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Statin Use is Associated with Better Cognitive Function in Elderly with Type 2 Diabetes

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Abstract

The pleiotropic contribution of statins on cognition is uncertain. From 840 patients in the cohort from the Israel Diabetes and Cognitive Decline Study, we identified 61 non-statin users and compared them with 45 patients who had used statins at least 90% of the time. Analysis of covariance was performed to compare mean cognitive z-scores between statin users and non-users while adjusting for socio-demographic, diabetes-related, and cardiovascular covariates which included change in cholesterol by year. Overall cognition, memory, and executive function was found to be significantly better in statin users ($p < 0.0008$). This suggests a positive effect of statins on cognitive function of type 2 diabetes patients that is independent of cholesterol levels.

Keywords

All cognitive disorders/dementia; Alzheimer's disease; case control studies; diabetes

INTRODUCTION

While efficacy of statins on cholesterol has been extensively studied [1], there is less information reported on their unintended effects. Recently, the U.S. Food and Drug Administration suggested that there may be an association between statins and cognitive impairment [2]. After a systematic review of 57 studies [3], the evidence remains inconclusive. The randomized controlled trial (RCT) at the lowest risk of bias ($n = 5,804$) demonstrated no significant difference in change in global cognitive performance assessed by Mini-Mental State Examination (MMSE) between statin- and placebo-treated patients

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[4]. Similarly, a recent review [5], which included two large randomized controlled trials, showed that statins had no benefit on the primary outcome measures of the Alzheimer's Disease Assessment Scale-cognitive sub-scale or the MMSE. In contrast, three cohort studies (total $n = 4,688$) suggested a significantly better global cognitive performance with statin use [6–8]; and a systematic review [9] of three RCTs of statins for treatment of dementia (748 patients with a mean age of 79 years, with probable or possible Alzheimer's disease, followed for 6 months or longer) showed no beneficial effect of statins, however, trends favored statins preventing cognitive decline.

The question of possible cognitive benefits of statins is particularly relevant to patients with diabetes since they have a significantly higher risk of dementia [10] and also take statins as a standard part of their treatment protocol. However, this has been difficult to investigate since statins reduce cholesterol levels, which is also associated with cognitive decline.

We report the results of a study of patients with diabetes in the Israel Diabetes and Cognitive Decline (IDCD) Study, an investigation of the relationships of type 2 diabetes characteristics with cognitive decline, and exploit the opportunity of examining the relationship of statins with cognition, above and beyond their effects on cholesterol [11].

METHODS

The IDCD is a collaboration between the Icahn School of Medicine at Mount Sinai, New York, the Sheba Medical Center, Israel, and the Maccabi Healthcare Services (MHS), Israel and is approved by all three relevant Institutional Review Boards. All participants gave informed consent. Community-dwelling elderly with type 2 diabetes, 65 + years old were recruited from approximately 11,000 patients living in central Israel, enrolled in the diabetes registry of MHS which has complete data collection for all patients from 1998. MHS is the second largest HMO in Israel, treating a representative cross-section of 2 million citizens. IDCD eligibility criteria were having type 2 diabetes; normal cognition at entry to the study; being free of any neurological, psychiatric, or other diseases that might affect cognition; having at least 2 HbA1c assessments, and having an informant. At entry to the IDCD study, participants were assessed by a physician experienced in assessment and diagnosis of dementia, and by a neuropsychologist, who administered a broad neuropsychological battery [12], which was the basis for the outcome measures. Factor analysis summarized the neuropsychological measures into four domains: episodic memory (immediate recall, delayed recall, and recognition), executive functioning (Trails A and Trails B, constructional praxis, and digit symbol), semantic categorization (similarities, letter fluency, category fluency), and attention/working memory (diamond cancellation, digit span forward, and digit span backwards). The neuropsychological tests scores were transformed into Z scores (reversed if necessary so that a high score represented good cognition) and summed for each domain. An overall cognition measure summed the scores of all four domains. This investigation includes historical diabetes-related data and the baseline cognitive and biochemical data collected from each patient as they were enrolled by the IDCD study. The socio-demographic variables were age at the time of cognitive assessment, years of education, and gender. The cardiovascular covariates were body mass index, triglycerides, diastolic and systolic blood pressure, and glomerular filtration rate. Diabetes-related

covariates were number of follow up years in the registry (an approximation of duration of type 2 diabetes), Hemoglobin A1c (HbA1c), and type 2 diabetes medications (defined as no medication, only non-insulin hypoglycemic medications, only insulin, and combination of insulin and hypoglycemic medications).

Using historical data prior to the date when patients entered the registry, we were able to tighten the eligibility criteria for this study such that for statin users we included only patients who had been taking statins for at least one year prior to their entry to the registry (which is the date that they were first diagnosed with diabetes). We computed the proportion of days in the registry that they were taking a statin medication, that is, the proportion of days covered (PDC). All statin data is from purchase data in our pharmacies. In view of the small number of subjects available for this study, we decided that days covered using statins was more important than type of statins. There was quite a large range of PDCs among these patients so we restricted the analysis to statin users with a PDC of at least 90%, reflecting consistent regular use of statins while in the registry (when they were diagnosed with diabetes). By restricting eligibility to users who had taken statins prior to entry to the registry and those who had a 90% PDC while in the registry, we observed comparable cholesterol levels between users and non-users, both at entry and over time, until their assessment in the ICDC study. For each cardiovascular covariate included in the model, we used the average of all measurements available in the MHS Diabetes Registry per subject.

Statistical analysis

As expected in a type 2 diabetes sample, there were many statin users ($n = 769$) and relatively few non-users ($n = 61$) with complete data on all covariates and outcome measures. Among the 769 statin users, there were 45 who had used statins at least 90% of their time in the registry (PDC = 90%) and had been on statins at least one year prior to their entry to the registry.

In addition to these inclusion criteria, we adjusted for cholesterol levels at entry to the registry as well as annual rates of change in cholesterol during time in the registry (subject-specific cholesterol slopes) among other covariates in our analysis of covariance (ANCOVA) model to control for any remaining differences with respect to these variables between groups.

ANCOVA was performed for each of the cognitive domains to estimate and compare mean cognitive z-scores between statin users and non-users, first in an unadjusted model (Model A), then adjusting for socio-demographic (Model B), and then also for diabetes-related covariates (Model C), and for cardiovascular covariates including subject specific cholesterol intercept and slopes (Model D). All statistical analyses were performed using SAS Version 9.2 (SAS Institute, Inc., Cary, NC). All hypothesis testing was conducted at the 5% (2-sided) level of significance.

RESULTS

Forty-five statin users and 61 non-users were identified among the 840 subjects in the registry with complete data on cognitive outcomes, socio-demographic, cardiovascular, and

diabetes-related characteristics Table 1. The 45 statin-users can be classified as regular users who had taken statins at least 90% of their time in the registry (range: 91%–98%) and who at entry to the diabetes registry had cholesterol levels comparable to the non-users since they had been taking their medications and thereby controlling their cholesterol levels for at least 1 year prior to entry. Statin-users and non-users had similar characteristics except that users had fewer years in the registry than non-users (7.2 versus 8.5); $p = 0.0184$ and experienced greater improvement in cholesterol level per year (-3.3 versus -2.4); $p = 0.0335$.

Table 2 shows that statin users had consistently better cognitive function than non-users. In each of the models, overall cognition, memory, and executive function was found to be significantly better in statin users. The domain of language, while not always significant, was also better in statin users. The cognitive domain of attention did not reach significance in any of the models.

DISCUSSION

In this study, the availability of long-term cholesterol measurements (averaging 18 cholesterol measurements per subject) in the years before enrolment in the study allowed us to estimate annual rates of change in cholesterol levels for each subject and to adjust the comparison of cognitive function between statin users and non-users not only for differences in cholesterol levels at entry to the registry but also for differences in the annual rates of change, thereby neutralizing the lipid lowering effects of statins and their possible effect on cognitive function. Statin users have on average a one unit greater improvement per year in cholesterol than non-users and this difference was statistically significant. However, when adjusting for the slope in the ANCOVA model, statin use remained significantly associated with better cognition suggesting that statin use has beneficial effects on cognition above and beyond its ability to lower cholesterol levels.

Our findings indicate a positive potential pleiotropic effect of statins on cognitive performance that is independent of cholesterol levels in patients with type 2 diabetes. This is in contrast to much of the literature for the general population, suggesting that in the context of the high risk for dementia in diabetes, with incipient brain compromise, statins may have a beneficial effect on cognition. The statins users group also received more combinations of insulin and hypoglycemic medication than non-users. This combination of diabetes medications has been associated with fewer neuritic plaques, the hallmark characteristic of Alzheimer's disease, compared to no medications or each alone, possibly explaining the cognitive benefits found in this study [13]. However, controlling for diabetes medications in our statistical models did not alter the results. The study is limited by a small number of subjects, having only one time point on cognitive performance, and the lack of neuroimaging that would examine whether the difference in cognition is reflected in neurodegeneration and cerebrovascular disease. It may be that the five percent of non-statin users in our cohort are in some way different from the rest of our sample with type 2 diabetes and thus our findings should be interpreted with caution. The study is strengthened by its broad neuropsychological battery permitting examination of overall cognition and specific cognitive domains. Israel has socialized medicine and the copayment is heavily subsidized; only 10% of the medication price at the Maccabi pharmacies, therefore data collection

regarding use of statins is complete. We were also able to identify use before entry to the diabetes registry. We avoid the dangers of over matching by presenting unadjusted estimates in users and non-users followed by multiple tiered adjustments eventually getting to the fully adjusted model; our results are consistently robust in all models. We show a positive pleiotropic effect of statins on cognitive function of type 2 diabetes patients that is independent of total cholesterol levels.

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Table 1

Description of matching Statin non-users and users

	Non-Statin N = 61	Statin N = 45	P-value	Overall
<i>Years in Registry</i>	8.5 (2.4)	7.2 (3.3)	0.0184	8.0 (2.9)
Mean (SD) [Min-Max]	[2.1–14.3]	8.4 [1.5–10.9]		9.1 [1.5–14.3]
<i>Current Age</i>	72.5 (4.6)	73.1 (4.0)	0.5084	72.8 (4.4)
Mean (SD) [Min-Max]	[66–85]	73 [67–84]		72 [66–85]
<i>Years of Education</i>	12.1 (3.2)	12.9 (3.1)	0.2047	12.5 (3.2)
Mean (SD)				
<i>Gender</i>	35 (57%)	25 (56%)	0.8516	60 (57%)
Male	26 (43%)	20 (44%)		46 (43%)
Female				
$\ddagger$ SBP	135.3 (8.8)	135.1 (8.6)	0.9229	135.2 (8.7)
Mean (SD)				
$\ddagger$ DBP	77.1 (5.2)	77.9 (4.3)	0.4244	77.5 (4.8)
Mean (SD)				
$\ddagger$ BMI	28.2 (5.1)	28.8 (3.8)	0.4839	28.5 (4.6)
Mean (SD)				
$\ddagger$ HbA1c	6.7 (0.9)	6.7 (0.7)	0.9665	6.7 (0.8)
Mean (SD)				
$\ddagger$ $\ddagger$ GFR	84.3 (28.2)	78.8 (23.2)	0.2884	82.0 (26.3)
Mean (SD)				
<i>Cholesterol Intercept</i>	176.6 (30.7)	184.5 (25.4)	0.1665	180.0 (28.8)
Mean (SD) [Min-Max]	[100.7–240.3]	[131.5–251.8]		[100.7–251.8]
<i>Cholesterol Slope</i>	−2.4 (2.0)	−3.3 (2.3)	0.0335	−2.8 (2.2)
Mean (SD) [Min-Max]	[−7.3–1.4]	[−9.0–1.7]		[−7.3–1.7]
<i>Diabetes Medication</i>	47 (77%)	31 (68%)	0.322	78 (74%)
Hypoglycemic Only	4 (7%)	7 (16%)		11 (10%)
Insulin+Hypoglycemic	10 (16%)	7 (16%)		17 (16%)
None				

 $\ddagger$ glomerular filtration rate (GFR). $\ddagger$ Mean value for all recorded values.

Table 2

Comparison of Statin non-users with Statin users and cognitive status PDC 90%

Model A	Non-Statins N = 61	Statin N = 45	P-value
Overall	-1.64 ± 0.97	2.82 ± 1.13	0.0036
Memory	-0.21 ± 0.27	0.82 ± 0.31	0.0148
Language	-0.52 ± 0.27	0.22 ± 0.31	0.0758
Attention	-0.10 ± 0.25	0.007 ± 0.29	0.7805
Executive	-0.64 ± 0.35	1.05 ± 0.41	0.0023
Model B	Non-Statins N = 61	Statin N = 45	P-value
Overall	-1.44 ± 0.88	2.55 ± 1.02	0.0040
Memory	-0.21 ± 0.26	0.82 ± 0.30	0.0115
Language	-0.47 ± 0.26	0.14 ± 0.30	0.1287
Attention	-0.04 ± 0.24	-0.08 ± 0.28	0.9030
Executive	-0.59 ± 0.33	0.98 ± 0.39	0.0028
Model C	Non-Statins N = 61	Statin N = 45	P-value
Overall	-2.45 ± 1.21	2.45 ± 1.15	0.0009
Memory	-0.22 ± 0.38	0.88 ± 0.36	0.0143
Language	-0.91 ± 0.35	0.02 ± 0.33	0.0268
Attention	-0.41 ± 0.33	-0.14 ± 0.32	0.4930
Executive	-0.73 ± 0.46	0.93 ± 0.44	0.0028
Model D	Non-Statins N = 61	Statin N = 45	P-value
Overall	-2.74 ± 1.32	2.62 ± 1.23	0.0011
Memory	-0.29 ± 0.40	0.98 ± 0.38	0.0104
Language	-1.08 ± 0.38	0.07 ± 0.36	0.0155
Attention	-0.46 ± 0.36	-0.0001 ± 0.33	0.2820
Executive	-0.63 ± 0.48	0.78 ± 0.45	0.0169

Mean ± SE shown. Model A: Unadjusted. Model B: Adjusted for age, education, gender. Model C: Adjusted for age, education, gender, years in diabetes registry, diabetes medication use, HbA1c. Model D: Adjusted for age, education, gender, years in diabetes registry, diabetes medication use, HbA1c, GFR, SBP, DBP, LDL, HDL, Cholesterol level at entry to diabetes registry, Cholesterol slope (change in cholesterol per year) during diabetes registry.