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Statins and Dementia

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Statins and dementia - a review of the research

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Do statins have any benefits against the two most common forms of late-onset dementia? Questions remain, but so far, the use of statins solely for the prevention or treatment of dementia is not warranted.

Dementia is the loss of cognitive function including memory, visuo-spatial and language skills, and executive function, sufficient to interfere with social or occupational activities.¹ The risk of dementia increases with age. About 1% of individuals aged 60-65 years are diagnosed with dementia, but by age 85 the prevalence can be greater than 35%. There are different forms of dementia, but the two that are most common in older adults are dementia associated with Alzheimer's Disease (AD) and dementia associated with vascular lesions (vascular dementia, VaD). Together they account for 70% of dementia in individuals 65 years and older.²

Dementia is already one of the most important causes of disability in people over 65 years.³ It is predicted that within one generation the number of Canadians living with dementia will roughly double from half a million to over 1 million.³

Why statins for dementia?

Cholesterol is believed to be involved in the pathophysiology of both AD and VaD. The

pathophysiology of AD is complex and not fully understood. One of the main pathophysiological processes, however, is thought to be the formation and deposition of a neurotoxic peptide called beta-amyloid (Ab) in brain tissue. Elevated cholesterol is thought to increase Ab formation and aggregation and reduce its clearance from the brain.^{4,5} Cholesterol's role in VaD may be more straightforward: elevated cholesterol causes vascular damage leading to cerebral hypoperfusion or stroke, causing cognitive decline.^{5,6} In addition, many patients with Alzheimer's disease have some degree of vascular dementia pathology and *vice versa*, and the effects of the different pathologies on cognitive decline are additive.⁴⁻⁷ Overall, there is epidemiological, genetic, and experimental laboratory evidence suggesting that cholesterol is a suitable target for dementia therapy. Statins are known to lower serum cholesterol and reduce the risks of cardiovascular and cerebrovascular disease. In addition to their cholesterol-lowering effects, statins may also have other beneficial modes of action such as antiplatelet and antithrombotic effects, anti-inflammatory effects, and effects on vascular endothelium.^{5,8}

Evidence for benefit in dementia

A number of observational studies have examined the association between statin use and the development of dementia, and many (but not all) of them have reported that statin use is associated with a reduced risk of dementia. A 2009 systematic review summarized the various studies on statins and dementia (AD and VaD) from the past decade, including the conflicting evidence from observational studies (with a brief discussion of the potential role of indication bias in the discordant results), and the results of the only two large-scale randomized controlled trials (RCTs) published at the time.⁵ Those two studies, the 5-year Health Protection Study (HPS)⁹ and the 3-year PROspective Study of Pravastatin in the Elderly at Risk (PROSPER),¹⁰ were mainly designed as cardiovascular and stroke prevention studies, but each also assessed aspects of cognitive function as tertiary outcomes. Neither study showed that statins (specifically simvastatin and pravastatin) prevented the development of dementia, although neither study used systematic clinical cognitive assessments.⁵ The PROSPER study, however, was not designed to test whether earlier use of statins (rather than in the PROSPER population who were 70 years or older) could have cognitive benefits later in life.¹⁰

More recent publications include an analysis from the Rotterdam Study¹¹ and the Lipitor's Effect in Alzheimer's Dementia (LEADe) study.¹²

The Rotterdam study

Since 1990, this population-based study has followed a cohort of individuals in Rotterdam, the Netherlands, for various disease outcomes. In one recent analysis of this cohort, statin use (assessed through pharmacy dispensing data) was associated with a reduced risk of diagnosis of Alzheimer's disease in over 7000 patients aged ≥ 55 over a roughly ten-year period (hazard ratio 0.57, 95% CI 0.37 to 0.90). All statins, whether lipophilic or lipophobic, were protective. However, no relationships between statin dose or duration of treatment and protective effect were observed.¹¹

LEADe

LEADe is the first large RCT looking at the effect of statins for the treatment of Alzheimer's disease. Six-hundred and forty patients aged 50 to 90 years with mild to moderate probable AD, who were already receiving treatment with the cholinesterase inhibitor donepezil, were randomized to receive atorvastatin 80 mg/d or placebo for 72 weeks. Patients did not have dyslipidemia or significant cardiovascular or cerebrovascular disease. Cognitive function was assessed every 3 months during the study using a variety of measures, the primary ones being the Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog) and the Alzheimer's Disease Cooperative Study Clinical Global Impression of Change (ADCS-CGIC). Cognitive function declined in both patient groups over time with no significant difference between groups in terms of cognitive performance.¹²

Conclusions

While statin use is associated with a reduced risk of dementia, evidence from controlled trials so far have not shown statins are effective at preventing dementia or treating existing dementia. Questions remain: could starting statins earlier in life help prevent dementia; is there a subset of patients with established dementia that *do* benefit from statins?¹³

For now, statins should be used where indicated for the prevention of cardiovascular and cerebrovascular disease according to established guidelines, and patients should be encouraged to adopt heart- and brain-healthy lifestyles. Taking statins solely for the prevention or treatment of dementia is not justified.

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