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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

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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 edema was 8.15(7.8-8.925) which was significantly higher than patients without macular edema 6.4(6-6.825). Mean LDL(mg/dL) in patients without macular edema was 99.1 ± 32.96 and patients with macular edema 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 edema. No significant association of stroke, smoking, cardiovascular disease and distribution of nephropathy with macular edema 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.© This is an open access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>) which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

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

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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 DR¹⁰⁻¹² 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 $\geq 250 \mu\text{m}$ attributable to DME.

The criteria for diagnosing diabetes mellitus was a fasting plasma glucose of $>126 \text{ mg/dL}$ (6.99 mmol/L) or a non-fasting plasma glucose of $>200 \text{ mg/dL}$ (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 $\pm$ 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 $\pm$ 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. ($p \text{ value}>.05$) (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. ($p \text{ value}>.05$) 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 edema. ($p=0.054$) (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 edema. This shows no significant association in the distribution of smoking with macular edema. (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 edema. This shows no significant association in the distribution of stroke with macular edema. (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 edema. This shows no significant association in the distribution of cardiovascular disease with macular edema. (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 edema. Significant association was seen in the distribution of use of pioglitazone with macular edema. (p value is 0.00006) (Table 8)

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

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 edema. The corresponding values for patients without macular edema 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 edema. [$p=0.014$]

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 edema. ($p<0.0001$). 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 edema. [$p=0.046$] 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 edema.

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 edema. ($p=0.054$) There was no significant association of urine Albumin Excretion (mg/ 24 hr) with macular edema. ($p=0.054$). 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 edema. (p value is 0.07) UKPDS showed a decrease in retinopathy progression

Table 1: Association of HbA1c (%) with macular edema.

HbA1c (%)	Patients without macular edema (n=96)	Patients with macular edema (n=14)	Total	P value	Test performed
<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	<.0001	Mann Whitney test; 110
Median(IQR)	6.4(6-6.825)	8.15(7.8-8.925)	6.55(6.1-7.2)		
Range	5.7-10.2	6.7-12.3	5.7-12.3		

Table 2: Association of lipid profile with macular edema

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 edema.

Urine Albumin Excretion (mg/ 24 hr)	Patients without macular edema (n=96)	Patients with macular edema (n=14)	Total	P value	Test performed
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 edema

Nephropathy	Patients without macular edema(n=96)	Patients with macular edema(n=14)	Total	P value	Test performed
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 edema

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

Table 6: Association of stroke with macular edema

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

Table 7: Association of cardiovascular disease with macular edema

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

Table 8: Association of use of pioglitazone with macular edema

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

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

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

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

Diabetic retinopathy status	Eyes without macular edema (n=192)	Eyes with macular edema (n=28)	Total	P value	Testperformed
Mild NPDR	58 (96.67%)	2 (3.33%)	60 (100%)	0.014	Fisher Exact test
Moderate NPDR	110 (85.27%)	19 (14.73%)	129 (100%)		
Severe NPDR	20 (80%)	5 (20%)	25 (100%)		
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 edema. ($p=0.11$)

We also studied the association of cardiovascular disease with macular edema. 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 edema. ($p=0.0006$) Proportion of patients with macular edema 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 edema. (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 edema. (p value <0.05) 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.

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