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A study conducted in western Maharashtra to evaluate the risk factors for diabetic macular edema in patients with type 2 diabetes mellitus

Chaitali Desai[1,*], O K Radhakrishnan[1], Namratha Judith Cardoza[1], Kavitha Mohankumar[1], Madhuvanthi Mohan[1]

[1] *Dept. of Ophthalmology, Dr. D.Y. Patil Medical College, Hospital & Research Centre, Pune, Maharastra, India*

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ABSTRACT

Aim: To study various risk factors (HbA1c levels, dyslipidemia, stroke, smoking, cardiovascular disease, nephropathy and use of pioglitazones) associated with Diabetic Macular Edema in patients with type 2 diabetes mellitus.

Materials and Methods: A total of 110 patients with type 2 diabetic mellitus of age group 30-70 years and both sexes participated in this study. Association between risk factors and diabetic macular edema was studied in analytical cross-sectional study conducted in a tertiary care hospital of Western Maharashtra.

Results: Median of HbA1c in patients with macular odema was 8.15(7.8-8.925) which was significantly higher than patients without macular odema 6.4(6-6.825). Mean LDL(mg/dL) in patients without macular odema was 99.1 ± 32.96 and patients with macular odema was 113.29 ± 32.35. Significant association was seen in the distribution of HbA1c($p<0.0001$), LDL ($p=0.046$) and the use of pioglitazone ($p = 0.00006$) with macular odema. No significant association of stroke, smoking, cardiovascular disease and distribution of nephropathy with macular odema was found.(p value>.05)

Conclusion: In patients with type 2 diabetes mellitus, multiple factors such as elevated HbA1c levels, LDL and use of pioglitazones were significant risk factors associated with Diabetic Macular Edema(DME). Also as many of the risk factors are modifiable, ophthalmologists and physicians should ensure that patients with DME receive appropriate assessment and treatment for these comorbidities.

1. Introduction

Diabetes mellitus (DM) is a chronic and progressive disease affecting all ages of the population. Diabetes mellitus is considered as an important cause of blindness worldwide and represents the leading reason behind severe loss of vision in people of working age in many of the countries.[1,2] Diabetic macular oedema (DME) is also a leading cause of the visual impairment which occurs with diabetic retinopathy. Over time, high blood glucose levels result in the development of diabetic macular edema and high blood pressure which might increase the risk of rapid progression and earlier onset of the disease.[2] Factors associated with the development of maculopathy are mostly unknown.

Since diabetic maculopathy is characterised by increased capillary leakage in the main retinal vessels and by alterations in the microcirculation of the macula,[3,4] several previous reports have suggested that poor metabolic control might be involved in haemodynamic changes of retinal circulation, and thereby lead to maculopathy. It is conceivable that increases in the retinal blood flow could play a part in haemodynamic changes of increased intracapillary retinal pressure and shear stress, thereby leading to diabetic maculopathy.[5,6]

Fenwick et al. showed that poor glucose and blood pressure control results in greater risk of developing diabetic retinopathy and macular edema than poor glycemic control alone.[7] Sometimes, patients having poor control of blood pressure and glucose may have a fulminant evolution of

* *Corresponding author.*
E-mail address: desaichaitali2@gmail.com (C. Desai).

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diabetic retinopathy and maculopathy.[8] In the Chennai Urban Population Study (CUPS), the diabetic subjects had a 3 times higher prevalence of hypertension i.e. 46.7% when compared to the overall prevalence of hypertension in the non-diabetic population which was 16.7%.[9]

Diabetic macular oedema involves the thickening of the macula which is central portion of the retina. It is typically associated with deposits of lipoproteins or hard exudates and will cause gradual loss of central vision as a result of deterioration of the retinal cells. Diabetic macular edema increases with the duration of diabetes and it is seen that the prevalence of DME is 5% within the first five years after diagnosis and at 15 years it is 15% (Aiello 1998). In the review of studies, it was found that the prevalence of clinically significant macular oedema (CSME) in people with diabetes ranges from 2% to 10% (Williams 2004).

Although numerous studies have assessed risk factors associated with DR[10–12] very few studies have assessed risk factors associated with a higher prevalence of DME. The objective of this study was to identify various risk factors associated with the presence of DME in the general adult population having type 2 diabetes mellitus.

2. Materials and Methods

A hospital based observational analytical cross sectional study was conducted in a tertiary hospital and research centre in Western Maharashtra from the period of September 2018 to August 2020 after clearance from the ethics committee of the institute. Inclusion and exclusion criteria taken into consideration, with a prevalence rate of 6.5% of macular edema in patients with type 2 Diabetes mellitus we proposed to take a sample size of 110.Well informed consent was procured from all the subjects. 110 patients with type 2 diabetic mellitus of age group 30-70 years and of both sexes were included in the study. A detailed work-up including a thorough medical history and a history of any previous ocular treatment was taken of each patient. The inclusion criteria included type 2 diabetic mellitus patients who are willing to give informed consent to participate in the study. Exclusion criteria was patients with type 1 diabetes mellitus, OCT not possible either due to hazy media or refusals, any prior ocular treatment, concomitant fundus pathology that could potentially affect the macula,

Thorough ophthalmic examination of both the eyes was done. Vision was assessed using illuminated Snellen's Chart. Detailed fundus examination was done in a dark room with indirect ophthalmoscope, direct ophthalmoscopy, and slit lamp biomicroscopy with +78D lens. OCT were performed using the Spectral domain Cirrus HD-OCT 500. (Zeiss, Jena, Germany): after appropriate pupillary dilatation, the patient was comfortably seated in a dimly lit room. After obtaining a fixation point for the patient the evaluation was done of eyes for clinically significant macular edema (CSME) which was defined by the Early Treatment Diabetic Retinopathy Study (ETDRS) and a central macular thickness (CMT) via OCT $\geq$ 250 μm attributable to DME.

The criteria for diagnosing diabetes mellitus was a fasting plasma glucose of >126 mg/dL (6.99 mmol/L) or a non-fasting plasma glucose of >200 mg/dL (11.1 mmol/L) and HBA1c of >6.5%; or when a patient is already on medication for diabetes. The following tests were done: 1) Urine albumin excretion for Nephropathy; 2) Fasting serum lipid and its components include total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL) and triglycerides (TG); 3) Fasting blood glucose (FBG); 4) HbA1c.

All details of participants were kept under strict confidentiality. Analysis was also anonymous and all personal identifiers were removed. Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then non parametric test was used. Microsoft Excel was used to enter data and statistical analysis was done using software Statistical Package for Social Sciences (SPSS) version 21.0.

3. Results

In this study, 0(0%) out of 51 patients whose HbA1c was < 6.5% and 14(23.73%) out of 59 whose HbA1c was >6.5% had macular odema. Median of HbA1c (%) in patients with macular odema was 8.15(7.8-8.925) which was significantly higher as compared to patients without macular odema 6.4(6-6.825). This shows significant association in the distribution of HbA1c (%) with macular odema. (p<0.0001)(Table 1)

In the current study, 6(8.22%) out of 73 patients with normal LDL values and 8(21.62%) out of 37 patients with deranged LDL values had macular odema. Mean ± SD of LDL (mg/dL) in patients without macular odema was 99.1 ± 32.96 and patients with macular odema was 113.29 ± 32.35. Significant association was seen in the distribution of LDL (mg/dL) with macular odema. (p=0.046) No significant association was seen in the distribution of Total Cholesterol(p=0.068), Triglycerides(p=0.057) and that of HDL(p=0.051) levels with macular odema. (p value>.05) (Table 2)

Median (IQR) of urine Albumin Excretion (mg/ 24 hr) in patients without macular odema was 16(12-23) and patients with macular odema was 30(16.5-177.25) with no significant association between them. This shows no significant association of urine Albumin Excretion (mg/ 24 hr) with macular odema. (p value >.05) 7(8.64%) out of 81 patients with no overt nephropathy, 5(21.74%) out of 23 patients with Microalbuminuria and 2(33.33%) out of 6 patients with Macroalbuminuria had macular odema. The corresponding values for patients without macular odema

are 74(91.36%), 18(78.26%) and 4(66.67%) respectively. This shows no significant association in the distribution of nephropathy with macular odema. (p=0.054) (Table 3)

Also,6(23.08%) out of 26 patients who are smokers and 8(9.52%) out of 84 who are non-smokers had macular odema. This shows no significant association in the distribution of smoking with macular odema. (p value is 0.07) (Table 5)

In the current study,6(21.43%) out of 28 patients with past history of stroke and 8(9.76%) out of 82 patients with no past history of stroke had macular odema. This shows no significant association in the distribution of stroke with macular odema. (p value is 0.11) (Table 6)

In the present study, 6(22.22%) out of 27 patients with past history of cardiovascular disease and 8(9.64%) out of 83 patients with no past history of cardiovascular disease had macular odema. This shows no significant association in the distribution of cardiovascular disease with macular odema. (p value is 0.088)(Table 7)

In our study, 6(40%) out of 15 patients who were using pioglitazone and 8(8.42%) of 95 patients who were not using pioglitazone had macular odema. Significant association was seen in the distribution of use of pioglitazone with macular odema. (p value is 0.00006) (Table 8)

Median (IQR) duration of diabetes mellitus (years) in patients with macular odema was 7(6-8) years which was significantly higher as compared to patients without macular odema 3(2-4) years. This shows significant association of duration of diabetes mellitus (years) with macular odema. [p<0.0001]

2 (3.33%) out of 58 eyes with Mild NPDR, 19 (14.73%) out of 129 eyes with Moderate NPDR, 5 (20%) out of 25 eyes with Severe NPDR and 2 (33.33%) out of 6 eyes with PDR had macular odema. The corresponding values for patients without macular odema are 58 (96.67%), 110 (85.27%), 20 (80%) and 4 (66.67%) respectively. This, shows significant association in the distribution of severity of diabetic retinopathy with macular odema. [p=0.014]

4. Discussion

Diabetic macular edema (DME) is a manifestation of diabetic retinopathy and is the leading cause of the visual impairment in patients with type 2 diabetes mellitus.[13] Worldwide prevalence of DME has been estimated to be 6.8%. Thus, about 27 million adults are affected by DME. Risk factors for the onset and development of diabetic retinopathy are well documented, but very few studies have investigated the risk factors associated with DME.

In our study, we found a significant association in the distribution of HbA1c (%) with macular odema. (p<0.0001). In the Diabetes Control and Complications Trial (DCCT), it was seen that in type 1 diabetes mellitus patients, the strict control of blood glucose led to a 29% decrease in the cumulative incidence of macular edema at the 9-year follow-up and this has reduced the application of focal laser treatment for DME upto half the previous times.[14] In the Epidemiology of Diabetes Interventions and Complications (EDIC) study, the level of glycemic control was studied. This study was an extension of the DCCT and it was observed that the former intensive control group was better than the former conventional control group. The CSME incidence in the former intensive control group, four years after the end of the DCCT was 2% whereas it was 8% in the former conventional control group ($p < 0.001$).[15]

Dyslipidemia plays a role in the development of DME. In our study, we found that a significant association was seen in the distribution of LDL (mg/dL) with macular odema.[p=0.046] No significant association was seen in the distribution of Total Cholesterol (p=0.068), Triglycerides (p=0.057) and that of HDL (p=0.051) levels with macular odema.

A recent study, the Madrid Diabetes Study has shown an association between low density lipoprotein cholesterol (LDLC) and incidence of DR.[16] Also in study done by Du et al, it was reported that increased levels of LDL may cause retinal-blood barrier injury through endoplasmic reticulum stress, apoptosis, oxidative stress and autophagy in patients with DR.[17] This can explain why LDL acts as the risk factors for both DR and DME. However, some studies suggest that the role of dyslipidemia in the pathogenesis of DME is relatively controversial.[18]

In the present study, no significant association was seen in the distribution of nephropathy with macular odema. (p=0.054) There was no significant association of urine Albumin Excretion (mg/ 24 hr) with macular odema. (p=0.054). The WESDR study did not report any significant associations between early stages of nephropathy and DME but only when there was gross proteinuria.[19] Another study by Knudsen et al. showed that albuminuria and the rate of transcapillary albumin escape correlates with diabetic macular edema.[20] The possible shared pathogenetic mechanism between the eye (DME) and the kidney (albuminuria) is vascular hyperpermeability.

In type 2 diabetes mellitus patients, transition from non-albuminuric to the albuminuric state may be caused by an increase in systemic inflammation which suggests that the retinal phenotype is caused by systemic factors causing a retina-specific response.[21] It is important that the patients with type 2 DM and albuminuria must be carefully followed up for any DME related changes and also the patients with DME must be evaluated for any kidney disease. DME being a multi-factorial and multi-pathogenic disease, its correlation with diabetic nephropathy will require further investigation.

In our study, no significant association was seen in the distribution of smoking with macular odema. (p value is 0.07) UKPDS showed a decrease in retinopathy progression

Table 1: Association of HbA1c (%) with macularodema.

HbA1c (%)	Patients without macular odema (n=96)	Patients with macular odema (n=14)	Total	P value	Testperformed
<6.5	51 (100%)	0 (0%)	51 (100%)	<.0001	Fisher Exact test
>=6.5	45 (76.27%)	14 (23.73%)	59 (100%)		
Mean ± SD	6.62 ± 0.87	8.56 ± 1.49	6.87 ± 1.16		
Median(IQR)	6.4(6-6.825)	8.15(7.8-8.925)	6.55(6.1-7.2)	<.0001	Mann Whitney test; 110
Range	5.7-10.2	6.7-12.3	5.7-12.3		

Table 2: Association of lipid profile with macular odema

Lipid profile	Patients without macular odema (n=96)	Patients with macular odema (n=14)	Total	P value	Testperformed
Cholesterol(mg/dL)					
Deranged	37 (80.43%)	9 (19.57%)	46 (100%)	0.068	Chi square test, 3.328
Normal	59 (92.19%)	5 (7.81%)	64 (100%)		
Mean ± SD	192.42 ± 53.57	220.57 ± 42.6	196 ± 52.98		
Median(IQR)	165.5(146-251)	238(184.5-253)	171(150-253)		
Range	130-285	150-266	130-285		
Triglycerides(mg/dL)					
Deranged	30 (78.95%)	8 (21.05%)	38 (100%)	0.057	Chi square test, 3.623
Normal	66 (91.67%)	6 (8.33%)	72 (100%)		
Mean ± SD	123.94 ± 37.88	152.29 ± 35.64	127.55 ± 38.63		
Median(IQR)	110(93.75-165)	170(133-179)	110(95-170)		
Range	75-200	76-192	75-200		
HDL(mg/dL)					
Deranged	14 (73.68%)	5 (26.32%)	19 (100%)	0.051	Chi square test, 3.818
Normal	82 (90.11%)	9 (9.89%)	91 (100%)		
Mean ± SD	64.86 ± 12.82	56.79 ± 14.61	63.84 ± 13.27		
Median(IQR)	68(65-74)	63(42.5-65)	68(64-70)		
Range	25-80	35-80	25-80		
LDL(mg/dL)					
Deranged	29 (78.38%)	8 (21.62%)	37 (100%)	0.046	Chi square test, 3.971
Normal	67 (91.78%)	6 (8.22%)	73 (100%)		
Mean ± SD	99.1 ± 32.96	113.29 ± 32.35	100.91 ± 33.08		
Median (IQR)	80(75-140)	130(81-140)	82(75-140)		
Range	65-160	70-150	65-160		

Table 3: Association of urine Albumin Excretion (mg/ 24hr) with macular odema.

Urine Albumin Excretion (mg/ 24 hr)	Patients without macular odema (n=96)	Patients with macular odema (n=14)	Total	P value	Testperformed
Mean ± SD	46.81 ± 82.08	109.21 ± 125.24	54.75 ± 90.44	0.054	Mann Whitney test; 458.5
Median(IQR)	16(12-23)	30(16.5-177.25)	17(12-40)		
Range	5-420	10-380	5-420		

Table 4: Association of nephropathy with macular odema

Nephropathy	Patients without macular odema(n=96)	Patients with macular odema(n=14)	Total	P value	Testperformed
Macroalbuminuria	4 (66.67%)	2 (33.33%)	6 (100%)	0.054	Fisher Exact test
Microalbuminuria	18 (78.26%)	5 (21.74%)	23 (100%)		
No overt nephropathy	74 (91.36%)	7 (8.64%)	81 (100%)		
Total	96 (87.27%)	14 (12.73%)	110 (100%)		

Table 5: Association of smoking with macular odema

Smoking	Patients without macular odema (n=96)	Patients with macular odema (n=14)	Total	P value	Testperformed
No	76 (90.48%)	8 (9.52%)	84 (100%)		
Yes	20 (76.92%)	6 (23.08%)	26 (100%)	0.07	Chi square test, 3.283
Total	96 (87.27%)	14 (12.73%)	110 (100%)		

Table 6: Association of stroke with macular odema

Stroke	Patients without macular odema (n=96)	Patients with macular odema (n=14)	Total	P value	Testperformed
No	74 (90.24%)	8 (9.76%)	82 (100%)		
Yes	22 (78.57%)	6 (21.43%)	28 (100%)	0.11	Chi square test, 2.56
Total	96 (87.27%)	14 (12.73%)	110 (100%)		

Table 7: Association of cardiovascular disease with macular odema

Cardiovascular disease	Patients without macular odema (n=96)	Patients with macular odema (n=14)	Total	P value	Testperformed
No	75 (90.36%)	8 (9.64%)	83 (100%)		
Yes	21 (77.78%)	6 (22.22%)	27 (100%)	0.088	Chi square test, 2.904
Total	96 (87.27%)	14 (12.73%)	110 (100%)		

Table 8: Association of use of pioglitazone with macularodema

Use of pioglitazone	Patients without macular odema (n=96)	Patients with macular odema (n=14)	Total	P value	Testperformed
No	87 (91.58%)	8 (8.42%)	95 (100%)		
Yes	9 (60%)	6 (40%)	15 (100%)	0.0006	Chi square test, 11.631
Total	96 (87.27%)	14 (12.73%)	110 (100%)		

Table 9: Association of duration of diabetes mellitus (years) with macular odema

Duration of diabetes mellitus (years)	Patients without macular odema (n=96)	Patients with macular odema (n=14)	Total	P value	Testperformed
Mean ± SD	3.13 ± 1.7	7.14 ± 1.56	3.64 ± 2.15		
Median(IQR)	3(2-4)	7(6-8)	3(2-5)	<.0001	Mann Whitney test;64.5
Range	0.08-9	5-10	0.08-10		

Table 10: Association of severity of diabetic retinopathy with macular odema

Diabetic retinopathy status	Eyes without macular odema (n=192)	Eyes with macular odema (n=28)	Total	P value	Testperformed
Mild NPDR	58 (96.67%)	2 (3.33%)	60 (100%)		
Moderate NPDR	110 (85.27%)	19 (14.73%)	129 (100%)		
Severe NPDR	20 (80%)	5 (20%)	25 (100%)	0.014	Fisher Exact test
PDR	4 (66.67%)	2 (33.33%)	6 (100%)		
Total	192 (87.27%)	28 (12.73%)	220 (100%)		

among smokers.[22] But consistent with our study, no association was found in multivariate analysis in other studies.[23,24]

A recent meta-analytical study reported that incidence of cardiovascular disease (CVD) and fatal CVD was more in type 2 diabetes patients with DME or PDR when compared to those without DME or PDR.[25] DME can be exacerbated by the fluid retention due to cardiac failure and is an important concern while managing DME.[26] In the current study, the relation of stroke with DME was studied. DME was detected in 21.43% patients with stroke and 9.76% without stroke and no significant association was seen in the distribution of stroke with macular odema. (p= 0.11)

We also studied the association of cardiovascular disease with macular odema. DME was detected in 22.22% patients with cardiovascular disease and 9.64% without cardiovascular disease but the difference was not statistically significant. (p=0.088). All these patients were not examined by a Cardiologist. It is therefore possible that subclinical findings in these patients may be missed or patients may not aware of their CVD. It is also possible that patients with these factors were missing the diabetic eye screening appointments more often than healthier patients and so were less frequently diagnosed with DME. (detection bias)

In the present study, significant association was seen in the use of pioglitazone with macular odema. (p= 0.0006) Proportion of patients with macular odema was 40% of patients in whom pioglitazone was used which was significantly higher as compared to 8.42% of patients in whom pioglitazone was not used. This result is consistent with previous case reports.[25–27] Although the mechanism of DME in patients using glitazones is not fully understood, the fluid retention caused by glitazones may be responsible for this effect. These drugs could possibly increase vascular endothelial growth factor levels which are high in DME.[28]

In our study, significant association was seen in duration of diabetes mellitus(years) with macular odema. (p value <0.05)[p<0.0001] Duration of diabetes has been observed as a significant factor in the progression of DME.[29] Some other studies have shown a lack of an association between duration of diabetes mellitus and DME incidence.[30] This could be attributed to the difficulty in dating the onset of diabetes mellitus and different survival rates in different groups of patients. Klein et al. also reported longer duration of diabetes mellitus in patients whose age at diagnosis was 30 years or older.[31]

One of the important ocular risk factors for occurrence of DME is severity of DR. In our study, significant association was seen between the severity of diabetic retinopathy and macular odema. (p value<.05) It is seen that although DME can occur during any stage of DR, increasing DR severity has been associated with an increasing prevalence of DME.[32]

5. Conclusion

In our study HbA1c and LDL level were found to have a significant association with the risk of developing DME. Use of pioglitazone was found to have significant association with the risk of DME. Total Cholesterol, Triglycerides, HDL levels, Microalbuminuria and overt nephropathy, smoking, stroke and cardiovascular disease were not found to have a significant association with the risk of developing DME in our study.

Further research is required to establish more risk factors associated with development of DME. Also as many of the risk factors are modifiable, Ophthalmologists and Physicians should ensure that patients with DR and DME receive appropriate assessment and treatment for these comorbidities.

6. Strengths of our Study

Our estimates of DME corroborate with the estimates recently published on a global scale as well as in India. Thus, this study adds to literature about the clinical and etiological profile of DME in type 2 diabetes patients Thus, our study can act as a basis for further larger studies of DME.

7. Limitations of Study

1. Our study was conducted in a hospital setting, and hence the results may not be representative of the entire population in terms of relevance and application. Its results cannot be extrapolated to the general population.
2. The sample size was smaller in comparison to previous studies.

8. Source of Funding

None.

9. Conflict of Interest

None.

References

1. World Health Organisation Prevention of blindness from diabetes mellitus: Report of a WHO consultation in Geneva, Switzerland, 9–11 November 2005.
2. Ballard DJ, Melton LJ, Dwyer MS, Trautmann JC, Chu CP, O'Fallon WM, et al. Risk Factors for Diabetic Retinopathy: A Population-Based Study in Rochester, Minnesota. *Diabetes Care*. 1986;9(4):334–42. doi:10.2337/diacare.9.4.334.
3. Arend O, Wolf S, Jung F, Bertram B, Postgens H, Toonen H, et al. Retinal microcirculation in patients with diabetes mellitus: dynamic and morphological analysis of perifoveal capillary network. *Br J Ophthalmol*. 1991;75(9):514–8. doi:10.1136/bjo.75.9.514.
4. Grunwald JE, Riva CE, Baine J. Total retinal volumetric blood flow rate in diabetic patients with poor metabolic control. *Invest Ophthalmol Vis Sci*. 1992;33:356–33.

5. Kohner EM, Hamilton AM, Saunders SJ, Sutcliffe BA, Bulpitt CJ. The retinal blood flow in diabetes. *Diabetologia*. 1975;11(1):27–33. doi:10.1007/bf00422814.
6. Patel V, Rassam S, Newsom R, Wiek J, Kohner E. Retinal blood flow in diabetic retinopathy. *BMJ*. 1992;305(6855):678–83. doi:10.1136/bmj.305.6855.678.
7. Fenwick EK, Xie J, Man REK, Sabanayagam C, Lim L, Rees G, et al. Combined poor diabetes control indicators are associated with higher risks of diabetic retinopathy and macular edema than poor glycemic control alone. *PLOS ONE*. 2017;12(6). doi:10.1371/journal.pone.0180252.
8. Wong T, Cheung C, Larsen M, Sharma S, Simó R, Diabetic. Diabetic retinopathy. *Nat Rev Dis Primers*. 2016;17(2):16012.
9. Deepa R, Shanthirani CS, Pradeepa R, Mohan V. Is the "Rule of Halves" in hypertension still valid? - Evidence from the Chennai urban Population Study (CUPS). *J Assoc Phys India*. 2003;51:153–7.
10. Hamman RF, Mayer EJ, Moo-Young GA, Hildebrandt W, Marshall JA, Baxter J. Prevalence and risk factors of diabetic retinopathy in non-Hispanic whites and Hispanics with NIDDM. San Luis Valley Diabetes Study. *Diabetes*. 1989;38(10):1231–7.
11. Varma R, Macias GL, Torres M, Klein R, Peña FY, Azen SP. Biologic Risk Factors Associated with Diabetic Retinopathy. *Ophthalmology*. 2007;114(7):1332–40. doi:10.1016/j.ophtha.2006.10.023.
12. West SK, Munoz B, Klein R, Broman AT, Sanchez R, Rodriguez J, et al. Risk factors for type ii diabetes and diabetic retinopathy in a mexican-american population: proyecto ver. *Am J Ophthalmol*. 2002;134(3):390–8. doi:10.1016/s0002-9394(02)01595-7.
13. Tan GS, Cheung N, Simó R, Cheung GCM, Wong TY. Diabetic macular oedema. *Lancet Diabetes Endocrinol*. 2017;5(2):143–55. doi:10.1016/s2213-8587(16)30052-3.
14. Diabetes Control and Complications Trial Research Group. Progression of retinopathy with intensive versus conventional treatment in the diabetes control and complications trial. *Ophthalmology*. 1995;102:647–61.
15. The writing team for the diabetes control and complications trial/ epidemiology of diabetes interventions and complications research group. *JAMA*. 2002;287:2563–9.
16. Salinero-Fort M, Andrés-Rebollo FJS, de Burgos-Lunar C, Arrieta-Blanco FJ, and PGC. Four-Year Incidence of Diabetic Retinopathy in a Spanish Cohort: The MADIABETES Study. *PLoS ONE*. 2013;8(10). doi:10.1371/journal.pone.0076417.
17. Du M, Wu M, Fu D, Yang S, Chen J, Wilson K, et al. Effects of modified LDL and HDL on retinal pigment epithelial cells: a role in diabetic retinopathy? *Diabetologia*. 2013;56(10):2318–28. doi:10.1007/s00125-013-2986-x.
18. Chew EY. Association of Elevated Serum Lipid Levels With Retinal Hard Exudate in Diabetic Retinopathy. *Arch Ophthalmol*. 1996;114(9):1079–84. doi:10.1001/archopht.1996.01100140281004.
19. Klein R. Diabetic Retinopathy and Nephropathy . In: Cortes P, editor. The diabetic kidney. Totowa, New Jersey: Humana Press; 2006. p. 473–98.
20. Knudsen ST, Bek T, Poulsen PL, Hove MN, Rehling M, Mogensen CE. Macular Edema Reflects Generalized Vascular Hyperpermeability in Type 2 Diabetic Patients With Retinopathy. *Diabetes Care*. 2002;25(12):2328–34. doi:10.2337/diacare.25.12.2328.
21. Forbes JM, Cooper ME. Mechanisms of Diabetic Complications. *Physiol Rev*. 2013;93(1):137–88. doi:10.1152/physrev.00045.2011.
22. Stratton IM, Kohner EM, Aldington SJ, Turner RC, Holman RR, Manley SE, et al. UKPDS 50: Risk factors for incidence and progression of retinopathy in Type II diabetes over 6 years from diagnosis. *Diabetologia*. 2001;44(2):156–63. doi:10.1007/s001250051594.
23. Hammes HP, Welp R, Kempe HP, Wagner C, Siegel E, Holl RW, et al. Risk Factors for Retinopathy and DME in Type 2 Diabetes—Results from the German/Austrian DPV Database. *PLOS ONE*. 2015;10(7). doi:10.1371/journal.pone.0132492.
24. Klein R, Knudtson MD, Lee KE, Gangnon R, Klein BEK. The Wisconsin Epidemiologic Study of Diabetic Retinopathy XXIII: The Twenty-five-Year Incidence of Macular Edema in Persons with Type 1 Diabetes. *Ophthalmology*. 2009;116(3):497–503. doi:10.1016/j.ophtha.2008.10.016.
25. Xie J, Ikram MK, Cotch MF, Klein B, Varma R, Shaw JE, et al. Association of Diabetic Macular Edema and Proliferative Diabetic Retinopathy With Cardiovascular Disease. *JAMA Ophthalmol*. 2017;135(6):586–93. doi:10.1001/jamaophthalmol.2017.0988.
26. Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema. Early Treatment Diabetic Retinopathy Study Report Number 2. Early Treatment Diabetic Retinopathy Study Research Group. *Ophthalmology*. 1987;94(7):761–74.
27. Kendall C, Wooltorton E. Rosiglitazone (Avandia) and macular edema. *CMAJ*. 2006;174:623.
28. Emoto M, Anno T, Sato Y, Tanabe K, Okuya S, Tanizawa Y, et al. Troglitazone Treatment Increases Plasma Vascular Endothelial Growth Factor in Diabetic Patients and Its mRNA in 3T3-L1 Adipocytes. *Diabetes*. 2001;50(5):1166–70. doi:10.2337/diabetes.50.5.1166.
29. Ozer PA, Unlu N, Demir MN, Hazirolan DO, Acar MA, Duman S. Serum lipid profile in diabetic macular edema. *J Diabetes Complications*. 2009;23(4):244–8. doi:10.1016/j.jdiacomp.2007.12.004.
30. Stratton IM, Kohner EM, Aldington SJ, Turner RC, Holman RR, Manley SE, et al. UKPDS 50: Risk factors for incidence and progression of retinopathy in Type II diabetes over 6 years from diagnosis. *Diabetologia*. 2001;44(2):156–63. doi:10.1007/s001250051594.
31. Klein R, Klein BEK, Moss SE, Davis MD, DeMets DL. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Ophthalmology*. 1984;91(12):1464–74. doi:10.1016/s0161-6420(84)34102-1.
32. Mohamed Q, Gillies MC, Wong TY. Management of Diabetic Retinopathy. *JAMA*. 2007;298(8):902–16. doi:10.1001/jama.298.8.902.

Author biography

Chaitali Desai, Resident

O K Radhakrishnan, Professor

Namratha Judith Cardoza, Resident

Madhuvanthi Mohan, Resident

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