International Journal of Research in Medical Sciences
Khan SA et al. Int J Res Med Sci. 2025 Jul;13(7):2902-2908
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20252025

Original Research Article

Association of use of statins with progression of diabetic retinopathy: a randomized controlled trial at a tertiary care centre in Southern India

Shehla Ashraf Khan[1]*, Adithya Andanappa[2], Hanisha Reddy Kukunoor[3], Sirapurapu Veera Venkata Laxmaiah Naidu[4], Abhijeeth Reddy Toodi[5]

[1]Bharati Vidyapeeth deemed university medical college, Pune, Maharashtra, India
[2]Mysore Medical College and Research Institute, Mysore, Karnataka, India
[3]Maheshwara Medical College and Hospital, Patancheruvu, Telangana, India
[4]Alluri Sita Ramaraju Academy of Medical Sciences, Eluru, Andhra Pradesh, India
[5]Mediciti Institute of Medical Sciences, Telangana, India

Received: 01 April 2025
Revised: 07 May 2025
Accepted: 22 May 2025

***Correspondence:**
Dr. Shehla Ashraf Khan,
E-mail: Shehlakhan555@gmail.com

ABSTRACT

Background: Diabetic retinopathy (DR) is a major microvascular complication of type 2 diabetes mellitus (T2DM) and a leading cause of vision impairment globally. Statins, beyond their lipid-lowering and cardiovascular benefits, may offer protective effects against DR by reducing inflammation, stabilizing endothelial function and modulating vascular endothelial growth factor (VEGF) expression. This study aimed to assess the impact of statin therapy on DR severity in patients with T2DM.
Methods: A randomized controlled trial was conducted at Government General Hospital, Srikakulam, between April 2024 and February 2025. A total of 120 patients with DR were enrolled and divided into two groups: those receiving statin therapy and those not on statins. DR severity was assessed using fundus examination findings and compared between the two groups.
Results: Among the 60 patients on statins, 62.2% had mild non-proliferative diabetic retinopathy (NPDR), while only 3.3% had proliferative DR (PDR) and 1.7% had diabetic macular edema (DME). In contrast, among non-statin users, only 18.2% had mild NPDR, while 29.1% had severe NPDR, 14.5% had PDR and 7.3% had DME. One patient also had vitreous hemorrhage.
Conclusions: Statin therapy appears to be associated with milder forms of DR in patients with T2DM. These findings suggest that statins may help slow DR progression, highlighting their potential as an adjunctive therapy for retinal protection in diabetes management.

Keywords: Diabetes, Diabetic retinopathy, Lipid lowering therapy, Retinal health, Statins

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia due to defects in insulin secretion, action or both. It remains a major global health challenge, with India alone accounting for approximately 79.4 million cases, a number projected to rise significantly in the coming decades.[1] Uncontrolled diabetes leads to multiple microvascular and macrovascular complications, significantly impacting morbidity and mortality. Among these complications, diabetic retinopathy (DR) is one of the most common and debilitating, potentially resulting in irreversible vision loss if left untreated.[2]

Diabetic retinopathy is a progressive microvascular complication of diabetes that affects the retinal vasculature, leading to increased vascular permeability, neovascularization and retinal damage. It is broadly classified into non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR), with diabetic macular edema (DME) being a major cause of vision impairment.[3]

Various treatment options, including laser photocoagulation, intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections and vitrectomy, are available for managing advanced DR.[4] However, there is growing interest in pharmacological approaches, particularly lipid-lowering therapies such as statins, to mitigate the progression of DR.[5]

Statins are widely recognized for their role in lowering cholesterol levels and reducing cardiovascular risks in diabetic patients. They function by competitively inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol biosynthesis, thereby decreasing low-density lipoprotein (LDL) levels and reducing atherosclerotic plaque formation.[6] Beyond their lipid-lowering effects, statins exert anti-inflammatory, antioxidative and endothelial-stabilizing properties, which may be beneficial in preventing or slowing DR progression.[7]

Emerging evidence suggests that statins may influence DR pathogenesis by modulating inflammatory and angiogenic pathways. Studies have demonstrated that statins can downregulate the expression of vascular endothelial growth factor (VEGF) and intracellular adhesion molecule-1 (ICAM-1), thereby reducing retinal inflammation and neovascularization.[8]

The fenofibrate intervention and event lowering in diabetes (FIELD) study provided substantial evidence supporting the role of lipid-lowering agents in DR management, showing a significant reduction in the need for laser treatment among patients receiving fenofibrate.[9] Similarly, animal model studies have suggested that statins, such as simvastatin and lovastatin, inhibit the proinflammatory transcription factor nuclear factor-kappa B (NF-κB), which plays a crucial role in retinal microvascular dysfunction.[10]

Several clinical studies have explored the potential benefits of statin therapy in DR. The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) identified a correlation between elevated serum cholesterol levels and the presence of hard exudates in DR patients, suggesting that lipid regulation could influence retinal health.[11]

Furthermore, a retrospective analysis from a tertiary care center in southern India found that statin users exhibited a significantly lower progression rate of DR compared to non-statin users, reinforcing the hypothesis of a protective effect.[12] Despite these promising findings, the role of statins in DR prevention and progression remains a topic of debate. Some studies have reported inconsistent results regarding the impact of statin therapy on diabetic macular edema and DR severity, highlighting the need for further large-scale, randomized controlled trials to establish definitive conclusions. Therefore, this study aims to investigate the association between statin therapy and the severity of DR in patients with type 2 diabetes mellitus (T2DM). By analyzing the impact of statins on DR progression, this research seeks to provide insights into their potential as an adjunctive treatment for DR management and prevention.

METHODS

Study design and study population

This randomized control trial was performed in the Government general hospital (GGH) Srikakulam, Andhra Pradesh 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 April 2024 to Feb 2025.

Inclusion and exclusion criteria

Patients who met the inclusion criteria and did not have any exclusion criteria were enrolled in the study. Informed consent was obtained from all participants. The study included patients over the age of 18 who had been diagnosed with diabetes and presented with diabetic retinopathy, as well as those who were willing to participate in the study.

Patients with a diagnosis of other ocular conditions, such as age-related macular degeneration (ARMD) and vasculitis, diabetic patients without retinopathy, ocular inflammation or infection, pregnant or lactating women, patients unable to attend follow-up appointments, individuals with known sensitivities to study medications and those who had undergone intraocular surgery within the six months prior to the study were excluded.

In the study, one eye (the affected eye) that met the inclusion criteria was designated as the study eye. In cases where both eyes were affected by diabetic retinopathy, both eyes received treatment, but only one eye was included in the study. The study protocol was approved by the institutional review board for ethical clearance and adhered to the ethical guidelines set forth by the World Medical Association's Declaration of Helsinki (1975, revised in 2000).

Written informed consent was obtained from all participants before the study commenced. A pretested questionnaire, with necessary modifications, was used to gather demographic, socioeconomic, medical and treatment history data from the patients. A total of 120

patients with diabetic retinopathy, who met the inclusion criteria, were selected for the study. Informed consent was obtained from each patient before inclusion. Detailed demographic data, medical and ocular history and prior treatment details were documented according to the study proforma. Clinical evaluation was performed at each visit during the treatment period, which included gathering a medical history (subjective symptoms), fundus examination using both direct and indirect ophthalmoscopy, slit lamp examination and slit lamp examination with 78 D/90 D lenses. The Yamane formula was used to determine the required sample size for the study, based on the average number of patients over the past two years (130 patients). The formula used is as follows.

n=N/1+N(e)2

Where,

n = sample size, N = total population (130), e = margin of error (0.033).

Calculating with these values, n=1301+130(0.05)2=114 n

Therefore, the sample size calculated was 114. However, to account for non-responses, an additional 5% was added, bringing the total sample size to 120 patients. A thorough ocular and medical history were obtained for each patient. A general physical examination was performed to rule out any contraindications to the study medications. The ocular examination included the following: Best-corrected visual acuity (BCVA) was assessed using a Snellen chart.

Examination of the eyelids, adnexa and lacrimal apparatus was performed with diffuse light. Fundus examination was carried out using indirect ophthalmoscopy and slit lamp bio microscopy with +78D or +90D lenses.

Statistical methods

Categorical variables were presented as frequency counts and percentages (%). Quantitative data were expressed as mean±standard deviation (SD) for normally distributed data and as medians with 25th and 75th percentiles (interquartile range) for non-normally distributed data. The normality of the data was assessed using the Kolmogorov-Smirnov test. For data that were not normally distributed, non-parametric tests were used. The Mann-Whitney test was applied to compare two groups, while the Kruskal-Wallis test was used for comparisons involving more than two groups.

For normally distributed data, comparisons between two groups were performed using the independent t-test and for more than two groups, ANOVA (Analysis of Variance) was employed. The association between qualitative variables was analyzed using the chi-square test. If any expected cell count was less than 5, Fisher's exact test was used instead. Data were entered into a Microsoft Excel spreadsheet and final analysis was performed using the Statistical Package for the Social Sciences (SPSS), IBM version 25.0 (Chicago, USA). A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 240 patients with type 2 diabetes and diabetic retinopathy (DR) were initially examined. Out of these, 120 patients met the inclusion criteria for the study and were included in the analysis. The remaining patients were excluded. Of the 120 patients, 60 were on statins and 60 were not exposed to statins.

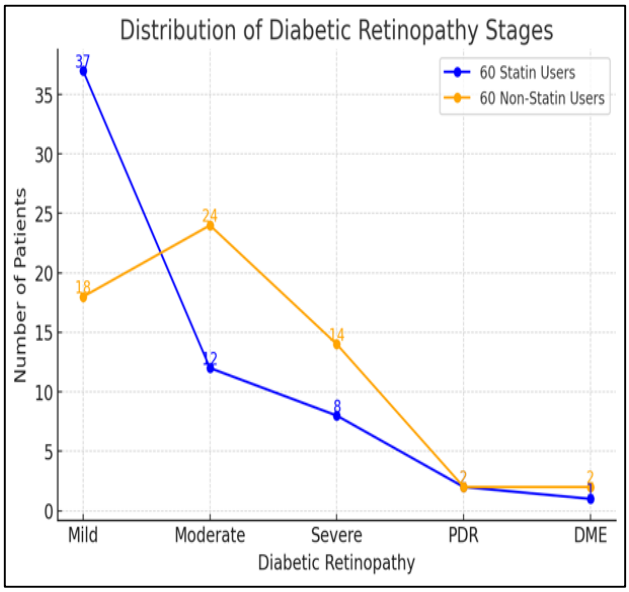

Figure 1: Line diagram representing various grades of diabetic retinopathy in patients taking statins and in those not taking statins.

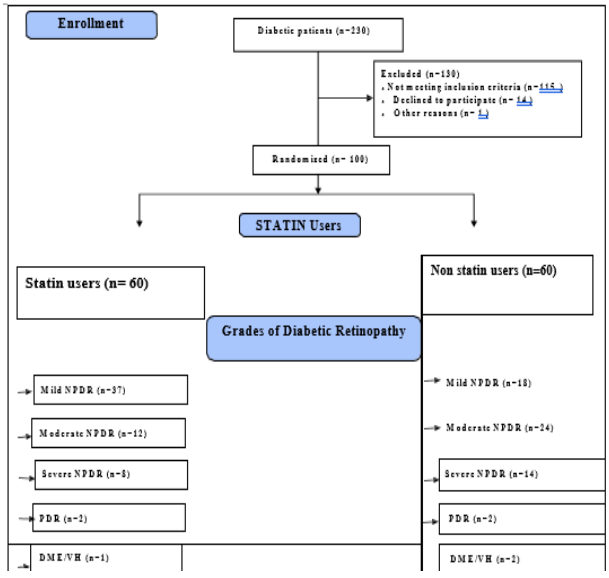

Figure 2: Represents the CONSORT diagram of the study participants.

The demographic and clinical profiles of the two groups are detailed in Table 1. Among the 60 statin users, there were 45 males and 15 females.

Among the 60 non-statin users, there were 30 males and 30 females. The mean age of all diabetic patients was 62.15 years, which was similar in both statin and non-statin users. The number of males taking statins was higher than females.

Hypertensive diabetic patients taking statins were 28, all of whom were male. Among those not taking statins, 33 hypertensive diabetic patients were identified, of which 24 were female and 9 were male. Out of the 60 statin users, 36 were smokers and 18 were alcoholics. Among the non-statin users, 32 were smokers and 8 were alcoholics.

The distribution of diabetic retinopathy severity in the two groups was among the 60 statin users, 37 (61.7%) had mild non-proliferative diabetic retinopathy (NPDR), 12 (20%) had moderate NPDR, 8 (13.3%) had severe NPDR, 2 (3.3%) had proliferative diabetic retinopathy (PDR), 1 (1.7%) had diabetic macular edema (DME).

Among the 60 non-statin users, 18 (30%) had mild NPDR, 24 (40%) had moderate NPDR, 14 (23.3%) had severe NPDR, 2 (3.3%) had PDR, 2 (3.3%) had DME. These findings are presented in Table 2 and Figure 1. The CONSORT diagram of the study participants is shown in Figure 2.

It was observed that patients who were prescribed statins had pre-existing hypertension and a higher predisposition to risk factors such as smoking and alcohol consumption compared to those not prescribed statins. Additionally, it was noted that patients not taking statins had higher HbA1c levels than those taking statins. Statistical analysis revealed that patients on statins had significantly lower grades of retinopathy compared to those not taking statins, with the difference being statistically significant (as shown in Figures 3 and 4).

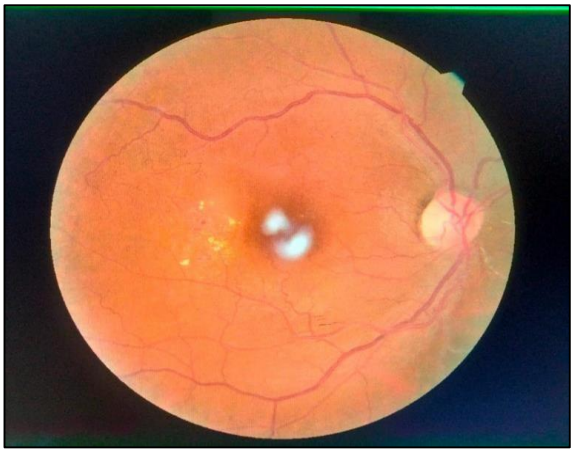

Figure 3: Fundus photo of a patient using statins showing hard exudates near the macula and few dot blot haemorrhages suggestive of mild grade of NPDR.

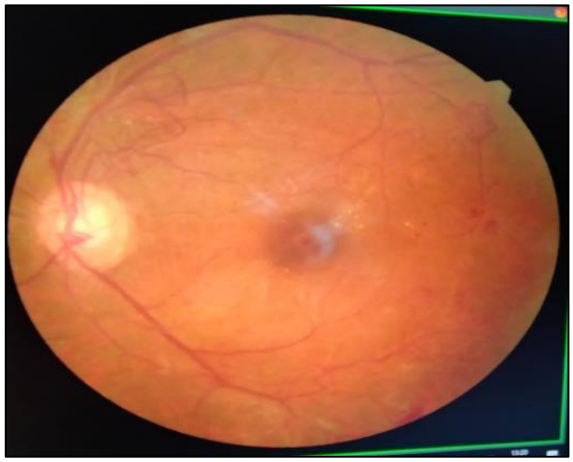

Figure 4: Fundus photo of a patient not using statins showing a higher retinopathy grade with neovascularisation else in the periphery and near the optic disc, hard exudates and dot blot haemorrhages suggestive of PDR.

Table 1: Demographic characteristics of the study population.

Characteristics	Statin users (n=60)	Non-statin users (n=60)
Sex		
Male	45	30
Female	15	30
Age (in years)		
55-60	20	12
61-65	30	36
66-70	10	12
Hypertension		
Male	28	24
Female	0	9
Smoking		
Male	36	16
Female	0	8

Continued.

Characteristics	Statin users (n=60)	Non-statin users (n=60)
Alcohol consumption		
Male	18	7
Female	0	1
HbA1c levels		
<7%	34	15
>7%	26	45

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

Grades of diabetic retinopathy	Statin users (%) (n=60)	Non-statin users (%) (n=60)
Mild NPDR	37 (61.7%)	18 (30%)
Moderate NPDR	12 (20%)	24 (40%)
Severe NPDR	8 (13.3%)	14 (23.3%)
Proliferative DR (PDR)	2 (3.3%)	2 (3.3%)
Diabetic macular edema (DME)/VH	1 (1.7%)	2 (3.3%)

DISCUSSION

Diabetes remains one of the most significant public health challenges, with diabetic retinopathy (DR) being a leading cause of vision impairment and blindness among individuals with type 2 diabetes mellitus (T2DM). The findings from this study indicate that statin therapy is associated with a lower severity of DR, suggesting a potential protective role against the progression of retinopathy.

Patients on statin therapy exhibited significantly lower grades of DR compared to non-statin users, with a higher proportion of mild non-proliferative diabetic retinopathy (NPDR) and a lower prevalence of severe NPDR, proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME). Statins are widely recognized for their lipid-lowering effects and their ability to reduce cardiovascular morbidity and mortality in diabetic patients. However, recent evidence also supports their role in modulating inflammatory processes, oxidative stress and endothelial dysfunction, which are central to the pathophysiology of DR.

The Wisconsin epidemiologic study of diabetic retinopathy (WESDR) demonstrated a correlation between elevated serum cholesterol levels and the presence of hard exudates in DR, emphasizing the role of lipid regulation in retinal health[10]. Similarly, a retrospective study from a tertiary care center in southern India found that DR progressed in 67% of non-statin users compared to only 37% of statin users, further supporting the protective role of statins.[13]

Several studies have investigated the impact of statin therapy on DR progression. A study by Gupta et al, highlighted that atorvastatin therapy significantly reduced hard exudates and sub-foveal lipid migration in patients with clinically significant macular edema (CSME), with 66.6% of statin users demonstrating regression compared to only 13.3% in the non-statin group.[12] Similarly, the ACCORD-EYE study found that fenofibrate combined with simvastatin was more effective in reducing DR progression than simvastatin alone, highlighting the potential benefit of combination lipid-lowering therapy.[11] The FIELD study also demonstrated that fenofibrate significantly reduced the need for laser treatment in DR patients.[16] The beneficial effects of statins in DR can be attributed to multiple mechanisms.

In addition to their lipid-lowering properties, statins have been shown to modulate inflammatory pathways by inhibiting nuclear factor-kappa B (NF-κB) activation and reducing vascular endothelial growth factor (VEGF) expression, which plays a crucial role in the pathogenesis of DR. By stabilizing endothelial function and reducing oxidative stress, statins may contribute to the maintenance of retinal microvascular integrity, thereby slowing the progression of DR.[18] Moreover, the anti-inflammatory properties of statins may help mitigate neurodegenerative processes in DR, which have been increasingly recognized as contributors to retinal damage[17].

Conversely, not all studies have uniformly supported the protective effects of statins against DR progression. A meta-analysis by Das et al, reviewed 21 studies and reported inconsistent findings regarding the impact of lipid-lowering therapy on diabetic macular edema.[14] Additionally, a large-scale Taiwanese cohort study involving 37,894 patients over five years found that while statin users had a significantly lower incidence of DR and macular edema, the absolute risk reduction was modest, suggesting that additional factors influence DR progression.[15]

These discrepancies underscore the need for further large-scale, long-term randomized controlled trials to establish the definitive role of statins in DR management. The findings from this study align with the growing body of evidence supporting the use of statins as an adjunctive

therapy for DR prevention and management. Given the high burden of diabetes and its complications, integrating statins into the standard of care for patients at risk of DR could be a cost-effective strategy to reduce the need for invasive and expensive interventions such as intravitreal anti-VEGF injections and laser photocoagulation.

Despite the promising findings, this study has several limitations. The sample size was relatively small, which may limit the generalizability of the results. Additionally, it was a single-center study conducted in India, so the findings may not be directly applicable to populations with different genetic, environmental and lifestyle factors. Another limitation is the absence of detailed information on statin dosage and duration of therapy, which could have influenced the outcomes

Future research should aim to address these limitations by employing multi-center, longitudinal study designs with larger and more diverse populations Such studies could help validate the current findings and provide deeper insights into the most effective statin regimens for the prevention of diabetic retinopathy.

CONCLUSION

This study highlights the potential protective role of statins in slowing the progression of diabetic retinopathy (DR) in type 2 diabetes mellitus (T2DM) patients. Statin users exhibited lower severity of DR, with reduced cases of proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME), suggesting anti-inflammatory and vaso-protective benefits beyond lipid-lowering effects.

Statin therapy may also decrease the need for invasive treatments like intravitreal anti-VEGF injections and vitrectomy, thereby improving visual outcomes and reducing healthcare burdens. Further large-scale studies are needed to confirm these findings and explore optimal dosing strategies. Incorporating statins into diabetes management could be a cost-effective approach to mitigating DR progression and preventing vision loss.

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

REFERENCES

1. World Health Organization. Prevention of Blindness from Diabetes Mellitus: Report of a WHO Consultation in Geneva, Switzerland, 9-11 November 2005. Geneva: WHO. 2006.
2. Antonetti DA, Klein R, Gardner TW. Diabetic retinopathy. N Engl J Med. 2012;366(13):1227-39.
3. Reddy SV, Husain D. Panretinal photocoagulation: A review of complications. Semin 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 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 Pharmacother. 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. Ophthalmology. 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 dyslipidemia: 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 Curr 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: Khan SA, Andanappa A, Kukunoor HR, Naidu SVVL, Toodi AR. Association of use of statins with progression of diabetic retinopathy: A randomized controlled trial at a tertiary care centre in Southern India. Int J Res Med Sci 2025;13:2902-8.