Original Article

DOI: 10.17354/ijss/2016/133

Risk Factors Associated with Clinically Significant Macular Edema in Patients with Type 2 Diabetes Mellitus

Gagan Sathya Prakash[1], Minal Kothari[2]

[1]Junior Resident, Intern, Bangalore Medical College, Bengaluru, Karnataka, India, [2]Post-graduate Student, Department of Ophthalmology, Kempegowda Institute of Medical Sciences and Research Centre, Bengaluru, Karnataka, India

Abstract

Introduction: Diabetic macular edema (DME) is the major cause of vision loss in diabetic retinopathy (DR). Apart from diabetes, a number of other systemic factors have an important role in occurrence and progression of DME. Control of these factors along with control of blood sugars can prevent or reverse the maculopathy, thereby restore the vision of diabetic patients.

Methodology: Cross-sectional comparative study. Patients with Type 2 diabetes were screened for DR. After thorough examination including fundus examination, patients were divided into two groups (Group 1 - Retinopathy with clinically significant macular edema [CSME] and Group 2 - Retinopathy without CSME). A detailed history of the duration of diabetes, treatment history, hypertension, and hyperlipidemia were taken. The mean values of three consecutive blood pressure (BP) readings were assessed. Following blood investigation, serum lipid profile, glycosylated hemoglobin (HbA1c), urine albumin, renal function test of the concerned patients were done. The significance of the above risk factors was compared in both the groups involved in the study.

Results: In the present study of 170 patients with DR, there was no significant difference in the age and gender distribution among two groups. The mean value of fasting blood sugar, postprandial blood sugar, and HbA1c were higher in the study group than control group. In this study, the mean value of systolic BP and diastolic BP were significantly higher in the study group compared to control group. Serum lipids, serum cholesterol, triglycerides, low-density lipoprotein (LDL), and very LDL levels were significantly higher in patients with CSME. Microalbuminuria and macroalbuminuria showed a correlation with CSME.

Conclusion: Systemic risk factor shows a significant association with CSME in DR. Thus, early detection of these risk factors and their control has a significant role in preventing the development and progression of maculopathy in DR patients thereby preventing severe visual loss.

Key words: Albuminuria, Clinically significant macular edema, Diabetic retinopathy, Glycosylated hemoglobin, Hypertension, Lipid profile

INTRODUCTION

Diabetic retinopathy (DR) is a chronic progressive, potentially sight-threatening disease of the retinal vasculature associated with the prolonged hyperglycemia and other conditions linked to diabetes mellitus (DM) such as hypertension.[1] It eventually afflicts virtually all patients with diabetes. It is estimated that diabetes affects 4% of the world's population, almost half of whom have some degree of DR at given time.[2,3] DR occurs in all Type 1 and 75% of Type 2 DM after 15 years of duration of diabetes.[2,4,5] Visual disability from DM is a significant public health problem. However, this morbidity is largely preventable and treatable.[2]

Diabetic macular edema (DME) is the most frequent cause of severe vision impairment in diabetic patients.[6] Diabetic maculopathy can occur at any level of retinopathy and alter the structure of macula, significantly affecting its function. Although treatment of established retinopathy can reduce

Access this article online

www.ijss-sn.com

Month of Submission : 01-2015
Month of Peer Review : 02-2016
Month of Acceptance : 02-2016
Month of Publishing : 03-2016

Corresponding Author: Dr. Gagan Sathya Prakash, No. 373, 43rd Cross, 5th Block, Jayanagar, Bengaluru, Karnataka, India.
E-mail: gagansp@gmail.com

the risk of visual loss by 60%, DR remains the leading cause of blindness among working-aged adults in the world.

The identification of risk factors is important for the evolution of better management strategies for DR. Previous studies have shown possible risk factors for retinopathy included diabetic duration, glycemic control, age of onset diabetic treatment, systemic hypertension, renal function/nephropathy, body mass, sex, human leukocyte antigen status, cigarette smoking, and elevated blood lipids.[4,5,7-17] Despite the recognized importance of maculopathy as a cause of visual morbidity in diabetes, risk factors for maculopathy have received considerably less attention in the literature. Diabetic duration, age, sex, age of diagnosis, insulin use, higher glycosylated hemoglobin (HbA1C), diuretic use, systemic hypertension, and proteinuria have been associated with DME.[14,18] Once diabetic maculopathy occurs, there is no satisfactory treatment and the prognosis of visual outcome is poor, so it is always better to prevent its development. Hence, there is a need for a study to find out the risk factors associated with the development of clinically significant macular edema (CSME) in diabetic patients, to control the same and subsequently reduce the incidence of diabetic maculopathy in future.

METHODOLOGY

This is a cross-sectional comparative study conducted in the Department of Ophthalmology from January 2014 to July 2015.

Inclusion Criteria

All patients (outpatients and inpatients) of either sex with Type 2 DM who will be screened for DR at ophthalmology outpatient department and found to have DR with or without CSME.

Exclusion Criteria

(1) Patients who have undergone any intraocular surgery in the past 3 months, (2) patients undergone any intraocular laser treatment or intraocular injection in the past 3 months, (3) patients with history of intake of drugs (corticosteroids, nephrotoxic) in the past 3 months or any non-diabetic renal disease, (4) patients suffering from non-diabetic maculopathy (age-related macular degeneration/macular dystrophy), (5) patients with chronic liver disease, (6) patients with significant media haziness preventing adequate visualization of the fundus, and (7) patients with insulin dependent DM or gestational DM.

All patients presenting with Type 2 DM were subjected to complete ophthalmologic examination by assessing the visual acuity with Snellen chart, slit lamp examination, intraocular pressure with I care tonometry. Fundus examination was conducted with a direct ophthalmoscope, indirect ophthalmoscope, and slit lamp biomicroscopy using +90D lens.

After fundus examination, only patients having retinopathy in at least one eye were selected for further study and subsequently divided into 2 groups (Group 1 - Retinopathy with CSME and Group 2 - Retinopathy without CSME). Informed consent was taken from the concerned patients. Fundus picture of the patients was taken with DRS and fundus camera. DR was classified according to early treatment DR study criteria. OCT was done in a few patients with CSME to quantify and find out the type of macular edema. FFA was done in a few patients to decide on the treatment plan.

A detailed history of the duration of diabetes, type of treatment, smoking/tobacco use, hyperlipidemia and hypertension were taken from the above-selected patients. The mean value of the three consecutive blood pressure (BP) reading was assessed. Following blood investigations (serum lipid profile, glycosylated Hb, urine albumin, and renal function test) of the concerned patients was done. HbA1c determination is based on the turbidimetric inhibition immunoassay. The significance of the above risk factors was compared in both the groups involved in the study like descriptive.

The data were analyzed using various statistical tests such as descriptive and inferential statistics, mean ± standard deviation (minimum-maximum), Student's *t*-test (two-tailed independent), and Chi-square or Fischer exact test.

RESULTS

In this comparative study, 85 patients were allotted in each group. The mean age of the patients in the study group (with CSME) was 57.02 ± 9.75 and in the control group (without CSME) mean age was 56.42 ± 9.25. There was no significant difference in age distribution between the two groups ($P = 0.681$) (Table 1). In the study group, 46 (54.1%) were males and 29 (34.1%) were females. In the control group, 56 (65.9%) were males and 29 (34.1%) were females. There was no significant difference in the gender distribution among the two group ($P = 0.117$).

In this study, 20% had duration <5 years, 27.1% in between 5 and 10 years, 25.9% in between 11 and 15 years, 16.5% in between 16 and 20 years, and 10.6% >20 years. In the control group, the majority of patients had duration <5 years (44.7%). This shows that the duration of diabetics is more in a study group with $P = 0.003$.

Table 2 shows the distribution of the patients in both the groups on the basis of treatment. In the study group, out of 85 patients, 2 (2.4%) have not received any treatment, whereas in the control group, none of the patients were there without ant treatment. The majority of the patients in both the groups were on treatment with oral hypoglycemic agents (57.7% in the study group and 74.1% in control group). In the study, 40% patients were on treatment with insulin, whereas in control group, 16.4% were on treatment with insulin.

Tables 3 and 4 compare the laboratory investigations between the two groups which are studied such as fasting blood sugars, postprandial blood sugar (PPBS), HbA1c, lipid profile, and urine albumin levels.

Table 5 shows the best corrected visual acuity (BCVA) in patients of both the groups (considering the BCVA of the worst eye). In the study group, out of 85 patients, none had BCVA of 6/6, whereas in the control group, 20 patients had BCVA of 6/6. The majority of patients in the study group had moderate visual impairment (51.76%), whereas in the control group, only 24.71% had moderate visual impairment. In the study group, out of 85 patients, 21 (24.71%) had severe visual impairment, whereas in the control group, only 1 patient (1.18%) had severe visual impairment.

Table 6 shows the severity of DR in both the groups (according to the worst eye). The majority of patients in

Table 1: The distribution of patients as per duration of DM

Duration of DM (years)	*n* (%)	
	Study group	Control group
<5	17 (20.0)	38 (44.7)
5-10	23 (27.1)	24 (28.2)
11-15	22 (25.9)	14 (16.5)
16-20	14 (16.5)	5 (5.9)
>20	9 (10.6)	4 (4.7)
Total	85 (100)	85 (100)

DM: Diabetes mellitus

Table 2: The distribution of the patients in both the groups on the basis of treatment

Treatment	*n* (%)	
	Study group (*n*=85)	Control group (*n*=85)
No treatment	2 (2.4)	0 (0.0)
OHA	49 (57.7)	63 (74.1)
Insulin	0 (0.0)	1 (1.1)
OHA+Insulin	34 (40)	13 (15.3)

OHA: Oral hypoglycemic agents

Table 3: Comparisons between the mean values of the parameters

Parameters	Study group	Control group	*P* values
FBS (mean)	151.62±51.54	153.54±53.34	0.812
PPBS (mean)	230.21±62.68	211.84±62.57	0.057
HbA1c (mean)	10.09±1.74	8.90±2.18	<0.001**
Lipid parameters			
Cholesterol	211.15±64.1	173.82±42.28	<0.001**
TGL	199.44±57.02	156.85±62.39	<0.001**
HDL	35.95±11.78	32.67±9.05	0.043
LDL	135.71±46.87	111.54±34.38	<0.001**
VLDL	35.82±12.18	30.28±9.40	0.001**

**: p<0.001, FBS: Fasting blood sugars, PPBS: Postprandial blood sugar, HbA1c: Glycosylated hemoglobin, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein, TGL: Triglycerides level

Table 4: Compares the levels of HbA1c values, lipid parameters, and urine albumin levels

Parameters	*n* (%)		*P* values
	Study group (*n*=85)	Control group (*n*=85)	
HbA1c			<0.001**
<6.5	0 (0)	10 (11.8)	
6.5-7.0	3 (3.5)	6 (7.1)	
>7.0	82 (96.5)	69 (81.2)	
Total cholesterol			<0.001**
<200	36 (42.4)	58 (68.2)	
200-240	25 (29.4)	21 (24.7)	
>240	24 (28.2)	6 (7.1)	
TGL			<0.001**
<150	19 (22.4)	36 (42.4)	
150-200	23 (27.1)	38 (44.7)	
200-500	43 (50.6)	11 (12.9)	
>500	0 (0.0)	0 (0.0)	
HDL			0.032*
<40	61 (71.8)	61 (71.8)	
40-60	18 (21.2)	24 (28.2)	
>60	6 (7.1)	0 (0.0)	
LDL			0.001**
<100	20 (23.5)	26 (30.6)	
100-130	29 (34.1)	34 (40.0)	
130-160	12 (14.1)	21 (24.7)	
160-190	18 (21.2)	3 (3.5)	
>190	6 (7.1)	1 (1.2)	
VLDL			0.029*
<30	28 (32.9)	42 (49.4)	
≥30	57 (67.1)	43 (50.6)	
Urine albumin			<0.001**
No albuminuria	5 (5.9)	38 (44.7)	
Microalbuminuria	11 (12.9)	2 (2.4)	
Macroalbuminuria	69 (81.2)	45 (52.9)	

*,**: p<0.001, HbA1c: Glycosylated hemoglobin, TGL: Triglycerides level, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein

Table 5: Comparison of BCVA in the study and control group

BCVA	*n* (%)	
	Study group (*n*=85)	Control group (*n*=85)
6/6	0 (0.0)	20 (23.53)
6/9-6/12	20 (23.53)	43 (50.59)
6/18-6/36	44 (51.76)	21 (24.71)
≤6/60	21 (24.71)	1 (1.18)

BCVA: Best corrected visual acuity

Table 6: Comparison of the severity of DR between the study and control group

Fundus	*n* (%)	
	Study group (*n*=85)	Control group (*n*=85)
Mild NPDR	10 (11.76)	32 (37.65)
Moderate NPDR	33 (38.82)	32 (37.65)
Severe NPDR	23 (27.06)	11 (12.94)
PDR	19 (22.35)	10 (11.76)

DR: Diabetic retinopathy, NPDR: Non-proliferative diabetic retinopathy, PDR: Proliferative diabetic retinopathy

the control group had mild and moderate non-proliferative DR (NPDR) (37.65% each). In the study group, only 11.76% had mild NPDR and 38.82% had moderate NPDR. Severe NPDR was present in 27.06% of patients in the study group, whereas 12.94% of patients in control group. Proliferative DR was present 22.35% in the study group and 11.76% in control group (**$P < 0.001$).

DISCUSSION

DR is the most common microvascular complication in diabetes which can produce a severe visual loss.[19,20] It is responsible for 4.8% of the 37 million cases of blindness throughout the world.[21] Severe visual impairment among diabetic patients may be caused by diabetic maculopathy. Since diabetic maculopathy is characterized by increased capillary leakage due to alterations in the microcirculation of the macula.[22,23] This study was conducted to find out the role of metabolic control and other systemic factors associated with CSME in Type 2 diabetic patients.

Age group of the patients included in the study ranged from 30 to 80 years. There was no significant difference in age and gender between two groups. Both groups were matched in terms of age and gender. In our study, it was found that majority of patients without CSME had duration of DM >5 years (80%). This shows that the duration of DM is significantly associated with CSME. Previous studies such as WESDR data also demonstrated the duration of DM as one of the risk factors for DME.[19,24]

Raised HbA1c levels have been shown to be a significant risk factor for DME in previous studies.[25-27] In this study, the mean HbA1c value was significantly higher in patients with CSME. None of the patients with CSME had HbA1c under control, and the majority of patients (96.5%) had suboptimal HbA1c. This correlates well with other studies, Jew *et al.* in their study concluded that HbA1c had a significantly high odds ratio of developing CSME.[28] Rema and Pradeepa in CURES study reported that for every 2% elevation of HbA1c, the risk of DR increases by a factor of 1.7. In this study, the mean PPBS value was also higher in CSME group though it was not statistically significant.

In this study, the mean systolic and diastolic BP were significantly higher in patients with CSME.

There has been increasing interest in the link between the serum lipids and maculopathy in view of the evolving medical treatment for hyperlipidemia. In this study, serum cholesterol, triglycerides level (TGL), low-density lipoprotein (LDL), and very LDL levels were significantly higher in patients with CSME. The association between serum lipids and CSME is biologically plausible. Several proposed mechanisms discussed in earlier reports include the direct involvement of serum lipids in endothelial dysfunction[29] which subsequently results in the breakdown of the blood-retinal barrier.

In our study, the incidence of microalbuminuria and macroalbuminuria is significantly more associated with CSME. 81.2% patients with CSME had macroalbuminuria and 12.9% patients with CSME had microalbuminuria. This shows that both clinical and subclinical nephropathy has an important role in diabetic maculopathy. Hypoalbuminemia, which may be secondary to renal loss of albumin, has been postulated to be one of the factors involved in the formation of macular edema.

CONCLUSION

In this study, duration of DM, uncontrolled glycemic status, systemic hypertension, albuminuria, serum cholesterol, TGL, LDL, and VLDL showed a significant association with CSME. However, serum high-density lipoprotein has not shown a correlation with CSME.

REFERENCES

1. The Royal College of Ophthalmologist Diabetic Retinopathy Guidelines, December 2012.
2. Rema M, Pradeepa R. Diabetic retinopathy: An Indian perspective. Indian J Med Res 2007;125:297-310.
3. Aiello LP, Gardner TW, King GL, Blankenship G, Cavallerano JD, Ferris FL 3rd, *et al.* Diabetic retinopathy. Diabetes Care 1998;21:143-56.
4. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. Arch Ophthalmol 1984;102:520-6.
5. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. Arch Ophthalmol 1984;102:527-32.
6. Sensio Sanchez VM, Gomez Ramirez V, Morales Gomezi I, Rodriguez I. Clinically significant macular oedema: Systemic risk factors. Arch Soc Esp Ophthalmol 2008;83:173-6.
7. Rand LI, Krolewski AS, Aiello LM, Warram JH, Baker RS, Maki T. Multiple factors in the prediction of risk of proliferative diabetic retinopathy. N Engl J Med 1985;313:1433-8.
8. Constable IJ, Knuiman MW, Welborn TA, Cooper RL, Stanton KM, McCann VJ, *et al.* Assessing the risk of diabetic retinopathy. Am J Ophthalmol 1984;97:53-61.

9. West KM, Ahuja MM, Bennett PH, Grab B, Grabauskas V, Mateo-de-Acosta O, *et al.* Interrelationships of microangiopathy, plasma glucose and other risk factors in 3583 diabetic patients: A multinational study. Diabetologia 1982;22:412-20.
10. Segato T, Midena E, Grigoletto F, Zucchetto M, Fedele D, Piermarocchi S, *et al.* The epidemiology and prevalence of diabetic retinopathy in the Veneto region of north east Italy. Veneto Group for Diabetic Retinopathy. Diabet Med 1991;8:S11-6.
11. Kostraba JN, Klein R, Dorman JS, Becker DJ, Drash AL, Maser RE, *et al.* The epidemiology of diabetes complications study. IV. Correlates of diabetic background and proliferative retinopathy. Am J Epidemiol 1991;133:381-91.
12. McLeod BK, Thompson JR, Rosenthal AR. The prevalence of retinopathy in the insulin-requiring diabetic patients of an English country town. Eye (Lond) 1988;2:424-30.
13. Mühlhauser I, Sawicki P, Berger M. Cigarette-smoking as a risk factor for macroproteinuria and proliferative retinopathy in Type 1 (insulin-dependent) diabetes. Diabetologia 1986;29:500-2.
14. Barnett AH, Britton JR, Leatherdale BA. Study of possible risk factors for severe retinopathy in non-insulin dependent diabetes. Br Med J (Clin Res Ed) 1983;287:529.
15. Nathan DM, Singer DE, Godine JE, Harrington CH, Perlmuter LC. Retinopathy in older Type 2 diabetics. Association with glucose control. Diabetes 1986;35:797-801.
16. Nelson RG, Wolfe JA, Horton MB, Pettitt DJ, Bennett PH, Knowler WC. Proliferative retinopathy in NIDDM. Incidence and risk factors in Pima Indians. Diabetes 1989;38:435-40.
17. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. Is blood pressure a predictor of the incidence or progression of diabetic retinopathy? Arch Intern Med 1989;149:2427-32.
18. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. IV. Diabetic macular edema. Ophthalmology 1984;91:1464-74.
19. Zander E, Herfurth S, Bohl B, Heinke P, Herrmann U, Kohnert KD, *et al.* Maculopathy in patients with diabetes mellitus Type 1 and Type 2: Associations with risk factors. Br J Ophthalmol 2000;84:871-6.
20. Klein R, Klein BE, Moss SE. Epidemiology of proliferative diabetic retinopathy. Diabetes Care 1992;15:1875-91.
21. Wirta O, Pasternack A, Mustonen J, Laippala P, Lähde Y. Retinopathy is independently related to microalbuminuria in Type 2 diabetes mellitus. Clin Nephrol 1999;51:329-34.
22. Arend O, Wolf S, Jung F, Bertram B, Pöstgens H, Toonen H, *et al.* Retinal microcirculation in patients with diabetes mellitus: Dynamic and morphological analysis of perifoveal capillary network. Br J Ophthalmol 1991;75:514-8.
23. Grunwald JE, Riva CE, Baine J, Brucker AJ. Total retinal volumetric blood flow rate in diabetic patients with poor glycemic control. Invest Ophthalmol Vis Sci 1992;33:356-63.
24. Ozer PA, Unlu N, Demir MN, Hazirolan DO, Acar MA, Duman S. Serum lipid profile in diabetic macular oedema. J Diabetes Complications 2009;23:244-8.
25. Uçgun NI, Yildirim Z, Kiliç N, Gürsel E. The importance of serum lipids in exudative diabetic macular edema in Type 2 diabetic patients. Ann N Y Acad Sci 2007;1100:213-7.
26. Knudsen L, Lervang HH, Lundbye-Christensen S, Gorst-Rasmussen A. The North Jutland County Diabetic Retinopathy Study (NCDRS) 2. Non-ophthalmic parameters and clinically significant macular oedema. Br J Ophthalmol 2007;91:1593-5.
27. Roy MS, Affouf M. Six year progression of retinopathy and associated risk factors in African American patients with Type 1 diabetes mellitus. Arch Ophthalmol 2006;124:1297-306.
28. Jew OM, Peyman M, Chen TC, Visvaraja S. Risk factors for clinically significant macular oedema in a multi-ethnic population with Type 2 diabetes. Int J ophthalmol 2012;5:499-504.
29. Landmesscr U, Hornig B, Drexler H. Endothelial dysfunction in hypercholesterolemia: Mechanism, pathophysiological importance and therapeutic interventions. Semin Thromb Hemost 2000;26:529-37.

How to cite this article: Prakash GS, Kothari M. Risk Factors Associated with Clinically Significant Macular Edema in Patients with Type 2 Diabetes Mellitus. Int J Sci Stud 2016;3(12):120-124.

Source of Support: Nil. **Conflict of Interest:** None declared.