Does tight control of systemic factors help in the management of diabetic retinopathy?

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Diabetic retinopathy (DR), one of the leading causes of preventable blindness, is associated with many systemic factors that contribute to the development and progression of this microvascular complication of diabetes. While the duration of diabetes is the major risk factor for the development of DR, the main modifiable systemic risk factors for development and progression of DR are hyperglycemia, hypertension, and dyslipidemia. This review article looks at the evidence that control of these systemic factors has significant benefits in delaying the onset and progression of DR.

Key words: Control of systemic factors, diabetic retinopathy, glycemic control

With the prevalence of Type 2 diabetes now reaching pandemic proportions, there is a concomitant increase in the prevalence of diabetic retinopathy (DR). There are approximately 93 million people with DR, 17 million with proliferative DR (PDR), 21 million with diabetic macular edema (DME), and 28 million with vision-threatening DR worldwide.[1] More than 75% of people who have diabetes for more than 20 years will have some form of DR despite all the advances in diabetes care.[2] The World Health Organisation has declared DR as the sixth leading cause of blindness, and as an important cause of avoidable blindness.[1] DR is associated with many systemic factors that contribute to its development, severity, and progression. Although the development of microvascular complications of diabetes including DR is dependent on the duration of diabetes to a great extent, there are other modifiable risk factors too, that influence the development of retinopathy.[1,3-5]

The Chennai Urban Rural Epidemiology Study (CURES) Eye Study showed that the major systemic risk factors associated with DR are the duration of diabetes, hyperglycemia, male gender, and macroalbuminuria.[3] Therapeutic approaches in people with retinopathy or at risk for DR include drug therapy to reduce modifiable risk factors, laser photocoagulation, and surgery. Recently, there have also been significant developments in pharmacotherapy in the management of DR. In this article, we look at the evidence for various systemic factors in the development of DR.

Glycemic Control in Diabetic Retinopathy

It is well known that hyperglycemia is one of the most important determinants of diabetic microvascular complications.[5,6] Hence, good glycemic control should indeed have a beneficial effect on the microvascular complications including retinopathy.

The CURES Eye Study demonstrated a significant increase in the prevalence of DR with increasing glycated hemoglobin (HbA1c) levels.[3] The multiple logistic regression analysis carried out using DR as a dependent variable showed a significant trend of increasing retinopathy at different quartiles of HbA1c (trend $\chi^2 = 51.6, P < 0.0001$) as shown in Fig. 1.

The long-term benefit of glycemic control has been evaluated by two large studies: The Diabetes Control and Complications Trial (DCCT) in Type 1 diabetes,[7] and the United Kingdom Prospective Diabetes Study (UKPDS) in Type 2 diabetes.[8] The DCCT and the UKPDS have demonstrated that intensive glycemic control (HbA1c ≤7%) reduced both the development and progression of DR, with the beneficial effects of intensive glycemic control persisting up to 10–20 years.

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of the two-step progression of DR and a 25% risk reduction, the intensive treatment group had significantly lower rates compared to the conventionally treated group. The benefits of intensive therapy were greater in patients with shorter duration of diabetes. Patients with no retinopathy at baseline (primary prevention cohort), the intensive treatment reduced the risk of the development of DR by 76% compared with conventional therapy ($P < 0.001$). In the secondary prevention cohort, intensive treatment slowed the DR progression by 54% relative to conventional treatment ($P < 0.001$). A 10% reduction in HbA1c level from baseline (for example from 8% to 7.2%) was associated with a significant reduction in progression of DR both in the intensive treatment group (43%) as well as in conventional treatment group (45%). The study also showed that the level of HbA1c at the start of the trial as well as the level achieved during the trial influenced the rate of progression of DR. Total glycemic exposure was a dominant factor associated with risk of retinopathy progression.

Many of the DCCT patients participated in follow-up trial namely, the Epidemiology of Diabetes Interventions and Complications (EDIC) study.[7] The main aim of the EDIC was to determine if the benefits achieved in the DCCT with intensive insulin therapy persisted. These risk reductions achieved during the trial influenced the rate of progression of DR both in the intensive treatment group (43%) as well as in the conventional treatment group (45%).[9] The study also showed that the level of HbA1c at the start of the trial as well as the level achieved during the trial influenced the rate of progression of DR. Total glycemic exposure was a dominant factor associated with risk of retinopathy progression.

The DCCT was performed in 1441 patients with Type 1 diabetes with no DR or with mild to moderate non-PDR (NPDR).[7] The DCCT reported that during the average treatment period of 6.5 years, the risk of developing DR was substantially lower in the intensive treatment group treated compared to the conventionally treated group.[7] The benefits of intensive therapy were greater in patients with shorter duration of diabetes. Patients with no retinopathy at baseline (primary prevention cohort), the intensive treatment reduced the risk of the development of DR by 76% compared with conventional therapy ($P < 0.001$). In the secondary prevention cohort, intensive treatment slowed the DR progression by 54% relative to conventional treatment ($P < 0.001$). A 10% reduction in HbA1c level from baseline (for example from 8% to 7.2%) was associated with a significant reduction in progression of DR both in the intensive treatment group (43%) as well as in conventional treatment group (45%).[9] The study also showed that the level of HbA1c at the start of the trial as well as the level achieved during the trial influenced the rate of progression of DR. Total glycemic exposure was a dominant factor associated with risk of retinopathy progression.

The UKPDS studied the impact of tight control versus conventional control on the microvascular and macrovascular complications in Type 2 diabetes.[8] After 6 years follow-up, the intensive treatment group had significantly lower rate of the two-step progression of DR and a 25% risk reduction in microvascular endpoints, including the need for retinal laser photoocoagulation. UKPDS showed that intensive blood glucose control, irrespective of the antidiabetic agents used, substantially decreased the risk of microvascular complications.

Studies like the Kumamoto study also evaluated the relationship between glycemic control and DR.[10] In this study, the glycemic threshold to prevent the onset and progression of diabetic microvascular complications was mentioned as: HbA1c ≤ 6.5%, fasting blood glucose concentration < 110 mg/dl and 2-h postprandial blood glucose concentration < 180 mg/dl.[11]

Two more clinical trials, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study, and the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) Retinal Measurements study, examined the effect of aggressive blood glucose lowering (HbA1c ≤ 6.5%) in people with Type 2 diabetes. In the ACCORD study, intensive glycemic control was associated with a lower rate of DR progression.[12] While the ACCORD Eye Study[13] showed a 33% reduction in the progression of DR in the intensive control group, after a period of 4 year follow-up, the ADVANCE study[14] and the Veterans Affairs Diabetes Trial[15] did not show any significant difference in the progression of microvascular changes after tight glycemic control.

Reversal of early retinopathy changes was seen with good glycemic control.[16] Tight glycemic control is most effective when initiated early in the course of diabetes. Intensive glycemic control can at times have adverse effects, including worsening of DR, possibly attributable to a rapid reduction in plasma glucose levels.[16] Early worsening of DR has been attributed to up-regulation of insulin-like growth factor-1.[16]

**Agents for glycemic control and diabetic retinopathy**

Insulin therapy has always been believed to be beneficial for delaying onset and progression of DR as it not only helps in achieving good glycemic control but also improves retinal blood flow and the vascular tone of retinal microvasculature.[16] The UKPDS showed that it was not the particular anti-diabetic drug used that was important, i.e., sulfonylurea or meforin or insulin but the degree of glycemic control which mattered for prevention of retinopathy.

There are some experimental studies which show that newer anti-diabetic drugs like sitagliptin (dipeptidyl peptidase-4 inhibitor) may decrease the retinal inflammatory state and neuronal apoptosis, thus suggesting a possible protective effect on diabetic retinal cells. However, no clinical studies have evaluated the effect of glitazones on retinopathy endpoints.[20]

Glitazones are a class of oral hypoglycemic agents that result in the activation of peroxisome proliferator-activated receptor-γ, a transcription factor located in the adipose tissue and retina. Glitazones should be used with caution in patients with DME. Fluid retention occurs in 5–15% of patients taking glitazones. Its use appears to be a cause for macular edema, and drug cessation appears to result in rapid resolution of DME.[20] It is important for ophthalmologists to check if the patients are on glitazones when treating DME.

There is very little evidence that any particular class of anti-diabetic drug is either beneficial or detrimental with respect to DR, independent of the glycemic control, i.e., the level of HbA1c achieved. The overall inference from various
Blood Pressure Control in Diabetic Retinopathy

Blood pressure (BP) control is an important component of risk factor modification in reducing the risk of retinopathy progression. Hypertension is very often coexistent with diabetes. The incidence of hypertension is 3 times greater in people with Type 2 diabetes when compared to those without diabetes. A review article showed that diabetes and hypertension coexist in people with Type 2 diabetes ranging from 20.6% in India to 78.4% in Thailand in South-East Asia.[22] The vascular damage due to hypertension has an additive effect on the severity of DR.

The UKPDS showed that, among patients with Type 2 diabetes, tight BP control (mean BP 144/82 mm Hg) resulted in a significant reduction in progression of DR (35%) as well as a significant decrease in vision loss and need for laser photoacoagulation compared to less control (mean BP 154/87 mm Hg).[23] At 9 years follow-up, the group with tight control of BP had a 47% reduction in risk of loss of three or more lines in the Early Treatment DR Study (ETDRS) visual acuity chart.[14] Gallego et al.[24] identified systolic and diastolic BP as predictors for the onset of DR in adolescents with Type 1 diabetes. A linear association was noted, an increase in systolic BP by 10 mm Hg was associated with 3–20% increase in risk for DR and an increase in diastolic BP by 10 mm Hg increased the risk by 2–30%.

The ACCORD and ADVANCE studies, where the mean BP was <140/80 mm Hg in both the active intervention and control groups, active treatment did not show any additional benefit on preventing progression of DR.[12,14] The ADVANCE study, however, showed the reduction in the occurrence of macular edema to be more significant.[14]

The Role of the Renin-Angiotensin System in Diabetic Retinopathy

A local renin-angiotensin system (RAS) in the eye is been found to be up-regulated in patients with DR resulting in increased vascular endothelial growth factor (VEGF). Hence, an RAS blockade appears to be a logical approach to control

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Intervention and Event Lowering in Diabetes, DM: Diabetes mellitus, ACE: Angiotensin converting enzyme, PPAR: Peroxisome proliferator-activated receptor, DME: Diabetic macular edema, DR: Diabetic retinopathy, PDR: Proliferative diabetic retinopathy
the progression of retinopathy. A number of trials have examined the effect of RAS blockade on DR development and progression. The findings of the EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes suggested that blockade of the RAS with the angiotensin converting enzyme (ACE) inhibitor lisinopril could reduce both incidence and progression of retinopathy in Type 1 diabetes. This benefit on the progression of retinopathy was noted even in normotensive patients [Table 1]. This drug possibly has a direct effect on retinopathy, outside of its BP-lowering mechanism.

In the RAS Study, ta
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taking enalapril, an ACE inhibitor or losartan, an angiotensin receptor blocker (ARB), reduced DR progression independent of BP change in normotensive, normoalbuminuric participants with Type 1 DM. This study showed that the night ambulatory diastolic BP was associated with increasing severity of DR and the protective effect of ACE inhibitors and ARBs was probably due to the effect on the BP at night.

The DR Candesartan Trials (DIRECT) Program, which evaluated the effect of the angiotensin II ARB candesartan 32 mg daily on the incidence of new DR in Type 1 diabetes (DIRECT-Prevent 1), and on the progression of DR in patients with Type 1 and Type 2 diabetes showed a change toward less severe retinopathy with the use of candesartan. A conclusion from these studies is that control of BP reduces the risk of progression of DR. Optimizing BP helps to reduce the risk of vision loss and the necessity of laser photocoagulation. Inhibition of the RAS by an ACE inhibitor or ARB, have effects on decreasing DR. It is important to remember that reduction of BP is more important than the type of BP-lowering medication. BP levels of about 135/80 mm Hg should be aimed for to reduce the risk of vision loss and the necessity of laser photocoagulation. Optimizing BP helps to reduce the risk of progression of DR. Nontraditional lipid markers in diabetic retinopathy

Studies have also been done to look into the serum lipoprotein(a) (Lp[a]) and serum apolipoproteins (Apo) profiles in DR. In patients with PDR, serum Lp(a) was significantly higher compared to patients without DR. In the retina, apo A1 is a key factor for preventing lipid accumulation and a potent scavenger of oxygen-reactive species for protecting the retina from the oxidative stress caused by diabetes. Apo B is the main component of LDL-C and is a reflection of atherogenicity. Low Apo A1/Apo B ratio in serum was found to be associated with PDR in Type 2 diabetic patients of long duration.

Renal Status and Diabetic Retinopathy

Microalbuminuria is found to be a reliable marker of DR. In the Sankara Nethralaya DR Epidemiology and Molecular Genetic Study (SN-DREAMS), subjects with microalbuminuria had a 2-fold higher risk of DR compared to those without microalbuminuria, and this risk increased to almost 6 times, in the presence of macroalbuminuria. In the CURES study, the risk of nephropathy was found to be significantly higher.
in sight-threatening DR group compared to the no retinopathy group (odds ratio [OR] 5.3, P < 0.0001). Hence assessment of the renal parameters-blood urea, serum creatinine and microalbumuria, is important, especially if DR is present. In a study done to assess the course of DR after renal transplant, it was found that renal transplant stabilized retinopathy in the majority (60%) of the diabetic patients and significant improvement in visual acuity was seen during the first 20 months postrenal transplant.[45]

The presence of DR is also a major risk factor for progression to overt diabetic nephropathy.[43] The EURODIAB study showed that DR in association with increased BP is an important independent risk factor for diabetic nephropathy progression.[44] Albuminuria and DR are considered important for renal prognosis in Type 2 diabetic patients.[46]

Anemia and Diabetic Retinopathy

Severity of DR was found to increase with severity of anemia.[44] In a recent study from China,[40] the prevalence of anemia was significantly higher in people with DR (27.3%) compared to those without retinopathy (19.7%, P < 0.001). The SN-DREAMS study identified the duration of diabetes >5 years (OR 1.56 [95% CI, 1.09–2.69]) and the presence of retinopathy (OR 1.82 [95% CI, 1.22–2.69]) as independent predictors for anemia in people with diabetes.[48]

Anemia leads to progression of DR by aggravating hypoxia in the retina, resulting in the production of growth factors such as VEGF.[49] In the ETDRS, low hematocrit was found to an independent risk factor for high-risk PDR and visual impairment.[50] Anemia is an important risk factor for clinically significant macular edema (CSME).[51] Hence, assessment of Hb levels is of utmost importance, especially in diabetic patients with sight-threatening retinopathy, PDR and CSME.

Intravenous administration of erythropoietin to treat anemia in diabetic patients with renal impairment showed a beneficial effect in DME and improvement in visual acuity.[52]

Cardiovascular Diseases and Diabetic Retinopathy

Association of cardiovascular disease (CVD) events and DR has also been established in many epidemiological studies worldwide.[53] DR in Type 2 diabetes is found to be associated with a 1.7-fold increased risk of cardiovascular events, such as stroke, coronary artery disease (CAD), and heart failure.[54] Presence of any DR doubled the risk of mortality and CVD events (OR 2.34) in people with Type 2 diabetes and quadrupled the risk in those with Type 1 diabetes (OR 4.1).[53]

The CURES study showed that the prevalence of CAD to be higher in DR versus no DR (P = 0.007).[55] Significant association was observed in subjects with HbA1c levels >7% (P = 0.002). It is likely that endothelial dysfunction, low-grade inflammation, and rheological abnormalities are common mechanistic denominators.[54]

DR has also been independently associated with the presence of carotid plaques (P = 0.045), an early sign of atherosclerotic burden.[56] Mean values of carotid intima-media thickness (0.93 ± 0.36 vs. 0.85 ± 0.21 mm, P = 0.001) and augmentation index (27.9 ± 8.9 vs. 25.8 ± 9.6%, P = 0.031) were also found to be significantly higher among patients with retinopathy compared with those without DR.[57]

Antiplatelet Therapy- Aspirin in Diabetic Retinopathy

A systematic review suggests that acetylsalicylic acid-aspirin therapy neither decreases nor increases the incidence or progression of DR.[58] Aspirin use does not appear to be associated with an increase in the risk of vitreous hemorrhage.

Pregnancy and Diabetic Retinopathy

Diabetic women in child-bearing age should be counseled regarding the risk of development and progression of DR.[59] Pregnancy may promote the onset of DR in about 10% of cases, as well as contribute to its worsening when already present.[60] Increasing systolic BP at first visit (OR 1.03, CI, 1.01–1.06, P = 0.02) and a greater drop in HbA1c between first and third trimesters of pregnancy (OR 2.05, CI, 1.09–3.87, P = 0.003) significantly increased the odds of retinopathy progression.[61] DR progression during pregnancy was higher in women with Type 1 diabetes than those with Type 2 diabetes (31.3% vs. 11.7%, P = 0.001).

Established sight-threatening DR should be treated at an earlier stage in pregnant women.[62] In a study of patients with no DR at onset, who then developed mild NPDR during pregnancy, 50% had complete regression, and 30% had partial regression of DR after delivery.[63] In another study,[64] two-thirds of women who experienced DR progression developed only mild NPDR. None of the women with normal retinal examination during the first trimester developed laser requiring sight-threatening DR during pregnancy.

Obesity and Diabetic Retinopathy

Obesity has been identified as an independent risk factor for DR. Persons with higher body mass index and larger neck circumference were found more likely to have DR and more severe DR.[64] In a study carried out in urban South Indian population, abdominal obesity and higher waist-to-hip ratio were associated with DR in women.[65] Obesity increases the prevalence of several risk factors involved in DR onset and development including inflammatory markers.[66] Elevated angiogenic factors including VEGF have also been observed in the serum of obese individuals.[67] Prevalence of retinopathy increased significantly with higher body weight (P < 0.05) with correlation to quality of metabolic control and systolic BP.[68] The Gutenberg Health Study has shown an association between vision-threatening DR and obesity.[69]

Conclusion

Good glycemic control and BP control are essential for the successful ophthalmic care of patients with diabetes. Early screening and tight glycemic control from the time of diagnosis of diabetes play an important role in the prevention of vision impairment due to sight-threatening retinopathy. Reduction of serum lipid levels by use of statins and fibrates and blockade of the RAS also add the beneficial effect in preventing development and progression of retinopathy. Association between microvascular and macrovascular complications of diabetes is well established. Optimal control of various systemic parameters that affect the onset and progression of DR through
a multidisciplinary healthcare team approach involving the physician, the ophthalmologist and the dietitian/counselor could help in reducing the morbidity due to DR.

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References


