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Study of the severity of Diabetic Retinopathy in patients with duration of Diabetes mellitus longer than 10 years – a study from a tertiary care hospital in North- India

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Abstract
Background: *Diabetic retinopathy is one of the most common complications of Diabetes Mellitus causing significant visual loss on a global scale.*
Purpose: *To evaluate the severity of Diabetic retinopathy in diabetics of duration of disease longer than 10 years.*
Materials and Methods: *This study was conducted over a period of one year from Nov. 2015 to Oct. 2016 in a tertiary care hospital of northern India, on 100 diagnosed patients of diabetes mellitus presenting to the Ophthalmology OPD. After detailed history, clinical examination and investigations, the patients were graded on basis of severity of diabetic retinopathy. The data analysis was performed using statistical software SPSS version 20. Relationship of diabetic retinopathy (dependent variable) was assessed employing univariate analysis. Chi-square test was used to assess statistical significance.*
Results: *Out of the 100 patients examined, 89 were having some form of retinopathy on presentation. The mean ages of patients with mild, moderate, severe NPDR and PDR were 54.85±10.02, 60.84±8.59, 64.77±10.97, 67.76±11.71 years respectively. The mean duration of diabetes mellitus in the study for mild, moderate, severe NPDR and PDR were 14.95±4.29, 17.76±3.89, 18.66±3.69 and 24.53±5.92 years respectively. Significant correlation were seen between severity of retinopathy and duration of DM, mean HbA1c, S.Creatinine, macroalbuminuria, anaemia and hypertension.*
Conclusion: *This study will be significant in determining risk factors for the causation of diabetic retinopathy and its progression. It will be a useful tool in identification of the modifiable risk factors which can help in prevention and progression of diabetic retinopathy.*
Keywords: *Diabetes Mellitus, Diabetic Retinopathy, severity of Diabetic Retinopathy.*

Introduction

Diabetes mellitus is a common metabolic disorder secondary to lack, diminished efficacy or both of endogenous insulin. An expert committee, in 1997 classified the disease into two distinct groups: Type 1 diabetes/IDDM (previously known as 'insulin dependent' or 'juvenile onset') which is characterized by complete or near total insulin deficiency and Type 2 diabetes/NIDDM (non-insulin dependent, adult onset) characterized by

insulin resistance in peripheral tissues and an insulin secretory defect of the beta-cells.

Among the various manifestations of DM, diabetic retinopathy is the most common cause of legal blindness between ages of 20 and 65 years (Bhavsar AR, 2002). Diabetic Retinopathy is a microangiopathy exhibiting features of both microvascular occlusion and leakage and is the most frequent and potentially blinding ocular manifestation of DM. Other important ophthalmic complications of diabetes include corneal abnormalities, glaucoma, neovascularisation of iris, cataract and optic nerve abnormalities. Involvement of macula by oedema, hard exudates or ischaemia known as diabetic maculopathy is the most common cause of visual impairment in diabetics.

Patients with diabetic retinopathy are 25 times more likely to become blind than non-diabetics (New York National Society to Prevent Blindness 1980). Approximately 25% of all diabetics have some form of retinopathy. The incidence and severity increase consistently over duration of diabetes so that more than 90% diabetics develop retinopathy at some time during their lives.

Prevalence Of Diabetic Retinopathy

The main determinants in the prevalence of diabetic retinopathy are the duration of the disease, the age of onset of disease and type of diabetes. As per WESDR (1991) at 20 years of duration of diabetes mellitus about 99% with type 1 and 60% with type 2 have some retinopathy:

Type 1 DM:

- No clinically apparent retinopathy in first 5 years
- 5 to 10 years->25 to 30% have some retinopathy
- 10 to 15 years->75% to 95% have some retinopathy
- 20 to 25 years-> 18% have PDR

Type 2 DM-NPDR:

- 23% - 11 to 13 years
- 43% -14 to 16 years
- 60% -16 years

PDR: 3%- 11 years (Yanko L, Goldbourt U et al. 1983)

Ref: (Klien R, Klien BEK, Moss SE et al. The WESDR study of DR 1984)

Severity grading of Diabetic Retinopathy is based on ophthalmoscopically visible signs of increasing severity, ranked into a stepwise scale from no retinopathy through various stages of non-proliferative or pre-proliferative disease to advanced proliferative disease. However, this may not accurately reflect functionally severe disease since maculopathy with severe visual loss may occur in the presence of moderate ophthalmoscopic signs. The two basic mechanisms leading to loss of vision are: retinopathy (risk of new vessels) and maculopathy (risk of damage to the central fovea). Diabetic Retinopathy is classified according to the presence or absence of abnormal new vessels as:

1. Non-proliferative (background/pre-proliferative) retinopathy
2. Proliferative Retinopathy

The ETDRS (1991) has classified Diabetic Retinopathy into:

A. Non Proliferative Diabetic Retinopathy

The retinal microvascular changes are limited to the confines of retina and do not extend beyond the internal limiting membrane,can be further classified as:

a. Mild NPDR: retinal microaneurysms in atleast one quadrant and at least one or more of retinal haemorrhage, hard exudates or soft exudates.

b. Moderate NPDR: haemorrhages or micro aneurysms or both in at least one quadrant and one or more of soft exudates, venous beading or IRMA

c. Severe NPDR: As defined by ETDRS in the 4-2-1 rule, presence of any one of diffuse intra-retinal haemorrhages or micro-aneursyms in four quadrants, venous beading in two quadrants and intra-retinal microvascular abnormalities in one quadrant.

d. Very severe NPDR: presence of any two of the features described above. It has 45% chance of progression to high risk PDR within a year.

B. Proliferative Diabetic Retinopathy

Characterized by presence of newly formed vessels and or fibrous bands, arising from the retina or the optic disc and extending along the inner surface or into the vitreous cavity. PDR is further described as early, high risk and advanced.

a. Early PDR: characterized by presence of newly formed blood vessels from the optic disc (NVD) or elsewhere (NVE), or vitreous/pre-retinal haemorrhages and NVE<1/2 disc area.

b. High Risk PDR: characterized by presence of one or more of:

1. NVD of 1/4 to1/3 or more of the disc area
2. Any NVD with vitreous/preretinal haemorrhage
3. NVE > than 1/2 disc area with vitreous or pre-retinal haemorrhage

c. Advanced PDR: High risk PDR, tractional RD involving the macula or vitreous haemorrhage obscuring the ability to grade NVD/NVE are characteristics of advanced PDR.

Clinically Significant Macular Edema (any one of the following):

1. Thickening of the retina located 500µm or less from centre of the macula
2. Hard exudates at 500µm or less from the centre of the macula with thickening of adjacent retina
3. Zone of retinal thickening, 1 disc area or larger in size, any portion of which is within on1 disc diameter or less from the centre of the macula

The worldwide prevalence of Diabetes Mellitus has risen dramatically over the past three decades, from an estimated 30 million cases in 1985 to 382 million in 2013; which will increase to 592 million by 2035. 175 million people with diabetes are undiagnosed (IDF, 2013). The Asian countries are presumed to have more than half of the world's diabetic population. The International Diabetes Federation (IDF, 2013) has projected that the no. of diabetics in India would rise from 65.1 million in 2013 to 109 million in 2035. WHO also estimates that DR is responsible for 4.8% of the 37 million cases of blindness throughout the World.

If detected early, blindness from diabetic retinopathy is a preventable complication of diabetes. Health care professionals providing primary care should have complete knowledge about the disease and the associated factors in order to guide the patients from the time of initial diagnosis, so that the modifiable risk factors can be avoided or controlled. Even if it develops, early detection and timely management can be done.

Materials and Methods

This study was conducted over a period of one year (November 2015 to October 2016) and 100 diagnosed cases of diabetes mellitus with duration of diabetes >10 years attending the OPD or referred from other specialties for ocular examination at the Upgraded Department of Ophthalmology, Govt. Medical College Jammu were selected at random and enrolled in the study. The cases were non selective with regards to age, sex, ethnic origin and occupation.

Inclusion Criteria: Patients with both type 1 and type 2 diabetes mellitus of either sex, who were willing to participate and had duration of diabetes mellitus greater than 10 years

Exclusion Criteria: Patients with duration of disease < 10 years, Patients with hazy media or in whom dilatation of pupils was contraindicated such as angle closure glaucoma, Patients on lipid lowering drugs or using drugs significantly affecting glucose metabolism (glucocorticoids, oral contraceptives etc., Patients who had received treatment for the retinopathy such as photocoagulation or anti VEGF agents.

A detailed history of each patient was obtained regarding age, year of diagnosis of diabetes,and duration of diabetes, family history, smoking, alcohol intake, hypertension or any associated illness.

Ocular Examination: UCVA and BCVA for both eyes along with slit lamp examination to visualize the anterior segment of both the eyes were done. IOP and gonioscopy were documented in both eyes. Fundus examination of both eyes was done and any changes attributable to diabetes were documented. Fundus photography and Fluorescin angiography was done where required.

The fundus findings were graded as: G0-No signs of retinopathy, G1-Mild non proliferative diabetic retinopathy, G2-Moderate non proliferative diabetic retinopathy, G3-Severe to very severe non proliferative diabetic retinopathy,G4-Proliferative diabetic retinopathy.

Biochemical Investigations: Hemoglobin was estimated using Cyanmethemoglobin method, Blood sugar (F) was estimated using Hexokinase/G6PDH enzymatic method(abnormal blood glucose fasting level :≥ 126 mg/dl,as per ADA 2014 guidelines), Serum creatinine was estimated using Kinetic Alkaline Picrate method (Normal range:- Males- 0.6-1.2 mg/dl and Females- 0.5-1.1 mg/dl, Pagana KD and Pagana TJ, 2010),Total Serum Cholesterol was estimated by enzymatic principle(Desirable < 200 mg/dl, as per NCEP 2001 guidelines),HbA1c estimated by enzymatic method. Serum magnesium levels were estimated by enzymatic method (Normal range:- 1.6-2.4 mg/dl), Urine for microalbuminuria and macroalbuminuria by Dirui H 11/MA urine reagent test strips. All these tests were done on Abbott Architect Systems automatic analyzer.

Statistical Analysis

The analysis was performed using statistical software SPSS version 20. Relationship of diabetic retinopathy (dependent variable) was assessed employing univariate analysis. Chi-square test was used to assess statistical significance. Crude Odd's ratio with 95 % CI was calculated to report strength of association.p value of <0.05 was considered as statistically significant. In addition, ANOVA was used to analyze the difference among means of variables for different grades of diabetic retinopathy.

Results

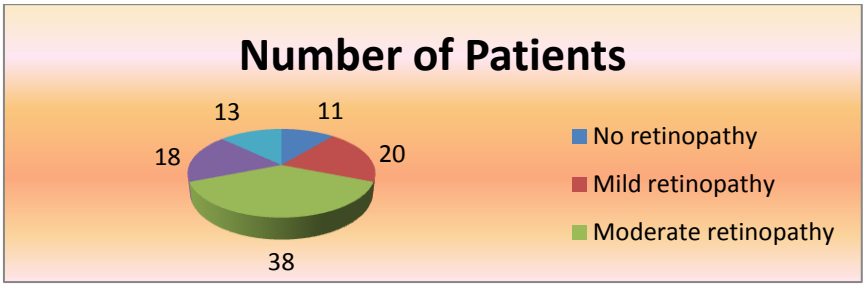

Fig.1: Distribution of diabetic patients according to the grade of diabetic retinopathy

Table 1: Distribution of diabetic subjects according to age and sex

Age (in years)	Males		Females		Total no. of patients	
	No.	%	No.	%	No.	%
≤20	0	0	0	0	0	0
21-30	0	0	1	2.38	1	1
31-40	2	3.45	1	2.38	3	3
41-50	14	24.14	9	21.43	23	23
51-60	19	32.76	13	29.54	32	32
61-70	16	27.59	12	28.57	28	28
≥71	7	12.07	6	14.29	13	13
Total	58	100	42	100	100	100
Mean ±SD	60.96±10.534					

Table 2: Distribution of subjects with different grades of diabetic retinopathy according to the duration of diabetes

Duration of diabetes (in years)	Mild NPDR		Moderate NPDR		Severe to very severe NPDR		PDR	
	No.	%	No.	%	No.	%	No.	%
10-15	13	65.00	9	23.68	4	22.22	2	15.38
16-20	4	20.00	21	55.26	9	50	1	7.69
21-25	3	15.00	7	18.42	5	27.77	5	38.46
26-30	-	-	1	2.63	-		3	23.08
≥31	-	-	-	-	-		2	15.38
Total	20	100	38	100	18	100	13	100
Mean±SD	14.95±4.29		17.76±3.89		18.66±3.69		24.53±+5.92	

χ^2=43.78
P<0.00001

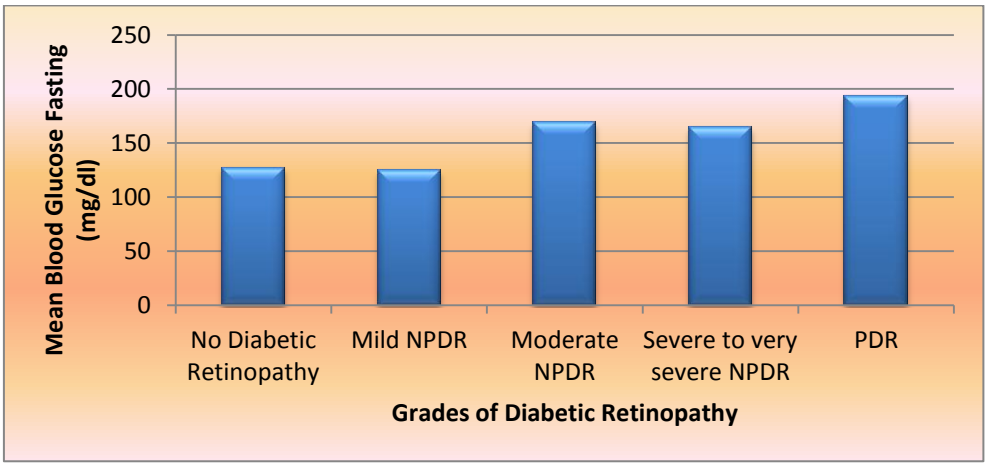

Fig.2: Mean blood glucose fasting level in different grades of diabetic retinopathy

Table 3: Distribution of subjects with different grades of diabetic retinopathy according to the level of glycosylated haemoglobin (HbA1c)

HbA1c (%)	Mild NPDR		Moderate NPDR		Severe to very severe NPDR		PDR	
	No.	%	No.	%	No.	%	No.	%
≤7	9	45.00	14	36.84	2	11.11	1	7.69
≥7	11	55	24	63.16	16	88.89	12	92.31
Total	20	100	38	100	18	100	13	100
Mean ±SD	7.07±0.58		7.62±0.85		8.32±0.92		9.08±0.94	

χ^2=9.2444
p=0.0262, significant

Table 4: Distribution of diabetic subjects according to presence of associated hypertension

Associated Hypertension	Retinopathy				Crude Odd's Ratio	95% Confidence Interval
	Absent		Present			
	No.	%	No.	%		
Absent	7	63.64	28	31.46	1.0(Ref)	
Present	4	36.36	61	68.54	3.81	1.03-14.09
Total	11	100	89	100		

χ^2=4.455
p=0.034

Table 5: Distribution of subjects with different grades of diabetic retinopathy according to the total serum cholesterol level

Total Serum Cholesterol (mg/dl)	Mild NPDR		Moderate NPDR		Severe to very severe NPDR		PDR	
	No.	%	No.	%	No.	%	No.	%
≤200	15	75	21	55.26	7	38.89	4	30.77
>200	5	25	17	44.76	11	61.11	9	69.23
Total	20	100	38	100	18	100	13	100
Mean±SD=	190.65±26.85		194.71±26.47		199.66±28.64		211.92±29.10	

χ^2=7.9777
p=0.0464

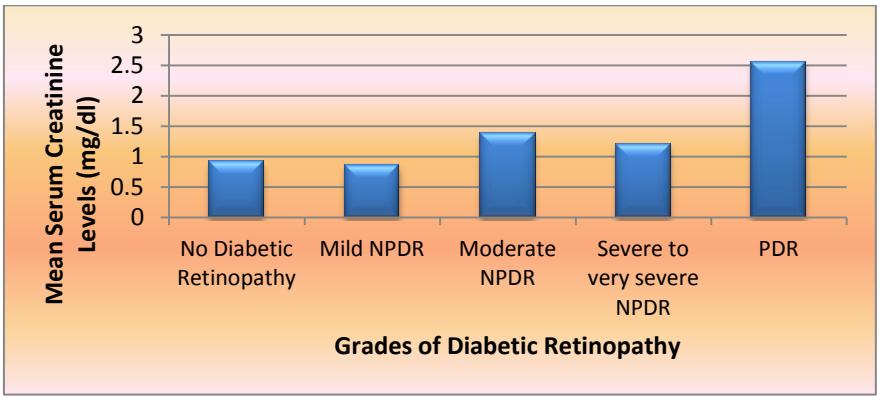

Fig.3: Mean Serum creatinine levels for different grades of diabetic retinopathy

Table 6 Distribution of subjects with different grades of diabetic retinopathy according to the serum creatinine levels

Serum Creatinine Levels	Mild NPDR		Moderate NPDR		Severe to very severe NPDR		PDR	
	No.	%	No.	%	No.	%	No.	%
Normal	16	80	26	68.42	6	33.33	1	7.69
Deranged	4	20	12	31.58	12	66.67	12	92.31
Total	20	100	38	100	18	100	13	100
Mean ±SD	0.86±0.25		1.39±0.98		1.20±0.37		2.56±0.98	

χ^2=22.99
p=0.00004057

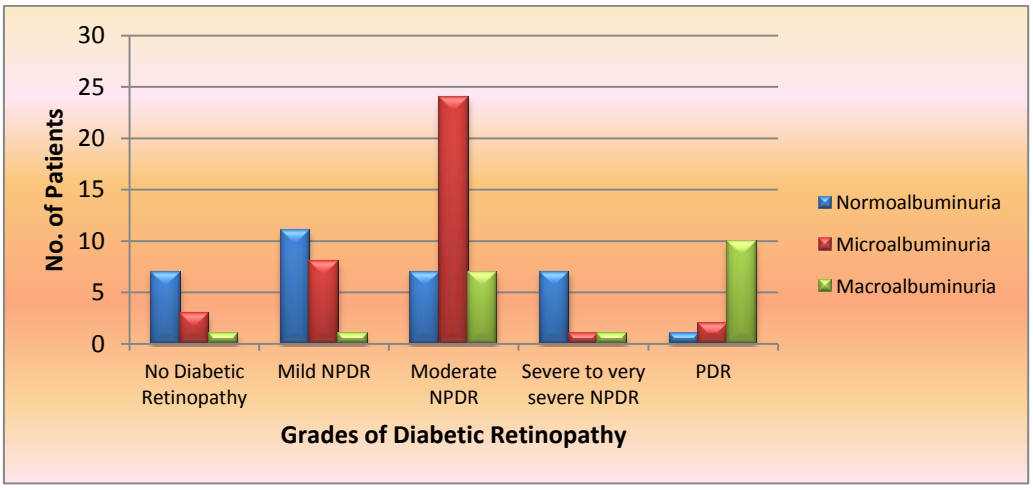

Fig.4: Type of proteinuria in different grades of Diabetic Retinopathy

Table 7: Distribution of subjects with different grades of diabetic retinopathy according to type of albuminuria

Albnuminuria	Mild NPDR		Moderate NPDR		Severe to very severe NPDR		PDR	
	No.	%	No.	%	No.	%	No.	%
Normoalbuminuria	11	55	7	18.42	7	38.99	1	7.692
Microalbuminuria	8	40	24	63.16	1	5.55	2	15.38
Macroalbuminuria	1	5	7	18.42	1	55.55	10	76.92
Total	20	100	38	100	18	100	13	100

χ^2=39.68

p=0.000000527

Discussion

The prevalence of diabetic retinopathy in the present study was 89%, with mild NPDR in 20% cases, moderate NPDR in 38% cases, severe to very severe NPDR in 18% cases and PDR in 13% cases. Kim et al. in their study found that the mean duration of diabetes in subjects with retinopathy was 11.0±0.3 years. Kaur P et al. found that 43.5% diabetic patients were having retinopathy with 16.5% having mild,9% moderate, 8.5% severe,4.5% very severe NPDR and 5% PDR. The probable reason for higher prevalence of diabetic retinopathy in our study could be that our study included only the patients with diagnosed diabetes mellitus of duration more than 10 years.

In our study 51 patients with diabetic retinopathy were males and 38 were females.74.15 % patients with diabetic retinopathy were in the age group > 50 years. The mean ages of patients with mild, moderate, severe NPDR and PDR as studied by Kaur P et al. was 60.17±11.16, 62.65±12.16, 63.70±13.33, 64.56±9.46 years respectively.

51% patients with diabetic retinopathy were males and 38% were females but association of severity of retinopathy with gender wasn't found significant (p=0.178). In studies conducted by Kaur P et al. and Venkatesh P et al. male preponderance was present in all grades of diabetic retinopathy.

In our study the presence and severity of diabetic retinopathy were significantly associated with duration of diabetes p<0.00001. Wong TY et al. with p<0.001, Kaur P et al. with p<0.001 and Raman R et al. with p<0.0001, reported similar significant association of severity of diabetic retinopathy with duration of diabetes mellitus. The mean duration of diabetes mellitus in our study for mild, moderate, severe NPDR and PDR were 14.95±4.29, 17.76±3.89, 18.66±3.69, 24.53±5.92 years respectively (p<0.00001).

Type 2 diabetics were found to be at a higher risk for developing retinopathy (p<0.05), but no significant association was found between severity of retinopathy and type of diabetes (p=0.793) in concordance with Venkatesh P et al.

Our study found out a significant relation between severity of diabetic retinopathy and treatment with Insulin (p<0.01). Similar findings were reported by Venkatesh P et al. and Raman R et al.

No significant association was found between fasting blood glucose levels with presence of retinopathy (p=0.351) or its severity (p=0.059) in our study. Zhang H et al. and Yue S et al. reported similar results. Blood glucose fasting levels indicate immediate control and not the long term control, this could be the reason for the association not being significant. But an increasing trend of mean fasting blood glucose levels in the our study was noted with increasing severity of retinopathy as in 124.45±31.03, 168.79±61.49, 164.67±57.90, 193.85±93.18 mg/dl in mild, moderate, severe NPDR and PDR respectively.

As per our study patients with HbA1c levels >7% were at 2.91 times higher risk of developing

diabetic retinopathy as compared to patients with levels within normal range. The association of severity of diabetic retinopathy with raised HbA1c levels was also found to be significant ($p<0.05$). These findings correlate well with studies conducted by Raman R et al. and Yue S et al.

Jindal K et al., Kaur P et al. and Yue S et al. found that mean HbA1c values increased proportionately with severity of diabetic retinopathy correlating well with our study.

As per our study diabetics with hypertension were at higher risk of developing retinopathy ($P<0.05$). Though the percentage of patients with hypertension increased with mild NPDR to severe NPDR except PDR, the association of hypertension with severity wasn't significant ($p=0.084$). Jindal K et al. and Venkatesh P et al. reported similar findings.

Kaur P et al. reported increase in mean cholesterol level with severity of diabetic retinopathy ($p<0.001$). Our study showed similar results as mean cholesterol levels of 190.65±26.85, 194.71±26.47, 199.66±28.64 and 211.92±29.10 mg/dl with mild, moderate, severe NPDR and PDR respectively($p<0.05$). Looker HC et al. and Zhang H et al. found that the risk of developing retinopathy was 1.32 and 1.14 times more with deranged cholesterol levels. In our study patients with serum cholesterol levels >200 mg/dl were at 1.30 times higher risk of developing retinopathy.

Patients with deranged creatinine levels were at 2.18 times higher risk of developing retinopathy than those with normal levels. The percentage of patients with deranged Serum creatinine levels increased significantly from mild NPDR to PDR group ($p<0.0001$), similar to Niveditha H et al. and Venkatesh P et al.

In our study patients with microalbuminuria were at 3.14 times more risk of developing retinopathy and those with macrolbuminuria were at 7.54 times more risk than patients with normoalbuminuria. Highly significant association was found between increasing severity of retinopathy and macroalbuminuria ($p<0.00001$). Rani PK et al. and Havange et al. reported similar associations.

Our study found that Diabetics with anaemia were at 1.94 times higher risk of developing retinopathy than those with normal Hb levels, but no statistically significant association was seen between development of retinopathy and anaemia ($p=0.298$) which in accordance with Corrêa ZMS et al. and Mohan VK et al. Anaemia was also found to have significant association with severe forms of retinopathy ($p<0.01$).

Our study showed hypomagnesaemia as a risk factor in development of retinopathy, but no association of it with severity of retinopathy was found ($p=0.374$). Patients with BMI $\geq$25 kg/m^2 were found to be at 1.29 times higher risk ,though no association between BMI and severity of retinopathy was found ($p=0.323$), correlating with Agroiya P et al. and Jindal K et al.

Conclusion

To conclude our present study will be significant in determining risk factors for the causation of diabetic retinopathy and most importantly its progression. It will be a useful tool in identification of the modifiable risk factors which can help in prevention and progression of diabetic retinopathy.

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Conflicts of interest: none declared

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