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(Article begins on next page)



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Medical management for the prevention and treatment of diabetic macular edema

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Abstract

Recent clinical trials have changed the management paradigm for diabetic macular edema (DME). There is an urgent need to identify the most effective ways of preventing retinopathy or intervening at an early, asymptomatic stage in order to preserve vision. The rise in the incidence of diabetes is a serious public health concern. Grading and screening programmes help to identify sight threatening diabetic retinopathy in the community early and facilitate timely referral to an ophthalmologist. Systemic therapies for DME target the key modifiable risk factors: metabolic and blood pressure control. There may also be a role for modification of the renin-angiotensin system and for lipid lowering agents. Improved glycemic and blood pressure control remain the most effective ways of reducing morbidity from DME. Fenofibrate also has beneficial effects, but the mechanism for this remains unclear. Multiple new treatments are in the pipeline, and these are expected to change our approach to DME for the first time in 30 years.

1. Introduction

Recent clinical trials (DRCR Protocol-I, RESOLVE) have changed the management paradigm for diabetic macular edema (DME). More sophisticated protocols than the ETDRS focal/grid laser for clinical significant macular edema (CSME) versus no laser will become more common. Given that most of the specifically ophthalmological treatments are suitable for fairly advanced disease in which vision has often already been lost, it is important to try to find ways of either preventing retinopathy or intervening at an early, asymptomatic stage in order to preserve vision. The prevention of ocular morbidity from diabetic retinopathy (DR) therefore requires that we consider other factors. These include the implications of the ways by which we grade the severity of DR and DME and the role played by screening programs. In addition, we need to consider carefully the effects of systemic treatment for diabetes on DR, and the potential for medical therapy to prevent the development or progression of DME. There have been mixed messages on the effects of systemic treatment on DR.²⁶ We highlight the key epidemiological issues, outline the role of grading systems and screening programs, and discuss the management options for DME in terms of systemic therapy that is directed at the key modifiable risk factors.

2. Epidemiology

In January 2011, over 220 million people worldwide had diabetes,^A and the World Health Organization projects that this will rise to 366 million by 2030.^B Type 2 diabetes in particular has reached epidemic proportions,⁹ the result of a combination of longevity and a rapid increase in obesity. This rise in the incidence of diabetes is a major public health concern⁸ and ³¹ because it is likely to be followed by a rise in its associated complications. DR is the most common microvascular complication of diabetes¹⁵ and is the leading cause of blindness in the working-age populations of developed countries.

The Eye Disease Prevalence Research Group at the National Eye Institute, Bethesda, estimated that, in March 2010, 4.1 million Americans had diabetic retinopathy and projected that by 2020 this would rise to

7.2 million.^C Analyzing data from several high quality ophthalmological studies, we estimate that one in every 12 Americans with diabetes aged 40 or older has vision threatening retinopathy. A recently published study of the prevalence of DR and vision-threatening DR in a nationally representative sample of U.S. adults aged 40 years or older showed that approximately 1.5% (95% confidence interval [CI], 1.1–2.2%) of adults with diabetes had proliferative DR and 2.7% (95% CI, 1.8–4.0%) had CSME.⁴¹ Over a 10-year period, non-clinically significant DME and CSME will develop in 14% and 10%, respectively, of Americans with known diabetes.²⁴ Approximately half of all patients with DME will lose two lines or more of vision within 2 years.¹⁴

Data from epidemiological studies, however, show remarkable improvements in the care and management of diabetes over the last 30 years.²³ These have been associated with significant decreases in the prevalence and incidence of DR and visual impairment in type 1 diabetics.²³ Only limited long-term epidemiological data are available to determine whether similar trends exist for type 2 diabetics.²³ The number of people with type 2 diabetes is growing, and this includes significant growth in communities where access to health care is poor. Epidemiologic studies have disclosed a high incidence of DR and the association of this with poor glycemic and blood pressure control, both of which are more common in these communities.

3. Standardized grading systems

The main symptom of diabetic retinopathy is reduced vision, but this occurs only when the condition is advanced and may be irreversible.³⁰ Early changes in DR are generally asymptomatic, and treatment may be needed long before patients are aware of losing any vision.³⁰ Early changes need to be targeted in order to provide the best chance of preserving good visual acuity.

Staging or grading of diabetic retinopathy can be done in many different ways. Although the ETDRS group provided grading guidelines that are considered to be the gold standard¹⁵ and that have often been used to grade DR in research studies,¹² the guidelines may be too complex for regular use in clinical practice.⁹ The International Clinical Diabetic Retinopathy and Diabetic Macular Edema Disease Severity Scales (Tables 1 and 2)⁹ and ³⁴ were therefore proposed. Derived from the ETDRS and the Wisconsin Epidemiologic Study of Diabetic Retinopathy, they are designed to be more clinically relevant and to facilitate communication between practitioners.⁹

Table 1.
The international clinical diabetic retinopathy severity scale

Proposed disease severity level	Findings observable upon dilated ophthalmoscopy
No apparent retinopathy	No abnormalities
Mild NPDR	Microaneurysms only
Moderate NPDR	More than just microaneurysms but less than severe NPDR
Severe NPDR	Any of the following: - >20 intraretinal hemorrhages in each of 4 quadrants

Proposed disease severity level	Findings observable upon dilated ophthalmoscopy
	<ul style="list-style-type: none"> - Definite venous beading in 2+ quadrants - Prominent intraretinal microvascular abnormalities in 1+ quadrant <p>And no signs of proliferative retinopathy</p>
PDR	<p>One or more of the following:</p> <ul style="list-style-type: none"> - Neovascularization - Vitreous/preretinal hemorrhage

Based on data from Fong et al¹⁵ and DRS report 7.³⁴

Table 2.

The international clinical diabetic macular edema disease severity scale

Proposed disease severity level	Findings observable upon dilated ophthalmoscopy
DME apparently absent	No apparent retinal thickening or hard exudates in posterior pole
DME apparently present	Some apparent retinal thickening or hard exudates in posterior pole
DME present	<p><i>Mild DME</i> (some retinal thickening or hard exudates in posterior pole but distant from the center of the macula)</p> <p><i>Moderate DME</i> (retinal thickening or hard exudates approaching the center of the macula but not involving the center)</p> <p><i>Severe DME</i> (retinal thickening or hard exudates involving the center of the macula)</p>

Based on data from Fong et al¹⁵ and DRS report 7.³⁴

The International Clinical Diabetic Retinopathy and Diabetic Macular Edema Disease Severity Scales when used in isolation, however, do not provide guidance as to how patients with the different levels of retinopathy should be managed. The American Diabetes Association guidelines recommend an annual ophthalmic examination, but adherence to this is poor.⁹ Patients at high risk of vision loss because of pre-existent DR or a long duration of diabetes have rates of adherence to this guideline as low as 61% and 57%, respectively.³ Statistics like this highlight the need for both doctors and patients to be educated about DR and its potential consequences.⁹ If early detection and treatment of DR is to be achieved, then screening programs, with standardized grading and referral of patients for ophthalmological review, are likely to be beneficial. Both doctors and patients need to understand the potential for loss of vision, the ways in which to detect this, and the interventions that reduce the risk of visual loss. Clinical outcome is better if patients are screened and treated early.²

4. Diabetic retinopathy screening programs

The purpose of a DR screening program is, therefore, to identify sight-threatening DR/DME early and facilitate timely referral to an ophthalmologist. Different approaches are taken in different countries. In the United Kingdom there are three DR screening programs. England and Wales share one, and Scotland and Northern Ireland each have their own. Screening is performed by digital fundus photography, and these photographs then undergo detailed analysis and grading by trained screeners who follow standardized guidelines (Table 3). They decide whether or not a particular patient needs to be referred to the hospital eye services, and/or when they next need to have their eyes photographed. Most patients can have their photographs taken without the use of dilating eye drops, but if this is not possible, then the pupils should be pharmacologically dilated. The details of the grading systems used differ slightly, but the aim is the

same: to enable those with sight threatening retinopathy, whether they are symptomatic or asymptomatic, to have their eye disease identified and then managed in a timely fashion to reduce their risk of visual loss.

Table 3.
Guidance for the early treatment of diabetic retinopathy

Grade of retinopathy	Management
No retinopathy (R0, M0)	Routine diabetes care Arrange annual screening
Background retinopathy (R1) <ul style="list-style-type: none"> • microaneurysm(s) • retinal hemorrhage(s) 	Routine diabetes care Arrange annual screening
Pre-proliferative retinopathy (R2) <ul style="list-style-type: none"> • venous beading, venous loop, or reduplication • intraretinal microvascular abnormality (IRMA) <ul style="list-style-type: none"> • multiple deep, round, or blot hemorrhages • (cotton wool spots—careful search for above features) 	<i>Achievable standard:</i> 95% seen by ophthalmologist in <13 weeks <i>Minimum standard:</i> 70% seen by ophthalmologist in <13 weeks 100% seen by ophthalmologist in <18 weeks
Maculopathy (M1) <ul style="list-style-type: none"> • exudate within 1 disk diameter (DD) of the center of the fovea • circinate or group of exudates within the macula • retinal thickening within 1 DD of the center of the fovea (if stereo available) • any microaneurysm or hemorrhage within 1 DD of the centre of the fovea only if associated with a best VA of $\leq 6/12$ (if no stereo) 	<i>Achievable standard:</i> 95% seen by ophthalmologist in <13 weeks <i>Minimum standard:</i> 70% seen by ophthalmologist in <13 weeks 100% seen by ophthalmologist in <18 weeks
Proliferative retinopathy/rubeosis iridis (R3) <ul style="list-style-type: none"> • new vessels on disk (NVD) <ul style="list-style-type: none"> • new vessels elsewhere (NVE) <ul style="list-style-type: none"> • pre-retinal or vitreous hemorrhage • pre-retinal fibrosis \pm tractional retinal detachment 	<i>Achievable standard:</i> 95% seen by ophthalmologist <2 weeks <i>Minimum standard:</i> 70% seen by ophthalmologist in <2 weeks 100% seen by ophthalmologist in <4 weeks
Very urgent <ul style="list-style-type: none"> • sudden loss of vision • retinal detachment 	Emergency referral to ophthalmologist (same day)

Adapted from the UK National Screening Programme for Diabetic Retinopathy Workbook 4.3, last updated June 2009.⁵

All diabetic patients who are not already attending the hospital eye services should be screened at least once a year. This reduces the risk of patients being lost to follow-up and may be easier for patients to remember and comply with than less frequent schedules. Some patients are, however, either unable or unwilling to attend. There are some for whom screening cannot be performed using digital photography (e.g., because of co-existing pathology that interferes with the ability of photographers to take gradeable photographs), and these patients have their annual review in the hospital eye service instead.

In the United States, DR screening programs have not been widely implemented. The Joslin Diabetes Center in Boston, however, has developed the Joslin Vision network to carry out screening via a remote imaging system, a centralized grading center, and a data storage system. Commercial services such as Inoveon (Oklahoma) and EyeTel (Virginia) transmit images to a reading center at the Wilmer Eye Institute, Baltimore.⁹

It is easier to detect DR than DME on digital photographs, particularly if non-stereoscopic images are used. Surrogate markers for DME, such as the presence of hard exudates, microaneurysms, or blot hemorrhages, have to be used to identify those at risk of sight threatening maculopathy. Now that spectral domain optical coherence tomography (SD-OCT) is becoming more widely available, we need to consider the potential role that this non-invasive imaging could play in identifying those at risk. The difficulty with SD-OCT is that it may pick up many patients with clinically insignificant macular edema who may not require any treatment. In addition, it would increase the costs associated with retinopathy screening, and operation of the SD-OCT would be an additional skill required by screening photographers. Whether the cost of the addition of SD-OCT to DR screening is justified has yet to be demonstrated. Fundus fluorescein angiography is more sensitive than photography for detecting DME,²⁹ but is not suitable as a screening tool because it is invasive, expensive, and carries a risk of adverse reactions.⁹

An alternative strategy for DR/DME screening is to use automated methods for detection of DR from digital photographs. As with other screening modalities that rely on imaging, these risk missing disease outside the photographic fields,⁹ but might, however, be helpful in determining which retinal lesions warrant further investigation by an ophthalmologist. The sensitivity and specificity of this technology have been reported to be 77.5–88.5% and 88.7–99.7%, respectively.¹⁷ In contrast, ophthalmoscopy can be used for screening purposes, but unsurprisingly is less sensitive than fundus photography in the hands of inexperienced doctors. With additional training for these doctors, it might be a clinically acceptable and cost-saving option for determining which patients should be referred to an ophthalmologist.⁹

5. Systemic therapy for DME

The main aims of systemic therapy in DR/DME are to reduce the risk of diabetic patients developing these conditions in the first place and to reduce the risk of progression of existing retinopathy or maculopathy to more severe, sight-threatening forms. Systemic therapies are designed to target the key modifiable risk factors, which in the case of both DR and DME are metabolic and blood pressure control. There may also be a role for modification of the renin-angiotensin system (RAS) and for lipid lowering agents. At present, the

major risk factors that cannot easily be modified include duration of diabetes, residual beta-cell function, insulin resistance, and genetic predisposition.

5.1. Modifying metabolic control

Improving glycemic control and lowering the level of glycosylated hemoglobin (HbA1c) is, at present, the most effective medical treatment to slow the progression of DR.¹⁵ Central to the discovery that optimal metabolic control could reduce the incidence and progression of DR were the Diabetes Control and Complications Trial (DCCT) in type 1 diabetics¹⁰ and the United Kingdom Prospective Diabetes Study (UKPDS) in type 2 diabetics.³⁷ Intensive glycemic control was found to have effects that persist well beyond the course of treatment.¹¹ The DCCT and UKPDS established optimizing metabolic control as a priority and led to the suggestion that it should be implemented early and maintained for as long as is safely possible.

There are, however, new approaches to metabolic control. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study was stopped because of increased all-cause mortality in people whose glucose was extremely tightly controlled with insulin and multiple oral agents.¹ Only mortality showed an adverse trend, and this was inconsistent with other outcomes. Inspection of the time-to-event curves suggests that chance is a likely explanation, but a real effect cannot be excluded.¹⁹ The UK national clinical guideline for management of type 2 DM recommends a glycosylated hemoglobin target of 6.5%,^D except where this requires combined intensive treatment with insulin and an oral agent, and where life expectancy is less than 5 years (not to be confused with old age).¹⁹

Many patients fail to achieve or maintain these levels of metabolic control. In those who do keep their HbA1c low, there is an increased risk of hypoglycemia. The incidence of severe hypoglycemia was three times higher in the DCCT intensive treatment group compared with the conventional treatment group, and for this reason seeking perfect control in type 1 diabetes is unrealistic. Fong and colleagues point out that intensive glycemic control in the DCCT was also associated with increased weight gain, an average of 4.6 kg more than those in the conventional treatment group.¹⁵ Optimal metabolic control in type 2 diabetes is also very difficult to achieve. Intensive treatment was also associated with increased hypoglycemic episodes and weight gain.¹⁵ In the UKPDS, metabolic control deteriorated over time, possibly as a result of progressive loss of islet beta cell function,³⁶ but this effect was not seen in ACCORD, leading to the suggestion that if titration of glucose-lowering treatments continues, even in non-intensive conditions, it may be possible to maintain glycosylated hemoglobin at target for at least 16 years from diagnosis.¹⁹

The American Diabetes Association and the European Association for the Study of Diabetes consensus statement in 2009²⁸ gives detailed guidance on the medical management of type 2 diabetes in the form of a treatment algorithm. Their recommendations emphasize the following:

- Achievement and maintenance of near normoglycemia (HbA1c <7.0%)

- Initial therapy with lifestyle intervention and metformin
- Rapid addition of medications, and transition to new regimens, when target glycemic goals are not achieved or sustained.
- Early addition of insulin therapy in patients who do not meet target goals.

A further approach to lowering HbA1c has been described by Trento and colleagues.³⁵ In their multicenter Rethink Organization to iMprove Education and Outcomes (ROMEIO) trial they demonstrated that seeing and educating type 2 diabetic patients in groups of 9 or 10 every 3 months has a statistically significant beneficial effect on their metabolic control. This approach is thought to be a feasible way of improving patient outcomes in everyday clinical practice and has been demonstrated to be reproducible in multiple clinical settings.

5.2. Modifying blood pressure ± the renin-angiotensin system

Hypertension is a major risk factor for DR and DME. The Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) found that progression of retinopathy was associated with higher diastolic blood pressure at baseline and an increase in diastolic blood pressure over a 4-year follow-up period.²²

The UKPDS demonstrated that control of blood pressure (systolic blood pressure <150 mm Hg) led to a reduction in the progression of diabetic retinopathy and reduced need for laser treatment in the tight blood pressure control group compared with the less tight control group.³⁸ In the UK, this finding has contributed to the establishment of a target blood pressure measurement in diabetic patients of 140/80 mm Hg. The American Diabetes Association and the National Institutes of Health recommend a target blood pressure of less than 130/80 mm Hg for diabetics.

The ACCORD study, however, produced contrasting findings to those of UKPDS in terms of the effects of intensive blood pressure control on the progression of DR.²⁰ In ACCORD, intensive blood pressure control did not reduce progression of DR. Tight or intensive blood pressure control was said to be a systolic blood pressure (SBP) <120 mm Hg, and standard control was SBP <140 mm Hg. Lim and colleagues²⁶ raised the question as to whether this could indicate a “floor” to the benefits of lowering blood pressure below normal ranges. The ACCORD authors accepted that it is possible that, in older patients with established type 2 diabetes, an efficacy “floor” for SBP has been reached.

At present there is no definitive evidence that any one method of lowering blood pressure is superior.³⁰ The Appropriate Blood Pressure Control in Diabetes (ABCD) trial, however, was a prospective randomized trial comparing the effects of intensive and moderate blood pressure control in hypertensive type 2 diabetic subjects.¹³ Nisoldipine, a calcium-channel antagonist, was compared with enalapril, an angiotensin-converting enzyme (ACE) inhibitor, as a first line antihypertensive agent for the prevention and reduction of progression of the complications of diabetes. Both drugs had similar effects on blood pressure control, but after using a multiple logistic regression model with adjustment for cardiac risk factors, the

authors found that nisoldipine was associated with a higher incidence of fatal and nonfatal myocardial infarctions. There was no difference between the moderate and intensive treatment groups with regard to the progression of diabetic retinopathy. The same drugs were used to investigate the effects of blood pressure lowering in normotensive subjects. Progression of DR was less frequent in those who were treated with either nisoldipine or enalapril and had blood pressure measurements <140/90 mm Hg at baseline ($p = 0.019$).

Attempts have been made to establish whether blockade of the RAS can reduce the incidence or progression of DR. On the basis that antihypertensive therapy, especially with ACE inhibitors, can slow progression of nephropathy, the EUCLID study group investigated the effect of lisinopril on progression of retinopathy in normotensive type 1 diabetics.⁶ They found that lisinopril can decrease retinopathy progression in non-hypertensive patients who have type 1 diabetes with little or no nephropathy. Whether this effect is due to RAS blockade or a benefit from incremental lowering of blood pressure in normotensive subjects remains unknown.¹⁵ As stated by Fong et al, other studies investigating the effect of ACE inhibitors on the progression of DR in type 1 diabetics have shown no significant benefits.⁴ and ²⁵

The Diabetic REtinopathy Candesartan Trials (DIRECT) were a group of large, randomized trials designed to assess whether blockade of the RAS with candesartan reduced the incidence or progression of diabetic retinopathy in normoalbuminuric normotensive patients.⁵ Almost 5 years of candesartan treatment in type 1 diabetes reduced the incidence of retinopathy by two or more steps (ETDRS) in severity by 18% ($p = 0.0508$) and, in a post hoc analysis, reduced the incidence of retinopathy by three-step progression by 35% ($p = 0.034$). In type 1 diabetes patients there was no effect on progression of established retinopathy. In contrast in type 2 diabetes, 5 years of candesartan treatment resulted in 34% regression of retinopathy ($p = 0.009$). Importantly, an overall significant change towards less-severe retinopathy was noted in both type 1 and 2 diabetes ($p \leq 0.03$). Although analysis was corrected by blood pressure values throughout the trial, it is impossible to prove conclusively that these effects were due to RAS blockade and not to blood-pressure-lowering effects.⁴⁰

The favorable effect of blocking the RAS was confirmed by the RASS study,²⁷ a multicenter, randomized, double-blind, placebo-controlled, investigator-initiated trial conducted on 285 normotensive patients treated with enalapril 20 mg/day, losartan 100 mg/day, or placebo and followed for 5 years. The end point was progression on a retinopathy severity scale of two steps or more. This occurred in 38% of patients receiving placebo, but only 25% of those receiving enalapril ($p = 0.02$), and 21% of those receiving losartan ($p = 0.008$). Enalapril and losartan increased the likelihood of slowing the progression of retinopathy by 65% and 70% respectively, apparently independent of changes in blood pressure.

5.3. Lipid-lowering agents

In 1991, Gordon et al¹⁸ found that lipid-lowering therapy reduced hard exudates and microaneurysms in DR. Lipid-lowering agents may decrease the risk of vision loss in patients with DR.⁷ In the UK the advice is to aim for total cholesterol less than 4 mmol/l or low density lipoprotein (LDL) cholesterol less than 2

mmol/l.³⁰ The American Diabetes Association has set desirable LDL cholesterol, HDL cholesterol, and triglyceride levels as <100, >40 in men/>50 in women, and <150 mg/dl, respectively. The first line of lipid-lowering therapy is usually treatment with a statin, and this is sometimes started even when cholesterol levels are within the normal range because cardiovascular disease is such an important cause of morbidity and mortality in diabetics. In cases where statins fail to lower lipid levels, fibrates might help to lower risk.³⁹

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study on the effects of long-term fenofibrate on cardiovascular events in patients with type 2 diabetes found beneficial effects on microvascular complications that included DR. There were significant benefits in terms of the requirement for first laser and development of DME. Fewer patients who received fenofibrate needed laser treatment than in the control group (3.4% vs 4.9%; $p = 0.0002$, 95% CI, 43–143).²¹ The protective effects of fenofibrate seemed to be independent of blood glucose, blood pressure, and baseline lipid values.³⁰ The conclusions from this study were, however, limited by uneven statin use.²⁶ The ACCORD-Eye study³³ confirmed the results of the FIELD study. In ACCORD-Eye, the addition of fenofibrate to basal statin therapy resulted in a significant reduction in the progression of retinopathy, in a similar manner to that observed with intensifying blood glucose control, but with a good safety profile and without increasing the risk of hypoglycemia.³² The fact that the effects of fenofibrate repeatedly appear to be independent of lipid concentration has raised more questions as to the mechanism of action of the drug and the pathogenesis of DR/DME.

6. Conclusion

Improved glycemic control and blood pressure control remain the most effective ways of reducing morbidity from DR and DME. New data from large, well-designed studies such as ACCORD and ACCORD-Eye have raised interesting questions about study design, methods of measuring outcomes, and even about the pathophysiology of DR and DME. In particular, the way in which fenofibrate produces its beneficial effects on DR and DME remains unclear. There may be a “floor” effect in the lowering of blood pressure in patients with established type 2 diabetes, although this would conflict with findings from older studies that demonstrated that lowering blood pressure, even in normotensive patients, has a beneficial effect in terms of progression of DR. Almost 10 years ago the Steno-216 study suggested that treating multiple risk factors in type 2 diabetic patients improved outcomes for both microvascular and macrovascular complications. Given that addressing the key risk factors for DR and DME involves systemic medical treatment, it is of paramount importance that ophthalmologists caring for patients with diabetic eye disease are familiar with this and can effectively discuss the options with patients and medical colleagues. Multiple new ophthalmological treatments are in the pipeline and are expected to significantly change our approach to DME in the eye clinic for the first time in 30 years.

7. Method of literature search

The literature search was conducted on PubMed, using the search terms diabetic macular (edema OR oedema) (management OR treatment), and covered all articles from January 2010 to June 2012. From the results of this search we reviewed all articles that were published in English and selected those that were

judged to be of clinical importance in terms of the medical management of diabetic macular edema. Where the key articles from our search cited other relevant peer-reviewed references, guidelines, press releases or reports then these were also included.

8. Disclosure

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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