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REVIEW

Managing diabetic macular edema: The leading cause of diabetes blindness

Pedro Romero-Aroca

Pedro Romero-Aroca, Ophthalmology Service, Hospital de Sant Joan Universtari, Institut de Investigació, Universitat Rovira i Virgili, Pere Virgili Health (ⅡSPV) Reus 43204, Spain
Author contributions: Romero-Aroca P contributed solely to the work.
Correspondence to: Pedro Romero-Aroca, MD, PhD, Ophthalmology Service, Hospital de Sant Joan Universtari, Institut de Investigació, Universitat Rovira i Virgili, Pere Virgili Health (ⅡSPV) Reus 43204, Spain. romeropere@gmail.com
Telephone: +34-977310300 Fax: +34-97732375
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Abstract

Diabetic macular edema (DME) is the leading cause of blindness in young adults in developed countries, affecting 12% of type 1 and 28% of type 2 diabetic patients. The gold standard DME treatment should be based on a good control of glycemia along with control of lipids and renal function. However, despite the systemic metabolic control values being essential for patients with diabetic retinopathy (DR), it has proven to be insufficient for DME if it appears. With these patients, additional measures are needed in order to avoid the subsequent loss of vision. While laser treatment of DME has been the only valid treatment so far, it has been inadequate in chronic cases. The introduction of new treatments, such as intravitreal corticosteroids or anti-VEGF drugs, have recently shown their safety and efficacy and together with laser photocoagulation are becoming the treatments of choice in the management of DME.

Key words: Diabetic macular edema; Diabetic retinopathy treatment

Peer reviewers: Rita Bortell, Dr., University of Massachusetts Medical School, Biotech 2, Suite 218, 373 Plantation Street, Worcester, MA 01605, United States; Ioannis Legakis, MD, PhD, Henry Dunant Hospital, Alimousion 33, Athens 11821, Greece

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INTRODUCTION

Diabetic macular edema (DME) is the leading cause of blindness in the diabetic population. Although its prevalence varies, the Diabetes Control and Complications Trial (DCCT) reported that 27% of type 1 diabetes (DM1) patients developed macular edema within nine years of onset[1]. Other studies indicate that in type 2 diabetic patients (DM2), prevalence increases from 3% within 5 years of diagnosis to 28% after 20 years[2]. DME tends to be a chronic disease, although spontaneous recovery is not uncommon. It is important to recognize that about 33% to 35% of patients resolve DME spontaneously after six months without treatment[3,4]. The disease is now believed to be multifactorial in origin with a number of systemic factors including hypertension, poor metabolic control of diabetes, dyslipemia and nephropathy playing a role in its pathogenesis.

EPIDEMIOLOGY

The prevalence of DME is generally higher in DM2 patients than in DM1 and our studies reflect that. Prevalence is 11.84% in DM1 and 27.15% in DM2[5]. The annual incidence of DME in DM1 ranges from 0.9% to 2.3%[6] and our studies show that the annual incidence in DM2 ranges 1.25% to 1.40%[2].

Epidemiological data for DME has shown changes with more intensive control of glycemia and blood pres-

sure. In the Wisconsin study[7], the incidence of DME at 25 years in DM1 patients decreased from 2.3% in the first 4 year cohort study (baseline between 1980-1982 and 1984-1986) to the current 0.9% incidence in a group of patients followed from years 14 to 25. The author's studies (in Spain) have also shown changes, where the prevalence of DME in DM1 has decreased from 12.90% to 11.84% and in DM2 from 7.86% to 7.15%. Furthermore, the percentage of patients treated by laser photocoagulation of the macular area has also reduced from 7.52% to 5.26% in DM1 patients and from 5.18% to 2.43% in DM2 patients[5].

Many large series studies have investigated the effect of different conditions on the incidence of DME. The frequency of DME increases with the duration of diabetes mellitus with two peaks, the first around 14 years and a second after more than 30 years[8,9]. Furthermore, poor metabolic control has been implicated with DME. Elevated diastolic blood pressure has been associated with DME and dyslipemia also increases prevalence. Our study group found a positive association with a high LDL-cholesterol and TC/HDL-cholesterol ratio in DM2 diabetics[10] and the LDL-cholesterol and TC/HDL-cholesterol ratio in DM1 diabetics was found to be a risk factor in the DCCT[11].

CLINICAL DESCRIPTION AND CLASSIFICATION

The two definitions of macular edema in diabetic patients currently used are: (1) Macular edema (ME); and (2) Clinically significant macular edema (CSME).

In diabetes related research studies, ME is often characterized by retinal thickening or the presence of hard exudates within a 1 disk diameter of the center of the macula.

To characterize the severity of macular edema, the term *clinically significant macular edema* (CSME) is used. Macular edema is clinically significant if one of the following conditions is present: (1) retinal thickening at or within 500 mm of the center of the macula; (2) hard exudates at or within 500 mm of the center of the macula if associated with thickening of the adjacent retina; and (3) a zone or zones of retinal thickening 1 disk area in size, at least part of which is within 1 disk diameter of the macular center, characterized by the retinal thickening of the macular area visible under biomicroscopy[12].

Concept of focal versus diffuse diabetic macular edema

DME is further classified into focal or diffuse, depending on the leakage pattern seen on the fluorescein angiogram (FA).

In focal DME, discrete points of retinal hyperfluorescence (leakage of intravascular liquid to interstitial space due to a vasopermeability) are present on the FA due to focal leakage of microaneurysms, the cause of retinal thickening. Commonly, these microaneurysms are surrounded by circular hard exudates[13]. A variation of this form is the multifocal macular edema which in some cases is confused with diffuse macular edema. This form appears under fluorescein angiography as multiple foci of leakage due to the presence of multiple foci of microaneurysms.

In diffuse DME, there are areas of diffuse leakage on the FA due to intraretinal leakage from dilated retinal capillary bed and/or intraretinal microvascular abnormalities (IRMA) and/or from arterioles and venules without foci of leaking microaneurysms.

Cystoid macular edema

Cystoid diabetic macular edema (CME) results from the generalized breakdown of the inner blood retinal barrier with fluid accumulation in the outer plexiform layer[14].

Classification attending OCT

The introduction of optical coherence tomography of the macular area has changed our view of DME and its classification. The visualization of the macular area and the interface between the vitreous and retina has allowed us to classify macular edema.

So now we can classify macular edema as follows[15]:

Spongiform: Sponge-like retinal swelling present in 88% of eyes with DME. This form is mostly confined to the outer retinal layers due to backscattering from intraretinal fluid accumulation, visible with hyporeflectivity at these levels.

Cystoid macular edema (CME): Large cystoid spaces involving variable depth of the retina with intervenint septae is present in 47% of all edemas and are initially mainly confined to the outer retina. In the OCT, the CME is represented by decreased intraretinal reflectivity and closely resembles its histopathology description. In eyes with long-standing cystoid macular edema, cystoid spaces fuse, resulting in a large cystoid cavity involving almost the entire retinal layer.

Serous retinal detachment (SRD): The SRD represents a 15% of all forms and is visible as an area of hyporeflectivity in the subfoveal region. This form is invariably associated to one of the two first described forms.

Tractional: Foveo-vitreal traction may result in detachment of the fovea. This can be diagnosed easily on OCT where the posterior vitreous is visible that caused traction on the fovea, resulting in underlying tractional retinal detachment.

Taut posterior hyaloid membrane (TPHM): The TPHM may result in recalcitrant macular edema with foveal detachment that can be diagnosed easily on OCT, even when subclinical. In advanced cases, it can be diagnosed clinically as a taut, shiny, glistening membrane with retinal striae on biomicroscopic retinal examination.

In the OCT, the hard exudates appear as areas of increased reflectivity with a trail of shadow behind. Furthermore, the OCT allows us to see if a macular edema is focal or diffuse.

In conclusion, the OCT gives us an *in vivo* histopathology of the retinal layers that helps in a better understanding of the disease and its pathogenesis. OCT is also a useful tool in monitoring the response to treatment.

DIAGNOSIS

The current gold standard for the diagnosis of DME is based on biomicroscopy and the ETDRS study group recommends that this diagnosis can be made if there is a thickening of the retina in macular area.

Fluorescein angiography (FA) is a standard method used for evaluating patients with DME. It is sensitive for qualitative detection of fluid leakage, even though leakage may not equate to clinical retinal edema. FA allows us to assess the severity of the characteristics of macular edema, such as fluorescein leakage and ischemic patterns[16,17].

FA is used for classifying DME into four categories: (1) Focal/multifocal leakage, well-defined focal or multifocal areas of leakage from microaneurysms; (2) Diffuse leakage, defined as the presence of widespread leakage from the retinal capillary bed or any intraretinal microvascular abnormalities (IRMA); (3) Diffuse cystoid leakage, where diffuse leakage and the pooling of dye in the cystic spaces of the macula in the late phase of angiogram is seen; and (4) Ischemic maculopathy. All these previous forms can be associated to areas of macular ischemia which can be seen as areas of capillary loss or an increase in the foveal avascular zone (FAZ). The presence of macular ischemia is an important finding in deciding the type of treatment needed and to help in those patients who suffer a loss of visual acuity of unknown origin.

Optical coherence tomography (OCT)

The current use of optical coherence tomography as a method of exploring the macular area has changed the way of diagnosing macular edema. As we said previously, OCT is an effective method of diagnosis of DME and in turn has become an essential technique for classifying the edema and observing the effect of its treatment. In the near future, OCT is likely to become the gold standard method of diagnosis and monitoring of patients with macular edema.

PATHOPHYSIOLOGY

Blood-retinal barrier concept

The pathway that results in DME is the disruption of the blood-retinal barrier (BRB). The BRB has two components: the outer and the inner barriers. The outer barrier is formed by tight junctions between retinal pigment epithelium (RPE) cells and includes zonula occludens and desmosomes. The inner barrier is formed by tight junctional complexes between retinal vascular endothelial cells and a well-differentiated network of glial cells (astrocytes and Müller cells). Several clinical studies[17-21] suggest that the inner barrier is the primary site of vascular leakage that results in DME. The disruption of the BRB leads to abnormal inflow of fluid into the neurosensory retina that can exceed the outflow and cause the accumulation of fluid in the intraretinal layers of the macula.

The mechanism of the BRB breakdown is multifactorial and secondary to changes in the tight junctions, pericyte and endothelial cell loss, retinal vessel dilatation and leukostasis and vitreo-retinal taut and traction.

Biochemical pathways

The pathogenesis includes the existence of chronic hyperglycemia, with the accumulation of free radicals, advanced glycemic end-products (AGE) proteins and protein kinase C formation and the subsequent activation of vascular growth factors (especially VEGF-A) and an increase in vascular permeability. Likewise, the appearance of areas of ischemia and inflammatory factors such as interleukin 6 also increases the synthesis of VEGF-A. All of these factors may be interrelated. For example, hypoxia and hyperglycemia upregulate VEGF-A production in diabetic retinopathy and this in turn increases vasopermeability by activating PKC. Hyperglycemia, however, can directly increase PKC and angiotensin Ⅱ, both of which cause vasoconstriction and worsening of hypoxia by their effect on endothelins[22].

One of the most important factors in the biochemical pathway is the formation of AGE, the consequence of chronic hyperglycemia. The AGE may be a primary contributor to diabetic microangiopathy. AGE has been found in the vitreous and in the ILM and can cause structural alterations in the posterior hyaloid that strengthens the vitreo-macular adhesion between the posterior hyaloid and the ILM[23]. In vascular endothelial cells, AGE may also affect the gene expression of endothelins (ET-1) and modify VEGF expression. The AGE also activates ICAM-1 in endothelial cells which increases leukocyte adhesion with the rupture of BRB[24].

Vasoactive factors

Cytokines, such as insulin-like growth factor-1 (IGF-1), on its own and in the presence of hyperglicemia (which enhances the response of retinal endothelial cells to IGF-1), overregulate the expression of VEGF in RPE cells and promote BRB disruption[25].

Other vasoactive factors, such as metalloproteases, pigment epithelium derived factor (PEDF), angiotensin Ⅱ, basic fibroblast growth factor (b-FGF) and platelet-derived growth factor (PDGF), have been implicated in the pathogenesis of DME. The matrix metalloproteinases (MMPs) regulate the degradation and modulation of the extracellular matrix that subsequently affects endothelial cell function and may cause the changes in vascular permeability. The effect of PEDF on vascular permeability is unclear despite a significant negative correlation between the vitreous level of PEDF and retinal thickness[26]. The b-FGF pathway is known to be activated in diabetes patients and plays a role in angiogenesis, stimulating endothelial cell production. Furthermore, b-FGF is produced mainly by the Müller cells in the retina and its activation results in a proliferation of astrocytes and hyalocites in the hyaloid, promoting a tight and taut hyaloid with subse-

quent DME[27]. Finally PDGF may be an important contributor to BRB maintenance by promoting the growth of retinal pericytes via PKC activation. There is evidence emerging that PDGF may be critical for the viability of pericytes[28].

Importance of Vascular endothelial growth factor-A (VEGF-A)

VEGF-A belongs to a family of different growth factors (A, B, C and D) and it has recently become accepted as one of the most potent factors in the induction of angiogenesis. Six major isoforms of VEGF-A exist: 121, 145, 165, 183, 189 and 206. VEGF-A 165 is the most important factor in the pathophysiology of DME.

VEGF is produced by RPE cells, ganglion cells, Müller cells, perycites, endothelial cells, glial cells, neurons and smooth muscle cells of the retina, of which the most important for producing VEGF are Müller cells. The upregulation of VEGF is produced by hypoxia, hyperglycemia (which itself can enhance the response of retinal cells) and cytokines, such as insulin-like growth factor 1, interleukin-6 and PKC-beta[29].

VEGF is reported[30] to produce changes in the tight junctions of retinal vascular endothelial cells with subsequent inner BRB rupture and promote angiogenesis and proinflammatory activity through the induction of ICAM-1 expression. Furthermore, in experimental models, the VEGF165 isoform injected into nonhuman primate eyes results in a rapid breakdown of the blood-retina barrier[30] accompanied by the formation of retinal microaneurysms, structures that are associated clinically with increased vascular leakage and the development of DME. Such data provides evidence that VEGF165 inhibition may not only be effective at preventing experimental diabetic blood-retina barrier breakdown, but may also have the potential to reverse DME once it has occurred.

Role of inflammation in DME

Inflammation is a nonspecific response to injury that includes a variety of functional and molecular mediators, including recruitment and activation of leukocytes. Many of the molecular and functional changes that are characteristic of inflammation have been detected in retinas from diabetic patients.

DME increases expression of ICAM-1 in the retina and produces an interaction between this adhesion molecule on retinal endothelia with the CD18 adhesion molecule on monocytes and neutrophils, contributing to the diabetes-induced increase in leukostasis within retinal vessels. This attraction and adhesion of leukocytes to the vascular wall are important components of inflammatory processes. Furthermore, leukostasis can contribute to the development of capillary nonperfusion in retinal vessels and it has been postulated that leukostasis is a factor in the death of retinal endothelial cells [31].

Importance of vitreo-retinal interface

Clinical evidence indicates that the vitreo-retinal interface may play a role in the pathogenesis of DME, the persistent vitreo-macular traction by vitreous cortex before posterior vitreous detachment (PVD) or the persistence of residual cortical vitreous (vitreoschisis) after PVD, and thickened and taut posterior hyaloid that may be adherent to internal limiting membrane (ILM), with a subsequent macular traction. In the macular area the vitreous and ILM have the strongest attachment and the ILM (which is the basement membrane of the Múller cells) is thinnest. A densely-packed collagen filament of posterior vitreous cortex penetrates the ILM in the macular area. Vitrectomy, removing all the posterior vitreous cortex and ILM peeling, has been shown to improve visual acuity and decrease macular thickening[32].

MANAGEMENT

Control of glycemia is essential in the management of diabetes mellitus to prevent and minimize the development and severity of diabetic retinopathy. The DCCT provided incontrovertible evidence that intensive management of hyperglycemia (demonstrated by the reduction of HbA1c to less than 7.0%) is associated with decreased rates of development and progression of DR in DM1 patients 833. In addition, the UKPDS showed that intensive blood control in DM2 patients resulted in a 25% risk reduction of microvascular development[34]. Therefore, the first line DME treatment should be based on good control of glycemia in diabetic patients. Furthermore, lipid and renal functional control also seems to be important in the management of patients with DME.

However, despite the systemic metabolic control values (glucose, lipids, control of renal function) being essential in patients with diabetic retinopathy, it is not sufficient if DME appears and so these patients have to take additional action in order to avoid the subsequent loss of vision.

Laser treatment

Currently the only proven treatment for DME is focal/grid laser photocoagulation. Laser treatment reduces the 3 year risk of moderate visual loss by half of 24% in untreated eyes to 12% in treated eyes[35]. Moderate visual loss is defined as a decrease in visual acuity score of 15 or more letters = 3 lines of ETDRS optotypes, corresponding to a doubling of the visual angle, e.g. from 20/20 to 20/40 in the optotypes scale.

The ETDRS have provided standard guidelines for focal laser photocoagulation, a direct treatment of microaneurysms located between 500 μ and 3000 μ off the center of the FAZ, with a spot of 75 to 100 μ and with sufficient power to bleach the retina without damaging it. A modified grid pattern of laser photocoagulation may be used for diffuse macular edema and in this form of treatment the burns are usually lighter (light gray) and smaller (50 μ).

In that edema, usually diffuse or multifocal in which the central macular laser therapy is difficult (which usually corresponds to values above 400 μ on OCT), anti-angiogenic therapy or intravitreal corticosteroids could be considered, followed by laser.

The mechanism of action of laser photocoagulation is unknown, a classical explanation being the laser-induced destruction of oxygen-consuming peripheral-retina photoreceptors with a subsequent increase in oxygen to the macular area photoreceptors. Another is a diffusion of oxygen through the laser scars to the inner retina. In the study of the diameter of retinal arterioles and venules before and after macular laser photocoagulation, around a 20% increase in constriction of the branches was observed, by which we can suppose that the improvement in retinal oxygenation leads to autoregulatory vasoconstriction which may improve DME.

Although laser photocoagulation has been shown to be beneficial, it is associated with an increase in retinal scars over time, with a possible involvement of the macular area and a decrease in vision[36].

Another laser therapy is the subthreshold micropulse diode laser photocoagulation (SMDLP), a technique that has some advantages as it requires no cooling system, is more compact, cheaper to maintain and has a long operating time. A micropulse laser has been suggested for the treatment of DME but so far there has been no definitive study to demonstrate it validity in this group of patients.

Vitreous surgery

Laser photocoagulation has no place in cases of tractional or taut DME. In such cases there is clinical evidence that vitrectomy will resolve the DME. The beneficial mechanisms may be: (1) to remove AGE ligand-induced mechanical traction between the posterior cortical vitreous and the ILM of macula and (2) to remove AGE that may also inhibit the activation of the RAGE axis and its proinflamatory effects.

Currently the discussion is centered on ILM peeling and it usefulness. It is not clear that ILM peeling is necessary for tractional-DME treatment as it may hinder the formation of epiretinal membranes but may help to remove all the cortical vitreous that may otherwise be left behind even after the posterior hyaloid is removed[37]. The complications encountered after vitrectomy include cataract, retinal detachment, epiretinal membrane, glaucoma and vitreous hemorrhage.

Intravitreal steroid injection

The use of corticosteroids as a means to treat ocular DME has emerged as an increasingly common treatment for certain patients. The Diabetic retinopathy clinical research network[38] reported 2 years' results of a multicentered, randomized, clinical trial comparing preservative free intravitreal triamcinolone (TA) and focal/grid laser for DME. In that study, 840 eyes with CSME were randomized into 3 groups: focal/grid laser, 1mg intravitreal TA and 4 mg intravitreal TA. The results showed that mean visual acuity (VA) at 2 years was better in the laser group than the two triamcinolone groups, although VA seemed to improve more rapidly in the 4 mg TA group than in the laser group. This randomized study indicates clearly that focal/grid laser is a better treatment than intravitreal TA in eyes with DME with VA between 20/40 and 20/30. The most frequent intravitreal TA complication is an increase in intraocular pressure (observed in 30% of patients) and cataract formation[38]. From this study and other non-randomized studies, we suggest that intravitreal TA is a promising therapy method for DME that is unresponsive to laser photocoagulation and for patients previously submitted for cataract surgery. Another corticosteroid currently undergoing phase Ⅲ trials is the fluocinolone intraocular implant (the RETISERT study). The preliminary 3 years' results show a higher rate of resolution in DME (about 58% responsive patients) and VA improvement of three or more lines in 28% of cases. However, 95% of phakic patients required cataract surgery and 35% of patients experienced medically uncontrolled increased intraocular pressure that needed removal of the implant or glaucoma-filtering surgery[39]. Finally, the dexamethasone intravitreal implant (Posidurex, Allergan®) is being investigated in a Phase Ⅱ trial[40]. The most important difficulty in this type of study is the safety and drug release profiles of this injectable implant. Further studies are warranted to assess its long-term efficacy and safety.

Anti VEGF therapy

In recent years, many clinical assays have been undertaken with anti VEGF drugs in order to establish the effectiveness and safety of these drugs in DME treatment.

Currently there are three VEGF inhibitors available in clinical practice: (1) Pegaptanib (Macugen®, Pfizer); (2) Bevacizumab (Avastin®, Genentech); and (3) Ranibizumab (Lucentis®, Novartis).

Pegaptanib is a VEGF-aptamer that binds the VEGF-165 isoform and has been shown to be safe with beneficial effects in the treatment of DME in a phase Ⅱ trial. This trial was based on an intravitreous pegaptanib (0.3 mg, 1 mg, 3 mg) or sham injections at study entry at week 6 and at week 12 with additional injections and/or focal photocoagulation as needed for another 18 wk. Final assessments were conducted at week 36. The results showed a safe tolerance of intravitreal injections and a reduction in retinal central thickness. The visual acuity outcomes were better in the pegaptanib group and this group was deemed less likely to need additional therapy with photocoagulation[41].

Bevacizumab is a complete full-length humanized antibody that binds to all isoforms of VEGF-A. Its use is off-label due to its oncological indication. There are currently no randomized control studies on its use in DME patients. The largest multicentered, retrospective study series was carried out on 78 eyes of 64 consecutive patients with a minimum follow-up of six months. The series received either 1.25 or 2.50 mg of intravitreal bevacizumab and the results showed an improvement in visual acuity from 0.87 to 0.6 log MAR VA with a significance of $P < 0.0001$. Furthermore, the central retinal thickness decreased from 387.0 ± 128.8 μm to 275.7±108.3 μm with a significance of $P < 0.0001$[42].

Ranibizumab is an anti-VEGF Fab fragment against all VEGF isoforms. A phase Ⅲ trial, the DRCR study, is

now finished and their results have been published[43]. It was a multicentered, randomized, clinical trial including 854 eyes of 691 patients with DME. The study aimed to evaluate intravitreal 0.5 mg ranibizumab or 4 mg triamcinolone combined with focal/grid laser compared with focal/grid laser alone for treatment of DME. The study reported that intravitreal ranibizumab with prompt or deferred laser is more effective over at least 1 year and in pseudophakic eyes and intravitreal triamcinolone-prompt laser seems more effective than laser alone but frequently increases the risk of intraocular pressure elevation.

The second study now completed is the 6 mo ranibizumab for DME, the READ-2 study, a phase Ⅱ study that was the first to compare the efficacy of ranibizumab with laser photocoagulation or a combination of both in patients with Ⅵ due to DME[44]. Ranibizumab led to significant improvements in mean VA (7.2 letters) compared with laser photocoagulation (-0.4 letters) or the combination (3.8 letters).

The third study now completed is the RESOLVE Ⅱ study, which was a 12 mo, multicentered, sham-controlled, double-masked study on DM1 and DM2 patients, with a retinal thickness [CRT] of ≥ 300 μm and best corrected VA of 73–39 ETDRS letters. The patients were randomly assigned to intravitreal ranibizumab (0.3 or 0.5 mg) or sham. The treatment schedule comprised three monthly injections, after which treatment could be stopped/reinitiated with an opportunity for rescue laser photocoagulation. Results from the RESOLVE study indicate that DME responds well to treatment with intravitreal ranibizumab over 1 year. It showed sustained improvements in BCVA and CRT over the 12 mo study period combined with a good safety profile.

In short, I now consider that in patients with focal or multifocal macular edema, focal laser treatment using the gold standard would be the best solution, whereas in patients with diffuse DME, a combination of anti-VEGF intravitreal injections with focal laser treatment would be suggested. Finally, in pseudophakic patients with diffuse DME, the intravitreal TA combined with the focal laser would be the best.

CONCLUSION

Today, blindness from diabetic retinopathy is largely preventable with timely detection and appropriate interventional therapy. However, diabetes mellitus is a systemic disease with numerous complications in organs other than the eye and concomitant disorders can exert significant influence on the development of diabetic macular edema. The first line therapy should include an optimized control of systemic considerations.

The next step would be the use of focal laser photocoagulation for focal or multifocal macular edema. Due to the poor results obtained with laser photocoagualtion in diffuse DME, we have sought alternatives to treatment. The use of intravitreal corticosteroids (for pseudophakic patients) and anti-VEGF drugs seems to be promising, although we must determine whether they can be used as a monotherapy or in combination with other treatments, such as laser photocoagulation. More clinical trials are needed that directly compare the efficacy and safety of anti-VEGF treatment with conventional laser therapy.

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