REVIEW

A review of the potential therapeutic role of statins in the treatment of Alzheimer's disease: current research and opinion

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Abstract: Alzheimer's disease is one of the most prevalent neurodegenerative disorders. However, there is no current treatment, which definitively influences disease progression over a sustained period. Numerous studies linking an increase in serum cholesterol, mainly during midlife, with the pathogenic process of Alzheimer's disease have been published. Therefore, the role of statins as a therapy in this disorder may be of great interest. The aim of the present review is to summarize of the role of statins in the treatment of Alzheimer's disease.

Keywords: animal models, epidemiology, HMGCoA-inhibitors, clinical trials, prevention, cognitive function

Introduction

Dementia affects an estimated 35.6 million people worldwide. This figure will triple in the next 40 years, with 115.4 million people expected to have this diagnosis in 2050.[1] The most prevalent type of dementia is Alzheimer's disease (AD), which is responsible for more than half of the cases.[2,3] AD is characterized by a progressive impairment of memory and other cognitive functions,[4] with moderate or rapid progression in many cases.[5] There is currently no effective therapy that can prevent deterioration. The combination of a high prevalence[2,3] accompanied by high burden[6] means that AD is a public health priority and the search for effective therapeutic agents a priority.[1] One of these potential therapeutic strategies is the use of cholesterol reducing medication (statins), as there appears to be a link between high serum cholesterol levels and AD.[7]

The aim of the present review is to summarize the possible role of statins in the treatment of AD.

Cholesterol and AD: the origins

Cholesterol is a basic compound of cell membranes, modulating their fluidity and permeability.[8] In the central nervous system uniquely, cholesterol is produced locally, as the blood–brain barrier effectively prevents the entrance of its circulating fraction.[9]

The first evidence highlighting a potential role of cholesterol in the pathological process underlying AD was based on experimental animal and cell-culture models. Additional evidence came from epidemiological studies that we will detail.

Cholesterol and the pathogenic process of AD: the amyloid hypothesis

One of the early research studies was a clinical-pathological study of necropsy specimens from individuals with/without heart disease, where a correlation between vascular

risk factors and the brain deposition of senile plaques containing the amyloid-β (Aβ)-peptide, the putative pathologic species in AD, was found.[10] Many experimental studies suggest that hypercholesterolemia accelerates the production of Aβ-peptide by shifting amyloid precursor protein metabolism from alpha to beta cleavage products, by β- and γ-secretases (Figure 1).[11–13] These secretases are embedded in a membrane structure known as a lipid raft, with high cholesterol content.[14] Cholesterol may influence this processing through the accumulation of proamyloidogenic forms that could trigger the pathogenic process of AD.[12,15–17]

Another type of evidence linking cholesterol and the pathogenic process of AD is that several lipoproteins involved in cholesterol metabolism are also related to amyloid deposition and AD.[18] One of these lipoproteins is apolipoprotein (Apo) E, which is one of the strongest genetic risk factors known for AD.[19] ApoE is a 35 kDa glycoprotein that exists in three isoforms differing by a single amino acid. One of these is ApoE4, which is estimated to be present in 14%–15% of the general population[20] and 37%–68% of patients with AD.[21] Heterozygote and homozygous carriers have, respectively, a threefold and eightfold increased risk of AD.[19,22] Recent attention has been directed to ApoJ (clusterin),[23] another lipoprotein protractedly associated with AD, and also to the low-density lipoprotein (LDL) receptor, which is related to the synaptogenic impairment found in AD.[24]

The mechanism whereby serum hypercholesterolemia leads to an increased neuronal content of cholesterol is unknown, but may be mediated by some cholesterol derivatives implied in its excretion pathways, known as oxysterols.[25] One of these products is 27-hydroxycholesterol (27-OHC), which is predominantly formed in the circulation and, in contrast to cholesterol, has the ability to cross into the brain.[26] 27-OHC is known to increase Aβ levels in both organotypic hippocampal slices and in neuronal preparations cultured from adult rabbits.[26] Some authors consider therefore, that 27-OHC is the link between circulating cholesterol and AD-like pathology in the brain.[26] Opposite to 27-OHC, 24-hydroxycholesterol (24-OHC) is brain-specific and is the main mechanism for eliminating cholesterol from the brain.[25] Plasma levels of 24-OHC are reduced in advanced AD and correlate with the degree of brain atrophy and neuronal loss.[25] There is evidence of the ability of 24-OHC to inhibit Aβ formation. Consequently, a reduced brain level of 24-OHC may accelerate the pathogenic process of AD.[25]

Epidemiological studies linking cholesterol with AD

Epidemiologic studies examining the association between cholesterol and AD have reported conflicting results.[27] Among longitudinal studies, high total cholesterol has been associated with both an increased[28,29] and decreased[30–32] risk of AD, as well as no effect.[33–35]

There are possible explanations for these conflicting results concerning cholesterol and dementia. First, such epidemiological studies could have yielded different results dependent on when cholesterol was measured (ie, midlife versus late life). In other outcomes such as cardiovascular disease, other studies have observed a similar pattern, in which high cholesterol in midlife,[36,37] but not late life,[38] is a risk factor. Second, an alternative explanation is that conflicting results may depend on whether cholesterol has been measured early versus late in the course of the disease process. The timing of measurements with respect to the disease process has been a factor in studies concerning the relationship between blood pressure and body mass index, and dementia. In studies with fewer than 10 years of follow up,[39–41] the null or opposite relationship has been observed. In studies with more than 10 years of follow up,[42–44] arterial hypertension and body mass index have been associated with an increased risk of AD. It has been hypothesized that several years before dementia begins, blood pressure and body mass index start to decline, perhaps as a result of preclinical AD pathology.[42] The same process may also be involved regarding cholesterol. Indeed, a decrease in cholesterol immediately before the dementia diagnosis could also be a predictor of dementia.[28] Finally, there is a possibility of mortality bias; however, this does not seem to be a likely explanation. Theoretically, hypercholesterolemic subjects may have an increased risk of mortality before dementia
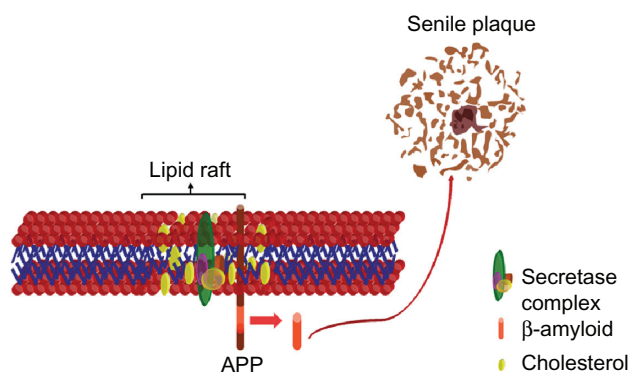

Figure 1 Amyloid processing by secretase and cholesterol interaction in lipid raft.
Notes: Hypercholesterolemia accelerates the production of amyloid-β-peptide, triggering the process of Alzheimer's disease with the formation of amyloid aggregates (senile plaque), by shifting amyloid precursor protein metabolism from alpha to beta cleavage products by β- and γ-secretases. These secretases are embedded in a membrane structure, known as a lipid raft, with high cholesterol content.
Abbreviation: APP, amyloid precursor protein.

begins and therefore less chance to develop dementia than subjects with low cholesterol. However, it has been noted in other studies, such as the Neurological Diseases in Central Spain (NEDICES),[45–48] that low cholesterol is also associated with mortality among the elderly (Sierra-Hidalgo and Bermejo-Pareja, unpublished data, 2012).

Animal models of beta-amyloid deposition

There are three main animal models where a link between cholesterol and AD has been established. One is a leporid exemplary (New Zealand White rabbit), used initially for coronary artery disease, where a 2% dietary intake of cholesterol induced amyloid brain deposition.[11] In both transgenic amyloid precursor protein and LDL receptor knock-out mice (which mimics human hypercholesterolemia), the same influence of cholesterol on amyloid pathology has been observed.[49,50] An additional model (Guinea pig) has shown indirect proof of cholesterol impact on Aβ-peptide after statin therapy.[13]

Cell culture evidence of cholesterol and AD

The experimental evidence linking cholesterol and AD is not limited to animal models. There are several in vitro studies in which an association between cholesterol and Aβ-peptide deposition has been observed.[12,15,51] The proposed mechanism is an increase of β- and γ-secretase activity that leads to increased levels of intracellular Aβ-peptide. By contrast, a negative impact of cholesterol lowering has been suggested by another experimental design, tangling the relationship between this lipid and the pathogenic process of AD.[52]

Conclusions regarding the association of cholesterol and AD

It seems likely that cholesterol has an influence on the AD pathological process, favoring Aβ-peptide brain deposition. This is based on different experimental evidence and epidemiological studies that individuals exposed to high levels, particularly during midlife, have an increased risk of AD. This evidence constitutes, at least, a rationale for the study of statin therapy as a potential tool to prevent and/or treat AD.

Statins and AD

Different authors have previously reviewed the role of statins in AD.[53–57] Here we review the outcomes of the main randomized clinical trials (RCT) conducted to date and explore future treatment possibilities for these therapeutic agents.

Basic concepts

The main effects of statins are based on their lipid-lowering capacity.[58] This is mediated through the inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase (an enzyme implied in cholesterol biosynthesis), which produces a decrease in low-density lipoprotein (LDL) cholesterol.[58] The effect depends on the dose and type of statin but, as an illustration, can range from a mean 1.5 mmol/L (59 mg/dL) decline with 20 mg simvastatin to 2.0 mmol/L (77 mg/dL) with 40 mg atorvastatin or even greater for higher doses or different agents.[58]

Although the lipid-lowering effect of statins has been the main feature addressed in AD, this is not the only potentially beneficial mechanism. Other recognized pleiotropic effects of statins are their anti-inflammatory and antiendothelial dysfunction activity, as well as their antioxidant, profibrinolytic, or antiproliferative properties.[59,60] A distinction is made between the lipophilicity and the chemical structure of the different statins, as this influences their ability to cross the blood–brain barrier.[60,61] Gathering these characteristics with the different hypocholesterolemic activity they may exert in neurons could be an explanation for the lack of effect found by some RCTs that used statins with low potential to influence the brain cholesterol content.[62] In a recent study, simvastatin was found to be the most efficient statin, considering all these features.[61]

Preliminary evidence revealing a protective effect of statins on AD

The first reports suggesting a potential therapeutic effect of statins were based on two independent observational studies in which a decreased risk of AD was found for the exposed group.[56,63] In a nested case-control design with information derived from 368 practices in the UK-based General Practice Research Database, the adjusted relative risk of dementia for those who were prescribed statins was 0.29 (0.13–0.63; $P = 0.002$).[63] In a cross-sectional analysis comparing the prevalence of probable AD in three groups of patients (the entire population, patients receiving statins, and patients receiving medications used to treat hypertension or cardiovascular disease) from hospital records, the prevalence of probable AD in the cohort taking statins over 23 months was 60%–73% ($P < 0.001$) lower than in the total patient population and lower than in those patients taking other medications typically used in the treatment of hypertension or cardiovascular disease.[56] After these initial reports, some other observational studies have yielded conflicting results with the great majority supporting this initial evidence, even

in predementia subjects;[64–71] whilst others have failed to show any differences.[72–74]

Main interventional trials

Preventive and therapeutic trials have tried to address the effects of statins on cognitive function.[57,62] In two large studies (Table 1), the neuroprotective effect on cognitive function was assessed as a secondary outcome.[75,76] Both failed to show any improvement for the treated subjects.[75,76] The enrolled patients had no overt cognitive impairment at baseline and had cardiovascular risk factors, including high cholesterol level. They received placebo or either 40 mg pravastatin with a mean 3.2-year follow-up[75] or 40 mg simvastatin, with a 5-year mean follow-up.[76] No differences were found in cognitive outcomes. Similarly, other studies have found no global effect on cognition.[77–83]

Other trials[84–89] are also summarized in Table 1. Several showed some kind of improvement in the treated groups. One of these was based on a secondary analysis of the main study and focused on the preventive efficacy of nonsteroidal anti-inflammatory drugs in AD, and it suggested a preventive effect, reducing AD incidence (67% hazard risk reduction)

in the 2528 normal elderly subjects studied and decreasing the worsening of neuropsychological measures (Mini-Mental State Examination) in a subset of mild cognitive impairment patients.[84,85] Carlsson et al[86] conducted a study in a population with an incremented risk of AD (siblings of diagnosed patients) and found a slight improvement in some neuropsychological tasks (verbal fluency and working memory) but no effect on cerebrospinal fluid amyloid (42 fraction). Some additional small studies found some beneficial effects on cognition in statins users.[90–92] In the DALI study,[90,92] a 24% improvement in a verbal memory test was observed in a group of diabetic patients treated with atorvastatin for 30 weeks. In another study,[91] 49 patients receiving 10 mg atorvastatin for a cardiovascular indication showed statistically relevant differences, compared with the placebo group, in the performance of different cognitive tests.

The therapeutic potential of statins in AD patients with an established diagnosis has been addressed in several RCTs (Table 2).[93–97] Simons et al[93] performed a small study of AD patients who were diagnosed according to National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association

Table 1 Preventive activity of statins on cognitive impairment

Study	Population	Statin	Outcome	Follow-up (months)	Conclusion	Comments
CRISP[87]	431 subjects (≥65 yrs) DL; CogNI	Lovastatin 20 and 40 mg	WAIS-R IADL	6	No effect	Prompt termination due to lack of funding
Muldoon et al[88,89]	194 subjects (24–60 yrs) DL; CogNI	Lovastatin 20 mg	Digit Span/ Symbol COWAT and TMT B plus others	6	No improvement	Attention/psychomotor speed results worst in lovastatin group
Muldoon et al[88,89]	308 subjects (35–70 yrs) DL; CogNI	Simvastatin 10 and 40 mg	Cognitive assessment battery	6	No improvement	Slight impairment in some tests. A negative effect proposed
MRC/BHF Heart Protection Study[76]	20,536 subjects (40–80 yrs) DL; CogNI	Simvastatin 40 mg	TICS-m	60	No effect	Cognitive effect secondarily evaluated
PROSPER[75]	5804 subjects (70–82 yrs) DL; CogNI	Pravastatin 40 mg	Stroop, LDT, PLT	42	No effect	Cognitive effect secondarily evaluated
Carlsson et al[86]	57 siblings of AD patients	Simvastatin 40 mg	Cognitive assessment battery	4	Improvement on verbal fluency and working memory	No effect on Aβ-42 CSF levels
ADAPT[84,85]	2528 subjects (≥70 yrs) DL and CogNI	Preventive trial of NSAIDs, but statin use permitted	Cognitive assessment battery	24	67% hazard risk reduction of Alzheimer's disease incidence	Cognitive effect secondarily evaluated

Note: Main interventional trials.
Abbreviations: DL, dyslipidemic; CogNI, cognitively not impaired; WAIS-R, Wechsler Adult Intelligence Scale-R; IADL, Instrumental Activities of Daily Living scale; COWAT, Controlled Oral Word Association; TMT B, Trail Making Test section B; TICS-m, modified Telephone Interview for Cognitive status; LDT, Letter-Digit Coding Test; PLT, 15-Picture Learning Test; AD, Alzheimer's disease; Aβ-42, amyloid-beta 42 fraction; CSF, cerebrospinal fluid; NSAIDs, non-steroidal-anti-inflammatory drugs.

Table 2 Statins and Alzheimer's disease

Study/Clinical Trial Number*	Population	Statin	Outcome	Follow-up (months)	Conclusion	Comments
ADCLT/NCT00024531[96,97,105]	67 patients (mild to moderate AD) ≥51 yrs (mean 78.2)	Atorvastatin 80 mg	ADAS-Cog, MMSE, CGIC	12	Fewer declines in ADAS-cog at 6 month	Six subjects in atorvastatin group and ten in placebo group were lost to follow-up
LEADe/NCT00151502[94,106]	640 patients (mild to moderate AD) ≥51 yrs (mean 78.2)	Atorvastatin 80 mg	ADAS-Cog, MMSE, CGIC; NPI, CDR-B	18	No effect	Normolipemic subjects
Simons et al[93]	44 patients (mild to moderate AD) >60 yrs (mean 68.0)	Simvastatin 80 mg	MMSE, ADAS-Cog, CSF Aβ	6.5	Better MMSE performance/augmented Aβ40	Showed less effect than the experimental model studied by the group
Sano et al/NCT00053599[95,107]	406 subjects (mild to moderate AD) >50 yrs (mean 74.6)	Simvastatin 40 mg	ADAS-Cog, MMSE, NPI, and others	18	No effect	Normolipemic subjects

Notes: Main interventional trials. *Clinical Trial Numbers are based on Burgos et al[57] and at http://ClinicalTrials.gov/.
Abbreviations: AD, Alzheimer's Disease; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive subscale; ADCLT, Alzheimer's Disease Cholesterol-Lowering Treatment trial; MMSE, Mini-Mental State Examination; CGIC, Clinical Global Impression of Change; NPI, Neuropsychiatric Inventory; CDR-SB, Clinical Dementia Rating-Sum of Boxes; CSF, cerebrospinal fluid; Aβ, amyloid-beta.

(NINCDS/ADRDA) criteria and randomly allocated to 80 mg simvastatin or placebo for a 26-week period. There was a significant effect on cognitive performance as well as an improvement in the Aβ-40 cerebrospinal fluid levels of the treated group.[93] Since this preliminary study, three other RCTs have been published.[94–97] The largest one included normolipemic AD patients who were randomly treated with atorvastatin 80 mg or placebo and assessed at 3-month intervals during 18 months.[94] No differences in the cognitive performance of the treated group were found; however, some marginal differences in the hippocampal-MRI assessment were detected.[94] Sparks et al[96,97] found modest differences in Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS)-Cog performance at the 6-month follow-up but not at 12 months, in a small group of AD patients randomly assigned to 80 mg atorvastatin. Sano et al[95] conducted a large RCT of 406 subjects with mild to moderate AD that failed to show any difference in the cognitive performance of patients taking simvastatin 40 mg versus placebo, incorporating an 18-month follow-up.

Since the larger trials have failed to show sustainable differences in cognitive performance or AD risk in the populations evaluated, the evidence suggests negligible benefit of statins at the current time. Some modest differences in subsets of patients might warrant further exploration. Another possibility that we will briefly comment on, are the methodological caveats that could influence the assessment of statin activity in AD. These could be an explanation for this inconclusive evidence, and several authors have highlighted this in the referred trials.[62]

Potential reasons for the lack of correlation between experimental evidences and therapeutic outcomes

Major concerns with statin research are the methodological issues that could influence the results. This is particularly important for the observational studies, where the lack of randomization introduces potential bias, commonly observed among statins users. Two of the most recognized are "indication bias" (in which a drug is prescribed to treat a condition that is associated with the variable of interest) and "cessation bias" (where some of the observed protective effects of a drug may be due to patients stopping the drug therapy after being diagnosed as having a condition).[98]

It has been also suggested that cohorts of statin users could be a selected population with a better-than-average health status, implying a decreased risk of AD. Alternatively, they could have worse health status and reduce the risk of AD through unrelated mortality. Other design issues could be related to the type, dose, and blood–brain barrier-crossing ability of the prescribed statin, as well as other pleiotropic effects, different from their lipid-lowering ability, which are not usually evaluated.[57,62] An additional possibility for the lack of homogeneous effect observed, supported by some groups, is that statins may themselves have a negative impact on cognition. This has been suggested by some observational studies,[99–101] and another

population-based analysis.[102] Also, one RCT found worse performance in cognitive testing, but it was not designed for this purpose.[88] This topic has been reviewed recently, especially after the Food and Drug Administration warning about this potential adverse outcome. The evidence so far, nonetheless, has been deemed inconclusive.[103,104]

Summary

Although a potential role of cholesterol in the pathogenic process of AD has been established through different experimental models, statin therapy has failed to show a clear general effect on the treatment or the prevention of this disease. In addition, we suggest future RCTs should test the use of statins with biomarkers, like amyloid (positron emission tomography [PET] tracers or cerebrospinal fluid levels) and others, as this is the main sustention of the bonds between cholesterol, and hence statins, and the AD pathological process. Upcoming studies should also consider all the methodological caveats reported so far. This could ensure that the target population at risk (midlife cholesterol exposure) is replicated and the appropriate product (statins with capability of influencing brain-cholesterol content) used.

Disclosure

The authors report no conflicts of interest in this work.

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