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Research Article

ADVANCED MANAGEMENT OF DIABETIC RETINOPATHY - A REVIEW

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ABSTRACT

Diabetic retinopathy (DR) has been established as one of the most significant risk factor for blindness worldwide. Blood pressure & metabolic control has been shown to significantly decrease the risk of retinopathy and remains a benchmark in the management of DR. There are many tools for preventing DR and its complications. Although treatment can help prevent blindness in majority of cases, still the key variable behind success of treatment stays with accurate diagnosis of patients with retinopathy before their vision is fully affected. Hence the key lies in the timely eye examination of diabetic patients. In the present review article the advanced pharmacological methods to target biochemical pathways causing DR are being evaluated here to overcome present treatment limitations.

Keywords :-Retinopathy, Eyeball, Diabetes, Patho-physiology.

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INTRODUCTION

Diabetic syndrome affects nearly 200 million people worldwide. Diabetic retinopathy has established itself as one of the leading causes of preventable blindness among working-age individuals [Klein et al. 1984]. Retinopathy causes between 12,000 and 24,000 new cases of blindness each year [Center for Disease Control and Prevention, 2007]. Diabetic retinopathy is the primary cause of blindness in patients who develop diabetes before the age of 30 & the primary cause in one-third of cases of blindness among those developing diabetes after the age of 30. Its prevalence increases with the duration of diabetes. In USA, reported cost of diabetic-related blindness in adults (aged 40 & above) is nearly $ 500 million annually1.

In recent years, advances in pharmacotherapy & surgical techniques have shown a promising way in the treatment of diabetic retinopathy. The present review article is an attempt to highlight various large scale clinical trial reports and the therapeutic advances related with diabetic retinopathy management.

Literature Review: A total of 43 articles were downloaded & analysed using the following

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meshwords retinopathy, eyeball, diabetes, patho-physiology searching pubmed & science direct data bases. 10 articles were finally selected and examined as per the requirement of the present review article on the advanced management of Diabetic Retinopathy.

Diabetic retinopathy: The pathogenesis of diabetic retinopathy is partially understood. Hyperglycemia results in retinal tissue micro vasculature damage. Diabetic retinopathy is separated into two stages: non-proliferative and proliferative diabetic retinopathy2.

Non-proliferative diabetic retinopathy: micro aneurysms, retinal hemorrhages, and cotton wool spots. Capillary closure results in retinal hypoxia, leading to increased production of vascular endothelial growth factor (VEGF) and other angiogenic factors.

Proliferative diabetic retinopathy:
(a) neovascularization elsewhere, cotton wool spots; (b)pre-retinal vitreous hemorrhage, neo-vascularization of the optic disc; (c) tractional retinal detachment. Diabetic macular edema can occur at any stage of diabetic retinopathy. Diabetic macular edema occurs as a result of increased vascular permeability due to a breakdown of the blood-retinal barrier, often with deposition of hard exudates in the macula. Fluorescein angiography of diabetic macular edema shows leakage of the blood vessels resulting in retinal edema, which can be seen in cross section with optical coherence tomography. The most common cause of moderate to severe vision loss from diabetic retinopathy results from proliferative diabetic retinopathy & diabetic macular edema.

Primary interventions:
Glycemic control: Poor glycemic control is directly related to diabetic retinopathy. The Diabetes Control and Complications Trial study group conducted a trial from 1983 to 1993 in 1441 patients with type 1 diabetes and nonproliferative diabetic retinopathy randomized to receive intensive glycemic control [median glycosylated hemoglobin A1c (HbA1c) 7.2%] or moderate control (median HbA1c 9.1%). The intensive treatment group had a reduction of diabetic retinopathy incidence of 76% and progression of 54% compared with the moderate treatment group [Diabetes Control and Complications Trial Research Group, 1993]3,4.

The study found two significant clinical drawbacks to tight glycemic control in patients with type I diabetes: an increased number of hypoglycemic episodes and early worsening of retinopathy. The effect on retinopathy was reversed by 18 months and did not result in serious visual loss. A careful ophthalmoscopic exam should be performed prior to institution of intensive glycemic control and at regular intervals of 3–6 months during this time [Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group, 2008].

Many clinical trials had established the foundations for management and treatment of diabetic retinopathy and were performed two to three decades ago. These trials provided compelling evidence that strict glycemic control is needed to prevent vision loss associated with diabetes. Innovations in monitoring diabetes such as home monitoring of glucose levels have contributed greatly towards more effective control of diabetes. Further, significant advances in treatment options, such as an insulin pump and a variety of oral antiglycemic agents, continue to improve the management of diabetes.

Hypertensive control: Tight control of blood pressure has been shown to reduce the progression of diabetic retinopathy in patients with type 2 diabetes [Schrier et al. 2002]. The UK Prospective Diabetes Study performed a subgroup analysis of 1148 patients with hypertension and type-2 diabetes; patients were randomized to less tight (< 180/105 mmHg) and tight (< 150/85 mmHg) blood pressure control with a mean follow-up period of 8.4 years. The tightly controlled patients had reduced progression of retinopathy in 34% and reduced deterioration in visual acuity by three lines in 47% compared with the conventional control group. The reduction in vision loss was primarily due to a 42% reduction in the incidence of macular edema. These effects were independent of glycemic control [UK Prospective Diabetes Study Group, 1998b]5.

Several antihypertensive agents have been studied for their effect on diabetic retinopathy. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have been shown in separate trials to reduce diabetic retinopathy progression in patients with normotensive type 1 diabetes and mild diabetic retinopathy6.

Secondary interventions:
Proliferative diabetic retinopathy: Laser and surgical interventions: Proliferative diabetic retinopathy is one of the major causes of severe vision loss. A recent meta-analysis pooled data from 28 studies and reported a trend of lower rates of proliferative diabetic retinopathy (cumulative: 11%; 1975–1985: 19.5%; 1986–2008: 2.6%) and severe vision loss (cumulative: 7.2%; 1975–1985: 9.7%; 1986–2008: 3.2%); this is likely related to improved diabetic monitoring and available therapy7.Pars planavitrectomy: Pars planavitrectomy, innovated in

the 1970s, is a surgical procedure that allows removal of the vitreous and manipulation of the retina. The procedure involves creating three small ports at the pars plana, an avascular zone of nonretinal tissue in the anterior globe. Conventionally, one port is for an infusion line to maintain the intraocular pressure. A light pipe typically occupies one of the remaining ports allowing endo-illumination. The final port allows access for a vitrector or other intraocular instruments. PRP can be performed intraoperatively with an endolaser.

More recently, intra-vitrealbevacizumab, an anti-VEGF agent, has been used as a preoperative- or peri-operative adjunct to vitrectomy. Anti-VEGF agents injected pre-operatively can reduce neo-vascularization and fibro-vascular adherence to the retina, which can reduce intra-operative bleeding and facilitate dissection of membranes; however, it has been associated with increased risk of traction and retinal tears [Oshima et al. 2009]8.

Diabetic macular edema: Laser, surgical and medical interventions: Diabetic macular edema is the principal cause of moderate vision loss (doubling of visual angle, i.e. 20/20 to 20/40) among patients with diabetes and nonproliferative diabetic retinopathy [Klein, 1992]. The pathophysiology of diabetic macular edema is multifactorial and includes increased levels of VEGF, loss of endothelial tight junctions & an increase in inflammatory mediators.

Macular laser treatment: Macular laser treatment was the first treatment shown to be of benefit for diabetic macular edema. It involves application of focal laser photocoagulation to localized leaking microaneurysms or in a grid pattern within a region of macular edema. The mechanism by which macular laser therapy improves diabetic macular edema is unknown, however it is hypothesized that it reduces retinal hypoxia, thus reducing the VEGF load and subsequent vascular permeability in the eye9.

Pars planavitrectomy: More recently, vitrectomy has been shown to have a role in the treatment of a specific subtype of diffuse diabetic macular edema resulting from vitreous traction on the central retina. Contraction of the posterior face of the vitreous, the hyaloid, over the macula can result in edema, which does not respond to focal laser photocoagulation. In some cases, an epiretinal membrane also contributes to traction and macular edema. Vitrectomy allows peeling of epiretinal membranes, often with peeling of the underlying internal limiting membrane, the innermost layer of the retina.

Corticosteroids: Corticosteroids have potent anti-inflammatory and antiangiogenic effects [Nauck et al. 1998]. The accumulation of fluid in the retina in diabetic macular edema is a result of increased vascular permeability factors, including VEGF [Funatsu et al. 2002], loss of endothelial tight junctions [Antonetti et al. 1998] & production of inflammatory mediators such as prostaglandins. Corticosteroids can inhibit these processes without the destruction of retina, an unavoidable consequence of laser photocoagulation. Injection of steroids into the vitreous cavity is effective in treating diabetic macular edema; however steroids can have significant side effects, including cataract progression and steroid-induced secondary glaucoma.

Triamcinolone: Intravitreal triamcinolone (Kenalog 40, Bristol-Myers Squibb, Princeton, New Jersey) has been used more frequently since 2002 for the treatment of diabetic macular edema. Gillies and colleagues [Gillies et al. 2006] conducted a randomized controlled trial in 69 eyes with persistent diabetic macular edema to receive either 4 mg intravitreal triamcinolone or sham injection; after 2-year follow up, 56% of triamcinolone-treated eyes had an improvement in visual acuity compared with 26% in the control group. However, many eyes required reinjection (mean 2.2). The incidence of steroid-induced glaucoma was significant in the treatment group, with an intraocular pressure rise of 5 mmHg occurring in 68% of eyes receiving intravitreal triamcinolone compared with 10% in the sham group; 44% of these eyes required glaucoma medications9.

Although intra-vitreal triamcinolone is useful in short-term anatomic and visual acuity improvement in diabetic macular edema, it requires repeat injections that subject the eye to significant ocular morbidity and the potential for endophthalmitis.

Other medications:

Anti-platelet agents: Studies have not shown a beneficial effect of aspirin (650 mg/day) on diabetic retinopathy progression [Chew et al. 1995; Early Treatment Diabetic Retinopathy Study Research Group 1991]. Patients receiving aspirin and dipyridamole in combination [Dipyridamole, Aspirin, Microangiopathy of Diabetes (DAMAD) Study Group, 1989] or ticlopidine [TiclopidineMicroangiopathy of Diabetes (TIMAD) Study Group, 1990] were shown to have a mild decrease in microaneurysms on fluorescein angiography compared with placebo; both may slow the progression of microaneurysm evolution in early diabetic retinopathy.

Lipid-lowering agents: Studies on fenofibrate monotherapy have demonstrated a potential effect of the drug in reducing diabetic retinopathy progression, and the need for laser treatment in CSME in patients with type 2 diabetes [Keech et al. 2007]. Other small, randomized controlled clinical trials have suggested a benefit of statins on reduction of diabetic retinopathy severity of diabetic retinopathy [Gupta et al. 2004; Sen et al. 2002] however the sample sizes in these studies were of insufficient power.

Hyaluronidase: Intravitreal purified ovine hyaluronidase (Vitrase, ISTA Pharmaceuticals, Irvine California) causes enzymatic vitreolysis. The dissolution of the vitreous is useful in the treatment of vitreous hemorrhage as a result of proliferative diabetic retinopathy, as the only two options currently available are observation or vitrectomy. Two large combined phase III randomized controlled clinical trials looked at 1125 eyes with vitreous hemorrhage of greater than 1 month duration and poor visual acuity (less than 20/200) treated with intravitreal ovine hyaluronidase compared with saline. The injected eyes had improved visual acuity and decreased vitreous hemorrhage density at 1 month which was sustained up to 3 months. This drug is still under evaluation for FDA approval10.

CONCLUSION

There is strong association between tight glycemic and blood pressure control with reduction in the incidence and progression of diabetic retinopathy hence reducing vision loss. In patients with proliferative diabetic retinopathy, PRP significantly reduces the risk of severe vision loss by 50%, especially in eyes with high-risk proliferative diabetic retinopathy. Early vitrectomy should be done in patients with persistent vitreous hemorrhage from proliferative diabetic retinopathy. In patients with diabetic macular edema, macular laser treatment must be done to reduce the risk of moderate vision loss by 50% hence visual improvement. Ongoing studies have shown a promising role for intra-vitreal anti-VEGF agents in diabetic macular edema treatment but at present is under clinical trial stage. Timely eye examinations & identification of high-risk patients still holds the key for prevention of vision loss in patients living with diabetes.

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