Neurodegenerative manifestations in diabetic retinopathy

Manifestações neurodegenerativas na retinopatia diabética

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ABSTRACT

Diabetic retinopathy is the leading cause of vision loss among working-age adults in the Western world. Although it has traditionally been considered a microvascular disease, growing evidence suggests that neurodegenerative changes may occur even before the appearance of microvascular damage. The aim of this review was to provide a comprehensive summary of the current evidence regarding neurodegenerative changes in diabetic retinopathy. This is a narrative review, in which we performed a comprehensive literature search from August 15, 1998, to June 20, 2025, using MEDLINE® (via PubMed®) and Lilacs (via the Virtual Health Library) to identify studies on neurodegenerative changes in diabetic retinopathy. The search strategy included combinations of keywords and MeSH terms such as „neurodegeneration" and „diabetic retinopathy". After screening titles and abstracts based on predefined criteria and removing two duplicates, we included 236 relevant publications, including reviews, case reports, randomized controlled trials, meta-analyses, and guidelines. Of these, 73 articles were selected for an in-depth qualitative review on the subject. Current evidence indicates that neurodegenerative changes play a significant role in the early stages of diabetic retinopathy in a substantial proportion of patients, supporting the understanding of the disease as a neurovascular disorder.

RESUMO

A retinopatia diabética é a principal causa de perda de visão entre adultos em idade laboral no mundo ocidental. Embora tradicionalmente tenha sido considerada uma doença microvascular, evidências crescentes sugerem que alterações neurodegenerativas podem ocorrer mesmo antes do aparecimento de danos microvasculares. O objetivo desta revisão foi fornecer um resumo abrangente das evidências atuais sobre alterações neurodegenerativas na retinopatia diabética. Esta é uma revisão narrativa, na qual realizamos uma busca abrangente na literatura de 15 de agosto de 1998 a 20 de junho de 2025, utilizando MEDLINE® (via PubMed®) e Lilacs (via Biblioteca Virtual em Saúde) para identificar estudos sobre alterações neurodegenerativas na retinopatia diabética. A estratégia de busca incluiu combinações de palavras-chave e termos MeSH, como "neurodegeneração" e "retinopatia diabética". Após a triagem de títulos e resumos com base em critérios predefinidos e a remoção de dois duplicados, incluímos 236 publicações relevantes, compreendendo revisões, relatos de casos, ensaios clínicos randomizados, meta-análises e diretrizes. Destas, 73 artigos foram selecionados para uma revisão qualitativa aprofundada sobre o tema. As evidências atuais indicam que alterações neurodegenerativas desempenham um papel significativo nos estágios iniciais da retinopatia diabética em uma proporção substancial de pacientes, apoiando a compreensão da doença como um distúrbio neurovascular.

INTRODUCTION

Diabetic retinopathy (DR), the leading cause of vision loss among working-age adults in the Western world, has traditionally been considered a microvascular disease. However, increasing evidence suggests that neurodegenerative changes may precede vascular damage.[1-3]

Diabetic retinopathy involves neurodegenerative changes such as neuronal apoptosis and glial activation, which can occur even without visible vascular damage. These changes have been found in diabetic patients with normal eye exams, indicating that neurodegeneration may precede clinical signs. Diabetes increases retinal neuron apoptosis – especially in ganglion cells – resulting in thinning of the nerve fiber layer.[4,5]

Diabetes can trigger apoptosis of retinal ganglion, amacrine, and Müller cells, likely due to chronic glutamate toxicity. Glutamate-induced excitotoxicity increases oxidative stress and inflammation, contributing to retinal neurodegeneration.[6] Glutamate accumulation in the diabetic retina may result from increased production by glial cells, reduced glutamate oxidation, and impaired clearance due to decreased glutamine synthetase activity in Müller cells.[7]

High glutamate levels lead to neuronal death by overactivating AMPA and NMDA receptors, increasing intracellular calcium and causing excitotoxicity. Diabetes also reduces neuroprotective factors like pigment epithelium-derived factor (PEDF), somatostatin (SST), and erythropoietin.[7]

Glutamate buildup and reduced neuroprotection increase vascular endothelial growth factor (VEGF) production, promoting blood-retinal barrier breakdown. Endothelial progenitor cell (EPC) dysfunction also contributes to microangiopathy and neurodegeneration.[8]

Glutamate buildup in DR is caused by reduced glutamine synthetase activity, impaired glutamate oxidation, and decreased glial clearance. These changes lead to excitotoxicity, a major factor in retinal neurodegeneration.[9-11] Neural dysfunction in DR can occur before microvascular damage, even without pericyte loss, challenging the view that vascular changes are the earliest signs of the disease.[12-14]

Diabetes-related neurodegeneration also affects avascular tissues like the cornea. Confocal microscopy shows reduced corneal nerve fiber density in patients with diabetic neuropathy, indicating neurodegeneration independent of vascular damage.[15,16] Neuronal changes in the retina can occur simultaneously with vascular alterations or may emerge prior to the development of microcirculatory dysfunction.[17]

The aim of this narrative review was to provide a comprehensive summary of the current evidence regarding neurodegenerative changes in DR.

METHODS

We conducted a comprehensive literature review covering the period from August 15, 1998, to June 20, 2025. Searches were carried out in the MEDLINE® database, via PubMed®, and Latin American and Caribbean Health Sciences (Lilacs), via the Virtual Health Library, to identify relevant studies on the neurodegenerative manifestations of diabetes. To ensure a thorough and sensitive search strategy, we used a variety of keyword and MeSH term combinations, including: ("neurodegeneration") AND ("diabetic retinopathy"); "diabetic retinopathy".

Titles and abstracts of all retrieved citations were screened for relevance and eligibility according to predefined inclusion criteria. Two duplicate articles identified across both databases were excluded. Following this, all publications categorized as reviews, case reports, randomized controlled trials, meta-analyses, and guidelines were selected, resulting in a final pool of 236 articles. From these, 73 articles were chosen for an in-depth qualitative analysis on the topic. Details of the search strategy are presented in table 1.

Table 1. Search strategies and number of articles retrieved from each database

Database	Search strategy	Articles retrieved
MEDLINE® (via PubMed®)	(«neurodegeneration») AND («diabetic retinopathy»)	684
Lilacs (via Virtual Health Library)	(«neurodegeneration») AND («diabetic retinopathy»)	2

RESULTS

Neurodegeneration, epigenetic regulation, and cellular mechanisms

Diabetic retinopathy starts before visible diabetes, driven by inflammation and angiogenesis. Chronic high blood sugar causes neuron damage and death through disrupted crystallin, microglial activation, and advanced glycation end product (AGE) accumulation, leading to inflammation and retinal ganglion cell loss via tumor necrosis factor-alpha (TNF-α) and nitric oxide. This causes excitotoxicity, vascular changes, and metabolic dysfunction worsened by sorbitol, oxidative stress, and apoptotic pathways. Early diabetes shows leukocyte adhesion, increased inflammatory cytokines, and barrier breakdown, promoting inflammation and abnormal blood vessel

growth. Genetics influence risk but do not fully explain the disease. Elevated AGEs worsen inflammation, hypertension, and fibrosis, advancing retinopathy.[18]

Retinal neurodegeneration occurs early in DR, before vascular damage, involving neuron apoptosis and glial activation. It is driven by glutamate excitotoxicity, mitochondrial dysfunction, oxidative stress, and inflammation. Hyperglycemia-related pathways also contribute. Experimental models aid understanding and treatment development. Neuroprotective therapies are promising but require early biomarkers, deeper disease insight, and clinical trials. AI tools may enhance early diagnosis and personalized treatment.[19,20]

Diabetic retinopathy goes beyond classical vascular changes, involving progressive degeneration of neural retinal tissue and disruption of retinal homeostasis. The retinal neurovascular unit (NVU) – comprising neurons, glial, vascular, and immune cells – is essential for neurovascular coupling and blood flow regulation. Chronic hyperglycemia disrupts these interactions early on, promoting oxidative stress, persistent inflammation, and cell death.[21,22]

Non-coding RNAs, especially lncRNAs, miRNAs, and piRNAs, act as important epigenetic regulators in DR. LncRNAs such as MALAT1, MEG3, H19, and NEAT1 modulate inflammation, neurodegeneration, and apoptosis by functioning as miRNA sponges, epigenetic modulators, or molecular scaffolds. Diabetic retinopathy, characterized as a chronic neurovascular inflammatory disease, involves hyperglycemia, oxidative stress, inflammation, programmed cell death, and epigenetic changes – all of which are promising targets for new therapies.[23-25]

Inflammation in DR begins early, with cytokines, leukocyte infiltration, and pro-apoptotic factors damaging the retinal endothelium, leading to ischemia and neovascularization. Chronic hyperglycemia increases AGEs and reactive oxygen species, activating pathways such as PKC, nuclear factor Kappa-light-chain-enhancer of activated B cells (NF-κB), and VEGF, which worsen inflammation and cellular injury. Early retinal neurodegeneration, linked to impaired insulin signaling (reduced Akt1 activity) and dysregulation of the mTOR pathway, causes synaptic dysfunction and cell death before vascular changes appear. Early visual deficits can be detected by electrophysiology. For research, the genetic db/db mouse model better mimics type 2 diabetes-related neurodegeneration than the STZ-induced model, which has neurotoxic limitations.[26,27]

Microglia, the retina's resident immune cells, normally support neural health through synaptic monitoring and immune defense. In DR, factors like high glucose and oxidative stress activate microglia, causing them to migrate, proliferate, and release inflammatory molecules, which can be either protective or damaging depending on disease stage. Early neuronal loss in DR is linked to disrupted neurotrophic factors such as insulin, insulin-like growth factor (IGF), VEGF, PEDF, brain-derived neurotrophic factor (BDNF), and NGF. While many of them support retinal health, imbalances, especially increased VEGF, can harm neurons. This underscores the potential of neuroprotective therapies to preserve vision in DR.[28,29]

EXAMS

The cross-sectional study from the EUROCONDOR consortium evaluated 449 patients with type 2 diabetes to investigate early neurodegenerative changes in DR and their relationship with microvascular damage. Neural function assessed by multifocal ERG (mfERG) showed that 58% of patients had dysfunction despite no visible retinopathy, with the P1 component of mfERG being a sensitive marker. Structural changes detected by OCT were correlated with functional deficits in early stages, but 32% showed no detectable changes, highlighting disease heterogeneity. Another EUROCONDOR study with 440 patients found that venular caliber increased in advanced DR stages, associated with thinning of neural retinal layers, indicating inflammation and blood-retinal barrier dysfunction. These findings reinforce DR as a neurovascular disease and suggest that non-invasive vessel measurements may serve as early biomarkers for diagnosis and personalized therapies.[30,31]

Animal models of diabetes indicate that neural damage in DR may arise before noticeable vascular abnormalities. In mice, inner retinal thinning and electrophysiological deficits are observed prior to visible microvascular pathology. In humans, although clinical evidence is still evolving, imaging techniques like optical coherence tomography (OCT) show early retinal layer thinning associated with DR progression, while functional assessments reveal subtle neuronal dysfunctions. OCT angiography (OCT-A) can detect early microvascular disturbances, such as decreased capillary density and enlargement of the foveal avascular zone, although findings are not always consistent across studies. Overall, current evidence suggests that neural and vascular changes may develop concurrently and interactively in the initial stages of DR.[32,33]

Patients with type 2 diabetes have a higher risk of neurodegenerative diseases such as Alzheimer's. Since

the retina originates from brain tissue, it provides a non-invasive way to monitor these changes. Diabetes and Alzheimer's share mechanisms including insulin resistance, inflammation, oxidative stress, and accumulation of AGEs, affecting both the brain and retina. Retinal imaging tools like OCT and microperimetry can detect early neurodegenerative signs linked to cognitive decline. In DR, neuronal damage– marked by gliosis and apoptosis of retinal cells–occurs before vascular changes, causing inner retinal thinning visible on OCT and early functional deficits detected by mfERG, which are associated with reduced visual function and quality of life.[34]

There is growing interest in using imaging methods such as OCT, OCT-A, and fluorescein angiography to detect retinal inflammation in vivo. Hyperreflective foci (HF), possibly activated microglial cells, increase with the severity of DR and diabetic macular edema (DME), correlating with retinal dysfunction. Vitreous HF and macrophage-like cells near vessels are also linked to disease progression. Specific DME patterns on OCT, such as subretinal fluid (SRF), indicate inflammation and respond better to corticosteroids (e.g., dexamethasone) than to anti-VEGF therapy. Choroidal biomarkers like choroidal HF and the choroidal vascularity index (CVI) help monitor treatment response. Macular perfusion is reduced in DME, especially in the deep capillary plexus. Despite technical limitations of OCT-A, corticosteroids appear to reduce vascular density without worsening ischemia, but further studies are needed.[35]

Neuroprotection and treatments

Current treatments for DR, such as laser therapy, anti-VEGF or corticosteroid injections, and vitrectomy, are effective but mainly used in advanced stages and can have side effects affecting quality of life. There is an urgent need for therapies targeting early DR to prevent irreversible retinal damage. Retinal neurodegeneration occurs early and independently, contributing to vascular injury through excitotoxicity, oxidative stress, and inflammation. Neurotrophic factors (BDNF, CNTF, NGF, IGF-1, and PEDF) show experimental neuroprotective effects. Early detection with advanced diagnostics like mfERG and OCT is crucial for timely intervention. Non-invasive treatments, including topical neuroprotective eye drops, are promising but require further clinical validation. Recognizing DR as a neurovascular disease highlights the importance of early neuroprotection to improve patient outcomes.[35,36]

Neuronal apoptosis in DR is driven by mechanisms such as glutamate excitotoxicity, hyperhomocysteinemia, kynurenic acid imbalance, and erythropoietin dysfunction. Advanced imaging reveals early photoreceptor loss, emphasizing the need for neuroprotective approaches like memantine, insulin receptor activation, and neurotrophic factors. Combined with strict blood glucose control and vascular risk management, these strategies may help preserve vision long-term, though more research is needed for effective clinical treatments.[37]

Neurodegeneration, including neuronal apoptosis, occurs before visible microvascular changes in DR, highlighting the crucial role of neural damage in vision loss. Thus, neuroprotection is a promising therapeutic target that extends beyond traditional vascular treatments.[38,39]

Stem cell therapies show potential to repair both neural and vascular damage in DR but face challenges from retinal inflammation and oxidative stress that limit cell survival. Approaches such as genetic enhancement of stem cells, early treatment, and combining different cell types are being investigated to improve effectiveness. Advances in imaging support personalized therapy, while ensuring safety through thorough evaluation of cell behavior and immune responses remains essential before clinical application.[40]

Innovative treatments for DR include stem cell therapies and targeted anti-inflammatory agents aimed at regenerating retinal cells and controlling inflammation. Experimental drugs such as NF-κB inhibitors, necroptosis inhibitors, circular RNAs, NOX4 inhibitors, finerenone, and miRNA-124 are promising in preclinical studies. In DME, corticosteroids effectively reduce inflammation, even when anti-VEGF treatments fail. Despite challenges from retinal toxicity and disease variability, personalized multimodal approaches combining anti-inflammatory and regenerative therapies, guided by advanced diagnostics, may improve vision preservation.[41]

Somatostatin, a neuropeptide with neuroprotective, antiangiogenic, and vascular-regulating properties, is significantly reduced in diabetic retinas, contributing to DR progression. Experimental studies indicate that topical SST prevents retinal dysfunction, neuronal apoptosis, glial activation, and excitotoxicity, suggesting its potential as an early-stage preventive therapy. Clinical trials are needed to confirm its safety and efficacy in humans.[42-44]

A European clinical study evaluating the effects of topical brimonidine and SST in patients with early or no signs of DR found no significant neuroprotective effects overall. However, individuals with subtle neuroretinal dysfunction showed disease stabilization. Additionally, patients with mild DR experienced dilation of retinal blood vessels,

indicating potential neurovascular improvements. These findings suggest that these topical therapies are safe and may serve as early, personalized interventions to slow disease progression and help maintain vision.[45,46]

In a related experimental study, retinal pericytes were found to predominantly express the SSTR1 receptor, identifying them as targets for SST. When exposed to diabetic-like conditions, both SST and brimonidine reduced apoptosis in endothelial cells, suggesting indirect protective benefits. Although these agents did not markedly affect neurovascular interactions, their lack of toxicity supports their potential use as safe treatments addressing both neural and vascular aspects of DR.[47]

Topical brimonidine demonstrates neuroprotective effects in DR by reducing retinal ganglion cell loss and glial activation in diabetic rat models. It activates the AKT survival pathway, decreases pro-apoptotic signals, increases anti-apoptotic proteins, and lowers retinal stress markers, possibly through enhanced BDNF production by Müller cells. This supports brimonidine as a promising localized treatment with minimal systemic side effects.[48]

Treatment for DR is evolving from traditional laser therapy to intravitreal corticosteroids and anti-VEGF agents. However, 30 to 40% of patients have poor responses, and long-term neurotoxicity is a concern. Novel therapies like anti-Scg3 antibodies, which selectively inhibit pathological angiogenesis without affecting healthy vessels or relying on VEGF, offer potentially safer and more targeted treatment. Though still in preclinical development, anti-Scg3 aims to protect both retinal vascular and neural tissues.[49]

Reduced levels of brain-derived neurotrophic factor in diabetic patients suggest its potential as a biomarker for the progression of DR. Both BDNF and Neurotrophin-4 (NT-4) support neuronal survival through the TrkB receptor; however, excessive BDNF can induce inflammation. To address BDNF's short half-life, nanoparticle-based delivery systems are being developed.[50]

Pigment epithelium-derived factor offers antioxidant and neurovascular protection by reducing neuronal damage and vascular leakage; related antiangiogenic peptides are undergoing clinical trials. Somatostatin demonstrates neuroprotection in animal models but has shown limited success in human trials. Glucagon-like peptide-1 (GLP-1) receptor agonists exhibit neuroprotective effects in preclinical studies but have not provided clinical benefits and may exacerbate DR.[50]

Fenofibrate, a Peroxisome Proliferator-Activated Receptor Alpha (PPARα) agonist, effectively slows DR progression by reducing inflammation and vascular damage, making it a promising early treatment targeting the NVU.[51]

Advanced Glycation End Products (AGEs) contribute to both vascular and neuronal damage in retinal diseases like DR and neurological disorders such as Alzheimer's. Anti-AGE therapies aim to protect the NVU by reducing AGE accumulation caused by chronic hyperglycemia. Effective treatments should combine antioxidant action, metal chelation, carbonyl scavenging, cross-link breaking, and Receptor for Advanced Glycation End Products (RAGE) inhibition; however, no current drug meets all these criteria without side effects. Natural compounds, though less potent, are safer and may be useful in early DR, but more research is needed to confirm their efficacy and safety.[51]

DISCUSSION

Dysfunction of the NVU is a critical early event in DR. Visual impairment often occurs before structural damage, highlighting the importance of neuroprotection to preserve visual quality. Advanced diagnostic tools such as mfERG and Fourier-domain optical coherence tomography (FD-OCT) are effective in detecting early neurodegeneration. Simpler, cost-effective methods like microperimetry, portable ERG, and OCT-A are also promising for clinical application. Emerging therapies targeting both neural and vascular damage – including GLP-1 receptor agonists, endothelin-1 blockers, and topical medications – are being explored. Overall, early DR management is shifting towards individualized strategies focused on protecting the NVU.[52]

While tight glycemic control reduces the risk of DR, overly aggressive glucose lowering may increase cardiovascular problems. Hemoglobin A1c (HbA1c) alone does not account for all DR progression, which involves additional mechanisms like hyperglycemia-induced neuronal apoptosis and glutamate excitotoxicity. Neuroprotective agents (e.g., latanoprost, memantine) and anti-inflammatory treatments (like minocycline) are promising in preclinical studies. Other strategies include protein kinase C (PKC) inhibition and localized delivery of neurotrophic factors (nerve growth factor [NGF], PEDF, BDNF, SST, topical insulin). Although animal studies are encouraging, clinical trials with functional vision outcomes are needed. DR should be treated as a complex sensory neuropathy requiring targeted ocular therapies.[53]

Diabetic retinopathy initiates with early neurodegeneration before vascular damage, making NVU protection

a crucial early intervention. Since multiple pathways contribute to neuronal death, combined neuroprotective treatments may be more effective. Axonal damage is mostly irreversible, limiting regeneration. Topical agents like brimonidine, SST, and citicoline with vitamin B12 are promising in preserving retinal function safely. Experimental therapies targeting glial activation and oxidative stress, such as arimoclomol, are being studied. Improved retinal imaging aids early detection and treatment guidance. More research is needed to confirm the effectiveness of these therapies.[54]

Recent studies show that DR involves multiple regulated cell death pathways – such as pyroptosis, ferroptosis, and necroptosis – that promote inflammation and disease progression beyond classic apoptosis. Since neuronal and pericyte loss are irreversible and disrupt retinal function, treatments must target these diverse death mechanisms for effective neuro- and vasoprotection. DR is now recognized as a complex disorder affecting neurons, glial cells, immune responses, and the retinal pigment epithelium. Traditional therapies focus on vascular complications but are often invasive and costly. Emerging treatments aim to protect the NVU using neurotrophic factors (PEDF, BDNF, IGF-1, and SST), antioxidants, anti-inflammatory agents, stem cells, and inhibitors of iNOS and endothelin-1 receptors. While promising, these therapies require further research to confirm long-term safety, efficacy, and optimal delivery methods before clinical use.[55,56]

Recent advances identify diabetic retinal neurodegeneration as a crucial component of diabetic retinal disease, involving molecular markers linked to inflammation, oxidative stress, and cell death. Neurodegeneration can occur despite stable HbA1c due to glucose fluctuations. Imaging techniques like OCT, microperimetry, and OCT angiography detect retinal structural and functional changes, highlighting the connection between neural and vascular damage. Experimental treatments include anti-inflammatory agents, antioxidants, neuroprotective drugs, stem cells, flavonoids, and RAS modulators. Diabetic retinal neurodegeneration results from oxidative stress, inflammation, AGEs, DNA damage, and programmed cell death. Although promising in preclinical studies, clinical application is difficult due to disease variability and diagnostic challenges. Multimodal therapies targeting several pathways and early neuroprotection are essential for vision preservation.[57-65]

Diabetic retinopathy begins with early neuronal and axonal injury. Topical neuroprotective treatments like SST and brimonidine showed limited success in the EUROCONDOR trial, possibly due to short follow-up and insensitive endpoints. However, combination therapies targeting multiple cell death pathways, such as citicoline, TUDCA, and NT-4, show better neuroprotection and nerve regeneration. Future research should focus on these multimodal neuroprotective and regenerative approaches.[57-67]

Optical coherence tomography (OCT) offers detailed, noninvasive imaging of retinal layers, revealing ganglion cell loss, neuronal apoptosis, glial activation, and inner retinal thinning. Type 2 diabetes may accelerate nerve fiber layer thinning. The close interaction between neurons, glia, and blood vessels explains the concurrent neuronal and microvascular damage – such as pericyte loss, basement membrane thickening, and capillary closure – contributing to vision loss.[58-69]

PERSPECTIVES

Strengths and limitations

The reviewed studies exhibited significant methodological variability, and this narrative review lacks standardized criteria for assessing study quality. It does not provide quantitative or statistical analysis, and author bias may have influenced study selection and interpretation.

Advanced imaging techniques like OCT angiography and adaptive optics enhance early detection and monitoring of DR. Early aggressive treatments are discouraged, while topical neuroprotective therapies are promising but require improved delivery methods and further clinical validation before routine use.[70]

Although neuroprotective treatments are promising in animal studies, their effectiveness in diabetic patients remains unconfirmed. This gap is due to differences between experimental models and human disease, clinical variability, delayed treatment initiation, challenges in drug delivery, and inconsistent clinical assessment methods. Numerous therapies have failed in clinical trials, underscoring the necessity for standardized protocols, multidisciplinary research efforts, and long-term studies, advanced imaging technologies, enhanced drug delivery systems, and meaningful clinical endpoints to establish their real-world efficacy.[71-73]

CONCLUSION

Diabetic retinopathy is a complex neurovascular disorder where neurodegeneration often occurs before vascular damage becomes apparent. Advances in imaging enable earlier diagnosis, but clinical use of neuroprotective and anti-inflammatory treatments faces challenges such as disease variability, late diagnosis, and drug delivery

issues. Combining neuroprotection, vascular support, and regeneration, guided by personalized diagnostics, offers the best chance to slow disease progression. Future efforts should focus on standardized methods, long-term trials, multimodal therapies, sensitive outcome measures, and multidisciplinary collaboration to improve patient care and preserve vision.

AUTHORS' CONTRIBUTION

Martins DGS: conceptualization (equal), data curation (equal), formal analysis (equal), investigation (equal), methodology (equal), project administration (equal), resources (equal), software (equal), supervision (equal), validation (equal), visualization (equal), writing-original draft (equal) and writing-review and editing (equal); Martins Thiago Gonçalves dos Santos: conceptualization (equal), data curation (equal), formal analysis (equal), investigation (equal), methodology (equal), project administration (equal), resources (equal), software (equal), supervision (equal), validation (equal), visualization (equal), writing-original draft (equal) and writing-review and editing (equal); Martins Thomaz Gonçalves dos Santos: data curation (equal), formal analysis (equal), investigation (equal), methodology (equal), project administration (equal), resources (equal), software (equal), supervision (equal), validation (equal), visualization (equal), writing-original draft (equal) and writing-review and editing (equal); and Schor P: conceptualization (equal), data curation (equal), formal analysis (equal), investigation (equal), methodology (equal), project administration (equal), resources (equal), software (equal), supervision (equal), validation (equal), visualization (equal), writing-original draft (equal) and writing-review and editing (equal). All authors actively contributed to discussion of the results from the study and reviewed and approved the final version of the manuscript to be released.

REFERENCES

1. Grauslund J, Green A, Sjolie AK. Prevalence and 25-year incidence of proliferative retinopathy among Danish type 1 diabetic patients. Diabetologia. 2009;52(9):1829-35.
2. Liew G, Michaelides M, Bunce C. A comparison of the causes of blindness certifications in England and Wales in working age adults (16–64 years), 1999–2000 with 2009-2010. BMJ Open. 2014;4(2):e004015.
3. Jonsson KB, Frydkjaer-Olsen U, Grauslund J. Vascular changes and neurodegeneration in the early stages of diabetic retinopathy: which comes first? Ophthalmic Res. 2016;56(1):1-9.
4. Carrasco E, Hernández C, de Torres I, Farrés J, Simó R. Lowered cortistatin expression is an early event in the human diabetic retina and is associated with apoptosis and glial activation. Mol Vis. 2008;14:1496-502.
5. van Dijk HW, Verbraak FD, Stehouwer M, Kok PH, Garvin MK, Sonka M, et al. Association of visual function and ganglion cell layer thickness in patients with diabetes mellitus type 1 and no or minimal diabetic retinopathy. Vision Res. 2011;51(2):224-8.
6. Lieth E, LaNoue KF, Antonetti DA, Ratz M. Diabetes reduces glutamate oxidation and glutamine synthesis in the retina. The Penn State Retina Research Group. Exp Eye Res. 2000;70(6):723-30.
7. Zhang Y, Bhavnani BR. Glutamate-induced apoptosis in neuronal cells is mediated via caspase-dependent and independent mechanisms involving calpain and caspase-3 proteases as well as apoptosis inducing factor (AIF) and this process is inhibited by equine estrogens. BMC Neurosci. 2006;7:49.
8. Kern TS, Barber AJ. Retinal ganglion cells in diabetes. J Physiol. 2008;586(18):4401-8.
9. Lieth E, Barber AJ, Xu B, Dice C, Ratz MJ, Tanase D, et al. Glial reactivity and impaired glutamate metabolism in short-term experimental diabetic retinopathy. Penn State Retina Research Group. Diabetes. 1998;47(5):815-20.
10. Reis A, Mateus C, Melo P, Figueira J, Cunha-Vaz J, Castelo-Branco M. Neuroretinal dysfunction with intact blood-retinal barrier and absent vasculopathy in type 1 diabetes. Diabetes. 2014;63(11):3926-37.
11. Kowluru RA, Engerman RL, Case GL, Kern TS. Retinal glutamate in diabetes and effect of antioxidants. Neurochem Int. 2001;38(5):385-90.
12. Sohn EH, van Dijk HW, Jiao C, Kok PH, Jeong W, Demirkaya N, et al. Retinal neurodegeneration may precede microvascular changes characteristic of diabetic retinopathy in diabetes mellitus. Proc Natl Acad Sci U S A. 2016;113(19):E2655-64.
13. Cogan DG, Toussaint D, Kuwabara T. Retinal vascular patterns. IV. Diabetic retinopathy. Arch Ophthalmol. 1961;66:366-78.
14. Hammes HP, Lin J, Renner O, Shani M, Lundqvist A, Betsholtz C, et al. Pericytes and the pathogenesis of diabetic retinopathy. Diabetes. 2002;51(10):3107-12.
15. Rosenberg ME, Tervo TM, Immonen IJ, Müller LJ, Grönhagen-Riska C, Vesaluoma MH. Corneal structure and sensitivity in type 1 diabetes mellitus. Invest Ophthalmol Vis Sci. 2000;41(10):2915-21.
16. Bitirgen G, Ozkagnici A, Malik RA, Kerimoglu H. Corneal nerve fibre damage precedes diabetic retinopathy in patients with type 2 diabetes mellitus. Diabet Med. 2014;31(4):431-8.
17. Harrison WW, Bearse MA Jr, Ng JS, Jewell NP, Barez S, Burger D, et al. Multifocal electroretinograms predict onset of diabetic retinopathy in adult patients with diabetes. Invest Ophthalmol Vis Sci. 2011;52(2):772-7.
18. Kadłubowska J, Malaguarnera L, Wąż P, Zorena K. Neurodegeneration and Neuroinflammation in Diabetic Retinopathy: Potential Approaches to Delay Neuronal Loss. Curr Neuropharmacol. 2016;14(8):831-9.
19. Simó R, Hernández C; European Consortium for the Early Treatment of Diabetic Retinopathy (EUROCONDOR). Neurodegeneration in the diabetic eye: new insights and therapeutic perspectives. Trends Endocrinol Metab. 2014;25(1):23-33.
20. Simó R, Simó-Servat O, Bogdanov P, Hernández C. Diabetic Retinopathy: Role of Neurodegeneration and Therapeutic Perspectives. Asia Pac J Ophthalmol (Phila). 2022;11(2):160-7.
21. Karpagavalli M, Sindal MD, Arunachalam JP, Chidambaram S. miRNAs, piRNAs, and lncRNAs: A triad of non-coding RNAs regulating the neurovascular unit in diabetic retinopathy and their therapeutic potentials. Exp Eye Res. 2025;251:110236.
22. Pu S, Xu Y, Li X, Yu Z, Zhang Y, Tong X, et al. LncRNAS-modulators of neurovascular units in diabetic retinopathy. Eur J Pharmacol. 2022;925:174937.
23. Callan A, Jha S, Valdez L, Tsin A. Cellular and Molecular Mechanisms of Neuronal Degeneration in Early-Stage Diabetic Retinopathy. Curr Vasc Pharmacol. 2024;22(5):301-15.
24. Gao S, Zhang Y, Zhang M. Targeting Novel Regulated Cell Death: Pyroptosis, Necroptosis, and Ferroptosis in Diabetic Retinopathy. Front Cell Dev Biol. 2022;10:932886.
25. Zhou J, Chen B. Retinal Cell Damage in Diabetic Retinopathy. Cells. 2023;12(9):1342.
26. Abcouwer SF, Gardner TW. Diabetic retinopathy: loss of neuroretinal adaptation to the diabetic metabolic environment. Ann N Y Acad Sci. 2014;1311:174-90.

27. Villarroel M, Ciudin A, Hernández C, Simó R. Neurodegeneration: An early event of diabetic retinopathy. World J Diabetes. 2010;1(2):57-64.
28. Altmann C, Schmidt MH. The Role of microglia in diabetic retinopathy: inflammation, microvasculature defects and neurodegeneration. Int J Mol Sci. 2018;19(1):110.
29. Whitmire W, Al-Gayyar MM, Abdelsaid M, Yousufzai BK, El-Remessy AB. Alteration of growth factors and neuronal death in diabetic retinopathy: what we have learned so far. Mol Vis. 2011;17:300-8.
30. Santos AR, Ribeiro L, Bandello F, Lattanzio R, Egan C, Frydkjaer-Olsen U, et al.; European Consortium for the Early Treatment of Diabetic Retinopathy (EUROCONDOR). Functional and structural findings of neurodegeneration in early stages of diabetic retinopathy: cross-sectional analyses of baseline data of the EUROCONDOR Project. Diabetes. 2017;66(9):2503-10.
31. Frydkjaer-Olsen U, Soegaard Hansen R, Simó R, Cunha-Vaz J, Peto T, et al.; EUROCONDOR. Correlation between retinal vessel calibre and neurodegeneration in patients with type 2 diabetes mellitus in the European Consortium for the Early Treatment of Diabetic Retinopathy (EUROCONDOR). Ophthalmic Res. 2016;56(1):10-6.
32. Sachdeva MM. Retinal neurodegeneration in diabetes: an emerging concept in diabetic retinopathy. Curr Diab Rep. 2021;21(12):65.
33. Simó R, Stitt AW, Gardner TW. Neurodegeneration in diabetic retinopathy: does it really matter? Diabetologia. 2018;61(9):1902-12.
34. Bianco L, Arrigo A, Aragona E, Antropoli A, Berni A, Saladino A, et al. Neuroinflammation and neurodegeneration in diabetic retinopathy. Front Aging Neurosci. 2022;14:937999.
35. Hernández C, Simó R. Neuroprotection in diabetic retinopathy. Curr Diab Rep. 2012;12(4):329-37.
36. Simó R, Hernández C; European Consortium for the Early Treatment of Diabetic Retinopathy (EUROCONDOR). Neurodegeneration is an early event in diabetic retinopathy: therapeutic implications. Br J Ophthalmol. 2012;96(10):1285-90.
37. Jindal V. Neurodegeneration as a primary change and role of neuroprotection in diabetic retinopathy. Mol Neurobiol. 2015;51(3):878-84.
38. Imai H, Singh RSJ, Fort PE, Gardner TW. Neuroprotection for diabetic retinopathy. Dev Ophthalmol. 2009;44:56-68.
39. Zhang X, Wang N, Barile GR, Bao S, Gillies M. Diabetic retinopathy: neuron protection as a therapeutic target. Int J Biochem Cell Biol. 2013;45(7):1525-9.
40. Lechner J, Medina RJ, Lois N, Stitt AW. Advances in cell therapies using stem cells/progenitors as a novel approach for neurovascular repair of the diabetic retina. Stem Cell Res Ther. 2022;13(1):388.
41. Bikbova G, Oshitari T, Bikbov M. Diabetic neuropathy of the retina and inflammation: perspectives. Int J Mol Sci. 2023;24(11):9166.
42. Hernández C, Simó-Servat O, Simó R. Somatostatin and diabetic retinopathy: current concepts and new therapeutic perspectives. Endocrine. 2014;46(2):209-14.
43. Hernández C, Simó R; European Consortium for the Early Treatment of Diabetic Retinopathy (EUROCONDOR). Somatostatin replacement: a new strategy for treating diabetic retinopathy. Curr Med Chem. 2013;20(26):3251-7.
44. Hernández C, García-Ramírez M, Corraliza L, Fernández-Carneado J, Farrera-Sinfreu J, Ponsati B, et al. Topical administration of somatostatin prevents retinal neurodegeneration in experimental diabetes. Diabetes. 2013;62(7):2569-78.
45. Simó R, Hernández C, Porta M, Bandello F, Grauslund J, Harding SP, et al.; European Consortium for the Early Treatment of Diabetic Retinopathy (EUROCONDOR). Effects of topically administered neuroprotective drugs in early stages of diabetic retinopathy: results of the EUROCONDOR Clinical Trial. Diabetes. 2019;68(2):457-63.
46. Grauslund J, Frydkjaer-Olsen U, Peto T, Fernández-Carneado J, Ponsati B, Hernández C, et al.; EUROCONDOR. Topical treatment with brimonidine and somatostatin causes retinal vascular dilation in patients with early diabetic retinopathy from the EUROCONDOR. Invest Ophthalmol Vis Sci. 2019;60(6):2257-62.
47. Beltramo E, Lopatina T, Mazzeo A, Arroba AI, Valverde AM, Hernández C, et al. Effects of the neuroprotective drugs somatostatin and brimonidine on retinal cell models of diabetic retinopathy. Acta Diabetol. 2016;53(6):957-64.
48. Jung KI, Kim JH, Han JS, Park CK. Exploring neuroprotective effects of topical brimonidine in experimental diabetic retinopathy. In Vivo. 2024;38(4):1609-20.
49. Ji L, Tian H, Webster KA, Li W. Neurovascular regulation in diabetic retinopathy and emerging therapies. Cell Mol Life Sci. 2021;78(16):5977-85.
50. Oshitari T. Neurovascular impairment and therapeutic strategies in diabetic retinopathy. Int J Environ Res Public Health. 2021;19(1):439.
51. Oshitari T. Advanced glycation end-products and diabetic neuropathy of the retina. Int J Mol Sci. 2023;24(3):2927.
52. Simó R, Simó-Servat O, Bogdanov P, Hernández C. Neurovascular Unit: A new target for treating early stages of diabetic retinopathy. Pharmaceutics. 2021;13(8):1320.
53. Stem MS, Gardner TW. Neurodegeneration in the pathogenesis of diabetic retinopathy: molecular mechanisms and therapeutic implications. Curr Med Chem. 2013;20(26):3241-50.
54. Fragiotta S, Pinazo-Durán MD, Scuderi G. Understanding neurodegeneration from a clinical and therapeutic perspective in early diabetic retinopathy. Nutrients. 2022;14(4):792.
55. Oshitari T. Neurovascular Cell death and therapeutic strategies for diabetic retinopathy. Int J Mol Sci. 2023;24(16):12919.
56. Nian S, Lo ACY, Mi Y, Ren K, Yang D. Neurovascular unit in diabetic retinopathy: pathophysiological roles and potential therapeutical targets. Eye Vis (Lond). 2021;8(1):15.
57. Pillar S, Moisseiev E, Sokolovska J, Grzybowski A. Recent developments in diabetic retinal neurodegeneration: a literature review. J Diabetes Res. 2020;2020:5728674.
58. Oshitari T. The Pathogenesis and therapeutic approaches of diabetic neuropathy in the retina. int J Mol Sci. 2021;22(16):9050.
59. Ciulla T, Amador A, Zinman B. Diabetic retinopathy and diabetic macular edema: pathophysiology, screening, and novel therapies. Diabetes Care. 2003; 26:2653-64.
60. Ciulla T, Harris A, Latkany P, Piper H, Arend O, Garzozi H, et al. Ocular perfusion abnormalities in diabetes. Acta Ophthalmol Scand. 2002;80:468-77.
61. Miyamoto K, Ogura Y. Pathogenetic potential of leukocytes in diabetic retinopathy. Semin Ophthalmol. 1999;14:233-9.
62. Slagle W, Musick A, Eckermann D. Diabetic papillopathy and its relation to optic nerve ischemia. Optom Vis Sci. 2009; 86: e395-e403.
63. Gardner TW, Davila JR. The neurovascular unit and the pathophysiologic basis of diabetic retinopathy. Graefes Arch Clin Exp Ophthalmol. 2017; 255(1):1-6.
64. Bearse MA Jr, Adams AJ, Han Y, Schneck ME, Ng J, Bronson-Castain K, et al. A multifocal electroretinogram model predicting the development of diabetic retinopathy. Prog Retin Eye Res. 2006;25(5):425-48.
65. Hardy KJ, Lipton J, Scase MO, Foster DH, Scarpello JH. Detection of colour vision abnormalities in uncomplicated type 1 diabetic patients with angiographically normal retinas. Br J Ophthalmol. 1992;76(8):461-4.
66. Greenstein VC, Thomas SR, Blaustein H, Koenig K, Carr RE. Effects of early diabetic retinopathy on rod system sensitivity. OptomVis Sci. 1993;70(1):18-23.
67. Jackson GR, Scott IU, Quillen DA, Walter LE, Gardner TW. Inner retinal visual dysfunction is a sensitive marker of non-proliferative diabetic retinopathy. Br J Ophthalmol. 2012;96(5):699-703.
68. Antonetti DA, Barber AJ, Bronson SK, Freeman WM, Gardner TW, Jefferson LS, et al.; JDRF Diabetic Retinopathy Center Group. Diabetic retinopathy: seeing beyond glucose-induced microvascular disease. Diabetes. 2006 Sep;55(9):2401-11.
69. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group; Nathan DM, Zinman B, Cleary PA, Backlund JY, Genuth S, Miller R, Orchard TJ. Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration: the diabetes control and complications trial/epidemiology of diabetes interventions and complications and Pittsburgh epidemiology of diabetes complications experience (1983-2005). Arch Intern Med. 2009;169(14):1307-16.

70. Hernández C, Dal Monte M, Simó R, Casini G. Neuroprotection as a therapeutic target for diabetic retinopathy. J Diabetes Res. 2016;2016:9508541.
71. Zafar S, Sachdeva M, Frankfort BJ, Channa R. Retinal neurodegeneration as an early manifestation of diabetic eye disease and potential neuroprotective therapies. Curr Diab Rep. 2019;19(4):17.
72. Budenz DL, Anderson DR, Varma R, Schuman J, Cantor L, Savell J, et al. Determinants of normal retinal nerve fiber layer thickness measured by Stratus OCT. Ophthalmology. 2007;114(6):1046-52.
73. Wong A, Chan C,Hui S. Relationship of gender, body mass index, and axial length with central retinal thickness using optical coherence tomography. Eye (Lond) 2004;19: 292-