Diabetic Macular Edema *(DME)*

Guidelines

Developed by the
DME Steering Committee from:

MINISTRY OF HEALTH
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Diabetes and blindness **due to DME**

Blindness, when it occurs has a heavy impact on the daily lives of not only patients, but also their immediate families and society at large. WHO data shows that, nearly half of diabetics in European countries have severe visual impairment. [1]Along with other major chronic diseases such as cancer and respiratory infections, blindness is among the leading disease burdens worldwide. It also carries a significant social and economic impact, as the majority of patients in which blindness occurs as a result of diabetic complications fall in relatively younger age groups.

As a large majority of the visually impaired will be unemployed, it becomes clear that blindness becomes a major burden to society. WHO reported that 85% of global visual impairment is avoidable. This includes diabetes induced vision loss as this can be controlled or prevented with existing and new diagnostic and treatment options. This, however, only can be achieved if steps are taken to monitor and detect diabetic retinopathy changes in the eye at an early stage.

Diabetes and blindness: **What is the link?**

Diabetic retinopathy is a complication of diabetes that results from damage to the blood vessels of the retina. The risk of related visual loss or visual impairment in the population with diabetes is up to 25 times higher than the population not affected by diabetes. Visual loss is the most feared complication of diabetes due to its functional effect on the patient.

There are two major stages of diabetic retinopathy: an early stage of non proliferative diabetic retinopathy and a later stage, proliferative diabetic retinopathy. In addition, fluid leakage into the area of the retina which is responsible for clear central vision is, results in Diabetic Macular Oedema (DME). This condition can occur in any stage of diabetic retinopathy, and in any patients with type 1 or type 2 diabetes. Diabetic Macular Oedema is a specific category of diabetic retinopathy. When the oedema involves the center of the retina,it can threaten sight and cause moderate to severe visual loss.

Even though DME only affects a certain percentage of diabetic patients, its burden is likely to increase worldwide. The diabetic population is projected to increase worldwide from 55.2 million in 2010 to 66.2 million in 2030 and it is anticipated that DME cases will increase proportionately.[2]

1. Visual impairment and blindness – Factsheet, World Health Organization http://www.who.int/mediacentre/factsheet/fs282/en/index.html
2. IDF Diabetes Atlas, International Diabetes Federation http://atlas.idf-bxl.org/ru/node/50

Diagnosis Options: **Prevention is possible**

Although the disease can permanently damage the retina and hence lead to visual impairment and even blindness, the sight can be restored if the two possible sight-threatening complications, DME or proliferative diabetic retinopathy, are diagnosed at early stages. Periodic eye screening/examination will ensure early detection of diabetic retinopathy or DME, thus preventing visual loss. The assessment can be done with a non mydriatic fundus camera or through dilated pupils by an Ophthalmologist or doctors trained to do an adequate examination.

Regular eye assessment is known to allow for early diagnosis and timely treatment, but the vast majority of diabetic patients as well as many doctors, are still unaware of the critical need to undergo regular eye checks. This possibly is due to lack of both comprehensive screening programmes and sufficient cooperation and communication between the different disciplines of the medical fraternity.

Treatment options **against DME**

Various treatments exist for patients with diabetic retinopathy or DME, involving both surgical and medical therapies. The control of blood sugar, blood pressure and possibly hyperlipidemia remains the key elements in the fight against visual loss due to DME or other form of Diabetic Retinopathy.

It must be recognized that laser will still have a role in some patients including the following: (1) if access to anti-VEGF therapy (see below) is not available, (2) in cases that have persistent macular edema despite at least 6 months of anti-VEGF therapy, and (3) as an option instead of observation or anti-VEGF therapy when DME involves the center of the macula but visual acuity is very good or excellent. It rarely improves vision when the visual acuity already is very good or excellent; it can improve vision when there is impairment approximately 30% of the time (not as often as with anti- VEGF therapy) and avoid vision loss in about 80% to 85% of cases but still results in vision loss in about 15% to 20% of cases over time.

Today, Anti vascular endothelial growth factor (VEGF) has proven to significantly improve visual acuity in patients with DME more often than laser and avoid vision loss more often than laser by preventing the blood vessels from leaking fluid and causing Macular Oedema. Some of these compounds have been licensed for several years to treat the neovascular or "wet" advanced stage of Age-related macular degeneration (AMD). These drugs have already gone through necessary clinical trials and have obtained regulatory approval to treat also DME patients

in indicated cases. Studies including The Diabetic Retinopathy Clinical Research Network (DRCR.net) available at www.drcr.ent conclusively show that combinations of anti-VEGF compounds with prompt laser treatment or deferral of laser for at least 6 months (and applied only after 6 months in cases where DME persists and no longer improves with anti-VEGF therapy) offer a higher chance of improving vision-related function and quality of life.

There may be a role for steroid in management of DME. While not superior to laser alone, intravitreal corticosteroids, alone, or in combination with laser are more effective than no treatment, and in cases which are pseudophakic, may be equally effective to anti-VEGF therapy (although intraocular pressure problems result in the need for additional management of that complication, precluding the decision to use corticosteroids prior to trying anti-VEGF in pseudophakic patients for many clinicians). Emerging evidence suggest that, in chronic oedema both in DME and RVO, there is an inflammatory cascade that is not necessarily addressed by anti-VEGF therapy; as such, corticosteroids may have a role in cases of persistent DME despite anti-VEGF therapy for at least 6 months, especially in pseudophakic patients where treatment would not result in cataract or the need to remove a cataract in the presence of a history of DME, when further vision loss may occur due to exacerbation of macular edema after cataract surgery. .

This guideline in management of DME is to standardize the best treatment options for the condition and to give the Ophthalmologist current knowledge on the latest practice patterns and the need to timely referral to retina specialists for further management when necessary.

Potential Patient Safety Concerns with **regards to unendorsed (off label) treatment**

As with any medication, new compounds used for DME or RVO (retina vein occlusion) should be formally approved and endorsed for use. Unendorsed treatment options of DME have become an issue of late. The drug used has been authorized for an altogether different indication, in a different dosage, form and route of administration. Here we use the term unendorsed or ‘off label’ to mean that.

It is therefore imperative that patients have a right to be adequately informed of the choices they have between approved and unendorsed medicines to treat their disease and of the consequences that this choice entails.

Guidelines for
Managing Diabetic Macular Edema

Central involved DME with vision impairment	• Ideally, licensed anti-VEGF (ranibizumab) with proven efficacy & safety is administered; role of bevacizumab with respect to efficacy and systemic as well as ocular safety remains controversial • If anti-VEGF not available, then focal/ grid laser
Central-involved DME with very good vision, *(3 options at this time, with community equipoise regarding best management)*	• Observation until vision impairment, then either focal/ grid laser or anti-VEGF therapy if DME persists • Focal/ grid laser until vision impairment, then anti-VEGF therapy if DME persists
Non-central involved DME	• Observation until central-involved DME, then see above Focal/ grid laser in selected cases where observation is judged to be inferior, such as during pregnancy or rapidly worsening cataract, or edema rapidly extending towards the center of the macula

**VEGF-Trap may have a future role in the treatment of DME. However, currently FDA & EMEA approval for VEGF-Trap to treat DME has not been obtained.*

How to apply the best of focal/ Grid laser

- *Typically laser is applied only to thickened areas of retina, with direct treatment to microaneurysms within thickened areas and grid treatment to other thickened areas without microaneurysms that have not been treated previously*
- *Focal/ grid laser generally should be repeated as often as every 3-4 months if edema persists or is not improving while giving anti-VEGF therapy (if available) (as long as it is believed that additional laser may be of benefit)*

How to apply anti-VEGF therapy:

Improving: After initiating therapy, if improving on OCT or VA after injection, inject again (improving = OCT central subfield thickness decreased by ≥ 10% or VA letter score improved by ≥ 5 letters, or ~1 line).

Stable: Not improving or worsening on OCT or VA: Sometimes inject, sometimes withhold injection

- If only stable since the last injection ➜ Inject at least one more time to be confident that both OCT and VA are stable and not improving
- If stable for at least 2 consecutive injections:
  - If OCT CSF (Stratus equivalent) <250 µm and VA 20/20 or better ➜ Defer injection, return in 4 weeks; if stable or improve, double follow-up to 8 weeks; if still stable or improve, double follow-up to 16 weeks; if worsen (see below), inject
  - OCT CSF ≥250 µm or VA worse than 20/20:
    - If less than 6 months of injections ➜ Inject
    - If ≥ 6 months of injections ➜ Defer injection
      - Consider focal/ grid laser if OCT CSF (Stratus equivalent) >250 µm
      - Return in 4 weeks
        - If stable or improve, double follow-up to 8 weeks; if still stable, double follow-up to 16 weeks
        - If worsen, inject (see below)

Worsening: After withholding injection, when stable, if worsening on OCT or VA, resume injections (worsening = OCT central subfield thickness increased by >10% or visual acuity letter score decreased by >5 letters, or ~1 line)

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