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Original Research Article

Comparison of Pharmacologic Mydriasis Achieved with Fixed Combination 0.8% Tropicamide + 5% Phenylephrine in Type 2 Diabetes Mellitus Versus Non-Diabetic Adults: A Prospective Comparative Study

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Abstract

Background: Adequate pupil dilation is essential for reliable posterior segment examination and retinal screening. Adults with type 2 diabetes mellitus (T2DM) may exhibit smaller baseline pupil diameter and reduced pharmacologic dilation due to autonomic dysfunction affecting iris musculature. Fixed-combination mydriatics (0.8% tropicamide + 5% phenylephrine) are widely used and considered safe and effective in routine ophthalmic practice.

Aim: To compare the magnitude and time course of mydriasis obtained with 0.8% tropicamide + 5% phenylephrine in adults with T2DM versus non-diabetic adults.

Methods: In this prospective comparative study (n=150), adults attending the ophthalmology outpatient services underwent standardized dilation using fixed combination tropicamide 0.8% + phenylephrine 5%. Pupil diameter (mm) was measured under uniform illumination at baseline and at 10, 20, 30, and 45 minutes after instillation. Primary outcome was mean pupil diameter over time; secondary outcomes included proportion achieving adequate mydriasis (≥6.5 mm) by time and predictors of inadequate mydriasis at 45 minutes. Comparative statistics and multivariable logistic regression were performed.

Results: Baseline pupil diameter was smaller in T2DM than non-diabetes (2.97 ± 0.45 vs 3.25 ± 0.54 mm; p=0.0006). At each time point after instillation, dilation was significantly lower in T2DM (all p<0.0001). At 45 minutes, mean pupil diameter was 6.19 ± 0.75 mm in T2DM vs 7.36 ± 0.69 mm in non-diabetes (p<0.0001). Adequate mydriasis (≥6.5 mm) at 45 minutes occurred in 32.0% of T2DM vs 90.7% of non-diabetes; T2DM had higher risk of inadequate mydriasis at 45 minutes (RR 7.29; 95% CI 3.54–15.00). In multivariable analysis, T2DM status (adjusted OR 29.39; 95% CI 8.76–98.57) and smaller baseline pupil diameter (per 0.5 mm increase, adjusted OR 0.18; 95% CI 0.09–0.37) independently predicted inadequate mydriasis.

Conclusion: With fixed-combination 0.8% tropicamide + 5% phenylephrine, adults with T2DM achieved significantly less and slower mydriasis than non-diabetics. Smaller baseline pupil diameter strongly predicted inadequate dilation. Diabetic patients may require protocol adjustments (additional dosing, extended waiting time, or adjunct regimens) to ensure reliable retinal evaluation.

Keywords: mydriasis; tropicamide; phenylephrine; type 2 diabetes mellitus; pupil diameter; autonomic neuropathy; retinal screening.

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Introduction

Pharmacologic mydriasis is fundamental to comprehensive ophthalmic assessment, enabling accurate optic nerve evaluation, retinal examination, and timely detection of sight-threatening conditions. In clinical workflows—particularly in settings managing high volumes of diabetic retinopathy screening—rapid and reliable pupil dilation improves diagnostic quality, reduces missed pathology, and enhances patient throughput. However, variability in dilation response is common and clinically relevant, with a subset of patients demonstrating inadequate mydriasis despite standard regimens. [6–8] Adults with diabetes mellitus represent a key group in whom pupil dynamics may differ from the general population. Several mechanisms contribute to altered pupillary behavior in diabetes. First, diabetic autonomic neuropathy can impair sympathetic and parasympathetic control of the iris, producing smaller resting pupil diameter, reduced dilation in

darkness, and altered pupillary light reflexes. Classic physiologic and clinical studies have demonstrated reduced pupillary reflex amplitudes and impaired dilation in diabetic individuals, supporting sympathetic dysfunction as a major contributor. [1,2] Subsequent work reinforced that pupillary abnormalities may appear even when other neuropathy markers are absent, indicating that ocular autonomic involvement can be an early or independent manifestation. [3] In practice, this may translate into reduced responsiveness to mydriatic drugs and a higher likelihood of suboptimal dilation during fundus examination.

Pharmacologic agents commonly used for diagnostic mydriasis include antimuscarinics (e.g., tropicamide) and adrenergic agonists (e.g., phenylephrine). Tropicamide inhibits parasympathetic stimulation of the iris sphincter muscle, while phenylephrine stimulates the iris dilator muscle via α-adrenergic receptors. Their combined use is intended to provide additive dilation by acting on complementary pathways. Multiple studies in diverse populations have evaluated the efficacy of combination regimens, often finding that combination therapy increases the magnitude and/or speed of dilation compared with monotherapy in routine settings. [7–9] Combination solutions have also been developed for convenience and to reduce dosing complexity, with evidence of effective dilation and workflow advantages. [8,9]

The fixed combination of 0.8% tropicamide with 5% phenylephrine has gained wide use in preoperative and diagnostic contexts. Safety evaluations have generally shown acceptable tolerability, with clinically manageable changes in vital parameters in most patient populations when used appropriately. [4] Contemporary ophthalmic guidance also supports the safety of pharmacologic dilation in diabetic retinopathy evaluation, emphasizing the low risk of acute angle-closure events when standard screening and precautions are applied. [6] Additionally, recent ophthalmic studies using this combination have examined ocular parameter changes and provide supportive evidence for its routine clinical deployment. [5] Despite the established role of combined mydriatics, the diabetic population remains clinically challenging. Prior work suggests that diabetic pupils may respond relatively poorly to tropicamide alone but better to combination regimens, implying that the adrenergic component may partly compensate for autonomic dysfunction—yet the degree of compensation may vary with disease duration, glycemic control, and baseline pupil size. [10,11] In Indian clinical settings, where dark irides are common and diabetes prevalence is high, these issues can be magnified, and inadequate mydriasis may directly affect the quality of retinal evaluation. Studies in darker-pigmented irides and diabetic cohorts have reported differences in mydriatic response and the need for tailored protocols. [11]

Given the public health burden of diabetes and the central role of dilated retinal examination, it is important to quantify real-world mydriatic response differences between diabetic and non-diabetic adults using the same fixed combination regimen. Such comparative data can guide practical adjustments—additional dosing, extended waiting time, or alternative regimens—especially in busy tertiary hospitals and screening programs. Therefore, the present study aimed to compare the time course and magnitude of pupil dilation achieved using fixed-combination 0.8% tropicamide + 5% phenylephrine in adults with type 2 diabetes mellitus versus non-diabetic adults at a government tertiary care hospital in Bihar, India.

Materials and Methods

This prospective comparative study was conducted in the Department of Ophthalmology, Jawaharlal Nehru Medical College, Bhagalpur, Bihar, India, from 10th April 2021 to 10th February 2023. A total of 150 adult participants were enrolled after clinical evaluation: 75 with diagnosed type 2 diabetes mellitus (T2DM) and 75 non-diabetic controls, matched pragmatically by outpatient attendance patterns. Participants with active ocular infection, significant corneal pathology precluding measurement, known hypersensitivity to study drugs, history of angle-closure glaucoma, prior intraocular surgery within the preceding months, or inability to comply with measurement timing were excluded. After baseline assessment, a fixed combination of tropicamide 0.8% + phenylephrine 5% was instilled following the unit's standardized dilation protocol used in routine practice. Pupil diameter (in mm) was measured under consistent ambient illumination using the same measurement technique and instrument throughout (standardized pupillary measurement approach), at baseline (0 min) and at 10, 20, 30, and 45 minutes post-instillation. The primary endpoint was mean pupil diameter at each time point and overall dilation trajectory. Secondary endpoints included the proportion achieving adequate mydriasis (defined a priori as ≥6.5 mm for reliable diagnostic fundus evaluation) by each time point, and predictors of inadequate mydriasis at 45 minutes. Statistical analyses included between-group comparisons using appropriate parametric tests, estimation of risk ratios for inadequate dilation, and multivariable logistic regression to identify independent predictors. A p value <0.05 was considered statistically significant.

Result

Table 1 presents the baseline demographic and clinical characteristics of the study participants. The mean age was slightly higher in the Type 2 diabetes

group compared to the non-diabetic group, while the gender distribution between the two groups was comparable. The baseline pupil diameter was significantly smaller in diabetic patients than in non-diabetics ($p < 0.001$), indicating a reduced resting pupillary size in diabetes. As expected, the mean HbA1c level was significantly higher in the diabetic group, reflecting poor glycemic control, and the median duration of diabetes was approximately four years among diabetic participants. These baseline differences provide important context for interpreting the variation in pharmacologic mydriasis observed between the two groups.

Table 1: Baseline Demographic and Clinical Characteristics of Study Participants (Type 2 Diabetes Mellitus vs Non-Diabetic Group)

Characteristic	T2DM (n=75)	Non-DM (n=75)	P value
Age (years), mean ± SD	58.59 ± 8.58	55.56 ± 7.81	0.0251
Male sex, n (%)	35 (46.7)	46 (61.3)	0.1014
Baseline pupil diameter (mm), mean ± SD	2.97 ± 0.45	3.25 ± 0.54	0.0006
HbA1c (%), mean ± SD	8.43 ± 1.24	5.45 ± 0.35	<0.0001
DM duration (years), median (IQR)	3.9 (2.5–7.0)	NA	

Table 2 shows the mean pupil diameter at baseline and at different time intervals (10, 20, 30, and 45 minutes) after instillation of the fixed combination of 0.8% tropicamide and 5% phenylephrine in both diabetic and non-diabetic participants. At baseline, diabetic patients had a significantly smaller pupil diameter compared to non-diabetic individuals. After administration of the mydriatic drops, pupil dilation increased progressively over time in both groups; however, the degree of dilation remained significantly lower in the diabetic group at all time points ($p < 0.0001$). These findings indicate that pharmacologic mydriasis occurs more slowly and reaches a smaller maximal diameter in patients with type 2 diabetes compared to non-diabetic subjects.

Table 2: Comparison of Mean Pupil Diameter at Different Time Intervals Following Instillation of 0.8% Tropicamide and 5% Phenylephrine

Time (minutes)	T2DM mean ± SD (mm)	Non-DM mean ± SD (mm)	Between-group P value
0	2.97 ± 0.45	3.25 ± 0.54	0.0006
10	4.95 ± 0.66	6.08 ± 0.71	<0.0001
20	5.73 ± 0.70	6.96 ± 0.69	<0.0001
30	6.04 ± 0.69	7.22 ± 0.68	<0.0001
45	6.19 ± 0.75	7.36 ± 0.69	<0.0001

Table 3 presents the proportion of participants achieving adequate mydriasis (pupil diameter ≥6.5 mm) at different time intervals after instillation of the fixed combination of 0.8% tropicamide and 5% phenylephrine. A significantly higher proportion of non-diabetic subjects achieved adequate pupil dilation compared to diabetic patients at all time points (20, 30, and 45 minutes). By 45 minutes, more than 90% of non-diabetic individuals achieved adequate mydriasis, whereas only about one-third of diabetic patients reached the same level of dilation. These findings suggest that pharmacologic pupil dilation is less effective and slower in patients with type 2 diabetes mellitus.

Table 3: Proportion of Participants Achieving Adequate Mydriasis (Pupil Diameter ≥6.5 mm) at Different Time Points After Mydriatic Instillation

Time (minutes)	Group	Adequate mydriasis ≥6.5 mm (n, %)	95% CI for proportion
20	T2DM	11 (14.7%)	6.7–22.7
20	Non-DM	54 (72.0%)	61.8–82.2
30	T2DM	19 (25.3%)	15.5–35.2
30	Non-DM	64 (85.3%)	77.3–93.3
45	T2DM	24 (32.0%)	21.4–42.6
45	Non-DM	68 (90.7%)	84.1–97.3

Table 4 shows the multivariable logistic regression analysis identifying predictors of inadequate mydriasis (pupil diameter <6.5 mm) at 45 minutes after instillation of the mydriatic combination. In the overall study population, the presence of type 2 diabetes mellitus was a strong independent predictor of inadequate dilation, while a larger baseline pupil diameter significantly reduced the risk of

insufficient mydriasis. In the subgroup analysis among diabetic patients, smaller baseline pupil size remained a significant predictor of inadequate dilation, whereas longer duration of diabetes showed a borderline association. These findings suggest that both diabetic status and baseline pupil diameter play an important role in determining the effectiveness of pharmacologic pupil dilation.

Table 4: Multivariable Logistic Regression Analysis of Predictors Associated with Inadequate Mydriasis (Pupil Diameter <6.5 mm) at 45 Minutes

Model	Variable	Adjusted OR	95% CI	P value
Model A (All participants)	Type 2 Diabetes vs Non-DM	29.39	8.76 – 98.57	<0.001
Model A (All participants)	Baseline pupil diameter (per 0.5 mm increase)	0.18	0.09 – 0.37	<0.001
Model B (T2DM only)	Baseline pupil diameter (per 0.5 mm increase)	0.19	0.08 – 0.47	0.0003
Model B (T2DM only)	Duration of diabetes (per year)	1.22	0.99 – 1.50	0.0643

Figure 1 illustrates the mean pupil diameter over time following instillation of the fixed combination of 0.8% tropicamide and 5% phenylephrine in both diabetic and non-diabetic participants.

The graph shows a progressive increase in pupil size in both groups; however, the diabetic group consistently demonstrates smaller pupil dilation at each time point compared to the non-diabetic group.

This indicates that pharmacologic mydriasis is slower and less pronounced in patients with type 2 diabetes mellitus.

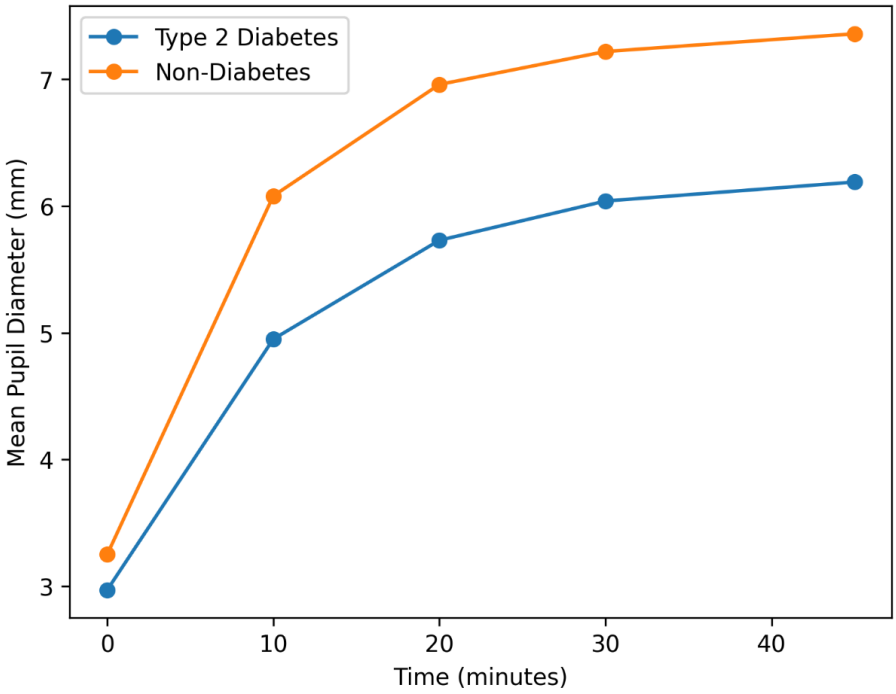

Figure 1: Mean Pupil Dilation over time Mydriatic Instillation

Figure 2 presents the percentage of participants achieving adequate mydriasis (pupil diameter ≥6.5 mm) at different time intervals after administration of the fixed combination of 0.8% tropicamide and 5% phenylephrine.

The figure demonstrates that a significantly higher proportion of non-diabetic participants achieved adequate dilation earlier and in greater numbers compared to diabetic patients.

Even at 45 minutes, the rate of adequate mydriasis remained markedly lower in the diabetic group, indicating reduced responsiveness to pharmacologic dilation in individuals with type 2 diabetes mellitus.

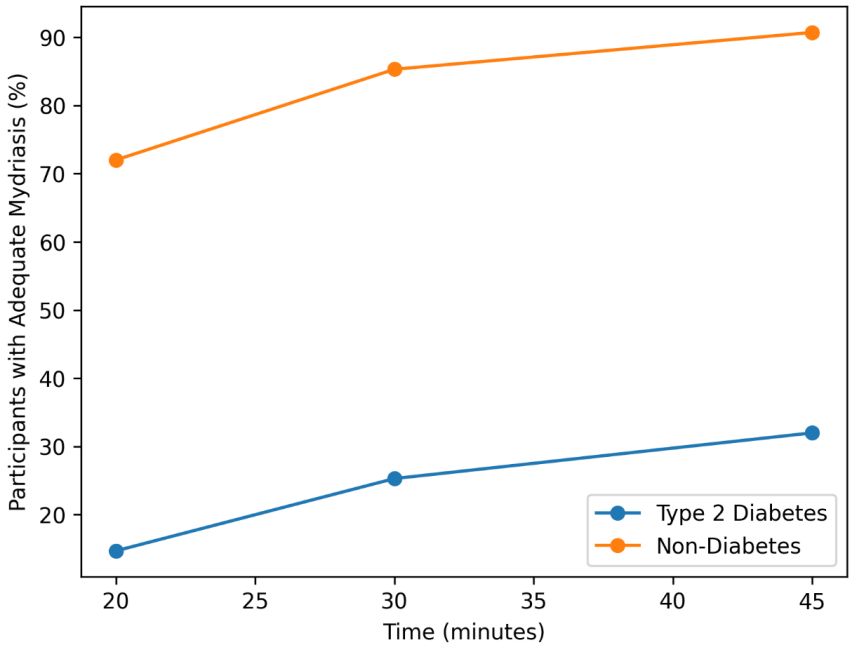

Figure 2: Proportion achieving adequate mydriasis (≥6.5 mm)

Discussion

This study demonstrates that adults with T2DM achieve significantly smaller and slower pharmacologic mydriasis than non-diabetic adults following a fixed combination of 0.8% tropicamide + 5% phenylephrine. Baseline pupil diameter was smaller in T2DM, and after instillation, the difference between groups remained pronounced at every measured time point. Importantly, when "adequate" diagnostic dilation was operationalized as ≥6.5 mm, only about one-third of T2DM participants met this criterion by 45 minutes compared with >90% of non-diabetics—an effect size that is clinically meaningful for retinal evaluation and diabetic retinopathy screening workflows.

These findings align with established evidence that diabetes affects pupillary function through autonomic neuropathy and related neurovascular mechanisms. Early landmark work described reduced pupillary reflex responses and impaired dilation in diabetics, suggesting sympathetic dysfunction and, in some cases, additional parasympathetic impairment. [1] Later studies supported that pupillary autonomic abnormalities can be present even without clear correlations to peripheral neuropathy or cardiovascular autonomic testing, emphasizing that pupillary dysfunction may represent an independent or early manifestation. [3] Observational and review-style discussions in ophthalmology have reiterated that diabetics—particularly those with subtle autonomic involvement—may show smaller pupil diameters and slower dynamics, which can become clinically apparent during attempted diagnostic dilation. [12,13] Our baseline pupil diameter differences and reduced dilation trajectory are consistent with these biologic expectations.

Combination mydriasis is widely used because tropicamide and phenylephrine act on different iris muscle pathways, and multiple studies report improved dilation with combination regimens. [7–9] Prior comparative work has shown superiority of combination therapy over phenylephrine alone and, in many settings, incremental benefit over tropicamide alone. [7] Fixed-combination solutions may also enhance usability and reduce sequencing errors, with studies demonstrating efficient dilation and practical advantages of single-bottle regimens. [8,9] Safety evidence for 0.8% tropicamide + 5% phenylephrine indicates overall tolerability, with clinically acceptable changes in systemic parameters in monitored settings. [4,5] In addition, professional statements addressing dilation for diabetic retinopathy evaluation support the overall safety of pharmacologic mydriasis when appropriate precautions are taken, with very low risk of acute angle-closure glaucoma in typical screening contexts. [6]

However, while combination therapy is effective in many patients, diabetic eyes may remain comparatively resistant due to impaired iris dilator responsiveness, altered receptor sensitivity, and structural or microvascular changes in the iris that accompany chronic hyperglycemia. Evidence from diabetic cohorts with pigmented irides has suggested that stronger or combined regimens may be needed to achieve satisfactory dilation, supporting the rationale that diabetics may respond poorly to tropicamide alone but more completely to combination therapy—though still with variability. [10,11] Our data extend this clinical message by

quantifying the gap between T2DM and non-diabetic adults under the same regimen and timing schedule in a tertiary government hospital population.

A key practical contribution of this study is the identification of predictors of inadequate mydriasis. In adjusted modeling across all participants, T2DM status remained a strong independent predictor, and baseline pupil diameter emerged as an especially powerful determinant of dilation adequacy. This is clinically intuitive: a smaller starting pupil likely reflects underlying autonomic or structural limitations and leaves less "reserve" for reaching target diameters within standard waiting times. Within the T2DM subgroup, smaller baseline diameter remained significant, and longer diabetes duration showed a borderline association—consistent with the concept that longer disease exposure increases the probability of autonomic dysfunction and iris changes. [2,12] Notably, HbA1c did not independently predict inadequate dilation in the T2DM-only model, which may reflect the complexity of cumulative exposure, interindividual susceptibility, and the fact that a single HbA1c snapshot may not fully capture long-term glycemic burden relevant to neuropathic change. From a service-delivery perspective, these findings suggest that "one-size-fits-all" dilation protocols may underperform in T2DM populations. Practical options include additional instillation cycles, longer waiting times, earlier triage of diabetics for dilation, or consideration of alternative/additional agents where clinically appropriate—balanced against safety considerations, blood pressure monitoring in selected patients, and contraindications. [4,6] The goal is not merely larger pupils but more consistent attainment of diagnostic adequacy to avoid missed retinopathy lesions and reduce repeated visits. This study has limitations. Measurements were made at defined time points rather than continuous pupillometry; lighting and measurement standardization were implemented but small variations can influence absolute diameters. The single-center nature may limit generalizability; nonetheless, the hospital setting and high diabetes burden enhance real-world relevance. Future work could incorporate objective autonomic testing or dynamic pupillometry and examine optimized protocols tailored to baseline pupil size and diabetes duration. Overall, the study supports a simple clinical inference: T2DM eyes dilate less and slower under standard fixed-combination tropicamide-phenylephrine protocols, and baseline pupil size can help anticipate those likely to need enhanced regimens.

Conclusion

Adults with type 2 diabetes mellitus achieved significantly reduced and delayed mydriasis compared with non-diabetic adults after fixed-combination 0.8% tropicamide + 5% phenylephrine. Smaller baseline pupil diameter strongly predicted inadequate dilation. In clinical practice, diabetic patients may require additional dosing and/or longer waiting time to reach diagnostically adequate dilation for retinal examination.

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