

Association of Use of Statins with Progression of Diabetic Retinopathy at a Tertiary Care Hospital in Southern India

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Abstract

Purpose: To study the role of statin therapy on diabetic retinopathy (DR) progression.

Methods: This retrospective study was carried out at a tertiary care hospital in southern India. Data were collected from the medical records of patients admitted from January 2013 to December 2018. Out of 1673 patients of DR enrolled in the study, 171 met the inclusion criteria. Patients' demographic data, drug history, clinical characteristics, and laboratory investigations were recorded as per the pro forma. The patients were divided into statin users and nonusers. The results were analyzed to compare the DR progression between the two groups.

Results: DR progressed in 67% of nonstatin users and 37% of statin users ($P < 0.001$). The use of statins decreased the risk of DR progression ($P < 0.001$). Center-involving macular edema was seen in 8 of 79 statin users (10%) and 16 of 92 statin nonusers (16%) based on optical coherence tomography findings during the follow-up period ($P = 0.17$).

Conclusion: In patients with type 2 diabetes, lipid-lowering therapy with statins has the potential to retard DR progression.

Keywords: Diabetes, Diabetic retinopathy, Dyslipidemia, Statins

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INTRODUCTION

India is one of the major contributors to the increasing global burden of diabetes,¹ and the number is expected to rise to 109 million in 2035.² An increase in early-onset diabetes along with uncontrolled hyperglycemia has raised the burden of various diabetic complications due to longer life spans.³ The microvascular complications associated with diabetes include neuropathy, retinopathy, and nephropathy, in addition to diabetic foot and cardiovascular disease. These complications are induced by chronic hyperglycemia, impaired lipid metabolism, and imbalance between the antioxidants and production of reactive oxygen species (ROS).⁴ Elevated

levels of ROS lead to DNA injury in retinal cells secondary to lipid peroxidation, thus leading to diabetic retinopathy (DR).⁵

DR is a neurovascular complication of diabetes. Its prevalence correlates with the duration of the disease and the level of glycemic control. The manifestations of DR result from microangiopathy, leading to retinal ischemia, development of new vessels, and an increase in retinal permeability.⁶ DR is currently the 6th most common cause of loss of eyesight in the country.⁷ Multiple risk factors are implicated in the development of DR.

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The treatment recommendations for DR include laser photocoagulation, which reduces the risk of vision loss and intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) for diabetic macular edema (DME).^{8,9} Deranged serum lipids have a role in the pathophysiology of DR,¹⁰ and lipid-lowering medications can reduce the overall DR risk. Most of the studies done to evaluate the role of serum lipids in DR progression are cross-sectional in nature and give minimal scope to confirm the causal relationship between the two. A cross-sectional study in Denmark showed a lower incidence of DR and neuropathy in patients on statins before diabetes diagnosis.¹¹ However, a study involving 11,247 adults in Australia did not show any significant association between serum lipid levels and DR.¹² Given the conflicting information on lipid-lowering therapies and DR progression from various studies and the susceptibility of Indians to diabetes, the present study was carried out to explore the association of statin therapy on DR progression in patients with Type 2 diabetes mellitus (T2DM). The study also aimed at exploring the effects of dyslipidemia and other risk factors on DR progression.

METHODS

This retrospective hospital-based study commenced after approval from the Institutional Ethics Committee, Kasturba Medical College, Manipal (ECR/146/Inst/KA/2013/RR-16), and complied with the Declaration of Helsinki. In this study, medical records of 1673 patients diagnosed with DR and Type 2 diabetes from January 2013 to December 2018 were reviewed. Patients of either gender, between the age of 18 and 80 years, and with DR and Type 2 diabetes were included in the study. Patients were excluded if they had follow-up of <1 year or were diagnosed with proliferative DR (PDR) at baseline or had been treated with laser photocoagulation or vitrectomy or had center-involving macular edema on presentation. Patients with other retinal diseases (hypertensive retinopathy, retinal vascular occlusion, retinal detachment, retinal tear, etc.), use of lipid-lowering agents other than statins (such as fenofibrate, niacin, or fish oil), statin compliance < 80%, and those whose records were incomplete were excluded.

On the basis of statin exposure, patients were grouped into statin users (exposed) and statin nonusers (unexposed). Statin exposure is defined as a regular intake of statin for a period of not <3 months. The severity of DR was graded as per the modified Early Treatment Diabetic Retinopathy Study (ETDRS) grading, considered a “gold standard” for grading the severity of the disease.⁹ The grading of DR was done by three consultants (K.R., S.V.B., and S.B.S.) who have an experience in retina service for more than 10 years. The grading was based on clinical judgment. Non-PDR (NPDR) as per ETDRS is classified into mild, moderate, or severe, depending on the presence of microaneurysms, hemorrhages, soft exudates, and venous bleeding.¹³ As per the medical records, the retinopathy grading was noted, and in case of variation in the grading of retinopathy between two eyes, the

higher grade of retinopathy was considered. Macular edema was assessed using a spectral-domain optical coherence tomography (OCT) images (Cirrus HD-OCT 4000 [Carl Zeiss Meditec, Inc., Dublin, USA]). The macular edema was classified as center-involving and noncenter-involving macular edema based on the OCT findings. The primary outcome measure was the progression of DR by two or more steps at 12 months.¹⁴ The two-step progression was considered only for NPDR and conversion to PDR (although one-step very-severe NPDR to PDR) was considered progression. Zero or one-step progression in NPDR was considered nonprogression.

The patients' data consisting of demographic characteristics, diabetic and drug history, clinical characteristics, serum lipid profile, serum glucose levels, liver function tests, and renal function tests were recorded at baseline, 6 months, and 12 months.

Statistical analysis

The collected data were analyzed using SPSS version 16 (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY, USA: IBM Corp.) and Numbers software (Apple v 5.1, [5683]). For baseline and demographic characteristics, descriptive analysis was used. Continuous variables were expressed as mean \pm standard deviation, and categorical variables were expressed as a number of patients and percentages (n, %). Chi-square test was carried out to find the association between statin use and progression of DR. An independent *t*-test was done to compare the continuous variables between the two groups (statin users and statin nonusers). Longitudinal data were analyzed using mixed analysis of variance. Univariate analysis followed by multivariate analysis was carried out to assess the strength of association between variables and DR progression. $P < 0.05$ was considered statistically significant. Entry criteria for variables into stepwise multivariate analysis by binary logistic regression method were $P < 0.26$, and those considered clinically relevant as per literature review were also included.

RESULTS

A total of 1673 patients with Type 2 diabetes and DR were assessed, and of these, 171 patients were enrolled for analysis, as shown in Figure 1.

Out of 171 patients, 79 (46%) patients were on statins, and 92 (54%) were not exposed to statins. The demographic and clinical characteristics of the two groups are summarized in Tables 1 and 2. Of the 79 statin users, 50 (63.29%) patients were on statins for more than 10 years. The percentage use of various statins and their doses in study population is shown in Figure 2. Following diagnosis of DR in T2DM patients, clinical parameters were recorded at various time points during follow-up [Table 3]. Total cholesterol (TC) and low-density lipoprotein (LDL) levels were significantly lower in patients on statins at both the time points ($P \leq 0.05$). In case of other parameters, no statistically significant difference was observed between the two groups.

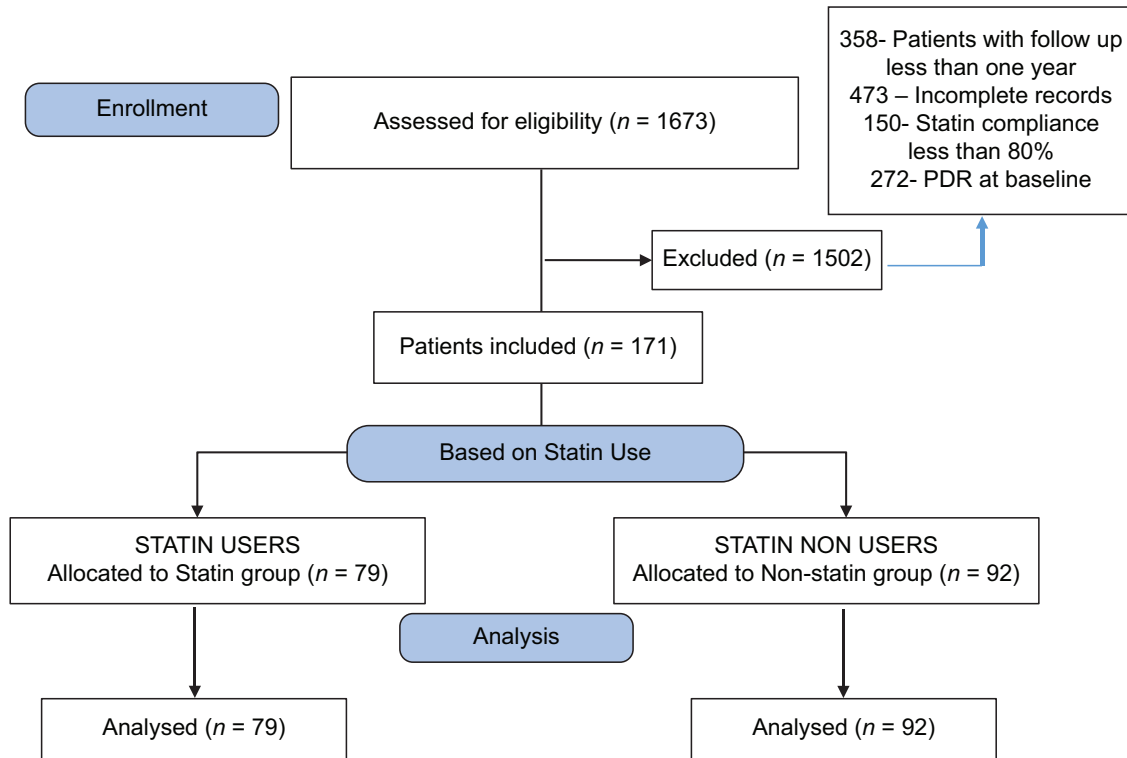


Figure 1: Patient allocation to the two groups

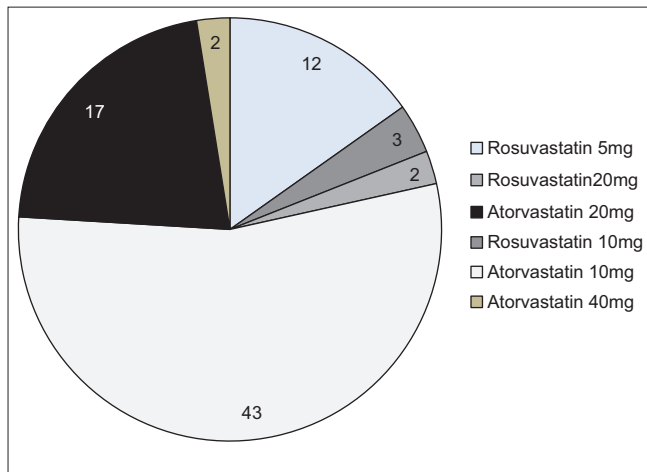


Figure 2: The percentage use of various statins and their doses in study population

Out of 171 patients, a total of 91 (53%) patients had DR progression as per ETDRS grading, whereas 80 (47%) patients did not show any progression at the end of follow-up [Table 4]. DR progressed in 67% of statin nonusers and 37% of statin users with a statistically significant difference ($P < 0.001$) at 12 months. Even though statins showed beneficial effect in DR progression, at any follow-up measurements, there was no statistically significant difference in lipid parameters or HbA1c levels between the patients whose DR progressed, and DR did not progress.

The demographic and clinical parameters between the two groups for univariate analysis are shown in

Tables 5 and 6. A significant difference was seen in duration of diabetes mellitus and presence of renal disorder between the two groups ($P < 0.26$), whereas no significant difference was seen in case of other variables. A statistically significant difference was seen in HbA1c, TC, and LDL levels between the DR progressed and DR not progressed groups [Table 6].

Binomial logistic regression analysis was carried out to evaluate factors associated with DR progression as shown in Table 7. With other variables such as renal disease, HbA1c, and lipid profile being adjusted, statin use was associated with significantly lower risk of DR progression (odds ratio [OR]: 0.25; 95% confidence interval [CI]: 0.09–0.68; $P = 0.007$). Diabetes duration of more than ten years increases the risk of DR progression (OR: 3.30; 95% CI: 1.06–10.25; $P = 0.039$). Triglyceride levels also increase the risk on DR progression (OR: 0.99; 95% CI: 0.97–0.99; $P = 0.02$)

Out of 171 patients, 24 (14%) patients had center-involving macular edema at the end of 12-month follow-up. Sixteen out of 92 patients (15%) in the nonstatin group developed center-involving macular edema as compared to 8 out of 79 patients (9%) in the statin group. The percentage of patients who developed center-involving macular edema was higher in the nonstatin group but the difference was not statistically significant ($P = 0.173$).

DISCUSSION

Dyslipidemia is one of the important risk factors in the development of DR.¹⁵ Lipid-lowering therapies are, thus, likely to prevent the progression of DR. In the present study,

Table 1: Baseline demographic characteristics of type 2 diabetes mellitus patients with diabetic retinopathy

	Nonstatin users (92)	Statin users (79)	SMD	P
Age (years) (mean±SD)	58.25±9.04	57.38±8.69	0.098	0.677 ^a
Gender (n)				
Female	30	29		0.574 ^b
Male	62	50		
Height (cm) (mean±SD)	162.09±7.17	158.57±5.28	0.565	0.250 ^a
Weight (kg) (mean±SD)	63.41±14.51	63.38±11.01	0.001	0.993 ^a
Smokers (n)	24	18		0.617 ^b
Nonsmokers (n)	68	61		
Alcoholics (n)	13	11		0.969 ^b
No alcoholics (n)	79	68		
SBP (mm Hg) (mean±SD)	140.97±19.29	136.56±20.39	0.221	0.162
DBP (mm Hg) (mean±SD)	85.76±8.64	85.41±10.72	0.035	0.818
RBS (mg/dl) (mean±SD)	259.37±138.79	265.89±127.12	0.049	0.788
FBS (mg/dl) (mean±SD)	172.76±71.70	178.47±75.11	0.077	0.645
PPBS (mg/dl) (mean±SD)	260.89±105.14	258.32±91.03	0.026	0.881
HbA1C (%) (mean±SD)	9.22±2.23	9.97±2.39	0.323	0.046 ^{a,*}
TC (mg/dl) (mean±SD)	164.63±39.59	170.84±49.79	0.136	0.388
LDL (mg/dl) (mean±SD)	98.54±34.58	98.83±40.59	0.007	0.962
HDL (mg/dl) (mean±SD)	35.12±10.92	37.45±14.58	0.182	0.257
TG (mg/dl) (mean±SD)	164.49±72.08	157.11±74.12	0.101	0.529

^aIndependent *t*-test, ^bChi-square test, **P*<0.05. SMD: Standardized mean difference, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, RBS: Routine blood sugar, FBS: Fasting blood sugar, PPBS: Postprandial blood sugar, HbA1C: Glycosylated hemoglobin, TC: Total cholesterol, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, TG: Triglyceride, SD: Standard deviation

Table 2: Baseline clinical characteristics of type 2 diabetes mellitus patients with diabetic retinopathy

Variable	Duration	Nonstatin (92)	Statin (79)	P
Diabetes duration (n) (years)	<10	45	29	0.108
	>10	47	50	
HTN (n)	No HTN	34	20	0.268
	<5 years	26	28	
	>5 years	32	30	
Dyslipidemia (n)	Yes	1	25	<0.001 ^a
	No	91	54	
Renal disorder (n)	Yes	29	19	0.278
	No	63	60	
Cardiovascular disorder (n)	Yes	5	28	<0.001 ^a
	No	87	51	
LFT (n)	Not Deranged	87	74	0.792
	Deranged	3	2	
RFT (n)	Deranged	37	24	0.204
	Not deranged	53	52	

^a*P*<0.05 (Chi-square test). HTN: Hypertension, LFT: Liver function test, RFT: Renal function test

an association between the use of statins and the progression of DR was evaluated.

In the present study, at 12 months of diagnosis of DR, 53% (91) of patients showed DR progression. Of these, 36% were statin users and 67.4% were nonusers. Statin use, thus, showed a significant association with reduction in DR progression (*P* < 0.001). A study by Chung *et al.*¹⁶ found that statins prevented progression of DR in patients

with Type 2 diabetes. Different studies done globally have shown concordance with our study results. A study in the US population via health claim data has reported that statin use was associated with less progression from NPDR to PDR.¹⁷ Similarly, in a Taiwanese population-based study, the use of statin in patients with diabetes was associated with decreased prevalence of DR. Statins also lowered the need for invasive treatment in severe cases.¹⁸ Patient adherence to statins and intensity of statins was directly proportional to the beneficial effects.¹⁸ Large-scale studies conducted across Japan, Taiwan, and the USA also found reduced development of DR, reduced DR progression, and requirement of less intensive therapies in patients on statins.^{10,17} A meta-analysis by the authors found that lipid-lowering drugs such as statins and fibrates reduced the risk of DR progression.¹⁹ However, no protective effect was observed in relation to visual acuity and hard exudates in DR with lipid-lowering therapy.¹⁹

Oxidative stress, dyslipidemia, endothelial dysfunction, and inflammation are involved in pathophysiology of DR.²⁰ Statins have shown to retard DR progression in patients with hypercholesterolemia²¹ and thus can have an effect mediated by regulating the levels of lipids. Statins at low doses have shown to promote vascular integrity and thus enhance retinal capillary endothelial survival, promote healing, and repair and prevent neovascularization. At high doses, cholesterol deficiency becomes a limiting factor for any of the repair mechanisms.²² The early features of DR are endothelial injury and blood retinal barrier breakdown, leading to increased vascular permeability in which leucocytes predominantly injure retina. Statins such as simvastatin have shown to inhibit leukocyte endothelial

Table 3: Clinical characteristics at 6 and 12 months of diabetic retinopathy diagnosis

Variables	Mean±SD		P
	Nonstatin	Statin	
At 6 months			
RBS (mg/dl)	268.59±123.29	245.74±105.32	0.320
FBS (mg/dl)	166.47±64.18	181.32±87.04	0.268
PPBS (mg/dl)	249.69±100.21	252.09±99.34	0.896
HbA1C (%)	9.12±2.10	9.57±2.3	0.245
TC (mg/dl)	177.33±45.71	159.73±46.29	0.052 ^a
LDL (mg/dl)	112.02±94.55	94.55±33.82	0.031 ^a
HDL (mg/dl)	36.56±13.22	36.04±8.82	0.814
TG (mg/dl)	172.70±67.37	155.25±59.83	0.162
At 12 months			
RBS (mg/dl)	255.18±113.65	263.57±133.47	0.713
FBS (mg/dl)	165.09±60.78	182.00±66.52	0.144
PPBS (mg/dl)	244.52±79.00	244.78±94.17	0.987
HbA1C (%)	8.94±2.23	9.03±1.91	0.790
TC (mg/dl)	175.76±41.37	159.98±52.00	0.054 ^a
LDL (mg/dl)	110.61±50.24	89.96±29.53	0.006 ^a
HDL (mg/dl)	34.55±12.56	36.57±8.92	0.300
TG (mg/dl)	182.49±75.21	159.02±80.66	0.087

^aP<0.05 (Independent t-test). RBS: Routine blood sugar, FBS: Fasting blood sugar, PPBS: Postprandial blood sugar, HbA1C: Glycosylated hemoglobin, TC: Total cholesterol, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, TG: Triglyceride, SD: Standard deviation

Table 4: Number of patients with diabetic retinopathy progression across the groups

	DR progression		P
	Not progressed	Progressed	
Nonstatin users (92)	30	62	<0.001 ^a
Statin users (79)	50	29	
Total (171)	80	91	

^aP<0.05 (Chi-square test). DR: Diabetic retinopathy

interaction and reduce vascular permeability independent of lipid-lowering mechanism.²³ Furthermore, by their antioxidant action, statins maintain the stability of blood–retinal barrier by reducing the generation of ROS, increasing nitrous oxide levels, and endothelial progenitor cells.^{24,25} Statins inhibit proinflammatory transcription factors such as nuclear factor kappa B, which in turn reduces the proinflammatory mediators such as VEGF and intercellular adhesion molecule and thus provide vasoprotection.²⁶ Thus, statins in addition to a lipid-lowering effect act by other pleiotropic mechanisms such as anti-inflammatory and antioxidant and maintain vascular integrity to prevent progression of DR.

Contrary to our results, many authors have reported that there is no association between statin use and reduced progression of DR. A retrospective cohort study from Malaysia found the incidence of DR to be more in patients using statins as compared to nonusers.²⁷ In a nested case–control study at Birmingham Veterans Affairs Medical Center, no association

Table 5: Demographic parameters in diabetic retinopathy (DR) progressed and DR not progressed groups

	Not progressed (n)	DR progressed (n)	P
	Sex		
Female	27	32	0.873
Male	53	59	
DM duration (years)			
<10	40	34	0.122 ^a
>10	40	57	
Drugs in DM			
Single therapy	45	45	0.443
Combination therapy	35	46	
Dyslipidemia			
No	65	80	0.287
Yes	15	11	
Hypertension duration			
No	26	28	0.932
<5 years	26	28	
>5 years	28	34	
Renal disorder			
No	64	59	0.04 ^a
Yes	16	32	
Cardiovascular disorder			
No	62	76	0.338
Yes	18	15	

^aP<0.26 (Chi-square test). DM: Diabetes mellitus

Table 6: Clinical parameters in diabetic retinopathy (DR) progressed and DR not progressed groups at follow-up

	Mean±SD		P
	DR not progressed	DR progressed	
RBS (mg/dl)	263.02±113.80	254.40±117.57	0.709
FBS (mg/dl)	168.09±69.74	179.50±82.67	0.395
PPBS (mg/dl)	247.81±87.48	253.72±110.16	0.747
HbA1C (%)	9.06±1.96	9.63±2.39	0.135 ^a
TC (mg/dl)	157.57±44.44	177.23±46.81	0.031 ^a
LDL (mg/dl)	91.62±31.03	112.52±46.93	0.010 ^a
HDL (mg/dl)	37.63±8.90	35.28±12.70	0.288
TG (mg/dl)	160.89±64.25	166.63±64.39	0.650

^aP<0.26 (Chi-square test). DR: Diabetic retinopathy, RBS: Routine blood sugar, FBS: Fasting blood sugar, PPBS: Postprandial blood sugar, HbA1C: Glycosylated hemoglobin, TC: Total cholesterol, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, TG: Triglyceride, SD: Standard deviation

was seen between statin use and DR. However, the authors concluded that as this study has a number of limitations, the results need to be confirmed further.²⁸

Hypertension accounts for one of the risk factors for progression of diabetic complications such as retinopathy.²⁹ In our study, hypertension was present in 73.4% of statin users and 63% of statin nonusers. Among hypertensives, more than 50% in the statin group had a history of hypertension >5 years. The incidence of hypertension in a retrospective study conducted in patients with vitreous hemorrhage in diabetic eye disease

Table 7: Logistic regression analysis between patients with and without diabetic retinopathy (DR) progression for variables associated with DR progression

	OR (95% CI)	P
Duration of diabetes	3.30 (1.062-10.25)	0.039 ^a
Statin use	0.25 (0.09-.068)	0.007 ^a
Renal disease	2.77 (0.91-8.41)	0.071
HbA1c	1.13 (0.902-1.43)	0.280
TC	1.00 (0.99-1.02)	0.546
LDL	1.01 (0.99-1.03)	0.110
HDL	0.98 (0.93-1.02)	0.301
TG	0.99 (0.97-0.99)	0.026 ^a

^a $P < 0.05$. OR: Odds ratio, CI: Confidence interval, HbA1C: Glycosylated hemoglobin, TC: Total cholesterol, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, TG: Triglyceride

was found to be 69%.³⁰ In the present study, at baseline, significantly higher number of patients on statins ($P < 0.001$) had cardiovascular morbidities as compared to nonstatin users (36% in statin and 5% in statin nonusers).

Overall, in our study population, 57% of patients had diabetes for more than 10 years' duration. Among statin users, 63.2% had diabetes for more than 10 years, whereas among nonstatin users, 51% of patients had diabetes for more than ten years. The mean duration of DM was found to be higher in patients using statins as compared to nonstatin users. The current study shows that patients with diabetes duration of more than 10 years are more susceptible to DR progression (OR: 3.30; 95% CI: 1.06–10.25; $P = 0.039$), implicating duration of diabetes as an important risk factor in DR progression. Diabetes duration as an independent risk factor is associated with DR progression as well as a rise in DR incidence in other studies.^{18,31}

ETDRS's report, which involved 2,709 patients, revealed that raised TC was twice as likely to develop severe forms of DR (OR: 2.00; 99% CI: 1.35–2.95). Elevated triglycerides were associated with development of PDR (OR: 1.23; 95% CI: 1.06–1.42).³² High levels of serum triglycerides and LDL are associated with progression of DR.³³

Association between triglycerides levels and DR has been reported earlier.³⁴ Raised LDL and triglyceride levels were associated with DR progression.³⁵ Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetic Study II study, involving 890 diabetic patients, observed higher triglycerides and high-density lipoprotein levels to be associated with progression to PDR.³⁶ A systematic review found serum triglyceride levels to be an independent risk factor for DR worsening.³⁷

DME is manifested as retinal thickening caused by the accumulation of intraretinal fluid, primarily in the inner and outer plexiform layers, and is secondary to hyperpermeability of the retinal vasculature.³⁸ Center-involving macular edema developed in 14% (24) of our patient population. Although more number of nonstatin users developed center-involving macular edema compared to statin users, the difference was not

statistically significant. This could be due to shorter follow-up duration as well as relatively a fewer number of patients with DR. Some studies have shown efficacy of statins in retarding the development of DME. In a randomized controlled trials, atorvastatin therapy reduced the severity of DME.³⁹ On the contrary, Shi *et al.* in their meta-analysis found no statistically significant protective effect of lipid-lowering therapies on DME.¹⁹ Meta-analysis by Das *et al.* involving 21 studies to evaluate the role of dyslipidemia in DME found conflicting evidence regarding the role of lipid-lowering therapies in DME.³⁷ Chung *et al.* in a retrospective analysis concluded statins to be protective against development of DME.¹⁶ Furthermore, a randomized multinational trial has shown that progression of retinopathy, macular edema, and need for laser treatment was reduced in patients treated with lipoprotein lipase activators such as fenofibrate as compared to placebo group in patients with T2DM.⁴⁰ For 40–75-year-old diabetics without any atherosclerotic cardiovascular disease, use of moderate intensity statin and lifestyle modification has been clearly recommended as per the latest ADA guidelines.⁴¹ Future studies are necessary to assess the effect of different types of statins and different dosages of statins on the progression of DR.

The retrospective design, different statins being used, and relatively small number of patients included as per the inclusion criteria are some of the limitations in the present study. Inadequate follow-up time could also have an impact on analysis of macular edema and its associated factors. Furthermore, this study relies on clinical grading without imaging confirmation. A large-scale, multicenter prospective study with longer duration of follow-up and large sample size can further investigate the role of serum lipids and other variables in DR.

To conclude, the present study exhibited a significant association between statin use and reduced progression of DR in a subset of Indian population. Risk factors such as serum triglycerides and diabetes duration show an association with progression of DR. Use of statins and modulating the risk factors such as serum triglycerides can play a role in retarding the overall progression of DR.

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Conflicts of interest

There are no conflicts of interest.

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