Lipids in Health and Disease

COMMENT

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Emerging risks of lipid-lowering therapy and low LDL levels: implications for eye, brain, and new-onset diabetes

Erkan Cure[1*] and Medine Cumhur Cure[2]

Abstract

Atherosclerotic cardiovascular disease remains a major global health burden. Current guidelines emphasize aggressive lipid-lowering strategies, particularly those that reduce low-density lipoprotein cholesterol (LDL-C) levels. While effective in lowering cardiovascular risk, excessively low LDL-C may have unintended health consequences. LDL-C plays a critical physiological role in cellular structure and hormone synthesis. Emerging evidence links low LDL-C and high HDL-C with increased glaucoma risk. Statins, which are commonly used to lower LDL-C, may further increase this risk, raising concerns for patients with coronary artery disease. Low LDL-C has also been associated with gestational diabetes and intracranial hemorrhage, while statin therapy may contribute to new-onset diabetes mellitus. These findings highlight the need to reassess the "lower is better" paradigm. A patient-centered, risk-based approach to statin therapy is recommended. Large-scale randomized controlled trials are urgently needed to establish safe lipid thresholds and optimize therapeutic strategies.

Keywords Cholesterol, LDL, Low-density lipoprotein, Glaucoma, Diabetes

Introduction

Atherosclerotic heart disease remains the leading cause of mortality worldwide, with its incidence continuing to rise [1–4]. Current guidelines strongly recommend statin therapy for individuals with low-density lipoprotein cholesterol (LDL-C) levels ≥ 190 mg/dL because of the associated elevated risk of cardiovascular disease (CVD) and mortality [5]. LDL-C thresholds for CVD risk stratification are defined as < 116 mg/dL for low-risk individuals, < 100 mg/dL for moderate-risk individuals, and < 70 mg/dL for high-risk individuals [6]. For patients at very high risk, intensive LDL-C reduction to approximately 55 mg/dL is advised [7]. Evidence suggests that for every 39 mg/dL (1 mmol/L) decrease in LDL-C, CVD risk is reduced by 20–25% [8–10]. The FOURIER trial further supported aggressive lipid lowering, demonstrating optimal cardiovascular protection at LDL-C levels below 20 mg/dL [11]. However, the potential harms of such low LDL-C levels and high-dose statin therapy have been increasingly debated. Although the concept of statin toxicity [12, 13] is not widely accepted, concerns persist among some researchers [14, 15].

Cholesterol is a fundamental component of human physiology and is essential for cell membrane structure and the synthesis of vital biomolecules. LDL-C plays a crucial role in transporting cholesterol to peripheral tissues. Excessive lowering of LDL-C may impair cholesterol distribution, with emerging evidence linking very low LDL-C levels (< 70 mg/dL) to increased cardiovascular

*Correspondence:
Erkan Cure
erkancure@yahoo.com
[1]Department of Internal Medicine, Istinye University, Gaziosmanpasa Medical Park Hospital, Gaziosmanpasa, Istanbul 34250, Turkey
[2]Department of Biochemistry, Medilab Laboratory and Imaging Center, Sisli, Istanbul, Turkey

and stroke-related mortality in large, long-term cohort studies [5, 16]. Furthermore, the *Lancet Commission* has highlighted growing public skepticism regarding the benefits and side effects of lipid-lowering therapies, stressing the need to address these perceptions [17]. A recent observational study associated low LDL-C with ocular conditions such as glaucoma [18], and statins have also been implicated in the development of hemorrhagic stroke and new-onset diabetes mellitus [19, 20]. While statins and aggressive LDL-C lowering have undeniably contributed to improved cardiovascular outcomes, the potential risks of extremely low LDL-C levels—particularly with respect to eye health, neurological function, and glucose metabolism—warrant further investigation. This study explored the potential adverse effects of low LDL-C on the eye and brain, as well as the relationship between statin therapy and new-onset diabetes. In light of these concerns, we advocate for a personalized, patient-centered approach to statin therapy tailored to individual risk profiles and clinical contexts.

LDL-C and ocular health

The relationship between cholesterol and ocular health—particularly the effects of statins on the eye—remains highly controversial in the literature. Importantly, LDL-C does not exert uniform effects on all ocular structures; its impact differs between the vascularized retina and the avascular lens. Retinal arteries are susceptible to atherosclerosis due to exposure to circulating LDL-C and triglyceride-rich particles, whereas high-density lipoprotein cholesterol (HDL-C) appears to have a minimal effect on the retinal vasculature [21, 22]. A study proving an association between LDL-C levels and retinal artery atherosclerosis in male patients revealed that atherosclerosis of the retinal arteries and coronary artery atherosclerosis were more or less at the same level and that multiorgan involvement by atherosclerosis was the rule rather than the exception [21]. This study revealed that detecting retinal artery atherosclerosis by ophthalmologists could help diagnose coronary artery atherosclerosis early. In a study evaluating patients' fundus examinations and concurrent coronary angiography, the prevalence and severity of retinal vessel atherosclerosis were strongly associated with the prevalence and severity of coronary artery disease [22]. Additionally, retinal vascular narrowing has been associated with an increased risk of developing glaucoma [23]. These findings suggest that LDL-C-induced retinal atherosclerosis may contribute to the pathogenesis of glaucoma and that statin therapy—by lowering LDL-C levels—could mitigate this risk by reducing retinal vascular damage.

In contrast, the eye lens lacks vasculature and is therefore not exposed to inflammatory changes in the same way. Consequently, elevated systemic cholesterol levels are unlikely to induce inflammation or significantly affect lens transparency [24]. This extremely high cholesterol content in eye lens fiber cell membranes plays a role in maintaining lens homeostasis and transparency rather than causing harm [24]. The retinal pigment epithelium and Müller cells circulate LDL-C into the retina via LDL receptors [25]. Findings have indicated that the retina can sustain cholesterol balance by employing LDL-C as a cholesterol provider in a laboratory model [25]. The retina was found to rapidly adjust the cholesterol balance, especially under stress conditions such as increased intraocular pressure [26]. This ability of the retina may reduce its vulnerability to hypocholesterolemia and hypercholesterolemia. The cholesterol content in the plasma membranes of eye lens fiber cells is much greater than that in the membranes of other tissues and organs in the human body, and the cholesterol content in the human lens has been shown to increase with aging [24]. Increased HDL-C is associated with age-related macular degeneration, whereas increased LDL-C is associated with decreased macular degeneration [27].

Cholesteryl ester transfer protein (CETP) is a hydrophobic glycoprotein that mediates the transfer of neutral lipids—primarily cholesteryl esters and triglycerides—from HDL-C to apolipoprotein B (ApoB)-containing proatherogenic lipoproteins such as very-low-density lipoprotein (VLDL) and LDL-C [28]. CETP is found within the interphotoreceptor matrix of the retina, suggesting the presence of a specialized retinal mechanism for processing HDL-C and related lipoproteins, thereby maintaining intraretinal lipid homeostasis [29, 30]. Given the high turnover rate of photoreceptor outer segment membranes, lipid metabolism within the retina is highly dynamic [30]. CETP inhibitors block the transfer of cholesteryl esters from HDL-C to VLDL and LDL-C, resulting in elevated HDL-C levels and reduced LDL-C concentrations [28]. These inhibitors are capable of crossing Bruch's membrane and reaching the retinal pigment epithelium [31]. Consequently, CETP inhibition has been implicated in the pathogenesis of macular degeneration [31, 32]. Collectively, these findings suggest that disruptions in retinal lipid homeostasis—caused by elevated HDL-C and reduced LDL-C levels—may contribute to retinal dysfunction and ocular complications.

A meta-analysis reported that elevated total cholesterol and reduced HDL-C levels were associated with an increased risk of primary open-angle glaucoma (POAG); however, no significant association was found between LDL-C levels and glaucoma in that analysis [33]. Another meta-analysis similarly identified low HDL-C as a risk factor for glaucoma but did not find a significant correlation with total cholesterol levels [34]. Importantly, both studies reported substantial heterogeneity, which may limit the generalizability of their findings. Additionally, a

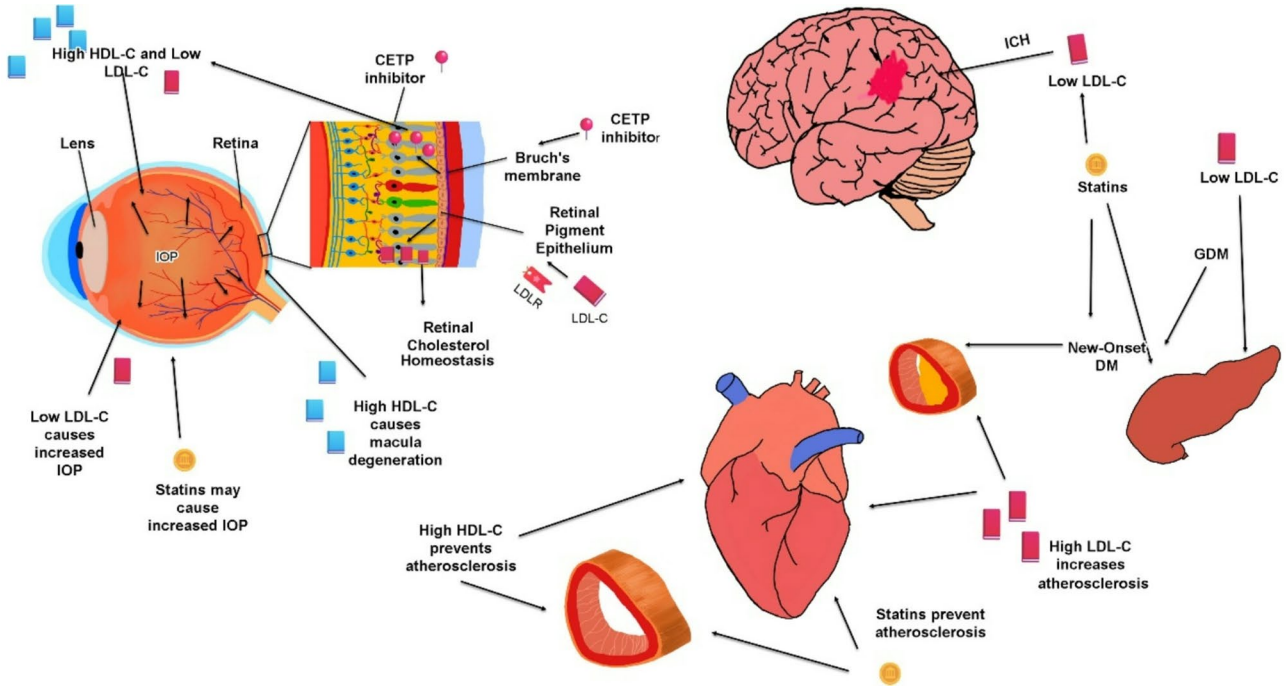

Fig. 1 Effects of LDL-C and statins on the eye, brain, cardiovascular systems, and glucose metabolism. **Abbreviations**: CETP, cholesteryl ester transfer protein; DM, diabetes mellitus; GDM, gestational diabetes mellitus; ICH, intracerebral hemorrhage; HDL-C, high-density lipoprotein cholesterol; IOP, intraocular pressure; LDL-C, low-density lipoprotein cholesterol

large-scale cohort study revealed an association between dyslipidemia and glaucoma development. In this analysis, individuals with elevated total cholesterol or those receiving lipid-lowering therapy were classified as having dyslipidemia. However, no subgroup analysis has been performed to specifically assess the impact of statins or LDL-C levels on glaucoma risk [35]. Furthermore, an extensive cohort study reported that higher levels of total cholesterol, HDL-C, and LDL-C were associated with elevated intraocular pressure (IOP) [36]. Genetic studies have also suggested a potential link between lipid metabolism and IOP through associations with single-nucleotide polymorphisms (SNPs) [36]. Collectively, these findings reflect the complex and inconsistent nature of the relationship between cholesterol levels and glaucoma, highlighting the need for further targeted research. Recent data suggest that the eye lens may not be affected by high blood LDL-C levels and may even require high LDL-C levels for health [18]. The authors analyzed 400,299 subjects and reported that increased HDL-C levels significantly increased the risk of glaucoma. In contrast, increased LDL-C, triglyceride, and total cholesterol levels are associated with a reduced risk of glaucoma [18]. HDL-C has several pleiotropic properties, including immune system modulation; anti-inflammatory, anti-apoptotic, and antioxidant functions; and cholesterol efflux [37]. However, excessively high HDL-C levels have also been associated with an increased risk of infectious disease, age-related macular degeneration, and death [37]. High levels of HDL-C and LDL-C may play opposite roles in the eyes, unlike in other organs. Local eye cholesterol metabolism and its relationship with glaucoma should be studied.

Figure 1 shows the effects of HDL-C and LDL-C on the eye and brain and on new-onset diabetes mellitus.

Statins and ocular health

A five-year large-scale cohort study demonstrated that statins did not reduce the risk of glaucoma in certain ethnic groups during the first year; however, a significant risk reduction was observed across all groups by the end of the study period [38]. In contrast, subgroup analyses from another trial revealed that although the overall incidence of glaucoma was similar between the statin and placebo groups, the risk of glaucoma increased in correlation with higher statin doses [39]. A 10-year population-based cohort study further revealed a strong association between long-term use (over three years) of rosuvastatin and an increased risk of glaucoma [40]. A meta-analysis also revealed that the use of specific statins—namely, rosuvastatin, simvastatin, and pravastatin—was linked to a heightened risk of glaucoma, whereas this association was not observed for all statin types [41]. A cross-sectional study supported the link between statin use and glaucoma, reporting that statin users had higher LDL-C levels than nonusers did and that the incidence

of glaucoma was particularly elevated among users aged 60–69 years [42]. Moreover, a recent observational study suggested a reduced risk of glaucoma with higher LDL-C levels, indirectly implicating statin-induced LDL-C reduction as a potential glaucoma risk factor [18]. The literature presents inconsistent findings regarding the ocular effects of statins. These discrepancies may stem from differences in study design, methodologies, duration of follow-up, and variations in primary versus secondary outcomes across studies [43]. Concerns have been raised regarding whether certain statins may increase glaucoma risk with prolonged use, particularly in older adults. Such uncertainties contribute to public skepticism about statin therapy—a challenge already acknowledged by the Lancet Commission [17]. A meta-analysis involving 4 million individuals reported that adverse statin-related effects, including intracranial hemorrhage (ICH), nephrotoxicity, and hepatotoxicity, occur in less than 5% of users—approximately 200,000 affected individuals [44]. Given the known increased incidence of glaucoma among patients with coronary artery disease [45], it is essential to clarify whether statins directly contribute to glaucoma development or whether a reduction in LDL-C plays a mediating role. As a significant proportion of individuals aged 60–69 years live with coronary artery disease—and considering the elevated glaucoma risk associated with statin use in this group—addressing this question is both urgent and necessary. Figure 1 illustrates the potential effects of statins on ocular health.

Clinical significance of LDL-C

Cholesterol is a crucial element of biomembranes and plays a key role in producing vitamin D, bile acids, steroid hormones, and many other essential biomolecules [46]. Every substance in the body is in balance: elements, cytokines, nitric oxide, oxidants, and antioxidants. For example, low and high calcium levels can be problematic for the body. Therefore, the calcium level is balanced between the upper and lower values determined by the body. In healthy individuals, the body maintains LDL-C levels within certain limits. Reducing LDL-C levels to prevent coronary artery disease can reduce the synthesis of many molecules necessary for the body, such as isoprenoids, sex hormones, and vitamin D [46, 47]. Since LDL-C carries cholesterol particles to cells, LDL-C levels below the basal level can disrupt the lipid balance, which is the cornerstone of the cell, and lead to many types of damage, such as disruption of cell integrity and conduction defects [47, 48]. Indeed, decreased cholesterol levels lead to increased movement of ceramide from the endoplasmic reticulum to the Golgi and thus increased sphingomyelin synthesis [49].

Total cholesterol levels below 120 mg/dL and LDL-C levels below 50 mg/dL are classified as hypolipidemia [50]. LDL-C values under 30 mg/dL are considered very low and have been associated with genetic lipid disorders, aggressive lipid-lowering therapy, and lipid apheresis [51]. The REGARDS study reported that all-cause mortality was lowest at LDL-C levels between 70 and 200 mg/dL, whereas mortality increased at LDL-C levels below 70 mg/dL [52]. Similarly, the PROVE-IT trial revealed that LDL-C concentrations below 40 mg/dL were linked to a higher incidence of certain cardiac events and stroke [53]. Conversely, other large clinical trials, including FOURIER, ODYSSEY OUTCOMES, and IMPROVE-IT, demonstrated that LDL-C levels under 20 mg/dL were not only safe but also associated with reductions in cardiovascular and stroke-related mortality [11, 54, 55]. These conflicting findings indicate a lack of consensus in the literature regarding the lower safety threshold of LDL-C. Given this uncertainty, we suggest that the minimum acceptable LDL-C limits be re-evaluated in light of emerging evidence.

LDL-C and intracranial hemorrhage

In the SPARCL study, LDL-C levels in the statin group were reduced to approximately 61 mg/dL [56]. After five years of follow-up, the incidence of hemorrhagic stroke nearly doubled in the atorvastatin 80 mg group compared with the placebo group (55 cases [2.3%] vs. 33 cases [1.4%]) [56]. Although this difference appears notable, it is relatively small when considering the total number of participants. Moreover, approximately 90% of the participants in both groups were on antiplatelet therapy, which may have contributed to the increased incidence of hemorrhagic events rather than statin use alone. The American Heart Association reported that the incidence of statin-associated hemorrhagic stroke is negligible and that low LDL-C levels do not independently increase this risk [57]. However, an extensive cohort study with 19 years of follow-up reported that women with LDL-C < 70 mg/dL had a 2.13-fold higher incidence of hemorrhagic stroke [58]. A key limitation of this study is that only 137 cases of hemorrhagic stroke occurred, and only 5% of the total cohort received statin therapy. Another 9-year longitudinal study revealed that the risk of hemorrhagic stroke increased progressively at lower LDL-C levels, with a 1.65-fold increase in individuals with LDL-C levels between 50 and 69 mg/dL and a 2.69-fold increase in individuals with LDL-C levels < 50 mg/dL [19]. A separate large-scale cohort study with a 5-year follow-up revealed that intensive statin therapy, which significantly lowered LDL-C, was associated with an increased risk of ICH [59]. Similarly, another study demonstrated that elevated ICH risk was more closely linked to reduced LDL-C levels than to a direct pharmacological effect of statins [60]. Importantly, cholesterol metabolism in the brain differs from that in peripheral vascular

structures. Additionally, many patients with atherosclerotic cardiovascular disease are prescribed both statins and antiplatelet agents, potentially compounding the risk of intracranial hemorrhage when aggressive LDL-C lowering is pursued. These findings underscore the need for well-designed, large-scale randomized controlled trials to elucidate the safety of intensive lipid-lowering strategies in patients receiving concurrent antiplatelet therapy.

LDL-C, Statins, and diabetes mellitus

In addition, excluding pravastatin, it has been reported that statin treatment (exclusively intensive statin treatment) may lead to new-onset diabetes in the range of 9–55%, and statin use with the combination of β-blockers and thiazides carries this risk to the upper limit [20]. Unfortunately, the mechanism of statin treatment has not yet been elucidated [20]. However, an association between low LDL-C levels and gestational diabetes mellitus has been described. For every 1 mmol/L increase in the serum LDL-C level, the risk of gestational diabetes mellitus decreases by 17.6% [61]. Impaired β-cell function reduces cellular cholesterol clearance, and disturbances in the metabolism of lipoproteins are the underlying mechanisms [61]. Among pregnant women diagnosed with gestational diabetes mellitus (GDM), the lifetime risk of progressing to type 2 diabetes is approximately 60%. Within this context, low LDL-C levels may indirectly contribute to the development of type 2 diabetes by increasing the risk of GDM [62]. Furthermore, in patients with coronary artery disease, aggressive lipid-lowering strategies—particularly those targeting very low LDL-C levels—have been associated with elevated glucose levels, thereby introducing an additional metabolic risk factor for this already vulnerable population.

Clinical implications

LDL-C, which is responsible for transporting cholesterol to cells, has target levels defined on the basis of CVD risk categories, and these values are periodically updated. However, existing evidence highlights several unresolved questions regarding lipid management that warrant further clarification. For example, in a study using coronary computed tomographic angiography to assess coronary artery calcium (CAC) scores, nearly half of the individuals with LDL-C levels either ≥190 mg/dL or <77 mg/dL had a CAC score of zero, suggesting no calcified plaque burden [63]. Although the presence of noncalcified plaques tends to increase with increasing LDL-C levels, this finding raises an important question: should lipid-lowering therapy be universally recommended for all individuals with LDL-C≥190 mg/dL, regardless of other clinical indicators? This calls for a more personalized approach to treatment [64]. Moreover, should cholesterol-lowering therapy be administered in individuals with elevated LDL-C due to Pattern A lipid profiles, which are considered less atherogenic [65]? These questions emphasize the need for individualized risk assessment in lipid management rather than a one-size-fits-all approach.

On the other hand, while some studies have suggested that LDL-C levels below 20 mg/dL do not cause significant harm, a growing body of evidence indicates potential adverse effects associated with very low LDL-C levels [11, 54, 55]. The impact of intensive LDL-C reduction and statin therapy on ocular and neurological health remains inconclusive, with conflicting findings in the literature. The roles of LDL-C, HDL-C, and CETP in the retina, along with their influence on the eye lens, intraocular pressure, and local cholesterol metabolism, are not yet fully understood. Emerging evidence also suggests a possible link between low LDL-C levels and an increased risk of hemorrhagic stroke, raising new concerns. As our understanding of localized lipid metabolism in the eye and brain continues to evolve, previously accepted assumptions may need to be revisited. Furthermore, the association between low LDL-C levels or statin use and new-onset diabetes mellitus has prompted renewed scrutiny of current lipid-lowering strategies. This has paved the way for exploring alternative cardiovascular risk reduction therapies, such as PCSK9 monoclonal antibodies and the recently emphasized lipoprotein(a) as novel antiatherogenic targets [17, 66]. These developments underscore the need for continued research to address unresolved questions in lipid biology and therapy.

Limitations in the literature

Most studies have focused on aggressive statin therapy and the benefit of lowering LDL-C levels [11, 54, 55]. The effects of low LDL-C levels and aggressive statin therapy on other organs have not been investigated in detail. The cholesterol metabolism and target cholesterol levels of organs, especially the eye and brain, have not been fully elucidated. The effects of low LDL-C on the synthesis of molecules such as sex steroids and vitamin D and on the cell membrane structure have not been investigated. The possible harms of high HDL-C cholesterol levels have not been studied. Lipid-lowering therapy, similar to diabetes treatment, has not been tailored to individual needs and has continued to be applied rigidly. Lipid metabolism, which has become a puzzle, can be elucidated with many randomized controlled trials, and lipid guidelines can be reorganized.

Conclusion

As a result, a significant proportion of the global population is affected by atherosclerotic cardiovascular diseases. Patients with established coronary artery disease, as well as those at high risk—particularly individuals with

diabetes mellitus—require lipid-lowering therapy. However, the potential adverse effects of low LDL-C levels and statin use on the eyes and brain remain insufficiently understood. Moreover, local cholesterol metabolism in organs such as the eye and brain has yet to be fully elucidated. The underlying mechanisms behind statin-associated new-onset diabetes also remain unclear. Addressing the public's concerns regarding lipid-lowering medications may be possible by offering further data. Therefore, large-scale randomized controlled trials are urgently needed to establish the optimal target range of lipid levels for atherosclerosis prevention and to determine appropriate statin dosages, considering the role of LDL-C metabolism in various organs. We strongly advocate for a personalized approach to statin therapy that is tailored to the individual risk profile of each patient. Finally, we call upon the scientific community to prioritize rigorous research efforts addressing these critical concerns.

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EC and MCC wrote this commentary entirely. EC and MCC drew the figure. The authors read and approved the final manuscript.

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