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Age-related Macular Degeneration and Current Therapies

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Abstract

Age-related macular degeneration (AMD) is degenerative retinal eye disease that affects central vision. It is estimated that by 2040, approximately 288 million people in the world might be affected by AMD. Considering the rapidly aging world population, the need for understanding the mechanism of progressive degeneration and developing appropriate treatment methods are increasing. Retinal degeneration in AMD is directly associated with many factors such as smoking, cardiovascular diseases, nutritional and genetic factors, and genes regulating complement, lipid, angiogenic, and extracellular matrix pathways. Studies on therapy development have limitations due to lack of knowledge of pathophysiological mechanism, multifactorial effects and disease progression is different in different patients. Although some therapy studies promise in treating AMD, huge effort is still needed for future drug development. This review focuses on the classification of AMD, underlying pathological mechanism, currently available and developing new treatment opportunities.

1. Introduction

Age-related macular degeneration, also known as AMD or “yellow spot disease”, is a retinal degeneration seen in individuals aged 50 years and older. AMD is considered one of the main causes of vision loss in developed countries (Ferris III et al., 2013). The macula is an area of approximately 5.5 mm in diameter, located posterior to the optic axis, close to the optic disc. Since there is a yellow xanthophyll pigment here, this area is also referred to as the "yellow spot" in some sources and is the most sensitive area of the retina. In the center of the macula is the fovea, a specialized retinal area responsible for clear and central vision. In the macula, only Cone photoreceptors are present, while blood vessels are not located in this area (Arunkumar, Gorusupudi, & Bernstein, 2020).

AMD is a degeneration characterized by the fact that the retina pigment epithelium (RPE) cells in the macula cannot fully perform their functions and, accordingly, lipids and metabolic wastes accumulate and cause inflammation with advancing age (Han et al., 2022). With the population continuing to age rapidly, it is predicted that 288 million people worldwide will have AMD by 2040 (W. L. Wong et al., 2014). Among the factors increasing the incidence of AMD are environmental conditions and living conditions of individuals, as well as age and race. High blood pressure, smoking, diabetes, cardiovascular diseases, high blood lipids, high long-term C-reactive protein (CRP), sedentary lifestyle and exceeded body mass index (BMI) are high-risk factors for AMD (Chakravarthy et al., 2010; Rastogi & Smith, 2016; Seddon, Gensler, & Rosner, 2010; Velilla et al., 2013). At the same time, it is known that some genetic characteristics increase the potential of having AMD. It has been reported that 38 different genes are involved in AMD (RetNet, 2022). In particular, complement factor H (CFH) and “high-temperature requirement protein A1” (HTRA1) are two significant gene loci associated with AMD (Haines et al., 2005; Lu et al., 2021). On the other hand, it has been revealed that a mediterranean-type diet, vitamin C, E, and D supplements, antioxidants and minerals such as lutein, zeaxanthin, and zinc reduce the risk of AMD development and also slow the progression of AMD (Humphries & Khachik, 2003; Merle, Silver, Rosner, & Seddon, 2017).

- **AMD-Driving Pathogenic Pathways**

AMD is caused by the death of photoreceptors and underlying RPE cells. Multifactorial interaction including metabolic, functional, genetic, and environmental factor may induce disfunction of both cell types in AMD (Kijlstra & Berendschot, 2015). Disruption of RPE cells changes the metabolic balance in the macular region and causes to accumulation of metabolic

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wastes in this area. The structure of the blood-retina barrier becomes dysfunctional over time, so that abnormal clusters form in the vitreous, retinal tissue damage appears, and the choroidal blood vessels progress into the macula (Bhutto & Lutty, 2012). In this case, calcifications, detachment, and tissue death occur in the retinal tissue and bruch's membrane as the retina cannot be adequately oxygenated (Abokyi, To, Lam, & Tse, 2020). This process induces the release of vascular endothelial growth factor (VEGF) from immune cells in retinal tissue. At the same time, the release of platelet-derived growth factor (PDGF) from cytokines that cause vasculogenesis, while the release of vasculogenesis inhibitors such as endostatin (ES) and tissue inhibitors of metalloproteinases (TIMP) are suppressed. This in turn results in new vascular structures in the retina and vitreous. These new vessels leak into the vitreous and prevent vision (Campochiaro, Soloway, Ryan, & Miller, 1999). Metabolic waste that disrupts the blood-retina barrier also increases the amount of reactive oxygen species (ROS) and consequently oxidative stress in retinal tissue. The accumulation lipofuscin of RPE cells in correlation with age may responsible for ROS production (Schmitz-Valckenberg, Fleckenstein, Scholl, & Holz, 2009). In addition, it is interesting and ironic finding that high-density lipoprotein (HDL), one of the cholesterol types, is a factor that promotes AMD; on the other hand, total cholesterol and triglycerides are factors that reduces the risk and severity of AMD (Wang et al., 2016). There is also a hypothesis that high blood lipids cause atherosclerosis by impaired structure of the choroidal vessels and thickening their walls in the retina leads to AMD (Bergen et al., 2019).

It has been shown that pro-inflammatory factors in the relevant tissue are increased in the early-stage of AMD cases. One of the causes of inflammation and angiogenesis in the macula is the C5a protein, which reaches the retinal tissue through impaired blood-retina barrier (Clark, McHarg, Tilakaratna, Brace, & Bishop, 2017).

In the AMD, lysosomal activity of RPE is also decreased due to the aging (Bowes Rickman, Farsiu, Toth, & Klingeborn, 2013). This reduces autophagy and increases metabolic deposits that need to be digested.

- **Classification and Clinical Features of AMD**

AMD is diagnosed with different imaging methods such as fundus imaging, optical coherence tomography (OCT), optical coherence tomographic angiography (OCTA), and fluorescent angiogenesis (FA). AMD is classified into different stages; in the first stage, it does not cause any symptoms or discomfort to the patient. RPE cells do not show any pigmentation and are characterized only by a few small bubbles (diameter <63 μm) in the

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macular area of the vitreous. These blisters are acellular and are yellowish-brown debris called "drusen" formed by the accumulation of metabolic wastes. In the second stage, while no pigmentation was observed in the RPE, the drusen grew slightly. Stage 3 has at least one large drusen (diameter >125 µm) and changes in RPE (Jager, Mieler, & Miller, 2008). The information that the diameter of the large drusen is approximately equal to the diameter of the retinal artery advancing towards the optic disc (Bird et al., 1995), and can be accepted as evidence that AMD rapidly endangers vision from this stage. Stage 4 is the last stage for AMD and is classified as "dry AMD" or "wet AMD". Dry AMD is known as geographic atrophy (GA) because of the structure created by the lost RPE cells and photoreceptors in the macula. This type of degeneration was named "dry-type" because there is no leakage of fluid or blood towards the macula. Dry-type AMD is characterized by yellowish-whitish droplets (drusens) in the macular area of the vitreous, and there is abnormal pigmentation in the RPE cells (Ferris III et al., 2013). On the other hand, in wet AMD, also called "neovascular" or "exudative" AMD, new blood vessels have formed in the macula (neovascularization) and leak from these vessels into the vitreous. It progresses faster and more aggressively than dry-type AMD (Jager et al., 2008) *(Figure 1).*

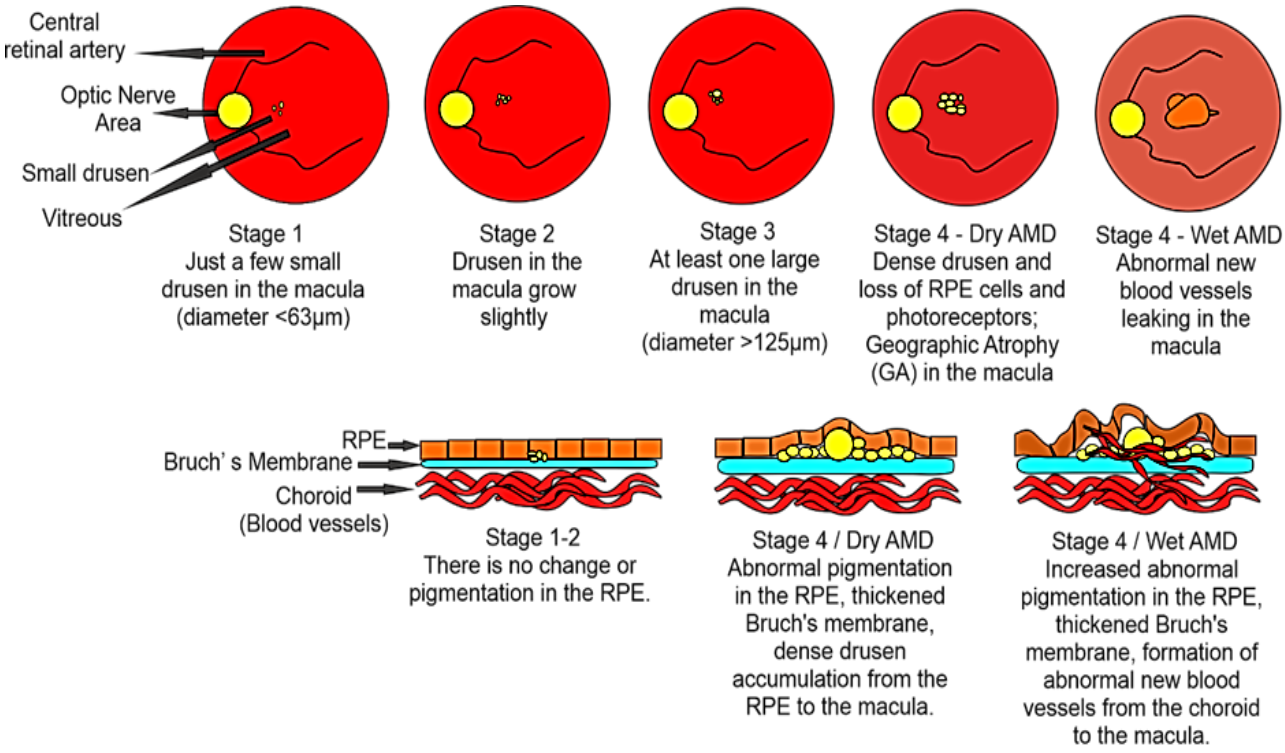

Figure 1. Stages of age-related macular degeneration (AMD) and the conditions of the blood-retina barrier at these stages (RPE: retinal pigment epithelium).

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However, wet AMD is also divided into two subclassifications; choroidal neovascularization (CNV) and polypoidal choroidal vasculopathy (PCV). Briefly, in CNV, it is seen that newly formed and unhealthy blood vessels pass through the RPE and extend into the inner layers, whereas in PCV, blood vessels only cross Bruch's membrane and do not exceed the RPE (Jager et al., 2008).

2. Current Therapies in AMD

In the current treatment of AMD, although there are no effective treatments to achieve complete recovery, its progression is limited by symptomatic and supportive treatment approaches according to the stage and classification of the disease (Al-Zamil & Yassin, 2017). For the first three stages, oral lutein, zeaxanthin, zinc, and vitamin C, D, and E supplements are recommended. Patients are guided to a life where they exercise regularly and keep blood glucose, lipid, and pressure values within the required range (Agrón et al., 2021; Group, 2001; K. H. Wong et al., 2022). A similar study conducted on 151 patients in Türkiye confirms these results and reveals that, especially in patients with AMD, daily cholesterol intake is higher and daily fiber intake is lower than in healthy subjects (Özgür & Aslı, 2018). For stage 4, there is no additional treatment other than what is recommended for dry AMD in the first three stages. Nevertheless, stem cell therapy was tried in 2012 in dry AMD. Retinal pigment epithelium (RPE) cells produced from human embryonic stem cells were transferred to AMD patients. In fact, the process was completed without complications, and the patients' vision improved (Schwartz et al., 2012). However, using local immunosuppressants in this method causes gene therapy not yet among the current treatment methods for dry AMD.

In wet AMD, current treatment methods include laser burning of these unhealthy blood vessels to prevent leakage into the vitreous after neovascularization, photodynamic therapy (PTD) and regular intravitreal anti-VEGF injections to prevent neovascularization (Schmidt-Erfurth et al., 2014; Yin, He, Yang, Cui, & Jiang, 2022). The anti-VEGFs used are predominantly ranibizumab, bevacizumab, pegaptanib, aflibercept, and conbercept (Chen, Cheng, Yeung, Yang, & Chen, 2020). These drug injections are also available in combination with laser or thermotherapy. The most preferred anti-VEGF is generally Ranibizumab. Anti-VEGF injections are administered to the posterior of the limbus under local anesthesia (Grzybowski et al., 2018). Depending on evidence that the physicians observe, injections can be performed monthly, every two months or every three months, and this method is called "extended-fixed". On the other hand, some physicians apply anti-VEGF treatment as needed according to the patient's controls.

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Table 1: Classifications of age-related macular degeneration (AMD) and current therapies

Stages of AMD	Characteristics of AMD	Current Therapy Method(s)
Stage 1	A few small drusen in the macula (<63 μm)	*For first three stages; no effective treatments. Oral lutein, zeaxnthin, zinc, and vitamin C, D, and E supplements are recommended. *Important keep under control blood pressure, glucose and lipid levels (Agrón et al., 2021; Group, 2001; K. H. Wong et al., 2022; Özgür & Aslı, 2018).
Stage 2	Drusen grows slightly, no irritation for the patient	
Stage 3	At least 1 large drusen in the macula (>125 μm)	
Stage 4a DRY-type	Dense drusen, Loss of RPE cells and photoreceptor cells, Abnormal pigmentation in RPE, Thickened Bruch's membrane, Geographic Atrophy (GA)	*Recommended the identical therapies in first three stages (Al-Zamil & Yassin, 2017). *In 2012, stem cell therapy as clinically study has been tried with no complication (Schwartz et al., 2012).
Stage 4b WET-type	Neovascularization, Blood vessels in the macula, Abnormal pigmentation in RPE, Thickened Bruch's membrane	*Burning abnormal new blood vessels with Laser, *Photodynamic therapy (PTD) with Verteporfin, *Intravitreal anti-VEGF injections (Ranibizumab, bevacizumab, pegaptanib, aflibercept, and conbercept) (Schmidt-Erfurth et al., 2014; Yin, He, Yang, Cui, & Jiang, 2022; Chen, Cheng, Yeung, Yang, & Chen, 2020) *Administration periods of anti-VEGFs: extended-fixed, pro re nata, treat and extend (Li, Donati, Lindsley, Krzystolik, & Virgili, 2020)

This method is named "pro re nata (PRN)". Another method called "treat and extend" is to continue the injections monthly when the recurrence of neovascularization is detected in the patient, and then the injection intervals arecontinued with an increasing course (Li, Donati, Lindsley, Krzystolik, & Virgili, 2020) *(Table 1)*.

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Photodynamic therapy, on the other hand, was first applied in the late 1990s. Verteporfin is an FDA-approved drug, also known as Visudyne. Verteporfin is activated by delivering a monochromatic laser light with a wavelength of 689-691 nm to the retina, following its intravitreal administration at a dose of 6 mg/m^2, depending on body area. Verteporfin activation works to destroy newly forming abnormal blood vessels by causing vascular endothelial damage through the production of ROS radicals (Scott & Goa, 2000; van den Bergh, 2001). According to the study conducted on 423 patients called ANCHOR (The Anti-VEGF Antibody for the treatment of predominantly classic choroidal neovascularization in Age-Related Macular Degeneration), when the results of the anti-VEGF injection therapy in which Ranibizumab is preferred and the photodynamic therapy with Verteporfin were compared, the visual acuity improvement in the patients who received anti-VEGF therapy was found to be significantly higher compared to those who received photodynamic therapy (Brown et al., 2009). In a similar study conducted with 28 patients with AMD in Türkiye, anti-VEGF therapy, in which Ranibizumab was preferred, was compared with the combined therapy of photodynamic therapy and Ranibizumab. As a result of this study, it was observed that photodynamic therapy did not have an extra advantage in increasing visual acuity, and both groups had similar visual acuity increases (Ünlü, Acar, Hazırolan, Acar, & Duman, 2010). In another study conducted in Türkiye with 80 patients with AMD, photodynamic therapy alone and a combined treatment regimen of photodynamic therapy, Ranibizumab anti-VEGF injection and intravitreal Triamcinolone injection were compared. This study showed that combined therapy was significantly more successful in improving visual acuity than photodynamic therapy alone (Selim, Koçak, Aslankara, & Kaynak, 2014). There are studies worldwide that the combined treatments of photodynamic therapy and anti-VEGF injection is found to be significantly more successful in improving visual acuity in wet AMD compared to photodynamic therapy alone (Kaiser et al., 2009; Lim et al., 2020).

On the other hand, both anti-VEGF injection treatments and photodynamic therapy have adverse effects and some negative sociological effects on the patient. Some of these effects are physical stress experienced by the patient, fear of injection, costs, continuous periods of treatment and the fact that this can only be achieved by going to certain health centers, sudden changes in blood pressure or shortness of breath during and after treatment, general restlessness and pruritus. In some cases, adverse effects such as the risk of photodynamic therapy damaging the neural retina and the risk of intraocular bleeding are also factors to be considered in treatment regimens for wet AMD (Falavarjani et al., 2013; Schnurrbusch, Jochmann, Einbock, & Wolf,

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2005; Ziemssen et al., 2020). According to a study conducted with 314 wet AMD patients in Türkiye, 39.8% of the patients could not continue anti-VEGF treatment for similar reasons in one-year period (Polat et al., 2017).

More radical and experimental treatment methods are RPE cell transplantation, gene therapies, and stem cell transplantations. In RPE cell transplantation, RPE tissue can be transplanted directly (MacLaren et al., 2007) or cultured RPE cells can be transplanted into the retina. For this transplantation method, various tools, heat-operated micro-thermal attachments, and implants that will enable the tissue graft to be delivered to the subretina are tested (Busik et al., 2009). In RPE cell suspension, the RPE cells are transferred to the retina with the help of a needle with a rounded glass tip (Hartman & Kompella, 2018). During this procedure, which causes much fewer complications compared to tissue transplantation, care should be taken in matters that require high sensitivity, such as the quality of the RPE cells to be transferred, their removal from dysfunctional tissue residues, their transfer to the retina via the correct pathway and with a correct technique (Alexander, Thomson, Luff, & Lotery, 2015).

Since the retina is a small tissue with a narrow microenvironment and can stay away from the effects of the immune system thanks to the blood-retina barrier, gene therapies have very promising potential for AMD. The aim of gene therapy applied to AMD patients is to ensure that the genetic material is produced directly by the patient. For this purpose, AAV2 viral vectors carrying VEGF binding proteins are used to prevent neovascularization in the retina. This method is known to be particularly effective in long-term, wet AMD patients (Heier et al., 2017). Some studies have shown that vectors carrying angiostatin and endostatin also give positive results in terms of treatment (C. C. Lai et al., 2005; L. J. Lai, Xiao, & Wu, 2007).

In addition to the human embryonic stem cell therapy tried in dry AMD (Schwartz et al., 2012), RPE cells produced from pluripotent stem cells have been transplanted into the retina for wet AMD. It was observed that this study did not have any positive or negative effects on vision improvement in patients compared to the study with human embryonic stem cells (Maeda, Sugita, Kurimoto, & Takahashi, 2021).

3. Conclusion

AMD remains a real concern for public health and important cause of blindness and is gaining more importance with today's rapidly aging world population. Knowledge on the physiopathology of this multifactorial neurodegenerative disease is limited. There is no cure to get back vision lost although very limited therapeutic options are exist to slow/delay the progression of the disease in AMD cases. Currently available therapeutic approaches are oral administration of antioxidant and vitamin

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supplements, intravitreal anti-VEGF injections, and photodynamic therapy with laser. While anti-VEGF injections are found to be more successful in improving patients' visual acuity compared to photodynamic therapy, combining both treatment regimens may be preferred on a case-by-case basis as a more effective method.

Considering that genetic background and ethnicity are also effective in AMD pathology, comprehensive and retrospective studies conducted by each country with a sufficient sample size may be effective in determining appropriate treatment methods for patients suffering from AMD. At the same time, AMD gene therapy studies for countries' own genetic pools have the potential to yield faster and more effective results.

Conflict of interest

There are no relevant conflicts of interest to disclose.

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