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Original Research Article

CLINICAL STUDY ON PATTERN OF MACULOPATHY IN NON-PROLIFERATIVE DIABETIC RETINOPATHY IN A TERTIARY CARE TEACHING HOSPITAL

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ABSTRACT:

Background: Diabetes mellitus (DM) is a well-documented major global medical problem which causesdiabetic retinopathy (DR) and macular edema. Proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME)is one among the leading causes of blindness in the world. DME represents a significant burdenwith increased incidence of DM and in the Indian subcontinent limited public health resources contributes for higher prevalence of DR and DME. Early detection and timely treatment of DMEis the key to prevent severe visual function loss from DR. Careful longterm follow-up and comprehensive DM care is needed to prevent the recurrence of DME, which mainly depends on the type of maculopathy.

Objective: To study the different patterns of diabetic maculopathy presentation in non-proliferative diabetic retinopathy patients

Material & Methods: This prospectivecross sectional observational study was conducted at tertiary care teaching hospital of Uttar Pradesh. After taking approval from institutional ethical committee 50 cases (100 eyes) who gave written consent were enrolled for the study. Detailed history of diabetes in terms of time of onset, duration and drug schedule was obtained. Demographic profile was recorded on predesigned Performa and visual acuity using Snellen's chart was done in all cases. Detailed anterior segment examination was done with slit lamp and fundus fluorescein angiography (FFA) was performed by injecting 10% fluorescein dye. Different types of macular edema or maculopathy were recognized with the analysis of the readings of FFA. Statistical analysis was done by using SPSS Version 20 and iindependent sample t-test/ one-wayANOVA analysis and Paired t- test were used to assess statistical significance. P values of <0.05 were considered statistically significant.

Results: Highest number of eyes (47%) had focal maculopathy followed by diffuse maculopathy with 33% and only $1/5^{th}$ of eyes had ischemic type of maculopathy. at the time of presentation 69 eyes had visual acuity better than 6/60, out of them 42 eyes had focal type of maculopathy.31 eyes had visual acuity less than 6/60, wherein 17 eyes had diffuse maculopathy and 10 eyes had ischemic maculopathy.More than ½ (54%) eyes developed

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diabetic maculopathy in less than 10 years of duration; however, 8% eyes had history of more than 21 years' duration.Hard exudate was present in 56% cases having total cholesterol levels of >180 in only 10% of such cases levels were <148 (normal value).Similarly, hard exudates were seen in 52% cases having high levels of LDL cholesterol (>114) and 56% cases having abnormal ratio of total: HDL cholesterol (>3.778).Only 10% cases with normal LDL cholesterol (<86) levels and 4% cases with total: HDL cholesterol ratio (<2.803), has hard exudates in their fundus.

Conclusions: Diabetic maculopathy specifically diffuse or ischemic are the commonest causes of visual loss in cases having diabetic retinopathy. Hard exudates were most abundant in cases having high levels of total cholesterol >186, LDL cholesterol >114 and a ratio of total: HDL cholesterol >3.778. Periodic follow up and ocular examination is necessary in all diabetics to detect the involvement of macular at an earlier stage.

Keywords: Diabetic maculopathy, Diabetic macular edema, Diabetic Retinopathy,Fundus Fluorescein Angiography,Hard Exudates

INTRODUCTION

Diabetes mellitus (DM) is one among the major global medical problems. The deleterious effects of DM on eyes, kidneys, heart and nervous system results in diabetic retinopathy, nephropathy,cardiomyopathy and neuropathy;respectively, due to the pathological changes of the microangiopathy. [1]Eyes are one of the utmost commonly involved organs in patients with diabetes mellitus. As the diabetic population in India is increasing day by day, it is common to see many diabetic patients presenting with a variety of ocular complications. All the parts of the eye are susceptible to the deleterious effects of this disease of glucose metabolism. [2]

The various ocular lesions in patients with diabetes mellitus are

- ***Eyelids and Lacrimal system:*** Increased occurrence of hordeolum externum, chalazion, xanthomas and xanthalesmas.There is decreased tear production in type 2 diabetics
- ***Cornea:***Decreased corneal sensitivity and increased occurrence of persistent epithelial defects were seen in diabetic patients.
- ***Glaucoma:*** Various studies had shown that the average IOP among diabetic patients is 1 to 1.5 mm higher than that of the average of the general population. Several studies have also shown the higher incidence of primary open angle glaucoma in diabetic patients;whereas some studies have shown the incidence to be the same as in the general population.
- ***Iris and Lens:*** Formation of iris neovascularization and 2 to 4 time's greater risk of cataract formation is present in diabetics than in non- diabetics. Senile cataract occurs at an earlier age in diabetics. True diabetic cataract occurs commonly in uncontrolled diabetes in juveniles and has been described as snow flake cataract.
- ***Retina and Optic nerve:*** Retina involve in the form of diabetic retinopathy varying from non- proliferative to proliferative diabetic retinopathy.Optic neuropathy described as diabetic papillopathy and increased incidence of non-arteritic ischemic optic neuropathy was seen in diabetic patients.

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- ***Extra ocular muscles and cranial nerves:*** Usually 3rd,4th and 6th nerve palsies occur in patients with uncontrolled diabetes.
- ***Refraction:*** Transient changes in refractive errors are common in type 2 diabetics.

Significant loss of visual function represents the most feared complications among diabetic patients, however several complications can be prevented once diagnosed in early stages.Diabetic Retinopathy (DR)pathophysiology includes the microangiopathy, which mainly affects the retinal precapillary arterioles, capillaries, and venules.Diabetic retinopathy (DR) in the form of proliferative diabetic retinopathy (PDR) and macular edema is one of the common causes of blindness in the world.[3]In the diabetic retinopathy cases macular edema is the leading cause of moderate reversible visual loss.Diabetic macular edema (DME) represents a significant burdenwith increased incidence of diabetes in the Indian subcontinent. Availability of the limited public health resources in India further contribute to the higher prevalence of DME. [4]

Severe visual function loss from diabetic retinopathy can be prevented by early detection and proper treatment of DME.Tight glycemic control and stricter control of hypertension had shown a clear effect on the development of micro vascular complications of diabetes such as PDR and macular edema. Most widely acceptedtreatment options for severe non-proliferate and proliferate from of Diabetic Retinopathy with DME were limited to pan retinal laser photocoagulation and vitrectomy.[5] In recent years the use of intravitreal injections of anti-vascular endothelial growth factors (anti VEGF) like Bevacizumab and Ranicizumab were considered for the treatment of DME, with encouraging results.[6] These treatment modalities can prevent significant visual function loss in cases of advance DR with DME.Careful longterm follow-up and comprehensive diabetes mellitus care firmly based on clinical evidence is needed to prevent the recurrence of DME, which mainly depends on the type of maculopathy. Older and newer pathogenesis based approaches to medical treatment are currently under evaluation by randomized controlled clinical studies but the results are still inconclusive.

With this background the present study was done to analyze the pattern of diabetic maculopathy in non-proliferative diabetic retinopathy cases presented in OPD of a tertiary care teaching hospital.

OBJECTIVE

To study the different patterns of diabetic maculopathy presentation in non-proliferative diabetic retinopathy patients

MATERIAL & METHODS

This prospective cross sectionalhospital based observational study was conducted at department of ophthalmology during Nov. 2021 - April 2022 in a tertiary care teaching hospital of North India. Approval for the study was obtained from the ethical committee of the institute. Sample size was calculatedusing formula $n = Z^2X\ pq\ /\ d^2$, where, at the confidence interval of 95%Z = 1.96, prevalence (p) of 40%, absolute precision (d) of 9,6% and q = 1- p the sample size (n) calculated was 100. Totally 50 cases(100 eyes) diagnosed as non-proliferative diabetic retinopathy with maculopathy and gave their written consent for this study were included. The patient'sdiagnosed with diabetic retinopathy without

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maculopathy or proliferative diabetic retinopathy orcentral retinal vein occlusion orhypertensive retinopathy (III & IV) were excluded from the study.

Demographic profile including age, sex and residential details were documented along with therelevant history of time of onset of diabetes, duration of diabetes, family history, drug schedule and dietary habits. Visual acuity using Snellen's visual acuity was recorded and detailed anterior segment examination using slit lamp was done in all the enrolled cases. Dilated fundus examination was done with direct and indirect ophthalmoscope and the diagnosis of non-proliferative diabetic retinopathy was established.

Fundus fluorescein angiography (FFA) using Zeiss FF450 plus fundus camera was performed by injecting 10% fluorescein dye in peripheral vein through the scalp vein set. Details of the FFA were recorded and saved to evaluate the status of macular edema and leakage. Different types of macular edema or maculopathy were recognized with the analysis of the readings of FFA. The findings of maculopathy were typed as focal, diffuse and ischemic on the basis of pattern of hyper fluorescein seen on FFA.

Urine sugar and albumin levels, random blood sugar levels and lipid profile investigations were donein all the study participants before performing the FFA.

Statistical Analysis

The data was collected, compiled and compared statistically by frequency distribution and percentage proportion. Quantitative data variables were expressed by using descriptive statistics (Mean ± SD). Qualitative data variables were expressed by using frequency and percentage (%). P values of <0.05 were considered statistically significant. Data analysis was performed by using SPSS Version 20. Independent sample t-test/ one-wayANOVA analysis and Paired t- test were used to assess statistical significance.

OBSERVATIONS & RESULTS

Table 1 shows the demographic profile of our study cases. Total numbers of cases in our study were 50 comprising 31 males and 19 females, with the sex ratio of M: F of 1.63:1.Nearly 2/3rd (66%) cases were above 50 years of age and only 7cases (14%) had maculopathy in juvenile onset diabetes mellitus.The mean age±SD of male cases was 53.451±14.01years and female cases was 57.842±8.08 years with an overall mean± SD of 55.2±12.2 years.

Table 1: Demographic profile of study cases

Variable	Subcategory	Number of cases (n = 50)		
Gender		**Male n (%)**	**Female n (%)**	**Total n (%)**
		31 (62%)	19 (38%)	50 (100%)
Age groups (years)				
	21-30	3 (6%)	-	3 (6%)
	31- 40	3 (6%)	1 (2%)	4 (8%)
	41 – 50	7 (14%)	3 (6%)	10 (20%)
	51 – 60	9 (18%)	8 (16%)	17 (34%)
	> 61	9 (18%)	7 (14%)	16 (32%)
Mean age ± SD (years)		**53.451±14.01**	**57.842±8.08**	**55.12±12.2**

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Table 2 shows the relationship between the duration of diabetes and various types of maculopathy in our study cases. More than ½ (54%) eyes developed diabetic maculopathy in less than 10 years of duration; however, 8% eyes had history of more than 21 years duration. Out of 54% eyes with history of less than 10 years' duration, 38 eyes had focal maculopathy and only 4 eyes had ischemic maculopathy. Between 11 and 20 years' duration history highest 19 eyes had diffuse maculopathy followed by 11 eyes with ischemic maculopathy and least 8 eyes with focal maculopathy were seen. Among ischemic maculopathy eyes (20) 80% eyes had history of diabetes more than 10 years' duration and among focal maculopathy eyes (47) only 20% eyes had similar duration history.

Table 2: Distribution of different types of maculopathy with duration of diabetes

Duration of diabetes (years)	Focal maculopathy n = 47 (%)		Diffuse maculopathy n = 33 (%)		Ischemic maculopathy n = 20 (%)		Total n = 100 (%)	
<1	4	8.51%	2	6.06%	-	-	6	6%
2-5	12	25.53%	4	12.12%	2	10%	18	18%
6-10	22	46.8%	6	18.18%	2	10%	30	30%
11-15	7	14.9%	13	39.39%	6	30%	26	26%
16-20	1	2.13%	6	18.18%	5	25%	12	12%
>21	1	2.13%	2	6.06%	5	25%	8	8%

Table 3 shows the patterns of maculopathy seen on fluorescein angiography in this study. Totally 100 eyes of 50 cases were evaluated on FFA, where highest number of eyes (47%) had focal maculopathy followed by diffuse maculopathy with 33% and only 1/5th of eyes had ischemic type of maculopathy.

Table 3: Patterns of maculopathy on FFA

Types of maculopathy	Number of eyes (n = 100)			
	Right eye	Left eye	Total	Percentage
Focal maculopathy	23	24	47	47%
Diffuse maculopathy	16	17	33	33%
Ischemic maculopathy	9	11	20	20%

Table 4 shows the distribution of different types of maculopathy with the visual acuity status at the time of presentation in 100 eyes of 50 cases. 69 eyes had visual acuity better than 6/60 at the time of presentation, out of them 42 eyes had focal type of maculopathy. 31% of eyes had visual acuity less than 6/60, wherein 17 eyes had diffuse maculopathy and 10 eyes had ischemic maculopathy; however, 4 eyes also had focal maculopathy with worst visual acuity than 6/60.

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Table 4: Visual acuity on presentation in different types of maculopathy

Visual acuity on presentation	Focal maculopathy n = 47 (%)	Diffuse maculopathy n = 33 (%)	Ischemic maculopathy n = 20 (%)	Total n = 100
6/6-6/9	11(23.4%)	-	-	11
6/12-6/18	21(44.6%)	4(12.1%)	2 (10%)	27
6/24-6/36	11 (23.4%)	12(36.3%)	8 (40%)	31
6/60-4/60	2(4.2%)	15(45.4%)	6 (30%)	23
<4/60	2 (4.2%)	2(6.06%)	4 (20%)	8

Table 5 shows the correlation of levels of total cholesterol, LDL cholesterol and ratio of total: HDL cholesterol in cases having hard exudates along with maculopathy. Total cholesterol levels of >180 was observed in 56% cases and only 10% cases had levels <148 (normal value). Similarly, the high levels of LDL cholesterol (>114) and abnormal ratio of total: HDL cholesterol (>3.778) was seen in 52% cases and 56% cases, respectively. Only 10% cases and 4% cases had normal levels of LDL cholesterol (<86) and total: HDL cholesterol ratio (<2.803), respectively.

Table 5: Distribution of cases with hard exudates in various lipids parameters

Total cholesterol			LDL cholesterol			Total / HDL cholesterol ratio		
Level	**Cases (n = 50)**	**%**	**Level**	**Cases (n = 50)**	**%**	**Level**	**Cases (n = 50)**	**%**
<148	5	10%	**<86**	5	10%	**<2.803**	2	4%
148-165	10	20%	**86-99**	7	14%	**2.804-3.283**	8	16%
166-181	7	14%	**100-114**	12	24%	**3.284-3.777**	12	24%
182-203	10	20%	**115-132**	10	20%	**3.778-4.429**	12	24%
>204	18	36%	**>133**	16	32%	**>4.429**	16	32%

DISCUSSION:

Worldwide diabetes mellitus remains the most serious challenges for the health care personnel as well as the patients.DM causes array of long term systemic complications, which have considerable impact on both the patient and the society because it typically affects individuals in their most productive years. This study included 100 eyes of 50 cases with maculopathy in Non-Proliferative Diabetic Retinopathy.

Age group and maculopathy: In our study predominant age group affected with maculopathy was 51-60 years (34%) followed by 61- 70 years (26%) and 41-50 years (20%); only 6% of 20-30 year aged had maculopathy due to its less incidence in juvenile onset diabetes mellitus. We found that in >41 years' age group 86% eyes had maculopathy; similarly the study done by Janaid S. Wani et al [(7)] 2003; on the incidence of maculopathy in non-Proliferative diabetic retinopathy, diabetic maculopathy was more prevalent in 41-75 years age group. Shetty KJ et

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al [8] (1987) also observed that the diabetic maculopathy was most prevalent in 51-60 years of age. Study conducted by Golubovic –arsovska M. et al [9] 2006 showed a correlation of diabetic maculopathy and level of diabetic retinopathy and resulted that the age group considered were 38 men from 49-73 years and 48 women at age of 51-74 years.

Gender Vs. maculopathy:The ratio of males and females in our study was 1.63:1. The predominant age group in which males and females were affected was between 51-60 years. This male predominance is correlated with, the Wisconisin epidemiological Study of diabetic retinopathy, 1984; which showed male female ratio was 1.5:1 [10]. Similarly, male predominance (Male: female-2:1) was shown in a study by Rema M et al, 1996; a study conducted in southern India [11]. In study conducted by Nanfack C et al [12] 2012 male female ratio was 1.33:1. These observations suggest that the diabetes mellitus is more prevalent in males and also the severity of disease in terms of maculopathy was more significant in male gender.

Duration of diabetes: Present study showed that 30% cases had diabetes in 6-10 years' duration, 26% of cases had diabetes in 11-15 years' duration. 24% of cases had diabetes in ≤ 5 years' duration. These findings are correlating with, the study by Zhang et al; showed that diabetic maculopathy often occurred within 10 years of diabetic duration [13]. In study by Wani JS et al; average duration of diabetes in patients with maculopathy in non-proliferative diabetic retinopathy is 14.4 years [14]. In Study by Shetty KJ et al; the duration of diabetes in patients with diabetic maculopathy ranged from 8-18 years [15].

Pattern of maculopathy: We found that the 47% cases had focal type of maculopathy, 33% cases had diffuse type of maculopathy and 20% cases had ischaemic type of maculopathy. These findings correlate with, study done by Wani JS et al; among maculopathy patients in non-proliferative diabetic retinopathy, where 62.5% of patients had focal maculopathy, 21.87% of patients had diffuse maculopathy and 15.62% of patients had ischaemic maculopathy [7]. Study done by Jian Wanchen et al. observed that out of 211 studied eyes, 126 eyes had focal edema (59.7%) and 60 eyes had diffuse edema (28.4%) [16]. In a study done by Espiritu et al. FA findings were macular staining (83.86%) and macular ischemia (10.76%); among macular staining micro aneurysms predominated over capillary leakage [17]. These finding concluded that the majority of cases with DR had focal maculopathy because the community is now well aware about the complications of diabetes and hence they present to an ophthalmologist in early stages of DR.

Visual acuity to the types of maculopathy: In our study 44.6% of eyes with focal maculopathy had visual acuity in the range of 6/12-6/18. Most of our cases with focal type of lesion had visual acuity in the range of 6/6 - 6/36. We observed that 45.6% of eyes with diffuse maculopathy had visual acuity between 6/60 - 4/60. Ourstudy showed that most of theeyes with ischaemic maculopathy had visual acuity between 6/24 - 6/60. These findings correlated withthe study done by Li-Yang L et al.who found that the loss of visual acuitywas significantly correlated with the degree of DME and the visual acuity was lower in patients with diffuse DME than those with focal DME [18]. Similarly, in study done by Zhang Huirong et al. showed that the visual acuity was worse in diffuse edema than focal edema [19]. In study by Espiritu R et al. vision was found to be marginally statistically different between normal and maculopathy group; however, the worst vision was seen in macular ischemia [17].

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Lipid profile, hard exudate and diabetic maculopathy: In our study the cases with total cholesterol levels of >204 mg/dl,36 % had hard exudates in comparison with 10% of cases with total cholesterol level <148 mg/dl. We saw hard exudates in 32% of cases with LDL cholesterol levels >133 mg/dl, in comparison with 10% of cases with LDL level <86% mg/dl. Similarly, the cases with total /HDL cholesterol ratio >4.42932% had hard exudates in comparison with 4 % of cases with ratio <2.803. This signifies that diabeticindividuals with higherlevels of total cholesterol, LDL cholesterol and more total /HDL cholesterol ratio are more prone to formation of hard exudates in their fundus. Thesefindings were correlated with, Chew EY et al, who showed that elevated serum lipid levels with an increase in cholesterol are associated with an increased risk of retinal hard exudates in persons with diabetic retinopathy [(20)]. Study by Idiculla J et al.also showed that elevated serum lipids are significantly associated with retinal hard exudates [(21)].

CONCLUSIONS:

Diabetic maculopathy is the commonest cause of visual loss in patient with diabetic retinopathy. Periodic follow up and ocular examination is necessary in all diabetics to detect the involvement of macular at an earlier stage. Early treatment with photocoagulation and anti VEGF injection can stabilize the visual acuity and also will prevent further visual loss.

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