Review Article

Age-Related Macular Degeneration: Pathogenesis, Genetic Background, and the Role of Nutritional Supplements

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Age-related macular degeneration (ARMD) is the leading cause of severe vision loss and blindness worldwide, mainly affecting people over 65 years old. Dry and wet ARMD are the main types of the disease, which seem to have a multifactorial background. The aim of this review is to summarize the mechanisms of ARMD pathogenesis and exhibit the role of diet and nutritional supplements in the onset and progression of the disease. Environmental factors, such as smoking, alcohol, and diet appear to interact with mutations in nuclear and mitochondrial DNA, contributing to the pathogenesis of ARMD. Inflammatory mediators and oxidative stress, induced by the daily exposure of retina to high pressure of oxygen and light radiation, have been also associated with ARMD lesions. Other than medical and surgical therapies, nutritional supplements hold a significant role in the prevention and treatment of ARMD, eliminating the progression of macular degeneration.

1. Introduction

Age-related macular degeneration (ARMD) is the leading cause of severe vision loss and blindness worldwide, given that its incidence ranges from 9 to 25% at ages between 65 and 75 years, leading to blindness of over 80% of affected patients after the age of 70 years [1, 2]. The risk of developing advanced ARMD lesions tenfolds in people over 85 years compared with those 70–74 years old [3]. ARMD is estimated to be responsible for 26% of cases of blind registration in the European Union, followed by glaucoma (20.5%) and diabetic retinopathy (8.9%) [1]. The beaver dam offspring study (BOSS), which was held in United States of America (USA), including 2810 subjects aged 21–84 years, revealed the incidence of early ARMD ranging from 2.4% among persons 21–34 years old to 9.8% in people over 65 years old [4]. In the same study, the incidence of early and advanced forms of

ARMD was estimated at 14.3% and 3.1%, respectively, among 3917 participants from 43 to 86 years old, increasing with age [5]. The risk of developing advanced ARMD lesions on the other eye of patients who had already such lesions in one eye was determined at 43% in age-related eye disease study (AREDS) [6]. In addition, the risk of unfavorable progression of ARMD in patients who suffered from early bilateral or unilateral lesions was assessed at 26.4% and 6.3%, respectively [6].

The retina is responsible for the conversion of light stimuli to neural impulses, which are transmitted to the visual cortex (occipital lobe). It consists of an outer pigmented layer (retinal pigment epithelium, RPE), which lays on Bruch membrane and an inner sensorineural layer (sensory retina), including the photoreceptors which transmit the electrical stimulus to nerve fibers layer, forming the optical nerve [7, 8]. The macula is located in the center of the retina and

FIGURE 1: Hard drusen at the temporal side of macula in patient with dry ARMD (a), geographic atrophy (b), and CNV in patient with wet ARMD (c).

displays the highest visual acuity due to the high concentration of photoreceptors. ARMD is classified, according to the severity of the disease, into (a) *mild*, characterized by the presence of single soft drusen (≥ 63 μ m), disorders of RPE, or a combination of these findings (dry ARMD) and (b) *advanced*, including geographic atrophy (advanced dry ARMD) and wet (exudative, neovascular) type [9]. There are no symptoms in the early stages of ARMD, but as far as the lesions are extended patients suffer from progressive visual loss, difficulty in reading and object recognition, central or paracentral scotomas, micropsia, and metamorphopsia [8].

Drusen are located between the RPE and Bruch's membrane of the macula or the peripheral retina and they mainly consist of phospholipids, triglycerides, cholesterol, cholesteryl esters, apolipoproteins, vitronectin, immunoglobulins, amyloid, and complement system components (Figure 1) [9, 10]. The atrophy of the RPE, choriocapillaris, and small vessels of the choroid are the main lesions of geographic atrophy, combined with thinning of the retina, drusen, hemorrhages, and peripapillary atrophy (Figure 1) [9]. The exudative type of ARMD is diagnosed by the presence of subretinal fluid or hemorrhage, fluid or hemorrhage beneath the RPE, accompanied with ipsilateral detachment of RPE, hard drusen, vitreous hemorrhage, a combination of the previous elements or geographic atrophy, and subretinal fibrosis (scar) in the final stages [11]. The progression of wet ARMD to choroidal neovascularization (CNV), classic or occult, detected as a grey membrane, is followed by scar formation and leads to severe visual loss (Figure 1) [9–11].

2. Pathogenesis of ARMD

2.1. Environmental and Nutritional Factors. The pathogenesis of ARMD is multifactorial, related to environmental factors, genetic background, and para-inflammation. Smoking is considered to be a major risk factor for the onset and the progression of ARMD, which has been positively correlated with the duration of smoking and the number of cigarettes [12]. The toxic effect of hydroquinone on retinal cells includes the accumulation of vascular endothelial growth factor (VEGF) and the decrease in macular pigment [13–15]. The levels of circulating antioxidants in smokers were found to be reduced

compared with nonsmokers by 25% for ascorbic acid, alpha and beta-carotene, and cryptoxanthin and by 16% for vitamin C, whereas vitamin E and carotenoids lutein, zeaxanthin, and lycopene were also decreased [16]. In addition, alcohol consumption is related to low levels of alpha-linolenic acid, which is an omega-6 fatty acid, necessary for the synthesis of arachidonic acid and cell membranes [17]. Daily intake of more than 20 g of alcohol increases the risk of ARMD (odds ratio = 1.21), regardless of gender [18]. The xanthophyll zeaxanthin and its isomer lutein are basic components of macular pigment, exhibiting protective role against light radiation and oxidative stress, as well as ARMD [19]. Vitamin D (concentrations over 38 nmol/L) reduces the risk of ARMD by 48%, due to its anti-inflammatory and antiangiogenic action and prevents the progression to the exudative form of ARMD [20]. Diet rich in cholesterol has been associated with accumulation of amyloid and induction of oxidative stress in the retina of rabbits with ARMD lesions [21].

High levels in serum of apolipoprotein B were related to inflammation and accumulation of drusen in the retina of patients suffering from wet ARMD [22]. Moreover, the consumption of red meat consists of a risk factor for the onset of early ARMD, while chicken and fatty fish (such as tuna, salmon, sardines, and herring) exhibit protective action against advanced ARMD [23, 24]. Red meat seems to be responsible for the induction of N-nitroso elements (toxic to the retina), heme iron, and advanced glycation end products (AGEs) [23]. Patients with ARMD appear to consume less fruit, legumes, fish, shrimp, poultry, and eggs [25]. The intake of large amounts of long-chain omega-3 polyunsaturated fatty acids reduces the risk of developing ARMD, due to their antiangiogenic and neuroprotective effects [26]. However, elevated concentrations of monounsaturated fatty acids increase the risk of drusen formation and disorders of RPE [26]. High glycemic index appears to be implicated in the onset of early ARMD, while cereal and bread consumption exerts a protective effect against ARMD [27]. In addition to diet, obesity, high diastolic pressure, low glomerular filtration rate, race (high incidence of drusen in white and blacks), and ocular factors (cataract excision, hyperopia) have been also related to the onset and progression of ARMD [28–32]. Above all, ARMD is directly dependent on the age of individuals [33].

2.2. Genetic Background of ARMD. Single-nucleotide polymorphisms (SNPs), mutations of mitochondrial DNA (mtDNA), and micro-RNAs (mi-RNAs) consist of the genetic background of ARMD. Polymorphisms of complement factor (CF) I (CFI, chromosome 1q32), C3 complement component (chromosome 19p13), CFV, and C2 complement component (chromosome 6p21), as well as ARMS2/HTRA1 (chromosome 10q26) genes, are primarily related to the incidence of ARMD in the western world [34–56]. Zinc supplements could be used in the treatment of ARMD, taking into account that the presence of zinc in the RPE is necessary for the normal retinal function, inhibiting the action of CFH [52]. Neurodegenerative diseases, including Parkinson disease and Alzheimer, Friedrich ataxia, and amyotrophic lateral sclerosis, have been associated with polymorphisms in mtDNA [57]. Mutations in mtDNA disrupt the function of antioxidant enzymes, repair mechanisms, and chaperones, which are responsible for the folding and unfolding of macromolecules in order to obtain their functional form [58]. Polymorphisms of mtDNA, such as 4917G (MTND2* LHON4917G), T8993G, and UNG uracil-DNA glycosylase, in patients with ARMD exhibited positive correlation with the severity of the disease [58–61]. The miR-30b and miR-30d are involved in the pathogenesis of ARMD inhibiting the antioxidant catalase, while miR-155, miR-146a, and miR-146b-5p are responsible for normal function of RPE [62, 63].

2.3. Inflammatory Mediators and Oxidative Stress. The presence of any harmful agent results in activation of parainflammation, which aims at homeostasis and normal tissue function. Prolongation of parainflammation leads to oxidative stress and degenerative processes, associated with diseases such as atherosclerosis, diabetes mellitus, and ARMD [64]. Activation and accumulation of microglial cells in the retina and subretinal space, potential disruption of the blood-retinal barrier, thickening of the choroid, accompanied by deposition of macrophages and mast cell activation, and fibrosis are some of the events observed in retinal parainflammation [64]. A variety of inflammatory mediators, including aldose reductase, platelet activating factor (platelet activating factor, PAF), cytokines, such as tumor necrosis factor- α (TNF- α), chemokines, arachidonic acid, and oxidative stress, seem to be involved in ocular diseases, including cataract, uveitis, retinal neovascularization, ARMD, and glaucoma [65–76]. Moreover, the complement system has been implicated in the pathogenesis of ARMD, as well as other neurodegenerative diseases, including Alzheimer disease and Parkinson [77]. The high pressure of oxygen in the retina, the daily exposure to the light, and the high concentration of fatty acids, including DHA (docosahexaenoic acid), favor the production of free radicals and oxidative stress [78]. The response of the immune system to oxygen free radicals and their active forms (reactive oxygen species, ROS) is called oxidative stress and is thought to participate in both aging process and ocular diseases, including keratitis, uveitis, cataract, retinopathy of prematurity, and ARMD [79].

Studies in aged RPE revealed high levels of VEGF and interleukins (IL) 12 and 10, although both of these

interleukins exhibit inverse effect, since the former promotes the production of interferon gamma, TNF- α , and T-lymphocytes, while the latter inhibits inflammatory mediators [80]. Reduced concentrations of proinflammatory cytokines, such as IL-8, IL-15, IL-6, granulocyte macrophage colony-stimulating factor (GM-CSF), and stromal cell-derived factor (SDF-1 α), were defined in aged RPE [80]. The expression of chemokines receptors CCR1 and CCR2 in CD14⁺ CD16⁺ monocytes appeared to be increased by 3.5 and 2.2 times, respectively, in patients with neovascular ARMD [81]. Peroxisome proliferator-activated receptors (PPARs) are implicated in the pathogenesis of ARMD, as well as other diseases, including obesity, diabetes mellitus, atherosclerosis, cancer, and neurodegenerative disorders [82]. PPARs- γ are expressed in the RPE and vascular endothelial cells of choroid, inhibiting VEGF and endothelin-1 and inducing the plasminogen activator inhibitor-1 [82]. Furthermore, PPARs- γ increase the expression of antioxidant enzymes and suspend proinflammatory factors and metalloproteinase (matrix metalloproteinase, MMP) 9, which degrades the extracellular matrix components. The hypoxia-inducible factors (HIFs) 1 and 2 (HIF-1, HIF-2) appear to be involved in the formation of neovascular membranes in exudative form of the disease, increasing VEGF [83].

Although lipofuscin is normally found in retinal epithelium, extremely elevated concentrations of this pigment have been associated with cell damage, induced by the formation of CEP proteins (carboxyethylpyrrole proteins) and bis-retinoids oxidation [78]. Bis-retinoids are responsible for parainflammation and the accumulation of AGEs [78]. Iron accumulation in RPE is a major cause of increased lipofuscin, degeneration of RPE, and subretinal neovascularization [84]. Amyloid (component of drusen) favors the expression of VEGF by interfering at the level of mRNA and proteins and suppresses pigment epithelium-derived factor (PEDF), which prevents angiogenesis [85]. The endocytosis of A2E (basic component of lipofuscin) and other components, including amyloid-beta, crystals of uric acid, and cholesterol, leads to destruction of lysosomes and activation of inflammasome NLRP3, which appears to affect the release of IL-1 β from A2E [86]. The A2E affects the interaction of cytochrome c and cytochrome oxidase (COX), promoting the detachment of cytochrome c from the inner mitochondrial membrane, followed by oxidative stress and insufficient production of ATP [87]. The anatomical and functional impairment of mitochondrial, which has been observed in patients with ARMD, seems to be associated with reduced energy, impaired apoptosis, ROS accumulation, and elimination of superoxide dismutase 2 (SOD2), leading to degeneration of RPE, shortening and thickening of Bruch's membrane, and degeneration of photoreceptors [88].

PAF (1-0-alkyl-2-acetyl-sn-glycero-3-phosphocholine) is a low molecular weight phospholipid, regulated by PAF acetylhydrolases (PAF-AHs), a group of phospholipases being responsible for hydrolysis and deactivation of PAF in blood and tissues, as well as by its receptor (PAF-R, flt-1), which is a transmembrane G-protein, being expressed in a wide range of cells (RPE cells, monocytes, lymphocytes, vascular

endothelial and smooth muscle cells, and keratinocytes) [89–93]. A variety of physiological processes, including platelet adhesion, activation of neutrophils and macrophages, calcium metabolism, pregnancy, implantation of the ovum, and ovulation, have been associated with PAF stimulation, which can, also, raise mechanisms involved in acute inflammation, asthma, systemic or cardiac anaphylaxis, infectious shock, and thrombosis [89–92].

Allergic conjunctivitis has been related to release of histamine and serotonin, vasodilation, increased vascular permeability and accumulation and degranulation of eosinophils, and neutrophils, caused by the ocular action of PAF [94–96]. Furthermore, PAF is involved in the healing of corneal epithelium, apoptosis of keratocytes and myofibroblasts, and binding of epithelial cells with the basement membrane, stimulating selective MMPs, serine proteases, transcription factors, and apoptotic agents [97–99]. PAF-induced corneal neovascularization takes place by the stimulation of arachidonic acid, lipid hydroperoxides, and the expression of VEGF in endothelial cells, as well as the migration of vascular endothelial cells, whereas PAF inhibits the antiangiogenic thrombospondin 1 (TSP-1) [100, 101]. Oxidative stress and free radicals, being involved in pathogenesis of ischemic retinopathies, such as retinal vein occlusion and diabetic retinopathy, are the stimuli for the release and activation of PAF [102]. PAF interacts with P-selectins of retinal and choroidal vascular endothelium, inducing endothelial damage and vascular thrombosis [103]. The migration of leukocytes to vascular endothelium and its subsequent disruption, the activation of phospholipases and proteases, and the disturbance of permeability of mitochondrial pores are implicated in the cytotoxic effect of PAF in retinal vascular endothelial cells [104–107].

3. Treatment of ARMD and Nutritional Supplements

3.1. Medical and Surgical Therapies in ARMD. Food supplements appear to be the basic therapy of dry ARMD, whereas exudative form is treated with the use of anti-VEGF and anti-inflammatory agents, as well as laser (laser photocoagulation or photodynamic therapy). Ranibizumab (Lucentis; Genentech, South San Francisco, CA/Roche, Basel, Switzerland, 2006), bevacizumab (Avastin; Genentech, South San Francisco, CA/Roche, Basel, Switzerland, 2005), pegaptanib sodium (Macugen; Eyetech Inc., Palm Beach Gardens, FL, 2004), and VEGF trap or Aflibercept (EYLEA; Regeneron Pharmaceutical Inc. and Bayer, Tarrytown, NY, 2011) are the major anti-VEGF agents used in treatment of wet ARMD [108]. The therapeutic effects of these agents include improvement of visual acuity, as well as decrease of subretinal or intraretinal fluid, central macular thickness, and neovascularization [109–113]. The most common complications of intravitreal injections of anti-VEGF include intraocular inflammation and increased intraocular pressure, whereas hypertension, thromboembolic (acute myocardial infarction, vascular incident), and hemorrhagic episodes are some of the systemic complications observed in low incidence

[114, 115]. The need for repeated injections and the inflammatory effect of photodynamic therapy (transient vascular occlusion, retinal and choroidal ischemia) led to the combination of anti-VEGF agents with steroids (such as triamcinolone) or photodynamic therapy [116]. Surgical treatment is applied on the complications of ARMD, including epiretinal membrane formation, subretinal hemorrhage, and retinal pigment epithelium detachment (PED), while transplantation of RPE cell is a new challenge in the treatment of ARMD.

3.2. The Role of Nutritional Supplements. AREDS study, conducted with 4757 participants aged 55–80 years, revealed that the daily intake of zinc (80 mg), copper (2 mg), and antioxidants (vitamin C: 500 mg, vitamin E: 400 IU, beta-carotene: 15 mg) reduces the risk of advanced ARMD lesions (OR: 0.75 and decrease of relative risk (RR) by 21% for an individual taking zinc, OR: 0.80 and RR reduction by 17% for individuals taking antioxidant components), preventing visual loss (OR: 0.72 and RR reduction by 25%) [117]. However, nutritional supplements should be used with caution, taking into account previous studies, which have related the intake of vitamin A and beta-carotene to increased incidence of cardiovascular diseases and lung cancer, especially in smokers and workers who have been exposed to asbestos [118, 119]. Supplements containing lutein, zeaxanthin, and DHA improve pigment concentrations in macula, providing extra protection against phototoxicity and oxidative stress [120, 121]. Folic acid and vitamins B6 and B12 appear to reduce homocysteine, which promotes, at high levels, dysfunction of vascular endothelium and development of ARMD lesions [122]. Overall, patients should include in their diet fruits, legumes, and fatty fishes, eliminating red meat, alcohol, and smoking, as it has been already mentioned.

The effect of vitamin supplements on the action and metabolism of PAF was recently investigated in rabbit's platelets and leucocytes. All supplements, including InShape (Farmex), Nutrof (Thea), Ocuvite (Bausch and Lomb), and Vitalux (Novartis), appeared to inhibit, even in low dose, the aggregation of platelets, which is closely related to the action of PAF [123]. The inhibitory action of these supplements was similar to that of potent PAF receptor antagonists, such as WEB2170, BN52021, and Rupatadine [123]. Particularly, Nutrof was the most potent inhibitor of PAF-induced aggregation, while Vitalux was the weaker one [123]. The implication of vitamin supplements in metabolism of PAF was determined by the levels of PAF-AHs, as well as PAF-cholinephosphotransferase (PAF-CPT) and lyso-PAF-acetyltransferase (lyso-PAF-AT) enzymatic activities (these enzymes catalyze the synthesis of PAF). The strongest suppression of PAF synthesis was achieved by Vitalux, through the elimination of PAF-CPT and lyso-PAF-AT levels, indicating significant anti-inflammatory activity [123]. On the other hand, Nutrof increased PAF-AHs activity more than the other supplements, exhibiting high antiangiogenic properties, but it had no effect on PAF synthesis and inflammatory process [123]. Ocuvite slightly increased PAF-AHs levels, as Vitalux did, but it had no anti-inflammatory properties [123]. Finally,

InShape seemed to have no interference in angiogenesis but a minor one in the inflammatory action of PAF [123].

4. Conclusion

The multifactorial background of ARMD complicates the treatment of the disease and generates the need for continuous research in ARMD therapy, taking into account that 80% of affected patients are blind after the age of 70 years. Numerous studies have highlighted the role of diet and vitamin supplements in inhibiting parainflammation and oxidative stress, which are involved in pathogenesis of ARMD. Changing dietary habits and eliminating smoking and alcohol could prevent the onset and the progression of ARMD, protecting the patients from vision loss and blindness.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper. The authors alone are responsible for the content and writing of the paper.

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