Editorial

New Perspectives in the Management of Diabetic Macular Edema

The prevalence of diabetes is increasing worldwide. With urbanization in the developing countries, and increasingly sedentary lifestyle, the incidence of diabetes is reaching an epidemic, particularly among the young. Prevalence of diabetes is estimated to double by 2025 in Pakistan to a staggering 11.6 million people. Pakistan will become the 4th most populous country in terms of the number of diabetics.[1] Rising prevalence means the burden of visual loss is likely to increase many folds. To identify sight-threatening retinopathy, systematic screening is recommended. Unfortunately, there is no effective screening programme for diabetic retinopathy in Pakistan. The two most common causes of visual loss in diabetes are proliferative diabetic retinopathy and diabetic macular edema (DME). DME is the commonest cause of visual loss among the working age group.

Good control of systemic risk factors is vital in managing diabetic retinopathy. Ophthalmologists, however, tend to focus mostly on local treatment modalities. It is worth remembering that a 10% 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, diabetics should have a regular evaluation of complete blood count, lipid profile, serum creatinine levels and random blood sugar. Anemia contributes to the ischemic injury caused by retinal non-perfusion in diabetics. High lipid levels cause direct endothelial damage. Microalbuminuria not only predicts nephropathy but also predicts myocardial infarction and stroke.

Smoking 20 cigarettes a day triples the risk of retinopathy. Passive smoking may double the risk. Similarly, sleep apnea, a treatable condition, contributes to DME and visual loss[2]. Certain medications such as glitazones, used to control blood sugar, cause fluid retention and macular edema[3]. Glitazones should be avoided in DME. Therefore, when a diabetic patient presents to an ophthalmologist, with visual impairment, the interaction is an opportunity for counselling about systemic risk factor control.

Statins are recommended for diabetics 40 year and older, if tolerated well, regardless of the cholesterol level. A fibrate such as finofibrate 200mg once daily may be advisable in patients with exudative maculopathy. In recent years two large randomized controlled trials, FIELD study[4] and ACCORD-Eye study[5], have reported efficacy of finofibrate in diabetic retinopathy. FIELD study reported reduced frequency of laser treatment for DME by 31% and PDR by 30% (40% in ACCORD – eye study). In ACCORD-Eye finofibrate was taken with simvastatin. This benefit was more marked in patients with pre-existing retinopathy. Finofibrate is not recommended as a prophylactic treatment to prevent diabetic retinopathy in patients with no pre-existing retinopathy.

Once systemic factors are looked at, what local treatment options are available to us in 2014?

Only a decade ago, macular laser was the only proven treatment for DME. EDTRS reported a 50% reduction in moderate visual loss with laser treatment. Back then the choice was simple; either treat with laser or observe. In 2014 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.

Laser photocoagulation was the standard of care for DME for more than 25 years. Focal macular laser still remains a viable treatment option for extra foveal DME, particularly to treat micro-aneurysms associated with circinate exudates. Focal laser may also be used as an adjunctive therapy to reduce number of anti-VEGF injections. Scatter laser of peripheral areas of FFA proven capillary non-perfusion may reduce the VEGF drive, important for vascular hyper-permeability and fluid accumulation at the macula.

In recent years, trials of intravitreal anti-VEGF agents in DME have shown their remarkable efficacy. Industry funded studies such as RISE, RIDE, VIVID-DME, and VISTA-DME, which evaluated ranibizumab and aflibercept, have all shown significant gains in vision when compared to laser treatment alone. RISE and RIDE are phase III multicenter randomized

controlled trials with identical methodology[6]. They enrolled 759 patients to evaluate efficacy and safety of ranibizumab versus sham injections in DME. Macular laser treatment was allowed as indicated. At 2 years mean gain in visual acuity was +12 letters and +2.5 letters in the ranibizumab and sham arms, respectively.

Similarly, VIVID-DME and VISTA-DME are two parallel phase III randomized controlled trials evaluating aflibercept versus laser treatment for DME.[7] At 1 year patients treated with aflibercept had a mean gain of +11 letters while the laser treated group had only +1 letter gain. There were no safety signals associated with aflibercept use. Ranibizumab and aflibercept are both approved by FDA for DME.

Bevacizumab is the most common intravitreal anti-VEGF used in Pakistan, and worldwide. The use of intravitreal bevacizumab for DME is off-label. The randomized trial of intravitreal Bevacizumab or Laser Treatment (BOLT) for DME,[8] reported +9 letters gain in the bevacizumab arm compared to +2.5 letters in the laser arm at 2 years. The median number of injections required was 9 and 4 in the first and second year of the study, respectively. Is the efficacy of bevacizumab, ranibizumab and aflibercept equal in DME? To date there are no randomized clinical trials, comparing head-to-head efficacy of the three compounds in DME. DRCR.net protocol T is designed to directly compare the efficacy and safety of these anti-VEGF agents in DME. Results are expected in 2016.

Because anti-VEGFs are angiostatic, repeated monthly injections are often times necessary. Unfortunately, patient compliance with a monthly treatment schedule is suboptimal. However, unlike macular degeneration, injections do not need to continue every month indefinitely. For example, the median number of injections in the DRCR. net protocol I (ranibizumab and deferred laser arm) were 9 in the first year, 3 in second year and 2 injection in the third year. Mean number of injections in this arm was 15 out of a possible maximum of 39 injections.

Intravitreal steroids are used off-label in DME when anti-VEGF therapy is not effective. In DRCR.net protocol I, when a subgroup analysis of pseudophakic eyes at baseline was performed, 4 mg triamcinolone and laser arm showed similar visual gains to ranibizumab and laser arm. Steroid therapy is associated with raised IOP, and cataract formation in phakic eyes. If patients are treated with intravitreal steroids, regular and long term follow up is warranted.

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) is a useful option in the management of DME. There are abundant case reports and case series, however, only a few high quality randomized control trials evaluating efficacy of vitrectomy in DME. A large case series[9] of vitrectomy outcomes in DME with co-existing vitreomacular traction (VMT) was reported by DRCR.net They reported reduction in central macular thickness in most eyes. Nearly half the patients had 10 or more letters gain. Significantly, one third of the patients lost 10 or more letters following surgery. Patel et al[10] in their randomized controlled trial included DME patients with no VMT. They reported no benefit of vitrectomy over laser treatment. It is worth noting that the prevalence of VMT in DME is low at 4%.

In summary, blindness caused by DME can be avoided by early detection, and timely treatment. In 2014 intravitreal anti-VEGFs are the gold standard treatments for center involving DME. For edema away from fovea, focal laser may be given. Intravitreal steroids may also be useful in pseudophakic eyes. Additionally, vitrectomy may be offered in select cases of VMT. To offer the most effective, individualized, treatment to our patients, we must keep a brace with the rapidly expanding scientific evidence about the emerging treatment modalities in DME.

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M. A. Rehman Siddiqui
Consultant Ophthalmologist and Retinal Surgeon
Shahzad Eye Hospital & South City Hospital, Karachi