Review Article

CMJ

www.cmj.ac.kr

Mechanistic Insight into Age-Related Macular Degeneration (AMD): Anatomy, Epidemiology, Genetics, Pathogenesis, Prevention, Implications, and Treatment Strategies to Pace AMD Management

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One of the most complicated eye disorders is age-related macular degeneration (AMD) which is the leading cause of irremediable blindness all over the world in the elderly. AMD is classified as early stage to late stage (advanced AMD), in which this stage is divided into the exudative or neovascular form (wet AMD) and the nonexudative or atrophic form (dry AMD). Clinically, AMD primarily influences the central area of retina known as the macula. Importantly, the wet form is generally associated with more severe vision loss. AMD has a systemic component, where many factors, like aging, genetic, environment, autoimmune and non-autoimmune disorders are associated with this disease. Additionally, healthy lifestyles, regular exercise, maintaining a normal lipid profile and weight are crucial to decreasing the risk of AMD. Furthermore, therapeutic strategies for limiting AMD should encompass a variety of factors to avoid and improve drug interventions, and also need to take into account personalized genetic information. In conclusion, with the development of technology and research progress, visual impairment and legal blindness from AMD have been substantially reduced in incidence. This review article is focused on identifying and developing the knowledge about the association between genetics, and etiology with AMD. We hope that this review will encourage researchers and lecturers, open new discussions, and contribute to a better understanding of AMD that improves patients' visual acuity, and upgrades the quality of life of AMD patients.

Key Words: *Macular Degeneration; Neovascularization; Inflammation*

Article History:
Received July 7, 2023
Revised August 15, 2023
Accepted August 16, 2023

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INTRODUCTION

1. Overview

Age-related macular degeneration (AMD) is known as a chronic illness characterized by gradual vision impairment caused by degeneration of the photoreceptor-dense central retina. First characterized in the clinical reports as "symmetrical central choroido-retinal illness appearing in elderly people" in 1874, the disorder was a major stimulator of blindness in a large number of people for more than a century since it was untreatable. In the 1980s, ophthalmologists began experimenting with thermal laser and photodynamic therapy, frequently bearing unsatisfactory results. According to this disease's pathophysiology, numerous medications have been utilized to treat this disease. Recent discoveries suggest that looking beyond the retina may help explain AMD's pathophysiology, consequences, therapy, and clinical course.[1] According to the pathogenesis of this disease, various drugs have been used to treat it, and some such as anti-VEGF agents for choroidal neovascularisation in early 2000s were a key advancement. Furthermore, it has been beneficial in maintaining or even restoring vision in a great number of cases.[2] Pegpleranib is an an-

https://doi.org/10.4068/cmj.2023.59.3.143

ti-platelet-derived growth factor (anti-PDGF) medication that joins PDGF-BB and inhibits PDGF binding to PDGF.[3] Pazopanib is a topical eye drop formulation of a strong and selective multi-targeted receptor tyrosine kinase inhibitor. Numerous regulatory authorities worldwide have authorized its use for renal cell carcinoma and soft tissue sarcoma.[4] Lampalizumab (INN) is an antigen-binding fragment of a humanized monoclonal antibody which adheres to complement factor D; it was modulated as a developing medication for geographic atrophy as a result of age-related macular degeneration.[5] Tandospirone, a topical ocular drop that acts as a partial 5-HT1A receptor agonist, has been widely utilized to treat Atrophic AMD.[6] Eculizumab, an inhibitor of complement protein C5, is an intravenous infusion of normal saline and a treatment for paroxysmal nocturnal hemoglobinuria (PNH).[7] Despite these optimistic developments, no definite or lasting treatment for AMD has been identified. Broad investigation of the fundamental disease pathways is necessary in order to identify fresh therapeutic goals. Novel discoveries have been trying to better comprehend the etiology, consequences, treatment, and medical progress of AMD, and researchers' approaches might have to expand further than the retina's local environment.[1] Therefore, in the subsequent sections of this review, the role of the pathogenesis, consequences, and treatment in AMD is extensively explored which are essential to the management of AMD; and hence, exploring the mediators of these sections could benefit its sufferers with important answers to AMD concerns and accelerate the management of this illness.

2. Structure and histology of the retina

The retina is known as a light-sensitive layer lining in the posterior portion of the human eye. The neuroretina, composed of photoreceptor cells, neuronal cells, and glia cells, is separated from the retinal pigment epithelium (RPE) by a virtual subretinal gap. The RPE forms the outer blood-retinal barrier (BRB), keeping extracellular fluid from the underlying choriocapillaris (a continuous layer of fenestrated capillaries) from seeping into the subretinal region, actively pumping fluid out, and controlling immune cell trafficking.[8] In addition, the RPE aids photoreceptor turnover by phagocytosis and lysosomal destruction of outer segments after shedding. The choriocapillaris emerges from branches of posterior ciliary arteries and serves the photoreceptor-RPE complex and outer neuroretina, whereas the central retinal artery supplies the interior portions of the neuroretina. Between the RPE and choriocapillaris is a membrane known as the Bruch membrane, which separates the two tissues. It appears that the integrity of the Bruch membrane is essential for preventing the invasion of capillaries from the choroidal circulation into the retina.[9] The macula (also known as macula lutea) is a region of the retina measuring around 5.5 mm in diameter and corresponding to the major temporal arcades. The macula is qualified for the middle 15 to 20 degrees of the visual field and has the best resolution of the eye.[9] Histologically, it varies from the peripheral retina in that it contains multiple layers of retinal ganglion cells, which are neurons dedicated to transferring visual input to areas of the brain cortex. In addition, mature RPE cells in the peripheral retina, but not the central retina, are efficient in multiplying and migrating to the senescent areas in the central retina.[10] In clinical practice, the macula can be viewed by ophthalmoscopy, which is frequently augmented by an imaging modality that permits more comprehensive inspections and reporting (Fig. 1).

3. AMD

1) Clinical features: In the industrialized era, AMD is the major reason for blindness. Generally, two types of AMD have been introduced: approximately 80% of AMD patients have the "dry" form, in which vision cells lose function, and 20% have the "wet" form, in which the macula is scarred due to leaking blood vessels.[11] Both variants are painless and are associated with diminished central visual acuity. The over-developed stage of AMD is "wet" (exudative) degeneration. However, in another approach, AMD could be divided into four distinct stages.[11] The initial phase consists of normal ageing distortion, with just little drusen and no pigment abnormalities. In this phase, the drusen have a diameter of 63 mm. At the following phase (which is referred to as early AMD), intermediate drusen with diameters between 63 mm and 124 mm are detectable, yet there are no visible abnormalities in the RPE cells. Extensive, moderate AMD presents as with at least one big drusen (125 mm in diameter; intermediate AMD) and RPE abnormalities. Fourth stage AMD, generally recognized as advanced AMD, is characterized by geographic atrophy (GA) of the fovea or other age-related symptoms of neovascular macular deterioration, in addition to causing vision loss. Liew established the strength of the AREDS simplified severity scale. Early AMD causes the least visual impairment, which is typically coupled with impaired studying abilities, optical distortion, and a central black or grey patch. Large or moderate vitreous wart membranes or poor pigmentation characterize mild AMD. Patients with severe AMD have significantly impaired central vision.[12]

In addition to the disciform scar, known as a sign of the final phase of advanced AMD, this phase is clinically split into two distinct subtypes: dry AMD (Fig. 2C) and wet AMD. GA is another name for dry AMD, in which no blood or serum leaking is evident. GA is distinguished with symmetrical eyes, distorted vision, disorganized macular pigmentation in both eyes, loss of foveal reflex, and variable posterior poles with yellowish-white drusen between Bruch membrane and RPE.[13] One might notice map-like atrophy of the posterior retina in some advanced patients. choroidal neovascularization (CNV, Fig. 2D) and polypoidal choroidal vasculopathy (PCV, Fig. 2E), the two phenomena that entail blood or serum leakage, are subtypes of wet age-related macular degeneration. Nonetheless, the occurrence of PCV in either wet or dry AMD is yet still debatable. From another point of view, PCV and CNV hold distinctive medi-

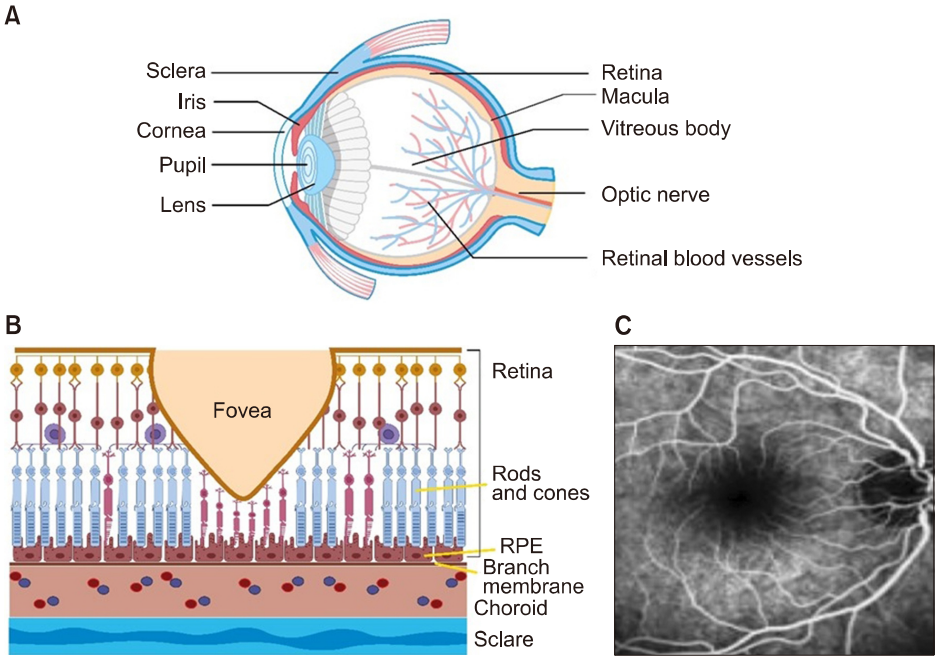

FIG. 1. Anatomy of the macula. The macula lies in the visual axis, temporal to the optic nerve (A). The fovea lies centrally in the macula and is responsible for sharp, central vision (B). Fundus angiography showing the macular region which coincides with the course of the major temporal arcades (C).

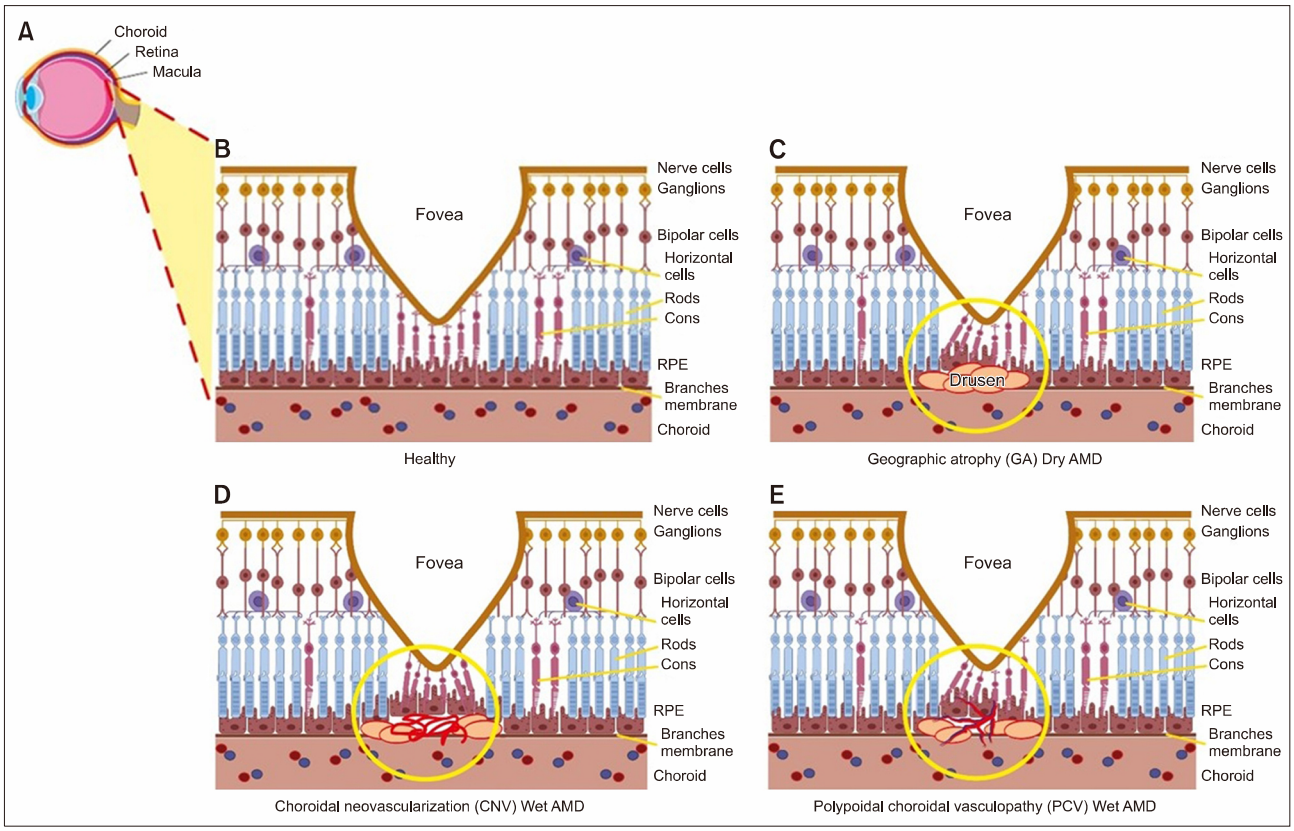

FIG. 2. Neovascularization and drusen formation. (A) A cross section of a normal human eye showing the location of the macula. An oval area with a diameter of 1.5 mm near the fovea is known as the macula. (B) It shows the important structure of the retina in the macular area. RPE cells have the function of removing metabolites produced by photoreceptors. The blood vessels in the choroid can transport nutrients and nourish the outer retina. (C) The formation and location of drusen is shown. Drusen formation will lead to retinal tissue atrophy and Bruch membrane calcification rupture, further leading to AMD. (D) This picture describes a choroid polypoid lesion. (E) This picture shows the proliferation of new blood vessels.

cal and epidemiological characteristics. In contrast, the combination of genetic and environmental factors for PCV and CNV are identical.

The visual acuity of patients suffering from wet AMD dropped more promptly than that of people suffering from dry AMD. The majority of people dealing with wet AMD notice signs and symptoms in one eye at the beginning of the vision impairment, and the other eye may not develop for several years.[14] Choroidal capillaries expand to RPE and Bruch membrane lesions in choroidal neovascularization, culminating in choroidal neovascularization.[15] Since the arrangement of neovascularization is not well-organized nor perfect, it often results in a succession of histological alterations, including exudation, bleeding, and scarring, the phenomena that subsequently result in the loss of central vision. Asians are prone to PCV infection to a greater extent than other ethnicities. PCV has been regarded as a distinct medical concept distinct from CNV because its clinical course is more consistent and its visual consequences are more positive than the outcomes of CNV. In PCV, polypoid neovascularization from the choroid layer could penetrate the Bruch membrane but not the RPE. Depending on the appearance of the lesions, PCV could be categorized into two types. Type I featured polypoid lesions at the point of the vascular network and an aberrant branching vascular network (BVN).[15] Type II was characterised by isolated or clustered polypoid tumours, yet lacked a branching vascular network or fine reticular veins. Secondary submacular or subretinal bleeding could arise in this disease.[16]

2) Epidemiology

(1) Prevalence: In accordance with racial and ethnic disparities, the prevalence of AMD is rising. From 1990 to 2010, the prevalence of AMD-related blindness and visual impairment rose. As the global population ages, it is projected that the number of AMD sufferers rose to 196 million in 2020 and consequently it would reach 284 million in 2040. Since Asia is home to about 42 percent of the global community, it is anticipated that the total count of patients suffering from AMD would reach 113 million by 2040. Due to the topmost prevalence of this illness in Europe, it is anticipated that the total count of future patients in this continent will outrun everywhere but Asia (Fig. 3).[17] AMD is more prevalent among whites than blacks.[18] The prevalence of AMD was 12.33% in Europe, 7.38 % in Asia, and 7.50% in Africa.[19] It has been reported that geographical latitude or longitude had a negative correlation with the original or age-standardized prevalence of this illness in the early and late phases ($p < 0.001$).[20] China accounts for around 18 percent of the global population and that the prevalence of AMD differs in various geographical settings in this country;[21] its prevalence is highest in the densest regions of south-central China, at 6.64% (95% CI Z 5.12e8.52) and 6.74% (95% CI Z 5.20e8.65) in 2000 and 2010, respectively, and increases with decreasing latitude.

(2) Risk factors: Demographic, environmental, genetic, and molecular risk variables are more useful in predicting AMD progression at earlier illness phases than phenotypic risk indicators like drusen and pigment abnormalities comparatively, which become more important as the disease progresses. Other characteristics, including sex, body mass index, and education, are insignificantly correlated with illness development compared to demographic and environmental risk factors including age and smoking tobacco.[22] Among all known AMD variations, rs10922109 and rs570618 in CFH, rs116503776 in C2/CFB/SKIV2L,[23] rs3750846 in ARMS2/HTRA1[24] and rs2230199 in C3[25] are the variants most consistently associated with disease progression. Nonetheless, it is probable that additional AMD variations contribute to ignition or progression of AMD to a lesser level. Rare variations likely possess a significant impact on the course of disease in families that are severely afflicted. In addition, present prediction models do not contain molecular and genetical risk variables, despite the fact that these components may be accurately tested in the blood. High-Density Lipoprotein Cholesterol (HDL-C),[26] Docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), zeaxanthin, and lutein[27] are possible promising molecular risk factors of AMD progression.

In prediction models, phenotypic, demographic, environmental, genetic, and molecular risk factors could be combined to predict disease progression; however, the selection of the appropriate risk factors for personalized risk prediction will probably vary between people and depend on their current disease phase.[28] Future prediction models are expected to incorporate a broader collection of genetic variations to identify genetic risk more precisely. In addition, uncommon variants ought to be considered in families with a high incidence of the disease.[29] Furthermore, the incorporation of molecular components into predictive models may lead to the development of preventative measures and individualized recommendations.[30]

Age, race, blood pressure, and lifestyle are all risk factors for AMD. Age is a significant factor for developing AMD. People with blue irises are more likely than people with brown irises to develop this illness. Systemic conditions such as cardiovascular disease are also risk factors for

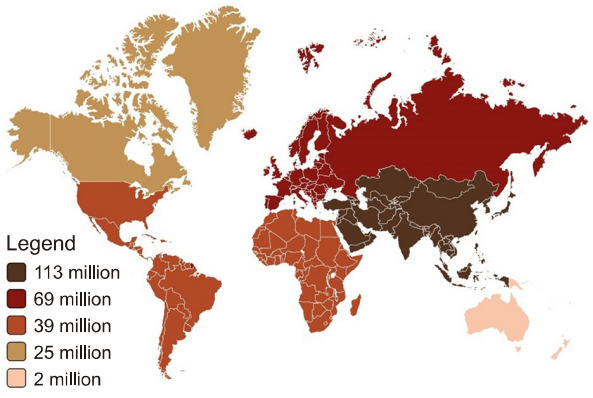

FIG. 3. The predicted global prevalence of AMD in 2040. This figure shows the estimated number of people worldwide with AMD in 2040.

AMD; hypertension and atherosclerosis can raise the risk of AMD as well.[31] Diabetic patients who suffer retinal complications, HDL, obesity, and high systolic blood pressure are also at increased risk for this illness.[32] In addition, the researchers observed that baseline blood cystatin C levels were related to the incidence of early AMD and wet AMD.[33] According to the literature, smoking tobacco and high alcohol consumption intensify the risk of AMD.[34] Lutein and zeaxanthin can reduce the incidence of AMD, as do vitamin C, vitamin E, vitamin D, and zinc oxide.[35] Increasing fish consumption can also lessen AMD risk.[36] DHA and EPA might inhibit the development of AMD.[37] Further, lunch breaks are related with a decreased risk of advanced AMD. Divorced or separated individuals were three times as likely as married individuals to suffer advanced AMD.[38]

3) Genetics

(1) Associated loci: The etiology of AMD is strongly influenced by genetic factors; numerous AMD-related genes and loci have been identified and their numbers are growing. CFH and HTRA1 loci are the two most important loci related with AMD. In 2005, scientists initially connected the 402H allele of CFH to a higher risk of AMD. The complement pathway regulator CFH is found on chromosome 1q32.[39] CFH 402H inhibits the extraction and transport of damaged lipids from the RPE layer, impairs the adjustment of CFH in preventing the cascade of conversion from C3 to C3b and eventually breaking from C3b, and thus increases AMD risk.[40] CFB and C2 are, respectively, triggers of alternative and classical pathways activation. CFB R32Q and R32Q/IVS10 haplotypes provide protection against AMD. The C3 mutation R102G (rs2230199) develops in the early stages of the disease to result in late AMD. The vitreous verruca membrane contains lysate C3a of C3. C3a can enhance the establishment of CNV and induce the production of VEGF.[41] CFI is a cofactor in the deactivation of C3b and is regulated by CFH. It has been reported that rs10033900, rs11728699, rs6854876, rs7439493, and rs13117504 have protective effects, but that rs2285714 can enhance the risk for AMD manifestation. HTRA1 is an additional important impact locus for AMD. The rs10490924 mutation in the HTRA1 promoter region could magnify the AMD risk 15-fold.[42,43] HTRA1 transgenic mice exhibited Bruch membrane and choroid challenge, as well as CNV and PCV pathology. Certain AMD-associated genes are generally involved in lipid metabolism. APOE is an important factor in cholesterol transport inside the nervous system. The APOE allele haplotypes are 2, 3, and 4. Carriers of the 4th genotype had a decreased risk of AMD progression than those with the 3rd genotype. If not for the high mobility of 4, fat, cholesterol, and RPE breakdown products would accumulate in the Bruch membrane, causing drusen and AMD. RPE cells appear to express more vascular and fibroblast growth factors when APOE 2 is present.[44] Consequently, APOE 4 can lower the incidence and development of degeneration relative to APOE 2. TIMP3 also plays a role in RPE ageing and sorbite dystrophy. The rs9621532 allele and adjacent TIMP3 polymorphisms are reported to be linked to an elevated risk of AMD. LIPC is also connected with AMD, with rs10468017 having the closest relationship.[45] CETP, LPL, and ABA1 were shown to express in the retina, this phenomenon might influence the development of drusen and be related with AMD. Rs2511989 encodes for C1INH in the SEPRING1 gene. C1INH inhibits activation of both the classical complement and lectin pathways. This is genetically close in accordance with AMD.[46] As determined by the GWAS Catalog (https://www.ebi.ac.uk/gwas/) and related literature, at least 103 loci related with AMD have been uncovered (Table 1). They play a role in complement factors, general lipid metabolism, angiogenesis, the immune system, cell motility, the cytoskeleton, cell growth and death, adhesions, collagen, and other processes. The majority of described genes have been reported to be involved in several functions and are related with all kinds of AMD. Only dry AMD is connected with TLR3, the receptor that is involved in non-specific immunity and serves as pathogen recognition component in RPE when cytokines promote apoptosis. The uncommon SNP rs77466370 in FGD6 is exclusively linked to PCV.[47]

(2) Inter-relation of genes and environmental variables: Certain genes and environmental variables (such as smoking) inter-relate to show an impact the incidence and progression of AMD. Smoking altered the linkage of CFH to C3, decreased the concentration of CFH in serum, and the rs1061170 variation altered the capacity of CFH to bind to C3b.[47] Thus, rs1061170 carriers had a greater effect on the chance of developing AMD among tobacco smokers.[48] Additionally, smoking raises the risk for all individuals with the HTRA1 genotype. A substantial relationship between CFH 402H and BMI was identified by AREDS.[49] 70 The Blue Mountains Eye Study discovered that increased fish consumption among CFH 402Y carriers had a greater protective impact against late AMD.[33] Individuals having a considerable genetic risk of CFH and HTRA1 loci had a lower risk of developing AMD if they consumed antioxidant foods. Similar to CFH variations, the risk of AMD increases when HTRA1 mutations and increased serum levels of C-reactive protein (CRP) concur.[50] Moreover, the possible association between chromosomes 6q16.2 and 18q22.1 and smoking dramatically elevated the incidence of AMD among long-term tobacco smokers. The literature also offers that APOE genotype influences the smoking-related risk of AMD and has a higher influence on CNV, and that smoking tobacco was more damaging to carriers of Apo e2.[51]

4) Etiology of AMD: The hallmark AMD lesions are drusen, which are detectable in clinic within the macula and periphery of the retina as well. Colour fundus photography and medical assessment could be employed to record drusen based on their size as hard (or small), medium (>63 μm), or large (>125 μm). Compound drusen could appear in the periphery of the retina, although their ramifications are unknown. On histopathology and electron microscopy, large drusen are associated with basal linear deposits containing membranous compounds and positioned between the foundation membrane of the retinal pigment epithelium

TABLE 1. Classification of AMD related genes

Type	Genes (region, SNP)
Complement factors	C9 (5p13.1, rs62358361), C3 (19p13.3, rs2230199), C2 (6p21.33, rs116503776), CFHR4 (1q31.3, rs2171106), CFH (1q31.3, rs10922109), MBL2 (10q21.1, rs6480975), CFI (4q25, rs10033900), CFB (6p21.33, rs116503776), CFHR2 (1q31.3, rs2171106)
Lipid metabolism	CETP (16q13, rs5817082), APOE (19q13.32, rs429358), LIPC (15q21.3, rs2043085), ABC41 (9q31.1, rs2740488), LHFP (13q14.11, rs8002574), ABHD2 (15q26.1, rs4932480), TIMP3 (22q12.3, rs9621532)
Angiogenesis	FILIP1L (3q12.1, rs13081855), VEGFA (6p21.1, rs943080)
Immune	PVRL2 (19q13.32, rs6857), CD34 (1q32.2, rs1967689), PILRB (7q22.1, rs7803454), SDK1 (7p22.2, rs55869773), ACKR3 (2q37.3, rs56072732)
Cell motion	POSTN (13q13.3, rs9646096), TNXB (6p21.32, rs12153855), CNN2 (19p13.3, rs67538026)
Cytoskeleton	CCSER2 (10q23.1, rs113544501), P005 (5q13.3, rs79069165), HTRA1 (10q26.13, rs3750846), ARMS2 (10q26.13, rs3750846)
Apoptosis and proliferation	TNFRSF10A (8p21.3, rs13278062), CTRB2 (16q23.1, rs72802342), NOTCH4 (6p21.32, rs2071277), FRK (6q22.1, rs1999930), PHACTR3 (20q13.32, rs843818), PKNOX2 (11q24.2, rs1077952), KRAS (12p12.1, rs73296436), IER3 (6p21.33, rs3130783), TRIM29 (11q23.3, rs61900473), TGFBR1 (9q22.33, rs334353)
Cell junction	GJA1 (6q22.31, rs9482193), CDH22 (20q13.12, rs6032755)
Mitochondrial	NDUFC2 (11q14.1, rs113553030), XRCC6BP1 (12q14.1, rs12368533), UQCRFSI (19q12, rs741449), TOMM40 (19q13.32, rs6857), 5OD2 (6q25.3, rs2842992), ACAD10 (12q24.12, rs61941274), MT-ND5 x ABHD2 (15q26.1, rs267606894 x rs4932480)
Ionic channel	KCNMA1 (10q22.3, rs76150532), KCNJ3 (2q24.1, rs1445653), TRPM1 (15q13.3, rs7182946), EFCAB14 (1p33, rs59182762), KCTD15 (19q13.11, rs10404384), TRPM3 (9q21.12, rs71507014)
Ubiquitination	NPLOC4 (17q25.3, rs6565597)
Transcription	PCF11 (11q14.1, rs4293143), TRIM24 (chr7:138166004, hg19), NELFE (6p21.33, rs116503776), RREB1 (6p24.3, rs11755724), GLI3 (7p14.1, rs2049622), KLF6 (10p15.1, rs12411753), ATF71P2 (16p13.13, rs28368872), BAZIA (14q13.2, rs6571690), EFCAB14 (1p33, rs59182762), KHDRBS3 (8q24.23, rs200534628), LYAR (4p16.3, rs150938341), NUPRIL (7p11.2, rs148800247), TLE4 (9q21.31, rs11545434)
Transport	SLC16A8 (22q13.1, rs8135665), SLC29A3 (10q22.1, rs7091537), SLC44A4 (6p21.33, rs12661281), TRAPPC9 (8q24.3, rs117659209), ADAMTS9 (3p14.1, rs6795735)
Nerve	SYN3 (22q12.3, rs5754227), CELSR1 (22q13.31, rs2337055), CNTN6 (3p26.3, rs77360121), DPF3 (14q24.2, rs12887388), MBP (18q23, rs1789110), TNR (1q25.1, rs58978565), HERC1 (15q22.31, 15q22.31)
Cluster protein family	PLXNC1 (12q22, rs17296444)
Helicases	SKIV2L (6p21.33, rs406936)
Adenylate cyclase	ADCY5 (3q21.1, rs6762009)
GTPase or ATPase	ARHGAP21 (10p12.1, rs12357257), ATP6V0D1 (16q22.1, rs1471142), FGD (12q22, rs10507047)
Tyrosinase	TYR (11q14.3, rs621313)
BBSsome	BBS9 (7p14.3, rs202162020)
Transmembrane protein	TMEM97 (17811.2, rs11080055), TSPANII (12p11.21, rs55916253)
DNA binding protein	RAD518 (14q24.1, rs61985136), TSN (2q14.3, rs72837798)
Transferase	KMT2E (7q22.3, rs1142), B3GALTL (13q12.3, rs9564692), UGT2B7 (4q13.2, rs112243525), HS3ST4 (16p12.1, rs79590629)
Collagen	COL8A1 (3q12.1, rs140647181), COL1041 (6q22.1, rs1999930), COL4A3 (2q36.3, rs11884770)
Noncoding RNA	ADAMTS9-A52 (3p14.1, rs62247658), LINC00470 (18p11.32, rs2186849), LINC00588 (8q12.1, rs72657107), LINC00900 (11q23.3, rs431911), PCDH9-A53 (13q21.32, rs1359191), L0C101060498 (4p14, rs12498917), L0C101927280 (5q23.1, rs61287758), L0C101927797 (21q21.1, rs2205502), L0C101929681 (5p13.3, rs139161960), L0C153910 (6q24.2, rs63337561), L00729987 (1p21.3, rs12727789)
Others	INHBB (2q14.2, rs6721654), ZPLD1 (3q12.3, rs17822656), HORMAD2 (22q12.2, rs713875), CST5 (20p11.21, rs4815244), CTRB2 (16q23.1, rs72802342), EX005 (14q22.3, rs75165563), IGFBP6 (12q13.13, rs11170417), PDHA2 (4q22.3, rs62315917), PRLR (5p13.2, rs114092250), RDH5 (12q13.2, rs3138141), STOX2 (4q35.1, rs11132213), TR/82 (2p24.3, rs10191751), C20orf85 (20q13.32, rs201459901), C4orf14 (4q12, rs1713985), C6orf223 (6p21.1, rs2295334), C80142 (8p23.3, rs722782), C9orf91 (9q32, rs41278671)

and the inner collagenous side of Bruch membrane.[52] Drusen are made up of numerous components, including neutral lipids with cholesterol esters in addition to free cholesterol (>40% of volume). More than 129 distinct proteins — including TIMP3, vitronectin, -amyloid, various apolipoproteins (E, B, A-I, C-I, and C-II), and proteins associated with complement system adjustment — and zinc and iron ions. Basal laminar deposits, a different form of retinal deposit linked to this illness, are located between the basement membrane of the retinal pigment epithelium and the proportional plasma membrane, and are composed of basement membranous proteins and long-spacing collagen.[53,54] These two sorts of deposits may indicate distinct reactions of the retinal pigment epithelium to oxidative responses, leading to the following early AMD exhibition: cataracts and retinal pigmentary irregularities. In regards to neovascular AMD (nAMD), subtypes of choroidal neovascularisation are defined based on the hypothesized source of retinal invasion.[54] As choroidal neovascularization proliferation arises underneath the retinal pigment epithelium, type 1 neovascularisation develops, which correlates with an unnatural choroidal neovascularisation with a vaguely understood presentation of leakage on fluorescein angiography. Type 2 neovascularisation denotes choroidal neovascularisation proliferation above the retinal pigment epithelium in the subretinal region, strong fluorescein leaking correlates to classic choroidal neovascularization. When the retinal blood supply is implicated, together with an anastomosis seen between choroidal and retinal circulations, type 3 neovascularisation develops.[55,56] Polypoidal choroidal vasculopathy, a subclassification of type 1 choroidal neovascularisation with a large aneurysmal component, is found more frequently in African and Asian people,[56] with an approximate frequency of 22% to 62% among individuals suffering AMD in Asian communities. A different late form of AMD, geographic atrophy is characterized by the loss of retinal pigment epithelium cells, photoreceptors, and choroidal capillaries. Histopathological findings imply in geographic atrophy, that the retinal pigment epithelium undergoes atrophy before the choriocapillaris degenerates.[57]

(1) Oxidative stress: The retina depends on the oxygen usage rate of all human tissues. Deposition of oxidative stress has a significant function in the pathophysiology of AMD. The mismatch between the synthesis and scavenging of reactive oxygen species (ROS) is the main source of RPE's increased oxidative damage. The oxygen-rich situation together with a greater content of polyunsaturated fatty acids, and photosensitizers could result in the overproduction of reactive oxygen species in the retina.[58] Lipofuscin is the primary generator of ROS, which build in the RPE by aging, hence raising retinal oxidative damage. Excessive lipofuscin is connected with AMD.[59] Also, the presentation of AMD was much higher in individuals who were exposed to direct sunlight for a longer duration than in the general community. Addressing oxidative challenges could be assumed as the objective of illness prevention and medication. Nevertheless, studies also shown the antioxidant mixture had only a minor influence on the progression rate of CNV. Hyttinen and others hypothesized that the modeling of the AMPK-mTOR axis could prevent the onset of AMD by facilitating the adaptation of cells to oxidative stress.[60]

(2) Inflammation and immunity: Multiple pro-inflammatory markers are present in AMD drusen, indicating that localized inflammation is an early indicator of AMD. The complement system is a crucial component of the non-specific immunity, particularly by offering a crucial function in intraocular microenvironment screening along with homeostasis maintenance. The quantity of CRP was observed to be greater in AMD patients. CRP could enlist CFH to eliminate necrotic tissue and inhibit the generation of pro-inflammatory mediators via recruiting CFH. As the protein 402H is paired with CRP, the patterns of interaction between 402H and CRP becomes less pronounced compared to that between 402Y in CFH and CRP, resulting in activation of the complement and inflammatory response.[61] Generally, complement mediators do not move across the Bruch membrane, however C5a produced by AMD complement activation diffuses via this membrane, causing an inflammatory state and angiogenesis. Increasing information suggests that the tailored modulation of complement-specific mediators will likely offer a treatment choice for AMD management. Local suppression of complement activation is viewed as a potentially effective therapy for progressive forms of AMD. Currently, several reports have identified possible complement cascade blockers that could delay the degeneration.[62] Additionally, Calippe et al.[63] discovered that the coupling of CFH and mononuclear phagocytes (MP) hindered CD47-mediated MPs clearance, whereas MPs maintained the stable status of the subretinal region. Consequently, inflammatory state and immunology are markedly associated with the development of AMD as well.[63]

(3) Neovascularization: VEGF is one of the major dangers associated with wet AMD, and it has a significant function in the development of CNV and PCV. The overexpression of vascular-promoting mediators (including VEGF and PDGF) plus the underexpression of inhibitory mediators (TIMP, etc.) might result in excessive neovascularization proliferation. Pulsatile ocular blood flow (POBF) and pulse amplitude (PA) are lower in exudative AMD cases than in nonexudative ones, according to some studies.[64,65] Bruch membrane thickening might result in higher choroidal vascular resistance, and decreased choroidal circulation could be associated to the establishment of CNV. Additionally, choroidal vitreous warts and aberrant pigmentation enhance the likelihood of developing AMD. The five-year risk of a second eye developing advanced AMD is believed to be between 30 and 40 percent, which importantly exceeds that of the general community.[66]

(4) Lipid metabolism: A high concentration of HDL-C was associated with an increased risk of AMD, whereas high levels of total cholesterol and low-density lipoprotein cholesterol correlated with a decreased change in AMD

development. Investigations have identified advanced lipid peroxidation end products (ALEs) in AMD patients' lipofuscin, vitreous warts, and Bruch membrane. Deposition of advanced lipid ALEs disrupts protein stability and induces photoreceptor and RPE apoptosis.[67]

(5) RPE cell senescence: AMD could be produced by a variety of RPE cell aging-related alterations. The aging RPE cells disrupt the equilibrium of enzymes in the macular area's extracellular matrix, which collects on the Bruch membrane. Metabolites collect on the Bruch membrane, producing vitreous warts, harming nearby retinal tissues, and diminishing the retina's circulation. The senescence of RPE cells causes immune cells to generate VEGF. Blood vessels are produced by calcification, rupture, and phagocytosis of the Bruch membrane, the phenomena that ultimately results in AMD.[68]

(6) Other mechanisms: Studies have also made effort to point out other variables, including autophagy, hemodynamics, and circadian rhythm, which could be considered to show close associations with the occurrence and progression of AMD. Autophagy is a lysosomal breakdown mechanism for cytoplasmic proteins and broken organelles. Through autophagy, protein aggregates are transferred to lysosomes. With increasing age and aging RPE cells, lysosomal enzyme activity diminishes. Autophagy is inhibited to eliminate mitochondria and protein aggregates in the intercellular space, hence speeding the buildup of lipofuscin and contributing to the progression of AMD. Golestaneh et al.[69] discovered that the autophagic flux of RPE in AMD cases was less than in healthy subjects.

Hemodynamics, a long-established system regarding the genesis and progression of AMD, posits that choroidal vascular dysfunction is the cause of degeneration. Today, atherosclerotic modifications in the circulation to the eyes are recognized as nAMD. Friedman's 1997 modern hemodynamic proposal states that AMD is the results of a change in choroidal blood flow resulting from an increase in choroidal and scleral sclerosis. Circulatory lipid deposition and atherosclerosis outcome in stiffness and thickening of the vascular wall, stenosis of the vascular lumen, which leads to reduced circulation to choroidal and irregular choroidal perfusions, leading to inadequate perfusion of RPE cells or Bruch membrane damage, and finally leading to AMD development. Recent medical and practical observations follow the hypothesis that choroidal hemodynamics leads to the progression of AMD. Some findings indicate that cyclic genes may regulate retinal vascularization signals in retinopathy. In proliferative neovascularization, retinal rhythm genes are not expressed. It has to be determined if circadian rhythm disruption would influence the incidence and progression of degeneration. Additionally, a disproportion in protein homeostasis would be of the potential causes of this illness (Fig. 4).[70]

5) Physical and mental health representation in AMD: AMD has far-reaching impacts on life quality. According to the literature, AMD cases report higher levels of life pressure, dissatisfaction, inactivity, and depression in relation to healthy age-matched individuals. Even among anti-VEGF-treated patients, depression is widespread when treatment outcomes fall short of expectations.[71] The reported health-related quality of life of individuals suffering AMD was comparable to or poorer than that of people with other major chronic health problems.[72] In older persons, AMD was found to be related with an elevated risk of functional impairment. Compared to individuals without AMD, participants who suffer AMD (at any stage) had a risk of deleterious impacts on usual daily activities that was about two times greater. AMD is considered to correlate with a higher risk of falling and other comparable injuries. A meta-analysis of 10 studies revealed that late AMD is cor-

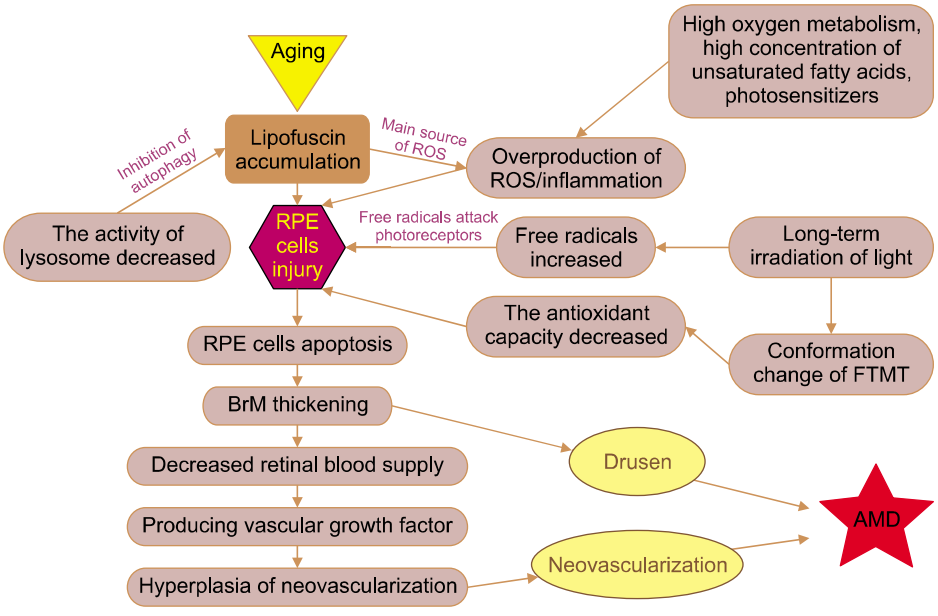

FIG. 4. The formation of AMD during aging. This diagram shows the non-genetic mechanisms of AMD induced by RPE cell senescence, oxidative stress, hemodynamics and so on during aging.

TABLE 2. Nutrients and their food sources capable of preventing the onset of AMD

Nutrients and food sources for AMD prevention	
Nutrients	Food sources
Vitamin C	Citrus fruits and juices, green peppers, broccoli, potatoes
Vitamin E	Whole grains, vegetable oil, eggs, nuts
β-Carotene	Carrots, kale, spinach
Zinc	Meat, poultry, fish, whole grains, dairy products
Lutein and zeaxanthin	Chicken egg yolk, leafy green vegetables
Omega-3 (DHA and EPA)	Fish and seafood, nuts and seeds, plant oils

Dietary modifications have demonstrated to be effective only in studies considering Western populations. Thus, these modifications do not necessary apply to people of other ethnicities.

TABLE 3. Mediterranean diet: a guide to daily food choices

Mediterranean diet	
Food types	Frequency of food servings
Whole grains, bread, beans, legumes, nuts, and seeds	Daily (35% of total daily calories)
Vegetables and fruits	Daily (30% of total daily calories)
Extra virgin olive oil	Daily (10% of total daily calories)
Fish and seafoods	Few times per week (20% of total daily calories)
Dairy products, eggs, poultry, and yoghurt	
Meat, sweets	Small amounts (5% of total daily calories)

Dietary modifications have demonstrated to be effective only in studies considering Western populations. Thus, these modifications do not necessary apply to people of other ethnicities.

related with a 20% rise in total mortality and a 46% rise in cardiovascular-related mortality.[73]

6) Prevention and treatment: Preforming preventive programs might be an ideal choice of management though the efforts being done to introduce novel medications suitable to change the medical progress of AMD have proven to be even more profitable than expected. The improvement of a dietary regime favoring antioxidant ingredients including vitamins C and E, lutein, and zeaxanthin, zinc, β-carotene, and polyunsaturated fatty acids has shown to attenuate the risk of AMD (Table 2). More particularly, it has been demonstrated that the Mediterranean Diet is beneficial in the prevention of this condition (Table 3).[74] Furthermore, changes in lifestyle, mainly stopping tobacco smoking, along with exercising on a regular basis, effective weight control, and regular sleeping circa around eight hours each night, revealed to be an efficient strategy in decreasing the risk of AMD development (Table 4). The significance of intraocular lenses and spectacles in avoiding AMD is not clearly understood and requires more clarification, however blue-light filters seem to preserve the retina from photochemical challenges. Lastly, a healthier lifestyle with a micronutrient-rich diet, abstinence from tobacco smoking, plus frequent physical activity may prevent the development of this illness.[75]

The Age-Related Eye Disease Study was a prospective, multicentric, randomised clinical study that examined the effects of a preformulated mixture of antioxidants and minerals from 1992 to 2006, significantly lowering the risk of advanced AMD in individuals at high risk, i.e. widespread, intermediate sized drusen, one or more big drusen, non-central geographic atrophy in at least one eye, or vision loss owing to AMD in one eye.[74] It has been claimed that this combination reduced the incidence of advanced AMD by 25% in individuals at a significant risk, and it has since been routinely advised to individuals at high risk of developing advanced AMD. AREDS-2 was initiated in 2006 to see if the addition of DHA/EPA (omega-3 fatty acids) or lutein and zeaxanthin (macular xanthophylls) could effectively halt development of AMD-related visual impairment. No additional reduction in advanced AMD risk was observed when DHA/EPA or lutein/zeaxanthin were added to the original AREDS regime. However, compared to individuals who received AREDS with beta-carotene, those

TABLE 4. Lifestyle modifications suggested to reduce the risk of AMD onset

Lifestyle and AMD prevention	
Activity/condition	What to do to prevent AMD onset
Smoking	Cessation
Sleep duration	7-8 h per night
Weight	Reducing obesity and overweight to normal Body Mass Index (BMI) values (18.5-24.9); reducing waist circumferences
Physical activity	At least three hours of moderate- to low-intensity physical activity per week

who took lutein/zeaxanthin instead had a slightly lower incidence of progressive AMD. Beta-carotene may be better replaced by lutein and zeaxanthin in current and ex-smokers due to the latter's and former's lower risks of developing lung cancer.[74] Unfortunately, there is currently no conclusive or established treatment for AMD management. A combination of supplements has been demonstrated to decrease the course of this illness, and direct reduction of VEGF locally is the cornerstone therapy for CNV. Several clinical trials have been filed to investigate treatment possibilities for geographic atrophy, nevertheless, no clear findings have yet been reported. Likewise, there is no beneficial therapy for the prevention or reversal of subretinal fibrosis in AMD.[76]

AMD-RELATED DISEASES (AMDRD)

Earlier studies have connected the pathophysiology of AMD to both adaptive and non-specific immune responses, suggesting that this condition could be an autoimmune disease. Autoantibodies against phosphatidylserine (PS) and carboxyethylpyrrole (CEP) adducts have been identified in AMD patient sera, as well as T-helper cell-associated cytokine production in peripheral blood mononuclear cells.[77] Also, mice immunized with CEP-adducted mouse plasma albumin developed pathologies comparable to that of dry AMD, demonstrating that this degeneration is partially mediated by the adaptive immune system.[78] Bearing in mind that there are certain similarities between AMD and autoimmune illnesses, research has been conducted to determine the prevalence of psoriasis, arthritis, and systemic lupus erythematosus (SLE) among AMD cases. In addition, the immune system may link AMD with non-autoimmune disorders that are closely associated with inflammation (i.e., cardiovascular issues, malignancies and diabetes).

1. Autoimmune diseases and correlation with AMD

1) Psoriasis: Males with a history of psoriasis were shown to have a higher frequency of wet AMD, however no correlation was seen in the female patient population. This disparity between two genders might be connected to prior research indicating that more men are prescribed biologics for the management of psoriasis, indicating a greater disease severity among men. Noticeably, the use of biologics was not included in the latter.[79]

2) Rheumatoid arthritis and systemic lupus erythematosus: Sufferers of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are predominantly female. In a research study utilizing linked hospital episode data from the English National Health Service, individuals with a history of RA had a 1.15 (95% CI, 1.12-1.19) greater probability of being diagnosed with AMD. SLE patients, like arthritic patients, were discovered to be related with AMD. Using reviewed clinical records from the General Practice Research database (GPRD), this was discovered with an odds ratio (OR) of 1.53 (95% CI, 0.95-2.47) between SLE cases and unspecified AMD.[80]

3) Rheumatoid arthritis and intestinal microbiota: A current study also indicates that gut microbes play a role in inflammatory diseases. Compared to healthy persons, newly diagnosed RA patients have increased intestinal microbiota, Prevotella copri, whereas Bacteroides, which is beneficial, is decreased. Comparable to people suffering RA, evaluation of the intestinal microbiota of AMD cases revealed an increase in Prevotella relative to cases without AMD. As microbiota are associated with chronic inflammatory status, our findings imply a function for systemic inflammation in the progression of AMD.[81]

2. Non-autoimmune diseases and AMD

1) Diabetes: Diabetes and AMD risk correlation has been studied as well. Evidently, diabetes causes a buildup of advanced glycation end products and elevated oxidative stress, two factors also associated with the etiology of AMD. A meta-analysis demonstrated a marginal risk for wet AMD (OR 1.10; 95% CI, 0.96-1.26) and an elevated risk in individuals with geographic atrophy (OR 1.58; 95% CI, 0.96-3.99).[82]

2) Hematological cancers: Myeloproliferative neoplasms have been shown to be interconnected with an elevated risk of (AMD) in a large cohort from the Danish National Patient Registry. Myeloproliferative neoplasms are also connected to persistent systemic inflammation, with data suggesting a role for an increased complement response and altered nuclear factor erythroid 2-related transcription signaling.[83] Since such components also have a role in the etiology of AMD, reports provide more evidence about the impact of chronic inflammation in the formation of this illness.

3) Cardiovascular disease: It is noteworthy that numerous protein complexes seen in atherosclerotic plaques are also present in the drusen of AMD cases. The results of studies examining whether cardiovascular conditions are possible factors for AMD development are contradictory. A systematic review reported that a total risk ratio (RR) of 1.18 (95% CI, 0.98-1.43) was found in various investigations, representing an augmented risk of AMD among cardiovascular patients. In contrast, another report by Cugati et al.[84] and colleagues did not concur with those findings (RR 0.75; 95% CI, 0.47-1.17). Similarly, coronary heart disease related with AMD was associated with an overall risk ratio of 1.17 (95% CI, 0.94-1.45),[85] although an individual analysis utilizing the Multi-Ethnic Study of Atherosclerosis (MESA) did not reveal a significant risk ratio of 1.01 (95% CI, 0.73-1.44).[86] Recent data from the European Eye Epidemiology (E3) collaboration under the European EYE-RISK project might be helpful for understandingsuch disparities.

4) AMD and dyslipidemia: Notably, SLE and RA are both linked with elevated pro-inflammatory HDL levels. HDL is hypothesised to give an advantageous protective anti-inflammatory effect under normal conditions, but to become proinflammatory in the presence of an enhanced non-specific immune response.[87] The results of the European Eye Epidemiology (E3) consortium within the European EYE-

RISK project indicate that elevated levels of HDL are correlated to larger drusen areas and an augmented risk of AMD development (OR 1.25; 95% CI, 1.14-1.29), and contrarily, elevated content of tryglycerides are correlated to smaller drusen sizes and a decreased risk of AMD (OR 1.14; 95% CI, 1.14-1.29). In contrast, HDL has a preventive impact against atherosclerosis;[88] therefore, it is probable that discrepancies in the relationship between AMD and cardiovascular disease did not adequately account for the HDL plasma level, phase of AMD, or prescription of cholesterol-lowering statin medicines.

TREATMENT OF AMD

1. Anti-VEGF medications and other anti-VEGF therapies

An effective therapy for nAMD relies on the suppression of a promoter of angiogenesis, VEGF, a factor generated in the retina and stimulated by many different means, mainly hypoxia. VEGF enhances retinal vascular permeability and encourages the formation of new blood vessels. The first anti-VEGF medicine applied in clinical trials for nAMD was the aptamer pegaptanib sodium, which adheres to VEGF. Ranibizumab is an antibody fragment that adheres to all VEGFA isoforms.[89] It has been utilized in the pivotal phase III trials MARINA[90] (for occult choroidal neovascularisation) and ANCHOR[91] (for classic choroidal neovascularisation) that resulted in the extensive application of ranibizumab for the nAMD control. Bevacizumab, another antibody that adheres to all isoforms of VEGFA, was first offered as an intravenous treatment for AMD and was later used intravitreally off-label. The Comparison of AMD Treatment Trials (CATT)[92] in the United States evaluated ranibizumab with bevacizumab in the management of nAMD and demonstrated comparable visual acuity results. The Inhibition of VEGF in Age-Related Choroidal Neovascularisation (IVAN) trial[93] in the United Kingdom demonstrated effects comparable to CATT, and the findings were validated by more clinical trials and a systematic study as well.[94] Worldwide, practitioners continue to manage this illness off-label using bevacizumab, for it is the significantly smaller cost of ranibizumab and what looks to be an equal successful rate.[95] Aflibercept, a recombinant protein including the binding domains of VEGF receptors 1 and 2, is of the recent significant novel chemicals to be applied in clinic on a global scale.[96] Aflibercept inhibits all VEGFA and VEGFB isoforms, as well as placental growth factors, the latter is yet to be considered useful. The VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW) trials showed that intravitreal aflibercept administered bimonthly after loading was comparable to monthly ranibizumab in terms of visual acuity gains and fluid resolution.[97] In several optical coherence tomography compartments (intraretinal, subretinal, sub-retinal pigment epithelium), fluid resolution was accomplished in a somewhat greater proportion of patients with 4-weekly aflibercept than with 8-weekly aflibercept after one year. These results are consistent with the medical findings that the majority of cases treated with aflibercept could possibly be prolonged with bimonthly treatment. For nAMD, the outcomes of clinical studies covering intravitreal treatment with conbercept or brolucizumab have been described previously.[98,99] The phase II trial85 of conbercept revealed comparable or better visual acuity improvements and injection frequency compared to the CATT study's ranibizumab. In phase II studies, brolucizumab was superior to ranibizumab, indicating potentially longer treatment periods than ranibizumab.[99] Brolucizumab also showed superior fluid resolution compared to aflibercept.[98] In a study on this matter, authors hypothesized that targeting the receptors of both platelet-derived growth factor (PDGF) and VEGF in tandem might impede the creation of pericyte scaffolds, hence enhancing the suppression of choroidal neovascularization. A number of clinical trials evaluated whether this dual antagonism may enhance the prognosis of nAMD against anti-VEGF monotherapy. In Phase IIb studies of the PDGF antagonist pegpleranib, combination treatment (pegpleranib+ranibizumab) showed a 62% larger incremental effect than anti-VEGF monotherapy.[100] Nonetheless, two phase III trials revealed no visual or structural advantage of combination treatment over ranibizumab therapy alone.[100]

1) Dosing regimens: After early loading phases of anti-VEGF treatment, the optimal maintenance regimen has been a topic of controversy. Although the early MARINA[90] and ANCHOR[91] studies declared monthly anti-VEGF therapy was required to preserve vision, the CATT[92] and IVAN[93] trials demonstrated monthly therapy was linked to merely marginally healthier end results compared to aggressive as-needed regimes requiring about eight injections through the first 24 months. Later studies of ranibizumab demonstrated optimal results for as-needed regimes, with 7-9 letter gains at 24 months from an average of 13-3 injections.[101] This research also revealed while the majority of patients responded favorably after three months, around one in eight individuals responded later. In addition to monthly and as-needed approaches, treat-and-extend regimes, the methods that combine scheduled therapy with flexibility of therapy intervals based on both visual and anatomic results, have gained popularity and are now the standard for anti-VEGF treatment in nAMD globally, mainly in the United States of America and Australia. The Lucentis Compared to Avastin Study (LUCAS) utilized a treat-and-extend regime and reported favourable 24-month results by about nine doses per year.[102] Following the findings of poor long-term results from as-needed regimes in several countries, treat-and-extend regimes are beginning to be substituted for the as-needed regimens commonly used in the UK97 and in other places.[103] In a seven-year follow-up of 65 patients who participated in a pivotal study of nAMD, 37% had visual acuity of 6/60 or lower.[104] In CATT study, after five years, such individuals were 20% plus the average visual acuity was three letters worse than at the start.[105] In a multicenter analysis of approximately 93,000 injections for nAMD in 11,000 patients, after 24 months of as-required

therapy, visual acuity improved to 56 letters (baseline 55) and decreased to 53 letters (−2 below baseline) after 36 months.[103] The average number of ranibizumab treatments fell from 5.7 in the first year to 3.7 in the second and third years, and baseline visual acuity was a significant predictor of results. 100, 16% of eyes, evaluated in the research were second-treated ones, where therapy began with improved baseline visual acuity (average 65 letters, near to driving-standard vision) and prolonged healthier vision than first-treated eyes for 36 months or even longer periods.[106] Involvement of the second eye was found in around 14% of AMD cases every year for colleague eyes with a baseline visual acuity of 6/60 or healthier conditions; for eyes with a baseline visual acuity of 6/18 or healthier, second-eye involvement was 50% after 36 months. Furthermore, the statistics imply that it is necessary that nAMD be discovered quickly, while vision is quite satisfactory since current vision is the most accurate predictor of eventual vision. Undertreatment of other eyes with nAMD is predictive of future vision loss.[107]

2) Population impact: In Denmark and Scotland, the incidence of blindness secondary to AMD has decreased considerably (about 50 percent) since the advent of anti-VEGF medication.[108,109] The United Kingdom AMD Electronic Medical Record System (EMR) Users Group found a cumulative rate of new blindness (worse than 6/60 in the treated eye) of 5% at 12 months, 9% at 22 months, 12% at 36 months, and 16% at 48 months among patients undergoing as-needed anti-VEGF medication.[110] These statistics were significantly lower than those previously mentioned in an investigation of the normal history of untreated nAMD. Additionally, the EMR Users Group research[110] discovered that the cumulative incidence of new visual loss was 30% at 12 months, 41% at 22 months, 49% at 36 months, and 54% at 48 months, indicating that there is much room for enhancement of the results. Complementary studies reveal that undertreatment of nAMD is common. AURA calculated that receiving a minimum of 5.1 ranibizumab treatments was required to maintain visual acuity from baseline to 12 months, and additionally, receiving more treatments (8.3 injections) was required to preserve visual acuity from months 12 to 24.[111] Overall, 5.4 injections were administered on average in year 1, but only 4.5 in year 2. Consequently, the total count of injections required to preserve sharpness was more than that generally delivered in AURA. A study conducted[112] by ranibizumab and aflibercept in treatment-naive individuals suffering nAMD who had comparable baseline features and generally decent beginning vision. In both groups, the mean numbers of injections (8.1 for ranibizumab and 8.0 for aflibercept) and clinic visits were comparable, as were the 1-year increases (+3.7 letters and +4.3 letters).

2. Management of subtypes of neovascular AMD

Individuals who deal with occult (MARINA) and classic (ANCHOR) choroidal neovascularisation lesions participated in the pioneering anti-VEGF studies for AMD.[90] Although antiVEGF medication is evidently helpful for choroidal neovascularisation, the data for its effectiveness in other subtypes of AMD, is less compelling. The 12-month results of therapeutic studies for polypoidal choroidal vasculopathy may provide light on these difficulties. The EVEREST I and II studies compared ranibizumab monotherapy with ranibizumab combined with verteporfin photodynamic therapy and reported comparable visual acuity results, but better histological findings including a higher proportion of eyes with complete regression of polyps (78% vs. 29%) and fluid-free retina in cases whom were injected with combination therapy.[113,114] However, the PLANET study revealed that aflibercept monotherapy was equivalent to aflibercept with rescue photodynamic treatment in aspects of eyesight improvement and inactive polyps (81.7% and 88.9%, respectively).[115] More than 85 percent of patients injected with intravitreal aflibercept monotherapy had improved visual or functional results, according to the PLANET study.[115] The photodynamic therapy accompanying intravitreal aflibercept injection led to no improvement in visual outcomes; however, due to the low sample size meeting the criteria for a suboptimal response to receive photodynamic therapy, the effects of adding photodynamic therapy for polypoidal choroidal vasculopathy could not be determined by one study hence more studies are needed to clarify this matter.

3. Treatment of geographic atrophy

It is believed that atrophic AMD (geographic atrophy, GA) accounts for 20% of legal blindness (20/200 or worse in the better eye) in the United States. GA often impairs driving vision as well as the abilities of reading and recognition of faces when it affects the foveal centre. On the other hand, visual acuity does not correspond well with the level of GA due to the fact that the fovea might be protected or encircled for lengthy durations. Consequently, the application of standard visual acuity as an outcome in different studies might not be a proper choice, since the research time might be excessively elongated due to the comparably slow progression of lesions in GA cases, especially in the early phases. Other medical objectives, such as enhanced recital indices,[116] GA growth characterised by fundus autofluorescence graphs, the optical coherence tomography index, and composite endpoints based on multimodal graphs, are now under investigation. Complement inhibition has been found as a promising possible therapy for AMD.[117] In phase 2 and phase 3 clinical studies, drugs interrupting the complement cascade, including aseculizumab and lampalizumab, have been evaluated. In the MAHALO phase II trial,[118] lampalizumab therapy was associated with a 20% drop in GA area development and a 44% attenuation in CFI risk-allelic carriers. Nonetheless, outcomes from the phase III studies[5] revealed that lampalizumab did not diminish GA enlargement following 48 weeks of therapy compared to a placebo. Furthermore, in the COMPLETE study,[119] eculizumab had no influence on the development of GA. Other medicines, including tandospirone eye drops,[120] had

no influence on the course of GA. Tandospirone is a partial agonist of the 5-HT1A receptor, a process thought to play a possible neuroprotection role against CNS injuries comparable to GA.

CONCLUSION

In summary, major advances have been made in our understanding of prevention, diagnosis, and treatment of AMD over the past decades, and the findings suggest that AMD has a systemic component, where many different factors such as genetic, environment, autoimmune and non-autoimmune disorders are involved in this disease. On the other hand, healthy lifestyles, including regular exercise, maintaining a normal lipid profile and weight are critical to decreasing the risk of AMD. Furthermore, therapeutic strategies for limiting AMD should encompass a variety of factors to avoid and improve drug interventions, and also need to take into account personalized genetic information. As a result, with the development of technology and research progress, visual impairment and legal blindness from AMD have be substantially reduced in incidence. This review article is focused on identifying and developing the knowledge about the association between genetics, and etiology with AMD. We hope that this review will encourage researchers and lectureres, and also new discussions and contribute to a better understanding of AMD that improve patients' visual acuity, and upgrade the quality of life of AMD patients.

CONFLICT OF INTEREST STATEMENT

None declared.

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