

## Association of severity of diabetic retinopathy with comorbidities in Type 2 diabetes mellitus

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### Abstract

**Introduction:** Diabetes mellitus is emerging as a multisystem disease culminating in various complications especially to the ocular system if not treated at the earliest. The role of various comorbidities in aggravating the severity of diabetic retinopathy is sparsely studied. This study was performed to throw light at this aspect of the need for early identification of comorbidities and its role in progression of diabetic retinopathy.

**Methods:** Study was conducted among 257 diagnosed type 2 diabetic patients with various grades of retinopathy as classified based on ETDRS classification. Clinical history and comprehensive systemic and ocular examination was done and laboratory profile of serum lipids and blood sugar values were collected. The analysis was carried out using SPSS software and results presented in percentages and p value <0.05 taken as significant.

**Results:** 257 patients were studied with a mean age of 58.8±10 years. Male female distribution 129:128. There were 221 non proliferative diabetic retinopathy, 33 proliferative diabetic retinopathy and 3 cases of advanced diabetic eye diseases. The study group had 48.6% smokers, 40.5% hypertensives, 13.6% coronary artery disease and 45.5% with serum lipid >200mg/dl. Present study revealed a positive association of retinopathy with hypertension (p value 0.034) and smoking (p value 0.002).

**Conclusion:** Comorbidities associated with Diabetes mellitus were contributing to worsening of diabetic retinopathy. Hence the need for prompt identification and control of these should form a part of the routine management of any stage of diabetic retinopathy to prevent sight threatening complications.

**Keywords:** Smoking, Coronary Artery Disease, Diabetes Mellitus, Diabetic Retinopathy, Hypertension.

### Introduction

Diabetes mellitus is a disease which is fast gaining the status of a potential epidemic ultimately resulting in an array of long term ocular and systemic complications.

Prevalence of diabetes has been steadily increasing for the past three decades and is growing most rapidly in low and middle income countries with more than 62 million diabetes individuals currently diagnosed with the disease. Kerala is the diabetic capital of India with prevalence of 11-19%, double the national average of 8%.

Diseases like hypertension and coronary artery diseases share common intertwined underlying risk factors including ethnicity, dyslipidemia and standard of living along with modifiable risk factors especially smoking. The complications which include both microvascular and macrovascular can be attributed to the direct effects of hyperglycemia in the tissues and to the co added effects of these risk factors. As our ocular system is immensely vascularised, the complications of diabetes quickly impairs the normal retinal functions leading to sight threatening retinopathy if not detected and treated at the earliest.

The eye is the most commonly affected organ by diabetes leading to Diabetic Retinopathy (DR). Endothelial damage and loss of pericyte caused by hyperglycaemic trigger is the primary event in the development of retinopathy. Further hypoxic changes and neovascularisation lead to proliferative retinopathy.

Atherosclerosis and smoking add on to the loss of vascular integrity. In the current scenario, around 93 million individuals have diabetic retinopathy accounting for 34.6% of which 10.2% have an advanced stage of disease.<sup>(1)</sup> The association of various risk factors with severity of diabetic retinopathy is well documented in developed countries.

In our study area, even though the prevalence of diabetes and its multitude of risk factors are high, clinical data regarding presence of any association between the severity of diabetic retinopathy with these risk factors is lacking. This effort constitutes the attempt to study the correlation of risk factors with severity of Diabetic Retinopathy among patients with type 2 diabetes in this area.

### Methods and Materials

**Study design and patient setting:** This cross sectional study was conducted among 257 type 2 diabetes mellitus (DM) patients attending Ophthalmology outpatient department at Government Medical College, Kozhikhode during a period of 6 months from January 2012 to June 2012 after getting approval from institutional research and ethics committee. An informed written consent is being taken from each patient before participation in the study.

**Inclusion criteria:** Type 2 diabetic Patients older than 40 years with diagnosed diabetic retinopathy.

**Exclusion criteria:** Patients with other retinal pathologies like vascular occlusions, optic atrophy. Patients whose fundus examination was not possible due to hazy media or inadequate dilatation or non-cooperative patients.

**Data collection:** A clinical history was taken with the help of a structured questionnaire including demographic data, duration of diabetes, history of coronary artery disease (CAD), smoking and systemic hypertension (HT). Comprehensive systemic and ocular examination was done including slit lamp and ophthalmoscopic evaluation. Fundus examination for grading the Diabetic retinopathy was done using direct, indirect ophthalmoscopy and slit lamp biomicroscopy with Volk +90D and graded based on ETDRS classification. Laboratory profile of complete haemogram, serum cholesterol level, fasting and post prandial blood sugar, renal function tests were also done.

**Statistical analysis:** Statistical analysis were performed using SPSS Version 18.0 (SPSS, Chicago, Illinois, USA) software and Chi square test was done to compare the variables. The stage of diabetic retinopathy in worse eye of patients, with each risk factor were analysed and results expressed in percentages.

## Results

A total of 257 patients with diabetic retinopathy were assessed and grouped depending on the severity of retinopathy. The mean age of the patients was 58.81 $\pm$ 10 years. Gender distribution being almost equal (males=129, females=128). All patients were diagnosed cases of type 2 diabetes with average duration of disease being 8.75  $\pm$  6.54 years.

Distribution among various stages of severity of retinopathy based on ETDRS classification were mild NPDR (Non proliferative diabetic retinopathy) 117, moderate NPDR 44, severe 28, very severe 32 (total NPDR 221), proliferative diabetic retinopathy (PDR) 13, high risk proliferative diabetic retinopathy (HRPDR) 20 (total PDR 33) and advanced diabetic eye disease (ADED) being 3. Among 257 patients,

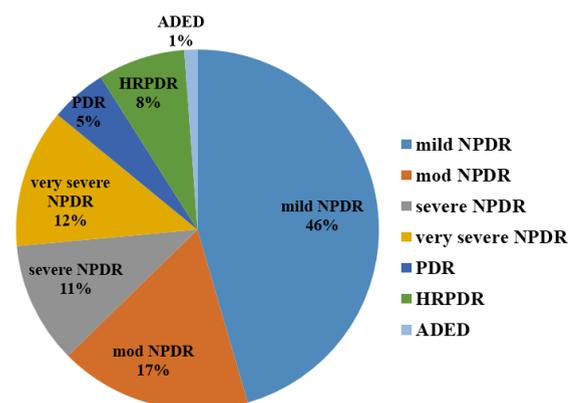


Fig. 1: No of patients in different stages of DR

125 (48.6%) patients were smokers, 104 (40.5%) patients had systemic hypertension, 35 (13.6%) patients were on treatment for coronary artery disease, 117 (45.5%) patients were having fasting total cholesterol more than 200mg%. There were 124 (48.2%) patients with multiple comorbidities.

Out of 257 diagnosed diabetic retinopathy patients, 104 (40.5%) had hypertension, of which 51 had mild NPDR, 26 had moderate NPDR, 8 severe NPDR, 10 very severe NPDR, 4 PDR, 4 HRPDR and 1 case of ADED. The proportion of hypertensives among various stages of diabetic retinopathy showed, 43.6% in mild NPDR, 59.1% in moderate NPDR, 28.6% in severe NPDR, 31.3% in very severe NPDR, 30.8% in PDR, 20% HRPDR and 33.3% in ADED. This association was statistically significant with a p value of 0.034.

Association with serum cholesterol levels in patients with diabetic retinopathy showed that 45.5% of the total subjects had hypercholesterolemia with serum cholesterol values more than 200mg. The distribution in the stages of DR were 42.7% in mild NPDR, 61.8% in moderate NPDR, 35.7% in severe NPDR, 34.4% in very severe NPDR, 53.8% in PDR, 55% in HRPDR and 33.3% in ADED group. The correlation was not significant (p value 0.137).

Out of 257 patients analysed, 125 (48.6%) had history of smoking, with the relative distribution of smokers among various grades of diabetic retinopathy being 36.8% in mild NPDR, 52.3% in moderate NPDR, 60.7% in severe NPDR, 50% among very severe NPDR, 92.3% in PDR, 65.% in HRPDR and 33.3% in ADED group. The statistical analysis showed a significant P value of 0.002.

35 patients (13.6%) out of 257 had coronary artery disease. The relative distribution among the groups was mild NPDR 12, moderate NPDR 12, severe NPDR 5, very severe NPDR 5, PDR1, HRPDR and ADED had no cases of CAD. The association of coronary artery disease with severity of Diabetic retinopathy had a p value of 0.051.

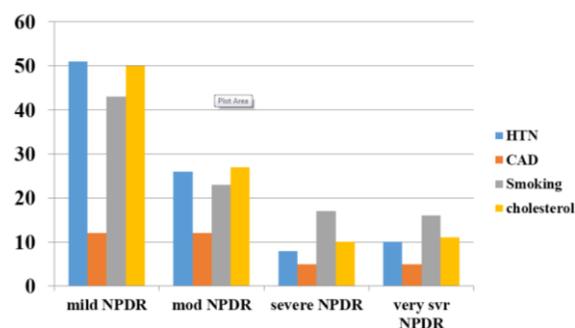


Fig. 2: Distribution of comorbidities in NPDR

**Table 1: Showing the distribution of patients with grades of diabetic retinopathy and its relation with comorbidities**

| Severity of retinopathy | No. of patients | Hypertension         | CAD                 | Smoking              | S cholesterol >200mg |
|-------------------------|-----------------|----------------------|---------------------|----------------------|----------------------|
| Mild NPDR               | 117             | 51<br>43.6%          | 12<br>10.2%         | 43<br>36.8%          | 50<br>42.7%          |
| Moderate NPDR           | 44              | 26<br>59.1%          | 12<br>27.3%         | 23<br>52.3%          | 27<br>61.8%          |
| Severe NPDR             | 28              | 8<br>28.6%           | 5<br>17.9%          | 17<br>60.7%          | 10<br>35.7%          |
| Very severe NPDR        | 32              | 10<br>31.3%          | 5<br>15.6%          | 16<br>50%            | 11<br>34.4%          |
| PDR                     | 13              | 4<br>30.8%           | 1<br>7.7%           | 12<br>92.3%          | 7<br>53.8%           |
| HRPDR                   | 20              | 4<br>20%             | 0                   | 13<br>65%            | 11<br>55%            |
| ADED                    | 3               | 1<br>33.3%           | 0                   | 1<br>33.3%           | 1<br>33.3%           |
| <b>TOTAL</b>            | <b>257</b>      | <b>104<br/>40.5%</b> | <b>35<br/>13.6%</b> | <b>125<br/>48.6%</b> | <b>117<br/>45.5%</b> |
| <b>P value</b>          |                 | <b>0.034</b>         | <b>0.051</b>        | <b>0.002</b>         | <b>0.149</b>         |

## Discussion

This study highlights the association between the various comorbidities like Hypertension, coronary artery disease, smoking and hypercholesterolemia with the occurrence and severity of diabetic retinopathy. The early detection and management of associated comorbidities may help in preventing future end organ complications and sight threatening problems.

Various studies including the UKPDS STUDY had suggested the prevalence of hypertension in 38% newly detected diabetic patients.<sup>(4,5)</sup> Increased peripheral vascular resistance and protein glycosylation in diabetic patients add on to the increased incidence of hypertension in this group. Since both diabetes and hypertension produce significant damage to vessel wall integrity, the likelihood of increased diabetic retinopathy is also more among subjects who suffer from both these diseases. The UKPDS study also recommended a blood pressure control of <150/80 to have a protective effect against progression of diabetic retinopathy. The Wisconsin Epidemiologic study of diabetic retinopathy reports the development of retinopathy within 5 years in 14% of type 1 and 33% with type 2 diabetes mellitus.<sup>(2)</sup> The presence of hypertension leads to coexistence of hypertensive retinopathy which ultimately magnifies the risk of vision loss in diabetic individuals. In the current study it was noted that 40.5% of the patients with various grades of retinopathy had underlying hypertension and this was present even in the severe grades. Hence the accelerating role of hypertension in the progression of severity of retinopathy has to be considered and the need for tight control of blood pressure to be emphasised.

The serum levels of cholesterol to the contrary do not seem to have a significant association with the

development of diabetic retinopathy. The Beijing eye study showed no association of increased serum lipids with diabetic retinopathy.<sup>(6)</sup> Our study also was in accordance with these results with a 45.5% having hypercholesterolemia. Hence it can be inferred that lipid changes do not directly appear to produce more microvascular damage but hyperlipidemia being major risk factor for the development of atherosclerosis and related cardiovascular events which can indirectly hamper the vessel wall function and retinal milieu. Thus the importance of diet quality of patients cannot be underestimated.

Smoking is one of the modifiable risk factor in diabetes. It increases oxidative stress and inflammation and results in the damage of endothelial cell function which aids in aggravating microvascular complications of diabetes especially, retinopathy.<sup>(7)</sup> Our study showed a significant correlation between smoking and diabetic retinopathy (p value 0.002), 48.6% patients had a history of smoking and this data also showed increased severity of diabetic retinopathy among smokers. It was observed that 92.3% of patients with proliferative diabetic retinopathy and 65% of high risk PDR patients were smokers. Even though Japanese study by Uchimoto et al have suggested a correlation of smoking with diabetes, no significant study could be quoted for the association for smoking with diabetic retinopathy.<sup>(8)</sup>

Hence this study would highlight the need for smoking cessation as an effective step in preventing the progression of diabetic retinopathy.

The study by Kawasaki et al on the relationship between CAD and diabetic retinopathy showed an increased prevalence of CAD with the progression of diabetic retinopathy.<sup>(11)</sup> In our study we could infer an

association between the two as our p value was 0.051. As diabetes is considered as one among the most important risk factors for coronary artery disease and progression of microvasculopathy is a predictor of health status of the coronary vessels as studied by Fawzia et al in Egyptian heart journal, early screening for diabetes retinopathy is warranted not only for preserving vision but also for early suspicion of CAD events.<sup>(9)</sup>

By these observations it should be emphasised that the role of metabolic factors and smoking in the progression of retinopathy should not be underestimated. As diabetic retinopathy is fast emerging as a major threat to vision and pathway for development of potential blindness, prompt measures for early identification of associated risk factors like hypertension, CAD, hyperlipidemia and smoking should be undertaken and treated at the earliest. Lifestyle modifications including smoking cessation and exercise promotion can help in a way to control these. Also interdisciplinary actions from the treating physician to motivate diabetic patients with hypertension and CAD for assessment of early retinopathy will also save the vision of these patients if referred timely for evaluation.

### Conclusion

Diabetic patients are at an increased risk of both microvascular and macrovascular complications. Our study highlights the need for targeting multiple risk factors including hypertension and smoking in effective control of the progression of severity of diabetic retinopathy. In particular all patients should be educated on the importance of smoking cessation and strict control of blood pressure levels to attain a beneficial reduction in the complications of diabetes. Hence timely screening for presence of retinopathy in all patients with coexistent risk factors including cardiovascular diseases and hypertension should be made mandatory. Also, any underlying risk factor in all diabetic patients should be thoroughly searched for and every measure to control the same initiated at the earliest.

**Limitations:** The study population represents the trends in diabetic retinopathy and its risk factors of a particular study area of 257 patients. Hence extrapolation to the entire population might depend on the geographic and other ethnic factors influencing the disease.

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