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Review Article

Aging Changes of the Retina in Age-Related Macular Degeneration

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Abstract

The anatomical and physiological changes associated with aging begin several years before the appearance of ophthalmic signs. Many of these alterations begin to appear gradually from the age of forty and continue until death. Physiologically, the senescence process causes the decline of all functions and then the aging of tissues. This literature review allowed us to understand, analyze and correlate age with retinal impairment, especially in AMD, including all factors associated with this disease.

Keywords: *Senile; Aging; Retina; AMD; Macular Degeneration*

Introduction

Age-related Macular Degeneration (AMD) is characterized by changes within the retina that occur as a process of aging. AMD has different clinical appearances, reflecting the different anatomical levels affected. The fundus may exhibit various types of drusen, abnormal choroidal vessels, signs of exudation, irregular pigmentation, and atrophy of the retinal pigment epithelium and outer retina [1]. Senescence causes the decline of the normal functions and homeostasis of the retina. Some of the anatomical and physiological changes associated with aging begin several years before the appearance of signs of AMD within the macula [2]. This article describes many of the age-related retinal changes that collectively merge into the visual decline and functional pathology that is seen in AMD.

Retinal anatomy

The retina is a delicate, transparent tissue-derived embryologically from the optic vesicles, which invaginate to form the bilayered optic cup. The neural retina arises from the inner layer of the optic cup, and the retinal pigment epithelium (RPE) arises from the outer layer. The neural retina is divided into nine layers as seen clinically on spectral-domain ocular coherence tomography (SD-OCT) B scan images: the outer and inner segments of photoreceptors (rods and cones), external limiting membrane, outer nuclear layer, outer plexiform layer, inner nuclear layer, inner plexiform layer, ganglion cell layer, nerve fiber layer, and internal limiting membrane. The RPE is a monolayer of cuboidal cells containing melanosomes that nourish the overlying outer neurosensory retina, by diffusing nutrients from the choroid and removing waste from the photoreceptors [3].

The basement membrane of the RPE comprises the inner layer of Bruch's membrane. Bruch's membrane (BM) is a thin and complex structure with five stratified layers that contain the basement membrane of the retinal pigment epithelium (RPE), the inner collagenous layer, the central elastic layer, the outer collagenous layer, and the basement membrane of the choriocapillaris endothelium (CCE) [4,5]. Bruch's membrane plays a critical role in the eye. Transport of oxygen, glucose, growth factors and fluids derived from choroidal vasculature to the retina/RPE and removal of waste materials from the RPE through BM supports the function of the RPE and photoreceptors [6-8]. Bruch's membrane also works as a tight barrier to prevent abnormal angiogenesis [9,10]. Thus, maintaining the five-layer structure of BM is essential for retinal health and normal visual function. Beneath BM lies the vascular network known as the choriocapillaris. Imaging the choriocapillaris *in vivo* is challenging because of highly pigmented choroidal melanocytes and its location below the RPE. In addition, unlike the blood vessels of the retina, the capillaries in the choroid are fenestrated which makes high-resolution choroid imagery with fluorescein and green indocyanine (ICG) angiography more difficult due to the leakage of dye [11]. Thus, most studies of the choroid are limited to post-mortem histology.

Aging retina

The structural alterations of the human retina during aging and in various pathological situations have a link with the pathogenesis of the disease. We see that most changes occur in the RPE, Bruch's membrane, and the choriocapillaris layer. These changes include the loss of the normal and essential characteristics of these cells and their progressive decline in function. Evidence shows that some of these changes may be mediated by the effects of oxidative stress, inflammation, and chronic exposure to light [12-16].

Age-related macular degeneration (AMD)

Age-related macular degeneration involves the posterior aspect of the retina known as the macula. The macula permits high-resolution visual acuity due to its dense concentration of cone photoreceptors. AMD has an early and late stage. The early stage is characterized by the formation of drusen and pigment abnormalities [17]. The late-stage is divided into two groups: a non-exudative or "dry" form and an exudative/neovascular or "wet" form. The non-exudative form is characterized by atrophic changes in the macula, known as geographic atrophy (GA) and has a slower deterioration with better preservation of visual acuity than exudative AMD. Exudative AMD involves choroidal neovascularization (CNV): formation of new abnormal blood vessels in the choriocapillaris that extend through Bruch's membrane. The presence of new abnormal blood vessels causes leaks and bleeding in the macula leading to irreversible damage to photoreceptors if not treated [17]. Therefore, the exudative form represents most of the cases of AMD with severe visual loss [18].

Incidence of AMD in aging adults

AMD is the leading cause of central blindness and visual disability in aging adults over the age of 55 years in developed countries. According to Gehlbach., *et al*. the prevalence is 12.2% in 55 - 64-year olds, 18.3% in 65 - 74-year olds and 29.7% in subjects over 74 years old [19]. These percentages include subjects with the early-stage disease without visual impairment. The advanced (exudative or atrophic) form of AMD is responsible for visual impairment in 7.8% of subjects older than 75 years. Under 70 years of age, the number of incident cases is similar in men and women. Over 70 years of age, the number of new cases of AMD (wet and dry) is consistently higher in women than in men. Women have a marginally higher rate of geographic atrophy (GA) than men [20].

Risk factors in AMD

Aging

In the Watermen Study, the prevalence of moderate to advanced forms of AMD doubles every decade after age 60 [21]. Rudnicki., *et al.* estimated from a recent meta-analysis of the American white population aged 50 - 97 years that the prevalence of advanced AMD is around 2.3% (95% confidence interval 1.7% - 3.2%) [16,20]. Overall, the annual incidence of late AMD in American whites is estimated to be 3.5 per 1000 individuals aged 50 - 97 years, and 7.8 per 1000 for individuals over age 65. The corresponding rates for GA and exudative

AMD are respectively 1.9 per 1000 and 1.8 per 1000, equating to about 293,000 new cases of late AMD each year. The estimated total of new cases rises rapidly from age 50 years to the mid-80s and then begins to drop.

Family history

AMD is most frequently found in Caucasians, followed by Hispanics and Asians with the lowest rate reported in African Americans [22]. Individuals with a positive family history of AMD had an increased risk than those of the general population [23].

Genetics and inflammation

AMD is a multifactorial disorder with a complex etiology involving both genetic and environmental factors. Lifestyle choices do contribute to the phenotype, although the specifics remain largely unresolved [24]. To date, 34 genetic loci including 52 gene variants have been identified that have been linked to AMD [25]. Advances in our understanding of the genetic basis of the AMD have identified risk and protective variants in several genes related to the complement pathway and chronic inflammation such as complement factor H (CFH). CFH interacting with oxidized phospholipids on the RPE membrane modulates cell functions, but the exact role of CFH in RPE cell death and survival remains poorly understood. Céline Borras and all reported in their study that only the full-length CFH protects RPE from oxidative stress-induced cell death.

Authors have mentioned different localisation and the pathway where the CHF is protective of RPE. CFH protects RPE tight junctions from oxidative stress-induced disruption. It preserves mitochondria and nucleus structure of RPE submitted to oxidative stress, protects RPE from caspase-dependent apoptosis finally it protects RPE from necrosis [26].

Chromosome 10q26 and specifically the Age-Related Maculopathy Susceptibility 2 (ARMS2) locus has been implicated as a second major genetic contributor to the AMD disease, beyond the complement pathway [27]. Biologic aging is characterized by a chronic low-grade level of inflammation. This phenomenon has been named "inflamm-aging". The most common theories of inflame-aging include redox stress, mitochondrial dysfunction, glycation, deregulation of the immune system, hormonal changes, epigenetic modifications, and telomere attrition. Inflamm-aging contributes to the initiation and progression of other age-related diseases such as type II diabetes, Alzheimer's disease, cardiovascular disease [28].

Lifestyle, diet, and nutrition

Lifestyle risk factors that have been attributed to AMD, in particular, include tobacco smoking, omega-6 fatty acid consumption, and high pulse pressure [29]. Smoking is the main modifiable risk factor. Smokers of > 40 years are two to four times more likely to develop AMD than non-smokers of the same age. There is conflicting evidence regarding sun exposure in the AMD occurrence. In a study comparing sun exposure of individuals with AMD in the final phase to non-affected spouses, researchers found no evidence of association [30]; however, other studies have shown that high-energy visible light can contribute to AMD [31,32]. Hogg., *et al*. examined the associations between adherence to a Mediterranean diet and the prevalence of age-related macular degeneration (AMD) in countries ranging from Southern to Northern Europe. Dietary intake during the previous 12 months was assessed by using a semi-quantitative food-frequency questionnaire (FFQ). Increasing Mediterranean Diet Score (MDS) had reduced odds of exudative AMD. For all early AMD stages, there was no relation with MDS. The authors concluded that interventions to encourage the adoption of the Mediterranean diet should be developed, and methods by which such a behavior change can be achieved and maintained should be investigated [33]. Chew., *et al*. reported that clinical trials showed no beneficial effect of omega 3 fatty acid supplementation in early AMD, but they added that fish consumption appeared to be important in many epidemiological studies [34]. In addition to maintaining a healthy lifestyle by controlling weight and eliminating tobacco use, patients should be encouraged to comply with a diet high in fish, vegetables, nuts, and green leafy vegetables. Oral supplementation with the Age-Related Eye Disease Study (AREDS) formulation (antioxidant vitamins C and E, beta carotene, and zinc) has been shown to reduce the risk of progression to advanced age-related macular degeneration (AMD).

Observational data suggest that increased dietary intake of lutein_zeaxanthin (carotenoids), omega-3 long-chain polyunsaturated fatty acids (docosahexaenoic acid [DHA]_eicosapentaenoic acid [EPA]), or both might further reduce this risk.

In AREDS 2 Participants consented randomly assigned to receive either the original AREDS formulation (vitamin [500 mg], vitamin E [400 IU], beta carotene [15 mg], zinc [80 mg, as zinc oxide], and copper [2 mg, as cupric oxide]),with lower, zinc dose (25 mg) during 5 years. The results were significant between participants randomized to receive placebo and participants treated, at the baseline serum levels of study nutrients were balanced across the treatment groups; the levels achieved during reported that, the median serum levels of lutein in participants randomized to receive lutein increased by 190% to 210% at years 1, 3, and 5 from baseline [35].

Recently, Tisdale., *et al*. investigated retrospectively the associations of dietary and supplemental calcium with the risk of AMD development and progression to late AMD (exudative AMD or GA) [36]. The authors evaluated this association with secondary analyses of participants enrolled in the Age-Related Eye Disease Study (AREDS). Prior epidemiologic analysis from the Blue Mountains Eye Study, a longitudinal (15-year) population-based study conducted in Australia, found that decreased dietary calcium intake and dairy product consumption conferred a higher risk for developing late AMD [37]. However, Tisdale., *et al*. found no evidence that calcium intake might be harmful in the development of AMD [34]. Further studies would be necessary to explore this association.

From pathophysiology of the aging retina to disease

The relationship between AMD and aging begs the same line of questioning geared towards all age-related diseases. What is it about aging that makes individuals susceptible to diseases? In the case of AMD, Ardeljan., *et al.* differentiated the anatomical, physiological, and biochemical changes common to every member of the elderly population from changes that cause disease [38].

Viable transport pathways for the translocation of nutrients and waste products across Bruch's membrane are essential for photoreceptor maintenance and survival. Gross structural and biochemical alterations from normal aging are postulated to form a diffusion 'barrier', compromising the transport functions of Bruch's membrane [39]. As such, the hydraulic conductivity of the membrane was found to decline exponentially with age but reaching levels in the elderly that were still enough to maintain normal photoreceptor physiology [40]. Further reductions associated with advanced aging are expected to lead to fluid pooling between Bruch's and the RPE, increasing the risk of RPE detachments which are commonly seen in AMD [41]. Age-related compromise in the transport of low molecular weight metabolites such as amino acids has also been demonstrated in Bruch's membrane with reductions of 58% for the hydrophilic glycine and 76% for the hydrophobic amino acid [42]. Despite dramatic alterations in age-related diffusional status, sufficient capacity was still maintained to avoid pathological insults, since, in this study, a normal elderly population without any signs of ophthalmic disease was examined [42].

Despite the absence of obvious disease, elderly subjects often show a slowing in rod-mediated dark adaptation because of delayed rhodopsin regeneration [43]. Similarly, early age-related maculopathy also shows clear delays in rod-mediated dark adaptation. The implications are that the constant phagocytosis of disc membranes and their subsequent degradation by lytic enzyme systems in the pigment epithelium eventually result in the progressive accumulation of debris within pigment epithelial cells. Recent histopathological studies on the retina of human donors with MRA have shown a predilection for photoreceptor loss of rods compared to cones on the parafoveal zone in the early non-exudative form of the disease [44].

Another more recent study was performed after an adaptation stimulus (complete darkness test with maximum adaptation time) that the patients presented, showed scotopic sensitivity deficits (rod-mediated) compared to photopic sensitivity (mediated by cones) [45]. Early ARM patients take more than 17 minutes longer to reach light sensitivity before bleaching than healthy participants. The alteration of the time constant of rod-mediated dark adaptation presented by ARM patients indicates a significant alteration in visual cycle sensitivity recovery. The authors thought that the hypothesis is the changes in Bruch's membrane-RPE complex linked to an ARM

arm may result in an insufficient intake of 11-cis-retinal to the outer segment of the stem, thereby slowing down the cycle Visuel [46]. An abnormality in the ABCR gene product (as in Stargardt's disease), which is a photoreceptor-based retinoid transporter [47], that could limit the availability of 11-cis-retinal to the outside of the stem.

By the fourth decade, extracellular debris is also seen accumulating in the inner, most layers of Bruch's membrane [48]. Sarks elegantly demonstrated in clinic pathological studies that in many individuals the extracellular deposits, possibly genetically predetermined, play a significant role in the generation of age-related macular disease [1]. The spectrum of disturbances in the aging retina ranges from extensive sub-RPE deposits to drusen to pigment epithelial detachments and subretinal neovascular complexes. Extracellular debris may not only be a causal agent in loss of functions in the aging macula but may also account for some variations or patterns seen on clinical examination. A recent article postulated the constant degradation of phospholipid waste by the pigment epithelium eventually results in an aggregation of lipids in the innermost layers of Bruch's membrane [43]. The presence of this hydrophobic layer impedes the passage of water moving from the retina towards the choroid. In the elderly, such a barrier may well be the causative agent of RPE detachments, since the RPE cannot pump the water from the subretinal space to the choroid through Bruch's membrane. Regarding the RPE, Sun., *et al*. demonstrated that rod outer segment phagocytosis activity in human retinal pigment epithelium is significantly higher in younger than in older patients [21]. Kuroda., *et al.* found that RPE cells gradually accumulate molecular debris over the course of a lifespan [49] Lipofuscin within RPE cells itself is composed of remnants of incompletely digested rod and cone membranes. Progressively, RPE cells become obstructed and associated with the extrusion of aberrant materials that accumulate in the Bruch membrane as basal laminar deposition [49].

Sarks in 1976 found histologically that these changes in aging could be detected at the level of the RPE, Bruch's membrane, and choriocapillaris before clinical abnormalities became apparent. Subsequent changes in these tissues were also correlated closely with the clinical progress of senile macular degeneration [1]. Gao., *et al.* analyzed the impact of aging on cell loss in the human retina of 35 donor eyes [50,51]. In their results, the authors indicated that equatorial rods, cones, and RPE cells decreased in density from the second to the ninth decade of life, and cone and RPE cells in the fovea appeared to be more stable over this same period. Their results suggest that cell loss during aging at the fovea and equator is dissimilar. The reasons for these different patterns of cell loss remain to be determined. Del Priore., *et al.* determined the effect of increasing age on the proportion of apoptotic RPE cells in each zone of the retina in the donor's eyes [51]. The authors found that the proportion of apoptotic cells started to increase in the sixth decade in the fovea and reached 50% of the maximum by 79 years. There was no significant increase in apoptosis with increasing age in the perifovea. The proportion of apoptotic RPE cells was higher in older eyes than in younger eyes in the fovea, while no difference was noted in the proportion of apoptotic cells in the peripheral retina of younger versus older eyes. Chong., *et al.* found in their experience with mice that with age, BM loses normal function and leads to degenerative changes [9]. Discontinuities of elastic fibers of BM were observed in senescence-accelerated mice (SAM), aging mice, and elderly people by numerous studies [9,52]. Increased length of discontinuities of the elastic lamina of BM may be the predilection for the occurrence of CNVs after the age of 75 years [9].

Choroidal changes with a tigroid appearance or pigmentary disturbance are also commonly observed. From this perspective, AMD could be viewed as a disease related to dysregulation and dysfunction of homeostatic processes which change as a function of aging. These processes include imbalances that arise in the photoreceptor, RPE, choriocapillaris, and choroid biologic systems [14,53].

Histological examination confirmed that the clinical prominence of the vessels was due to the thinning of the choroid, particularly loss of the middle layer so that the larger vessels occupied almost the full thickness of the choroid [1]. Degenerative changes were also noted in some choroidal arteries similar to those seen in cerebral vessels, particularly in the plexus. Many histological studies have investigated the interrelation between photoreceptors, RPE, Bruch's membrane, and choriocapillaris in AMD [12]. Although histologic studies have shown alterations in the choriocapillaris secondary to changes in the RPE in non-exudative AMD, it is still possible that one of the earliest changes

detectable in the retina *in vivo* could be alterations in choriocapillaris circulation and/or structure [13,14]. In addition, in exudative AMD, changes in the choriocapillaris may occur before changes in the RPE and could be the primary cause of subretinal neovascularization [15]. Nateras., *et al.* analyzed and determined the changes in choroidal blood flow (ChBF) with age in humans. Blood flow was high around the macula and dropped off peripherally. They reported that an increase of ocular perfusion pressure (OPP) and mean arterial pressure (MAP) was correlated negatively with retinal leukocyte velocity and measurement of ChBF and blood volume with laser Doppler flowmeter [54]. Their findings corroborated with the results of Grunwald., *et al* [55]. However, when multiple regression analyses for age, MAP, and OPP were performed, choroidal hemodynamics only significantly correlated with age. These results suggest that possible changes in MAP or OPP due to age may not have much effect on ocular perfusion [56].

Oxidative stress with aging

Oxidative stress is an attack of cells by free radicals, also called "reactive oxygen species" (ROS). They have important biological functions, notably by intervening in cell signaling. However, when in excess, free radicals can attack essential cells and promote chronic diseases such as AMD, cataracts, cancer, etc [57]. Excessive ROS and accumulation of oxidative stress appear to play a central role in the pathogenesis of AMD, with RPE cells being a critical site of oxidative injury [58]. Although the retina and RPE cells are rich in both enzymatic and non-enzymatic antioxidants, ROS levels increase in the aging retina. Increased levels of ROS and attenuated antioxidant cell defense systems damage photoreceptors, RPE cells, and choriocapillaris with apoptosis, disrupting the delicate homeostasis of the retina [58,59].

Conclusion

AMD is a chronic, complex, and multifactorial neurodegenerative disease. Advanced age presents a variety of biological challenges, including physiologic cell apoptosis, tissue involution, inflammatory processes, cumulative lifestyle exposures, and epigenetic changes. As described, alterations in the macular structure at multiple levels have been well demonstrated to occur with advancing age. The mechanisms proposed to explain these effects of normal ageing could also be applied to better understand the degenerative changes of AMD. Although AMD seems inextricably bound to the ageing process, the lack of universality suggests that genetic susceptibility and lifestyle factors triggering and exacerbating inflammation, oxidative stress, apoptosis, and debris accumulation in the cellular level may accelerate the progression to degenerative changes of AMD in some elderly individuals.

Conflict of Interest

None.

Search Sources

PubMed, Medicine Library of Chicago University hospital, Association for Research in Vision and Ophthalmology meeting abstracts, ClinicalTrial.gov.

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