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Evaluating The Protective Role Of Dapagliflozin In Diabetic Retinopathy Among Well-Controlled Type 2 Diabetes Mellitus Patients: A Prospective Cohort Study

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Abstract

Background:
Diabetic retinopathy (DR), a major microvascular complication of diabetes mellitus (DM), is a leading cause of preventable blindness worldwide. Despite significant advancements in glycemic control strategies, DR prevalence remains high, particularly in low-resource settings like India. Dapagliflozin, a selective SGLT2 inhibitor, is widely used for glycemic management and has shown promise in mitigating microvascular complications.

Objective:
To compare the prevalence and progression of diabetic retinopathy in well-controlled Type 2 DM patients treated with dapagliflozin versus those not receiving it, and to assess its potential protective effect on retinal health.

Methods:
This prospective cohort study enrolled 216 patients with T2DM (HbA1c <7%), divided equally into two groups: Group-D (Metformin + Glimepiride + Dapagliflozin) and Group-M (Metformin + Glimepiride). Patients underwent baseline and follow-up retinal evaluations using indirect ophthalmoscopy and optical coherence tomography (OCT), along with glycemic, lipid, and renal profiling. DR prevalence, retinal thickness changes, and progression were monitored over 24 months.

Results:
Group-D showed significantly lower prevalence of DR (29.6%) compared to Group-M (42.6%), with 70.4% vs. 57.4% having no DR, respectively ($p = 0.038$). Progression of DR was also less frequent in Group-D at 12 months (16.7% vs. 25.9%, $p = 0.039$). Furthermore, Group-D exhibited a significantly smaller increase in retinal thickness over 24 months (+6.3 µm vs. +13.1 µm, $p < 0.001$).

Conclusion:
Dapagliflozin may offer protective effects against the development and progression of diabetic retinopathy. Its integration into standard therapy could enhance long-term retinal outcomes in patients with T2DM.

Keywords: Diabetic Retinopathy,Dapagliflozin,Type 2Diabetes Mellitus ,SGLT2 Inhibitors ,Retinal Thickness

INTRODUCTION

Diabetes mellitus (DM) has become a pressing global health concern, with 382 million adults affected in 2013 and projections estimating 592 million cases by 2035. The steepest rise is expected in Asia and Sub-Saharan Africa due to urbanization, sedentary habits, and poor diets. India, with 77 million diabetics, ranks second globally, behind China. Diabetic retinopathy (DR), a leading microvascular complication of DM, accounts for nearly 5% of global blindness, impacting around 2 million people [1]. Risk factors such as long-standing diabetes, poor glycemic control, hypertension, and dyslipidemia heighten susceptibility to DR. Despite advancements in diabetes care in developed nations, countries like India continue to face challenges in DR management due to inadequate awareness, limited screening programs, and delayed diagnosis [2,3]. Early identification and timely intervention—including regular screenings, glycemic control, and treatments like laser photocoagulation and anti-VEGF injections—are crucial for preventing vision loss [4].

Nearly half of all individuals with DM are expected to develop some form of DR during their lifetime [5]. Functional retinal changes may precede vascular manifestations, with early neuroretinal damage detected via ERG, EOG, and VEP techniques [6]. Hyperglycemia triggers oxidative stress, inflammation, and endothelial dysfunction, leading to increased vascular permeability, ischemia, and neovascularization—hallmarks of DR [7]. The diversion of glucose into the polyol pathway in hyperglycemic states results in harmful byproducts that further aggravate retinal damage [8–10]. While treatments like pan-retinal photocoagulation and anti-VEGF agents have shown efficacy, they are most beneficial in advanced DR stages and are not uniformly effective across all patients [11]. Consequently, there is growing interest in exploring novel therapeutic strategies that offer earlier, more effective intervention.

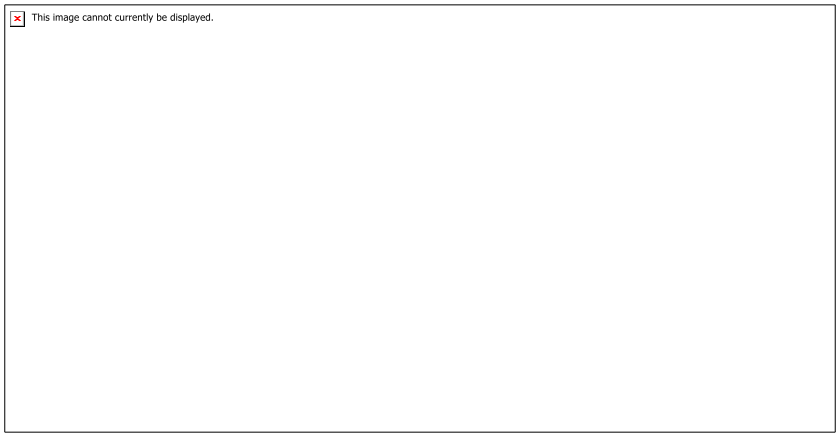
Dapagliflozin, a selective SGLT2 inhibitor, is widely used in DM management and has demonstrated cardiovascular and renal protective effects [12,13]. Emerging research indicates that SGLT2 is expressed in retinal microvasculature, and dapagliflozin may offer neuroprotective and anti-angiogenic benefits. Studies on SGLT2 inhibitors like phlorizin and ipragliflozin show reduced retinal gliosis, better ERG results, and even cataract prevention [14,15]. Dapagliflozin has been found to improve visual acuity in diabetic macular edema and reduce pathological changes in retinal arterioles [16]. Its multifactorial benefits include improved glycemic control, reduced HbA1c, body weight, and blood pressure, alongside enhanced retinal microvascular health [17]. This study aims to compare the prevalence of DR in well-controlled Type 2 DM patients receiving dapagliflozin (Group-D) versus those not receiving it (Group-M), to evaluate its potential protective role against DR development and progression.

METHODOLOGY

This prospective cohort study was conducted in the Department of Medicine in collaboration with the Department of Ophthalmology at S.N. Medical College, Agra, over 1.5 years (June 2023–January 2025). A total of 216 patients with Type 2 Diabetes Mellitus (T2DM) meeting the inclusion criteria (age 30–70 years, diabetes duration ≥5 years, dual oral hypoglycemic therapy, and HbA1c <7%) were enrolled after obtaining written informed consent. Patients with diabetic nephropathy, non-diabetic retinopathy, Type 1 DM, or unwillingness to participate were excluded. Sample size was calculated using standard formulae with a 95% confidence level and 5% margin of error, based on DR prevalence of 16.9% from Vashist et al. [2021]. Participants were randomized into two equal groups: Group-D (Metformin + Glimepiride + Dapagliflozin, n=108) and Group-M (Metformin + Glimepiride, n=108).

All participants underwent baseline evaluation including indirect ophthalmoscopy (Heine Indirect Ophthalmoscope) and Optical Coherence Tomography (Zeiss OCT) to assess retinal structure and detect diabetic retinopathy (DR). Laboratory tests included fasting blood glucose, HbA1c (measured using Beckman Coulter DxC 700 AU via HPLC), lipid profile, and renal function tests. Blood pressure was recorded, and Mean Arterial Pressure (MAP) was calculated. Comorbidities such as cardiovascular disease and CKD were assessed using the Charlson Comorbidity Index. Follow-up visits were scheduled every 6 months for repeat retinal imaging, glycemic monitoring, BP measurement, and review of medications. Primary outcomes included progression of DR, changes in retinal thickness, and their correlation with glycemic control and comorbidities. All findings were systematically documented and analyzed.

RESULTS



The bar graph illustrates the distribution of sociodemographic characteristics among study participants in Group-D (Metformin + Glimepiride + Dapagliflozin) and Group-M (Metformin + Glimepiride), each comprising 108 individuals. The age distribution was nearly identical across both groups, indicating an age-matched population that minimizes potential bias in age-related retinal outcomes. Gender distribution also showed a comparable pattern, with a slightly higher percentage of males in Group-D (57.4%) versus Group-M (53.7%), while females represented 42.6% and 46.3% in Group-D and Group-M respectively, suggesting a balanced gender representation.

In terms of educational status, a slightly greater proportion of participants in Group-M were illiterate compared to Group-D, though the difference was not markedly large. Participants with primary education were somewhat more frequent in Group-D (31.5%) than Group-M (27.8%), while both groups had an equal share of participants with secondary education (51.9%). Overall, the two groups were demographically similar in terms of age, sex, and educational attainment, indicating that the baseline sociodemographic factors were well-matched. This comparability reinforces the reliability of subsequent analyses by reducing the likelihood of confounding effects related to participant background characteristics.

Table 1: Prevalence of Diabetic Retinopathy in Group-D (Metformin + Glimepiride + Dapagliflozin)

Retinopathy Severity	Group-D [n=108]
No DR	76 (70.4%)
Mild NPDR	22 (20.4%)
Moderate NPDR	8 (7.4%)
Severe NPDR	2 (1.9%)

Table 2: Prevalence of Diabetic Retinopathy in Group-M (Metformin + Glimepiride)

Retinopathy Severity	Group-M [n=108]
No DR	62 (57.4%)
Mild NPDR	30 (27.8%)
Moderate NPDR	12 (11.1%)
Severe NPDR	4 (3.7%)

In Group-M, a higher percentage of patients exhibited signs of DR, with only 57.4% showing no DR, indicating comparatively higher DR prevalence than Group-D.

Table 3: Comparative Prevalence of Diabetic Retinopathy Between Groups

Retinopathy Severity	Group-D [%]	Group-M [%]	p-value
No DR	70.4	57.4	0.038
Mild NPDR	20.4	27.8	0.214
Moderate NPDR	7.4	11.1	0.342
Severe NPDR	1.9	3.7	0.682

A statistically significant difference (p=0.038) was observed in the prevalence of 'No DR' between groups, favoring Group-D. Other severity grades showed no significant intergroup variation.

Table 4: Progression of Diabetic Retinopathy at 12 Months

Outcome	Group-D [%]	Group-M [%]	p-value
No Progression	77.8	66.7	0.048
Worsening of NPDR	16.7	25.9	0.039
Macular Edema	5.6	7.4	0.782

Group-D demonstrated significantly lower progression of NPDR and greater stability in retinal status over 12 months, indicating the potential protective role of dapagliflozin.

Table 5: Change in Retinal Thickness (OCT) at 24 Months

Parameter	Group-D (Mean ± SD)	Group-M (Mean ± SD)	p-value
Baseline Retinal Thickness [µm]	252.3 ± 16.8	254.1 ± 17.2	0.452
Retinal Thickness at 24 Months [µm]	258.6 ± 18.4	267.2 ± 20.1	0.012
Change from Baseline [µm]	+6.3 ± 4.2	+13.1 ± 5.6	<0.001

Over 24 months, Group-D exhibited a significantly smaller increase in retinal thickness than Group-M ($p<0.001$), suggesting slower structural deterioration with dapagliflozin therapy.

DISCUSSION

The present study revealed a notably lower prevalence of diabetic retinopathy (DR) in Group-D (dapagliflozin-based regimen) compared to Group-M (non-dapagliflozin regimen). Specifically, 70.4% of participants in Group-D had no evidence of DR, whereas this figure dropped to 57.4% in Group-M ($p = 0.038$). These findings align with global estimates indicating a DR prevalence of around 35–40% among individuals with diabetes, though this can vary by geography and disease control [1,6]. Studies by Rema and Pradeepa [12] and Katulanda et al. [11] reported similar findings in Indian and South Asian populations, reinforcing the high burden of DR in conventional therapy groups. The superior outcomes in Group-D suggest a potential protective effect of SGLT2 inhibitors like dapagliflozin against early retinal damage, possibly due to better metabolic and vascular control.

While the proportion of mild, moderate, and severe NPDR cases was slightly lower in the dapagliflozin group, these differences did not reach statistical significance ($p > 0.05$). However, the directionality of data is consistent with earlier findings that aggressive glucose-lowering therapies reduce microvascular complications over time [5,7]. The American Diabetes Association highlights the importance of early and aggressive interventions to reduce progression from mild to more severe stages of DR [5]. Moreover, Solomon et al. emphasized that the shift in DR stages is often influenced not only by glycemic control but also by lipid and blood pressure management—factors known to be favorably influenced by SGLT2 inhibitors [5,10].

Longitudinal data from the 12-month follow-up demonstrated that Group-D had significantly better retinal stability, with 77.8% of patients showing no progression of DR compared to 66.7% in Group-M ($p = 0.048$). Additionally, worsening of NPDR was higher in Group-M (25.9%) than in Group-D (16.7%, $p = 0.039$). This outcome is particularly important in light of literature indicating that DR progression is linked to cumulative metabolic insult, inflammatory processes, and endothelial dysfunction [13,14]. The lower progression rate in the dapagliflozin group may be partially attributed to the anti-inflammatory and antioxidative effects of SGLT2 inhibitors, which could counteract VEGF-driven neovascularization and endothelial permeability [14,16]. These results suggest that dapagliflozin could serve as a stabilizing agent in DR by modifying pathogenic pathways beyond glycemic control.

Retinal thickness, a surrogate marker for disease severity and macular edema, showed a significantly smaller increase in Group-D than Group-M over 24 months (+6.3 µm vs +13.1 µm; $p < 0.001$). This finding is of high clinical relevance as increased retinal thickness is closely associated with macular edema—a primary cause of visual impairment in DR [7,9]. The Wisconsin Epidemiologic Study of Diabetic Retinopathy demonstrated that retinal swelling correlates with lipid abnormalities and poor glucose regulation [9]. Our findings are consistent with these observations and further support the role of dapagliflozin in reducing microvascular leakage, possibly via modulation of VEGF pathways and endothelial stabilization [15,16]. Thus, Group-D not only showed less progression but also a lower degree of structural retinal compromise.

The protective trends seen in Group-D across DR prevalence, progression, and retinal structural integrity mirror the broader global push for multifactorial risk reduction in diabetes management. Studies by WHO and Shaw et al. have emphasized that DR remains a preventable cause of blindness if early screening and optimized pharmacotherapy are implemented [2,4]. Dapagliflozin's impact in this cohort resonates with findings from recent meta-analyses showing that comprehensive control of glycemia, lipids, blood pressure, and inflammation is pivotal in mitigating microvascular complications [6,13]. In this context, the present study contributes valuable Indian data to the emerging body of evidence suggesting that SGLT2

inhibitors may serve as disease-modifying agents for diabetic retinopathy by halting or slowing its progression through systemic and local vascular effects.

CONCLUSION

This study demonstrated that patients treated with dapagliflozin (Group-D) had a significantly lower prevalence and slower progression of diabetic retinopathy compared to those on conventional therapy (Group-M). Group-D also showed less retinal thickness increase over time, indicating better structural retinal preservation. Glycemic control and sociodemographic variables were comparable between groups, minimizing confounding effects. These findings suggest a potential protective role of dapagliflozin against diabetic retinal complications. Incorporating SGLT2 inhibitors may offer added ocular benefits in managing type 2 diabetes.

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