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Correlating Factors of Eye Disease-Age related Macular Degeneration (AMD) with cardiovascular diseases (CVD)

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Abstract

The major reason behind permanent blindness in individuals over 50 is AMD. Studies in genetics, epidemiology, & molecular biology are starting to reveal complicated processes behind this illness, which link way of lipid factors to disease onset & progression pathophysiology. Numerous inherited & environmental threat elements for AMD also increase risk of other complicated age-related degenerative illnesses, such as CVD. This review provides epidemiological data linking AMD to many genes involved in cardiovascular symptoms, & pertinent environmental exposures. Age, smoking, hypertension, hypercholesterolemia, postmenopausal oestrogen usage, diabetes, & dietary consumption of lipids, alcohol, & antioxidants are all known risk factors for cardiovascular disease which have been linked to AMD. To create most personalised medical treatment for ageing persons, researchers must not only elucidate diverse contributions of these variables to AMD & also relationships between (b/w) AMD & CVD.

Keywords: *AMD, CVD, Hypertension, Retina, Cholesterol, Basic Metabolic Index, Antioxidants, Genetic factor*

1. Background

AMD is a slowly blinding condition for which there is now no solution. In its most severe forms, it renders a person incapable of doing everyday tasks including reading, identifying people, & driving. Patients who have cardiovascular risk factors can minimise their chance of experiencing adverse cardiovascular events by changing their lifestyle & using medicines. But, many people may not get proper diagnosis until they experience major incidents like myocardial infarction or stroke. Finding subclinical ischemia indicators can help doctors find people with hidden cardiovascular disease [1]. Retinal macular (central) area is most frequently impacted by AMD, a neurodegenerative condition. Eye diseases are related to cardiovascular diseases such as Retinal vascular occlusions are more likely to occur in people with cardiovascular disease. quantity & size of drusen, in addition to hyper- or hypo pigmentary alterations, & whether there is evidence of choroidal neovascularization, are used to classify a disease as early, moderate, or advanced. drusen deposits, which are lipid & protein-rich & accumulate b/w Bruch's membrane & RPE, are signs of early illness. Geographic atrophy (GA), a late stage, & early or intermediate phases are all collectively referred to as "dry AMD."A slow photoreceptor & central vision loss is caused by advanced GA stage, which is characterised by RPE & choroid loss in retinal macular region at least. CNV occurs when new BVs grow from choroid into typically avascular sub-RPE & sub-retinal areas, resulting in neovascular AMD [2]. Although neovascular AMD accounts for a tiny part of all AMD cases, it causes bulk of AMD-related blindness. A thorough ocular examination is necessary for accurate diagnosis & staging. This examination must include fundus imaging of retina to see signs such precipitation of drusen, degeneration & loss of RPE & neural retina, and/or exudative alterations in retina [3]. Fluorescein angiography, which shows blood vessels (BVs), is used to validate existence or absence of CNV

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during further imaging. To validate a diagnosis, one can also use other imaging methods like optical coherence tomography (OCT). With use of these data, doctors & researchers may classify progression using a common grading system; AREDS method, which assigns eyes a score b/w 1-4. Non-AMD eyes fall under class 1(AREDS1) designation in AREDS grading system. Class 2 (AREDS2) eyes are those with early AMD instances that only had a single little druse (also known as a "hard" druse) measuring less than 63 micrometres, an intermediate-sized druse measuring b/w 63 & 124 micrometres, and/or pigmentary alterations. Eyes in class 3 (AREDS3) comprise those with more widespread drusen, such as many intermediate drusen, GA without touching central macula, and/or min. 1 big druse >124 m ("soft" druse).The central macula and/or CNV are affected by GA in class 4 (AREDS4) eyes. Most current therapies for AMD are aimed at neovascular stage, after damage has been done, & they work by blocking production of vVEGFA utilising antibodies. These treatments produce stable to increased visual acuity in a limited patient ratio without requirement for ongoing care. However, most patients need ongoing care or show illness progression in spite of treatments [5].

With hope that they would ultimately enhance results & lessen burden of therapy on those who are afflicted, new therapies have been developed for wet & dry forms of disease. Devastating consequences of blindness may be mitigated with use of treatments that halt progression of illness from its earliest to its intermediate and/or advanced stages. Molecular mechanisms underlying aetiology and progression of AMD will need data from gene expression, epigenetic, molecular, biochemical, and genetic epidemiology studies. [6]. Discovering causes of illnesses that may have overlapping pathophysiology or that are comorbid with AMD may be possible by studying their interactions. Individual vulnerability to ARMD is influenced by a complex interplay of several genetic, environmental, and lifestyle variables. BMI, smoking, nutrition, and blood lipid and cholesterol levels are all epidemiological risk markers for AMD that may be enhanced. However, factors; sex, ethnicity, and age, as well as genotype at a given risk locus are now fixed. This review study emphasises relationship b/w eye diseases & prevalent risk factors for cardiovascular illnesses, such as smoking, nutrition, & insufficient exercise, lipid metabolism, cholesterol which also contribute to pathogenesis of AMD.

2. Pathogenesis of AMD

One hypothesis suggests that severe neovascular AMD develops when a buildup of drusen cuts off blood flow to retinal pigment epithelium (RPE) & choroidal macula (Mac)[7]. Hypoxia stimulates synthesis of VEGF & other pro-angiogenic proteins, which in turn promote development of new blood vessels. However, there is more evidence than can be accommodated by this model indicating significance of local inflammation, complement activation, oxidative stress (OS), & lipid homeostasis in pathogenesis of AMD. According to one theory, abnormal lipid inflow into & outflow from RPE causes development of drusen deposits [8]. composition & buildup of drusen also seem to be similar toatherosclerotic plaques. However, precise molecular origins of AMD pathogenesis are still unknown. Despite fact that candidate genes, GWAS, & epidemiological research have connected lipid metabolism-cholesterol pathway to pathogenesis of AMD, function is ambiguous & occasionally contradictory.

2.1Drusen buildup & development of atherosclerotic plaque

The characteristic lesions of AMD are drusen. size & quantity of drusen deposits often indicate severity of disease & likelihood that it may proceed to an advanced stage.Studies examining makeup of drusen have shed light on mechanisms involved in drusenogenesis & shown similarities with other degenerative processes including creation of atherosclerotic plaque. Bruch's membrane & RPE

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function similarly to blood brain barrier in that they enable nutrients & oxygen to cross from choroidal blood supply into retina.In conclusion, drusen proteins seem to originate from choroidal cells & serum, whereas drusen lipid components appear to originate mostly from RPE & photoreceptors & choroidal blood supply. In contrast, lipids, proteins, & lipoproteins that make up fatty atherosclerotic plaque lesions are derived from circulatory system. In addition, drusen & atherosclerotic plaques have many of same pathological features. These components include calcium, apolipoproteins, esterified & unesterified cholesterol, MMPs, amyloid (beta, P), & complement components like VTN & complement component 3 (C3). After noticing similarities b/w drusen & atherosclerotic plaques about 20 years ago, Dr Friedman established "hemodynamic model" of AMD, which he refined over subsequent ten years [9].This model detailed parallel pathways that lead from lipid accumulation in sclera & Bruch's membrane to CNV & atherosclerotic plaque formation. According to Friedman's hypothesis, scleral lipid deposition increases scleral stiffness & choroidal vascular resistance, which in turn reduces choroidal blood flow & raises choriocapillary pressure, resulting in CNV [10]. Elastin, collagen, basal deposits, & drusen all degenerate along with lipid accumulation in Bruch's membrane. Degeneration of elastin & collagen causes calcification, fracture, overexpression of VEGFA, & eventually CNV. According to this theory, first stage in course of disease is accumulation of lipids. However, this model suggests that drusen deposits themselves cause RPE atrophy rather than CNV & are not cause of development of neovascular illness. More research into roles of chronic inflammation, endothelial dysfunction, & OS in AMD & atherosclerosis has shifted focus away from viewing these diseases solely as lipid-deposition disorders. In a recent review, it was revealed that pathologic lipid buildup in AMD causes immune system activation [11]. Previous research suggested that collection of sub-retinal deposits is a natural part of ageing process & becomes pathogenic when normally regulated, healthy inclusion of complement system is disturbed (possibly due to OS), uncontrolled, & thereby helps cause cellular harm & death. Although it has not been demonstrated that build-up of drusen deposits causes advancement of pathological illness, it does precede it. Similar to how dyslipidemia, hypertension, or pro-inflammatory cytokines are considered to interact with alterations in artery endothelial cell lining to cause atherosclerotic plaques, agents, encourages build-up of LDL-C particles & additional immunological involvement, which in turn causes smooth muscle migration, plaque destabilisation, & finally thrombosis.

3. Prevalence of AMD with Cardiovascular Diseases

White Europeans who are non-Hispanic & do not identify as European have highest disease burden. Recent population-based research has been combined into a meta-analysis spanning many ethnic groups, researchers showed that among people aged 45 to 85, AMD prevalence was greatest within people with European ancestry, rising from 12.3% to 30% as one became older [12]. disease burden is remains quite high among Hispanics (10.4%), Africans (7.5%), & Asians (7.4%), despite a minor decline. Despite fact that evidence suggests that incidence of AMD varies by race and ethnicity, it is less clear how genetic variations, environmental exposures, & their interactions contribute to determining AMD susceptibility.

4. Correlation with cardiovascular health epidemiology

Numerous recent researches have examined connection b/w incidence of AMD & cardiovascular-related disorders, often yielding seemingly contradicting results. Over time, researchers have used a wide range of approaches to learn more about links b/w AMD phenotypes & cardiovascular diseases & risk factors. Smoking & advancing age are well-known contributors to CVD & age-related macular degeneration. Research revealing epidemiological relationships b/w AMD phenotypes & other CV risk factors will be highlighted in sections that follow. Range of CV-associated & AMD phenotypes

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utilised to reflect threats or results, as well as challenge of obtaining solid AMD phenotypes, are complicating considerations in these investigations.

Different AMD phenotypes have been inconsistently linked to various CVD outcomes like coronary heart disease/coronary artery disease, myocardial infarction/heart attack, & angina. According to findings from EDCCS Group & other investigations, there is no correlation b/w AMD & cardiovascular disease [13]. A 2004 analysis of a combined data set from BDES, BMES, & Rotterdam Study concentrating on incident GA, neovascular AMD, & any late AMD. Several significant associations were found b/w AMD & specific research groups, but in aggregated dataset, there was no significant association b/w AMD & a history of MI [14]. Despite this, several additional studies have shown important links b/w AMD & CVD, including links b/w different AMD subtypes & symptoms & CV outcomes in various ethnic groups. Research studies revealed that significant associations b/w AMD & a history of CVD. ARCS found a substantial correlation b/w incidence CHD & late AMD in a group at high risk for CHD [15]. In CVHS, a group of white & black Americans, early AMD was associated with a greater prevalence of CHD. researchers discovered that participants with late AMD had an elevated threat of CVD even in cases where they restricted their analysis to prospective trials. Age, smoking, hypertension, hypercholesterolemia, postmenopausal oestrogen usage, diabetes, & dietary consumption of lipids, cholesterol, alcohol, & antioxidants are all known risk factors for cardiovascular disease which affect eye diseases are discussed in following section.

4.1 Lipid Metabolism

This is one of risk factors of CVD which affect AMD. Genetic evidence b/w AMD with lipid metabolism-cholesterol pathway first emerged in candidate gene & subsequent GWAS studies. In addition to previously discovered genes with genome-wide significance, research uncovered genes involved in lipid pathway, such as ABCA1, ABCA7, APOC2, APOC4, & PLTP; complement pathway VTN gene; & angiogenesis-associated MMP9 gene [15]. first gene to be linked to a single subtype of AMD is MMP9, which has been explicitly proven to be connected with neovascular subtype. GWAS has previously demonstrated that a number of additional lipid-associated pathway genes, such as those encoding APOE, CETP, & LIPC, are associated with AMD. Several candidate gene studies have also linked other genes involved in lipid metabolism to disease. These include RORA, ROBO1, LPL, LDL LRP5, LRP6, VLDLR, FADS1-3, & ADIPOR1. varied nature of AMD, variety of populations, & necessity for more stringent & standardised phenotyping within large, multi-centre cohorts necessary for genome-wide analysis may all be factors in lack of genome-wide important relationships for candidate genes. Given investigation determined lipid pathway genes, such as ABCA1, ABCA7, APOC2, APOC4, & PLTP, in addition to previously identified genes with genomewide significance. complement pathway VTN gene; & MMP9 gene associated with angiogenesis. MMP9 was found to be specifically associated with neovascular subtype of AMD, making it first gene to be linked to a particular AMD subtype. Other lipid associated pathway genes, including as those encoding APOE, CETP, & LIPC, have also been linked to AMD by GWAS in past. In reality, several genes; ABCA1, ABCA7, APOE, CETP, LIPC, & MMP9, have been linked to AMD via molecular or candidate gene research. Other lipid metabolism genes, including those for RAR RORA, ROBO1, LPL, LRP5, LRP6, VLDLR, FADS1-3, & ADIPOR1, have also been linked to disease involvement in several candidate gene studies. When all types of AMD were considered, PAGE study found that Mexican, Asian & African Americans, & non-Hispanic White Europeans appear to have different AMD risk with regard to lipid metabolism & cholesterol-related genes. In

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fact, after correction for multiple testing, no big threat version for AMD, such as HTRA1, ARMS2, or CFH, were important in non-white European populations. However, this was likely because of study's small sample size. lipid metabolism-cholesterol pathway is linked to AMD pathogenesis in GWAS & epidemiological research; however exact involvement is still unclear & sometimes contradictory. Further research must be put into figuring out population-specific molecular mechanisms that may affect way that each patient responds to therapeutic interventions & how disease develops, given variations in AMD genetics, prevalence, & pathology that exist within & among ethnic populations. In order to simulate some of these genes in vivo, transgenic & knockout animal models of ABCA1, ABCA7, APOE, CETP, LIPC, MMP9, & PLTP have been developed.

4.2 Stroke

In a cohort of 1.3 million Medicare adults without significant CVD at baseline, considerable associations were found b/w AMD, neovascular AMD, & non-neovascular AMD & incident stroke; ischemic & hemorrhagic stroke [16]. Based on further data from BMES, patients with late AMD had a tenfold rise in stroke mortality relative to controls lacking AMD among patients 75 years of age, yet not in patients < 75 yrs [16]. It was challenging to understand connections discovered b/w several AMD phenotypes & particular stroke diagnostic characteristics since they differed from research to study, much as phenotypes previously described.

4.3 Hypertension

Decreased choroidal blood flow has been linked to onset of AMD, which is in turn linked to systemic hypertension, indicating that there may be systemic contributions to AMD's onset and/or progression [17]. Multiple studies have found strong correlations b/w AMD phenotypes & BP measurements. There is a lack of consistency in reported blood pressure measurements & other cardiovascular parameters in these studies. Correlation b/w hypertension & AMD is complicated by fact that hypertension status might alter during a person's life.

4.4Triglycerdides Level, phospholipids

The EDCCS Group consortium reported in 1992 - higher serum cholesterol levels were substantially linked with an increased incidence of neovascular AMD. Later research revealed conflicting results on association b/w blood cholesterol & triglyceride levels & AMD, similar to other cardiovascular disorders. [18]. A strong correlation b/w dietary cholesterol, high HDL levels, & neovascular AMD was found by AMD Risk Factors Study Group. Biracial CVHS found a big correlation b/w initial AMD & reduced total serum cholesterol.

4.5 Obesity, Basic Metabolic Index & bodily activity

Many studies examined associations b/w phenotypes associated with AMD & weight & physical activity. findings of connections b/w AMD & weight/activity measurements have been conflicting, much like data given for other cardiovascular risk factors. Given that physical activity & weight are controllable traits, further study is needed to understand connection b/w these two factors & AMD [19]. Due to these features' wide range during a person's lifespan, it is more difficult to assess correlations b/w weight/activity metrics & illness condition. If these variables are shown to affect AMD onset and/or progression, however, they might be targeted in order to slow or stop disease.

5. Prevention of AMD

5.1 Utilisation of antioxidants & other dietary supplements

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OS has been related to development & progression of AMD & CVD. Antioxidants such as docosahexaenoic acid & eicosapentaenoic acid, and the macular xanthophylls lutein and zeaxanthin, have been investigated for their potential use in preventing the progression of age-related macular degeneration [20]. High concentrations of essential nutrients lutein & zeaxanthin are present in mammalian retina.

5.2 Statin Application

AMD protection by statin (HMG-CoA reductase inhibitor) therapy was first shown in 2001. In a similar vein, research published in 2005 found a substantial prospective link b/w statin use & reduced rates of CNV, while research published in 2004 found a significant retrospective correlation b/w statin consumption & reduced rates of ARMD. But, further look into connection b/w statin usage & AMD have been uniformly unfavourable.

6. Conclusion

It comes to reason that not all disease contributions are shared b/w cardiovascular diseases & AMD, given their complexity & variability. Given wealth of epidemiological evidence for shared genetic & environmental risk factors across these illnesses, as well as parallels b/w them at molecular level, it would seem that these two sets of contributors overlap significantly. Defining biochemical, physiological, & pathological roles of each of components described below in genesis & progression of AMD is crucial for understanding this potentially blinding disorder. Understanding underlying biological factors that contribute to illness progression, such as epigenetic factors (DNA methylation or histone changes), can also help to create better treatment interventions. These investigations are essential for expanding existing knowledge beyond only identifying illness associations to uncovering fundamental cause & effect linkages that underlie disease, allowing for appropriately focused therapeutic intervention.

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