

# International Journal of Health Science

Acceptance date: 15/01/2025

## RELATIONSHIP BETWEEN DIABETES MELLITUS AND GLAUCOMA: PATHOPHYSIOLOGY, RISK FACTORS AND MULTIDIMENSIONAL THERAPEUTIC APPROACHES

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***Fernando Soares de Moraes***

Universidade Nove de Julho Campus Bauru  
(UNINOVE) - Bauru/SP  
<https://orcid.org/0009-0006-9052-9849>

***Laura Martins Paressa Alves***

Centro Universitário Presidente Antonio  
Carlos (UNIPAC) - Juiz de Fora//MG  
<https://orcid.org/0009-0004-1181-2124>

***Larissa Ferreira Horta***

São Leopoldo Mandic Araras (SLMA) -  
Araras/SP  
<https://orcid.org/0009-0001-5529-2448>

***Anna Carolina de Oliveira Carone Bissoli***

Universidade Estácio de Sá (UNESA) - Rio  
de Janeiro/RJ  
<https://orcid.org/0009-0000-1319-9053>

***Anna Palméria Santilhana de Souza Moraes  
França***

Faculdade de Minas BH (FAMINAS) - Belo  
Horizonte/MG  
<https://orcid.org/0009-0003-7443-1938>

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**Luiz Eduardo Ferreira Domingues**

Universidade Estácio de Sá (UNESA) - Angra dos Reis/RJ

<https://orcid.org/0009-0006-2524-1160>

**Viviane Thaís Gaidarji Nesvera**

Atitus Educação (ATITUS) - Passo Fundo/RS

<https://orcid.org/0009-0004-6739-1576>

**Sofia Pimenta Silluzio**

Universidade José do Rosário Vellano

(UNIFENAS) - Belo Horizonte/MG

<https://orcid.org/0000-0002-0756-5915>

**Júlia Mallmann Monteiro**

Pontifícia Universidade Católica do Paraná

(PUCPR) - Curitiba/PR

<https://orcid.org/0009-0009-0057-0728>

**Carolina Corrêa Magnavita**

Escola Bahiana de Medicina e Saúde Pública

(EBMSP) - Salvador/BA

<https://orcid.org/0009-0008-7701-5960>

**Priscila de Jesus Santana**

Universidad Nacional de Rosario (UNR)

Rosario - Argentina

<https://orcid.org/009-0002-5018-1455>

**Abstract: Objective:** To investigate the relationship between diabetes mellitus (DM) and the increased risk of developing glaucoma, analyzing pathophysiology, prevalence, diagnostic methods and specific treatment strategies. **Methodology:** Structured bibliographic review based on the PVO strategy. The search was carried out in the PubMed/MEDLINE database, using the terms “diabetes mellitus”, “diabetes”, “mellitus”, “glaucoma” and “glaucomas”, combined with the Boolean operators AND and OR. Thirteen articles were selected for critical analysis. **Discussion:** Diabetes mellitus is considered a risk factor for increased intraocular pressure (IOP) and vascular dysfunction, although there are conflicting data on its direct impact on the development of primary open-angle glaucoma (POAG). Insulin plays a protective role in retinal ganglion cells and has an anti-inflammatory action, but it is not enough to prevent cell damage. According to some studies, metformin is associated with a reduction in the risk of GPAA, while others have found no significant impact. Neovascular glaucoma is treated with panretinal photocoagulation and intravitreal injections of anti-VEGF agents, which reduce IOP and prevent irreversible damage. However, a multidimensional approach, including strict glycemic control, is essential, considering the stage of the disease and the underlying conditions. **Final thoughts:** More robust research is needed to validate the efficacy of specific drugs. However, early screening for diabetic retinopathy remains an essential strategy to optimize early diagnosis and improve effective preventive approaches.

**Keywords:** Diabetes Mellitus, Glaucoma, Risk Factors.

## INTRODUCTION

Diabetes mellitus (DM) is one of the most prevalent metabolic diseases in the world, projected to affect 634 million people by 2030, and represents a growing public health challenge due to its chronic complications. These complications include eye diseases such as diabetic retinopathy (DR), cataracts, ocular surface changes and glaucoma (Mahmood *et al.*, 2023).

Studies suggest that individuals with DM have a higher risk of developing glaucoma, even after adjusting for confounding factors. This association reinforces the importance of integrated prevention and early diagnosis strategies, as well as strict glycemic control, aimed at mitigating the impacts of DM on ocular health. These measures are essential for preserving patients' quality of life and minimizing the visual and systemic consequences of the disease (Zhaoxia; Yu, 2024). Primary open-angle glaucoma (POAG), in particular, is characterized by progressive and irreversible damage to the optic nerve and is the leading cause of irreversible blindness worldwide (Jung *et al.*, 2020).

DM and GPAA represent global public health challenges due to their high prevalence and impact on the quality of life of affected individuals. DR and GPAA share pathophysiological mechanisms, such as retinal neurodegeneration and vascular impairment, which increase the risk of irreversible visual loss (Kjærsgaard; Grauslund; Vestergaard; Subhi, 2022).

Although glaucoma has the devastating potential to cause irreversible blindness, universal population screening for the disease is considered economically unfeasible due to its low prevalence compared to DM and DR. However, screening programs for DR, which are already well established in many countries, offer an opportunity to incorporate the detection of glaucomatous changes. This integrated approach would make more efficient use of existing resources and could address

the underdiagnosis of glaucoma at early stages, increasing the effectiveness of early interventions and reducing the global burden of these interrelated eye diseases (Aldarrab; Al Jarallah; Al Balawi, 2023).

The projected increase in cases of these diseases in the coming decades, coupled with late diagnosis and underreporting, justifies the need for studies that integrate the understanding of these pathologies. Identifying and addressing shared risk factors can optimize clinical management strategies and prevent serious complications, especially in vulnerable populations (Aldarrab; Al Jarallah; Al Balawi, 2023).

The aim of this review is to explore the association between DM and primary open-angle glaucoma (POAG), focusing on shared pathophysiological mechanisms, risk factors and clinical implications. In addition, it seeks to identify opportunities for integrating early detection of POAG into screening programs for DR, optimizing resources and increasing the prevention of serious visual complications.

## METHODOLOGY

This study is a literature review based on the PVO strategy, which includes the following elements: population or research problem, variables and outcome. This strategy was used to formulate the research question: *"How does diabetes mellitus influence the risk of developing glaucoma, and what are the pathophysiological mechanisms, prevalence, most effective diagnostic methods and recommended treatment strategies for diabetic patients with glaucoma?"*.

The searches were carried out in the PubMed - MEDLINE (*Medical Literature Analysis and Retrieval System Online*) database, using search terms combined by Boolean operators "AND" and "OR". The search strategy applied was: ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields])) OR "diabetes mellitus"[All Fields] AND ("glaucoma"[MeSH Terms] OR "glau-

coma”[All Fields] OR “glaucomas”[All Fields] OR “glaucoma s”[All Fields]). From this initial search, 605 articles were found and submitted to selection criteria.

The inclusion criteria involved articles in English, published between 2019 and 2024, which addressed the proposed themes, including randomized studies, meta-analyses, systematic reviews and integrative reviews. The exclusion criteria included duplicate articles, articles available only as abstracts and articles that did not directly address the study proposal. After rigorously applying these criteria, 13 articles were selected from the PubMed database to make up the collection of this review.

## DISCUSSION

### PATHOPHYSIOLOGICAL MECHANISMS AND RISK FACTORS ASSOCIATED WITH DIABETES MELLITUS AND GLAUCOMA

DM has been widely linked to pathophysiological changes that can contribute to the development of glaucoma. According to Su *et al.* (2023), DM acts as a risk factor for increased IOP by interfering with the function of the trabecular meshwork. This effect is amplified by chronic hyperglycemia, which, associated with the process of ischemia and reperfusion in the retina, generates retinal hypoxia. These events induce the production of pro-neovascularization factors, unbalancing the processes of pro-angiogenesis and anti-angiogenesis, which can lead to structural and functional alterations in the ocular system.

Tang, Shi and Fan (2023) reinforce that chronic hyperglycemia can cause loss of pericytes, apoptosis of endothelial cells, thickening of the basement membrane and impairment of cell adhesion, culminating in the breakdown of the blood-retinal barrier. These structural processes favor the propagation of pro-angiogenic and inflammatory factors, ag-

gravating vascular dysfunction. These mechanisms are critical in the progression of ocular diseases, including glaucoma, and highlight the complex interaction between metabolic alterations and inflammation in ocular pathophysiology.

Maestroni *et al.* (2023) highlight the additional complexity of the role of IOP in the pathogenesis of glaucoma. Despite being frequently associated with the disease, high IOP is not a pathognomonic feature, considering that up to 40% of patients develop glaucoma with normal IOP. These findings indicate that, in addition to intraocular pressure, other factors, such as chronic inflammation and vascular dysfunction, play significant roles in glaucomatous optic neuropathy, especially in diabetic patients.

Additionally, Lee, Jeon, Kang and Kim (2024) suggest that, in addition to the impact of DM, neuroretinal hypertension can exacerbate the pathogenesis of glaucomatous optic neuropathy. These authors identified advanced age as one of the main risk factors for glaucoma. On the other hand, although they found subtle variations related to gender, these differences were not clinically significant, suggesting that the impact of metabolic and vascular factors is predominant.

According to George, Asokan and Vijaya (2021), diabetic individuals have, on average, higher IOP than non-diabetic individuals, with an average difference of 1.85 mmHg. Alterations such as greater corneal rigidity and hysteresis have been identified as potential contributors to increased IOP in diabetics, reinforcing the relationship between DM and glaucoma. However, these authors emphasize that, despite these correlations, diabetes should not be considered in isolation as the main risk factor, as other factors, such as advanced age and ocular hypertension, also play critical roles.

## **THERAPEUTIC AND NEUROPROTECTIVE EFFECTS OF METFORMIN AND INSULIN IN THE CONTEXT OF GLAUCOMA**

Insulin has been studied for its potential neuroprotective effects in the context of glaucoma. According to Hou, Moghimi, Baxter and Weinreb (2021), insulin plays a crucial role in the survival of retinal ganglion cells (RGCs), contributing to the reduction of oxidative stress and the maintenance of mitochondrial homeostasis. These effects are complemented by anti-inflammatory properties, which may mitigate the damage associated with the pathophysiology of glaucoma. However, Maestroni *et al.* (2023) point out that the loss of RGCs in diabetic patients is comparable to that observed in glaucoma, suggesting that insulin, although promising, may not be sufficient as an isolated neuroprotection strategy in cases of patients with both conditions.

Metformin, widely used in the management of type 2 diabetes mellitus, has also been associated with potential neuroprotective benefits in glaucoma. Hou, Moghimi, Baxter and Weinreb (2021) reported that the use of metformin significantly reduces the risk of developing GPAA in a dose-dependent manner. However, Virtanen, Haukka, Loukovaara and Harju (2023) reinforced these findings by observing that diabetic patients treated with metformin had a lower incidence of GPAA. This effect suggests that metformin may mitigate the risks related to the vascular pathophysiology of diabetes mellitus.

On the other hand, studies carried out in specific populations, such as in southern India, found no significant association between the use of metformin and a reduction in the risk of POAG. George, Asokan and Vijaya (2021) evaluated diabetic patients using metformin and found no significant impact on IOP reduction or the prevention of primary open-angle glaucoma. These conflicting re-

sults highlight the need for greater methodological standardization and analysis of confounding factors to clarify the therapeutic and neuroprotective effects of metformin in different populations.

## **MULTIDIMENSIONAL THERAPEUTIC APPROACHES AND CLINICAL MANAGEMENT OF NEOVASCULAR GLAUCOMA**

Neovascular glaucoma (NVG) is an aggressively progressive condition often associated with proliferative diabetic retinopathy (PDR), central retinal vein obstruction (CRVO) and ocular ischemic syndrome (OIS). Tang, Shi and Fan (2023) point out that the combination of panretinal photocoagulation and intravitreal injections of anti-VEGF agents is key to controlling neovascularization in the early stages of the disease. These treatments help to reduce IOP and prevent irreversible damage to vision. However, their effectiveness decreases in advanced stages, which often results in high rates of surgical failure, as observed in trabeculectomy procedures.

Senthil *et al.* (2021) reinforce the relevance of panretinal photocoagulation and anti-VEGF agents in the management of neovascular glaucoma, pointing out that these interventions are particularly effective in reducing IOP in early cases of neovascularization. In a study of 100 eyes undergoing trabeculectomy, the authors identified PDR as the most prevalent cause of NVG (59%), followed by CRVO (25%) and OIS (16%). These findings highlight the importance of a multidimensional approach, taking into account the stage of the disease and underlying conditions.

Complementary approaches, such as Acupuncture and yoga exercises, have also shown benefits in the management of glaucoma. Ismail and El-Azeim (2021) reported a significant reduction in IOP in patients with primary open-angle glaucoma after applying these alternative therapies. However, the authors point out that



the beneficial effects were only observed in the short term, and the lack of prolonged follow-up limits the application of these methods as isolated interventions. These results point to the need for further studies to assess the feasibility of these strategies in the integrated management of neovascular glaucoma.

Furthermore, Su *et al.* (2023) emphasize that strict glycemic control should be integrated into therapeutic strategies in the treatment of neovascular glaucoma. Population studies indicate that patients with type 2 diabetes mellitus are more likely to develop angle-closure glaucoma, the progression of which can be aggravated by differences in iris volume. These pathophysiological factors should be considered when establishing clinical management plans.

Finally, Chang *et al.* (2022) point out that the correlation between type 2 diabetes mellitus and primary open-angle glaucoma should be considered in the context of the therapeutic management of NVG. Multivariate analyses of clinical data suggest that diabetes is independently associated with a higher risk of developing glaucoma, reinforcing the need for management strategies that address both the underlying conditions and the specific manifestations of neovascular glaucoma.

## FINAL CONSIDERATIONS

The relationship between diabetes mellitus DM and GPAA has been highlighted, highlighting shared pathophysiological mechanisms such as microvascular alterations and retinal neurodegeneration, as well as the impact of strict glycemic control and specific therapies in the prevention and management of these diseases. However, methodological limitations, controversies over the efficacy of certain drugs and the scarcity of robust longitudinal data make it difficult to draw definitive conclusions. Integrating screening for diabetic retinopathy with the early detection of glaucoma has emerged as a promising strategy, allowing for the optimization of resources and more effective interventions. In addition, the improvement of preventive approaches, the implementation of early interventions and the use of neuroprotective therapies have the potential to significantly reduce the burden of these diseases on global eye health. Further studies, with robust methodologies and representative samples, are needed to strengthen this evidence and contribute to the development of integrated and personalized clinical strategies.

## REFERENCES

ALDARRAB, A.; AL JARALLAH, O. J.; AL BALAWI, H. B. Association of diabetes, fasting glucose, and the risk of glaucoma: a systematic review and meta-analysis. **European Review for Medical & Pharmacological Sciences**, v. 27, n. 6, 2023.

CHANG, Ya-Wen *et al.* Risk of Glaucoma Associated with Components of Metabolic Disease in Taiwan: A Nationwide Population-Based Study. **International Journal of Environmental Research and Public Health**, v. 19, n. 1, p. 305, 2022.

GEORGE, Ronnie; ASOKAN, Rashima; VIJAYA, Lingam. Association of metformin use among diabetics and the incidence of primary open-angle glaucoma–The Chennai Eye Disease Incidence Study. **Indian Journal of Ophthalmology**, v. 69, n. 11, p. 3336-3338, 2021.

HOU, Huiyuan; MOGHIMI, Sasan; BAXTER, Sally L.; WEINREB, Robert N. Is diabetes mellitus a blessing in disguise for primary open-angle glaucoma?. **Journal of glaucoma**, v. 30, n. 1, p. 1-4, 2021.

JUNG, Younhea *et al.* Metabolic health, obesity, and the risk of developing open-angle glaucoma: metabolically healthy obese patients versus metabolically unhealthy but normal weight patients. **Diabetes & metabolism journal**, v. 44, n. 3, p. 414-425, 2020.

KJAERGAARD, Marianne; GRAUSLUND, Jakob; VESTERGAARD, Anders Højslet; SUBHI, Yousif. Relationship between diabetic retinopathy and primary open-angle glaucoma: a systematic review and meta-analysis. **Ophthalmic Research**, v. 65, n. 4, p. 377-386, 2022.

LEE, Sun Jung; JEON, Jae-Sik; KANG, Ji-Hyuk; KIM, Jae Kyung. Prediction of the Cause of Glaucoma Disease Identified by Glaucoma Optical Coherence Tomography Test in Relation to Diabetes and Hypertension at a National Hospital in Seoul: A Retrospective Study. **Diagnostics**, v. 14, n. 13, p. 1418, 2024.

MAESTRONI, Silvia *et al.* Diabetes has no additional impact on retinal ganglion cell loss in a mouse model of spontaneous glaucoma. **European Journal of Ophthalmology**, v. 33, n. 3, p. 1418-1424, 2023.

MAHMOOD, Tauseef *et al.* Ocular Complications Associated with Diabetes and The Risk of Sustainable Blindness; A Real World Analysis. **J Pak Med Assoc**, v. 73, p. 1453-1456, 2023.

SENTHIL, Sirisha *et al.* Trabeculectomy for neovascular glaucoma in proliferative diabetic retinopathy, central retinal vein occlusion, and ocular ischemic syndrome: Surgical outcomes and prognostic factors for failure. **Indian Journal of Ophthalmology**, v. 69, n. 11, p. 3341-3348, 2021.

SU, Ying *et al.* Assessment of iris volume in glaucoma patients with type 2 diabetes mellitus by AS-OCT. **International Journal of Ophthalmology**, v. 16, n. 5, p. 743, 2023.

TANG, Yizhen; SHI, Yan; FAN, Zhigang. The mechanism and therapeutic strategies for neovascular glaucoma secondary to diabetic retinopathy. **Frontiers in Endocrinology**, v. 14, p. 1102361, 2023.

VIRTANEN, Aapo; HAUKKA, Jari; LOUKOVAARA, Sirpa; HARJU, Mika. Diabetes mellitus and risk of open-angle glaucoma—A population-based follow-up study. **Acta Ophthalmologica**, v. 101, n. 2, p. 160-169, 2023.