Systemic Medical Management of Diabetic Retinopathy

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ABSTRACT

Diabetes mellitus (DM) has assumed epidemic proportions and as a consequence, diabetic retinopathy is expected to be a major societal problem across the world. Diabetic retinopathy (DR) affects the vision by way of proliferative disease that results in vitreous hemorrhage and traction retinal detachment or by way of diabetic maculopathy (DME). The present-day management of diabetic retinopathy revolves around screening the diabetics for evidence of retinopathy and treating the retinopathy with laser photocoagulation. DME is treated with laser photocoagulation and/or intra- vitreal injection of anti-vascular endothelial growth factor (VEGF) agents or steroids. Laser remains the mainstay of treatment and is potentially destructive. Systemic management aims at preventing or delaying the onset of retinopathy; reversing the early retinopathy; or delaying the progression of established retinopathy. Evidence from multiple studies has confirmed the protective role of rigid control of blood glucose and blood pressure. The evidence for lipid control versus maculopathy was less definitive. However, the use of fenofibrates (originally used for lowering serum lipids) has shown a benefit on both proliferative disease and maculopathy outside their lipid-lowering effect. Other drugs being tried are the Protein Kinase C (PKC) inhibitors, other peroxisome proliferator-activated receptors (PPAR) agonists, Forsoklin (which binds GLUT 1 receptor), minocycline (for its anti inflammatory effect), and Celecoxib (Cox-2 inhibitor).

Key words: Diabetic Retinopathy, Diabetic Maculopathy, Dyslipidemia, Fenofibrates, Hypertension, Systemic Management

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INTRODUCTION

The World Health Organization estimates the prevalence of diabetes worldwide across all age groups at 4.4% in year 2030 – an increase by about 1.6% from the year 2000.[1] This should amount to an increase from 171 million to about 366 millions in actual numbers.

Diabetic retinopathy (DR) affects 1 in 3 persons with diabetes and is the leading cause of vision loss in adult persons of working age. Patients with DR have been reported to have poorer quality of life reduced physical, emotional and social wellbeing, and to utilize more healthcare resources.[2]

In the US, among the adults 40 years or older with diabetes mellitus, the prevalence of DR has been estimated at 40.3% and that of vision-threatening retinopathy, which includes diabetic macular edema (DME), is estimated at 8.2%.[3] Globally, it has been estimated that up to 100 million people have DR and more than 20 million will have vision-threatening retinopathy.[4]

The present-day management of DR revolves around laser photocoagulation for proliferative disease; laser photocoagulation, intra-vitreal anti-vascular endothelial growth factor (VEGF) agents and steroids for DME. Vitreo retinal surgery is reserved for the more serious complications such as vitreous hemorrhage, traction and combined retinal detachment, premacular vitreoretinal traction.[5]

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While most agree that microvascular changes including DR are duration dependent to a great degree, there are obviously other factors that influence the onset and progression of the retinopathy. In this regard, many ocular treatments are indicated only when retinopathy has set in, and is akin to "fire fighting". Laser photocoagulation, for example, remains the first and often repeated modality of treatment in most countries; unfortunately this modality is destructive in nature and leads to variable loss of peripheral field in an attempt to preserve some central vision.

Thus, systemic therapy could be preventive and hence potentially could have more impact on the overall public health outcome for the society at large.[6] Systemic approaches to treatment are aimed at preventing retinopathy, delaying the onset of retinopathy, reversing retinopathy (in some cases), or delaying the progression of early to advanced stages of retinopathy.

In this article we discuss some of the current concepts related to systemic therapy in diabetic retinopathy using the evidence from various clinical trials [Table 1].

Glycemic control

Considering the fact that diabetes is primarily defined by raised blood glucose levels, it makes logical sense that good glycemic control should have beneficial effect on secondary effects of diabetes including microvascular complications and retinopathy.

The evidence

Two major trials- the Diabetes control and complications trial (DCCT)[7] involving insulin-dependent diabetics and the United Kingdom prospective diabetes study group (UKPDS)[8] involving non-insulin-dependent diabetics have answered the question in the affirmative. The DCCT has shown that a 10% reduction in HbA1c (e.g., 8-7.2%) is associated with a 43% reduction in progression of retinopathy in the intensive treatment group and 45% reduction in progression of retinopathy in the conventional treatment group- indicating that it is ultimately the control of blood glucose that is important. The study also showed that both the levels of HbA1c at start of the trial as well as the level achieved during the trial influenced the rate of progression of retinopathy. However, significantly the intensive treatment group had more incidence of hypoglycemic episodes. Follow-up studies on this group of patients have shown that the benefit of tight control on the progression of retinopathy was maintained, despite reducing difference in the values of HbA1c between the groups over time- a concept of "metabolic memory".[9]

The UKPDS[8] studied similar tight control versus conventional control for type 2 diabetes. After 6 years of follow-up, the intensive treatment group had significantly smaller rate of the two-step progression of diabetic retinopathy (even if need for photocoagulation was excluded).

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was designed primarily to study the affect of even more intensive glycemic control (than DCCT) on cardiovascular and microvascular events in patients with type 2 diabetes. The ACCORD eye study group has found a 33% reduction in the progression of DR in the intensive control group after a short period of 4 years.[10]

In contrast, the Veterans affairs diabetes study did not show any significant difference in the progression of microvascular changes after tight control of glycemia. Specifically, the study noted that the incidence of new ocular procedures; conversion to proliferative disease; and occurrence of macular edema were similar in both the groups while a non-significant beneficial trend was noted in terms of two-step progression of the retinopathy.[11]

Most reports mention halted or delayed progress of retinopathy but not reversal of established retinopathy. Very early retinal changes (such as increased fluorescein leak on vitreous fluorometry) has been shown to get reversed with intense glycemic control.[12]

An important issue to note is that tight control of blood glucose has been reported to cause early worsening of diabetic retinopathy and this has been attributed to up regulation of insulin-like growth factor-1 (IGF-1).[13-15] There are also case reports of rapid progression to florid retinopathy in insulin-dependent young diabetics, when put on intensive control of glycemia with continuous subcutaneous insulin infusion.[16] However, these patients also had significant other co-existing problems such as severe nephropathy. The ACCORD trial has shown increased risk of hypoglycemic episodes requiring medical assistance in the group with intensive treatment (aiming at $<$6% HbA1c). There was also increased rate of death from any cause in the group with intensive treatment -5% versus 4% in the conventional treatment.[10]

The inference

From a clinical practice perspective, it is perhaps impossible to replicate on a daily basis, the rigorous regimen of blood glucose control practiced in DCCT, ACCORD, and other trials. The message, however, is clear: better glucose control is associated with less risk of progression of DR. Good glycemic control right from diagnosis is beneficial in preventing the onset of diabetic retinopathy as well as in delaying the progression of the retinopathy. A 'good' control of glycemia is aimed at but not necessarily below normalcy. The long-term benefits of good control of glycemia outweigh the small risk of early worsening of retinopathy.

Control of hypertension

Hypertension is very often coexistent with diabetes. In a review publication by Mohan *et al.*, the incidence of hypertension

Table 1. Summary of clinical trials related to systemic treatment in diabetic retinopathy

Title	Intervention	Results
DCCT (Diabetes control and complications trial)	Maintaining near normal blood glucose (intensive treatment) compared to usual control in insulin dependent diabetes	43% reduction in risk of progression of retinopathy for 10% reduction in HbA1c. (from 8 to 7.2%) Metabolic memory-benefit of tight control maintained despite losing tight control later on
UKPDS (UK prospective diabetes study group)	Tight Vs conventional control of blood glucose in type 2 diabetes	25% reduction in microvascular end points (mostly due to reduced need for photocoagulation)
ACCORD (Action to control cardiovascular risk in diabetes) and ACCORD eye study group	Intensive control of blood glucose (more intensive than in DCCT), intensive blood pressure control, and combination therapy for dyslipidemia in type 2 diabetes	Glycemia control-Progression of DR7.3% vs 10.4% in standard therapy (33% reduction) Use of Fenofibrate-6.5% progression of DR vs 10.2% with placebo Intensive blood pressure control-10.4% progression of DR vs 8.8% with standard therapy
VADT (Veteran affairs diabetes trial)	Tight control of glycemia with goal of absolute reduction of 1.5 percentage points in HbA1c	No affect on the progression to Proliferative DR No affect on progression to DME Non-significant trend towards benefit in reducing progression of DR by two steps
HDS (part of UKPDS) dealing with hypertension control	Additional tight control of hypertension (150/85 or lower) with captopril or atenolol	At 7.5 yrs, 34% reduction in risk of deterioration of DR by two steps At 9 years follow-up, 47% reduction in risk of reduced vision by 3 or more lines on ETDRS
Prospective cohort study from Australia (Donaghue *et al.*)	Follow up study on type 1 diabetics (median follow up 4 yrs)	Higher systolic and diastolic blood pressures contribute to early DR development independent of glycemic control BP had a continuous rather than threshold affect 10 mm/hg higher systolic BP associated with 3-20% higher risk of DR 10 mm/hg higher diastolic BP associated with 2-30% higher risk of DR
ADVANCE trial (action in diabetes and vascular disease: Preterax and diamicron MR controlled evaluation)	Effect of blood pressure lowering and intensive blood glucose control on incidence and progression of DR in type 2 DM	BP lowering: Incidence and progression of DR lowered-but not to a significant degree (P=0.12) BP lowering: Significant reduction in occurrence of macular edema Intensive glucose control-had no affect on incidence and progression of DR Borderline reduction in risk of hard exudates and macular edema
EUCLID trial (EURODIAB controlled trial of lisinopril in Insulin-dependent diabetes mellitus)	Use of lisinopril (ACE inhibitor) in insulin dependent diabetics	Non-significant reduction in occurrence of DR Significant reduction in progression of DR Affect seen in normotensive patients as well
DIRECT (Diabetic retinopathy candesartan trials) Prevent 1-studied incidence of DR in type 1 DM Protect -1-Studied progression of DR in type 1 DM Protect-2-studied progression of DR in type 2 DM	Candesartan (angiotensin convertase inhibitor) used	Prevent 1-Reduction incidence of DR to just short of significant levels (P=0.0508); *post hoc* analysis showed significant reduction in 3 step deterioration of DR Protect-1-No significant affect on DR progression but final vision better Protect-2-Non significant affect on progression of DR; Significantly regression of established mild DR No affect on PDR or DME
RASS	Renin angiotensin blockade with enalapril (ACE inhibitor) or losartan (angiotensin receptor blocker) in normotensive type 1 diabetics	Significant reduction in risk of progression of DR by two steps for both drugs The effect remained after adjusting for the mean blood pressure
FIELD study (fenofibrate intervention and event lowering in diabetes)	Fenofibrate-a PPAR-α agonist and lipid lowering agent used in type 2 diabetics	Requirement for first laser was lowered Significant reduction in two-step progression of DR No effect on the incidence of DR The effect not related to lipid lowering
STENO-2 study	Intensive multifactorial target driven intervention in high risk type 2 DM with microalbuminuria Factors targeted were the BP, HbA1c, LDL cholesterol, triglycerides	About 50% reduction in risk of retinopathy, nephropathy, and cardiovascular risk

among type 2 diabetics was quoted at 20.6% in India, 78.4% in Thailand, 9.7% in Nigeria and 70.4% in Morocco.[17] Other studies have reported a three times greater incidence of hypertension among type 2 diabetics compared to age and sex-matched population without diabetes. Considering the known vascular damage that occurs with hypertension, there is expected to be additive affect of hypertension on the severity of diabetic retinopathy.

The evidence

The UKPDS studied the role of tight control of blood pressure on various end points – one of which is the retinopathy and visual loss.[18] There was a 35% reduction in the progression of retinopathy by 2 or more steps in the group with tight control of blood pressure. At 9 years follow-up, the group with tight control of blood pressure had a 47% reduction in risk of loss of 3 or more lines of vision (on ETDRS chart). Control of

hypertension was also shown to have beneficiary affect on other end points such as myocardial infarction, stroke, renal failure, etc., In a prospective cohort study, Gallego *et al*. have identified systolic and diastolic pressure as predictors for onset of diabetic retinopathy in type 1 diabetes.[19] The association was found to be linear- an increase by 10 mm/hg in systolic blood pressure was associated with 3-20% increased risk of retinopathy and an increase by 10 mm/hg in diastolic blood pressure increased the risk by 2-30%.

In contrast to glucose control, follow-up studies on this group of patients have shown that the benefit of tight blood pressure control on the progression of retinopathy was not maintained over time; thus, blood pressure control has to be sustained throughout life.[20]

The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation trial (ADVANCE) used perindopril-indapamide combination versus placebo for control of blood pressure in addition to glycemic control. The study, however, has shown only marginal benefit on the onset or progression of retinopathy with the pressure-lowering drugs.[21] The reduction in occurrence of macular edema was more significant.

The role of the renin-angiotensin system in the pathogenesis of DR has been of increasing interest. A local renin-angiotensin system has been identified to be functional in the eye and has been found to be upregulated during DR resulting in increased VEGF and other growth factors. Hence blockade of this system appears to be a logical approach to control the progression of retinopathy. Lisinopril, an angiotensin convertase enzyme (ACE) inhibitor, has been used in the EURODIAB trial (EUCLID Controlled trial of Lisinopril in Insulin-Dependent Diabetes Mellitus) and has been shown to have non-significant reduction in the occurrence of retinopathy (although not a primary end point) and significant reduction in progression of retinopathy.[22] This benefit on progression of retinopathy was noted even in normotensive patients with type 1 diabetes. This raises the possibility of direct effect of this drug on the retinopathy, outside of its blood pressure-lowering affects.

The DIRECT study is a large trial conducted to test the efficacy of Candesartan (an angiotensin receptor blocker) on diabetic retinopathy. The study had three components. The prevent-1 that studied the role of this drug in preventing diabetic retinopathy in type 1 diabetics and Protect-1 and Protect-2 that studied the effect of the drug in halting the progression of diabetic retinopathy in type 1 and type 2 diabetes, respectively.[23,24] Treatment with Candesartan was able to reduce the incidence of retinopathy by 18% (a marginally significant achievement $P = 0.0508$). Progression of retinopathy could not be influenced to a significant degree in both type 1 and type 2 diabetes. However, regression (reduction by 2 steps) of early stage retinopathy was achieved to a significant degree in type 2 diabetes. In general, it is believed that the treatment has reduced the retinopathy to a less severe variety more often than in the placebo group.

Yet another study- the Renin Angiotensin System Study (RASS) was designed to primarily study the occurrence of diabetic nephropathy, with retinopathy as additional end point. The study compared ACE inhibitor Enalapril or Angiotensin II receptor blocker Losartan with a placebo. Progression of retinopathy was significantly less with the both medications compared to placebo even when adjusted for blood pressure-lowering affect of the drugs.[25] The study has also demonstrated that the night ambulatory diastolic blood pressure is associated with increasing severity of diabetic retinopathy and this was attributed to the dysfunctional autonomic system in diabetics. The authors believe that the protective effect of ACE inhibitors and Angiotensin II receptor blockers could be due to the affect on the night time blood pressure rather than a direct affect on the rennin-angiotensin system in the eye.[26]

The inference

Control of blood pressure, along with good glycemic control, reduces the risk of progression of retinopathy. Furthermore, inhibition of the rennin-angiotensin pathway by an ACE inhibitor or angiotensin II receptor blocker seem to have effects beyond the impact of blood pressure control.

Control of dyslipidemia

The association between lipids and DR has been less well demonstrated compared to the role of hyperglycemia and hypertension.[27]

The evidence

The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) has not shown any association of cholesterol levels with the severity of DR but showed significant association with severity and occurrence of hard exudates in young diabetics.[28] The ETDRS study found a two-fold increase in risk of retinal hard exudates with increased levels of cholesterol.[29] High serum triglycerides have also been shown to be associated with increased risk of development and progression of retinopathy by Hadjadj *et al*.[30] The DCCT has shown significant association between occurrence of clinically significant macular edema and levels of LDL as well as total cholesterol- HDL ratio.[31] Low levels of HDL cholesterol have been known to be a risk factor for cardiovascular disease but the ADVANCE study did not show similar relationship between low levels of HDL cholesterol and retinopathy although there was a relationship with nephropathy.[32]

The statins and the fibrates have been in use clinically to reduce the lipid levels. Statins primarily reduce the LDL cholesterol. Gupta *et al*. had a good success with use of atorvastatin in the reduction of

diabetic macular edema.[33] Reduction in hard exudates was noted in as high as 66.6% cases with statins versus only 13.3% in control group. In a study by Gordon *et al*. of six patients, reduction in hard exudates was achieved with pravastatin along with reduction in total cholesterol and low-density lipoproteins.[34]

Peroxisome proliferator-activated receptors agonists

Peroxisome proliferator-activated receptors (PPAR) belong to a large super family of nuclear receptors.[35] These are ligand inducible transcription factors and serve as receptors for thyroid hormones, steroids, etc., They regulate the genes involved in carbohydrate and lipid metabolism and hence affect the insulin sensitivity and lipid homeostasis.[36] PPAR-α and γ are specifically of importance for this discussion. Drugs such as rosiglitazone, pioglitazone belonging to the group of thiazolidendiones are agonists of PPAR-γ and have serum glucose-lowering ability.[37] The fibrates are agonists of PPAR-α and have predominantly lipid-lowering function. Drugs such as Muralglitazar have dual (α/γ receptor agonists) affect and are expected to be even better since they have affect on lipid control as well as improving insulin sensitivity.[38]

PPAR-γ agonists are also suggested to have anti-inflammatory role since they have been shown to reduce the inflammatory markers such as serum C-reactive protein, IL-6, plasminogen activator-1, etc.[39]

Fenofibrates and diabetic retinopathy

Fibrates are PPAR- α agonists and have been extensively tested for diabetes and retinopathy.[40,41] The FIELD study (Fenofibrate Intervention and Event Lowering in Diabetes) is essentially a cardiovascular trial. However, the effect on reduction of myocardial infarction and coronary death was not found to be significant. There was beneficial effect on overall cardiovascular events. Study of diabetic retinopathy was actually a tertiary end-point, but showed a significant result. The need for first as well as repeat laser treatment for proliferative retinopathy and macular edema was significantly reduced with use of fenofibrate compared to placebo. A sub-study of 1012 patients who had baseline and follow-up fundus photographs was also carried out. This analysis revealed a markedly significant reduction in the need for laser photocoagulation, and also showed a significant reduction in 2-step progression of retinopathy. Incidence of macular edema showed non-significant trend toward reduction.

The mechanism by which fibrates achieved this beneficial effect on the retinopathy is, however, unclear. While lipid lowering is the identified primary action of fibrates, the actual levels of lipid lowering achieved in the study was not significant over time (although at 4 months there was significant reduction). The benefit on diabetic retinopathy progression was achieved against the backdrop of use of ACE inhibitors in both groups, as well as more use of statins in the placebo group over time.[42]

The ACCORD study also showed beneficial effect of fenofibrates. When added to statins, they significantly slowed the progression of diabetic retinopathy in type 2 diabetes mellitus.[10] Some of the mechanisms by which fenofibrates probably act are listed below.

- Inhibitory affect on the VEGF pathway.[43]
- Regulation of retinal endothelial cell survival and prevention of apoptotic death[44]
- Anti-inflammatory effect: There is enough evidence that inflammation plays a role in the pathogenesis of DR.[45] The vitreous of PDR patients has been demonstrated to have elevated levels of proinflammatory cytokines, such as Interleukins- IL-1β, IL-6 and IL-8; TNF-α and vascular cell adhesion molecule-1.[46-48] Increased VEGF and IL-6 levels were also detected in the aqueous humor of diabetic patients with macular edema.[49] Reduced concentrations of TNF-α, Interleukin-6, and interleukin-1β have been seen with fenofibrates.[40,50,51]
- Antioxidant property: Fenofibrates were shown to reduce the concentrations of melondialdehyde- a lipidperoxide formed due to reactive oxygen species.[52]

Considering the evidence of benefit of fenofibrates in DR, Treacy *et al*. suggest the exploration of intraocular delivery of the same along with anti-VEGF drugs in the management of DR. Currently available fenofibrate (oral) is converted to the active form by esterases. Hence bioavailability becomes an issue if administered intravitreally. A choline salt (ABT-335) has been identified that does not need activation by esterases.[53] Hopefully the future should see the conversion of this possibility into reality.

The inference

Control of dyslipidemia, possibly with fenofibrate, reduces the risk of progression of retinopathy.[54]

Multifactoral intervention

Most previous trials targeted only a single risk factor for DR. The effect of a multifactorial approach was investigated in the Steno-2 study in patients with type 2 diabetes and microalbuminuria.[55,56] The Steno-2 study encompassed treatment goals similar to those recommended in the American Diabetes Association guidelines. After 7.8 years of intensive treatment, the study group achieved lower systolic and diastolic blood pressures, lower HbA (1c), lower fasting serum total and low-density lipoprotein cholesterol, lower fasting serum triglycerides, and lower 24- hour urine albumin excretion. As a percentage of total energy, fat intake was less and carbohydrate intake was more. This resulted in significant reduction in microvascular events including diabetic retinopathy by about 50%.[55]

The inference

A multifactorial approach, targeting control of hyperglycemia, blood pressure, and dyslipidemia will reduces the risk of onset and progression of DR.

Other approaches to systemic medication

Anti-platelet agents

These have been the first to be tried for DR with no proven efficacy. Aspirin, ticlopidine, and dipyridamole have been tried.[57,58]

PKC inhibitors

Activation of Protein kinase C has been shown to have a role to play in development and progression of diabetic retinopathy. Ruboxistaurin – a selective PKC inhibitor has been tried for DR as well as DME.[59-61] Although the study revealed some beneficial affect in moderate and severe diabetic retinopathy, the drug has not been approved by the USA-FDA pending further trials.

Suppression of GLUT1

GLUT1 transports glucose between blood and the retina. Inhibiting the same by intra-ocular injection of siRNAs that inhibit the mRNA (that codes for GLUT) has been shown to reduce the retinal glucose levels.[62] Forskolin (which binds to GLUT1) when administered systemically has been shown to reduce retinal glucose levels in mice. Hence, GLUT1 can be a potential target for medical treatment- both locally and systemically.

Minocycline

A novel connection between bone marrow neuropathy, inflammation, and DR has been proposed.[63] Bone marrow neuropathy is supposed to increase the synthesis of inflammatory cells. This induces a sort of systemic inflammation that affects hypothalamus among other organs, and adversely affects the microvascular and macrovascular events. Minocycline (100 mgs twice a day)- a well-tolerated anti-inflammatory agent has been shown to have some benefit in improving visual acuity in type 2 diabetics with morbid obesity. In a pilot study of five patients with DME, Cukras *et al*. have found significant reduction in central macular thickness and improvement in vision.[64]

Rosiglitazone

As alluded to above, PPAR- γ agonist Rosiglitazone is primarily used for better control of diabetes. 65 Shen *et al*. have shown a 59% reduction in progression to proliferative DR from severe non-proliferative DR (47.4% vs 19.2%) with use of this drug over a 3-year period. 66 However, DME has been reported as a complication of use of this drug as well as with Pioglitazone.[67-69] However, Tatti *et al*. did not find any increased incidence of DME in patients being treated with Rosiglitazone.[70]

Celecoxib

Celecoxib is a Cyclo-oxygenase-2 (COX-2) inhibitor. Since COX-2 has been shown to upregulated in DR, inhibiting the same was thought to have benefit in DR. However, a placebo-controlled trial of Oral Celecoxib (200 mgs twice a day) has failed show any beneficial effect on the DME. Some decrease in fluorescein leakage was noticed.[71]

Adenosine receptor agonists or adenosine reuptake inhibitors

Adenosine has been shown to have anti-inflammatory affect. However, systemic administration of adenosine has severe side effects of hypotension, bradycardia, and sedation. Hence, agents that can inhibit its uptake or which mimic its action could be potential drugs for treatment of DR. This approach is at a concept level.[72]

Other agents that are under trial are canakinumab, a human anti–interleukin β monoclonal antibody (administered subcutaneously), Darapladib – a selective lipoprotein-associated phospholipase A2 inhibitor (administered orally) and Darbepoetin alpha (recombinant erythropoietin).

CONCLUSIONS

The present day treatment of established diabetic retinopathy mainly involves laser photocoagulation, which is basically a destructive treatment. Preventing the onset of DR or delaying the progression of DR can go a long way in preserving good vision and avoiding the laser photocoagulation. Normalizing the blood glucose levels, rigid control of blood pressure, reduction in LDL cholesterol by use of statins, use of fenofibrates and blockade of renin angiotensin system have all shown some benefit in the occurrence or progression of DR. The concept of multifactorial approach to simultaneously target each of the important issues that face a diabetic seem to be important since the cumulative benefit is very significant. The challenge is in implementing the study regimens in the general population so as to extract maximum mileage from the studies, in terms of reduction in societal burden of visual impairment caused by diabetes.

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