Cholesterol Level and Statin Use in Alzheimer Disease

I. Review of Epidemiological and Preclinical Studies

Nina E. Shepardson, MS; Ganesh M. Shankar, MD, PhD; Dennis J. Selkoe, MD

During the last 2 decades, evidence has accumulated that a high cholesterol level may increase the risk of developing Alzheimer disease (AD). With the global use of statins to treat hypercholesterolemia, this finding has led to the anticipation that statins could prove useful in treating or preventing AD. However, the results of work on this topic are inconsistent: some studies find beneficial effects, but other studies do not. In this first segment of a 2-part review, we examine the complex preclinical and clinical literature on cholesterol level and AD. First, we review epidemiological research on cholesterol level and the risk of AD. Then, we assess studies correlating cholesterol level with neuropathological AD type. The potential molecular mechanisms for the apparent adverse effects of cholesterol on the development of AD are then discussed. Third, we review preclinical studies of statin use and AD. Therefore, this first part of our review provides the background and rationale for investigating statins as potential therapeutic agents in patients with AD, the subject of the second part.

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As longevity continues to rise, diseases of aging loom large as a major threat to public health. Among these, Alzheimer disease (AD) takes a great toll, with up to 5 million Americans affected, and the prevalence by 2050 is expected to reach more than 13 million. Over the past 2 decades, numerous studies have implicated a high cholesterol level as an apparent risk factor for AD. Statins, a class of drugs in widespread use for the treatment of hypercholesterolemia, have demonstrated some apparent promise as potential preventive agents or treatments for AD. However, the results of this work have been mixed, as detailed in this 2-part review. Herein, we examine the epidemiological and neuropathological literature on the putative connection between high cholesterol level and AD, which forms the basis for hypothesizing that lipid-lowering agents like statins might decrease the risk of AD or slow its progression. Then, we assess preclinical research on statin use and the mechanism of AD. In the second part of the review (published in the next issue of the Archives), we will review clinical studies of statin use and AD. In that issue, we will discuss whether the complex and inconsistent trial results to date may be explained in part by the differential abilities of statins to cross the blood-brain barrier, as well as several other confounding factors. Overall, we conclude that a principal basis for reported differences in the association of AD with cholesterol level and in the effects of cholesterol-lowering drugs across studies is the variable relationship between the time of cholesterol measurement or statin initiation and the time of onset and severity of AD. These and other findings lead us to recommend a set of specific criteria for conducting much-needed clinical trials of potentially important but still unresolved effects of cholesterol regulation on AD incidence and progression.

Author Affiliations: Center for Neurologic Diseases, Department of Neurology, Brigham and Women’s Hospital and Harvard Medical School (Ms Shepardson and Drs Shankar and Selkoe), and Department of Neurological Surgery, Massachusetts General Hospital (Dr Shankar), Boston, Massachusetts.
We performed an unbiased search of the PubMed database for relevant English-language studies, without regard to publication date. Additional studies were identified from citations in the resultant articles and by the recommendations of consultants (identified in the “Additional Contributions” subsection of the “Acknowledgments” section). We included all articles that described well-controlled studies and clearly interpretable conclusions about our topic. Studies of the effects of statin use in humans (part 2) were required to include at least 50 persons, and human studies examining lipid-lowering agents were required to specify which lipid-lowering agents were investigated.

CHOLESTEROL LEVEL AS AN AD RISK FACTOR

High levels of cholesterol, particularly low-density lipoprotein cholesterol (LDL-C), are a well-established risk factor for developing coronary artery disease and stroke. An impression is emerging that these may also be an AD risk factor based on human epidemiological studies, human neuropathological studies, and experiments using animal models of AD, each of which we will review in order herein.

With regard to human epidemiological studies, a high total cholesterol level in serum has been reported to increase the risk of developing AD. In one study, this relationship was strengthened when apolipoprotein E (APOE) genotype was controlled for. In another study, high levels of total cholesterol or LDL-C were reported to correlate with lower Modified Mini-Mental State Examination scores in patients without clinical dementia. High total cholesterol level at midlife has been associated with an almost 3-fold (odds ratio, 2.8; 95% confidence interval, 1.2-6.7) increase in the likelihood of developing AD, even after controlling for APOE genotype. It has been further suggested that cholesterol level exerts some influence on the well-established correlation of the APOE-4 allele with AD risk. Solomon et al found that total cholesterol level at midlife (mean age, 50.4 years) was higher in persons who ultimately developed mild cognitive impairment or dementia than in those who did not, and this relationship was unaffected by APOE status. Similarly, Whitmer et al concluded that high total cholesterol level at midlife (mean age, 42 years) substantially increased the risk of late-life (age range, 61-83 years) dementia (hazard ratio, 1.42; 95% confidence interval, 1.22-1.66). Patients with AD having high total cholesterol or LDL-C level can experience faster cognitive decline than those having normal cholesterol measures, as can those with an APOE-4 allele. For APOE-4 non-carriers, high levels of high-density lipoprotein cholesterol (HDL-C) also contributed to faster cognitive decline; triglycerides level did not significantly affect the rate of decline in the latter study population, regardless of APOE-4 status. In another epidemiological study, high levels of neutral lipids in peripheral blood mononuclear cells were much more common in patients with AD than in healthy age-matched control subjects, and plasma HDL-C levels were reduced. Zambron et al concluded that individuals with familial hypercholesterolemia were more likely than healthy persons to develop mild cognitive impairment, the amnestic form of which is commonly a harbinger of AD.

Although the findings of these diverse studies suggest a consensus that high cholesterol level confers an increased risk of developing AD, some reported results do not fit with this conclusion. For example, Reitz et al found that high total cholesterol level in persons 77 years and older decreased the risk of AD (hazard ratio, 0.48; 95% confidence interval, 0.26-0.86). However, the individual effects of HDL-C and LDL-C levels were not significant. In a 2005 study, this group of researchers observed no significant effects of cholesterol (total, HDL, or LDL) level or triglycerides level on cognitive ability in healthy older persons. A later study by Reitz et al demonstrated that a high total cholesterol or LDL-C level was associated with a decreased risk of developing mild cognitive impairment in persons 65 years and older, although this was dependent on which factors were adjusted for. Similarly, Mielle et al found that a high total cholesterol level between age 70 and 79 years reduced the risk of developing dementia between age 79 and 88 years.

Two major caveats must be considered when evaluating the epidemiological studies of cholesterol level and AD risk. First, many such studies measured only total cholesterol and could not detect differing effects of HDL-C and LDL-C. Second, when participants already have AD at study enrollment, it can be difficult to determine whether a change in cholesterol level is having an effect on the progression of the disease or, conversely, whether the pathophysiological changes that accompany AD alter cholesterol level. This second consideration is particularly important because many published studies have been conducted late in the lives of participants, when substantial neuropathological AD type may already be present. As shown in the Figure, studies finding a negative correlation of cholesterol level with dementia risk (gray balloons) were principally conducted late in the patients’ lives, whereas studies finding a positive correlation (red balloons) tended to be conducted earlier (the left end of each balloon represents the mean age at study start; the horizontal dimension of each balloon indicates the length of follow-up).

In addition to clinical epidemiological evidence, correlational human neuropathological studies have been conducted. Early work in this area demonstrated that pathological amyloid was more common in patients with heart disease than in healthy persons. A neuropathological study noted differences in the distribution of pathological AD type associated with high cholesterol level at different ages: high HDL-C level both at midlife and in late life was associated with increased pathological neurofibrillary tangles in the neocortex, but only late-life HDL-C level was associated with increased pathological plaque in hippocampus or neocortex. This is a notable observation because HDL-C is generally considered atheroprotective. The authors speculated that alterations in HDL-C metabolism could change neuronal membrane composition, and in this context they suggested that HDL-C might affect amyloid β-protein (Aβ) production, aggregation, or clearance, possibly through an APOE-mediated mechanism. They also noted that APOE genotype did not influence the effects of cholesterol level on pathological AD brain. Another study
found a link between high cholesterol level and pathological brain amyloid in persons aged 40 to 55 years but not in older individuals, suggesting that cholesterol level during the presymptomatic stage (particularly in middle age) is important.

Some of these human neuropathological results seem to be borne out in animal models of AD. Feeding amyloid precursor protein (APP) transgenic mice a high-fat high-cholesterol diet increased the number or size of amyloid plaques and led to higher Aβ levels in formic acid extracts of brain. One of these studies observed a positive correlation of murine APOE plasma level with Aβ deposition in mice expressing the Swedish mutation of human APP. Feeding rabbits a high-cholesterol diet doubled Aβ levels in the hippocampal cortex (although this effect did not reach statistical significance) and caused damage to the blood-brain barrier. Notably, returning rabbits to a normal diet after several weeks of a high-cholesterol diet reversed the increase in Aβ levels.

**POTENTIAL MECHANISMS FOR THE APPARENT ADVERSE EFFECTS OF CHOLESTEROL ON THE DEVELOPMENT OF AD**

There are several possible mechanisms that could explain the findings of studies reviewed in the previous section that seem to connect high cholesterol level with the development of neuropathological AD. Cholesterol may increase the activity of the β- or γ-secretase enzymes that generate Aβ from APP, decrease the flux of APP through the nonamyloidogenic α-secretase pathway, or affect various nonamyloid factors, such as local inflammation or tau metabolism.

Partial repression of the nonamyloidogenic α-secretase pathway is a route postulated from animal study findings by which high cholesterol level could increase AD risk. Application of exogenous cholesterol to human embryonic kidney cells overexpressing human APP decreased the α-cleavage product of APP (APPα), and did feeding mice a diet high in fat and cholesterol. Conversely, treatment of human embryonic kidney cells, human neuroglioma cells, or APP-overexpressing astrogliaoma cells with the cholesterol-extracting agent methyl-β-cyclodextrin (MβCD) increased the secretion of APPα. Another study found that progesterone, which decreases transport of cholesterol from the plasma membrane to the cytosol, did not alter the cholesterol-mediated inhibition of APPα secretion. This result suggests that cholesterol may act on APP primarily at the cell surface.

Cholesterol could also exert its effects more directly by influencing the β- and γ-secretase cleavages that produce Aβ. Depletion of cholesterol from human APP-expressing rat hippocampal neurons by applying lovastatin and MβCD strongly decreased the amount of Aβ produced. This effect occurred without changing the levels of APPα and was reversed by restoring cholesterol. The authors suggested the following 2 possible reasons why cholesterol depletion could affect β-cleavage but not α-cleavage: intracellular transport of APP might be affected in such a manner that APP colocalizes less with β-secretase, or β-secretase may be principally active in cholesterol-rich lipid rafts. The application of cholesterol-lowering agents to APP-overexpressing human embryonic kidney cells has also been shown to inhibit β-cleavage of APP; conversely, the addition of exog-
enous cholesterol enhanced β-cleavage and led to increased secretion of both Aβ40 and Aβ42.25 Notably, treating neuronal cells with compounds that interfere with intracellular cholesterol transport inhibited β-secretase activity but promoted γ-secretase activity.26 In a separate study,27 removal of cholesterol seemed to decrease γ-secretase activity, an effect that could be reversed by restoration of cholesterol.

Once Aβ has been produced, the cholesterol level could influence its aggregation state. Increased interactions of Aβ with the cell membrane under low cholesterol conditions may allow greater internalization and degradation of the peptide; conversely, high cholesterol level could make it more difficult for Aβ to associate with the cell surface, leading to its accumulation and aggregation in the extracellular space.28 Furthermore, a group of researchers who had previously described a novel 5-kDa form of Aβ (Aβ monomer is 4 kDa) having unique properties that were dependent on the presence of cholesterol demonstrated that this Aβ isoform could act as a seed for fibrillar aggregation when it was incubated with synthetic Aβ peptides.29 Treatment of cells with compactin (a hydroxymethylglutaryl coenzyme A reductase inhibitor) or filipin (an antibiotic that binds to cholesterol) inhibited this seeding effect, and that inhibition was countered by application of exogenous cholesterol. The authors suggest that this special 5-kDa “seeding form” of Aβ is likely produced in lipid rafts.

In addition to its apparent effects on APP processing and Aβ, cholesterol exerts a range of pleiotropic effects on physiological characteristics of neurons. For example, cholesterol depletion had adverse effects on dendrite growth and axonal branching, even when the chemical used to deplete cholesterol did not interfere with the synthesis of downstream isoprenoids.30 In view of this and many other reports that well-regulated cholesterol level helps maintain healthy neurons, there has been great interest in whether the use of statins, which lower LDL-C level by inhibiting hydroxymethylglutaryl coenzyme A reductase, or other lipid-lowering agents may alter the risk of developing AD or may be beneficial in its treatment.

PRECLINICAL STUDIES AND THE CURRENT STATE OF KNOWLEDGE ON STATIN USE AND AD

Because statins are already in widespread use, the possibility that they might be useful for AD treatment or prevention must be rigorously confirmed or denied. In the years since the connection between cholesterol level and AD was elucidated, many studies have investigated the potential use of statins as AD-modulating compounds. However, the results of these studies have often been inconsistent, in large part due to major differences in study design and data analysis. Although these methodological differences make it difficult to synthesize the results from various studies, we have endeavored to identify factors that could explain the observed variation in study outcomes.

Results of several cell culture studies (Table) have indicated that statin use can reduce Aβ levels. Application of lovastatin (along with MβCD) to rat hippocampal neurons expressing human APP decreased Aβ production without affecting the quantity of APPsα or the p3 peptide that arises from α- followed by γ-secretase cleavage.31 Another study32 found that inhibition of cholesterol synthesis with lovastatin decreased Aβ formation. Yet another study33 reported that treatment of various cell lines with lovastatin increased a-secretase activity and that treatment of human astrogliaoma cells with lovastatin decreased Aβ production. Furthermore,
Aβ-induced release of lactate dehydrogenase from human neuroblastoma cells was abolished by application of mevastatin. In hippocampal or mixed cortical neurons from rats, treatment with simvastatin or lovastatin reduced levels of both intracellular and extracellular Aβ40 and Aβ42. That study also demonstrated that lovastatin and MBCD increased levels of C-terminal fragment α in primary neurons carrying the Swedish missense mutation in APP, suggesting a stimulation of α-secretase processing. Together, the results of these cell culture studies suggest that statin use can lower Aβ generation.

Animal models of AD have generally yielded complementary findings (Table). Administering simvastatin to guinea pigs for 3 weeks resulted in decreased brain and cerebrospinal fluid levels of Aβ, an effect that was reversed by discontinuing the treatment. In another study, lovastatin and pravastatin sodium each decreased the amount of Aβ in the brains of transgenic mice while simultaneously increasing levels of APPs. Transgenic mice treated with simvastatin performed better in the Morris water maze test than their untreated counterparts.

The large body of literature on a putative connection between elevated cholesterol level and increased AD risk suggests that lowering cholesterol level might be a viable strategy for AD treatment or prevention, although differences among studies in the ages of participants are a complicating factor. Based on this evidence, numerous researchers have investigated the potential therapeutic effects of lipid-lowering agents, with a focus on statins. The results of preclinical research on this topic are encouraging, but human studies have been far more inconsistent in outcomes. In the forthcoming second part of this review, we will examine these clinical studies in detail, elucidate possible reasons for this observed variability, and make recommendations for future human studies on this important topic.

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Correspondence: Dennis J. Selkoe, MD, Center for Neurologic Diseases, Department of Neurology, Brigham and Women’s Hospital, Harvard Medical School, Harvard Institutes of Medicine, Room 730, 77 Ave Louis Pasteur, Boston, MA 02115 (dseelko@rics.bwh.harvard.edu).

Author Contributions: Dr Selkoe had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Shankar. Acquisition of data: Shepardson and Shankar. Analysis and interpretation of data: Shepardson and Selkoe. Drafting of the manuscript: Shepardson and Shankar. Critical revision of the manuscript for important intellectual content: Selkoe, Shepardson, and Shankar. Obtained funding: Selkoe. Study supervision: Selkoe.

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REFERENCES


**Correction**

**Error in Notation.** In the article titled “Association of Low Ejection Fraction With Impaired Verbal Memory in Older Patients With Heart Failure” by Festa et al, published in the August issue of the Archives (2011;68[8]:1021-1026), percentages were incorrectly noted in 3 places. On page 1023, left-hand column, third complete paragraph, lines 6 through 8 should have read as follows: “Among patients 63 years or older, an EF below 30% decreased the MCS on average by 0.95 (95% confidence interval, 0.18-1.72; P = .02).”