





REVIEW ARTICLE

Dyslipidemia in age-related macular degeneration

Jonathan B. Lin¹, Omar A. Halawa¹, Deeba Husain¹, Joan W. Miller ¹ and Demetrios G. Vavvas ¹✉

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Lipid-rich drusen are the *sine qua non* of age-related macular degeneration (AMD), the leading cause of blindness in older adults in the developed world. Efforts directed at uncovering effective therapeutic strategies have led to the hypothesis that altered lipid metabolism may play a pathogenic role in AMD. This hypothesis is supported by the fact that: (1) drusen, the hallmark histopathologic feature of AMD, are composed of lipids, (2) polymorphisms of genes involved in lipid homeostasis are associated with increased odds of AMD, (3) metabolomics studies show that patients with AMD have alterations in metabolites from lipid pathways, and (4) alterations in serum lipid profiles as a reflection of systemic dyslipidemia are associated with AMD. There is strong evidence that statins, which are well described for treating dyslipidemia and reducing risk associated with cardiovascular disease, may have a role for treating certain cohorts of AMD patients, but this has yet to be conclusively proven. Of interest, the specific changes in serum lipoprotein profiles associated with decreased cardiovascular risk (i.e., high HDL levels) have been shown in some studies to be associated with increased risk of AMD. In this review, we highlight the evidence that supports a role for altered lipid metabolism in AMD and provide our perspective regarding the remaining questions that need to be addressed before lipid-based therapies can emerge for specific cohorts of AMD patients.

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INTRODUCTION

Age-related macular degeneration (AMD) is a leading cause of blindness in older adults [1]. Early AMD is characterized by focal accumulation of lipids and proteins between Bruch's membrane and the retinal pigment epithelium (RPE) known as drusen. The presence of multiple large drusen is a risk factor for progression to either advanced nonexudative/dry AMD, characterized by photoreceptor and RPE cell death known as geographic atrophy (GA), or advanced exudative/wet AMD, characterized by abnormal blood vessel growth beneath the eye known as choroidal neovascularization (CNV). Both forms of advanced disease cause devastating vision loss.

Despite the significant morbidity associated with AMD, there are limited treatment options for nonexudative AMD, which affects the vast majority of patients. Nutritional supplements in the form of vitamins and antioxidants may have a small role in slowing progression to advanced neovascular AMD but do not have a definitive role in treating nonexudative AMD [2, 3]. Anti-vascular endothelial growth factor agents have revolutionized the treatment landscape for patients with exudative AMD, but there is no equivalent option for patients with the nonexudative form of the disease.

This lack of treatment options for most AMD patients has led to significant efforts to identify cellular and molecular pathways involved in AMD pathogenesis. Numerous lines of evidence suggest that altered lipid homeostasis may contribute to AMD pathogenesis, including biochemical studies revealing that drusen are predominately composed of lipids [4–6], genetic studies that have identified polymorphisms in genes involved in lipid metabolism that are associated with AMD [7–11], and studies

reporting that patients with AMD have altered serum lipoprotein profiles [12–15]. Nonetheless, since not all studies have yielded the same results, there is still not clear consensus regarding the specific role of dyslipidemia in AMD pathogenesis. In this review, we summarize the evidence that supports a role of altered lipid homeostasis in AMD pathogenesis and provide our perspective regarding important remaining research questions. This research may lead to much-needed, novel lipid-based therapies for early to intermediate AMD to prevent progression to advanced disease and blindness.

Biochemical evidence of altered lipid homeostasis in AMD

One of the most prominent clinical and histopathologic features of AMD is the focal accumulation of extracellular material between the inner collagenous layer of Bruch's membrane and the basal lamina of the RPE. When present in a thin linear pattern, these accumulations are referred to as basal linear deposits (BLinD) [16, 17]. In contrast, when they are present in a focal, dome-shaped lesion, these accumulations are known as drusen (Fig. 1). BLinD and drusen are considered to be alternative forms of the same entity, and patients with AMD are orders of magnitude more likely to have BLinD and large drusen (>125 μm) compared with age-matched controls [16, 18]. Classical drusen are typically found within the fovea in association with cone photoreceptors and Müller cells. This is in contrast with another type of lipid-rich, AMD-associated lesion known as subretinal drusenoid deposits, which are located between the photoreceptors and the RPE and mainly in rod photoreceptor-rich regions of the macula [6, 19, 20]. There is speculation that these distinct lipid-rich lesions of the retina may reflect different underlying pathobiological processes of AMD.

¹Retina Service, Department of Ophthalmology, Mass Eye and Ear, Harvard Medical School, Boston, MA, USA. ✉email: demetrios_vavvas@meei.harvard.edu

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The presence of a few small (less than 63 μm in diameter) drusen, also called drupelets, is considered a part of the normal aging process of the eye. Small drusen are associated with a rather small risk (i.e., <1%) of developing late AMD [21]. However, the presence of numerous medium (between 63 and 125 μm in diameter) or large (>125 μm in diameter) drusen, especially with indistinct borders, defines the transition from normal aging to early/intermediate AMD by multiple disease classification criteria, including that of the Age-Related Eye Disease Study and the Beckman Initiative for Macular Research Classification Committee (Table 1) [21, 22]. The reason why medium and large drusen define the transition from normal aging to disease is because they are associated with increased risk of progression to vision-threatening advanced AMD, including exudative AMD and GA [23, 24]. The estimated rate of progression to advanced AMD within 5 years approaches 50% for patients with large drusen and pigmentary abnormalities in both eyes [21].

The specific composition of drusen has been investigated in numerous biochemical and histological studies. Cumulatively, these studies reveal that drusen are highly heterogeneous but have significant lipid composition, supporting that altered lipid metabolism contributes to AMD pathogenesis [4]. Lipoprotein-derived particles that contain the physical forms of cholesterol seen in the core of atherosclerotic plaques with apolipoprotein B100, as well as various immunologic effectors, such as complement and molecules that promote macrophage migration, are

seen in drusen and thought to contribute to the progression from nonexudative to exudative AMD. Almost a decade ago, Curcio et al. proposed the “oil spill” model to characterize the process by which lipids accumulate within the retina during physiologic aging and in the transition to AMD, culminating in drusen formation and progression to advanced AMD (Fig. 2) [5, 6]. Although the specific mechanism by which drusen biogenesis leads to GA and CNV remains an area of active investigation, there is a clear link between altered lipid homeostasis in the retina, formation of pathologic drusen, and the development of early/intermediate AMD.

Identification of specific proteins within drusen also support a role for altered lipid homeostasis in AMD pathogenesis [25]. Bergen et al. recently combined multiple published studies to curate a list of 89 drusen proteins [26]. Pathway analysis performed on this curated list of drusen proteins revealed that three of the five most significantly enriched canonical pathways involve lipid and cholesterol metabolism: liver X receptor/retinoid X receptor (LXR/RXR) activation, farnesoid X receptor (FXR)/RXR activation, and atherosclerosis signaling (Table 2).

Genetic evidence of altered lipid homeostasis in AMD

Near the turn of the millennium, polymorphisms in the apolipoprotein E gene (APOE) were found to be associated with AMD [7, 8]. Specifically, the APOE- ϵ 4 allele was associated with decreased risk of AMD, while the APOE- ϵ 2 allele was associated with increased risk of AMD, although one recent study challenged this idea by identifying a protective role for APOE- ϵ 2 within a Northern Spanish population [27]. Interestingly, these risk profiles are opposite to those that have been identified for Alzheimer disease (AD), wherein the ϵ 4 allele is associated with increased risk of AD and the ϵ 2 allele is associated with decreased risk of AD. Two companion genome-wide association studies (GWAS) provided further associations between AMD and variants located near or within genes for hepatic lipase gene (LIPC), cholesterol ester transfer protein (CETP), ATP binding cassette subfamily A member 1 (ABCA1), and lipoprotein lipase (LPL) [9, 10]. A more recent, large GWAS of 16,144 patients and 17,832 non-AMD controls confirmed these associations between AMD and variants located near or in the ABCA1, APOE, CETP, and LIPC genes [11]. Table 3 summarizes the function of the proteins encoded by these genes. Recent meta-analysis of multiple GWAS confirmed that many AMD-associated loci were located near or within genes involved in high-density lipoprotein particle remodeling, cholesterol transporter activity, and macrophage foam cell differentiation, among other processes [28]. Although the specific cellular and molecular consequences of these variants remain under active investigation, these associations suggest that altered lipid homeostasis may contribute to AMD pathogenesis. Notably, the magnitude of altered risk associated with these gene variants is rather small, suggesting that these changes may occur in tandem with other biological processes that remain to be discovered.

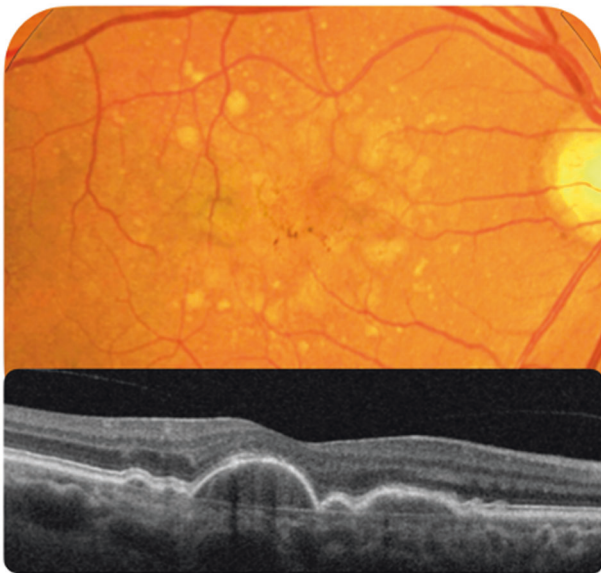


Fig. 1 Drusen are the *sine qua non* of age-related macular degeneration. Example of large, soft, confluent drusen visualized by ophthalmoscopy (top panel), and optical coherence tomography (OCT; bottom panel).

Table 1. Classification of age-related macular degeneration (AMD) per Beckman Initiative for Macular Research Classification Committee and the Age-Related Eye Disease Study (AREDS) based on drusen size and pigmentary abnormalities.

Classification per Beckman	Classification per AREDS	Drusen size	Pigmentary abnormalities
Normal aging	AREDS 1–2, no to early AMD	None	None
		Small (<63 μm)	None
Early AMD	AREDS 2–3, early to intermediate AMD	Medium (63–125 μm)	None
Intermediate AMD	AREDS 3, intermediate AMD		Yes
		Large (>125 μm)	None
			Yes
Late AMD	AREDS 3–4, intermediate to advanced AMD	Exudative AMD or geographic atrophy	Not applicable

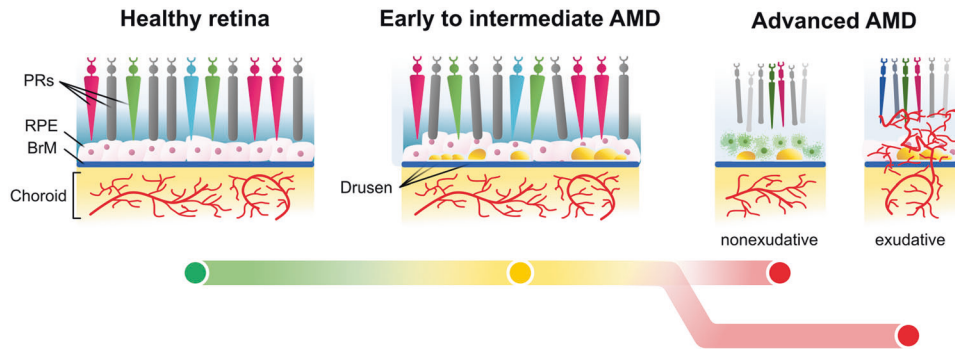


Fig. 2 Schematic detailing lipid accumulation in the retina in the form of drusen leading to progression from normal/healthy retina to early/intermediate age-related macular degeneration (AMD) and then to either advanced nonexudative or exudative AMD. PRs photoreceptors, RPE retinal pigment epithelium, BrM Bruch's membrane.

Table 2. Top enriched canonical pathways after performing Ingenuity pathway analysis on curated list of 89 drusen proteins.

Pathway name	P value	Overlap
Acute phase response signaling	7.51×10^{-15}	14/170 (8.2%)
Liver X receptor/retinoid X receptor (LXR/RXR) activation	2.29×10^{-12}	11/121 (9.1%)
Farnesoid X receptor (FXR)/RXR activation	9.39×10^{-11}	10/126 (7.9%)
Atherosclerosis signaling	2.35×10^{-9}	9/127 (7.1%)
IL-12 signaling and production in macrophages	1.42×10^{-7}	8/146 (5.5%)

Data reproduced from Bergen et al. [26].

Plasma metabolome

Untargeted plasma metabolomics studies also support the hypothesis that lipid homeostasis is altered in patients with AMD. In one cross-sectional, case-control study of 90 patients with AMD compared with 30 non-AMD controls, 87 plasma metabolites were found to be significantly different between patients with AMD versus controls. Of these 87 metabolites, the majority (82.8%) were lipid species, especially from the glycerophospholipid pathway [29]. A more recent and larger study of 2267 patients with AMD compared with 4266 non-AMD controls also identified 60 plasma metabolites that were significantly associated with AMD [30]. These metabolites included various lipoproteins, such as large and extra-large high-density lipoprotein (HDL) subclasses and very low-density lipoprotein (VLDL), which facilitate circulation of hydrophobic lipid species within the hydrophilic bloodstream.

Serum lipoprotein profiles in AMD

Given the many shared risk factors for patients with cardiovascular disease and AMD, many studies have focused on examining serum lipoprotein profiles in patients with AMD compared with non-AMD controls. Despite numerous studies that have examined this question, there is no clear consensus, though most recent studies tend to report an association between increased serum HDL and increased risk of AMD (Table 4).

To our knowledge, the first study to examine the association between serum cholesterol and AMD was a small study by Albrink and Fasanella, which found that patients with AMD ($N = 11$) had similar serum total cholesterol (257 ± 52 mg/dL) compared with young healthy controls (210 ± 32 mg/dL) and older healthy controls (238 ± 43 mg/dL) [31]. Twenty years later, Vidaurri et al. examined the association between cardiovascular risk factors and drusen in Jewish patients with AMD (Israel) [32]. When comparing patients with and without drusen, they found a statistically

significant difference only in systolic and diastolic blood pressure ($P = 0.011$, $P = 0.025$, respectively). Interestingly, this was the first study to note a tendency towards a negative association between HDL, LDL, and drusen area.

The first large population-based studies to examine serum lipid levels in AMD were based on the National Health and Nutrition Examination Survey (NHANES) [33] and the Framingham Eye Study [34]. Although both failed to find any significant association between serum cholesterol and AMD, they found that blood pressure may be associated with AMD. Interestingly, the NHANES data suggested that there may be a trend towards higher cholesterol having a protective effect against AMD [33]. In contrast to these two studies, a subsequent large population-based study, the Eye Disease Case-Control Study, reported a significant association between elevated cholesterol and AMD [35]. The next large study to look into serum lipoprotein levels and AMD was the Beaver Dam Eye Study, which did not find strong associations between cardiovascular risk factors and AMD but did identify an association between elevated serum HDL and incidence of GA [36, 37]. This association between elevated serum HDL and AMD was also identified by the Age-Related Macular Degeneration Risk Factors Study Group [38].

Given that both the Beaver Dam Eye Study and the Age-Related Macular Degeneration Risk Factors Study Group identified elevated serum HDL as a risk factor for AMD, van Leeuwen et al. were the first to examine the relationship between serum lipoprotein profiles and APOE genotype and the risk of early and late AMD. In the Rotterdam Study, they found that elevated serum HDL, but not total cholesterol, was indeed associated with increased risk of AMD and that this association remained even after controlling for APOE genotype [39]. A pooled analysis of the largest studies at the time from three continents was unable to provide a clear hypothesis to explain disparate conclusions regarding the association between serum cholesterol and AMD [40]. Dashti et al. suggested that these contradictory findings may stem from the fact that cholesterol and apolipoproteins found in drusen may arise from intraocular rather than systemic origin [41].

In the subsequent decade, emerging genetic evidence of variants in lipid-related genes conferring increased risk of AMD continued to fuel research into the association between serum lipids and AMD. A meta-analysis of three large, population-based cohorts, including data from the Blue Mountains Eye Study, the Beaver Dam Eye Study, and the Rotterdam Study found no associations between cholesterol measures and the incidence or progression of AMD when controlling for known risk alleles in lipid pathway genes, further muddling an already confusing picture regarding how systemic lipid profiles may influence AMD pathogenesis [42].

In 2016, Wang et al. performed a systematic review and meta-analysis examining the association between serum lipoprotein levels and AMD, analyzing 82,966 participants from 19 studies

Table 3. Variants in lipid-related genes associated with AMD.

Gene name	Function	Variant	OR	P value
Apolipoprotein E (APOE)	Major apoprotein of chylomicrons, catabolism of triglyceride-rich lipoprotein constituents	rs429358	0.70	2.4×10^{-42}
Hepatic lipase (LIPC)	Triglyceride hydrolase and ligand for receptor-mediated lipoprotein uptake	rs2043085	0.87	4.3×10^{-15}
Cholesterol ester transfer protein (CETP)	Reverse transport of cholesterol from high-density lipoprotein to other lipoproteins	rs5817082	0.84	3.6×10^{-19}
ATP binding cassette subfamily A member 1 (ABCA1)	Cholesterol efflux pump in cellular lipid removal pathway	rs2740488	0.90	1.2×10^{-8}

Data reproduced from Fritsche et al. [11].
OR odds ratio.

published at the time of their writing [12]. They identified a significantly increased risk of AMD associated with higher serum HDL (relative risk [RR]: 1.18 per 1 mmol/L increase; 95% confidence interval [CI]: 1.01–1.35). In contrast, higher serum total cholesterol (TC), LDL, and triglycerides (TG), were associated with a decreased risk of AMD (RR: 0.92–0.95). These findings challenge the paradigm that LDL is “bad” cholesterol and that HDL is “good” cholesterol, as is case in the context of cardiovascular disease, although an earlier meta-analysis reported no clear associations [43].

Some recent studies that were published after this meta-analysis have yielded similar results. For example, a multi-center European cross-sectional study of 32,483 subjects found that higher serum HDL was associated with increased risk of AMD (odds ratio [OR]: 1.21 per 1 mmol/L increase; 95% CI: 1.14–1.29), whereas higher serum TG was associated with decreased risk of AMD (OR: 0.94 per 1 mmol/L increase; 95% CI: 0.91–0.97) [13]. Similarly, the Tsuruoka Metabolomics Cohort Study in Japan, which included 3,988 participants, reported a significant association between AMD and increased serum HDL (OR: 1.61 per 1 mmol/L increase; 95% CI: 1.17–2.23) and between AMD and decreased serum TG (OR: 0.78 per 1 mmol/L increase; 95% CI: 0.64–0.96) in male participants [44]. In female participants, however, there was an association between early AMD and elevated TC (OR: 1.21; 95% CI: 1.01–1.44) and elevated serum LDL (OR: 1.26; 95% CI: 1.03–1.53) [44].

Other studies have corroborated the association between AMD and elevated serum HDL but not with other serum lipoproteins. A prospective cohort study of 5,344 participants from the United Kingdom found a similar association with elevated serum HDL conferring a higher risk of AMD (OR: 1.15 per 0.5 mmol/L increase, 95% CI 1.01–1.30) but no similar association with serum LDL and AMD [14]. Similarly, a Mendelian randomization investigation using published data from the International Age-Related Macular Degeneration Genomics Consortium with 33,526 participants of predominately European ancestry found evidence that serum HDL is a causal risk factor for AMD (OR: 1.22 per 1 standard deviation increase; 95% CI: 1.03–1.44) but no evidence of a causal association of serum LDL or TG with AMD [15]. Other Mendelian randomization studies in both European and Asian populations have further corroborated that serum HDL may be a causal factor in AMD pathogenesis [45, 46].

Notably, other recent cross-sectional and cohort studies have reported no significant associations between serum lipoprotein profiles and AMD [47, 48]. It remains unknown whether these discrepancies are due to differences in underlying study design, lack of appropriate sample size for sufficient statistical power, differences in case definition, or due to uncontrolled confounding. Taken together, although not all studies have yielded the same results, there is some evidence that there may be a link between systemic dyslipidemia and AMD, especially with HDL. This link between HDL and AMD is supported by mechanistic studies in disease models that suggest that targeting HDL interactions with Bruch’s membrane may slow the pathologic processes that leads to lipid accumulation, drusen biogenesis, and ultimately, development of AMD [49].

Cholesterol modulation as a therapeutic strategy in AMD

Given these possible associations between dyslipidemia and AMD, some have proposed the use of cholesterol modulation to treat early AMD. Observational studies in the last few decades have yielded inconsistent results. Some studies have reported a protective effect of statins on AMD, while others have reported a null result or even an adverse result whereby statins cause increased risk of exudative AMD; there is insufficient high-quality evidence to make definitive conclusions [50–53]. These discrepancies are likely due to underlying methodological limitations and bias. Moreover, there are numerous types of statins with differing lipophilicity, bioactivity, and dosage schemes. Since

Table 4. Summary of selected studies examining the association between elevated serum high-density lipoprotein (HDL) levels and increased risk of age-related macular degeneration (RR relative risk, OR odds ratio, CI confidence interval, SD standard deviation).

Study authors, Ref.	Location	N	Effect Size	95% CI
Wang et al. (meta-analysis) [12]	Various	82,966	1.18 per 1 mmol/L increase (RR)	1.01–1.35
Colijn et al. [13]	Europe	32,483	1.21 per 1 mmol/L increase (OR)	1.14–1.29
Sasaki et al. [44]	Japan	3988	1.61 per 1 mmol/L increase (OR) in males only	1.17–2.23
Yip et al. [14]	UK	5344	1.15 per 0.5 mmol/L increase (OR)	1.01–1.30
Burgess and Davey Smith [15]	Europe	33,526	1.22 per 1 SD increase (OR)	1.03–1.44
Lüdtke et al. [47]	Pomerania	4420	1.06 (RR; no units specified)	0.79–1.42
Mao et al. [48]	China	6830	1.35 (OR; no units specified)	0.84–2.17

animal studies have confirmed that not all statins are able to penetrate the blood-retina barrier to the same extent [54], it is possible that the statin type and dose must be optimized to achieve the desired clinical outcome.

Our recent open-label, prospective clinical study reported that the use of high-intensity atorvastatin (80 mg daily) may lead to regression of drusen in some patients with associated improvement in visual acuity and no progression to advanced exudative AMD [55]. The patients in our study had, on average, a baseline cholesterol level of 208 ± 35 mg/dL with an average reduction of 62 ± 35 mg/dL. Of note, those who had regression of drusen volume after high-intensity atorvastatin ($N = 10$) showed a trend towards less reduction in total cholesterol after statin therapy compared to those who did not show change in drusen volume ($N = 13$) (-49 ± 31 mg/dL versus -71 ± 36 mg/dL; $P = 0.14$). In comparison, an earlier study by Guymer et al. reported that patients randomized to moderate-intensity simvastatin (40 mg daily; equivalent to atorvastatin 20 mg) had significantly reduced odds of AMD progression after adjusting for age, sex, smoking, and unilateral AMD status at baseline ($P = 0.05$), especially among patients who were homozygous for the AMD risk-conferring Y402H genotype of the complement factor H (CFH) gene [56]. Large randomized controlled trials and prospective cohort studies are necessary to definitively answer the question of what role statins and other lipid-lowering medications such as fibrates [57] may have in treating AMD. These future studies must consider the numerous heterogeneous subtypes of AMD, patients' genetic profiles that contribute to differing levels of underlying risk, and lipid subspecies that may play disparate roles in disease pathogenesis. High-intensity statin therapy may be necessary to achieve regression of drusen burden and slow AMD progression. This would align with work in the cardiovascular field, which has suggested that intensive as opposed to moderate statin therapy may be necessary to stop atheroma growth and to yield the greatest protection against further cardiovascular events [58, 59].

Remaining questions

Taken together, there are multiple lines of evidence that support the idea that altered lipid homeostasis contributes to drusen biogenesis, which ultimately leads to the transition from physiologic aging to AMD. Although they have relatively small effect sizes, polymorphisms in genes involved with lipid metabolism perturb lipid and cholesterol homeostasis and thereby predispose individuals to developing AMD. Finally, although not all studies have reported consistent results, these perturbations in lipid homeostasis can be measured systemically based on serum lipoprotein profiles. Of interest, this evidence supports the idea that therapies targeted at restoring lipid homeostasis may have efficacy in reducing drusen biogenesis, preventing development of early AMD, or slowing development of advanced disease. However, there are numerous issues that need to be addressed before lipid therapies become a reality.

Challenging the paradigm of HDL as “good” cholesterol and LDL as “bad” cholesterol. Serum HDL is classically considered “good” cholesterol, as it is responsible for cholesterol transport from tissues to the liver, where it can be removed from the circulation. In contrast, serum LDL is considered ‘bad’ cholesterol, as it circulates cholesterol and can contribute to pathologic build-up of atherosclerotic plaques in the vasculature. Nonetheless, although not all studies have yielded the same results, this dogma has been challenged in studies of patients with AMD. In direct contrast with the pattern observed for cardiovascular disease, there is significant, yet not conclusive, evidence for elevated HDL as a risk factor for AMD. This notion of HDL as “good” cholesterol is also being challenged in the cardiovascular field as well. Most recently, the cardiovascular field has been moving toward the analysis of protein-defined subspecies of HDLs [60]. HDL particles contain small amounts of functional proteins that are used to define single subspecies. It appears that subspecies containing proteins involved in inflammation, immune response, thrombosis, and lipid metabolism are associated with higher risk of cardiovascular disease, whereas subspecies containing apolipoprotein C1 or E are associated with lower risk. Thus, risk determination should be made not by the total HDL level alone but by determining the balance between beneficial versus detrimental HDL subspecies and their local distribution. Future studies that measure lipids should take this into account. Increased efforts should also be made to identify and determine risk-conferring characteristics of HDL subspecies within the framework of AMD.

AMD: a disease of altered local or systemic lipid homeostasis or both?. Further studies are also necessary to determine the extent to which systemic modulation of lipid homeostasis may affect lipid homeostasis within the retina. This is especially important in the context of studies suggesting that local biosynthesis is the primary source of cholesterol within the retina [61]. Although systemic statin therapy has been well established as a therapy for dyslipidemia and can produce measurable improvements in serum lipid levels, it has not been definitively established that systemic statin therapy can alter local lipid profiles within the retina in humans. Moreover, local therapies may be necessary not only for improved bioavailability but also for the ability to optimize both systemic and local lipid profiles for patients with concomitant cardiovascular disease and AMD. Systemic lipid-lowering therapies may still be needed for AMD to create a permissive state for lipid efflux from the tissues, as well as for improving the function of circulating scavenger macrophages that are otherwise impaired by the accumulation of lipid material [62]. Targeting dyslipidemia may also have broad applicability for other neurodegenerative disorders beyond the retina, such as in AD, where dyslipidemia may also play a pathogenic role [63, 64].

Drusen: an innocent bystander or causative factor?. There is no doubt that the presence of multiple large drusen defines the transition from normal aging to early/intermediate AMD and

Table 5. Key points regarding role of dyslipidemia in age-related macular degeneration (AMD).

Central themes
1 Multiple lines of evidence, including histopathologic, genetic, and metabolomic data, support a role for altered lipid homeostasis in AMD pathogenesis
2 Although there is not clear consensus, patients with AMD have evidence of elevated high-density lipoprotein (HDL), which is complicated by the identification of HDL subspecies with different risk-conferring properties along with the question of whether systemic lipoprotein profiles reflect local lipid homeostasis in the eye
3 Lipid-lowering therapies, including statins, likely have therapeutic potential for certain patients with AMD, although the specific drug type, dosage, delivery, and timing require further study and optimization

increases risk of progression to advanced AMD. However, to date, it remains unclear whether drusen are a by-product of the underlying pathologic process or causative in the disease pathway or both. Future studies that carefully characterize the natural history of AMD and explore the effect of lipid-based therapies in reducing not only the quantity and size of drusen but also the risk of progression to advanced disease are essential to provide further insight into this issue.

CONCLUSIONS

Multiple lines of evidence support a role for altered lipid metabolism in AMD pathogenesis, from AMD lesion composition to systemic lipid changes and genetic risks associations. The exact association is far more complex than initially hypothesized with the most notable example being the association of elevated HDL with increased AMD risk being complicated by the importance of local lipid production and dyshomeostasis, as well as identification of HDL subspecies with potentially different risk profiles. Key takeaways are highlighted in Table 5. Although further research is necessary, the development of therapies that target alterations in lipid homeostasis and thereby address the underlying cellular and molecular pathophysiology of AMD would be revolutionary for many AMD patients.

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ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Demetrios G. Vavvas.

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