Review Article

Medical Management of Diabetic Retinopathy: An Overview

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Abstract

Diabetes mellitus is a global health problem affecting 366 million people worldwide and its prevalence is growing rapidly. Diabetic eye disease is present in up to 25% of diabetic subjects.

Diabetic retinopathy is a chronic complication of diabetes that can result in blindness. Generally, there are two stages of diabetic retinopathy, non-proliferative and proliferative. The longer a person has diabetes and the poorer metabolic control, the higher the chance of developing diabetic retinopathy. The majority of people with type 2 diabetes will ultimately develop diabetic retinopathy.

Multifactorial therapy targeted to lifestyle modification and optional glycemic control reduces the risk. However, diabetic retinopathy develops or progresses with time.

Primary (preventive) strategies include glycemic, lipid, and blood pressure control.

Glycemic control effectively reduces the incidence of diabetic retinopathy. In additional, its effect on progression of diabetic retinopathy has been demonstrated in randomized clinical trials.

Furthermore, tight control of blood pressure significantly reduces the progression of retinopathy and visual loss. However, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study Group has shown that intensive blood pressure control has no beneficial effect on reducing the rate of diabetic retinopathy in subjects with type 2 diabetes.

Elevated serum lipids and dyslipidemias are associated with a higher risk of diabetic retinopathy. The beneficial effects of lipid-lowering agents on the progression of retinopathy have been reported. Intensive combination therapy for dyslipidemia has been shown to effectively reduce the rate of progression of diabetic retinopathy in type 2 diabetes.

Secondary strategies are focused on various pathophysiologic approaches such as blockade of the renin angiotensin system (RAS), anti-vascular endothelial growth factor agents, somatostatin analogues, protein kinase inhibitors, and anti-inflammatory agents.

The purpose of the current overview is to look into the medical management of diabetic retinopathy, and to explore the primary (preventive) measures as well as secondary strategies proposed to be effective in its medical management.

Keywords: Diabetes, management, retinopathy

Cite the article as: Malek M, Khamseh ME, Aghili R, Emami Z, Najafi L, Baradaran HR. Medical Management of Diabetic Retinopathy: An Overview. *Arch Iran Med*. 2012; **15(10):** 635 – 640.

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Introduction

Diabetes mellitus is a global health problem that affects 366 million people worldwide[1] and its prevalence is growing rapidly.[2] Up to 25% of diabetic subjects are affected by diabetic eye disease, a figure that might double by 2025.[3] In Iran, the prevalence of ophthalmic complications is estimated to be 37% and per capita direct cost of these complication is about 215 ± 140 million USD.[4]

Diabetic retinopathy is the leading cause of blindness among the working population in the UK and United States.[5,6] Prevalence of diabetic retinopathy depends on various factors including ethnicity, type of diabetes, state of metabolic control, and diabetes duration.[3] In the Wisconsin Epidemiological Study of Diabetic Retinopathy, all subjects with type 1 diabetes of 20 years duration have been reported to have background diabetic retinopathy.[7] In type 2 diabetic subjects, up to 60% will develop some degree of retinopathy ten years after diagnosis.[7]

Generally, diabetic retinopathy is classified into two phases, non-proliferative and proliferative. The presence of microaneurysm and retinal hemorrhages are hallmarks of the non-proliferative stage, while proliferative diabetic retinopathy is characterized by new blood vessel formation on the retinal surface.[3]

Intensive glycemic control is considered a mandatory component of primary prevention strategies. However, it does not eliminate the risk.[3] On the other hand, secondary strategies focus on progression of diabetic retinopathy and loss of vision.[8]

Primary (preventive) strategies

Glycemic control

In non-Western countries, the current state of glycemic control seems to be poor with HbA1c levels between 9.3%–9.9%.[9]

Glycemic control effectively reduces the incidence of diabetic retinopathy and its effect on progression of diabetic retinopathy has been demonstrated in randomized clinical trials.[10,11] In Diabetes Control and Complications Trial (DCCT), intensive glycemic control reduced the incidence of diabetic retinopathy and its pro-

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Accepted for publication: 20 June 2012

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gression by 76% and 54%, respectively, compared with conventional treatment.[12] In type 2 diabetes, up to 25% reduction in microvascular end points have been reported by intensive treatment in the United Kingdom Prospective Diabetes Study (UKPDS).[13] The ACCORD Eye Study Group[14] reported a 7.3% rate of retinopathy progression after four years of intensive glycemic control (target HbA1c < 6%) compared to 10.4% in those with standard treatment (target HbA1c = 7%–7.9%).

Improvement of patient self-management behavior leads to better metabolic control in relation to HbA1c and fasting blood glucose levels.[15]

Blood pressure control

In the hypertensive diabetic population, alterations of auto-regulation and increases in retinal perfusion pressure are considered to be responsible for the progression of diabetic retinopathy.[16] Release of vascular endothelial growth factor (VEGF) has been reported to be responsible for attenuation of retinal endothelial autoregulation and subsequent increase in perfusion pressure.[17] Strict control of blood pressure significantly reduces the progression of retinopathy and visual loss.[18,19] In the UKPDS, a 34% reduction in diabetic retinopathy progression has been reported in patients with strict control of blood pressure compared with those who had conventional control.[13] However, the ACCORD Eye Study Group showed that intensive blood pressure control (target systolic blood pressure < 120 mmHg) has no beneficial effect on reducing the rate of diabetic retinopathy in subjects with type 2 diabetes.[14]

It has been suggested that some antihypertensive drugs might have an additional preventive effect on the progression of diabetic retinopathy, an effect that seems to be not related to their blood pressure lowering effect.[20,21]

Lipid control

Elevated serum lipids and dyslipidemia are associated with a higher risk of diabetic retinopathy.[22] There is a positive correlation between dyslipidemia and worsening of retinopathy, development of hard exudates and macular edema in diabetic subjects.[23,24] The beneficial effect of lipid-lowering agents on progression of retinopathy has been reported[25] Intensive combination therapy for dyslipidemia with fenofibrate plus simvastatin has been shown to effectively reduce the rate of progression of diabetic retinopathy in type 2 diabetes.[14]

Secondary strategies

Blockade of the renin angiotensin system (RAS)

The contribution of the renin angiotensin system (RAS) to diabetic retinopathy has been suggested elsewhere.[26,27] RAS has been considered as a potential angiogenic factor, both systematically and locally.[28] Possible explanations for this contribution include local production of angiotensin,[29] the presence of RAS in ocular tissue,[6] high levels of ACE and angiotensin II in animal models,[30] and lower levels of vascular endothelial growth factor (VEGF) in the vitreous of patients with proliferative diabetic retinopathy treated by ACE inhibitors.[29]

In the EUCILD study, a significant reduction in diabetic retinopathy progression has been shown in subjects with type 1 diabetes, even when normotensive.[31] However, subjects randomized to lisinopril had lower baseline HbA1c levels. In type 2 diabetes the results are not convincing because of the changes that occur in blood pressure and glucose control.[31]

In the Heart Outcomes Prevention Evaluation (HOPE) study, ramipril had a non-significant effect on the requirement for laser therapy.[32] In another study[33] captopril was reported to prevent the progression of retinopathy in type 2 diabetic subjects. In the Diabetic Retinopathy Candesartan Trials (DIRECT)[34,35] it was hypothesized that inhibition of RAS was effective on diabetic retinopathy, independent of the blood pressure-lowering effect of the drug. The trial had three components:

- In DIRECT-Prevent 1, a reduction in three-step deterioration of retinopathy was shown in type 1 diabetes, which remained significant after adjustment for small changes in blood pressure.
- Protect 1 described the progression of established retinopathy in type 1 diabetes. The results showed no significant effect of candesartan on the progression of retinopathy in this group.
- Protect 2 failed to show any significant effect on the progression of retinopathy in type 2 diabetic subjects. However, a significant regression of established mild diabetic retinopathy was reported, which remained after adjustment for changes in blood pressure. Candesartan had no beneficial effect on the progression of moderate and severe diabetic retinopathy.

Considering the evidence from the EUCLID and DIRECT trails, primary prevention of retinopathy by blocking RAS could be considered in high-risk type 1 diabetic subjects with the following[28]:

- HbA1c > 8% without retinopathy after six years, even when normotensive.
- Hypertension
- Diabetic retinopathy

In type 2 diabetes, blocking RAS should be considered in subjects with:

- Background or pre-proliferative retinopathy, even when normotensive
- Hypertension
- Diabetic retinopathy

Anti-vascular endothelial growth factor (VEGF) agents

VEGF is responsible for retinal neovascularization[36–38] and increased vascular permeability in patients with diabetic retinopathy[38] and is targeted by various therapeutic approaches.[39–42] Breakdown of the blood-retinal barrier and retinal neovascularization are the leading causes of vision loss in diabetic retinopathy.[43] Blockade of receptor binding by high-affinity antibodies, reduction of VEGF formation or free VEGF available for binding to its receptor, and interruption of the VEGF signaling pathway are major therapeutic options.[44] Specific anti-VEGF monoclonal antibodies[45,46] such as ranibizumab and bevacizumab reduce the availability of free VEGF. Bevacizumab is effective for the treatment of diabetic retinopathy.[46–48] Ranibizumab is a recombinant monoclonal antibody fragment that has been approved for age-related macular degeneration. [46–48] It is also effective for the treatment of diabetic macular edema, In the READ 2 study ranibizumab has been shown to improve visual acuity in diabetic subjects with macular edema. Regeneron (VEGF trap) interrupts the interaction of VEGF and its receptor. Intravitral injection of the VEGF trap is effective for the treatment of diabetic macular edema.[17]

Fenofibrate

Although the primary use of fibrates in treatment of hypertriglyceridemia is a common clinical practice, it has been shown that

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fenofibrate reduces the rate of photocoagulation in patients with proliferative diabetic retinopathy and macular edema.[49–51] Experimental studies suggest some possible mechanisms for the effects of fenofibrate[52]:

- Reduction of retinal endothelial cell apoptosis
- Inhibition of the VEGF pathway
- Reduction of pro-inflammation and oxidative stress

Development of cotton-wool spots and retinal hemorrhage have been reported to be associated with combined dyslipidemia in diabetic subjects.[53] Considering the subclasses of lipoproteins, there is a positive association between LDL, apolipoprotein B and triglyceride levels and the severity of diabetic retinopathy.[24]

Atorvastatin has been shown to reduce laser therapy in type 2 diabetes.[54] The ACCORD-EYE study evaluated the effect of intensive lipid control on progression of diabetic retinopathy. The intensive treatment consisted of simvastatin plus fenofibrate versus the standard treatment (simvastatin plus placebo). The intensive group showed a reduction in the rate of progression of retinopathy at four years.[55]

The effect of fenofibrate on diabetic retinopathy was explained in the FIELD Ophthalmology Substudy.[56] In a cohort of 1012 subjects with type 2 diabetes, fenofibrate treatment was associated with a 22% reduction in two-step progression of retinopathy which was significant in those who had pre-existing retinopathy. Significant treatment benefit was also observed for the first laser therapy in diabetic proliferative retinopathy. Although the absolute event rates were small, this study shows beneficial effect of fenofibrate in subjects with established diabetic retinopathy at baseline.[56]

GH/IGF1 inhibitors

Angiogenic stimulation is postulated as a mechanism for angiogenesis and subsequent blood-retinal barrier breakdown in diabetic retinopathy.[57,58]

Some observations suggest a possible correlation between the GH/IGF1 pathway and retinopathy such as:

- Progression of retinopathy during puberty[59]
- GH-deficient dwarfs do not develop serious retinopathy[59,60]
- Improvement of diabetic retinopathy following hypophysectomy[61]
- Increased ocular levels of insulin growth factor in patients with severe diabetic retinopathy[62]

Hence, it could be hypothesized that somatostatin analogues might have a beneficial effect on prevention and progression of diabetic retinopathy by inhibiting angiogenesis in the retina of affected subjects. Randomized Clinical Trials (RCTS) has led to conflicting results on the beneficial effect of octreotide on prevention and progression of diabetic retinopathy.[63–67]

Protein kinase C (PKC) inhibitors

Activation of protein kinase C (PKC) enzymes through synthesis of diacylglycerol is a known phenomenon induced by hyperglycemia and theoretically this activation may have some role in the pathogenesis of diabetic retinopathy.[68] The PKC-B inhibitor ruboxistouzin (RBX) is the most researched PKC inhibitor in cellular, animal and human studies.[69] RBX can normalize retinal blood flow in diabetic patients that have less than a ten-year history of diabetes and no evidence of clinical retinopathy.[70]

PKC-DRS determined RBX has been shown to significantly delay the occurrence of moderate visual impairment but could not reduce progression of proliferative diabetic retinopathy.[71]

In addition, PK-DMES showed no significant effect by RBX on the progression of diabetic macular edema[72]; however, in PKC-DRS2, RBX (32 mg/day) reduced the risk of vision loss by about 40%.[73]

Treatment with RBX might preserve visual acuity by reduction of capillary permeability or targeting the neural retina.

Overall, these data suggest that inhibition of the PKC alone is not enough to stop the early metabolic changes that seem to accelerate the progression of pre-proliferative diabetic retinopathy.[69]

Prevention of advance glycation end product (AGES) formation and/or action

Accumulation of advance glycation end products (AGES) in the vitreous and retina has been shown in diabetic patients.[74] These products have deleterious effects on the retina and its vasculature and might lead to a breakdown of the blood-retinal barrier.[75] Decreases in AGE formation and/or its receptor binding have been shown to delay the progression of diabetic retinopathy.[76] However, safety issues are major concerns in this regard.

Aldose reductase inhibitors

Increased activity of aldose reductase and subsequent increases in intracellular concentrations of sorbitol by high levels of glucose is defined elsewhere.[74] It has been postulated that intracellular accumulation of sorbitol and subsequent osmotic flow might be harmful for vascular cells.[77] Nevertheless, inhibition of the enzyme's activity has been shown to be ineffective in reducing the incidence and/or progression of diabetic retinopathy.[78–81]

Reducing oxidative stress

Oxidative injury is linked to diabetic retinopathy.[82,83] The major reactive oxygen species, superoxide and nitric oxide, are involved in oxidative cell damage[84] and high levels of VEGF in diabetic patients.[85] Nevertheless, the effect of antioxidants on prevention and progression of diabetic retinopathy is not promising.

Anti-inflammatory agents

Current evidence supports the role of pro-inflammatory cytokines in the pathogenesis of diabetic retinopathy. Pro-inflammatory cytokines such as TNF-α, IL13, IL6, and COX-2 are increased in the vitreous humor and retina of diabetic patients.[86,87]

The inflammatory process results in leukostasis, a process that may contribute to capillary non-perfusion in diabetic retinopathy. In addition, leukostasis may be involved in endothelial cell death and breakdown of the blood-retinal barrier. Blood-retinal barrier leakage that occurs in patients with diabetes can cause retinal edema and visual defects.[88,89]

Some reports support the role of COX-2 and its metabolic products such as prostaglandin E2 (PGE2) and thromboxane A2 (TXA2) as regulators of angiogenesis.[90] It has been shown that NOS and COX-2 act together to contribute to retinal cell death and development of diabetic retinopathy. Both animal and human studies have shown that prostaglandins increase locally in the eyes of those who suffer from diabetic retinopathy.[91–94]

Thus, systemic and local inhibition of ocular inflammation have been proposed to inhibit the inflammatory mechanisms involved in diabetic retinopathy.[87]

In animals, treatment with NSAIDs has been reported to have some beneficial effects on the prevention of diabetic retinopa-

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thy.[95–98] Initial observations in patients with rheumatoid arthritis have shown that high doses of salicylate reduce the incidence of diabetic retinopathy.[99]

Although a number of studies have reported some beneficial effects of aspirin, dipyridamole, and ticlopidine on non-proliferative diabetic retinopathy, Early Treatment Diabetic Retinopathy Study (ETDRS) results did not confirm the protective effect of aspirin on progression of diabetic retinopathy or impaired visual acuity in patients with severe non-proliferative diabetic retinopathy.[60,100] However, it has been reported that aspirin taken by patients with proliferative diabetic retinopathy did not increase the risk of bleeding.[85] Overall, there is insufficient evidence to recommend the use of NSAIDs as a prophylactic measure or as primary treatment of diabetic retinopathy, necessitating additional studies.[101]

Intravitreal corticosteroids provide high concentrations of steroids over a prolonged period of time.[102] In diabetic macular edema, intravitreal injection of triamcinolone is a promising treatment.[103,104] Intravitreal steroid implants need further studies regarding their safety and efficacy compared to intravtreal triamcinolone acetonide (IVTA).[105]

Thiazolidinedione

A prospective observational study has shown that rosiglitazone could delay the onset of proliferative diabetic retinopathy in type 2 diabetes.[106,107] On the other hand, there are some reports regarding the role of rosiglitazone on the development of macular edema.[108,109]

Pentoxifylline

Some studies have shown a lower incidence of retinal neovascularization in diabetic patients treated with pentoxifylline.[110] However, randomized clinical trials are needed to investigate this hypothesis.

Antihistamines

Preliminary data suggest some role for histamine receptor-mediated increase in blood-retinal barrier permeability and a probable effect of astemizole, an antihistamine agent, on its prevention.[111] However, the beneficial effect of astemizole on the progression of diabetic retinopathy needs further investigation.

In conclusion, diabetic retinopathy is one of the most important and prevalent complications of diabetes mellitus. Multifactorial therapy focused on lifestyle modification and optional glycemic control reduces the risk.

Primary (preventive) strategies effectively reduce the incidence of diabetic retinopathy. They are effective on its progression as well.

Secondary strategies are targeted at various pathophysiologic approaches. Current evidence is in favor of blockade of the renin angiotensin system (RAS), use of Specific anti-VEGF monoclonal antibodies, and intravitreal corticosteroids for the treatment of diabetic retinopathy, especially macular edema.

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