Cholesterol and Cognitive Performance in Normal Controls and the Influence of Elective Statin Use after Conversion to Mild Cognitive Impairment: Results in a Clinical Trial Cohort

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Key Words

Alzheimer's disease · Mild cognitive impairment · Cholesterol · Lipid-lowering agents

Abstract

Background: We reported a significant 67% reduction in the hazard risk of incident Alzheimer's disease (AD) with elective statin use in the AD Anti-inflammatory Prevention Trial (ADAPT), without a reduction in risk of incident mild cognitive impairment (MCI). **Objective:** To assess if cholesterol levels are associated with cognitive performance and determine if statin use alters cognitive performance after onset of MCI. **Design:** Fractionated cholesterol levels, neurological and cognitive status were evaluated annually. Comparisons of non-LLA (lipid-lowering agent) users or statin-LLA users were performed blind to the ADAPT medication randomization. Pearson's correlations were validated using a time-dependent linear mixed model. **Results:** The MMSE performance significantly declined over time in non-LLA users, and, after adjusting for this, a significant positive correlation between MMSE and HDL was identified ($p = 0.0002$). A negative correlation between total and LDL cholesterol, and im-

mediate and delayed recall of the Rivermead paragraph was significant (total cholesterol, $p < 0.003$; LDL, $p < 0.02$). Pilot data suggest a positive signal on delayed recall of both the Hopkins word list and Rivermead paragraph with deterioration in the non-LLA users and improvement in the statin users after conversion to MCI. **Conclusion:** Cholesterol levels may be associated with differential performance on the MMSE and measures of learning or memory. The trend for improved delayed recall in statin users with MCI compared to non-LLA users with MCI may have contributed to the reduced hazards risk of incident AD without reducing the risk of MCI.

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Introduction

Most clinical data suggest that statin treatment may reduce the risk of Alzheimer's disease (AD) later in life. The last three large cohort studies of over 10,000 total subjects [1–3] found significantly reduced risk of incident AD with elective statin use. Data from the Rotterdam study, the largest cohort investigation to date [3], indicate

Fig. 1. Plot of estimated performance on delayed recall of the Hopkins word list among individuals with MCI taking statins (dashed line) and those not taking an LLA (solid line) versus time (0–30 months). p value for slope of the statin line is 0.083; p value for slope of the non-LLA line is 0.24; p value for difference in slope is 0.039.

a reduction in the risk of incident AD with elective statin use regardless of an individual's ApoE genotype or statin BBB permeability.

Our study of the effect of elective statin use on the risk of AD comes from the findings in individuals enrolled in the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) who were allowed the elective use of statins and other lipid-lowering agents (LLAs) [2]. Cognitive performance was not influenced by statin use in cognitively normal controls [2]. We also reported that elective statin use was associated with a significant reduction in the risk of AD associated with ongoing statin use, but there was no reduction in the risk of mild cognitive impairment (MCI) [2]. The objective of the current study was to determine if cholesterol levels were associated with differences in cognitive performance among the 1,309 cognitively normal ADAPT participants not using an LLA during the trial, and to determine if cognitive performance was altered by statin use after conversion to MCI.

Methods

ADAPT was a randomized, double-blind, placebo-controlled, primary prevention trial testing whether NSAIDs prevent or delay incident AD. Specifics regarding study design and eligibility criteria are available elsewhere [4]. Persons regularly using NSAIDs were excluded, but LLA use was permitted and recorded at each scheduled visit.

Eligible participants were randomly assigned to receive NSAIDs or matching placebos irrespective of LLA use. The effect of statin use was analyzed without regard to or knowledge of the primary treatment assignment.

Procedures and outcome assessments are detailed elsewhere [2]. Briefly, the eligibility of prospective participants was established using specified health criteria and scores on an Eligibility Battery, which included the MMSE [5]. Eligible individuals returned for a baseline visit testing their cognitive and functional abilities using a Cognitive Assessment Battery [4], which included delayed recall on the Hopkins Verbal Learning Test and immediate and delayed recall of the Rivermead paragraph. Participants with abnormal cognition received diagnoses of AD using NINCDS/ADRDA criteria, or MCI using published methods [6].

Total cholesterol (TC), LDL, and HDL were correlated with each of the cognitive variables (MMSE, Hopkins word list, Rivermead paragraph) at each visit by calculating Pearson's correlation coefficients and determining if each correlation is statistically significant. We also employed an alternative analysis which relies on a linear mixed model (LMM) in which each clinical variable is regressed on time on study and one of the cholesterol values to determine if that cholesterol measurement is consistently correlated with the end point after adjusting for the decline in the scores over time. The LMM addresses inflation of the type I error rate and accounts for repeated measures made over time.

Analysis of the effect of statins was restricted to the 31 participants who converted to MCI and had at least one observation on their cognition after the date of this diagnosis. Cognitive scores analyzed were limited to all scores after diagnosis as well as the last visit before conversion. Each clinical variable was then regressed on time, statin use (yes or no) and the interaction between statin use and time. Particular interest centered around the interaction, since this would indicate whether decline varied significantly with statin use.

Results

We report the effect of cholesterol levels on cognitive performance in non-LLA using controls and elective statin use compared to non-LLA in MCI, blind to primary anti-inflammatory or placebo use in ADAPT. Based

Fig. 2. Plot of estimated performance on delayed recall of the Rivermead paragraph among individuals with MCI taking statins (dashed line) and those not taking an LLA (solid line) versus time (0–30 months). p value for slope of the statin line is 0.23; p value for slope of the non-LLA line is 0.23; p value for difference in slope is 0.096.

on this reclassification, we considered two groups of ADAPT participants in the current study: 1,309 non-LLA users and 759 statin LLA users. Demographic data are reported elsewhere [2]. Of the 50 individuals (33 non-LLA and 17 statin users) converting to MCI, 16 non-LLA users returned for a clinical follow-up visit; 4 were longitudinally assessed, and 15 of the statin-using individuals returned for a follow-up clinical visit; 5 were longitudinally assessed.

MMSE scores declined significantly over time in the non-LLA population. There was a significant positive Pearson's correlation between HDL-cholesterol and MMSE, and after adjusting for time-dependent decrease in MMSE the significant positive correlation between MMSE and HDL remained after LMM analysis ($p = 0.0002$). The negative correlation between TC and LDL cholesterol, and immediate and delayed recall of the Rivermead paragraph remained significant using the LMM analysis (TC, $p < 0.003$, and LDL, $p < 0.02$).

Although there was no significant difference between the non-LLA and statin-LLA users prior to or after conversion to MCI in performance scores on any of the four cognitive measures, the pilot data suggest there is a positive signal on both delayed recall of the Hopkins word list (fig. 1) and the Rivermead paragraph (fig. 2), and the MMSE (not shown) with deterioration in the non-statin users and improvement in the statin users after conversion to MCI. The difference in slope between statin use and non-LLA use groups achieved significance for the Hopkins word list ($p = 0.039$), trended toward significance for the Rivermead paragraph ($p = 0.096$), and was not significant for the MMSE ($p = 0.19$).

Discussion

A modest but significant decrease in global function (MMSE) was identified using a time-dependent assessment (LMM) which was not apparent for measures of learning or memory (Rivermead immediate and delayed recall, and Hopkins delayed recall). Our data tend to confirm previous reports of a positive relationship between HDL cholesterol and cognitive performance, and disclosed a significant deterioration in learning and memory (Rivermead) with increased total and LDL cholesterol.

Consistent with the two very large prospective studies published in 2002 suggesting statins produced no positive effect on cognition in younger individuals at risk for heart disease [7, 8], we found no differences in the mean MMSE performance [2], or recall of the Hopkins word list and Rivermead paragraph between statin users and non-LLA users prior to conversion to MCI. After onset of MCI, elective statin use produced a positive signal on clinical measures of cognition (fig. 1, 2). The trend for improvement on delayed recall of the Hopkins word list and the Rivermead paragraph in statin users with MCI compared to non-LLA users with MCI may have contributed to the reduced hazard risk of incident AD without reducing the risk of incident MCI previously reported [2].

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