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OXIDANTS AND THE BLOOD-RETINAL BARRIER: THE PROGRESSION AND MOLECULAR MECHANISMS OF DIABETIC RETINOPATHY

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ABSTRACT

Diabetic retinopathy is a microvascular complication of the eye that arises as a result of poor control of hyperglycemia in patients with diabetes mellitus. This condition is characterized by progressive damage to the blood vessels of the retina, leading to increased vascular permeability, microaneurysms, intraretinal hemorrhages, and, in more advanced stages, neovascularization. Depending on its degree of progression, it can be classified into a non-proliferative form, which is more common in the early stages, and a proliferative form, which appears in advanced stages and is associated with an increased risk of severe visual loss. In terms of its pathophysiology, chronic hyperglycemia triggers a number of harmful metabolic and molecular pathways, such as the accumulation of reactive

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oxygen species, which cause oxidative stress and jointly contribute to endothelial damage and blood-retinal barrier dysfunction. Patients with this complication need strict and continuous glycemic control by hypoglycemic drugs capable of reducing the osmolar disorders characteristic of diabetes, combined with specific ocular therapies such as endothelial growth factor inhibitors, which slow down neovascularization and, consequently, reduce the likelihood of blindness. However, even with treatment protocols, diabetic retinopathy remains the leading cause of blindness in adults worldwide, underscoring the importance of prevention and early diagnosis. This study was based on the bibliographic method, compiling scientific medical data from specialized journals such as PUBMED and Scielo published between 2018 and 2023. The results highlight the close relationship between hyperglycemic states and diabetic retinopathy, thus concluding that it is essential to develop new therapies that target not only the advanced symptoms of the disease, but also the early molecular changes that occur during the early stages of diabetic retinopathy, effectively combating the cause and effect of the pathology.

Keywords: Endothelial dysfunction. Neovascularization. Retinal hypoxia. Macular edema and diabetes mellitus.

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INTRODUCTION

Retinopathy is a debilitating eye condition characterized by affecting the layer of tissue responsible for sensitivity to light, located in the posterior portion of the eye1, 2, 3. Its main characteristic is damage to the retinal microvasculature, and depending on the severity of this involvement, the damage may become irreversible2, 3.

Its interaction with hyperglycemic states is extremely close, considering that there are 146 million people worldwide with diabetic retinopathy, according to the Light for the World International 2021 report, and 537 million diabetics, according to the Diabetes Atlas published in the same year. It is suggested that 27% of the diabetic population is in some stage of this disease2, 4.

As presented in the 2021 World Vision Report, diabetic retinopathy is the pathology that most frequently affects vision in people active in the labour market2. Although the exact number is unknown, estimates suggest that 11.9 million people worldwide have complete or partial visual impairment from diabetic retinopathy2, 5.

The pathophysiology of this condition is strongly related to chronic hyperglycemia, which triggers a series of molecular and cellular events detrimental to the structure and function of the retina, such as the increase in reactive oxygen species (ROS), mainly from mitochondrial metabolism, which play a crucial role in the oxidative stress of cells3, 6, 7.

In addition to molecular mechanisms, microvascular endothelial dysfunction is a critical component in diabetic retinopathy, affecting the integrity of the vascular endothelium, causing increased permeability and, consequently, edema, being one of the main causes of visual loss in diabetic patients6, 7.

Angiogenesis is another characteristic reaction of this condition, occurring as a pathological response to hypoxia, resulting from microaneurysms, thickening of the basement membrane and capillary occlusion3, 7. As the pathological response progresses, the vessels are not able to supply the need for local oxygen, triggering, as a response of glial cells and pigmented epithelium, the release of vascular endothelial growth factors, which increases vessel formation and endothelial proliferation7.

This pathology is divided into two presentations: nonproliferative diabetic retinopathy in the early stages and proliferative diabetic retinopathy in more advanced cases.2, 3, 7 The mildest form, nonproliferative retinopathy, shows signs of microvascular injury, such as microaneurysms and exudates, and is mainly related to macular edema. In the proliferative

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form of the pathology, the formation of new abnormal vessels is observed in response to hypoxia3.

Clinically, patients with this condition present general symptoms of diabetes, such as polyphagia, polydipsia, and polyuria3, 6, 8. With the chronicity of hyperglycemia, patients report vision deterioration, presenting blurred vision, loss of central visual acuity, scotomas and metamorphopsia, which worsen over time2, 3, 9.

It is necessary to use an ophthalmoscope for the examination of the fundus, a clinical equipment consisting of adjustable lenses and a lamp, which allows the presence of retinal alterations, such as microaneurysms, hemorrhages and neovascularization, to be detected1, 3. Although positive signs are present in clinical evaluation with an ophthalmoscope, there are limitations of the equipment, such as low detail resolution and restricted field of view, which makes it difficult to stratification of damage to the microvasculature1.

For this reason, fluorescent angiography is recommended, a technique that uses a tomograph accompanied by contrast administration, whose sensitivity is special for mapping and detecting the ocular vasculature1, 7. Local biopsy can also be used, although it is not the gold standard for screening due to its high cost and aggressiveness. Under microscopy, characteristic signs such as thickening of the basement membrane and the folded part of the ciliary body are observed7.

Therefore, detection and diagnosis play a fundamental role in the management of diabetic retinopathy in the community, implementing programs for early detection and educational programs aimed at both health professionals and patients, emphasizing rigorous glycemic control and regular eye monitoring, training patients to actively participate in their care1, 4, 10.

With these trainings, health professionals tend to implement appropriate practices in prevention and management, reducing medical errors12. Once you fail to adopt proper practices, it can result in legal complications, as vision loss due to medical malpractice typically results in compensation for the affected party and loss of medical license. In addition, the economic impact for these patients is high, including the direct costs of treatment and the indirect costs related to lost productivity11, 12.

Understanding the delicate relationship between hyperglycemic status and retinopathy, it is important to monitor mainly the diabetic population so that it is possible to delay this complication6, 7, 13. Pharmacological treatment is carried out by combining

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antidiabetic drugs, such as insulin, and specific medications for retinopathy, such as Aflibercept or Ranibizumab, responsible for inhibiting microvascular angiogenesis, as presented by the Brazilian protocol JOINT PORTARIA DIABETIC RETINOPATHY SAES/SCTIE/MS nº 17, 202114.

Against this backdrop, understanding the mechanisms underlying diabetic retinopathy, as well as implementing effective diagnostic and treatment strategies, becomes essential to reduce the incidence of serious visual complications. This study aims to analyze in detail the pathophysiological and pathological factors involved in diabetic retinopathy, in addition to evaluating the efficacy of current management approaches and discussing the legal and economic implications associated with the disease.

MATERIALS AND METHODS

The bibliographic method was used to collect scientific data from sources such as Scielo, The Lancet and PubMed, by searching for keywords such as "Endothelial dysfunction", "Neovascularization", "Retinal hypoxia", "Macular edema" and "Diabetes Mellitus" in the last 5 years. The study included ophthalmoscopy images, obtained from Ophthalmic Hospital/science photo library, that demonstrate the parallels between proliferative and nonproliferative retinopathy. To support this information, reference books were consulted, such as Porth CM. Physiopathology (9th ed. Rio de Janeiro: Guanabara Koogan; 2014) and Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J, editors. Harrison's Internal Medicine (19th ed. Porto Alegre: AMGH Editora; 2017), in addition to relevant articles available on the websites of global diabetes support organizations, such as the International Diabetes Federation.

THEORETICAL FRAMEWORK

Diabetic retinopathy is a progressive and debilitating disease that affects vision, triggered by the consequences of elevated blood glucose levels1, 2. Its main characteristic is microvascular damage to the retina, which can be reversible in the initial phase, known as non-proliferative diabetic retinopathy, and irreversible in the advanced phase, called proliferative diabetic retinopathy2, 3.

With the chronic progression of the disease, there is a partial or total loss of the visual field, significantly impacting the quality of life of patients2, 3. This condition, caused by chronic hyperglycemia, can manifest itself in proliferative and non-proliferative forms2, 7.

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The severity of the disease is associated with the degree of microvascular involvement, with neovascularization as a response to local hypoxia being a prominent feature in the proliferative phase7. In this phase, the newly formed vessels are fragile and prone to ruptures, leading to complications such as hemorrhages and retinal detachment, further aggravating the visual picture6.

The relationship between diabetic retinopathy and hyperglycemic states is extremely intimate. According to the 2021 Light for the World International report, there are an estimated 146 million people in the world with diabetic retinopathy, in a context in which there are 537 million diabetics2, 4.

Chronic hyperglycemia generates an increase in reactive oxygen species (ROS), mainly originating in the mitochondria, which causes cellular oxidative stress [3]. This, in turn, leads to microvascular endothelial dysfunction, compromising vascular integrity, increasing permeability and causing edema, factors that directly contribute to progressive visual loss3, 6, 7. In more advanced stages, prolonged hyperglycemia causes significant tissue damage, and patients frequently report gradual deterioration of vision, initially with loss of visual acuity, followed by blurred vision and, eventually, loss of central vision2, 3, 9.

Early diagnosis of diabetic retinopathy is crucial. The use of the ophthalmoscope for the examination of the fundus of the eye allows the detection of initial alterations in the retina, such as microaneurysms and hemorrhages, which can be reported by patients as blurred vision, loss of central vision and metamorphopsia, a condition in which there is difficulty in distinguishing objects and people1. However, the ophthalmoscope has limitations in stratification of the degree of retinopathy and in the evaluation of its progress1, 3.

Recently, research and development of new therapies have advanced in the search for control of the progression of diabetic retinopathy, with emphasis on the treatment of neovascularization and macular edema1. Antiangiogenic agents, particularly vascular endothelial growth factor (VEGF) inhibitors, have been shown to be effective in reducing disease progression in the proliferative phases and in preventing severe visual complications12.

These treatments, by promoting the control of edema and the formation of abnormal vessels, help preserve vision and improve the quality of life of patients. The implementation of evidence-based clinical protocols for the use of anti-VEGF agents reinforces treatment adherence and contributes to more positive visual outcomes in the long term1, 12.

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For this reason, fluorescein angiography is frequently recommended for a more detailed analysis of the retinal microvasculature. This examination helps to identify areas of ischemia, neovascularization and macular edema, which are fundamental elements for therapeutic planning1, 7. The use of standardized clinical protocols is essential to ensure effective management of diabetic retinopathy1, 4.

A clinical case published in 2023 in the Brazilian journal Pro-Universus tells the story of a 33-year-old patient, diagnosed with type 1 diabetes since she was 6 years old. At age 27, the patient noticed blurred vision in her right eye, accompanied by a "black line" and "floaters." Subsequently, she was diagnosed with bilateral proliferative diabetic retinopathy. In 2018, at the age of 29, he underwent a corneal transplant in his left eye. The following year, she evolved to total blindness in the left eye and perception of shadows in the right eye15.

Due to the severity of this condition, screening and early diagnosis are essential for the effective management of diabetic retinopathy12. Early detection programs and education for both health professionals and patients are critical. When health professionals are adequately trained, the implementation of appropriate preventive and management practices tends to significantly reduce medical errors and improve clinical outcomes11, 12.

Failure to adopt proper prevention and management practices can result in legal complications. Vision loss due to medical negligence often leads to legal proceedings, the economic consequences for patients are considerable, including direct costs with medical treatment and indirect costs, such as lost productivity at work, severely impacting their lives13.

RESULTS AND DISCUSSION

The results reinforce the close relationship between chronic hyperglycemic states and the development of diabetic retinopathy1. Inadequate glycemic control accelerates the involvement of the retinal microvasculature, which initially progresses in a non-proliferative manner, characterized by recurrent microaneurysms and exudates2, 3. In the advanced stages, proliferative retinopathy manifests with pathological neovascularization in response to tissue hypoxia1, 2, 3.

The increase in cases of diabetic retinopathy among the economically active population confirms the statistics mentioned in the 2021 World Vision Report, demonstrating that this condition is one of the main causes of visual loss in people inserted

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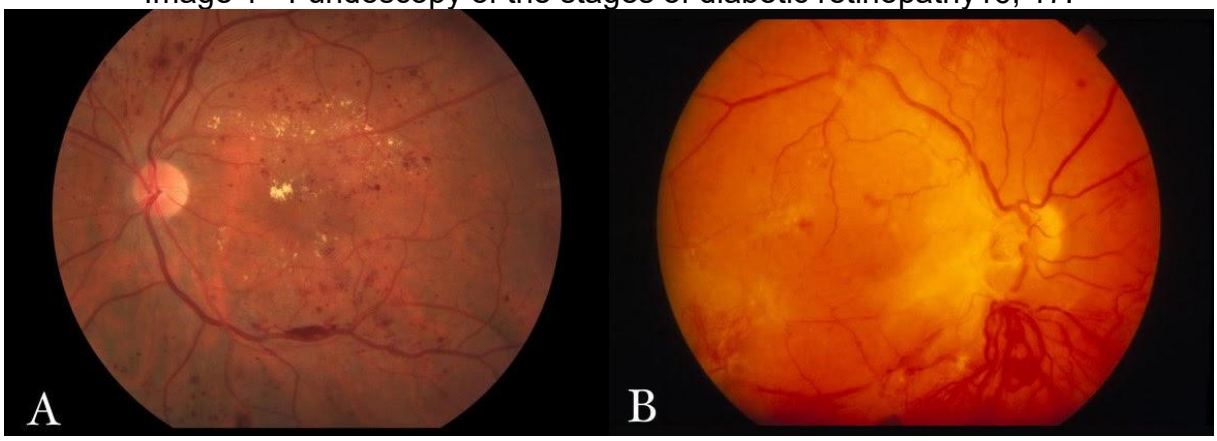
in the labor market, so early diagnosis is essential, both for the country's economy and for the quality of life of the population2, 5.

To make the initial clinical diagnosis possible, the ophthalmoscope is used, a piece of equipment equipped with adjustable lenses and focal points of light, which has proven to be efficient in the identification of initial microvascular lesions, although insufficient for the complete stratification of the damage1, 3.

Image 1 - Fundoscopy of the stages of diabetic retinopathy16, 17.



In the first image, identified as A, we observe non-proliferative diabetic retinopathy. This initial phase of the disease presents a series of microvascular alterations within the retina12. Microaneurysms are observed, which appear as small dark spots caused by the dilation of the capillaries. Intraretinal hemorrhages are also visible, evidenced by irregular and dark spots, resulting from the extravasation of blood from the compromised vessels1, 10, 16. In addition, the presence of hard exudates, small yellow or white dots that indicate accumulation of lipids in the retinal layers is noted. These findings reflect the progressive deterioration of microcirculation in the retina, with no new blood vessels observed12. 16.

In the second image, identified as B, we observe proliferative diabetic retinopathy, a more advanced and severe stage of the disease. At this stage, the retina undergoes the formation of neovessels, i.e. new blood vessels that arise as a response of retinal tissue to oxygen deficiency (hypoxia)[6, 12]. These abnormal and fragile vessels tend to develop on the surface of the retina and along the optic nerve9. On imaging, neovascularization is evident, and these new vessels are prone to ruptures, which can cause vitreous hemorrhages12.

Thus, fluorescein angiography stands out as the essential complementary examination for the exploration and detailed evaluation of retinal vascularization, being able to map areas of ischemia and neovascularization efficiently, helping in the choice of

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appropriate management, depending on the presentation of diabetic retinopathy1, 7, 18. Tissue biopsy can also be performed, although it is not the most common due to its high cost and aggressiveness, where characteristic signs such as thickening of the basement membrane and thickening of the ciliary body are found in microscopy7, 19.

The main pillar of the pathophysiology of diabetic retinopathy is chronic hyperglycemia, which affects the retinal microvasculature through the increase in the production of reactive oxygen species, mainly from the mitochondria due to the state of local hypoxia, which leads to oxidative stress and, consequently, cellular damage7, 9, 19. This oxidative state promotes the thickening of the basement membrane of capillaries as a form of adaptation to resist stress, combined with the loss of pericytes, cellular components responsible for the integrity of the vasculature[7, 9, 19].

The endothelial dysfunction that accompanies this process generates an increase in vascular permeability, combined with the osmolar disorders specific to hyperglycemia6, 7, 9. Consequently, retinal edema forms and, with the chronicity of fluid leakage in the extravascular environment, capillary circulation is compressed and blocked, resulting in tissue ischemia and hypoxia3.

This is the main event in the evolution of non-proliferative diabetic retinopathy towards proliferative presentation, since, in response to hypoxia, the body compensates for the local hypoperfusion of the retinal endothelium with the formation of new blood vessels, releasing neoangiogenic factors, such as Vascular Endothelial Growth Factor (VEGF)[9, 19]. However, this adaptive response is insufficient, generating abnormal and fragile capillaries, with a great propensity to rupture, which causes episodes of hemorrhages and complications such as retinal detachment1, 7, 9.

Clinically, continuous and rigorous monitoring of the diabetic patient is essential. These individuals present characteristic symptoms of defects in blood osmolarity derived from hyperglycemia, manifesting the cardinal symptoms of diabetes, such as polyphagia, polyuria and polydipsia3, 6, 8. In the more advanced stages, prolonged hyperglycemia causes significant tissue damage, and patients frequently report a gradual deterioration of vision, initially presenting with loss of visual health, followed by blurred vision and, eventually, loss of central vision3, 7.

For the treatment of these patients, in addition to information on vision, hyperglycemia control with hypoglycemic drugs should be considered assertively, to control osmolar traumas and prevent edematous leakage. For the treatment of retinopathy,

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medications that inhibit VEGF, a growth factor responsible for the formation of neovascularization, are used14.

These medications are Ranibizumab and Aflibercept, both of which are administered directly through the intravitreal route14. The first drug is given in monthly injections of 0.5 mg for two years, or until maximum visual accuracy is reached or no signs of disease activity; The second indicated medication follows a fixed schedule of 5 mg per month, followed by bimonthly injections of 2 mg14, 20.

This class of endothelial growth factor inhibitor drugs effectively demonstrates the slowing of disease progression and the prevention of serious complications, such as macular edema20. However, the combined treatment of endothelial growth factor inhibitors together with hypoglycemic agents is crucial to adequately control the cause and effect of the pathology14, 20.

The absence of adequate diagnosis and treatment can result in medical malpractice lawsuits, especially when vision loss occurs due to failures in early management11, 12. In addition to glycemic control and the use of anti-VEGF agents, the management of diabetic retinopathy should consider an individualized approach, adjusting treatment to each patient according to the comorbidities present, such as hypertension and dyslipidemia14.

Rigorous control of these systemic risk factors has been associated with reduced disease progression and improved therapeutic outcome. Recent studies indicate that, by treating these factors in an integrated manner with antiangiogenic therapy, it is possible to enhance vision preservation and minimize serious ocular complications, promoting a more comprehensive and effective treatment approach for patients with diabetic retinopathy11, 14, 21.

Education of patients and professionals about glycemic control and ophthalmological monitoring is crucial to prevent complications of diabetic retinopathy11. Early detection programs and interventions can reduce disease progression and improve quality of life, avoiding irreversible damage and legal risks.

FINAL CONSIDERATIONS

Diabetic retinopathy, a devastating complication of diabetes mellitus, continues to affect millions of people worldwide, demonstrating worryingly the severe and prolonged impact of hyperglycemia on the microvasculature, especially the retinal. Although technological advances, such as fluorescein angiography and VEGF inhibitors, offer

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valuable tools for diagnosis and treatment, insufficient glycemic control remains the biggest obstacle to effective prevention.

The alarming increase in cases of diabetic retinopathy among the economically active population not only reveals significant failures in clinical management, but also highlights the inadequacy of public policies and preventive programs. The emphasis on late interventions, when visual loss is already imminent, fails to reduce the impact of the disease, resulting in high rates of irreversible blindness and a growing socioeconomic cost.

In this scenario, it is imperative to prioritize rigorous glycemic control and early ophthalmological monitoring. Without a drastic change in prevention and awareness strategies, the burden imposed by diabetic retinopathy will continue to increase, requiring coordinated and incisive actions to mitigate its devastating consequences for both patients and society.

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