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A Holistic Approach To Diabetic Retinopathy

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ABSTRACT

Threatening Diabetic Retinopathy (DR) is projected to nearly triple in the next forty years1. DR is predominantly a microangiopathy in which small blood vessels are particularly vulnerable to damage from high glucose levels. Direct hyperglycemic effects along with many angiogenic stimulators (like vascular endothelial growth factor) and inhibitors have a role to play in the causation of DR. A consistent screening with timely metabolic control helps prevent ocular disease in diabetic patients, thereby decreasing the need for intravitreal anti-VEGFs and steroids, laser photocoagulation and vitrectomy with or without epiretinal membrane removal or peeling of internal limiting membrane. Therefore, a tight regulation of blood glucose, blood pressure, serum lipids, albuminuria (signifying diabetic nephropathy), anemia is important. Additional risk factors that need to be taken care of include- smoking in males with type1 diabetes, puberty, pregnancy, duration of disease.

Keywords: diabetic retinopathy, hyperglycemic effects, anti-VEGFs, metabolic control

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INTRODUCTION

Approximately, one-third of people with diabetes develop some degree of diabetes-related eye damage, or retinopathy[1]. In the absence of adequate diabetes care, and without good metabolic control, high rates of retinopathy and other complications are likely to ensue[1]. All over the world, there were 382 million diabetic patients in 2013, which may rise to 592 million patients by 2035[1]. According to the WHO estimates- 19% of the world's diabetic population lives in India and 80 million people in India will have diabetes by the year 2030[1] . The prevalence of type 2 diabetes mellitus (DM) is increasing more rapidly than type 1 DM due to sedentary lifestyles, obesity, industrialization and ageing of the population.

Shaw *et al.* concluded that the world prevalence of diabetes among adults (aged 20-79 years) was 6.4%, affecting 285 million adults, in 2010, and that it would increase to 7.7%, and 439 million adults by 2030. Between 2010 and 2030, there will be a 69% increase in numbers of adults with diabetes in developing countries and a 20% increase in developed countries[2]. A population based assessment of diabetic retinopathy conducted by Dandona *et al.*[3] in an urban population in southern India showed the prevalence of diabetic retinopathy (DR) in India to be 17.6% to 28.2% (1999). Raman *et al*. calculated the overall prevalence of DR in diabetics as 18.0%, the prevalence of DR in known diabetics as 20.6% and the prevalence of DR in the newly diagnosed as 6.0%. The age and gender-adjusted prevalence of DR came out to be 3.5% (for the urban Chennai general population (2009))[4].

The medical aspects of diabetic retinopathy which are usually forgotten, and need to be taken care of to reduce the incidence of DR in diabetic patients are :Age at the diagnosis of diabetes, duration of diabetes, poorly controlled DM, pregnancy, associations with: hypertension, nephropathy, hyperlipidemia, obesity, anemia, smoking.

Diagnosis of diabetes mellitus:

Symptoms of diabetes + random blood glucose concentration ≥ **11.1 mmol/L (200mg/dL**) *or*

Fasting plasma glucose ≥ **7.0 mmol/L (126mg/dL)** *or*

Hemoglobin A 1c ≥ **6.5%***or*

2-hour plasma glucose ≥ **11.1 mmol/L (200mg/dL)** during an oral glucose tolerance test[5].

AN OVERVIEW OF THE MANAGEMENT OF DM:

A timely management of DM done under the following three criteria can minimize the occurrence of DR and other complications of DM:

Individualized glycemic control:

Diet/Lifestyle modification, exercise, medication

Treat associated conditions:

Dyslipidemia, hypertension, obesity, coronary heart disease

Screen for / manage complications:

Retinopathy, cardiovascular disease, nephropathy, neuropathy, other complications.

Diet / Lifestyle Modification

A diabetic patient's diet should be a high calorie/ high fiber/ low fat diet with food items having a low glycemic index which helps to reduce blood cholesterol and triglyceride level. Monounsaturated fats (canola, olive and peanut oils) also help lower triglyceride level. The sucrose consumption should be done with appropriate insulin adjustments. Fructose is preferred over sucrose or starch. A use of non-nutrient sweeteners should be made. The **supplements containing vitamins, antioxidants or trace elements should not be advised.**

Exercise regimen:

A physical exercise regimen may have a detrimental effect on advanced diabetic retinopathy. Therefore, it should be individually tailored. Anderson *et al. saw* that 84% of vitreous haemorrhage were associated with exercise as mild as walking[6].

Glycemic control:

A tight glycemic control reduces both the incidence and progression of diabetic retinopathy. The treatment goals are:

1. HbA1c < **6.0%**
2. Preprandial capillary plasma glucose**: 80-130mg/dL**
3. Peak postprandial capillary plasma glucose **<180mg/dL**

The Diabetes Control and Complications Trial (DCCT) Research Group demonstrated that the intensive treatment reduced the incidence of diabetic retinopathy by 76% and progression by 54% as compared with the conventional treatment[7]. But the trial also revealed a risk of early worsening (in the first six months) of DR, (as seen in DCCT[8)] :13.1% of the intensive treatment group against 7.6% of the conventional treatment group.

Blood pressure control:

The patients having tight control had 34% reduction in DR progression, 47% reduction in visual acuity deterioration and 35% reduction in laser photocoagulation as compared to those having conventional control[9]. These effects can be produced with a target B.P. of**<130/80 mmHg** or **<125/75 mmHg** if proteinuria is **>1.0 g/24 h** with increased serum creatinine, which can be achieved by using drugs that block the effect of renin-angiotensin-aldosterone system.

In a trial (EUCLID[10]), **Lisinopril** reduced the progression of DR by 50% and progression to proliferative DR by 80%. Similarly, a small RCT conducted by Knudsen *et al*. reported a worsening of DME among patients treated with the angiotensin II receptor blocker, **Losartan**, compared with the controls[11].

Currently, ongoing RCTs include:Action in Diabetes and Vascular Disease (**ADVANCE**): to study the effect of **perindopril-indapamide** combination on the incidence of DR[12], and Diabetic Retinopathy Candesartan Trial (**DIRECT**): to evaluate the angiotensin II receptor blocker, **Candesartan**[13].

Lipid-lowering therapy:

Sen *et al.*concluded that simvastatin shows a nonsignificant trend in visual acuity improvement in patients with DR[14]. Similarly, Cullen *et al*. demonstrated a reduction in hard exudates but no improvement in visual acuity in patients with clinically significant DME, taking clofibrate[15]. On the contrary, as revealed by Keech *et al*., in their study on effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus, fenofibrate improves macular edema and reduces the need for laser treatment[16].

Atorvastatin has no effect in reducing DR progression[17, 18]. Ongoing RCT, Atorvastatin Study for Prevention of Coronary Endpoints (**ASPEN**)[19], will also evaluate the effects of atorvastatin on DR.

Diabetic nephropathy:

All renal anatomical end points were associated with increasing severity of diabetic retinopathy (*Klein et al*.), while controlling for other risk factors. These data demonstrate a significant association between diabetic retinopathy and preclinical morphologic changes of diabetic nephropathy in type 1 diabetic patients[20].

Pregnancy and Dr:

Moloney *et al.* showed prevalence increasing from 62 to 77% in pregnant diabetic women[21]. A worsening of DR is noted during the course of pregnancy. Also, the presence of hypertension compounds DR in pregnancy. An early laser photocoagulation may be needed to treat DR in pregnancy. Sometimes, a normal delivery may be converted to a caesarean[22].

Role of anemia:

The prevalence of anemia (Hb < 12 g/dl in women and <13 g/dl in men) among diabetic patients was **12.3%**. Between 40 and 49 years of age, prevalence of anemia was **higher in women** than in men (26.4 % vs 10.3%). **Men with anemia** had **2** times the risk of developing diabetic retinopathy (Ranil *et al.)*[23]. A Multivariate analysis revealed independent predictors for anemia[23]:

1. age group more than 69 years
2. duration of diabetes of more than 5 years
3. presence of diabetic retinopathy

Anemia is a relevant factor related to the progression of proliferative diabetic retinopathy, which can be treated with the help of physician[24].

Antiplatelet agents:

Aspirin: As demonstrated by ETDRS **650mg/day** has no beneficial effect on DR progression or loss of visual acuity[25,26]. It is **not** associated with an increased rate of **vitrectomy**[25,26]. A reduction in microaneurysms is reported with the use of aspirin alone or in combination with dipyridamole[27]. A similar trend was observed in a small RCT[28], evaluating **ticlopidine**, although the results were not statistically significant.

ROLE OF CALCIUM DOBESILATE:

Calcium dobesilate (2,5-dihydroxybenzenesulfonate), the only **angioprotective** agent that reduces the progression of this disease[29].Recent studies have shown that calcium dobesilate is a potent **antioxidant**, against the highly damaging hydroxyl radical. In addition, it improves diabetic **endothelial dysfunction, reduces apoptosis, and slows vascular cell proliferation[29].**

PROTEIN KINASE C INHIBITORS:

The patients treated with **32mg** of ruboxistaurin had a significant reduction in the risk of moderate visual loss[30].There was a reduction in clinically significant DME among patients treated with **32mg** ruboxistaurin with a larger effect seen in patients with HbA1c levels of less than 10% (when patients with HbA1c levels of **10% or greater** were excluded)[31,32].

GROWTH HORMONE/ INSULIN LIKE GROWTH FACTOR INHIBITORS:

Octreotide (a synthetic analogue of somatostatin) blocks the growth hormone and reduces the severity of retinopathy[33], but, a **continuous subcutaneous infusion** of octreotide has not shown any significant benefits[34]. The results obtained were inconclusive even when a **long-acting release** octreotide injection was used[35].

ALDOSE REDUCTASE INHIBITORS:

Two aldose reductase inhibitors, **sorbinil** and **tolrestat**, did **not** show any statistically significant effect in reducing DR incidence or progression in RCTs of 3 to 5 years' duration[36].

ROLE OF ERYTHROPOIETIN:

Intravenous EPO to treat anaemia in diabetic patients with renal impairment has shown a remarkable effect in macular edema and **improvements in visual acuity**[37]. It works mainly due to the **neuroprotective** mechanism[39].Some studies have evaluated the **intravitreal** effect of EPO in the eyes of patients with diabetic macular and severe chronic oedema[38], and patients benefitting from this treatment have shown an improvement in their eyesights. A study has also suggested that EPO may reduce the loss of pericytes in the early stages of DR, and therefore, could be used as a new therapeutic agent for the initial forms of DR based on its **anti-oxidant, antiapoptotic, and neuroprotective properties**[39].

MICRONUTRIENTS:

Chromium supplementation improves **glucose intolerance, gestational diabetes, and corticosteroid-induced diabetes**[40,41]. Likewise, if one suspects zinc deficiency, especially in high-risk patients such as those with prolonged **glycosuria and diuretic therapy**, one can consider supplementation of zinc sulfate, **220 mg three times daily.** This should be initiated for no more than **3 months** because prolonged zinc supplementation may inhibit copper absorption and adversely affect lipid profiles[42,43].

The rationale for the use of **vitamin C** in a diabetic population is based on its potential effects in reducing atherosclerotic plaque formation, **preventing microangiopathy**, improving vascular integrity, and aiding in wound healing[44,45,46].

Plasma homocysteine concentration in type 2 diabetes correlates with age, creatinine, folate, and vitamin B12 but not with diabetes-related variables such as duration, current degree of control, or presence of complications[47]. Interventional trials with folate and vitamin B6 and B12 supplementation have failed to prevent cardiovascular events despite lowering homocysteine levels[48,49].

CONCLUSION

In a nutshell, for the management of DR, one must try becoming a physician first. A holistic approach to treat diabetes provides for the timely management of DR. Firstly, a reduction in glycosylated Hb by 10%, reduces DR by 35%, thereby achieving a tight metabolic control a necessity. Secondly, a lowering of systolic blood pressure by 10 mm Hg, reduces DR by 11%. Hence, a BP below 130/80 mm Hg should be targeted at. Thirdly, the anti-lipidemic drugs improve DR/DME on a long term basis, thereby, justifying its use to delay the progression of DR. The patients on drugs like rosiglitazone or Losartan should be monitored for an incorrigible macular edema. The treatment of anemia reduces DR by 50%. About half of the diabetic patients are anemic, thereby making the control of anemia an important aspect in the management. The renal function tests should be taken care of, because nephropathy correlates with retinopathy. The drugs like Calcium dobesilate, protein kinase C inhibitors, minerals, and vitamin C should be used efficiently, to minimize the occurrence and progression of DR. The antioxidants have a negative impact on DR and therefore, must not be used extravagantly. A timely medical management of DM may reduce the occurrence of DR, dependency on Anti VEGFs (to control the symptoms of DR) and markedly improve DR in a cheaper & effective way with a long term beneficial result.

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