (Staphylococcus epidermidis) after TA-assisted vitrectomy. Four days after surgery, endophthalmitis associated with anterior chamber hypopyon was noticed, the patient’s vision had deteriorated to hand motion. In the spite of severe cell infiltration, the ciliary injection and ocular pain were not significant. Additional vitrectomy with irrigation of antibiotics was performed, and then the endophthalmitis was soon resolved. On the other hand Jonas and Bleyl (Jonas and Bleyl 2004) reported that some eyes with endophthalmitis after IVT show a marked destruction of the whole globe. The most striking histologically finding can be that some areas show a massive infiltration by granulocytes, while other areas can be almost completely devoid of inflammatory cells (Jonas and Bleyl 2004). As a steroid, TA may inhibit the immigration of the inflammatory cells into those areas in which the TA crystals are present, which may be paralleled by the clinical observation that patients with infectious endophthalmitis after an IVT injection usually show almost no pain which is rather uncommon for infectious endophthalmitis in eyes without intraocular steroids (Nelson et al. 2003). Sterile endophthalmitis after IVT injection have been reported (Nelson et al. 2003, Parke 2003, Roth et al. 2003). It was suggested that it could be related to the solvent agent. Jonas and associates (Jonas et al. 2000), Sutter and Gillies (Sutter and Gillies 2003), and Kreissig and associates (Kreissig et al. 2006) documented cases with pseudo-endophthalmitis after IVT injection. If TA crystals are washed from the vitreous cavity into the anterior chamber, they deposit down in the inferior anterior chamber angle mimicking a hypopyon, which is difficult to differentiate from the painless
hypopyon caused by a post-injection infectious endophthalmitis. Using high magnification slit lamp biomicroscopy may reveal the crystalline structure of TA. They have reported that TA crystals in the anterior chamber usually disappear spontaneously and may not need to be removed. In our third study we documented acute bacterial endophthalmitis (Staphylococcus epidermidis) in 1/32 (3.1%) eye required additional vitrectomy with intravitreal application of antibiotics and injection of silicon oil.

TA injected into the vitreous cavity may lead to de-arrangement of the structure of the vitreous body, which may exerts traction on the retina leading to a rhegmatogenous retinal detachment. If TA is injected during vitrectomy and rhegmatogenous retinal detachment occurred after the surgery, it is more likely that retinal detachment is related to the vitrectomy not to the TA. In a recent study on 348 eyes receiving 20 mg TA none of the eyes developed rhegmatogenous retinal detachment or retinal lesions (Jonas et al. 2004). In our third study we documented retinal detachment in 1/32 (3.1%) required additional peripheral vitrectomy with fluid-gas (16 % C3F8) exchange.

Jonas and associates (Jonas et al. 2005) reported that in elderly patients, 20 mg IVT injection leads to clinically significant cataract in about 15% to 20% of eyes within about one year after the injection. If TA injected at the end of vitrectomy, cataract formation could be related to the both procedures, IVT and the vitrectomy. In our third study we documented cataract formation in 2/32 (6.25%) eyes during the fellow-up period (mean 5.5 months). These results suggest that IVT injected at the end of vitrectomy may induce cataract formation in fewer cases than only IVT injection without vitrectomy. The rate of cataract formation in our study was small compared to Jonas’s study but this might be related also to the shorter follow-up period in our study.

IVT seems a promising treatment for refractory diffuse DME, but further studies are required to demonstrate strong evidence about its efficacy and safety.
relapse may justify retreatment, whose tolerance and frequency will also have to be evaluated. IVT injected into the eye at the end of vitrectomy may be effective in reducing DME, however includes some risks related to the corticosteroid suspension. IVT for DME is a new treatment option and long-term experience has not been available yet. For date there are many open questions about the use of IVT for DME unanswered yet.

Bloom and Balazs (Bloom and Balazs 1965) named the cell located in the vitreous body as a hyalocyte. However, it has been known that the hyalocyte is not a single species of cell but contains a large variety of cells such as macrophages, fibroblasts, plasma cells, and hypertrophic glia cells (Tenz 1969, Freeman 1970, Lazarus et al. 1994, Ogawa 2002). In our histopathologic study the features of cellular elements attached to the ILM mostly resembled macrophage. Asami and associates (Asami et. al. 2004) ultrastructurally observed collagen fibers on the vitreous side of the surgically removed ILM from eyes with DME. Heparan sulphate proteoglycan (HSPG) is a component of the basement membrane in various tissues together with fibronectin, laminin, and type IV collagen (Leblond et al. 1989, Timpl 1993). It is known that HSPG plays a role of the charged barrier in basement membrane in many tissues and that the qualitative and quantitative changes of HSPG in basement membrane induce the disorder of transportations of the many biomaterials (Timpl 1993, Kjellen et al. 1991, Chakravarti et al. 1999). In the ILM of the human diabetic retina, it has been already reported that the amount of other extracellular matrix components such as fibronectin (Kohno et al. 1987, Ljubimov et al.1996), laminin (Kohno et al. 1987), and Type I, III, IV and collagen (Ljubimov et al.1996) are increased, therefore the ILM thickening in eyes with DME may be induced by increasing accumulation of various extracellular matrices including HSPG (Asami et al. 2004). Tano (Tano 2000) has reported that ILM taken from DME cases were indeed almost twice as thick as the ILM taken from MH cases. Avci (Avci et al.2004) did not found any
differences in the thickness between ILM peeled from eyes with DME and those with MH. In our histopathologic study the thickness of the peeled ILM in the DME group and the MH group was increased. Some cellular elements (mostly resembled macrophage) were observed on the vitreous side of the peeled ILM in the both groups; however, they were not seen on the retinal side. In agreement with previous studies (Asami et al. 2004, Avci et al. 2004) we conclude that ILM thickening and cell abundance on the vitreous surface might contribute to the course and the pathogenesis of DME and idiopathic MH.

Strategies to block the formation of VEGF or to prevent its action in the human eye might be promising treatments for DR and DME. However, systemic anti-VEGF therapy would have potential clinical disadvantages (Duh et al. 1999). Whereas neovascularization is harmful in several tissues of the eye, the formation of new blood vessels is beneficial in the coronary circulation and in the legs, which may be affected in patients with diabetic vasculopathy. Intraocular application of agents that block neovascularization may be preferable; however using intravitreal injection is a potential injurious procedure.
Diabetic macular edema is the most common cause of visual impairment in diabetic patients. Precise pathophysiology of diabetic macular edema is unclear and seems to be multifactorial and includes pericyte loss, microaneurysm formation, basement membrane thickening and focal closure of the capillary bed, vitreomacular traction, and ultimately breakdown of the blood-retinal barrier with increased vascular permeability. Risk factors for clinical significant diabetic macular edema are hyperglycemia, hypertension, hyperlipidemia, duration of diabetes, and pregnancy. The increasing number of individuals with diabetes worldwide suggests that diabetic macular edema will continue to be major contributors to vision loss and associated functional impairment in the working-age population of most developed countries. Although eyes with diffuse macular edema carry a particularly poor prognosis despite laser photocoagulation, laser treatment is still the first choice of treatment for diabetic macular edema as it is safety and less invasive that other surgical options. Diffuse diabetic macular edema is characterized by diffuse leakage from extensive areas of the posterior retinal capillary bed, a scarcity of hard exudates, and often the formation of cystoid spaces. Focal macular edema, in contrast, is characterized by focal leakage from microaneurysms and dilated capillary segments and is more responsive to laser photocoagulation. Laser photocoagulation for diabetic macular edema is mainly sight preserving and not sight resorting. The failure of laser photocoagulation in a substantial subgroup of patients has prompted interest in other treatment methods, including surgical treatment with vitrectomy with or without peeling of the internal limiting membrane, and application of the intravitreal steroids. In conclusion:

1. The findings of our first study in agreement with previous studies support the effectiveness of vitrectomy with or without internal limiting membrane peeling in resolving diabetic macular edema in majority of eyes. This however, is not always associated with
visual acuity improvement. Better outcomes were achieved in eyes with evident vitreomacular traction and with short duration of the edema. The discrepancy between anatomic and functional results may relate to irreversible changes of the macula due to long-standing macular edema, therefore optimal timing of the surgery seems to be important prognostic factor. We confirm that DME is good indication for vitrectomy, especially in eyes with vitreomacular traction by the adherent thickened posterior hyaloid following a partial posterior vitreous detachment. Eyes with attached posterior hyaloid in the macular region, but without thickening and without traction on the macula and eyes with detached posterior hyaloid could also benefit (but in less percentage) from vitrectomy. Vitrectomy might involve the multifactorial pathogenesis of diabetic macular edema.

2. The findings of our second pilot study demonstrated that in eyes with diabetic macular edema, refractory to laser treatment and without evident epimacular proliferation, vitrectomy without internal limiting membrane peeling was as effective in reducing the foveal thickness and improving the visual acuity as vitrectomy with internal limiting membrane peeling. We conclude that peeling of the internal limiting membrane is not essential for anatomic and visual success in diabetic macular edema surgery. Internal limiting membrane peeling might be indicated on a case- by- case base, not as a standard procedure during vitrectomy for diabetic macular edema. Furthermore iatrogenic macular hole or lamellar defect can be associated with ILM peeling in eyes with large cystoid spaces composed of thin inner retinal layer.

3. In our third study and in according with previous studies we found that application of triamcinolone acetonide into the vitreous cavity at the end of vitrectomy may have a positive effect in reducing the macular edema and improving the visual acuity, however the complications of triamcinolone may include serious complication as endophthalmitis. Vehicle removal and triamcinolone application must be performed under strict sterile
conditions. Because of the novelty of this therapy, one has to be very careful since long-term experience has not been available yet. There are many questions unanswered yet, such as the optimal dosage, the mode of application, are there other complications than those already reported? Is it necessary to remove the solvent agent prior to the intraocular injection and how should be removed.

4. In our fourth study and in agreement with previous studies we conclude that enhanced thickening of the internal limiting membrane and cell abundance on the its vitreous surface might contribute to the course and the pathogenesis of diabetic macular edema and idiopathic macular hole.

5. Vitrectomy and creating of posterior vitreous detachment for diabetic macular edema refractory to laser treatment might be more effective than traditional management of observation or further laser and might offer a longer lasting effect than injection of triamcinolone. These surgical results have made us considerably reduce the use of laser photocoagulation for diabetic macular edema and decide for earlier intervention in selective cases. However, one should keep in mind that vitrectomy requires a significant surgical intervention with its inherent risks, recovery time, and expense.
### 7. ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>DR</td>
<td>Diabetic retinopathy</td>
</tr>
<tr>
<td>PDR</td>
<td>Proliferative diabetic retinopathy</td>
</tr>
<tr>
<td>NPDR</td>
<td>Nonproliferative diabetic retinopathy</td>
</tr>
<tr>
<td>AAO</td>
<td>American academy of ophthalmology</td>
</tr>
<tr>
<td>DME</td>
<td>Diabetic macular edema</td>
</tr>
<tr>
<td>ILM</td>
<td>Internal limiting membrane</td>
</tr>
<tr>
<td>CSME</td>
<td>Clinical significant diabetic macular edema</td>
</tr>
<tr>
<td>CME</td>
<td>Cystoid macular edema</td>
</tr>
<tr>
<td>ETDRS</td>
<td>Early treatment diabetic retinopathy study</td>
</tr>
<tr>
<td>OCT</td>
<td>Optical coherent tomography</td>
</tr>
<tr>
<td>BCVA</td>
<td>Best corrected visual acuity</td>
</tr>
<tr>
<td>IMH</td>
<td>Idiopathic macular hole</td>
</tr>
<tr>
<td>PD</td>
<td>Optic disc diameter (1500 µm)</td>
</tr>
<tr>
<td>VEGF</td>
<td>Vascular endothelial growth factor</td>
</tr>
<tr>
<td>IVT</td>
<td>Intravitreal triamcinolone</td>
</tr>
<tr>
<td>TA</td>
<td>Triamcinolone acetonide</td>
</tr>
<tr>
<td>VA</td>
<td>Visual acuity</td>
</tr>
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</table>


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9. RELATED PUBLICATIONS AND PRESENTATIONS

 RELATED PUBLICATIONS


Surgical treatment of diabetic macular edema
Aboutable T, Kalvodová B, Dvořák J
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Diagnosis and treatment of diabetic retinopathy and its complications
Kalvodova B, Sklenka P, Varchálová D, Aboutable T
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DMEV, Czech, www.tigis.cz/dmev/dmev104/08.htm

 RELATED PRESENTATIONS

Pars plana vitrectomy for cystoid macular edema
Aboutable T, Kalvodová B, Štěpánková J, Nováková D
The X. Annual Meeting of the Czech Society of Ophthalmology, Hradec Králové 2003

Vitrectomy for diabetic macular oedema. Results of 72 cases.
Aboutable T and Kalvodova B

A controlled study of internal limiting membrane peeling for diabetic macular oedema without evident epimacular proliferation.
Aboutable T

Is removal of internal limiting membrane always necessary during surgery for diabetic macular oedema without evident epimacular proliferation?
Aboutable T
Ist die Entfernung der Membrana limitans interna (ILM) immer erforderlich bei Patienten mit dem therapierefraktären diffusen diabetischen Makulaödem ohne Nachweis von epimakulären Proliferationen?

Is Removal of Internal Limiting Membrane always Necessary during Surgery for Refractory Diffuse Diabetic Macular Edema without Evident Epimacular Proliferation?

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Bibliografie
ISSN 0023-2165
Zusammenfassung

**Hintergrund:** Untersucht wurde, inwieweit sich das Peeling der Membrana limitans interna (ILM) bei Patienten mit diabetischem Makulaödem ohne nachweisbaren epimakulären Proliferationen oder Zellophanmakulopathie und ohne Erfolg nach zentraler Laserkoagulation, auf den Visusverlauf auswirkt. **Patienten und Methoden:** In einer prospektiven Studie untersuchten wir 10 Augenpaare mit gleichen Schweregrad und Dauer der diabetischen Makulopathie. Die postoperativen Kontrolluntersuchungen wurden über 6 Monate hinaus durchgeführt. Es wurden bilaterale Vitrektomien mit und ohne ILM Peeling durchgeführt. Die ILM wurde mit ungefähr 0,3 ml der Trypan-Blue, 0,2 % gefärbt. Die Ergebnisse wurden mittels Biomikroskopie, OCT und Visus aufgezeichnet und verglichen. Intra- und postoperative Komplikationen wurden dokumentiert. **Ergebnisse:** Am Anfang, am Augen mit dem ILM –Peeling war die am besten korrigierte Sehschärfe (BCVA) von 20/50 bis 20/400 (Mittelwert 20/110) und die Makulastärke von 430 bis 840 µm (Mittelwert 618 µm), und am Augen ohne ILM-Peeling war die BCVA von 20/40 bis 20/400 (Mittelwert 20/120) und die Makulastärke von 390 bis 910 µm (Mittelwert 623 µm). Es gab keinen statistisch signifikanten Unterschied zwischen beiden Gruppen im Anfangsvisus (P = 0.4691, Wilcoxon Rank Sum Test) sowie in der Makulastärke (P = 0.8204, Wilcoxon Rank Sum Test). Die Kontrolluntersuchungen nach 6 Monaten zeigten, dass der Mittelwert der BCVA verbesserte sich bedeutend in beiden Gruppen, von 20/110 zu 20/60 (P = 0.0427, Wilcoxon Signed Rank Test) in den Augen mit dem ILM-Peeling, und von 20/120 zu 20/80 (P = 0.0482, Wilcoxon Signed Rank Test) in den Augen ohne den ILM Peeling. Der Mittelwert der Makulastärke reduzierte sich signifikant von 618 µm zu 265 µm (P = 0.0050) in Augen nach dem ILM Peeling und von 623 µm zu 311 µm (P = 0.0050) in Augen ohne den Peeling. Der Visus verbesserte sich um zwei oder mehr Linien in 5 Augen (50 %) beider Gruppen. Kein statistisch signifikanter Unterschied in der Visusverbesserung (BCVA) und Makulastärkeverringerung (Wilcoxon Rank Sum Test, P = 0.9083, respektiv P = 0.2720) wurde bemerkt. In einem Auge entstand ein Makulaforamen in Folge der Ruptur einer größeren Zyste während des ILM Peelings. **Schlussfolgerung:** Die Vitrektomie mit oder ohne das ILM-Peeling kann das Visus verbessern und die Makulastärke verringern. Es wurde nicht festgestellt, dass das ILM-Peeling die Sehstärkeverbesserung nach der Operation weiter verbessern kann. Eine größere Studie ist nötig, um festzustellen, ob das ILM-Peeling während der Operation für das diabetische Makulaödem ohne epimakulären Proliferationen oder Zellophanmakulopathie notwendig ist.

**Schlüsselwörter**
Diabetisches Makulaödem – Pars Plana Vitrektomie – ILM-Peeling - Membrana limitans interna.

**Kurze Zusammenfassung:**
In einer prospektiven Studie werden die Ergebnisse von Vitrektomie und ILM-Peeling beim therapierefraktären diffusen diabetischen Makulaödem verglichen.

**Abstract**

**Purpose:** To evaluate the effect of the internal limiting membrane (ILM) peeling in eyes with diabetic macular edema (DME) without evident epimacular proliferation or cellophane maculopathy, unresponsive to laser photocoagulation. To determine whether ILM peeling is always essential in DME surgery and whether improves the functional...
outcome.

**Patients and Methods:** In a prospective controlled study ten patients with similar degree and duration of DME in both eyes were followed up for more than 6 months after bilateral vitrectomy with and without ILM peeling. Trypan blue 0, 2% was used to stain the ILM during surgery. We evaluated anatomical outcome detected by biomicroscopic evaluation and optical coherence tomography (OCT) and visual outcome. Intraoperatively and postoperatively complications were documented. **Results:** Baseline BCVA and foveal thickness ranged, respectively, from 20/50 to 20/400 (mean 20/110) and 430 to 840 µm (mean 618) in eyes that underwent ILM peeling, 20/40 to 20/400 (mean 20/120) and 390 to 910 µm (mean 623 µm) in eyes without ILM peeling. There were no significant differences between the both groups in baseline BCVA (P = 0.4691, Wilcoxon Rank Sum Test) or foveal thickness (P= 0.8204, Wilcoxon Rank Sum Test). At six-months follow-up, mean BCVA improved significantly in both groups, from 20/110 to 20/60 (P = 0.0427, Wilcoxon Signed Rank Test) in eyes that underwent ILM peeling and from 20/120 to 20/80 (P= 0.0482, Wilcoxon Signed Rank Test) in eyes without ILM peeling. Mean foveal thickness decreased significantly from 618 to 265 (P= 0.0050) in eyes with ILM peeling and from 623 to 311 (P= 0.0050) in eyes without ILM peeling. Visual acuity improved by two or more lines in five eyes (50%) of each group. There were no significant differences in the improvement of BCVA and decreasing of foveal thickness between the both groups (Wilcoxon Rank Sum Test, P = 0.9083, P = 0.2720, respectively). Cyst rupture with formation of macular hole was documented in one eye after ILM peeling. **Conclusions:** Vitrectomy with or without ILM peeling may improve BCVA and decrease foveal thickness. ILM peeling was not found to enhance the improvement of VA postoperatively. A larger study is required to determine whether ILM peeling is essential in surgery for DME without epimacular proliferation or cellophane maculopathy.

**Key words**
Diabetic macular edema – pars plana vitrectomy – ILM peeling- internal limiting membrane peeling.

**Einleitung:**


Das diabetische Makulaödem ist die häufigste Ursache für eine Sehverschlechterung in Patienten mit Diabetes mellitus [25,32]. Ein Makulaödem, ein-oder beidäugig, findet sich bei ca. 29% der Diabetiker mit einer Krankenanzahl von 20 Jahren oder mehr [25]. Der genaue Pathomechanismus des diffusen, klinisch signifikanten Makulaödems ist nicht bekannt [5,14,33,44]. Ursache für das chronische Makulaödem könnte die Dysfunktion der Blut Retina Schranke und vitreomakuläre Traktionen sein [42,50]. Mehrere Faktoren können die Ausbildung eines Makulaödems beeinflussen, so z.B. Herzkreislauf -oder Nierenerkrankungen, entgleister arterieller Hypertonus, Schwangerschaft und panretinale Laserkoagulation [6]. Auch wenn sich in einigen Fällen das Makulaödem spontan resorbieren kann, so wird doch ein früher Therapiebeginn befürwortet, da sonst mit irreparablen Schäden und somit dauerhafter Visusminderung bis vollständiger Verlust der...

**Patienten und Methode**

Diese Studie wurde gemäß den ethischen Standards der Erklärung von Helsinki in 1964 durchgeführt. Patienten wurden vollständig über alle Therapiemöglichkeiten aufgeklärt. Die Einverständniserklärung lag uns vor Aufnahme in die Studie vor. Alle Patienten wurden in unserer Klinik im Zeitraum April 2003 bis Januar 2005 operiert. Folgende Kriterien mussten erfüllt sein um in die Studie aufgenommen zu werden: (1) klinisch signifikantes Makulaödem beidseits mit vergleichbarem Schweregrad und gleicher Dauer des Bestehens der Erkrankung (Abweichung der Sehschärfe nicht mehr als 3 Zeilen); (2) keine Verbesserung durch Laserkoagulation; (3) keine epimakulären Proliferationen oder Zellophanmakulopathie; (4) Anliegen des hinteren Glaskörpers, keine vitreoretinalen Traktionen. Ausgeschlossen aus der Studie wurden: (1) andere Augenerkrankungen, welche mit einem Makulödem einhergehen, so z.B. Uveitis und Astvenen -oder Zentralvenenverschlüsse; (2) dichte Medientrübungen, wie z.B. Katarakt, Glaskörperblutung; (3) fibrovaskuläre Proliferationen mit Ablatio retinae und/oder Makuladistorsion; (4) vorangegangene Vitrektomien. In unserer Studie diente das Partnerauge (an diesem Auge wurde die Vitrektomie ohne ILM- Peeling durchgeführt) als Kontrolle, so dass wir den Verlauf und die Auswirkung des ILM Peelings gegenüber des nicht operierten Auges vergleichen konnten. Die präoperative gemessene foveale Dicke und der best korrigierte Visus (Best Corrected Snellen visual acuity, BCVA) waren in allen Augen (mit bzw. ohne ILM Peeling) gleich. Die folgenden präoperativen Angaben wurden

Am Ende der Operation verabreichten wir Dexamethason 2 mg und Gentamycin 4mg subconjunctival. Postoperativ wurden die Augen mit Gentamycin 3 mg für 1 Woche; Dexamethason 1 mg und Atropin 1% für 1 Monat getropft. Eine erneute Operation war bei keinem Patienten erforderlich. Die Kontrolluntersuchungen dauerten mindestens 6 Monate postoperativ oder länger an. Wir untersuchten die Augen auf den best korrigierten Visus (BCVA), Resorption des Makulaödems bzw. Bestehenbleiben oder Rezidiv des Ödems. Untersucht wurde mittels Biomikroskopie 1 Woche; 1, 3 und 6 Monate postoperativ. Aufzeichnung mittels OCT erfolgte 6 Monate postoperativ. Wilcoxon Rank Sum Test und Wilcoxon Signed Rank Test wurden für statistische Analyse benutzt.

**Ergebnisse:**


Tab.1 Patientendaten:
Befunde der Optischen Kohärenz Tomographie

<table>
<thead>
<tr>
<th>Patient Nr.</th>
<th>Alter (Jahre)</th>
<th>Geschlecht</th>
<th>Dauer des DMÖ (Monate) ±2M</th>
<th>Linsezustand</th>
<th>zystische Veränderungen</th>
<th>seröse Netzhautablösung</th>
<th>Länge der Beobachtung (Monate) mit P</th>
<th>ohne P</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>54</td>
<td>M</td>
<td>15</td>
<td>IOL</td>
<td>Ja</td>
<td>Ja</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>52</td>
<td>W</td>
<td>12</td>
<td>Phak</td>
<td>Ja</td>
<td>Ja</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>W</td>
<td>10</td>
<td>Phak</td>
<td>Ja</td>
<td>Nein</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>57</td>
<td>M</td>
<td>21</td>
<td>Phak</td>
<td>Ja</td>
<td>Ja</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>W</td>
<td>18</td>
<td>IOL</td>
<td>Ja</td>
<td>Nein</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>6</td>
<td>55</td>
<td>M</td>
<td>8</td>
<td>IOL</td>
<td>Ja</td>
<td>Ja</td>
<td>16</td>
<td>20</td>
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<tr>
<td>7</td>
<td>58</td>
<td>M</td>
<td>6</td>
<td>IOL</td>
<td>Ja</td>
<td>Nein</td>
<td>20</td>
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<tr>
<td>8</td>
<td>62</td>
<td>M</td>
<td>14</td>
<td>Phak</td>
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<td>Nein</td>
<td>15</td>
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<tr>
<td>9</td>
<td>45</td>
<td>W</td>
<td>6</td>
<td>Phak</td>
<td>Nein</td>
<td>Nein</td>
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<tr>
<td>10</td>
<td>55</td>
<td>M</td>
<td>9</td>
<td>Phak</td>
<td>Ja</td>
<td>Nein</td>
<td>12</td>
<td>8</td>
</tr>
</tbody>
</table>

DMÖ = diabetischer Makulaödem  
M = männlich  
W = weiblich  
P = ILM Peeling

Acht Augen (40%) mit proliferativer diabetischer Retinopathie wurden präoperativ mittels panretinaler Laserkoagulation therapiert; 12 Augen (60 %) mit NPDR erhielten präoperativ eine fokale Laserkoagulation. Die zentrale Laserkoagulation brachte in keinem der Augen eine präoperative Visusverbesserung. Grid Laser führten wir aufgrund der limitierten Erfolge in Patienten mit diffusen bzw. zystoiden Makulaödemen nicht durch [3,40].

Am Anfang, am Augen mit dem ILM –Peeling war die am besten korrigierte Sehschärfe (BCVA) von 20/50 bis 20/400 (Mittelwert 20/110) und die Makulastärke von 430 bis 840 µm (Mittelwert 618 µm), und am Augen ohne ILM-Peeling war die BCVA von 20/40 bis 20/400 (Mittelwert 20/120) und die Makulastärke von 390 bis 910 µm (Mittelwert 623 µm). Es gab keinen statistisch signifikanten Unterschied zwischen beiden Gruppen im Anfangsvisus (P = 0.4691, Wilcoxon Rank Sum Test) sowie in der Makulastärke (P= 0.8204, Wilcoxon Rank Sum Test). Die Kontrolluntersuchungen nach 6 Monaten zeigten, dass der Mittelwert der BCVA verbesserte sich bedeutend in beiden Gruppen, von 20/110 zu 20/60 (P = 0.0427, Wilcoxon Signed Rank Test) in den Augen mit dem ILM-Peeling, und von 20/120 zu 20/80 (P= 0.0482, Wilcoxon Signed Rank Test) in den Augen ohne den ILM Peeling. Der Mittelwert der Makulastärke reduzierte sich signifikant von 618 µm zu 265 µm (P= 0.0050) in Augen nach dem ILM Peeling und von 623 µm zu 311 µm (P= 0.0050) in Augen ohne den Peeling. Der Visus verbesserte sich um zwei oder mehr Linien in 5 Augen beider Gruppen. Kein statistisch signifikanter Unterschied in der Visusverbesserung (BCVA) und Makulastärkeverringerung (Wilcoxon Rank Sum Test, P = 0.9083, respektiv P = 0.2720) wurde bemerkt. In einem Auge entstand ein Makulaforamen in Folge der Ruptur einer größeren Zyste während des ILM Peelings. Die Sehschärfe verbesserte sich 2 Zeilen oder mehr in 50% der Fälle mit und ohne ILM Peeling (Tab. 2).

Tab. 2 Anatomische und funktionelle Ergebnisse:

<table>
<thead>
<tr>
<th>No.</th>
<th>DMÖ mit ILM peeling</th>
<th>DMÖ ohne ILM peeling</th>
<th>Sehschärfe (BCVA) mit ILM peeling</th>
<th>Sehschärfe (BCVA) ohne ILM peeling</th>
</tr>
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<tr>
<td>1</td>
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<td>resorbiert</td>
<td>verbessert ≥ 2 Zeilen</td>
<td>verbessert ≥ 2 Zeilen</td>
</tr>
<tr>
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<td>vermindert</td>
<td>vermindert</td>
<td>unverändert</td>
<td>unverändert</td>
</tr>
<tr>
<td>3</td>
<td>resorbiert</td>
<td>resorbiert</td>
<td>verbessert ≥ 2 Zeilen</td>
<td>verbessert ≥ 2 Zeilen</td>
</tr>
<tr>
<td>4</td>
<td>unverändert</td>
<td>unverändert</td>
<td>unverändert</td>
<td>unverändert</td>
</tr>
<tr>
<td>5</td>
<td>resorbiert</td>
<td>resorbiert</td>
<td>verbessert ≥ 2 Zeilen</td>
<td>verbessert ≥ 2 Zeilen</td>
</tr>
<tr>
<td>6</td>
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<td>verbessert ≥ 2 Zeilen</td>
</tr>
<tr>
<td>7</td>
<td>vermindert</td>
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<td>9</td>
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<td>10</td>
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Intraoperative Komplikationen waren wie folgt: (1) peripheres Netzhautforamen in 1 Auge (5%) welche mittels Laserkoagulation behandelt wurde; (2) Ruptur einer Makulazyste in 1 Auge (5%) mit Folge Ausbildung eines Makulaforamens. Es wurde 20%iges Sulfur Hexafluorid injiziert und eine Bauchlage für 14 Tage eingehalten. Postoperativ wurden weder epiretinale Membranen noch ein Rezidiv eines Makuläomens beobachtet. Wir beobachteten, dass die abgelösten ILM dicker wurden und eine große Adhäsion zu der Netzhaut aufwiesen. Infolge dessen, war das Peeling gewöhnlich schwieriger als in Augen mit Makulaloch und dauerte länger wegen der Tendenz zu reißen, besonders im Falle des zystoiden Makulaödems mit größeren Zysten.

Zusammenfassung:

Die ETDRS konnte zeigen, dass eine fokale Laserkoagulation in Augen mit diabetischem Makulaödem das Risiko des Sehverlustes um 50 % reduzieren kann; gleichzeitig wurde gezeigt dass auch das Auftreten eines chronischen Makulaödems durch die Laserbehandlung deutlich reduziert wird und die BCVA verbessert werden kann. Trotz Laserbehandlung reduziert sich in 15 % der Augen die Sehschärfe nach 3 Jahren [11,12]. In einer anderen Studie, bei der 302 Augen mit diffusen Makulaödems behandelt wurden, konnte gezeigt werden, dass mittels Grid-Laserkoagulation in 75.4% der Augen eine Stabilisierung bzw. sogar eine Verbesserung der BCVA erreicht wurde. In 24.6% der Augen trat trotz Laserbehandlung ein Sehverlust nach 3 Jahren auf [30]. In mehreren Studien konnte gezeigt werden, dass es keinen Vorteil der Lasertherapie im Gegensatz zum natürlichen Verlauf der Erkrankung gibt. Auch bei Patienten, die anfängs durch die Grid-Lasertherapie profitierten, mussten nach 3 Jahren mit einer erneuten Sehverschlechterung rechnen [4,20,38].


Netzhautdefekte bei ILM Peeling an Augen mit großen zystoiden Höhlen in der dünnen inneren Netzhautschicht als Komplikation in Betracht ziehen. Größere multizentrische Studien sind letztendlich erforderlich um klare Richtlinien darüber geben zu können, ob ILM Peeling als Standardtherapie in Patienten mit diabetischem Makulaödem in Betracht gezogen werden kann.

**Literatur**


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Surgical treatment of diabetic macular edema
Aboutable T, Kalvodová B, Dvořák J
Oftalmochirurgie, Czech, 2006, in press.
Chirurgická léčba diabetického makulárního edému

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(Oční klinika VFN a 1. LF UK v Praze, přednost doc. MUDr. Bohdana Kalvodová, CSc.)

Úvod

Diabetický makulární edém (DME) je charakterizován ztlustěním sítnice v makulární oblasti, které je způsobeno nemocí, při které dochází k zvětšení sítnice v makulární oblasti, které je způsobeno nahromadením tekutiny ve vnitřní a vnější plexiformní vrstvě. DME je nejčastější přičinou zhoršeného vidění u diabetiků (17). DME postihující jedno nebo obě oči vzniká přibližně u 29 % diabetiků, jejichž onemocnění trvá 20 a více let (17).

Patogenetický mechanismus DME nebyl dosud objasněn. Zvýšená permeabilita sítnicových cév na podkladě porušení hematoretinální bariéry a vitreomakulární trakce jsou pravděpodobně nejvýznamnější faktory, které se podílejí na vzniku DME (26, 37). Bylo prokázáno, že některé systémové a lokální faktory mohou exacerbovat difuzní DME, například retence tekutin způsobená onemocněním kardiovaskulárního systému či ledvin, neléčená hypertenze, těhotenství a panretinální fotokoagulace (5). DME klasifikujeme na fokální, difuzní i cystoidní. Podle optické koherenční tomografie (OCT) rozlišujeme tyto struktury DME: houbovitý edém, cystoidní edém a serosní odchlípení sítnice (27). I když se může DME v ojedinělých případech spontánně vyskytovat (38), většina autorů doporučuje včasnou léčbu ještě před vznikem funkčních ztrát (7, 9, 10, 16, 21, 29). Nové operační postupy vedly v posledních několika letech k prudkému rozvoji chirurgické léčby DME. Cílem této práce je přehled současných poznatků o možnostech chirurgické léčby DME.

Laserová fotokoagulace

Early Treatment Diabetic Retinopathy Study (ETDRS) potvrdila přínosný terapeutický účinek fokální laserové fotokoagulace (LK) v léčbě klinicky signifikantního DME (7). Hlavním výsledkem LK je zajištění dostatečného očního zrakového ostrosti (CZO). LK snižuje riziko stěžejních ztrát CZO a je účinná u pacientů s DME v ojedinělých případech spontánně vzniklého DME (5), když se může DME v ojedinělých případech spontánně vyskytovat (38), většina autorů doporučuje včasnou léčbu ještě před vznikem funkčních ztrát (7, 9, 10, 16, 21, 29). Nové operační postupy vedly v posledních několika letech k prudkému rozvoji chirurgické léčby DME. Cílem této práce je přehled současných poznatků o možnostech chirurgické léčby DME.

Pars plana vitrektomie

Mnozí autoři referovali o tom, že pars plana vitrektomie (PPV) je přínosná u DME, zejména u očí s ztlustělou a napjatou zadní plochou sklivce, u kterých byla premakulární vitreoretinální trakce uvolněna během PPV (9, 10, 16, 21, 29). Byla vyšložena hypotéza, že DME vzniká následkem tangenciální trakce ztlustělé a přiložené zadní plochy sklivce, která způsobuje velmi ploché oční odehlípení makuly obdobné tomu, které je patrné u pacientů s makulární dírou (10, 12, 21). Jiní autoři prokázali, že PPV může být účinná dokonce i tehdy, když nejsou patrné změny zadní sklivcové membrány (13, 20, 33, 40), a to dokonce i tehdy když byla zadní plocha sklivce v oblasti zadního pólu odloučena (13). Většina těchto studií byla retrospektivní a nekontrolovaná.

Otani a Kishi (28) porovnávali v ojedinělé kontrolované studii 7 očí, které podstoupily PPV, přičemž u všech operovaných očí regresi DME a přítomnost foveální deprese, zatímco u 5 ze 7 kontrolních neoperovaných očí DME
zůstal stejný a u 2 očí nepatrně regredoval. CZO se zlepšila o 2 a více řádků u 4 ze 7 operovaných očí a zůstala stejná u 3 očí. CZO se zlepšila u 1 neoperovaného oka, u 3 očí zůstala stejná a zhoršila se u 3 očí.

Přínos PPV u očí s DME bez vitreomakulární trakce lze vysvětlit několika důvody. Sklicev může působit jako možný rezervoár zánětlivých substancí nebo růstových faktorů, jako je například vascular endothelial growth factor (VEGF), produkovaný glíaálními buňkami, který také zvyšuje cévní permeabilitu (3). Odstranění těchto substancí může zlepšit DME. Jiné možné vysvětlení je, že PPV zlepšuje zásobení sítnice kyslíkem (32).

Kalvodová podala zprávu o příznivém účinku PPV na ústup DME a zlepšení CZO. Pilotní studie v České republice týkající se PPV u DME byla publikována v roce 2002(16). Kalvodová podala zprávu o příznivém účinku PPV na ústup DME a zlepšení CZO.

Chirurgické výsledky byly ověřeny metodou OCT.

V prospektivní studii provedené na Oční klinice VFN a 1. LF UK v letech 2001 až 2003 jsme hodnotili výsledky PPV provedené u 72 očí s cystoidním DME, který nereagoval na léčbu LK. Vitreomakulární trakce byla hodnocená biomikroskopicky, ultrazvukovým vyšetřením v B-modu a OCT u 21 očí. Úplné odloučení zadní plochy sklicev (PVD) mělo 15 očí a 36 očí mělo částečnou PVD v periferii. Byla provedena PPV s přerušením vitreomakulární tangenciální a axiální trakce. Všichni pacienti byli sledováni minimálně po dobu 6 měsíců. Po operaci byly anatomické výsledky uspokojivé u 96 % očí, výsledná CZO se zlepšila u 2 a více řádků u 63 % očí. Nejlepší výsledky byly dosaženy u DME s dominantní vitreomakulární trakcí složkou a u očí, u kterých cystoidní DME trval méně než 6 měsíců (1). Výsledky naší studii se shodují s prací Lewis (21), který jako první prokázal kladný účinek PPV u DME. Ve shodě s dřívějšími studiemi (10, 16) jsme zjistili, že kratší časový interval od počáteční diagnosty DME k PPV může souviset s lepší konečnou CZO. Horší výsledky pozorované u očí s dlouhodobě trvající DME může být na podkladě destruktivního účinku dlouhodobého DME na vrstvy sítnice.

Takagi a spol. (34) zjistili kladný vliv odstranění submakulárních rozsáhlých transudátů na regresi serosního ochlípení sítnice v makule a zlepšení funkce u pacientů s nízkou CZO při DME. Takaya a spol. (35) však podali zprávu, že zlepšení CZO nemůže být po odstranění submakulárních transudátů u většiny pacientů dlouhodobě dosaženo a doporučili léčit diabetickou makulopatii dříve než se vytvoří rozsáhlá deposita transudátů v makule.

PPV s odstraněním vnitřní limitující membrány

I když předchozí autoři uvádějí velmi dobré a slibné výsledky PPV u DME vyvstává otázka, zda PPV a peeling vnitřní limitující membrány (ILM) dále kladně ovlivní funkční a anatomické výsledky. Gandorfer (9) jako první publikoval v roce 2000 výsledky PPV a peelingu ILM u DME. Dosud bylo o peelingu ILM u DME publikováno jen málo a jeho indikace není dosud jednoznačně stanovena. Někteří autoři (4, 18, 30) jej provádějí vždy u pacientů s DME, zatímco jiní (1, 20) pouze u očí, u kterých je patrna viditelná epimakulární proliferace a celofánová makulopatie. Avci (4) a Kuhn (18) referovali o příznivém anatomickém a funkčním výsledku PPV a peelingu ILM u DME. Kumagai (19) zjistil, že odstranění ILM u DME při PPV s odstraněním ILM u DME nemůže být na podkladě destruktivního účinku dlouhodobého DME na vrstvy sítnice. Předem bylo o lokalizaci ILM u DME s viditelnou epimakulární proliferací a celofánovou makulopatií.

Jakým způsobem může odstranění ILM ovlivnit DME není jednoznačně stanoveno. K diskutovaným mechanismům patří úplné uvolnění trakčných sil a zamezení proliferace
fibrózních astrocytů (9, 29). Tano (36) publikoval, že ILM odebraná od pacientů s DME byla dvakrát tak silnější než ILM u očí s makulární dírou. Proto bylo navrženo, že abnormálně ztušťelá ILM může působit jako bariéra příznaku cytokinů do sklivce, jako je např. VEGF a jiné, které vedou k poruchám permeability kapiláří. Radetzky (30) uvedl, že odstranění ILM neovlivnilo patofyzioologické změny jako jsou tvorba růstových faktorů nebo porušená dynamika tekutin. Je však mnohem pravděpodobnější, že odstranění ILM výrazně zlepšuje difúzi štítnicových substance do sklivce a je tedy účinnější u pacientů s již existujícími poruchami vitreomakulárního rozhraní. Ústup DME po operaci je možno přičíst jak PPV tak ILM peelingu.

V prospektivní kontrolované studii provedené na Oční klinice VFN a 1. LF UK v letech 2003 a 2004 jsme hodnotili vliv odstranění ILM u očí s DME bez zjevně epimakulární proliferace nebo celofánové makulopatie. Sledovaný soubor tvořili deset pacientů s obojí stranným DME, který přetrvával po LK. Stupněm DME a doba jeho trvání byly obdobné na obou očích. Pacienty byli sledováni déle než 6 měsíců po obojí stranné PPV nebo bez odstranění ILM (2). Hodnotili jsme anatomické výsledky biomikroskopicky a pomocí OCT a konečnou CZO. Tato studie je jistě omezena malým počtem operovaných očí. Jde o první kontrolovanou studii zabývající se odstraněním ILM u DME bez zjevně epimakulární proliferace či celofánové makulopatie. Celkové parametry jako je glykémie, krevní tlak a přítomnost nefropatie se u jednotlivých pacientů liší a mohou ovlivnit výsledky operací. Tyto parametry jsme vzhledem k tomu, že jsme použili druhé oko jako kontrolní klinicky s DME v porovnání s obojí stranným DME bez zjevné ILM (2). Hodnotili jsme anatomické výsledky biomikroskopicky a pomocí OCT a konečnou CZO. Tato studie je jistě omezena malým počtem operovaných očí. Jde o první kontrolovanou studii zabývající se odstraněním ILM u DME bez zjevně epimakulární proliferace či celofánové makulopatie. Celkové parametry jako je glykémie, krevní tlak a přítomnost nefropatie se u jednotlivých pacientů liší a mohou ovlivnit výsledky operací. Tyto parametry jsme vzhledem k tomu, že jsme použili druhé oko jako kontrolní nez hodnotili. V sledovaném souboru se DME vstřebal u 90 % očí s odstraněním ILM a u 70 % očí bez odstranění ILM. CZO se zlepšila o 2 a více řádků u 50 % očí obou skupinách. U jednoho oka byl operační a pooperační průběh komplikován rupturou cysty a vznikem makulárního defektu.

Pendergast (29) pozoroval vznik epiretinální membrány po odstranění zadní plochy sklivce bez odstranění ILM pro DME u 6 z 59 očí, také Tachi a Ogino (33) uvedli tuto pooperační komplikaci u 6 z 59 očí. Tato komplikace nebyla pozorována v studii Gandorfera (8) na konci sledovací období po PPV s odstraněním ILM. V sledovacím souboru jsme vznikem tato komplikace nepozorovali.

Při operacích makulární díry bylo prokázáno, že odstranění ILM je proveditelný a bezpečný postup, který přináší slibné anatomické a funkční výsledky (6). Odstranění ILM u očí s DME je v porovnání s očima s makulární dírou obtížnější. ILM u edematózní sítnice slibně adherovala k sítnice a byla rezistentní k natržení, zejména u DME s většími cystoidními dutinami. Ruptura cystoidní dutiny během odstraňování ILM a vznik makulárního defektu je závažnou komplikací. Proto je za těchto podmínek třeba pečlivě zvážit indikace peelingu ILM.

**Peroperační intravitreální aplikace indocyaninové zeleně**

Peroperační aplikace indocyaninové zelené (ICG) vyvolá výrazný kontrast mezi neobarvenou sítnicí a zbarvenou ILM. Obarvení ICG usnadnilo a urychlovalo odstraňování ILM. Možný toxický vliv ICG aplikované přímo do sklivcového prostoru je kontroverzní. Zatímco někteří autoři podali zprávu o morfologickém a funkčním poškození sítnice u krysích očí (8) nebo o skotomech v zorných polích u pacientů po intravitreálním barvení ICG (11, 38), jiní nezjistili nežádoucí vliv ICG na funkci sítnice při operaci makulární díry (38). Byla vyslovena domněnka, že toxická může záviset na její koncentraci a délce kontaktu tkáně s ICG (11, 38). Proto je nezbytné, aby chirurgové zvážili rizika a přínos barvení do doby než se prokáže, že peroperační aplikace je bezpečná a vede k porovnatelným dobrým výsledkům, jakých je dosahováno při odstraňování ILM s jinými barvivy. V naší studii jsme používali trypanovou modř (Membrane Blue).
Operační komplikace

Různé peroperační a pooperační komplikace byly publikovány po PPV u pacientů s DME. Ke komplikacím patřily peroperační trhliny sítnice (33), peroperační rhegmatogenní odchlípení sítnice (9, 21, 33), neovaskulární glaukom (33), pooperacení hemoftalmus (9, 21), pooperacení vznik epiretinální membrány (21, 32), katarakta (9, 21, 33) a ischemie makuly (10).

O lamelárním makulálním defektu související s PPV a odstraněním epiretinální membrány, ale bez zamyšleného odstranění ILM bylo referováno pouze jednou (40). Ruptura cysty s následným makulálním defektem související s odstraněním ILM byla dokumentována také pouze u jednoho oka s velkými cystoidními změnami (10). Také pouze u protrahované léčby byla uvedena také v naší studii (2). Odlučit byly u protrahované léčby pouze u jednoho oka s velkými cystoidními membrány, ale bez zamýšleného odstranění cysty s následným makulárním defektem související s odstraněním cystinového sklovodu (10).

O kortikoidech je známo, že tlumí nitrooxygenační koncentrace steroidů dostatečně vysoká, aby dosáhla terapeutických hladin, nebo celkové vedlejší účinky byly u prodlouhované léčby příliš výrazné. Aby se vyhnuli těmto omezením steroidní oční léčby, začali někteří autoři injikovat steroidy do sklivce (22). Někteří autoři používali rozpustný kortison, který se ale z oka vstřebá během přibližně 24 hodin po jedné intravitreální injekci. Machemer doporučoval použití triamcinolon acetonidu, který jako krystalický steroid má výrazně delší dobu absorpce než injekce rozpustného kortisonu (23).

Oko tvoří přibližně 0,01 % objemu lidského těla. Předpokládáme-li rovnoměrnou distribuci triamcinololu acetonidu v těle, pak intravitreální injekce 4 mg odpovídá intragluteální injekci 40 g a intravitreální aplikace 25 mg triamcinolon acetonidu odpovídá 250 g aplikovanému intragluteálně (15). Intravitreální aplikace triamcinolon acetonidu (IVT) může být kombinována s jinými nitrooxygenačními výkony jako jsou operace katarakty či PPV. Od roku 2001 bylo v mnoha studiích navrženo, že IVT se může spolupodílet na zlepšení CZO a zmenšení DME (14, 15, 25). Při užití dávky okolo 20 mg triamcinolon acetonidu bylo zlepšení CZO nejvíce patrné během prvních 3-6 měsíců po injekci a bylo možné jej sledovat po dobu 6-9 měsíců (14, 15). Při užití dávky 4 mg triamcinolon acetonidu byla doba, po kterou byla snížena makulární absorpce OCT kratší než 6 měsíců. Na konci sledovacího období se CZO vratila k výchozím hodnotám bez signifikantního rozdílu mezi výchozími hodnotami a výsledky získanémi na konci sledovacího období (25). Jestliže se CZO po IVT zlepší a eventuálně znovu poklesne, může být injekce opakována. Doba účinnosti jedné IVT injekce je v rozmezí 2-9 měsíců (15). Ke komplikacím léčby IVT patří sekundární oční hypertenze u asi 40 % očí, vznik katarakty, pooperační infekční a neinfekční endoftalmitida a pseudoendoftalmitida (15).

V prospektivní studii provedené na Oční klinice VFN a 1. L. F. UK v roce 2005 jsme strhnuti účinnost a bezpečnost PPV s aplikací triamcinolon acetonidu u DME, který byl odstraněn po 24. Tato studie zahrnovala 32 očí 32 diabetiků. Po PPV kombinované s aplikací 4 mg triamcinolon acetonidu (0,1 ml 40 mg Triamcinolon acetonid) jsme vyhodnotili anatomické a funkční výsledky a komplikace. Nemocné jsme sledovali od 4 do 7 měsíců (průměrně 5,5 měsíců). Zlepšení a stabilizace CZO jsme pozorovali u 28 očí (87 %).
DME regredoval u 23 očí (72%). Pooperační průběh byl u 1 nemocného komplikovaný časnou bakteriální endofoamitidou (Stafylococcus epidermidis).

Macugen Diabetic Retinopathy Study Group (24), která zkoumá účinnost intravitreální aplikace Pegaptanibu (anti-VEGF preparát) na DME, podala v posledních měsících 2005 zprávu o ústupu DME a zlepšení CZO po jeho aplikaci. Anti-VEGF preparáty se dosud v široké klinické praxi nepoužívají.

Závěr

PPV s peelingem nebo bez peelingu ILM je účinný operační postup, který vede ke resorbci DME u většiny očí. Resorbce DME není vždy doprovázeno zlepšením CZO. DME je indikací k operaci, bez ohledu na stav zadní plochy sklivce. PPV má pravděpodobně děle trvající účinnost než samotné aplikace IVT. Odstranění ILM pro DME u očí bez evidentní epimakulární proliferace nebo celofánové makulopatie může urychlit resorbci DME, ale nezda se, že by bylo významným faktorem ovlivňujícím pooperace CZO. Ruptura cystoidní dutiny a vznik makulárního defektu mohou souviset s peelingem ILM u očí s rozsáhlými cystoidními prostory tvořenými tenkými vitálními síticími vrstvami.

Zlepšení CZO u očí s DME bez zjevné epimakulární proliferace může být dosaženo PPV s odloučením zadní plochy sklivce bez odstranění ILM. Peeling ILM by mělo být individuálně indikován. Rozdíl mezi anatomickými a funkčními výsledky může souviset s nevraťnými změnami v makule vzhledem k dlouhotrvajícímu DME a proto je vhodné načasování operace důležité. Tyto výsledky operací nás vedly u konkrétních případů k rozhodnutí indikovat PPV jako primární postup ještě před zahájením LK.

IVT je slibná podpůrná léčebná metoda u očí s DME. Avšak, jako u jakékoliv jiného nového postupu léčby, je třeba být v jejím používání velmi opatrnný, protože dosud nejsou dlouhodobé zkušenosti. Dosud nejsou známy optimální dávkování, způsoby podávání a nutnost filtrace.

Jsou žádány další randomizované, prospektivní, dvojitě slepé, multicentrické studie s větším počtem pacientů a standardizovaným vyšetřováním zrakové ostrosti ke stanovení vztahů mezi všemi možnými chirurgickými léčebnými možnostmi DME.

Literatura


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