RESEARCH PAPER

Impact of Long-Term Statin Therapy on the Severity and Treatment of Diabetic Retinopathy in Type 2 Diabetes Mellitus

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ABSTRACT

Background: Diabetic retinopathy (DR) is one of the leading microvascular complications of type 2 diabetes mellitus (T2DM) and remains a major cause of preventable vision loss worldwide. In addition to glycemic control, dyslipidemia has been implicated in the progression of retinal vascular damage. Statins, widely prescribed for lipid-lowering therapy, may provide additional protective effects against the development and progression of diabetic retinopathy.

Aim: To assess the role of statin therapy in diabetic retinopathy among patients with type 2 diabetes mellitus.

Methods: A cross-sectional study was conducted among 110 patients with T2DM. Comprehensive ophthalmic evaluation, including dilated fundus examination and optical coherence tomography (OCT) of the macula, was performed in both eyes. Among the participants, 80 patients had been receiving statin therapy for more than 10 years, while 30 patients had never received statin therapy. The prevalence and severity of diabetic retinopathy and diabetic macular edema (DME) were compared between the two groups.

Results: The mean duration of diabetes was 17.5 ± 6.7 years. The overall prevalence of diabetic retinopathy was 46.35%. Mild non-proliferative diabetic retinopathy (NPDR) was observed in 20% of patients, moderate NPDR in 10.9%, severe NPDR in 6.36%, and proliferative diabetic retinopathy (PDR) in 9.09%. Diabetic macular edema was present in 20% of participants. Patients receiving long-term statin therapy demonstrated a lower incidence of diabetic macular edema and reduced need for treatment of diabetic retinopathy compared with those not receiving statins.

Conclusion: Long-term statin therapy appears to be associated with a reduced risk of sight-threatening diabetic retinopathy and diabetic macular edema in patients with type 2 diabetes mellitus. These findings suggest that lipid-lowering therapy may contribute to delaying disease progression and reducing the need for vision-saving interventions.

Keywords: Diabetic retinopathy, statin, diabetic macular edema, optical coherence tomography.

How to cite this article: Navya D, Swathi G, Dhanush HC. Impact of long-term statin therapy on the severity and treatment of diabetic retinopathy in type 2 diabetes mellitus. Int J Drug Deliv Technol. 2026;16(74s): 2016-2024. DOI: 10.25258/ijddt.16.74s.160

INTRODUCTION

Diabetic retinopathy is a major complication of diabetes and a significant cause of visual impairment worldwide, with sight threatening disease present in approximately 10% of persons with diabetes[1-9]. DME can be either secondary to focal leakage of microaneurysms or due to diffuse edema that occurs from extensive breakdown of the blood–retinal barrier with leakage of both microaneurysms and ischemic retinal capillaries. DME contributes to more vision loss. Hypergycemia and hypertension partly account for the risk of development and progression of diabetic retinopathy, suggesting that other pathogenetic mechanisms also play a role[10-12].Patients with diabetes

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mellitus are known to have severe lipid abnormalities, namely hypercholesterolemia and elevated serum triglycerides. Some observational studies suggested that elevated serum low-density lipoprotein cholesterol levels and elevated triglyceredemia are associated with increased incidence for diabetic retinopathy[13-15] but not in others. Statins reduce serum LDL-C levels and also modulates pathogenetic mechanisms involved in diabetic retinapathy. Statins exihibit antiangiogenic action in retinal endothelial cells by suppressing VEGF phosphorylation and preserve blood retinal barrier[16,17]. Conflicating results in observational studies and small interventional studies, randomized trials was seen. Hence the study was undertaken.

MATERIALS AND METHODS

This was a Cross Sectional study at Department of Ophthalmology from May 2019 to December 2019. 110 type 2 Diabetic patients referred from Departments of Medicine, endocrinology, nephrology were included in the study. 80 Type 2 diabetes mellitus on statin therapy for systemic diseasewere included in this study. Associated systemic factors Hypertension, Cardiovascular disease, Chronic kidney disease were included were included in this study. Type 2 Diabetes mellitus less than 10 years on statin therapy, Other retinal pathologies, Type 1 diabetes mellitus, Gestational diabetes mellitus were excluded from this study.

Ophthalmic examination and grading of DR

All patients were dilated with Tropicamide (0.8%w/v) + phenylephrine (5%w/v) and examined and fundus photography done. Grading of DR and macular edema was done with International clinical Diabetic retinopathy severity level. The level of retinopathy was graded based on worse eye. Stratus domain-OCT -macula of both eyes was done and central subfield thickness was noted.

Biochemical Parameters

Blood samples (2-3 mL) were taken from all subjects enrolled in this study by healthcare professionals following aseptic precautions through venipuncture technique using anticoagulant ethylenediaminetetraacetic acid (EDTA) tube for determination of glycated hemoglobin (HbA1c). Blood samples taken were carefully agitated to prevent any clot formation and sent immediately to the clinical biochemistry laboratory for testing. Levels of HbA1c were determined using an established method, for example, high performance liquid chromatography (HPLC) or automated immunoturbidimetric assay method in accordance with the manufacturer's recommendations and laboratory standard operating procedures. Internal quality control samples and regular calibration procedures were used in order to provide accuracy and reliability in measurements. The results obtained were presented as HbA1c concentration (% of total hemoglobin) for each individual subject.

Statistical Analysis

All collected data were entered into Microsoft Excel and verified for accuracy prior to statistical analysis. The statistical analysis was done using SPSS (Statistical Package for the Social Sciences, IBM SPSS Statistics, Version 26.0, IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean ± SD while categorical variables were presented as frequency (%). Distribution of the data was tested for normality using the Shapiro-Wilk test. Comparisons of two independent groups were done using independent samples Student's t-test for normally distributed data or the Mann-Whitney U test for non-normally distributed data. Comparisons of more than two groups were done using one-way analysis of variance (ANOVA) followed by a suitable post-hoc test. Relationship between categorical variables was done using Chi-square test or Fisher's exact test, as required, and relationship between HbA1c and other variables was done using Pearson or Spearman correlation, depending on the distribution of the data.

Ethical Approval

Ethical approval for the study was obtained from the Institutional Health Research and Ethics Committee before the initiation of the study. The study was carried out in line with the ethical standards stated in the Declaration of Helsinki and pertinent national guidelines on biomedical research involving human subjects. Detailed information on the aims, processes, benefits, and risks of participation in the study were provided to all qualified participants before recruitment into the study. Informed consent was obtained in writing from all participants before sample collection and data acquisition. Participation in the study was purely voluntary, and the participants were advised that they had the freedom to leave the study at any time without facing any penalty. Confidentiality and anonymity of all information about the participants were ensured by using unique identification codes and storing the records of the study securely. Biological samples and study data were used only for the purpose of the current study and could be accessed only by the researchers conducting the study.

III.RESULTS

Demographics

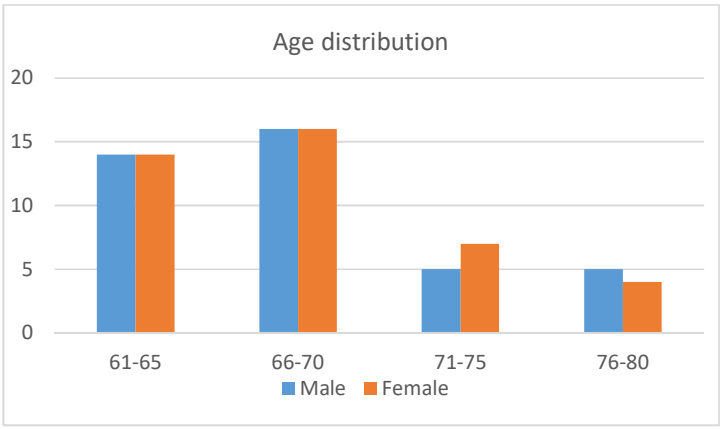


Figure 1. Age Distribution of Study Participants by Gender

A total of 110 patients-50% males and 50% females. The Mean Duration of diabetes was 17.50 years (SD-6.73 years). The majority of participants were in the 66–70 years age group for both males and females. Similar numbers of males and females were observed in the 61–65 and 66–70 years categories. Fewer participants were present in the 71–75 and 76–80 years age groups, with a slightly higher proportion of females in the 71–75 years category.

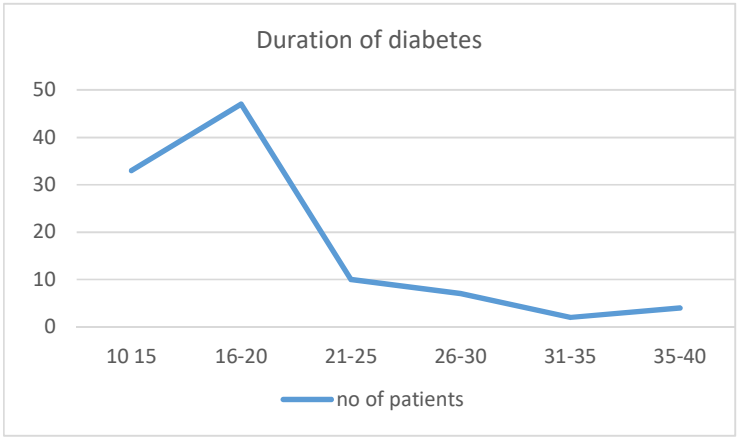
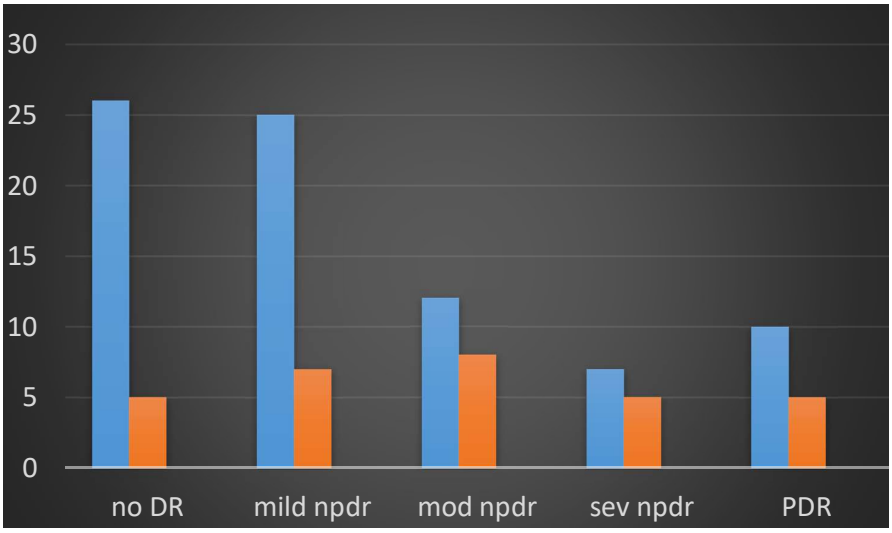


Figure 2. Distribution of Participants by Duration of Diabetes

The highest proportion of patients had a diabetes duration of 16–20 years, followed by 10–15 years. The number of patients gradually decreased with increasing duration beyond 20 years. Only a small proportion of participants had diabetes for 31–40 years.

Prevalence of Diabetic Retinopathy

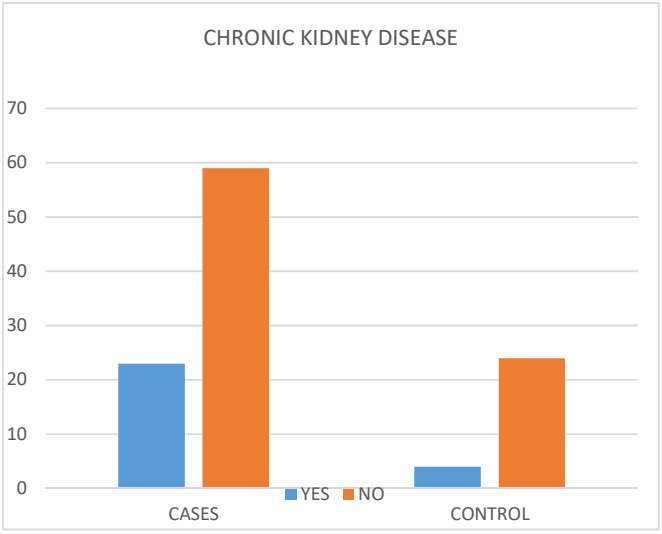


Statstically not significant p value< 0.05

Figure 3. Distribution of Diabetic Retinopathy Severity

The largest proportion of participants had no diabetic retinopathy, followed by mild NPDR. The frequency of patients decreased with increasing severity from moderate NPDR to severe NPDR and PDR. These findings indicate that early-stage diabetic retinopathy was more common than advanced disease in the study population.

Chronic Conditions

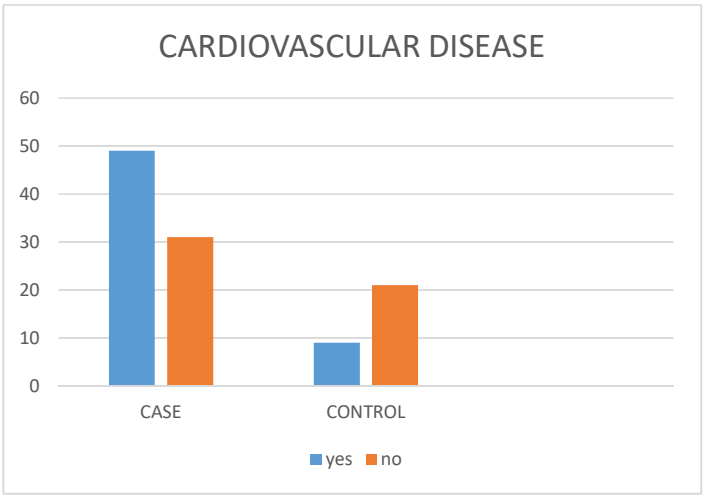


Statstically not significant p value> 0.05

Figure 4. Prevalence of Chronic Kidney Disease Among Cases and Controls

Among 29% of cases and 13% of Chronic kidney disease, Chronic kidney disease (CKD) was more prevalent among cases than controls. Most participants in both groups did not have CKD. The findings indicate a higher burden of CKD among cases compared to the control group.

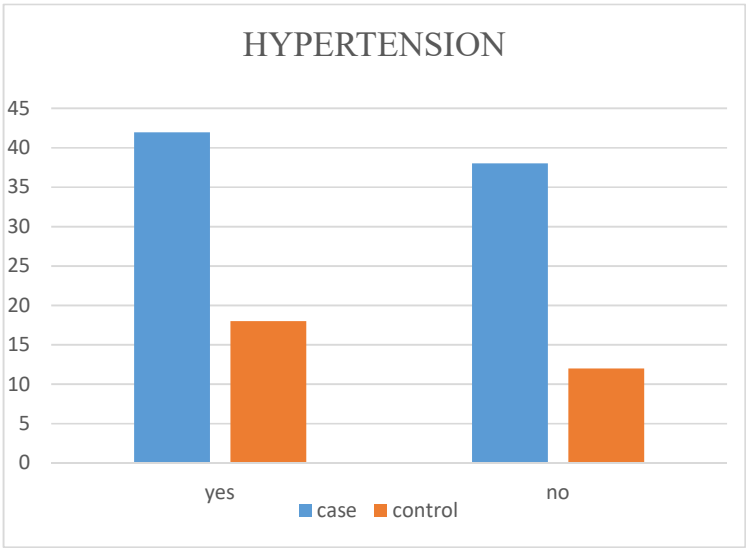
Cardiovascular Condition



Statstically significant p value< 0.05

Figure 5. Prevalence of Cardiovascular Disease Among Cases and Controls

Among 61% of cases and 30% cases of cardiovascular disease, Cardiovascular disease was more common among cases than controls. A greater proportion of controls did not have cardiovascular disease. These findings suggest an increased burden of cardiovascular disease among the case group.



Statstically significant p value< 0.05

Figure 6. Prevalence of Hypertension Among Cases and Controls

Among 52% of cases and 60% of controls of hypertension, Hypertension was more prevalent among cases than controls. In both groups, a greater proportion of participants had hypertension compared to those without hypertension. These findings indicate a higher burden of hypertension in the case group.

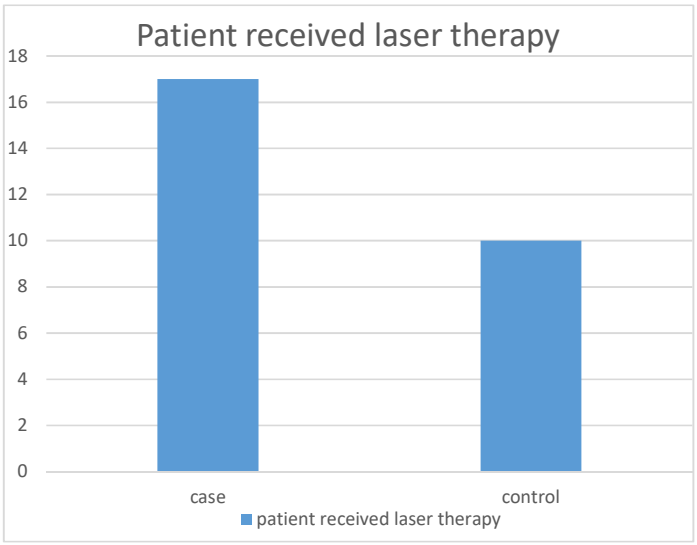
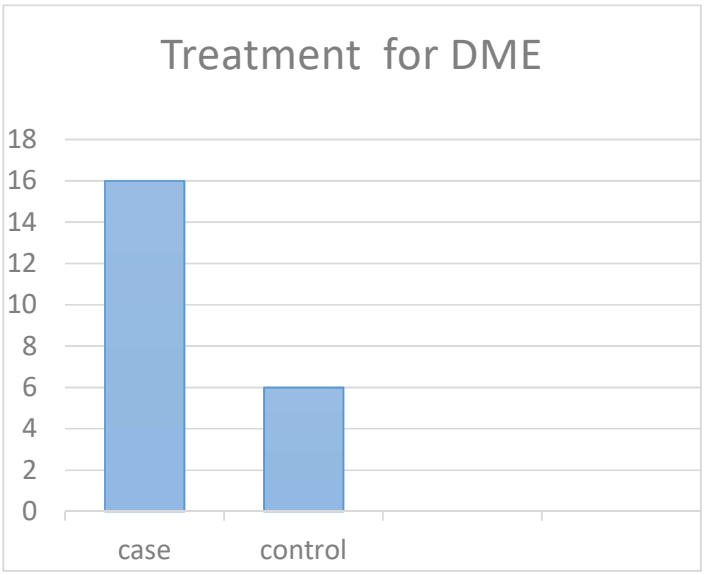


Figure 7. Patients Receiving Laser Therapy in Cases and Controls

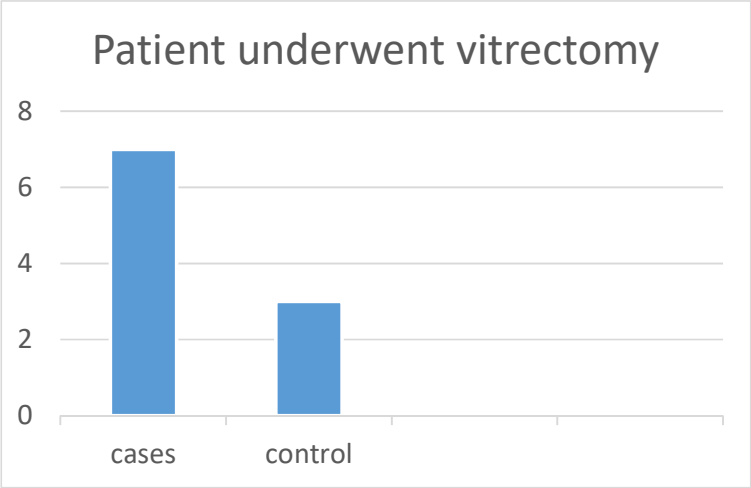
A higher number of cases received laser therapy compared to controls. This suggests that retinal disease requiring laser treatment was more common among cases. The findings indicate a greater need for therapeutic intervention in the case group.



Statstically significant p value< 0.05

Figure 8. Patients Receiving Treatment for Diabetic Macular Edema (DME)

A greater number of cases required treatment for diabetic macular edema compared to controls. The need for DME treatment was considerably lower in the control group. These findings suggest that sight-threatening macular involvement was more common among cases.



Statstically significant p value< 0.05

Figure 9. Patients Undergoing Vitrectomy in Cases and Controls

A higher number of cases underwent vitrectomy compared to controls. The requirement for vitrectomy was relatively low in the control group. These findings suggest that advanced diabetic retinopathy requiring surgical intervention was more common among cases.

DISCUSSION

The present study evaluated the association between long-term statin therapy and diabetic retinopathy (DR) among patients with type 2 diabetes mellitus and demonstrated that although the overall prevalence of diabetic retinopathy was not significantly different between statin users and non-users, patients receiving statin therapy for more than 10 years had a lower incidence of diabetic macular edema (DME) and a reduced requirement for laser or intravitreal treatment. These findings suggest that the beneficial effects of lipid-lowering agents may primarily involve slowing the progression of sight-threatening retinal complications rather than preventing the initial development of diabetic retinopathy. Dyslipidemia has been recognized as an important contributor to retinal endothelial dysfunction, oxidative stress, inflammation, and vascular leakage, all of which play critical roles in the pathogenesis of diabetic macular edema. Beyond lowering serum cholesterol, statins possess pleiotropic properties including anti-inflammatory, antioxidant, anti-thrombotic, and endothelial-stabilizing effects, which may reduce retinal vascular permeability and inhibit progression to advanced retinopathy. Similar observations were reported in the FIELD study, where fenofibrate significantly reduced the need for laser treatment despite showing only modest effects on the overall incidence of diabetic retinopathy, suggesting that lipid-lowering therapy mainly delays disease progression rather than disease onset [12-13]. Likewise, the ACCORD Eye Study demonstrated that intensive lipid management with fenofibrate combined with statins significantly reduced the progression of diabetic retinopathy over four years compared with statin therapy alone [8]. A recent systematic review and meta-analysis further concluded that lipid-lowering therapy exerts a protective effect against DR progression and is associated with a lower risk of developing diabetic macular edema, supporting the observations of the present study [10].

Despite the beneficial effects observed with statin therapy, no significant difference was found in the overall occurrence of diabetic retinopathy between the two study groups. This finding is consistent with several observational studies suggesting that while statins may not prevent the onset of DR, they can reduce retinal vascular leakage and delay progression to vision-threatening complications [4,5]. It is also important to consider the influence of confounding factors in the present study. Patients receiving long-term statin therapy had a higher prevalence of hypertension and cardiovascular disease, both of which are well-established independent risk factors for diabetic retinopathy progression through mechanisms involving endothelial dysfunction, impaired retinal perfusion, and chronic inflammation [11]. Furthermore, many patients in the statin-treated group were concurrently receiving low-dose aspirin (Ecosprin) for cardiovascular protection. Although evidence from the Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated that aspirin does not increase the risk of retinal or vitreous hemorrhage and should not be withheld when clinically indicated, its concurrent use may still represent a potential confounding factor when evaluating retinal outcomes [15]. Therefore, while the findings of the present study support the beneficial role of lipid-lowering agents in reducing diabetic macular edema and treatment requirements, the cross-sectional design precludes establishing a causal relationship. Larger multicenter prospective studies and randomized controlled trials controlling for cardiovascular comorbidities, glycemic status, and concomitant medications are required to better define the independent role of statins in preventing the progression of diabetic retinopathy.

CONCLUSION

In conclusion, the present study suggests that long-term statin therapy may play a beneficial role in reducing the progression of sight-threatening diabetic retinopathy in patients with type 2 diabetes mellitus. Although no significant difference was observed in the overall prevalence of diabetic retinopathy between statin users and non-users, patients receiving statins for more than 10 years demonstrated a lower incidence of diabetic macular edema and a reduced requirement for retinal interventions such as laser therapy. These findings indicate that the protective effect of lipid-lowering agents is primarily associated with limiting disease progression rather than preventing the onset of diabetic retinopathy. Hypertension, cardiovascular disease, and concomitant medications such as aspirin may have influenced retinal outcomes and should be considered as potential confounding factors. Overall, the study supports the incorporation of statin therapy as an adjunct to optimal glycemic and cardiovascular risk management for reducing vision-threatening complications in patients with type 2 diabetes mellitus. However, larger multicenter prospective studies and randomized controlled trials are warranted to establish a definitive causal relationship and further clarify the independent role of statins in the prevention and progression of diabetic retinopathy.

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