International Journal of Clinical Trials
Chhabra N et al. Int J Clin Trials. 2025 Feb;12(1):1-6
http://www.ijclinicaltrials.com
pISSN 2349-3240 | eISSN 2349-3259
DOI: https://dx.doi.org/10.18203/2349-3259.ijct20250128

Original Research Article

Correlation of statin therapy and severity of diabetic retinopathy at a tertiary care hospital in Northern India: a randomised control trial

Neha Chhabra[1], Rohit Raina[2]*

[1]Department of Ophthalmology, Government Medical Patiala, Punjab, India
[2]Department of General Medicine, All India Institute of Medical Sciences, Bathinda, Punjab, India

Received: 01 August 2024
Revised: 24 November 2024
Accepted: 02 December 2024

***Correspondence:**
Dr. Rohit Raina,
E-mail: rohitraina103@yahoo.com

ABSTRACT

Background: Aim was to study the correlation between statin therapy and the severity of diabetic retinopathy.
Methods: A randomised control trial was performed at a tertiary care hospital in northern India. The severity of diabetic retinopathy was compared between statin and non-statin users from the fundus examination and medical records of patients presenting to the Outpatient department from July 2022 to May 2023. A total of 100 patients with diabetic retinopathy were enrolled in the study, all meeting the inclusion criteria. The patients were divided into statin users and nonusers. The results were analysed to compare the severity of DR between the two groups.
Results: Out of 45 statin users, 28 (62.2%) had mild non-proliferative diabetic retinopathy (NPDR), 10 (22.2%) had a moderate grade of NPDR, 5 (11.1%) had severe NPDR, 1 (2.22%) had PDR and 1 (2.22%) patient had diabetic macular edema (DME). Out of 55 non-statin users, 10 (18.18%) had mild diabetic NPDR, 16 (29.09%) had a moderate grade of NPDR, 16 (29.09%) had severe NPDR, 8(14.54%) had PDR and 4 (7.27%) patients had DME and 1 (1.81%) patient presented with both DME and vitreous haemorrhage (VH).
Conclusions: In type 2 diabetic patients, patients on statins had significantly lower grades of retinopathy as compared to those who were not taking statins. Thus, statins can be given prophylactically to lower the severity of diabetic retinopathy.

Keywords: Diabetes, Diabetic retinopathy, Statins

INTRODUCTION

Diabetes is one of the most common metabolic diseases characterised by hyperglycemia. The WHO reported that there are 79.4 million cases of diabetes, if not controlled by 2030 then India would be the diabetic capital of the world.[1] Diabetes presents with many macrovascular complications mainly cerebrovascular disease, cardiovascular disease, and peripheral artery disease that often leasd to high morbidity and mortality. Among microvascular complications, one of the most common is diabetic retinopathy which can potentially lead to vision loss in T2DM patients.[2]

There are many surgical interventions for vision-threatening diabetic retinopathy, including laser, intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections, and vitrectomy.[3]

Medical treatment to lower the severity of diabetic retinopathy would be tried apart from surgical interventions.[4] Statins have been demonstrated to reduce the risk of cardiovascular events in patients with diabetes in many clinical trials.[5,6] Statins exert their action through competitive binding to 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) thereby lowering cholesterol and triglyceride levels.[7] Several studies also showed that statins can control retinal inflammation by upregulating

various inflammatory factors and cytokines like VEGF and ICAM and thus statins can be useful to treat diabetic retinopathy through their vaso-protective action.[8] The fenofibrate intervention and event lowering in diabetes (FIELD) study conducted in 2005 showed the effectiveness of fenofibrate in diabetic retinopathy by diminishing the requirement of laser treatment.[9] In various animal model trials, simvastatin and lovastatin have been shown to exert their proinflammatory action by inhibiting transcription factor NF-κB and diminishing the expression of VEGF and VEGF-induced intercellular adhesion molecule 1.[8] The present study is conducted to correlate statin therapy and the severity of diabetic retinopathy.

METHODS

This randomised control trial was performed at a tertiary care hospital in northern India. The severity of diabetic retinopathy was compared between statin and non-statin users, from the fundus examination and medical records of patients presenting to the outpatient department from July 2022 to May 2023. The patients fulfilling the inclusion criteria and not presenting with any exclusion criteria were enrolled in the study. Proper consent was taken from the patients. Patients aged more than 18 years, diagnosed diabetic patients presenting with retinopathy, and patients willing to get enrolled in the study were included. All patients with an established diagnosis of other ocular diseases like ARMD and vasculitis, diagnosed diabetic patients not presenting with retinopathy, ocular inflammation, ocular infection, pregnant and lactating females, patients unable to attend follow-up, any known sensitivity to study drugs, patients with a history of intraocular surgery within six months before the study were excluded in the study. In the study group, one eye (the affected eye) fulfilling the inclusion criteria was considered the study eye. If both eyes have diabetic retinopathy, both eyes were treated, but only one eye was studied. The study protocol for all procedures was approved by the institutional review board for ethical clearance and was included and performed by the code of ethics of the world medical association according to the declaration of Helsinki of 1975, as revised in 2000. Informed and written consent was obtained from all the patients before the commencement of the study. The questionnaire was conducted to obtain the pretested data with modifications made before its use in the study. The patients were interviewed and requested their demographic, socioeconomic status, medical history, and previous history of taking any medications and supplements.

A hundred patients with diabetic retinopathy were selected after fulfilling the inclusion criteria. Informed consent was taken from the patients included in the study. In addition, demographic data, detailed ocular, and medical history were noted, and the past treatment history as per the proforma. Clinical evaluation of each patient on each visit during treatment was done as: History: any subjective symptoms, fundus examination, both direct and indirect ophthalmoscopy, slit lamp examination and slit lamp examination with 78 D/90 D.

Sample size calculation

Yamane formula was used to determine the necessary number of participants for the study using the average number of last two-year patients (130 patients), and the formula as follows;

$n=N/1+N(e)^2$

n=denotes the sample size, N is the number of people.

Alpha level=significant level

If this formula is calculated using the sample shown above, where N=130 and e=0.05

Consequently, yields; N=98

Therefore, the sample size is 98 but 5% was added to take care of non–responses. The total sample size then became 100 respondents.

A detailed ocular and medical history were obtained. A careful general physical examination was done to rule out any contraindications to the drugs. An ocular examination was done as follows: Best-corrected visual acuity (BCVA) was done with a Snellen chart. Examination of lids, adnexa and lacrimal apparatus was done using diffuse light. Fundus examination through Indirect ophthalmoscopy and slit lamp indirect biomicroscopy with +78D or +90D lens was done.

Statistical method

The presentation of the Categorical variables was done in the form of number and percentage (%). On the other hand, the quantitative data were presented as the means±SD and as median with 25^{th} and 75^{th} percentiles (interquartile range). The data normality was checked by using Kolmogorov-Smirnov test. The cases in which the data was not normal, we used non parametric tests. The association of the variables which were quantitative and not normally distributed in nature were analysed using Mann-Whitney test (for two groups) and Kruskal Wallis test (for more than two groups) and variables which were quantitative and normally distributed in nature were analysed using independent t test (for two groups) and ANOVA (for more than two groups). The association of the variables which were qualitative in nature were analysed using chi-square test. If any cell had an expected value of less than 5 then Fisher's exact test was used.

The data entry was done in the Microsoft excel spreadsheet and the final analysis was done with the use of statistical package for social sciences (SPSS) software, IBM manufacturer, Chicago, USA, ver 25.0.

For statistical significance, p value of less than 0.05 was considered statistically significant.

RESULTS

A total of 240 patients with type 2 diabetes and DR were examined, and of these, 100 patients were taken for analysis fulfilling the criteria for our study, the rest were excluded. Out of 100 patients, 45 patients were on statins, and 55 were not exposed to statins. The demographic and clinical profiles of the two groups are mentioned in Table 1. Out of 45 diabetic patients taking statins, there were 33 males and 12 females. Out of 55 diabetic patients who were not taking statins, there were 24 males and 31 females. The mean age of all diabetic patients is 62.15 years which is similar in both statins and non-statins users. Males taking statins are more as compared to females. Hypertensive diabetic patients taking statins were 28, and all were males. Hypertensive diabetic patients not taking statins were 33 out of which 24 were females and 4 were males. Out of 45 statin users, 36 were smokers and 18 were alcoholics. Among non-statin users, 32 were smokers and 8 were alcoholics.

Out of 45 statin users, 28 (62.2%) had mild NPDR, 10 (22.2%) had a moderate grade of NPDR, 5 (11.1%) had severe NPDR, 1 (2.22%) had PDR and 1 (2.22%) patient had DME. Out of 55 non-statin users, 10 (18.18%) had mild diabetic NPDR, 16 (29.09%) had a moderate grade of NPDR, 16 (29.09%) had severe NPDR, 8 (14.54%) had PDR and 4 (7.27%) patients had DME and 1 (1.81%) patient presented with both DME and VH as shown in Table 2 and Figure 1. The CONSORT diagram of the study participants is represented in Figure 2.

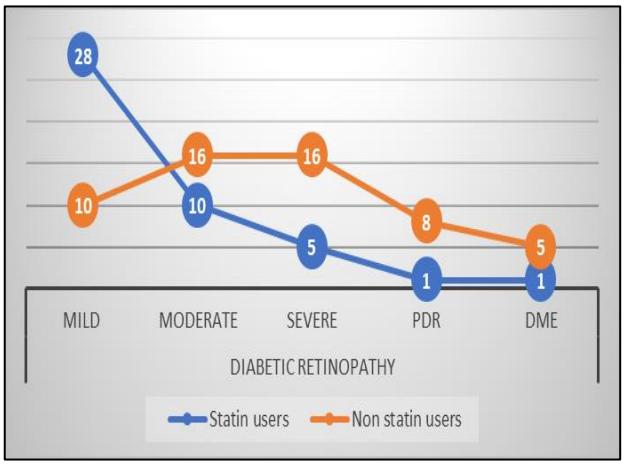

Figure 1: Line diagram representing various grades of diabetic retinopathy in patients taking statins and in those not taking statins.

Patients who were prescribed statins also had preexisting hypertension and more predisposition to risk factors like smoking and alcohol as compared to patients who were not prescribed statins. It is also reported that patients who were not taking statins had high HbA1c levels as compared to those who were taking statins. Patients on statins had significantly lower grades of retinopathy compared to those who were not taking statins, thus statistically significant. (Figure 3 and 4).

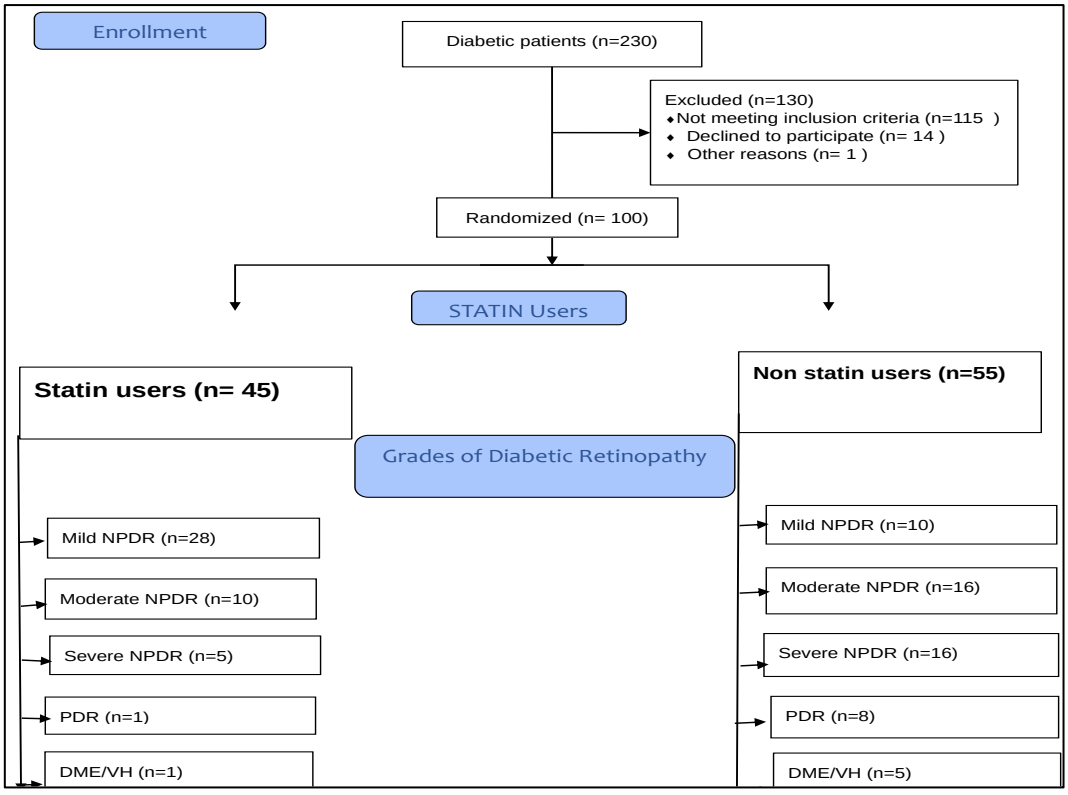

Figure 2: Represents the CONSORT diagram of the study participants.

Table 1: Demographic data and clinical profile of diabetic patients.

Sex		Age (in years)			Hypertension		Smoking		Alcohol		HbA1c	
Statin users												
M	F	55-60	61-65	66-70	M	F	M	F	M	F	<7%	>7%
33	12	17	20	8	28	0	36	0	18	0	24	21
Non-statin users												
M	F	55-60	61-65	66-70	M	F	M	F	M	F	<7%	>7%
24	31	8	36	11	24	9	16	8	7	1	11	44

Table 2: Grades of diabetic retinopathy in patients taking statins and in those not taking statins.

Grades of diabetic retinopathy	Mild NPDR	Moderate NPDR	Severe NPDR	PDR	DME/VH
Statin users	28	10	5	1	1
Non-statin users	10	16	16	8	5

Figure 3: Fundus photo of a patient using statins showing hard exudates near the macula and few dot blot haemorrhages suggestive of mild grade of NPDR.

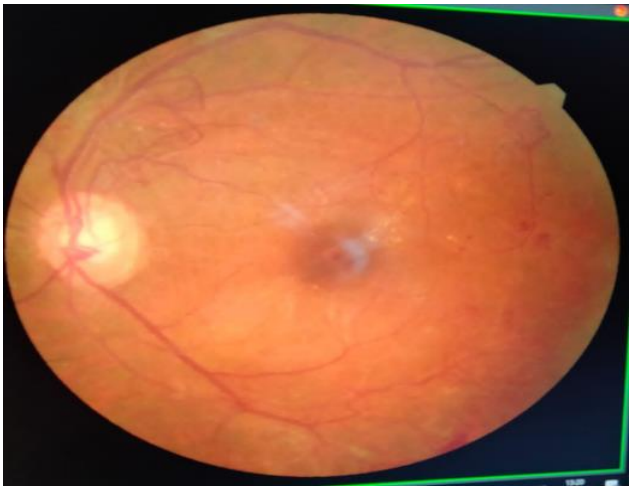

Figure 4: Fundus photo of a patient not using statins showing a higher retinopathy grade with neovascularisation else in the periphery and near the optic disc, hard exudates and dot blot haemorrhages suggestive of PDR.

DISCUSSION

Diabetes is one of the leading causes of blindness in diabetic patients. The present study concluded that diabetic patients who were taking statins had lower severity of diabetic retinopathy as compared to those patients who were non-statin users. So, statins are beneficial in retarding the progression of diabetic retinopathy.

The Wisconsin epidemiologic study of diabetic retinopathy (WESDR) concluded that there is an association between serum cholesterol levels and hard exudates seen in diabetic retinopathy.[9] Several studies showed similarities to our study results. One such study in the US reported less progression of NPDR to PDR in patients taking statins.[10] Fenofibrate combined with simvastatin was compared with simvastatin alone in the treatment of diabetic retinopathy in the ACCORD-EYE study (Action to control cardiovascular risk in diabetes-EYE) which showed that the combination was more effective as compared to single drug therapy and thus highlighting the use of statins in the treatment of DR.[11] Another study conducted by Gupta et al concluded that oral atorvastatin therapy in patients with type 2 diabetes with dyslipidaemia reduces the severity of hard exudates and subfoveal lipid migration in clinically significant macular edema where patients with type 2 diabetes with clinically significant macular edema were assessed and among those treated with atorvastatin showed a reduction in hard exudates in 66.6% as compared to 13.3% who were not treated with atorvastatin and regression of macular edema was also more in the patients treated with atorvastatin.[12] A retrospective study carried out at a tertiary hospital in southern India showed that DR progressed in 67% of nonstatin users and 37% of statin users and centre-involving macular edema was reported in 10% of statin users as compared to 16% of nonstatin users and thus the study concluded that statins have the potential to slow the progression of DR.[13] However, Das et al published a meta-analysis involving 21 studies that demonstrated the effect of dyslipidaemia in DME and the

meta-analysis conflicted with the evidence regarding the role of lipid-lowering therapies in DME.[14] In another study conducted by Kang et al 37,894 Taiwanese patients were assessed over 5 years and it was that 10.6% of the statin group and 12% of the non-statin group developed diabetic retinopathy. Patients in the statin group had a significantly lower rate of diabetic retinopathy and macular edema than the non-statin group.[15] The FIELD study revealed that if fenofibrate is given as an add-on therapy in type 2 diabetes patients then the need for laser treatment was significantly reduced and fenofibrate also retards the progression of diabetic retinopathy.[16]

The pathophysiology involved in DR is underlying oxidative stress and inflammation, imbalance in lipid levels and endothelial dysfunction.[17] Thus, statins by regulating the lipids levels have been demonstrated to slow down the progression of DR.[18]

Limitations

The main limitation of the present study is the small number of participants. The study involved an Indian population, so these data may not be conclusive for other populations. Also, it lacks information on eye laterality, so whether the right or left eye is similarly affected or not yet clear.

CONCLUSION

Thus, the present study concluded that statins should be given as an add-on therapy to prevent the development of diabetic retinopathy and prophylactically to slow down the progression of diabetic retinopathy. The present study also concludes that statins may reduce central involving macular edema in diabetic patients thus improving vision. The study also concluded that statins by slowing the progression of DR reduce the need for various invasive and costly procedures like intravitreal anti-VEGF injections and vitrectomy required in severe and advanced stages. Statins also appear to be a beneficial medical alternative to laser photocoagulation.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Prevention of Blindness from Diabetes Mellitus: Report of a WHO Consultation in Geneva, Switzerland, 9-11 November 2005. World Health Organization: Geneva. 2006.
2. Antonetti DA, Klein R, Gardner TW. Diabetic retinopathy. N Eng J Med. 2012;366(13):1227-39.
3. Reddy SV, Husain D. Panretinal photocoagulation: A review of complications. Seminars Ophthalmol. 2018;33(1):83-8.
4. Kang EYC, Chen TH, Garg SJ, Sun CC, Kang JH, Wu WC, et al. Association of statin therapy with prevention of vision-threatening diabetic retinopathy. JAMA Ophthalmol. 2019;137(4):363-71.
5. Heart Protection Study Collaborative Group Heart. Protection Study Collaborative GMRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 20,536 high-risk individuals: A randomised placebo-controlled trial. Lancet. 2002;360:7-22.
6. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HAW, Livingstone SJ, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative atorvastatin Diabetes Study (CARDS): A multicentre randomised placebo-controlled trial. Lancet. 2004;364(9435):685-96.
7. Patel KK, Sehgal VS, Kashfi K. Molecular targets of statins and their potential side effects: Not all the glitter is gold. Eur J Pharmacol. 2022;922:174906.
8. Julius A, Hopper W. A non-invasive, multi-target approach to treat diabetic retinopathy. Biomed Pharmacotherapy. 2019;109:708-15.
9. Klein BE, Moss SE, Klein R, Surawicz TS. The Wisconsin epidemiologic study of diabetic retinopathy. XIII. Relationship of serum cholesterol to retinopathy and hard exudate. Ophthalmol. 1991;98(8):1261-5.
10. Vail D, Callaway NF, Ludwig CA, Saroj N, Moshfeghi DM. Lipid-lowering medications are associated with lower risk of retinopathy and ophthalmic interventions among United States patients with diabetes. Am J Ophthalmol. 2019;207:378-84.
11. Hermans MP, Fruchart JC. Reducing vascular events risk in patients with dyslipidaemia: An update for clinicians. Therap Adv Chronic Dis. 2011;2(5):307-23.
12. Gupta A, Gupta V, Thapar S, Bhansali A. Lipid-lowering drug atorvastatin as an adjunct in the management of diabetic macular edema. Am J Ophthalmol. 2004;137(4):675-82.
13. Priyadarshini P, Chogtu B, Bhandary SV, Kabirdev, Magazine R. Association of use of statins with progression of diabetic retinopathy at a tertiary Care Hospital in Southern India. J Current Ophthalmol. 2022;34(2):234-40.
14. Das R, Kerr R, Chakravarthy U, Hogg RE. Dyslipidemia and diabetic macular edema: A systematic review and meta-analysis. Ophthalmology. 2015;122(9):1820-7.
15. Kang EYC, Chen TH, Garg SJ, Sun CC, Kang JH, Wu WC, et al. Association of statin therapy with prevention of vision-threatening diabetic retinopathy. JAMA Ophthalmol. 2019;137(4):363-71.
16. Keech AC, Mitchell P, Summanen PA, O'Day J, Davis TM, Moffitt MS, et al. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): A randomised controlled trial. Lancet. 2007;370(9600):1687-97.

17. Bloomgarden ZT. Diabetic retinopathy and diabetic neuropathy. Diabetes Care. 2007;30(3):760-5.
18. Sen K, Misra A, Kumar A, Pandey RM. Simvastatin retards progression of retinopathy in diabetic patients with hypercholesterolemia. Diabetes Res Clin Pract. 2002;56(1):1-11.

Cite this article as: Chhabra N, Raina R. Correlation of statin therapy and severity of diabetic retinopathy at a tertiary care hospital in Northern India: a randomised control trial. Int J Clin Trials 2025;12(1):1-6.