Management Strategies for Diabetic Macular Oedema

a report by

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Diabetic retinopathy remains the major cause of blindness in working-age adults in developed nations. Diabetic retinal lesions are still reversible at the initial stage of mild non-proliferative diabetic retinopathy, opening real opportunities for effective intervention. Four main alterations characterise the early stages of diabetic retinopathy:

- microaneurysms/haemorrhages;
- alteration of the blood–retinal barrier (BRB);
- capillary closure; and
- alterations in the neuronal and glial cells of the retina.

These alterations may be monitored by red-dot counting on eye fundus images, and by leakage and retinal thickness measurements.[1,2] A combination of these methods through multimodal macula mapping has contributed to the identification of three phenotypes[2] showing different patterns of evolution:

- pattern A, including eyes with reversible and relatively little abnormal fluorescein leakage, a slow rate of microaneurysm formation and normal foveal avascular zones;
- pattern B, including eyes with persistently high leakage values and high rates of microaneurysm accumulation; and
- pattern C, including eyes with variable leakage, high rates of microaneurysm accumulation and abnormal foveal avascular zones.

The identification of different phenotypes in the initial stages of the disease opens the door for genotype characterisation, development of targeted treatments and personalised approaches to management strategy.

Retinopathy screening in patients with diabetes is now accepted as an essential step in the appropriate management of diabetic retinopathy.

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First of all we have to identify the patients at risk of developing progressive retinopathy. The fundamentals of diabetic retinopathy management are:

- the identification of patients at risk of diabetic retinopathy;
- encouragement of patient and primary care physician involvement in the management of the patient's systemic disorder, with special attention to blood sugar control, serum lipids and blood pressure; and
- to treat patients at risk of visual loss.

Diabetes is characterised by poor glycaemic control and is frequently associated with hypertension and abnormally increased blood lipid vessels. Therefore, first-line therapy must be directed at controlling these risk factors, and must include regular eye examinations to detect progression in retinal vascular disease. This is particularly important since not all diabetic patients develop progressive retinopathy, and may remain with minimal retinopathy changes and good vision for their entire lifetime. However, how the retinal vasculature is affected in diabetes is still not clear and appears to be a multifactorial process, probably conditioned by genetic factors. At least four mechanisms are now considered to be involved: non-enzymatic glycation, oxidative-reductive stress, aldose-reductase deprivation and diacylglycerol-mediated activation of protein-kinase C (PKC). Increased production of vascular endothelial growth factor (VEGF) has also been shown to be present, at least when ischaemia predominates. Furthermore, an inflammatory component probably associated with an attempt to repair the disease damage is considered to play an important adjunctive role.[3]

The most frequent cause of progressive visual loss due to diabetes is diabetic macular oedema. It may affect central vision from the early stages of the retinopathy, particularly when it involves the central foveola. Diabetic macular oedema may cause a significant decrease in visual acuity in the absence of severe retinopathy. Retinal oedema occurs when there is any increase of water in the retinal tissue resulting in an increase in its volume, i.e. thickness. This increase in water content of the retinal tissue may initially be intracellular or extracellular.

In the retina a specialised structure exists – BRB – that regulates the movements of fluids in and out of the retinal tissue. In diabetes, the inner BRB (retinal vascular endothelium) opens, resulting in increasing movements of fluids and molecules into the retina. In a situation of open BRB there is extracellular retinal oedema and the situation of immune privilege is altered, creating the condition for a systemic inflammatory repair response. When the BRB is open, the retinal oedema accumulation follows Starling's Law.[4] With an open BRB any loss of equilibrium among hydrostatic, oncotic and tissue pressure gradients across the retinal vessels contributes to increased water movements and more oedema formation.

We are now able to measure changes in retinal thickness and identify, using non-invasive instrumentation, the evolution of macular oedema. Optical coherence tomography (OCT) provides cross-sectional retinal images and contributes to the visualisation of retinal oedema by showing cystoid oedema spaces and serous retinal detachment. More importantly, it measures retinal thickness. Maps of retinal thickness can be displayed topographically, identifying the areas of oedema and their distance to the foveola.

It is now possible to closely follow changes in retinal oedema and to characterise diabetic macular oedema by considering the following factors.

- The distribution of the oedema – is it focal or diffuse?
- Is it recent or chronic?
- Is the foveola preserved or is it involved, and if so how much?
- Is the BRB open (vascular leakage)?
- Are there signs of retinal pigment epithelium (RPE) dysfunction?
- Is there diffuse oedema with RPE signs of damage?
- Are there OCT 'cysts' (an indication of low tissue pressure facilitating oedema progression)?
- Are there signs of vitreo-retinal traction on OCT?
- Are there signs of capillary closure and ischaemia in the fovea?
- Are glycosolated haemoglobin (HgA1c) values frequently higher than 8%?
- Is the blood pressure higher than 130/80mmHg even after medication?

All these factors are crucial and must be considered in order to design the most appropriate treatment for a specific type of diabetic macular oedema. We now have more options than ever at our disposal for treating diabetic retinopathy and particularly diabetic macular oedema.[5] Laser treatments and vitrectomy surgery have been effective in reducing the incidence of blindness due to diabetes.[6] Improved metabolic control and advances in diabetes therapy have decreased the incidence and severity of diabetic retinal complications. However, diabetic retinopathy remains a major cause of vision loss. Therefore, it is essential to see each patient as an individual and each type of macular oedema as a specific case where the evolution, previous treatments, quality of metabolic control and all of the previously identified characteristics of diabetic macular oedema are taken into account. Therapies directed at the causative and associated mechanisms of diabetic retinal vascular disease are currently being investigated in clinical trials, and appear to be close to being accepted for clinical use. These include anti-VEGF therapies, intravitreal steroid administration and ruboxistaurin, an orally active PKC inhibitor.

Inhibition of the enzyme PKC represents a particularly exciting therapeutic approach because its mechanism of action is directed at the early stages of the diabetic retinal disease when the disease is still reversible.[7] The first clinical studies of PKC inhibition, especially with ruboxistaurin, an orally active inhibitor of the B1 and B2 isoforms of PKC, demonstrated that it can be used safely by patients.[8] Clinical trials have shown that its administration reduces the progression of macular oedema and reduces vision loss. However, the difficulties associated with relatively short-term clinical trials, and the relative lack of progression of the retinopathy in the placebo-controlled population, led the US Food and Drug Administration (FDA) to indicate the need for further studies.

Intravitreal steroids have been used with some success in advanced situations of chronic diffuse diabetic macular oedema.[9] They are effective only in the short term, and are associated with complications such as cataracts and glaucoma. Their efficacy demonstrates that inflammation is an important component of diabetic retinal disease, particularly when there is a situation of open BRB. Therefore, intravitreal steroids may be used as another treatment option when the diabetic macular oedema is characterised by its chronicity with poor response to laser therapy and there is a situation of open BRB and diffuse involvement of the fovea, suggesting that an important inflammatory repair response is present. The combination of intravitreal steroids with conventional laser therapy has been shown to be another interesting alternative. An increase in VEGF has been repeatedly demonstrated in the vitreous body of advanced cases of diabetic retinopathy. Their role in angiogenesis is well known, and therefore anti-VEGF agents are clearly indicated when ischaemia predominates. Intravitreal administration of VEGF inhibitors such as pegaptanib sodium (Macugen) or ranibizumab (Lucentis) are now being evaluated for the treatment of diabetic macular oedema with visual loss.[10,11] A variety of other anti-VEGF agents will be undergoing clinical trial evaluation in the near future based on the promising results observed. There are numerous available management strategies to treat diabetic macular oedema and prevent irreversible visual loss. The following factors should also be taken into consideration:

- early detection by using regular screening procedures and new diagnostic tools;
- characterisation of the type of diabetic macular oedema;
- monitoring of retinal thickness values and their topography, particularly regarding progression of the oedema in the direction of the fovea and foveola;
- if the BRB remains tight and there are no signs of vascular leakage, close metabolic control must be the goal;
- if the BRB opens, blood pressure also needs to be closely monitored and laser treatment, either conventional (Early Treatment Diabetic Retinopathy Study guidelines) or sub-threshold, should be considered where there are signs of impending foveal involvement;
- if the oedema becomes chronic and diffuse with progressive involvement of the fovea and visual loss, intravitreal steroids or intravitreal VEGF inhibitors should be considered; and
- particular attention should be given to the presence of ischaemia in the fovea and presence of vitreo-retinal traction. The demonstration of vitreo-retinal traction is a clear indication for vitrectomy, whereas the presence of ischaemia is, at present, mainly a call for caution, but may be an indication for targeted anti-VEGF therapy.

These new therapeutic approaches, together with improved screening and control of the diabetic metabolic alterations, have opened new perspectives for patients with diabetic retinopathy. ■

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