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Role of SGLT2 Inhibitors in Diabetic Retinopathy

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ABSTRACT

Objectives: To determine the role of SGLT2 Inhibitors in diabetic retinopathy by comparing the incidence and severity of retinopathy in patients using SGLT2 inhibitors with those using other antidiabetic therapies. **Study design:** Case-control study. **Place and duration of study:** This study was conducted at the department of Medicine, PAF Hospital, Islamabad from Apr 2024-March 2025. **Methods:** A total of 300 type 2 diabetic patients using SGLT2 inhibitors (Dapagliflozin, Empagliflozin) for at least 3 consecutive years with HbA1c ≤7.5% were included as the study group. Another 300 patients on non-SGLT2 antidiabetic regimens, matched for treatment duration and glycemic control, were included as the control group. Primary objective was set as the incidence and severity of diabetic retinopathy. These primary outcomes were compared between the two groups to find the role of SGLT2 Inhibitors in diabetic retinopathy. **Results:** The mean age in this study was 53.76 ± 8.82 years (ranged from 34 to 70 years). Comparison of the incidence and severity showed a significantly lower incidence of diabetic retinopathy (<0.01), non-proliferative retinopathy (p=0.02) and proliferative retinopathy (p=0.04) in the study group compared to the control group. However, difference was non-significant for the presence of advanced retinopathy or macular abnormalities (p=0.78). **Conclusion:** SGLT2 inhibitors demonstrated substantial preventive benefits in reducing the incidence and progression of diabetic retinopathy compared to other antidiabetic therapies, particularly for non-proliferative and proliferative retinopathy stages.

INTRODUCTION

Diabetic retinopathy (DR) represents predominant and devastating microvascular sequelae of diabetes mellitus (DM), distinguished by gradual deterioration of retinal vasculature, estimated to affect 33% of the global diabetic population. Despite the available strategies for controlling glycaemia and recent advances in ophthalmological interventions, DR remains a primary contributor of preventable blindness with forecasts suggesting a rise from 103 million to 160 million from year 2020 to year 2045. Current strategies focus on a good control of blood glucose levels, blood pressure, and lipid levels, yet the progression of DR continues in a significant number of diabetic patients and reinforce the urgent need for other therapeutic modalities in addition to commonly employed management startegies.[1,2]

The pathophysiology of DR involves complex mechanisms which are initially triggered by chronically raised glycemic levels. This leads to increased free radical activities, production of oxygen-derived reactive molecules, raised inflammatory responses, synthesis of advanced glycation end products (AGEs), stimulation of protein kinase C and elevated vascular endothelial growth factor (VEGF). These changes cause damage to the vasculature in shape of disruption of the blood-retinal barrier, thickening of capillary basement membrane, loss of perivascular supportive cells, and pathological angiogenesis. There is ultimate capillary leakage, neovascularization and macular edema.[3,4]

Sodium-glucose co-transporter 2 (SGLT2) inhibitors is a class of antidiabetics that have provided a new approach towards type 2 diabetes mellitus (T2DM) management. SGLT2 Inhibitors counteract the pathophysiological processes triggered by chronic hyperglycemic conditions and reduce oxidative stress, decrease inflammation, while improve the endothelial function.

SGLT2 inhibitors act by blocking glucose reabsorption in the proximal renal tubules, the process causes glycosuria leading a reduction in plasma glucose levels by enhancing urinary glucose excretion. Besides their effect of lowering blood glucose, studies have shared the pleiotropic benefits of SGLT2 inhibitors such as cardiovascular (CV) risk reduction and renal protection that extend beyond glycemic control.[5,6] Randomized clinical trials have shown that SGLT2 inhibitors significantly reduce adverse cardiovascular events, hospitalizations due to heart failure, and progression of diabetic kidney disease in large group of patients.[6,7]

Several preclinical studies, conducted on the basis of above mentioned macrovascular benefits, have shared the potential retinoprotective effects of SGLT2 inhibitors. In studies conducted with animal models, the molecules like empagliflozin and dapagliflozin have shown to slow down the process of retinal neurodegeneration, reduce retinal vascular leakage, and regulate the biomarkers related to inflammation.[8,9] Clinical data regarding the impact of SGLT2 inhibitors on DR in human is still limited and under debate, where some observational studies have suggested a protective effect, while others have reported neutral outcomes.[10]

An early intervention which can reduce the vision loss will improve the quality of life (QOL) of diabetic patients and help to cut the overall healthcare costs. Our research was therefore aimed to evaluate the role of SGLT2 inhibitors in reducing the incidence and progression of DR. The findings of this work will assist the healthcare professionals in diabetes care centers for recommending evidence-based treatment strategies that not only ensure effective glycemic control but also help to prevent future complications of diabetes.

METHODOLOGY

This case-control study was conducted at the department of Medicine, PAF Hospital, Islamabad from April 2024 to March 2025 over a period of 1 year.

The approval of conducting the study was received from the ethical committee of the hospital.

The sample size was calculated as per following details:

Alpha = 5% (two-sided), power = 80%.

p1 (risk of sight-threatening DR in SGLT2 Inhibitor group) = 51%

p2 (risk of sight-threatening DR in other antidiabetic group) = 63%.[11]

The Estimated sample size: n1 = 267, n2 = 267. We however added 300 patients in each group.

A total of 300 type 2 diabetic patients reporting at outpatient department using any SGLT2 inhibitor (among the molecules commonly used in Pakistan like Dapagliflozin and Empagliflozin) as a part of their treatment regimen for at least 3 consecutive years and having their HbA1C levels ≤7.5% (to minimize the confounding impact of uncontrolled hyperglycemia on retinopathy progression) were enrolled in the study group.

Another 300 type 2 diabetic patients reporting at outpatient department using antidiabetics other than SGLT2 inhibitors as a part of their treatment regimen and with same treatment details and blood glucose control were enrolled in the control group. Both groups were matched for key confounding variables including age, gender, duration of diabetes and baseline HbA1c. Confirmation of adherence to medication was based on self-reported questionnaire (defined as ≥80% of prescribed doses taken).

Exclusion criteria was set as patients with type 1 diabetes, advanced renal impairment (eGFR <45 ml/min/1.73m^2), any pre-existing ocular diseases not related to diabetes (e.g., glaucoma, macular degeneration), or a history of ocular surgery in the recent past.

A written consent was received from each participant before enrolment in this study.

All the related demographic details, medical history and current clinical assessments were recorded on the predesigned performa. An on-site ophthalmologist assessed DR through direct and indirect ophthalmoscopy performed and graded as per the standard clinical classification system, categorizing it as non-proliferative, proliferative, or macular edema. Visual acuity measurements were recorded and Snellen chart was used to evaluate functional vision. Moreover, Vision-threatening complications, such as advanced retinopathy or macular abnormalities, were identified through fundoscopy. In cases of clinical suspicion of severe complications, optical coherence tomography (OCT) was conducted by referring to ophthalmology unit for further confirmation.

Primary objective was set as the incidence of DR, non-proliferative retinopathy, proliferative retinopathy and severity of the incidence (presence of vision-threatening retinopathy such as macular edema). These primary outcomes were compared between the two groups to assess the role of SGLT2 Inhibitors in DR.

All collected data were analyzed using SPSS version 26. Quantitative variables such as age, duration of diabetes, and HbA1c levels were expressed as mean ± standard deviation and compared between the two groups by applying independent t-test. Categorical variables including gender, presence and severity of DR (non-proliferative, proliferative, or macular edema), and other baseline characteristics were calculated for frequencies and percentages and then compared using the chi-square/Fisher's exact tests. Stratification was applied to determine these effects based on the duration of diabetes>5 years. A p-value<0.05 was considered statistically significant for all these comparisons.

RESULTS

The mean overall age of study participants was 53.76 ± 8.82 years (ranged from 34 to 70 years). The group wise demographics and clinical characteristics are shared in Table-I which shows that both the groups were well matched for the confounding factors.

Table 1

Baseline Characteristics of Study Participants (n=600)

Demographics and clinical characteristics		Study group (n=300)	Control group (n=300)	p-value
Age (Mean±SD) years		53.52±8.95	54.01±8.68	0.49
Gender	Male n (%)	163 (54.33)	166 (55.33)	0.31
	Female n (%)	137 (45.66)	134 (44.66)	
Body mass index (Mean±SD) Kg/m^2		28.77±2.77	29.02±2.81	0.27
Hypertension n (%)		62 (20.66)	73 (24.33)	0.28
Duration of diabetes (Mean±SD) years		8.79±2.75	9±2.74	0.35
HbA1C levels (Mean±SD) %		7.05±0.35	7.1±0.33	0.07

The comparison of incidence and severity of DR showed significantly lower incidence of DR (<0.01), non-proliferative retinopathy (p=0.02) and proliferative retinopathy (p=0.04) in the study group compared to the

control group. This difference was however not significant for the presence of advanced retinopathy or macular abnormalities (p=0.78) as shown in Table-II.

Table 2

Comparison of incidence and severity of DR between groups (n= 600)

Incidence and grades of DR*		Study group (n=300)	Control group (n=300)	p-value
Presence of DR	Yes n (%)	116 (38.7)	161 (53.7)	<0.01
	No n (%)	184 (61.3)	139 (46.3)	
Non- proliferative DR n (%)		61 (20.3)	85 (28.3)	0.02
Proliferative DR n (%)		49 (16.3)	69 (23)	0.04
Advanced retinopathy or macular abnormalities n (%)		6 (2)	7 (2.3)	0.78

Diabetic retinopathy*

The stratification of results for patients having duration of diabetes>5 years also showed significant difference regarding the incidences of all stages of DR in the study group compared to the controlled group except for the advanced retinopathy or macular abnormalities as shown in Table-III.

Table III

Incidence and severity of DR in patients with duration of diabetes>5 years (n= 531)

Incidence and grades of DR*		Study group (n=261)	Control group (n=270)	p-value
Presence of DR	Yes n (%)	111 (42.5)	147 (54.4)	< 0.01
	No n (%)	150 (57.5)	123 (45.6)	
Non- proliferative DR n (%)		52 (20)	75 (27.8)	0.03
Proliferative DR n (%)		43 (16.5)	64 (23.7)	0.04
Advanced retinopathy or macular abnormalities n (%)		0 (0)	2 (0.7)	0.25

Diabetic retinopathy*

DISCUSSION

The results of our study demonstrated that patients using SGLT2 inhibitors had significantly lower incidence of DR compared to those using other antidiabetic medications (38.7% vs 53.7%, p<0.01). Same results were observed for other grades of retinopathy including non-proliferative (20.3% vs 28.3%, p=0.02), and proliferative retinopathy (16.3% vs 23%, p=0.04). This was also true for the subgroup of patients with the duration of diabetes >5 years. However, this difference was not significant for advanced retinopathy or macular abnormalities between the two groups (p=0.78), suggesting that while SGLT2 inhibitors may help prevent or delay the onset of retinopathy, they may not affect its progression once advanced stages are reached or duration of use of SGLT2 inhibitor was not sufficient to show a significant impact on this stage of DR. These findings align with emerging evidence suggesting that SGLT2 inhibitors may provide retinoprotective benefits beyond their glycemic control.

Preclinical studies over the topic have proposed plausible mechanisms for these observed benefits, indicating a direct effect of this class of antidiabetics on retinal structure and functions. Herat LY et al. and Matthews J et al. in their reviews worked on the retinal microvascular/neural damage in diabetic mice and mentioned a positive effect of SGLT2 inhibitor (Dapagliflozin and Empagliflozin respectively) alongside improved glucose tolerance. Retinal SGLT1 upregulation in diabetic subjects suggested SGLT1/2 inhibition as a novel therapeutic strategy for preventing diabetic retinopathy.[12,13]

A review published by Sha W et al. in 2020, discussed that this new class of antidiabetics has potential dual role in both glucose management and diabetic retinopathy prevention, pointing towards a new therapeutic direction for clinical research.[14]

Several clinical studies have further worked and reinforced the retinoprotective effects of SGLT2 inhibitors based on population data and use of imaging modalities. Mieno H et al. conducted a study with 10 eyes and found that SGLT2 inhibitors after 12 months of treatment significantly reduced central retinal thickness (p<0.01) and improved vision in vitrectomized eyes with chronic diabetic macular edema, suggesting potential structural benefits.[15]

Sabaner MC et al., made the assessment with optical coherence tomography and found that SGLT2 Inhibitors combined with metformin in patients with HbA1c>7% may help prevent preclinical diabetic retinopathy by preserving retinal microvascular structure.[16]

A cohort study by Yen F et al. compared the risk of sight-threatening diabetic retinopathy (STDR) in patients with T2DM treated with SGLT2 inhibitors versus other glucose-lowering drugs (DPP-4 inhibitors, pioglitazone, and sulfonylureas). SGLT2is significantly reduced the risk of STDR by 25-43% compared to other glucose-lowering medications. Kaplan-Meier analysis confirmed lower cumulative STDR incidence with SGLT2is $P < 0.001$) suggesting that SGLT2is may slow retinopathy progression in T2DM, beyond their known renal benefits.[11]

A comprehensive study on this topic was conducted by Lin TY et al. in 23,378 type 2 diabetic patients which compared SGLT2 inhibitors and GLP-1 receptor agonists for DR risk. While both showed similar overall incidence (SHR 0.90; 95% CI 0.79-1.03), SGLT2is demonstrated superior protection against vision-threatening complications, reducing proliferative DR risk by 47% (SHR 0.53; 95% CI 0.42-0.68) and vitreoretinal intervention need by 42% (SHR 0.58; 95% CI 0.48-0.70) compared to GLP-1 RAs. These findings suggest that SGLT2is may offer better protection against advanced DR complications, offering a major advantages for the diabetic patients.[17]

Lahoti S et al. discussed the possible mechanism of action of above mentioned retinoprotective effects of SGLT2I proven in different studies and explained them by reduction in inflammation, oxidative stress and hyperglycemia-induced vascular damage and emphasized the need of large-scale clinical trials utilizing standardized outcomes (e.g., visual acuity, OCT changes) to establish their role in DR management. Our trial partly fulfilled this need and confirmed the efficacy of this class in preventing the development and slowing the worsening of retinopathy in T2DM.[18]

In summary, the results of our study and the studies discussed above suggest that SGLT2 inhibitors not only improve glycemic control but also confer retinal

protection, especially in early stages of DR, which emphasize their potential supporting role as part of comprehensive diabetes management strategies.

The case-control design and the reliance on self-reported medication adherence were among the major limitations of this study. Additionally, three-year treatment duration may not fully capture the long-term outcomes of the SGLT2 Inhibitors use in DR.

CONCLUSION

SGLT2 inhibitors demonstrated substantial preventive benefits in reducing the incidence and progression of DR compared to other antidiabetic therapies, particularly for non-proliferative and proliferative retinopathy stages. This protective effect is persisted in patients with duration of diabetes exceeding five years or above. Future diabetes management should, therefore consider early initiation of SGLT2 inhibitors, particularly in patients at higher risk for microvascular complications. Multidisciplinary approaches including regular ophthalmologic screening with therapies having impact on future complications can potentially reduce the burden of diabetes related complications including retinopathy.

REFERENCES

1. Kropp, M., Golubnitschaja, O., Mazurakova, A., Koklesova, L., Sargheini, N., Vo, T. K., De Clerck, E., Polivka, J., Potuznik, P., Polivka, J., Stetkarova, I., Kubatka, P., & Thumann, G. (2023). Diabetic retinopathy as the leading cause of blindness and early predictor of cascading complications—risks and mitigation. *EPMA Journal*, *14*(1), 21-42. https://doi.org/10.1007/s13167-023-00314-8
2. Shukla, Unnati V., and Koushik Tripathy. "Diabetic Retinopathy." *PubMed*, StatPearls Publishing, 2023, www.ncbi.nlm.nih.gov/books/NBK560805/
3. Chen, Y., Radke, N. V., Amarasekera, S., Park, D. H., Chen, N., Chhablani, J., Wang, N., Wu, W., Ng, D. S., Bhende, P., Varma, S., Leung, E., Zhang, X., Li, F., Zhang, S., Fang, D., Liang, J., Zhang, Z., Liu, H., ... Lam, D. S. (2025). Updates on medical and surgical managements of diabetic retinopathy and maculopathy. *Asia-Pacific Journal of Ophthalmology*, *14*(2), 100180. https://doi.org/10.1016/j.apjo.2025.100180
4. Haydinger, C. D., Oliver, G. F., Ashander, L. M., & Smith, J. R. (2023). Oxidative stress and its regulation in diabetic retinopathy. *Antioxidants*, *12*(8), 1649. https://doi.org/10.3390/antiox12081649
5. Padda, Inderbir S., et al. "Sodium-Glucose Transport Protein 2 (SGLT2) Inhibitors." *PubMed*, StatPearls Publishing, 2023, www.ncbi.nlm.nih.gov/books/NBK576405/
6. Sarzani, R., Giulietti, F., Di Pentima, C., & Spannella, F. (2020). Sodium-glucose Co-transporter-2 inhibitors: Peculiar "hybrid" diuretics that protect from target organ damage and cardiovascular events. *Nutrition, Metabolism and Cardiovascular Diseases*, *30*(10), 1622-1632. https://doi.org/10.1016/j.numecd.2020.05.030
7. McGuire, D. K., Shih, W. J., Cosentino, F., Charbonnel, B., Cherney, D. Z., Dagogo-Jack, S., Pratley, R., Greenberg, M., Wang, S., Huyck, S., Gantz, I., Terra, S. G., Masiukiewicz, U., & Cannon, C. P. (2021). Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes. *JAMA Cardiology*, *6*(2), 148. https://doi.org/10.1001/jamacardio.2020.4511
8. Wołos-Kłosowicz, K., Matuszewski, W., Rutkowska, J., Krankowska, K., & Bandurska-Stankiewicz, E. (2022). Will GLP-1 analogues and SGLT-2 inhibitors become new game changers for diabetic retinopathy? *Journal of Clinical Medicine*, *11*(20), 6183. https://doi.org/10.3390/jcm11206183
9. El Mouhayyar, C., Riachy, R., Khalil, A. B., Eid, A., & Azar, S. (2020). SGLT2 inhibitors, GLP-1 agonists, and DPP-4 inhibitors in diabetes and Microvascular complications: A review. *International Journal of Endocrinology*, *2020*, 1-11. https://doi.org/10.1155/2020/1762164
10. Bonora, B. M., Avogaro, A., & Fadini, G. P. (2020). Extraglycemic effects of SGLT2 inhibitors: A review of the Evidence. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, *13*, 161-174. https://doi.org/10.2147/dmso.s233538
11. Yen, F., Wei, J. C., Yu, T., Hung, Y., Hsu, C., & Hwu, C. (2023). Sodium-glucose Cotransporter 2 inhibitors and risk of retinopathy in patients with type 2 diabetes. *JAMA Network Open*, *6*(12), e2348431. https://doi.org/10.1001/jamanetworkopen.2023.48431
12. Herat, L. Y., Matthews, J. R., Ong, W. E., Rakoczy, E. P., Schlaich, M. P., & Matthews, V. B. (2022). Determining the role of SGLT2 inhibition with Dapagliflozin in the development of diabetic retinopathy. *Frontiers in Bioscience-Landmark*, *27*(12). https://doi.org/10.31083/j.fbl2712321
13. Matthews, J., Herat, L., Rooney, J., Rakoczy, E., Schlaich, M., & Matthews, V. B. (2022). Determining the role of SGLT2 inhibition with Empagliflozin in the development of diabetic retinopathy. *Bioscience Reports*, *42*(3). https://doi.org/10.1042/bsr20212209
14. Sha, W., Wen, S., Chen, L., Xu, B., Lei, T., & Zhou, L. (2020). The Role of SGLT2 Inhibitor on the Treatment of Diabetic Retinopathy. *Journal of Diabetes Research*, *2020*, 1–6. https://doi.org/10.1155/2020/8867875
15. Mieno, H., Yoneda, K., Yamazaki, M., Sakai, R., Sotozono, C., & Fukui, M. (2018). The efficacy of sodium-glucose Cotransporter 2 (SGLT2) inhibitors for the treatment of chronic diabetic macular oedema in vitrectomised eyes: A retrospective study. *BMJ Open Ophthalmology*, *3*(1), e000130. https://doi.org/10.1136/bmjophth-2017-000130
16. Sabaner, M., Duman, R., Dogan, M., Akdogan, M., Vurmaz, A., Bozkurt, E., & Beysel, S. (2021). Do SGLT2 inhibitors prevent preclinical diabetic retinopathy? A prospective pilot optical coherence tomography

angiography study. *Journal Français d'Ophtalmologie*, *44*(8), 1159-1167. https://doi.org/10.1016/j.jfo.2021.01.005

17. Lin, T.-Y., Kang, E. Y.-C., Shao, S.-C., Lai, E. C.-C., Garg, S. J., Chen, K.-J., Kang, J.-H., Wu, W.-C., Lai, C.-C., & Hwang, Y.-S. (2023). Risk of Diabetic Retinopathy between Sodium-Glucose Cotransporter-2 Inhibitors and Glucagon-Like Peptide-1 Receptor Agonists. *Diabetes & Metabolism Journal*, *47*(3), 394–404. https://doi.org/10.4093/dmj.2022.0221
18. Lahoti, S., Nashawi, M., Sheikh, O., Massop, D., Mir, M., & Chilton, R. (2020). Sodium-glucose Co-transporter 2 inhibitors and diabetic retinopathy: Insights into preservation of sight and looking beyond. *Cardiovascular Endocrinology & Metabolism*, *10*(1), 3-13. https://doi.org/10.1097/xce.0000000000000209