OCULAR FACTORS ASSOCIATED WITH RESISTANCE TO THE DEVELOPMENT OF DIABETIC RETINOPATHY IN TYPE 2 DIABETIC PATIENTS

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BACKGROUND
Though duration of diabetes mellitus (DM) and degree of hyperglycaemia have been consistently identified as predictors of diabetic retinopathy (DR), some patients suffering from same condition, do not develop such microvascular complication for a prolonged duration of the disease. The purpose of this study is to find-out the influencing role of different ocular factors creating resistance to the development of DR.

METHODS
300 patients of type 2 DM of more than 20 years without having DR were recruited as cases in the study, whereas 300 patients of similar disease, duration and glycaemic status, having DR, were included as controls. Diagnosis and grading of DR, measurement of axial length and refractive condition, determination of cup-disc ratio and intraocular pressure and evaluation of chorioretinal scarring were performed following standard methods.

RESULTS
Among the cases, 60% were myopic, 26.67% suffered from primary open angle glaucoma, and 13.33% had chorioretinal scarring.

CONCLUSIONS
Resistance to the development of DR was seen in diabetic subjects who had myopia, glaucoma and chorioretinal scar.

KEYWORDS
Diabetes Mellitus (DM), Diabetic Retinopathy (DR), Myopia, Glaucoma, Chorio-Retinal Scarring.

ABSTRACT
Microangiopathy in retina of diabetes mellitus (DM) is the most frequent single cause of blindness among adults in the age group of 20 to 75 years and it affects 4 percent of world population.1 India ranks second in the prevalence of diabetes globally and the reported prevalence of DR ranges from 17% to 28.2%.2,3 Hyper glycaemia is the major risk factor for the development of diabetic retinopathy. The exact mechanism by which diabetes mellitus causes diabetic retinopathy is still elusive. Increased vessel wall dilation and retinal blood flow have been associated with DR progression. Chronic hyperglycaemia, hypoxemia, damage and leakage of retinal microvessels, thickening of capillary basement membrane, haemorrhage, ischemia and neovascularization are the collective factors that aggravate the process of retinopathy.4 Some patients of type 2 DM do not develop this complication for a prolonged period.5 Population-based, cross-sectional study showed that myopic refraction and longer axial length are associated with a lower risk of DR. Suppressive effect of glaucoma on diabetic retinopathy did not exist in patients with only ocular hypertension. High cup-to-disc ratio also appears to suppress the progression of retinopathy. Diabetic eyes with retino choroidal scaring and myopia suppress the development of DR possibly by inducing haemodynamic and metabolic changes in order to alter changes of natural course of diseases.6,7,8 Some ocular factors may be responsible for protection from the development of this complication.9 Despite advances in the diagnosis and treatment of DR, it is still causing blindness at a frightening rate. So, better understanding of the pathogenesis of this complication is essential for control of blindness due to DR. Identification of these protective factors is important for better understanding of pathomechanisms and management of diabetic retinopathy.

Aims and Objectives
This study was undertaken to find out the effects of different ocular factors producing resistance to the development and progression of DR in type 2 DM. Objective of this study is...
also to add further information related to resistance to the development of this microvascular complication.

METHODS
It is a case-control study and it was carried-out at Regional Institute of Ophthalmology, Kolkata. Study Population included subjects attending the retinal research clinic and outpatient department at Regional Institute of Ophthalmology, Kolkata, for ophthalmoscopic examination and those referred patients from diabetic clinic of Medical College, who need comprehensive eye examination, were included in this study.

Study Period
Study period was from January 2015 to August 2016.

Sample Size
300 patients of Type 2 DM without retinopathy were enlisted as cases and 300 patients of type 2 DM with diabetic retinopathy were recruited as controls. Subjects were selected sequentially according to the inclusion criteria.

Inclusion Criteria
- Patients of type 2 DM of more than 20 years.
- Patients of type 2 DM having diagnosed glaucoma.
- Patients of type 2 DM having myopia, chorioretinal degeneration.
- Patients of type 2 DM having retino choroidal scar were included in the study.

Exclusion Criteria
- Patients of type 2 DM having recent acute infection.
- Type 2 diabetic subjects suffering from Eales’ disease or central and branch venous occlusion.
- Diabetic patients suffering from hypertension or hyperlipidaemia or ischemic heart disease were excluded from the study.

Parameters Studied
Axial length measurement by USG A scan, Cup-disc ratio evaluation by stereoscopic disc photography, Visual field assessment by Humphrey Field Analyser, diabetic retinopathy grading and evaluation of chorio retinal scarring in retina were carried out following standard methods. Intraocular pressure measurement by applanation tonometry, fundus examination by slit lamp biomicroscopy with +90 D lens, direct and indirect ophthalmoscopy were performed meticulously. Dilated stereoscopic fundus photography was done to document the specific retinal picture.

Method of Data Collection
After obtaining informed written consent from diabetic individuals who fulfilled inclusion and exclusion criteria, study and control subjects were recruited in this case-control study following the declaration of Helsinki. Approval from Ethics Committee of Calcutta Medical College and Hospital was obtained. Detailed clinical history was recorded regarding age, sex, age of onset of diabetes, duration of diabetes, HbA1c level and treatment of DM. Presence or absence of DR was assessed by dilated stereoscopic fundus photography and graded according to criteria of modified Airlie House classification. Axial length of eye ball was measured by A scan of USG and spherical equivalent refraction was performed by objective auto refraction and subjective verification. Myopia of 5 dioptres or more with axial length 25-28 mm were included in the study. Findings of retina regarding retino choroidal scar were documented by two experienced ophthalmologists and adjudicated by consensus. Maximum retino choroidal scarring were produced by old chorioretinal inflammation due to infectious chorioretinitis or traumatic chorioretinitis. Some portion of scar was also created by laser photocoagulation during sealing of the retinal breaks. All the scarring areas were located in the temporal retina. No scar owing to degenerative disorders was seen in this cross-sectional study.

RESULTS
This is a case-control study with total number of cases being 300 and controls being 300. Among the cases of this study 60% of the subjects had myopia, 26.67% had glaucoma and 13.33% had chorioretinal scarring. The data was collected for a period of one year. The following data were tabulated from the study details. Myopia of five dioptres or more with axial length of 25 to 28 mm were seen to have beneficial effect on the course of development of diabetic retinopathy. Maximum subjects in case were 62% male while that of the controls were 58.67%. According to demographic pattern of the age distribution, the maximum number of subjects belongs to 50-59 years in cases and in control also. The Mean age of cases was 53.15±11.07 years and control were 52.82±11.47 years. The maximum duration of diabetes, in case group was 25-29 years and in control group was 25-29 years. The mean year of duration of diabetes in case group was 24.75±4.33 and in control group was 24.19±4.22. The glycaemic status in maximum number of subjects of case and control group lied in the range of HbA1c 8.5-9.5%.

Chi-square test was performed to find out the any association between development of diabetic retinopathy and age, sex, duration of diabetes and glycaemic status. There was no association between age, sex, duration of diabetes and glycaemic status at the significant level of p<0.05. The maximum 67% subject was myopic in cases and the maximum 64% subject was non-myopic. Chi-square test shows that there was association between the cases and myopia at the significant level of p<0.0001. Frequency rate of cases was definitely higher among diabetic subjects with myopia than diabetic individuals without myopia. Relative risk 2.00 showed that case was more likely to develop in myopic diabetic patient than non-myopic diabetic patient at the significant level p<0.0001. Odd ratio 3.5 also demonstrated that myopic diabetic patient was 3.5 times as likely as develop case than non-myopic diabetic patient at the significant level p<0.0001. Mann-Whitney test shows that case in the myopic diabetic patient is significantly higher.
that the non-myopic diabetic patient (P<0.0001). The maximum 67% subject had glaucoma in cases and the maximum 54% subjects had no glaucoma in control group. Chi-square test shows that there was an association between the cases and glaucoma at the significant level of 0.0001. Frequency rate of cases was definitely higher among diabetic glaucomatosus patient than diabetic subject without glaucoma at the significant level p<0.0001. Odd ratio 2.36 suggested that glaucomatous diabetic patient was 2.36 times more likely to develop case than non-glaucomatous diabetic patient at the significant level p<0.0001. Mann-Whitney test shows that case in the glaucoma patient is significantly higher than the non-glaucomatous diabetic patient at the significant level of P<0.0001.

In cases 67% subject had chorio-retinal scarring and in control group 54% subject had no chorio retinal scarring. Chorioretinal scar of more than two-disc area in the temporal retina exercised protective effect or resistance to the development of DR. Chi-square test shows that there was association between the cases and chorio-retinal scarring at the significant level of p<0.0001. Frequency rate of cases were definitely higher among diabetic patients having chorio-retinal scarring than diabetic patients with no chorioretinal scarring. Relative risk 1.7 showed that case was more likely to develop in diabetic subjects with chorio-retinal scarring than diabetic patients with no chorio-retinal scarring at the significant level p<0.0001. Odd ratio 2.36 demonstrated that chorio-retinal scarring in diabetic patient was 2.36 times more likely to develop case than diabetic patients with no chorio-retinal scarring at the significant level p<0.0001. Mann-Whitney test shows that case in the chorio retinal scarring patient is significantly higher than the diabetic patients with no chorio retinal scarring at the significant level of P<0.0001. Chi-square result and regression coefficient results show that diabetic retinopathy was statistically significantly associated with axial length, C/D ratio, and chorio retinal scaring. Odd ratio shows that the risk of no development of diabetic retinopathy is higher in AL (0.71, 95% CI 0.63 to 0.81), C/D ratio (0.12, 95% CI 0.03 to 0.52), and chorio retinal scarring (0.53, 0.25 to 1.11). In this study, diabetic subjects with optic atrophy or amblyopia were not screened and therefore these ocular factors were not included in the analysis. In this study, the case that is No-DR was significantly higher in myopia, glaucoma and retina with chorio-retinal scaring.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>Standard Error</th>
<th>p-Value</th>
<th>ODD Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myopia</td>
<td>-0.34</td>
<td>0.06</td>
<td>&lt;0.0001</td>
<td>0.71</td>
<td>0.63 to 0.81</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>-2.12</td>
<td>0.75</td>
<td>0.0047</td>
<td>0.12</td>
<td>0.03 to 0.62</td>
</tr>
<tr>
<td>Chorioretinal Scarring</td>
<td>-0.63</td>
<td>0.34</td>
<td>0.09</td>
<td>0.53</td>
<td>0.25 to 1.11</td>
</tr>
</tbody>
</table>

This logistic regression test suggests that myopia, glaucoma and chorioretinal scarring are strongly correlated with the resistance to the development of DR.

Chi-square is 23.7, Degree of freedom is 8, Significance level p= 0.0026

**DISCUSSION**

Chronic hyperglycaemia and duration of diabetes are considered to be the primary contributors for development of diabetic retinopathy. Many ocular factors are associated with decreased prevalence of diabetic retinopathy and these are amply elucidated in this study. In our study diabetic patients with myopic fundus did not manifest diabetic retinopathy in 60% cases. So myopia is a protective factor against the development of diabetic retinopathy. The same message was declared in the observation of Jain IS et al, Lim LS et al and Man RE et al.10,11,12 A population-based, cross-sectional study showed that myopic refraction and longer axial length are associated with lower risk of DR (OR, 0.86; 95% CI, 0.75-0.99; p=0.041, per 1 mm increase), particularly vision-threatening retinopathy.10 Our study shows that diabetic patients suffering from glaucoma did not develop diabetic retinopathy over a certain duration of diabetes mellitus. Similar picture was depicted in the studies of Becker and Williams et al.6,7 Our observation suggests that chorioretinal scarring reduced the development of diabetic retinopathy in diabetic patients of prolonged duration. The same observation inspired Aiello et al to apply panretinal photocoagulation treatment for proliferative diabetic retinopathy.2 Although persistent hyperglycaemia is considered to be the most important and decisive factor related to the development of DR, all patients of type 2 DM with persistent hyperglycaemia for a prolonged period, do not develop the attendant complication of this disease.13,14

Medalist Study showed that significant numbers of diabetic patients could live without severe complications for an extreme duration of the disease, suggesting that they may...
possess factors that can neutralize the adverse effects of hyperglycaemia.\textsuperscript{15} Theories of myopia against the development of DR are revolving around the reduced blood flow and reduced retinal oxygen demand. The reduction of blood flow from the stretching of the eyeball along it's choroid and retina reduce the chances of obstructive rupture of retinal blood vessel.\textsuperscript{12} In glaucoma retrograde axoplasmic transport block due to elevated intraocular pressure can deprive the retinal ganglion cells of the supply of brain-derived neurotrophic factor (BDNF) for cell metabolism and cell survival. Deficiency of BDNF leads to progressive apoptosis of ganglion cells which is further modulated by increased release of growth inhibiting factor which blocks the VEGF (vascular endothelial growth factor) action. VEGF is the crucial driver for development of DR. In a retrospective study of 150 eyes of 75 patients with diabetes mellitus glaucoma status was determined by clinical examination of cup-to-disc ratio and measurement of intraocular pressure by application tonometry. This study demonstrated that patients with high cup-to-disc ratio (p<0.05) were significantly different in the severity of retinopathy than normal patients based on chi-square analysis. Normal patients were not significantly different in the severity of retinopathy than patients of ocular hypertension. Suppressive effect of glaucoma on diabetic retinopathy did not exist in patients with only ocular hypertension. High cup-to-disc ratio only appears to suppress the progression of retinopathy.\textsuperscript{7} Pathophysiology of chorioretinal scarring from trauma, inflammatory disease or laser photocoagulation creates a clinical background where reduced retinal metabolism, particularly decreased need for oxygen protects the retina from development of diabetic microangiopathy. Other factor may be inability of gliotic muller cells to create calcium weaves which are necessary for action of VEGF. Some investigators suggest that retinal cells may produce growth-inhibiting factors or reduce production of growth-promoting factors in response to injury to retina due to trauma, inflammation or photocoagulation.\textsuperscript{16} So ocular conditions which create resistance to the secretion or activation of VEGF inhibit the development of diabetic retinopathy.

CONCLUSIONS
The ability of retinal tissue to produce growth promoting factors is also a deciding factor for the development of diabetic retinopathy in type 2 diabetes mellitus. Resistance to the development of DR was seen in diabetic subjects who had myopia, glaucoma and chorioretinal scar.

REFERENCES