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DIABETIC RETINOPATHY AND ITS SYSTEMIC RISK FACTORS

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ABSTRACT

Diabetes mellitus (DM), commonly referred to as diabetes, is a group of metabolic disorders with complications that include sight-threatening diabetic retinopathy, also known as diabetic eye disease. To implement an effective prevention the risk factors of diabetic retinopathy are essential to understand. This research aims to examine the association between the commonest complications of diabetes namely Diabetic retinopathy and its risk factors. Studies show there is a poor glycemic control in patients of diabetic retinopathy as reflected by a raised glycated hemoglobin, longer standing diabetes, and use of injectable insulin for treatment. Among other risk factors, hypertension has association with prevalence and progression of diabetic retinopathy whereas the effects are not so well established for cholesterol, and lipid control, inflammatory markers, sleep-disordered breathing, obesity and exercise. Myopia was a protective factor for the development of diabetic retinopathy. Several genetic polymorphisms are also associated with an increased risk for development of diabetic retinopathy.

KEYWORDS: Diabetic retinopathy, Hypertension, Cholesterol, Exercise, Obesity, Sleep-disordered breathing, Anemia, Sex Hormones.

INTRODUCTION

Diabetes mellitus (diabetes) includes a group of metabolic disorders in which raised and dysregulated blood glucose levels result from either decreased production of insulin or insulin resistance.[2] Diabetes in India is fast gaining the status of an epidemic with around more than

62 million diabetic individuals currently diagnosed with the disease. The prevalence of diabetes is predicted to double globally from 171 million in 2000 to 366 million in 2030 with a maximum increase in India]. Diabetes mellitus may afflict upto79.4 million individuals in India by 2030, while China and the United States will also see significant rise in those suffering from the disease. Even with increasing number of treatment modalities for diabetic retinopathy, the best method of minimizing its impact is prevention of ocular complications. Insulin resistance, being at the heart of pathology of diabetes mellitus is not the only problem but is one of the components of this metabolic syndrome. Other features of the metabolic syndrome including dyslipidemia, hypertension, abdominal obesity, prothrombotic and a proinflammatory state are more likely to be found in a diabetic subject.[4] If one or more of these components are present in the patient suffering from diabetes there is an increased risk of diabetic complications, including retinopathy.[5] At the forefront of managing the disease are primary care physicians, endocrinologists and ophthalmologists who help to motivate patients to control their disease. The time of diagnosis of diabetic eye disease can be a pivotal moment in the patients' lives. Subjects with threat of vision loss is a wake-up call for them to invest in habits that will maintain their overall health and the health of their eyes. Various risk factors that affect one of the most important complications of Diabetes ie.diabetic eye disease has been studied in this research.

MATERIAL AND METHOD

This research was carried out by searching various classical text books along with medical database like PubMed, Google scholar. The authors each independently carried out a narrative literature review and findings were discussed. Literature was identified via searches of PubMed, Google and Google Scholar, with relevant publications selected after discussion. An important consideration was that papers either had risk factors for diabetic retinopathy or contained a detailed description of diabetic retinopathy. For PubMed and Google searches, similar terms were used. For example, the PubMed strategy consisted of title and abstract searches for: ((diabetic retinopathy) OR ((diabetic retinopathy AND risk factors)). Also searched upon were the recommendations of conferences and seminars, and reference lists from key publications.

RESULTS AND DISCUSSION

Glycemic control

The effects of raised blood sugar have been found to show the most significant effect on the progression of diabetes and the development of its complications particularly microvascular complications.[6] In Action to Control Cardiovascular Risk in Diabetes (ACCORD)trial, patients were randomized to an intensive blood sugar control regimen with a target HbA1c level of 6.0 % were found to have a significantly lower rate of progression of diabetic retinopathy as compared to those with a HbA1c target level of 7.0–7.9 % (7.3 vs 10.4 % progression rate).[7] Similar levels were found in subjects on a regimen of intensive control of glucose in type 2 diabetics in Cochrane review.[8] For every 10 % decrease in HbA1c, there is an associated 42 % decreased risk of retinopathy progression. Whereas for every 10 % increase in Hba1c, the risk of retinopathy progression increased by 64 %.[9] This study results are similar to previous studies, which also found a reduction in the risk of retinopathy with strict glycemic control.[10,11] The beneficial effects of tight glycemic control seems to last for a longer time, as similarly managed patients in the Epidemiology of Diabetes Interventions and Complications Trial (EDIC) extension to the Diabetes Control and Complications Trial (DCCT) had a significantly lower risk of retinopathy progression if they were previously randomized to strict insulin therapy vs. conventional therapy (39 vs 56 % progression over 3 years).[12] A new therapeutic modality for diabetes has emerged in form of pancreas transplantation. This has dramatic effects on blood sugars, with a number of patients achieving a euglycemic state. Cases have been reported on decreased progression or even regression of diabetic retinopathy after transplantation of pancreas.[13,14] A class of medications used for control of blood sugar namely thiazolidinedione are considered to be controversial because of their ocular adverse effects including diabetic macular edema and resistant peripheral edema as its systemic side effect.[15,16] However the ACCORD trial, compared the rates of macular edema with or without exposure to these drugs and saw no effect.[17] Conclusively, strict control of blood sugar levels is definitely helpful in decreasing the progression of complications of Diabetes, particularly Diabetic retinopathy. The ideal levels of HbA1c target for diabetics still remains controversial. The American Diabetes Association advocates for a goal 7.0 % where as in ACCORD trial a HbA1c goal of 6.0 % was used and similarly a goal of 6.5 % was used by the ADVANCE trial.[7]

Arterial Hypertension

BP control is an important component of risk factor modification in lowering the risk of progression of diabetes to develop retinopathy. Hypertension is very often coexistent with diabetes. Hypertension is three times more common in patients with diabetics as compared to non-diabetics. With respect to the risk for developing cardiovascular disease, diabetics are particularly susceptible to effects of hypertension. There are multiple hypotheses for why this may be. A review article showed that diabetics and hypertension coexist in people with type 2 diabetes mellitus in a range from 20.6% in India to 78.4% in Thailand in south East Asia. One of the implicated mechanism is the interactions between blood sugar control by hormones and the renin-angiotensin- aldosterone system (RAS) at many levels and in both directions; those with diabetes have elevated RAS leading to hypertension, and those with hypertension have higher rates of developing diabetes. The reduced risk of developing diabetes in hypertensive subjects and also reduced in risk of developing hypertension in previously normotensive diabetics has been seen with pharmacologic blockade of the RAS.[19] An increased mortality rate, largely due to cardiovascular disease has been associated with combination of hypertension and diabetes in subjects. Diabetics with optimal blood pressure control have only 70 % risk of mortality as compared to poorly controlled hypertensive subjects, who have almost double the risk of death from cardiovascular disease.[21] Naturally enough coexisting hypertension and diabetes have a higher incidence of developing retinopathy. Studies on diabetics with hypertension have shown that the relative risk of developing diabetic retinopathy is 1.7.[21,23] One study shows that the risk of diabetic retinopathy increased by 1.23 times and by 1.19 times for a vision-threatening retinopathy for every increase in systolic blood pressure by 10 mmHg.[24] A reduced risk with increasing diastolic blood pressure was identified in the same study that shows a 0.71 relative risk of diabetic retinopathy and 0.65 relative risk of vision-threatening retinopathy for every 10 mmHg increase in diastolic blood pressure.[24] The rate of progression of diabetic retinopathy showed to reduce by 34 % over 7.5 years with treatment of hypertension (goal blood pressure less than 150/85).[22,25] Also, efforts of reducing the blood pressure in hypertensive diabetics reduced the risk of vision loss of three lines or more by 47 %. There are beneficial effects of treatment of increased blood pressure to prevent diabetic retinopathy but not for slowing its progression as found in a Cochrane review.[26] Subjects on intensive blood pressure control (goal systolic blood pressure 120 mmHg) and those on standard management (goal 140 mmHg) showed no significant difference in rate of progression diabetic retinopathy in the

ACCORD trial. As per the regulations of Joint National Committee 8, the control of blood pressure to a level of 140/90 mm of Hg is recommended.[27]

High Cholesterol and Hyperlipidemia

Elevated levels of serum cholesterol and lipid are pillars of the metabolic syndrome. Studies show that an increased serum cholesterol and lipid levels have been linked to an elevated risk of vision loss in diabetic retinopathy. The average baseline cholesterol level of 244 was found in subjects with a persistent drop in vision to 5/200 or worse, as compared to a level of 228 in those who did not develop such loss in one of the study.[28] Diabetics with macular edema have increased levels of total cholesterol, low-density lipoproteins, and serum triglycerides as shown in a meta-analysis.[29] Elevated levels of lipids and cholesterol are associated with increased rates of hard retinal exudates. Study showed that the subjects with cholesterol level 240 mg/dL were twice as likely to have hard retinal exudates as compared to those with a cholesterol level 200 mg/dL. Also those with low-density lipoprotein cholesterol of 160 mg/dL as compared to those with\130 mg/dL, have double chances to have hard retinal exudates. Subjects with very-low density lipoprotein cholesterol level of 61 mg/dL— have a 1.84 times risk of having hard retinal exudates as compared to those with 18 mg/dL.[28] Statically a non-significant effects of high-density lipoprotein cholesterol and triglycerides was seen in the in this study. Effect of cholesterol and lipids on risk to develop diabetic eye disease has not been found in other studies.[24,30] A commonly used treatment for elevated cholesterol is statins (HMG-CoA reductase inhibitors) whose use prior to diagnosis of diabetes is significantly associated with a reduced rate of development of diabetic retinopathy[31] and its use in those with existing retinopathy has been associated to improved average visual acuity[32] A class of medications for the treatment of hyperlipidemia is fibrates. In the ACCORD trial, there were 10,251 participants with type 2 diabetes enrolled in this randomized trial. In the lipid arm of ACCORD study,5518 patients with dyslipidemia were assigned randomly to receive simvastatin in combination with either fenofibrate or matching placebo .At 4 years ,the rates of progression of diabetic retinopathy were 7.3% with intensive glycaemia treatment(HbA1c<6.0%) versus 10.4%with standard therapy (HbA1c level,7.0 to 7.9%,p=0.003);6.5% with fenofibrate for intensive dyslipidemia therapy ,versus 10.2% with placebo(p=0.006);and 10.4%with intensive blood pressure therapy, versus 8.8% with standard therapy(p=0.29).[7] The study found a reduction in chance for laser treatment for diabetic retinopathy for those who received fenofibrate as compared to those only on a placebo.[33] An additional retinal benefits may be offered by fibrates for a diabetic patients

but further study is required for this medication to be ideal for managing of retinopathy in diabetes.

Obesity

Association between obesity and diabetes exists. There is a five times higher chance of developing diabetes in individual with class 3 obesity (body mass index of 40) as compared to one with a normal weight.[35] There is an increased chance of developing diabetic retinopathy in those having high body mass index.[36] An increased body mass index and obesity may have a protective effect as shown by few studies [37–39]. An increased rate of diabetic retinopathy has been found in those with a higher waist-to-hip ratio, which is a reliable marker for abdominal obesity.[40,41] Both, the severity and the risk of diabetic retinopathy has been found to be higher in presence of increased neck and waist circumference.[41] The major component of metabolic syndrome is obesity and the subjects should be motivated to lose weight and keep a check. Bariatric surgery and its effects on diabetic retinopathy is not well defined and appears to be unpredictable.[42,43]

Inflammatory markers

Various markers of inflammation are associated with increased risk of neoplasia and cardiovascular disease. An association with diabetic retinopathy is also found. An elevated level of CRP was shown in patients of diabetic retinopathy as compared to those without diabetic retinopathy.[36,44] The risk of retinal hard exudates and clinically significant macular edema are high and are associated with increased CRP levels.[39,44]

Sleep-disordered breathing

Obstructive sleep apnea (OSA) or Sleep-disordered breathing causes frequent upper airway obstructions leading to blood oxygen desaturation and sleep disruption. It can lead to morbidity and is frequently associated with obesity. In one of the studies, after an overnight oximetry monitoring, it was found that 86 % of obese diabetic patients met the criteria for diagnosis of obstructive sleep apnea[45] Frequent and repeated hypoxia is associated with OSA can lead to oxidative stress at the endothelial level which can later progress to vascular dysfunction and angiogenesis.[46] An increased rate of diabetic retinopathy has been seen in subjects with Obstructive sleep apnea (OSA).[47,48] Obstructive sleep apnea (OSA) and macular edema may be linked as shown in study;[50] and a poor response has been shown with use of anti-vascular endothelial growth factor agents.[51]

Exercise

Studies show that there is a 75 % decreased risk of developing diabetic retinopathy with a daily 10 minutes exercise of moderate to vigorous category and a 94% reduction in risk in women with a daily 20 minutes exercise.[52] There is no statistical significance difference for men. Low intensity leisure time physical activity. Low-frequency leisure time physical activity shows 1.49 times higher risk for diabetic retinopathy and can lead to a 2.58 elevated rate of diabetic retinopathy.[53] 60 minutes of physical activity daily is the current recommendation for adults and it should comprise of at least 15 min of work related activity, 15 min of muscle strengthening exercises and 30 minutes of moderate intensity aerobic activity.

Anemia

Anemia is more common in patients with diabetes than in persons without diabetes. There is an early onset of anemia and is of more severity in patients with diabetes as compared with patients having renal functions impaired due to causes other than diabetes. According to the recommendations of the World Health Organization (WHO), one should investigate for anemia in women if Hb level is less than 12 g/dL and in women if it is less than 13g/dL in men. As per these guidelines nearly 1 out of 4 patients suffering from type 1 or type 2 diabetes were found out to have associated anemia. There is found to be an association of anemia with the increased incidence and progression of both microvascular and macrovascular complications of diabetes. The reason for the aforementioned problem can be because of falsely low levels of HbA1c in patients having anemia and eventual under treatment of hyperglycemia and hence more rapid development and progression of the complications of diabetes including retinopathy. According to Quing Quio et al, there is a reported odds of 5 for severe retinopathy with presence of anemia. Similar risk between the two was also reported by Shorb in a case series.

Sex Hormones

Gupta et al[62] showed that there is dissimilarity in ocular pathophysiology between females and males of humans. Such differences are seen in the lacrimal and associated glands, crystalline lens, ocular surface, and retinochoroid complexes. These differences are mainly due to sex steroid hormones and physiological conditions, such as age, menstrual cycles, pregnancy, and menopause or andropause, where there is alteration of the hormone milieu that affects the vision.

There is ample evidence that sex hormones do play a role in development and progression of diabetic retinopathy in humans and a study by Anjum A et al[63] also showed that sex hormones do play a role at several different stages of retinopathy and that sex hormone stimulation or modulation, can offer promise to control diabetic retinopathy. Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) were done with predominantly white cohorts (Klein et al;[64] Klein et al[65] and the 25 year results of this WESDR showed that being a male was an independent risk factor for progression of diabetic retinopathy. A study by Haffner et al,[66] suggested that changes in sex hormones may influence the development of diabetic retinopathy. They measured serum testosterone, estradiol, DHEA-S and sex hormone binding globulin levels in subjects with type I diabetes from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), and found that the serum testosterone concentrations were significantly higher in male diabetic subjects with proliferative retinopathy than in male diabetic subjects with minimal or no retinopathy. A study in India by Raman et al[67] also demonstrated increased risk of diabetic retinopathy for men who develop diabetes over the age of forty.

Diabetic retinopathy presents a major problem during child bearing years and deleterious effects of diabetic retinopathy during pregnancy have been documented. A study by Vargas et al[70] showed that 10% of all pregnancies have complications as a result of diabetes mellitus in United States. The occurrence and progression of retinopathy were related to the mean blood glucose levels and the serum concentrations of prolactin, human placental lactogen, estradiol and progesterone in pregnant insulin-dependent diabetic patients was shown by Larinkari J et al.[68] Throughout gestation, serum prolactin concentrations were significantly lower in diabetic patients than in healthy subjects. Further, the influence of hormonal alterations during pregnancy on the worsening of diabetic retinopathy was studied by Sone et al.[69] They examined the effects of estradiol (E2) and progesterone (P4) on the production of vascular endothelial growth factor (VEGF) in bovine retinal pigment epithelial cells in culture. As the increase in serum P4 levels during pregnancy is reported to be greater in pregnant diabetic patients with progressive retinopathy, their findings suggested that P4 may contribute to the worsening of diabetic retinopathy during pregnancy by up-regulating intraocular vascular endothelial growth factor (VEGF) levels. An in depth understanding of role of sex hormones in development and progression of diabetic retinopathy is of importance.

CONCLUSIONS

Diabetic retinopathy is the most common complication of diabetes mellitus that impairs the individual functioning and diminishes the quality of life. It ultimately imposes sever health burden on society and can cause significant morbidity if not addressed appropriately. The modifiable and non-modifiable risk factors are found to be the reason for the development of the diabetic retinopathy. The treatment modalities for management of diabetic retinopathy are available and found to be efficacious in different controlled studies, but the best treatment is prevention and strict control of the risk factors. In conclusion, overall health of the patients affects the development of diabetes and diabetic retinopathy. Health education about the maintenance of good systemic health and motivation of patients to strive for better management of issues related to health is a shared responsibility of ophthalmologists and other eye care providers.

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