ABSTRACT

Dyslipidemia refers to an abnormal amount of lipid in the blood, and the total cholesterol level is defined as the sum of high-density lipoprotein cholesterol, low-density lipoprotein (LDL) cholesterol, and very-LDL cholesterol concentrations. In Korea, the westernization of lifestyle habits in recent years has caused an increase in the incidence of dyslipidemia, which is an important risk factor of cardiovascular disease (CVD). Several studies have been conducted on how dyslipidemia affects not only CVD, but also chorioretinal diseases such as age-related macular degeneration (AMD) and diabetic retinopathy. Recently, a pathological model of AMD was proposed under the assumption that AMD proceeds through a mechanism similar to that of atherosclerotic CVD. However, controversy remains regarding the relationship between chorioretinal diseases and lipid levels in the blood, and the effects of lipid-lowering agents. Herein, we summarize the role of lipids in chorioretinal diseases. In addition, the effects of lipid-lowering agents on the prevention and progression of chorioretinal diseases are presented.

Keywords: Age-related macular degeneration; Cholesterol; Diabetic retinopathy; Lipids; Hypolipidemic agents

INTRODUCTION

Since 2015, Korean Society of Lipid and Atherosclerosis has published “Dyslipidemia Fact Sheets in Korea” based on the Korea National Health and Nutrition Examination Survey conducted by the Ministry of Health and Welfare and the Korean Centers for Disease Control and Prevention. According to the “Dyslipidemia Fact Sheets in Korea, 2018,” the prevalence of elevated levels of low-density lipoprotein (LDL) cholesterol, hypertriglyceridemia, and reduced levels of high-density lipoprotein (HDL) cholesterol among adults aged 30 years or older is 17.6%, 17.5%, and 19.4%, respectively.¹ The above results show a decrease in hypertriglyceridemia, a decrease in hypo-HDL-cholesterolemia, and an increase in hyper-LDL-cholesterolemia compared to a report published in 2015. Because dyslipidemia is recognized as a prominent risk factor for cardiovascular disease (CVD),² current guidelines focus on lowering LDL cholesterol levels through statins in both primary and secondary intervention settings.³,⁵
Conflict of Interest
The authors have no conflicts of interest to declare.

Author Contributions
Conceptualization: Park DH; Data curation: Park DH; Formal analysis: Park DH; Methodology: Park DH; Resources: Park SJ, Park DH; Supervision: Park DH; Validation: Park DH; Writing - original draft: Park SJ, Park DH; Writing - review & editing: Park SJ, Park DH.

The retina, a structure composed of the neurosensory layers in the eyes, is a highly metabolic tissue, and lipid metabolism plays a critical role in maintaining the homeostasis of various kinds of cells. Previous studies have reported the role of lipids in various chorioretinal diseases, including diabetic retinopathy (DR) and age-related macular degeneration (AMD), although some controversies remain.

In this review paper, we discuss the associations between lipids and various chorioretinal diseases and present an evaluation of whether lipid-lowering agents could affect disease progression or prevention.

BACKGROUND

1. Cholesterol and lipoproteins
Cholesterol plays many diverse roles in the body, including serving as a contributor to the structure of cell membranes, a precursor for steroid hormones, a regulator of gene transcription, and a component involved in the formation of neuronal synapses. For lipid transportation through the systemic circulation, lipoproteins are required. Lipoproteins are complex plasma particles that include a core composed of cholesterol esters and triglycerides (TG) and a surface composed of apolipoproteins, phospholipids, and unesterified cholesterol. According to their size, structure, and apolipoprotein content, lipoproteins are classified as chylomicrons, very-LDLs, intermediate-density lipoproteins, LDLs, HDLs, and lipoprotein (a).

2. Distribution of cholesterol in the retina
The retina consists of 10 layers, from its internal limiting membrane to the retinal pigment epithelium (RPE). In addition to retinal vessels, the choroidal vasculature, which is connected to the systemic circulation, supplies the blood to the retina, especially outer the retina. To achieve physiological structure and function, the retina receives cholesterol from endogenous biosynthesis and the systemic circulation across the RPE.

For lipid transportation, the RPE rapidly takes up lipoproteins from the systemic circulation, and it contains receptors for LDL (e.g., LDL-R) and HDL (e.g., SR-BI and SR-BII) on the basolateral side, which contacts the choroid.

AMD

1. AMD specific lesions: drusen and basal linear deposits (BLinDs)
AMD is the most common cause of blindness in developed countries and accounts for 8.7% of all cases of blindness worldwide. In AMD, central vision is gradually reduced by changes in the macular region of the retina. According to the Beckman classification, AMD is classified into early, intermediate, and late AMD. Early AMD is diagnosed based on the presence of medium-sized drusen (>63 and ≤125 μm) and no retinal pigmentary abnormalities (hyperpigmentation or hypopigmentation). Intermediate AMD is defined as the presence of large drusen (>125 μm) and/or any pigmentary abnormalities. Late AMD is defined by geographic atrophy (GA) or neovascular AMD. Neovascular AMD is characterized by choroidal neovascularization (CNV), and GA is characterized by a sharply defined area of RPE degeneration in which the choroidal blood vessels are visible. Drusen are focal, dome-
shaped lesions between the RPE basal lamina and the inner collagenous layer of Bruch’s membrane (BrM) and are observed as yellow-white deposits on a fundus examination.\textsuperscript{22}

BrM, which is the basement membrane of the RPE, has unique characteristics in terms of cholesterol content and is relevant to AMD. As aging progresses, BrM thickens and develops basal deposits. Depending on its location, a basal deposit is classified as a basal laminar deposit (BLamD) or a BLinD. BLamD is considered as a stereotypically thickened area of the RPE basal lamina. BLinD is located in the sub-RPE space, bounded internally by the basal lamina and externally by the inner collagenous layer of BrM. Drusen and BLinD are 2 forms of an AMD-specific lesion, in the shape of a lump and thin layer, respectively.\textsuperscript{23-30} BLinD and soft drusen are considered to be alternative forms of the same entity because these lesions are located in the same plane and contain the same materials.\textsuperscript{31,32} Curcio and Millican\textsuperscript{32} reported that eyes with AMD were 24 times more likely to have BLinD and large drusen (>125 μm) than age-matched controls.

These lesions contain lipoprotein-derived particles that have the physical forms of cholesterol seen in the core of atherosclerotic plaques,\textsuperscript{33-35} a mark of atheroma maturity. The formation of AMD lesions has thus been considered to share mechanisms with the formation of atherosclerotic plaques.\textsuperscript{36,37} In atherosclerosis, trapped apolipoprotein B100 lipoproteins within the arterial wall initiate a cascade of pathological events, including innate immune system-mediated inflammation.\textsuperscript{38} This launches various downstream deleterious events, including macrophage recruitment, cytokine release, and neovascularization.

Similarly, in AMD, lipoprotein particles from multiple resources accumulate during aging. Those particles could fuse to form lipoprotein-derived debris such as soft drusen and BLinD. These processes may be accompanied by oxidative stress and inflammation, which contribute to the progression from non-neovascular AMD to neovascular AMD.\textsuperscript{39}

2. Serum lipids, cholesterol-lowering medication, and AMD

Since the early 1960s, the correlations of AMD with concentrations of plasma cholesterol or apolipoproteins have been evaluated.\textsuperscript{40} Several clinical studies of the associations between lipids and AMD are summarized in Table 1. Klein et al.\textsuperscript{41} reported that carotid artery intima-media thickness and carotid plaques had a weak relationship with the incidence of late AMD. The Eye Disease Case Control Study reported a 4-fold increased risk of exudative AMD in patients with high total cholesterol levels (≥6.749 mmol/L).\textsuperscript{42} Reynolds et al.\textsuperscript{43} reported lower mean HDL cholesterol levels and higher LDL cholesterol levels in patients with advanced AMD than in controls. In addition, high total cholesterol and LDL cholesterol levels were found to be related to an increased risk of AMD after adjusting for environmental and genetic covariates.

Several studies have investigated the relationship between the risk of AMD and a specific lipid profile, such as HDL cholesterol. van Leeuwen et al.\textsuperscript{44} reported that elevated HDL cholesterol levels increased the risk of AMD. Klein et al.\textsuperscript{45} reported that high serum HDL cholesterol levels were associated with GA, and that a high total cholesterol/HDL ratio was associated with the incidence of RPE depigmentation and GA. The Pathologies Oculaires Liées à l’Age study reported that high HDL cholesterol and apolipoprotein A1 were associated with an increased risk of soft drusen.\textsuperscript{46} A large clinical study with 1,235 patients in North America showed an interesting finding that only neovascular AMD was associated with high HDL cholesterol levels, while non-neovascular AMD was unrelated to serum lipid levels.\textsuperscript{47}
Table 1. Clinical studies of associations between lipid profiles and age-related macular degeneration

| References          | Study design | Disease phenotypes                                      | Lipid profiles                                      | Results                                                                                                                                 |
|---------------------|--------------|---------------------------------------------------------|-----------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Klein et al. 41      | Cohort study | No AMD, early AMD, late AMD                             | IMT and presence of plaque of carotid artery Angina, MI, stroke | Mean IMT was associated with the 10-year incidence of pure GA, but not exudative AMD. The number of sites with plaque was related to the incidence of late AMD, but not to early AMD. |
| van Leeuwen et al. 44| Cohort study | Neovascular AMD including both early and late            | Total cholesterol, LDL-C, HDL-C, TG                 | Higher total cholesterol and LDL-C were associated with increased risk of AMD.                                                         |
| Klein et al. 45      | Cohort study | Early AMD, late AMD, progression of AMD                 | Total cholesterol, HDL-C                             | Higher HDL-C at baseline was associated with pure GA. A higher serum total cholesterol-to-HDL-C ratio was associated with the incidence of RPE depigmentation, pure GA, and late AMD. |
| Delcourt et al. 46   | Cohort study | Soft drusen, pigmentary abnormalities, late AMD          | Total cholesterol, TG, apolipoprotein A1, apolipoprotein B | High concentrations of HDL-C and apolipoprotein A1 were associated with an increased risk of soft drusen.                                 |
| Hyman et al. 47      | Case-control study | Neovascular AMD, non-neovascular AMD                  | Total cholesterol, HDL-C, TG, total cholesterol/HDL-C ratio | Neovascular AMD, but not non-neovascular AMD, was associated with elevated HDL-C.                                                        |
| Abalain et al. 49    | Case-control study | Early AMD, large soft indistinct drusen, large drusen area, any pigmentary abnormality, late AMD, pure GA, exudative AMD | Total cholesterol, HDL-C, phospholipid, TG, apolipoproteins | No differences in total cholesterol, TG, phospholipids, HDL-C, LDL-C were observed between AMD and controls.                             |
| Klein et al. 50      | Meta-analysis | Early AMD, large soft indistinct drusen, large drusen area, any pigmentary abnormality, late AMD, pure GA, exudative AMD | Total cholesterol, HDL-C, non-HDL-C, total cholesterol/HDL-C ratio, Statin use, lipid pathway genes | There were no associations between serum lipids, history of statin use, or lipid pathway genes and the incidence or progression of AMD. |

AMD, age-related macular degeneration; APOE, apolipoprotein E; GA, geographic atrophy; HDL-C, high-density lipoprotein cholesterol; IMT, intima-media thickness; LDL-C, low density lipoprotein cholesterol; RPE, retinal pigment epithelium; TG, triglycerides.

However, other epidemiological studies have not reported an association between serum lipid profile and AMD risk. 46-49 The discrepancies in results among previous studies could be due to the different lipid profiles that were analyzed or the diverse clinical characteristics of the enrolled patients, such as different stages of AMD.

Several studies have evaluated the effect of lipid metabolites in an in vivo model of CNV. The ω-3 and ω-6 long-chain polyunsaturated fatty acids (LCPUFAs) are 2 classes of essential fatty acids that have opposing effects. Metabolites generated by the cytochrome P450 (CYP)—epoxygenase pathway are potent modulators of inflammation and angiogenesis. Yanai et al. 50 reported that dietary supplementation with ω-3 LCPUFAs decreased CNV lesions in a mouse model of neovascular AMD. Furthermore, mice fed ω-3 LCPUFAs showed suppressed leukocyte recruitment and adhesion molecule expression in CNV. 50 Hasegawa et al. 51 reported that the CYP-derived lipid metabolites 17,18-epoxyicosatetraenoic acids and 19,20-epoxydocosapentaenoic acids play a vital role in alleviating CNV severity by regulating leukocyte recruitment and the inflammatory microenvironment in CNV lesions. Recently, the combined dietary intake of ω-3 LCPUFAs and lutein was found to attenuate CNV in an additive manner, which was related to suppression of inflammatory mediator production, reactive oxygen species generation, and NADPH oxidase 4 expression. 52

Regarding lipid metabolites from humans, Lains et al. 53 evaluated the plasma metabolomics profiles of AMD from 2 cohorts, including Boston in the United States and Coimbra in Portugal. Meta-analyses showed that 28 plasma metabolites differed between patients with...
AMD and controls and most of the significant metabolites were lipids. In particular, the metabolites mapping to glycerophospholipid pathways were altered in AMD subjects. Li et al. also stated that the glycerophospholipid pathway was one of the most significant pathways in their study group of polypoidal choroidal vasculopathy, a subtype of neovascular AMD.

Statins, which are 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, have been used to control blood cholesterol levels. In AMD, statins have several potential effects such as preserving the blood supply to the outer retina, downregulation of LDL cholesterol and peroxidized lipids, and anti-inflammatory properties. Previous studies evaluated whether cholesterol-lowering agents have a therapeutic effect on AMD, although the results are inconsistent. Vavvas et al. reported that high-dose statins (80 mg of atorvastatin daily) may result in the regression of drusenoid pigment epithelial detachments and a vision gain of 3.3 letters, without progression to advanced AMD such as GA or CNV. Barbosa et al. suggested a possible beneficial effect of statin intake for the prevention of AMD in individuals 68 years or older. Guymer et al. also reported a decrease in the risk of progression in the simvastatin group, and the most prominent effect was observed in individuals who were homozygous for the at risk C allele at Y402H of the complement factor H gene.

However, the effects of statins remain controversial. van Leeuwen et al. and Klein et al. did not find an association between statin use and the risk of AMD. In addition, a meta-analysis of 3 clinical trials showed no correlation between statin use and the incidence or progression of AMD.

**DR**

1. **Serum lipids, cholesterol-lowering medication, and DR**

DR, which is one of the most common microvascular complications of diabetes, is characterized by retinal hemorrhage and yellowish retinal exudates. DR is broadly classified into nonproliferative DR and proliferative DR (PDR) according to the presence of neovascularization of the disc or elsewhere, or vitreous hemorrhage. Diabetic macular edema is the most common cause of vision loss in patients with diabetes, and of particular note, the Early Treatment of Diabetic Retinopathy Study introduced the term “clinically significant macular edema” (CSME), which is defined upon slit lamp biomicroscopy as “1) thickening of the retina at or within 500 μm of the center of the macula; 2) hard exudate at or within 500 μm of the center of the macula associated with thickening of adjacent retina; or 3) a zone of retinal thickening 1 disc area or larger, any part of which is within 1 disc diameter of the center of the macula.”

Table 2 summarizes several studies that have been conducted on the associations between lipids and DR. Many studies reported risk factors for the development of DR, including the duration of diabetes, glucose control, and the presence of hypertension. The effect of fat intake on exudative maculopathy has been studied. Ernest et al. reported that retinal exudates decreased in 8 diabetic patients after consumption of a low-fat diet for 2–3 years. Several studies have suggested that serum lipids may cause the development of retinal exudates. Patients with diabetes who had severe exudative maculopathy demonstrated higher levels of serum TG than those with nonexudative retinopathy, although serum cholesterol levels did not differ between the 2 groups. A case-control study reported that patients with maculopathy tended to have higher mean serum HDL cholesterol and total cholesterol levels over 7 years, but the difference was not significant.
Several studies have reported that serum lipid levels were not associated with DR severity or the presence of macular edema. Cetin et al. reported that serum lipid levels were not correlated with DR severity despite their correlation with mean blood glucose and hemoglobin A1c levels. Klein et al. reported that there was no association between serum total cholesterol or HDL cholesterol levels and the incidence of PDR, or macular edema after adjusting for covariates.

Interestingly, however, some studies have reported that serum lipid levels were associated with CSME. Benarous et al. stated that although serum lipids were not associated with the presence and severity of DR, levels of serum lipids including total cholesterol, LDL cholesterol, non-HDL cholesterol, the LDL-to-HDL cholesterol ratio, and the total-to-HDL cholesterol ratio were independently associated with CSME after adjustment for traditional DR risk factors and lipid-lowering medications. Raman et al. also reported associations of serum lipids with CSME and non-CSME; specifically, high serum LDL cholesterol levels were related to non-CSME, and high serum total cholesterol levels were associated with CSME.

CSME, clinically significant macular edema; DME, diabetic macular edema; DR, diabetic retinopathy; ETDRS, Early Treatment Diabetic Retinopathy Study; HDL-C, high-density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; ME, macular edema; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; TG, triglycerides; VLDL-C, very-low-density lipoprotein cholesterol.
p-chlorophenoxyisobutyrate and androsterone, reduced serum cholesterol and TG levels in patients with ischemic heart disease.\textsuperscript{64} Duncan et al.\textsuperscript{85} reported that atromid only reduced the rate and extent of new exudate deposition in exudative DR, but did not improve visual acuity due to established exudates. Since then, statins and other lipid-lowering medications have been extensively studied as treatments for DR.

Statins reduced the risk of DR and reduced the number of patients who required laser photocoagulation treatment.\textsuperscript{86} Furthermore, statins decreased the cumulative incidence of DR.\textsuperscript{87} Denniston et al.\textsuperscript{88} reported that statins were associated with lower rate of diabetic vitreous hemorrhage at 1 year. However, Liinamaa and Savolainen\textsuperscript{89} reported that statins were associated with high levels of vascular endothelial growth factor in patients with PDR. In contrast, Zhang and McGwin\textsuperscript{90} reported no association between the use of statins and development of DR. Atorvastatin and simvastatin also showed different results depending on the study. Atorvastatin reduced hard exudates and fluorescein leakage in DR\textsuperscript{91} and simvastatin slowed the progression of DR.\textsuperscript{92}

Fenofibrate, a peroxisome proliferator-activated receptor alpha agonist, lowers plasma TGs and increases HDL, and 2 randomized controlled clinical trials have analyzed its effects on DR. In 2007, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study reported long-term effects of fenofibrate on DR in patients with type 2 diabetes mellitus.\textsuperscript{93} A multinational randomized trial of 9,795 patients were randomly assigned to receive fenofibrate (200 mg/day) or placebo. The cumulative percentage of patients who required a first round of laser treatment was lower in the fenofibrate group compared to the placebo group. Moreover, if DR was already present, the progression of retinopathy was higher in the placebo group than in the fenofibrate group. However, there was no difference in plasma concentrations of lipids between groups, so the mechanism of this effect does not seem to be related to plasma concentrations of lipids. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) eye study, published in 2010, compared the progression of DR in a simvastatin plus placebo group and a simvastatin plus fenofibrate (160 mg/day) group. At 4 years, the rate of progression of DR was lower in the fenofibrate group than in the placebo group.\textsuperscript{94}

However, Narang et al.\textsuperscript{95} reported that subjects with normal serum lipid levels did not show any relationship between atorvastatin use and reduction in hard exudates, macular edema, or visual acuity. The Collaborative Atorvastatin Diabetes Study trial also reported no added benefits of atorvastatin in DR; however, the treatment group needed less laser treatment, although the difference was not significant.\textsuperscript{96} Fried et al.\textsuperscript{97} reported that simvastatin medication did not affect the progression of DR.

CONCLUSION

It is well known that dyslipidemia is an important risk factor for CVD, and lipid-lowering agents are used according to standardized criteria. However, although chorioretinal diseases such as AMD and DR share common aspects of vascular pathology, the role of lipids is underestimated in these diseases, most likely due to the discordant results reported in many clinical and epidemiological studies. Likewise, studies of the association between lipid-lowering medications and chorioretinal disease have been inconsistent. Moreover, there is no clear evidence from randomized controlled clinical trials that lowering plasma lipid levels reduces the risk of DR onset or progression. The FIELD and ACCORD studies suggested that
fenofibrate may play a potential role in reducing the risk of DR progression, but it is not clear whether the process of plasma lipid changes is involved in its mechanism.

However, some repeated findings could be observed among the inconsistent data, namely the relationship between serum lipid levels and the incidence of hard exudates and CSME and the relationship between lipids and chorioretinal disease has not yet been identified, more large-scale clinical studies are expected to provide additional benefits to patients. These studies will contribute to the understanding of pathophysiology of AMD and DR and can serve as a basis for identifying future biomarkers and precision medicine for these conditions that cause blindness.

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