

New perspectives in the management of diabetic retinopathy

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The incidence of diabetes is rising worldwide. With urbanization in the developing countries, and increasingly sedentary lifestyle, the figures of diabetes are reaching a high proportion, particularly among the young. The incidence of diabetes is estimated to double by 2025 in Pakistan to a staggering figure of 11.6 million people. Pakistan will become the 4th most populous country in terms of number of diabetics.¹ Rising incidence means an increase in the burden of visual loss to increase many folds. Diabetic retinopathy is the major ocular complication associated with diabetes, and represents the leading cause of legal blindness in the working-age population in developed countries. To identify sight-threatening retinopathy, systematic screening is recommended which is not available in Pakistan. Visual loss in diabetic retinopathy is caused by diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR).

Good control of systemic risk factors is vital in managing diabetic retinopathy. Ophthalmologists, however, tend to concentrate mostly on ocular treatment. It is worth noting that a 1% decrease in HbA1c, say from 8% to 7.2%, reduces diabetic retinopathy by 40%, progression to vision threatening retinopathy by 25%, need for laser therapy by 25% and blindness by 15%. In addition to HbA1c, people with diabetes should have a regular evaluation of complete blood count, lipid profile, serum creatinine levels and random blood glucose. Anaemia contributes to the ischaemic injury caused by retinal non-perfusion in this group. High lipid levels can lead to direct endothelial damage. Microalbuminuria not only predicts nephropathy but also myocardial infarction and stroke.

Smoking 20 cigarettes a day triples the risk of retinopathy and passive smoking may double the risk. Similarly, sleep apnoea, a treatable condition, contributes to DME and visual loss.² Certain medications such as glitazones, prescribed to control blood glucose, cause fluid retention and macular edema.³ Glitazones should be used with caution in DME.

Statins are recommended for people with diabetes 40

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years and older, if tolerated well, regardless of the cholesterol level. A fibrate such as fenofibrate 200mg once daily may be advisable in patients with diabetic maculopathy with lipid exudates. In recent years two large randomized controlled trials (RCTs), FIELD study⁴ and ACCORD-Eye study,⁵ have reported efficacy of fenofibrate in diabetic retinopathy. Fenofibrates are not recommended as a prophylactic treatment in patients with no pre-existing retinopathy.

A decade ago, macular laser was the only proven treatment for DME. In 2016 we are fortunate to have many treatment modalities at our disposal. However, this also makes it difficult to decide which treatment option is best for a particular patient. In recent years, trials of intravitreal anti-VEGF agents in DME have shown their remarkable efficacy. Industry funded studies such as RISE, RIDE,⁶ VIVID-DME, and VISTA-DME,⁷ which evaluated ranibizumab and aflibercept, have all shown significant gains in vision when compared to laser treatment alone.

Bevacizumab is the most common intravitreal anti-VEGF used in Pakistan, and worldwide. The use of intravitreal bevacizumab for DME is off-label. In DRCR.net Protocol T, the three anti VEGF agents were compared in DME.⁸ If the initial visual acuity (VA) was 20/32 to 20/40, the mean improvement was +8.0 letters with aflibercept, +7.5 letters with bevacizumab, and +8.3 letters with ranibizumab. But if the initial VA was 20/50 or worse, the mean improvement was +18.9 letters with aflibercept, +11.8 letters with bevacizumab, and +14.2 letters with ranibizumab. It seems in DME Aflibercept is superior if VA is 20/50 or worse.

Because anti-VEGFs are angiostatic, repeated monthly injections are often — necessary. Unfortunately, patient compliance with a monthly treatment schedule is suboptimal. However, unlike macular degeneration, injections do not need to continue every month indefinitely.

Intravitreal steroids are used off-label in DME if anti-VEGF therapy is not effective.

Steroid therapy is associated with raised IOP, and cataract formation in phakic eyes.

The observation that DME prevalence is higher among

patients with attached vitreous, and that a posterior vitreous detachment in patients with pre-existing DME may result in resolution of DME has led many to believe that vitrectomy (with removal of any antero-posterior and tangential traction) may be a useful option in the management of DME. There are abundant case reports and case series, however, only a few high quality RCTs evaluating efficacy of vitrectomy in DME. Patel et al⁹ in an RCT included DME patients with no vitreo macular traction (VMT). They reported no benefit of vitrectomy over laser treatment. It is worth noting that the prevalence of VMT in DME is as low as 4%.

Diabetic Retinopathy Study (DRS) investigated whether panretinal photocoagulation (PRP), compared to indefinite deferral, could reduce the risk of vision loss from PDR. After 2 years, photocoagulation was shown to significantly reduce severe visual loss from PDR¹⁰ and the benefit persisted through the entire duration of follow up.

Anti-VEGF therapy has also been found to be effective in rapid regression of retinal neovascularization seen in patients with PDR;^{7,11} however, the effects of anti-VEGF agents appear to be transient, and therefore PRP may be necessary to ensure permanent regression of new vessels. Caution is necessary when injecting anti-VEGF agents in patients with PDR and significant fibrovascular proliferation as these agents may worsen traction retinal detachment (TRD).

With recent advancements in vitrectomy fluidics, port optimisation of vitreous cutters, and sutureless nature of vitrectomy surgery; patients with recurrent/ persistent vitreous haemorrhage or TRD, achieve better visual outcome with vitrectomy.

In summary, blindness caused by diabetic retinopathy can be avoided by early detection, and timely treatment. In 2016 intravitreal anti-VEGFs and PRP are the gold standard treatments for center involving DME and PDR

respectively. Vitrectomy may be offered in recurrent/ persistent vitreous haemorrhage, TRD or selected cases of VMT. To offer the most effective, individualized, treatment to our patients, we must keep abreast with the rapidly expanding scientific evidence about the emerging treatment modalities in diabetic retinopathy.

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