Age-related macular degeneration: an overview

Degeneração macular relacionada à idade: um panorama geral

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ABSTRACT

Age-related macular degeneration is the most important cause of irreversible vision loss in the elderly and has been considered a severe public health problem. Current treatments have only been successful in delaying the loss of central vision. Due to increased life expectancy, governments and researchers have been challenged to seek more efficient and successful treatments for age-related macular degeneration. Considering its relevance for public health and the need of further research, this article aims to address age-related macular degeneration objectively, tackling on the current knowledge about its pathophysiology, potential molecular biomarkers, main prevention procedures and treatments, as well as introducing possible molecules that may be a therapeutic target in this disease.

RESUMO

Degeneração macular relacionada à idade é a causa mais importante de perda irreversível da visão em idosos, e é considerada um sério problema de saúde pública. Os tratamentos atuais são bem-sucedidos apenas ao postergar a perda da visão central. Devido à maior expectativa de vida, os governos e pesquisadores têm dificuldade de encontrar tratamentos mais eficientes e exitosos para degeneração macular relacionada à idade. Considerando sua relevância para saúde pública e a necessidade de mais pesquisas, este artigo procura abordar a degeneração macular relacionada à idade de forma objetiva, abordando os conhecimentos atuais sobre sua fisiopatologia, potenciais biomarcadores moleculares, principais procedimentos de prevenção e tratamentos, e apresentar possíveis moléculas que podem ser alvo terapêutico nessa doença.

LITERATURE SEARCH METHODS

Aiming to address age-related macular degeneration pathophysiology, use of possible biomarkers, as well as its prevention and treatment, a comprehensive literature review was performed through Cochrane Database, PubMed, MedlinePlus Health Information, and Elsevier Science. We used the following keywords and their synonyms in various combinations: age-related macular degeneration, oxidative stress, chronic inflammation, retinal pigment epithelium, biomarkers, primary prevention, secondary prevention, therapy. Articles cited in the reference list of publications obtained through this search were also reviewed, whenever relevant.

INTRODUCTION

Age-related macular degeneration (AMD) is one of the main causes of irreversible vision loss in the elderly.[1] It is a complex, multifactorial disease, associated with aging, and genetic, nutritional, and environmental alterations.[2] Due to the highly impactful nature of this disease, several studies have correlated it with depression, recommending immediate need of psychological support.[3,4]

AGE-RELATED MACULAR DEGENERATION PATHOPHYSIOLOGICAL MECHANISMS

The macula region of the retina is responsible for visual acuity and color vision, and it is a place where all light beams converge to form an image. It is exposed to a high concentration of oxygen, polyunsaturated fatty acid content, high incidence of light rays (between 400 nm and 700 nm), and has photosensitive molecules, such as rhodopsin and lipofuscin. These characteristics induce a continuous production of oxygen reactive species (ROS).[5] Conversely, the sensory retina and retinal pigment epithelium (RPE) cells present an antioxidant machinery coordinated by the nuclear factor erythroid 2-related factor 2 (Nrf-2), which neutralizes the physiologically or pathologically originated ROS,[6] maintaining proteostasis.[7] With aging, oxidative damage gradually increases since the antioxidant capacity decreases concurrently in mammals. As a result, the inherent repair capacity of RPE cells becomes compromised.[8-10] This resultant redox imbalance plays an important role in triggering and progression of AMD,[11] inducing the accumulation of lipofuscins in the RPE cells, decreasing their function,[12-14] and increasing oxidative stress and retinal inflammation.[15,16] The dysfunction of RPE cells, on its turn, leads to failure in degradation of products resulting from phagocytosis of the photoreceptor cell outer segments, causing pathological accumulation of lipids in the Bruch's membrane (BM).[17] The low-density lipoproteins (LDL) undergo oxidation, making the endothelial and RPE cells increase the expression of vascular adhesion molecules (P-selectin, intercellular adhesion molecule 1 and vascular cell adhesion molecule 1), interleukin 8 (IL-8), which, along with the monocyte chemoattractant protein-1 ligands (MCP-1) and their C-C chemokine receptors type 2 (CCR2), improve activation and recruitment of monocytes to phagocytize oxidized LDL.[18-20] The macrophages, as well as the endothelial and RPE activated cells, induce an increased expression of cytokines, enzymes, and growth factors, closely related to progression of the macular degenerative disease.[21-23] Simultaneously, alterations in the BM interfere in the RPE cell nutrition, causing RPE and choriocapillaris atrophy,[24-26] and consequently triggering the choroid geographic atrophy. The reduction in choriocapillaris layer leads to hypoxia and resulting death of the photoreceptors, and major damage to RPE cells.[27] Hypoxia induces release of vascular endothelial growth factor (VEGF)[28] and develops subretinal neovascularization,[2] hence, typifying wet AMD.

POTENTIAL MOLECULAR BIOMARKERS

Considering the several molecules involved in AMD genesis, important studies have been performed aiming to validate biomarkers that may provide prediction, diagnosis, stratification, monitoring of treatment, and drug development for AMD. The most promising biomarkers belong to the oxidative stress pathway, the complement system, and to a lesser extent, to lipid metabolism. Many studies reported decreased antioxidant levels and elevated levels of oxidized proteins or lipids indicating oxidative stress in AMD. Malondialdehyde, a marker for lipid peroxidation, homocysteine, an intermediate in the oxidative stress pathway, and the involvement of the complement system have provided more consistent results as AMD biomarkers.[29] Nevertheless, a variety of differences between studies, including methodological differences (fasting *versus* non-fasting blood), different populations (Caucasian/Asian/Mediterranean) with diverse dietary habits, different study designs, different analytical methods, and correction factors offer contradicting, difficult-to-interpret results, suggesting the need for large well-conducted prospective studies to further clarify these findings. Additionally, because of the presence of the blood-retinal barrier, biomarkers might be only locally dysregulated inside the eye with no measurable systemic effect.[29] Other

biomarker types in AMD, such as genetic factors, imaging biomarkers, or visual function measurements, are currently of key importance for proper clinical diagnosis, stratification, and treatment of AMD.[29]

PREVENTION

From a preventive perspective, healthy diet, regular physical activities, wear of glasses with filters that protect against harmful rays present in the visible light, even oral hygiene, have been recommended to prevent the onset and/or progression of AMD.[30-35] Nevertheless, the main modifiable factor for AMD is smoking, and quitting smoking is highly recommended.[36,37] Regarding the use of synthetic antioxidants, it has been demonstrated they are not effective for prevention of primary AMD; that is, they do not prevent drusen or pigmental alterations in the macular region, reported to be the first manifestations of the disease.[38] Nevertheless, in secondary prevention, when the disease has already developed, the Age-Related Eye Disease Study (AREDS) has concluded that (a) without nutritional supplements, patients with intermediate AMD had an 18% chance of progressing to advanced AMD, in one or both eyes, over 5 years; (b) without nutritional supplements, patients with advanced AMD in one eye had a 43% chance of progressing to advanced AMD in the other eye; (c) with nutritional supplements, high-risk patients decreased their risk of progressing to AMD by 25 % (in the case of advanced AMD in one eye, this decreased risk refers to the other eye); (d) with nutritional supplements, risk of moderate or severe vision loss decreased by 19%, over 5 years; (e) nutritional supplements did not slow progression from early AMD to intermediate AMD; (f) there was no evidence that vision loss or disease progression was reversed in any treatment group; (g) compared to placebo, addition of lutein/zeaxanthin and/or omega-3 fatty acids to the previous AREDS formulation showed no significant effect on AMD progression or visual acuity loss. The adopted nutritional supplementation formula included a dose of 500 mg of Vitamin C, 400 IU of vitamin E, 10 mg of lutein, 2 mg of zeaxanthin, 80 mg of zinc and 2 mg of copper.[39]

TREATMENT

In the treatment of advanced AMD, with the geographic atrophy of the choroid, blocking complement activation reduced its rate by 29%.[40] Other approaches, such as the cell-based therapy, have also been considered.[41,42] Regarding wet-AMD, the treatment with anti-VEGF was revolutionary, enabling vision preservation in many patients.[43] However, the need of periodic interventions, discomfort and high cost make this treatment still not available to most people.[44]

CONCLUSION

A more comprehensive understanding of AMD pathophysiology in the last decades has been of outmost importance in the quest for new treatments.[2] Changes in lifestyles have been reported as one of the major factors in longevity and vision preservation.[45] The nutritional supplementation is of great importance in cases of intermediate AMD.[39] The malondialdehyde biomarkers, homocysteine and the complement system are potential aids in prediction, diagnosis, stratification, monitoring of treatment, and drug development for AMD. Local inhibition of complement activation has been considered a promising approach for treatment of both forms of late AMD. In light of the probable role of complement system in the development of AMD, many clinical trials investigating the effect of complement inhibitors have been conducted or are in progress. The results of clinical trials, in which often only a subgroup of patients responded favorably, have shown careful stratification of indications and patient cohorts will be critical to identify patients who may benefit from complement-mediated therapies.[46] Overly complex molecular mechanisms found in the endothelial and in RPE cells, in microglia of the sensory retina and in macrophages, such as the Nrf2,[6] nuclear factor kappa β (NF-κβ),[15] inflammasome,[47] NADPH-oxidase (NOX),[15] complement system,[40,48] among others, are likely to become future therapeutic approaches, improving prognosis of AMD.

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