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A Pilot Study: The Beneficial Effects of Combined Statin-exercise Therapy on Cognitive Function in Patients with Coronary Artery Disease and Mild Cognitive Decline

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Abstract

Objective Hypercholesterolemia, a risk factor in cognitive impairment, can be treated with statins. However, cognitive decline associated with “statins” (HMG-CoA reductase inhibitors) is a clinical concern. This pilot study investigated the effects of combining statins and regular exercise on cognitive function in coronary artery disease (CAD) patients with prior mild cognitive decline.

Methods We recruited 43 consecutive CAD patients with mild cognitive decline. These patients were treated with a statin and weekly in-hospital aerobic exercise for 5 months. We measured serum lipids, exercise capacity, and cognitive function using the mini mental state examination (MMSE).

Results Low-density lipoprotein cholesterol levels were significantly decreased, and maximum exercise capacity (workload) was significantly increased in patients with CAD and mild cognitive decline after treatment compared with before. Combined statin-exercise therapy significantly increased the median (range) MMSE score from 24 (22-25) to 25 (23-27) across the cohort ($p<0.01$). Changes in body mass index (BMI) were significantly and negatively correlated with changes in the MMSE. After treatment, MMSE scores in the subgroup of patients that showed a decrease in BMI were significantly improved, but not in the BMI-increased subgroup. Furthermore, the patients already on a statin at the beginning of the trial displayed a more significant improvement in MMSE score than statin-naïve patients, implying that exercise might be the beneficial aspect of this intervention as regards cognition. In a multivariate logistic regression analysis adjusted for age >65 years, sex, and presence of diabetes mellitus, a decrease in BMI during statin-exercise therapy was significantly correlated with an increase in the MMSE score (odds ratio: 4.57, 95% confidence interval: 1.05-20.0; $p<0.05$).

Conclusion Statin-exercise therapy may help improve cognitive dysfunction in patients with CAD and pre-existing mild cognitive decline.

Key words: statins, exercise, cognition, coronary artery disease

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Introduction

The number of dementia cases in developed countries is dramatically increasing, and rising health care costs related to dementia are a large social problem (1). Cardiovascular diseases, as well as their risk factors, are strongly associated with cognitive decline (2). Development of effective therapeutic strategies for cognitive dysfunction in coronary artery disease (CAD) patients is therefore an urgent issue.

Statins are effective in reducing cardiovascular events and are recommended for secondary prevention in all patients who have CAD and tolerate statin therapy (3). However, the US Food and Drug Administration and several reviews have raised concern regarding potential adverse cognitive effects associated with statins (4-7). Exercise therapy is recommended as a protective factor for cognition in older adults, as well as CAD patients (8).

We previously reported that exercise combined with statins is clinically useful and an effective treatment for CAD patients (9-11). However, the effects of statin-exercise therapy on cognitive function in CAD patients have not been fully clarified.

In the present study, we examined whether or not statin-exercise therapy is beneficial for managing cognitive decline in patients with CAD and pre-existing mild cognitive impairment.

Materials and Methods

Study population

We performed a prospective observational study to investigate the clinical significance of regular exercise and statin treatment in CAD patients with mild cognitive decline. We recruited 43 consecutive CAD patients with mild cognitive decline (mini mental state examination [MMSE] score <25). All patients were referred to our hospital for low-density lipoprotein (LDL) cholesterol-lowering therapy with statins in order to achieve guideline goals and underwent cardiac rehabilitation therapy at the Division of Cardiology, Hitoyoshi Medical Center between April 2011 and August 2014. Patients who could not perform cardiopulmonary exercises or undergo MMSE tests during the study period were excluded.

Study design

The patients performed weekly 30-minute in-hospital aerobic exercises on ergometer-equipped bicycles. The aerobic exercises were based on anaerobic thresholds that were evaluated with cardiopulmonary exercise tests. Patients performed the exercises for 5 months. An experienced registered exercise rehabilitation instructor instructed all of the patients regarding the performance of 30-minute walking or cycle ergometer exercises at home to a Borg scale rating of 12-13. All of the patients were treated with one of a variety of statins to achieve guideline goal levels for LDL (<70 mg/dL). Thirty statin-naive subjects were started on a *de novo* statin. Ten patients with pre-existing statin treatment remained on their current dose and statin, two patients were switched to similar-intensity therapy, and one patient had their dose increased. The protocol of the Hitoyoshi Cardiovascular Rehabilitation Study (HARVEST), which is evaluating the efficacy of exercise therapy on patients with cardiovascular disease and is registered with the UMIN protocol registration system (identification number UMIN 000015544; https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&recptno=R000018044&type=summary&language=E), was approved by the Institutional Review Board of the Hitoyoshi Medical Center in Kumamoto, Japan. A signed consent form was obtained from each patient. The methods in this study were performed in accordance with approved guidelines.

Home exercise instructions

All of the patients were instructed to perform exercises at home under the supervision of a registered exercise rehabilitation instructor, as previously described (9). The patients maintained personal healthcare logs in which they recorded their daily blood pressure, body weight, and exercises that were performed at home. Patients who did not complete the home exercises received repeat instruction and were asked again to perform the training.

Blood biochemistry

Venous blood samples were collected before the exercise test.

Cognitive assessment

The MMSE test, a brief 30-point questionnaire, was conducted by a single trained technician at baseline and at the end of treatment. Subjects who scored below 25 were considered to have mild cognitive impairment.

Cardiopulmonary exercise test

An individually optimized 5-, 10-, 15-, and 20-Watt ramp-up exercise protocol on an electromagnetically braked cycle ergometer (Well Bike BE-250; Cat Eye Co., Osaka, Japan) with blood pressure and heart rate monitoring was performed in a temperature-controlled room (23-25°C), as previously described (9). Respiratory gas was sampled from a mouthpiece, and minute ventilation, carbon dioxide in expired air, oxygen in inspired air, ventilatory equivalent for carbon dioxide, and ventilatory equivalent for oxygen were measured for each breath using a breath-by-breath gas analyzer (AE310S; Minato Medical Science, Osaka, Japan). Peak oxygen uptake, anaerobic threshold, and maximum workload were evaluated at baseline and at the end of treatment.

Statistical analyses

We used the Shapiro-Wilk test to determine whether the

Table 1. Patients' Characteristics.

All patients (n = 43)	
Age (years)	71 ± 8
Male, n (%)	35 (81)
Angina pectoris, n (%)	9 (21)
Myocardial infarction, n (%)	29 (67)
Heart failure, n (%)	11 (26)
Cerebral stroke, n (%)	3 (7)
Risk factors	
Hypertension, n (%)	32 (74)
Diabetes mellitus, n (%)	15 (35)
Dyslipidemia, n (%)	34 (79)
Chronic kidney disease, n (%)	20 (47)
Current smoking, n (%)	5 (12)
Medical therapies	
Aspirin, n (%)	42 (98)
Anticoagulant, n (%)	9 (21)
Angiotensin II receptor blocker, n (%)	13 (30)
Angiotensin-converting enzyme inhibitor, n (%)	23 (53)
Diuretic, n (%)	12 (28)
Calcium channel blockers, n (%)	20 (47)
β-blockers, n (%)	24 (56)
Nitrate, n (%)	9 (21)
Oral hypoglycemic agents, n (%)	6 (14)
Insulin, n (%)	4 (9)

Data are mean ± SD or n (%).

samples were normally distributed. Depending on the distribution of data, the paired Student's *t*-test or Wilcoxon test was used to analyze the effects of 5 months' treatment. Pearson or Spearman correlation tests were used to analyze correlations between changes in the MMSE and changes in other parameters. To determine the independent association between changes in the MMSE and changes in body mass index (BMI), we adjusted for the effects of other covariates on the cognitive function with multivariate linear regression analysis with forced inclusion of the variables of age, sex, and the presence of hypertension, diabetes mellitus, and cerebral stroke. Univariate and multivariate logistic regression analyses were used to assess the baseline parameters, risk factors, and medications that were correlated with an elevation in MMSE score (ΔMMSE = [MMSE score after 5 months] - [baseline MMSE score]; cutoff value of ΔMMSE = 1.0, median). There were a total of four missing data-points for HbA1c in non-diabetic patients (two missing baselines, and two separate patients missing 5-month data). The data are expressed as the mean±standard deviation, or median value. A value of $p<0.05$ was considered statistically significant. All statistical analyses were performed using the IBM SPSS Statistics software program, Version 21.0 (IBM Corp., Armonk, NY, USA).

Results

Patients' characteristics

The patients' baseline characteristics are shown in Table 1. Forty-three CAD patients (aged 71±8 years, 81% male) were included.

Effect of statin-exercise therapy on the cognitive function and other parameters

Five months of combined statin-exercise therapy significantly improved the cognitive decline on average, as measured by the MMSE test (Figure A). Table 2 shows the effects of statin-exercise therapy on various parameters. The cardiopulmonary function, as measured by the maximum workload capacity, significantly improved after treatment. The average total cholesterol and LDL cholesterol levels were significantly decreased after treatment compared with before treatment.

Effect of pre-treatment statin and statin types on cognitive outcome

Thirteen patients were on pre-existing statin therapy at the beginning of the statin-exercise therapy period. Overall, this subgroup experienced little-to-no changes in their statin regimen at the initiation of the trial. These patients displayed a significant increase in the MMSE score ($p<0.009$), which was not observed in the statin-naïve patients (Figure B). Notably, the average BMI was not markedly different between the pre-existing statin treatment and statin-naïve groups after treatment (25.8±4.2 to 26.1±3.6 kg/m^2, p=0.521; 23.6±3.2 to 23.5±3.2 kg/m^2, p=0.611, respectively).

Further, the mean (range) MMSE score of lipophilic statins users (n=26) increased significantly from 24 (22-25) to 25 (23-28) (p=0.005). In contrast, hydrophilic statin users (n=17) saw no marked changes (25 [22-26] to 24 [23-27], p=0.217).

Baseline diabetes mellitus and improvement of the cognitive function

Fifteen diabetic CAD patients were included in this study. Six diabetic patients were taking oral glycemic agents, while four separate patients were taking insulin (Table 1). While the anti-diabetic agents might have had effects on BMI and cognition, a univariate logistic regression analysis showed that neither oral hypoglycemic agents nor insulin correlated with an increase in the MMSE score (Table 3) or a decrease in the BMI (odds ratio: 1.85, p=0.489; and 0.53, p=0.601, respectively). Further, although the baseline fasting blood glucose level, HbA1c level, and oral hypoglycemic agents were not associated with cognitive response (Table 3), a univariate logistic regression analysis showed that the presence of diabetes mellitus (DM) was significantly negatively correlated with an increase in the MMSE score (odds ratio: 0.24, $p<0.05$). The MMSE in non-diabetic CAD patients significantly increased after treatment compared with before treatment, with no marked changes in the diabetic patients (Figure C).

Effects of statin-exercise therapy-associated changes in BMI on cognitive decline

Although the average BMI did not change markedly across the study group (Table 2), changes in the BMI were

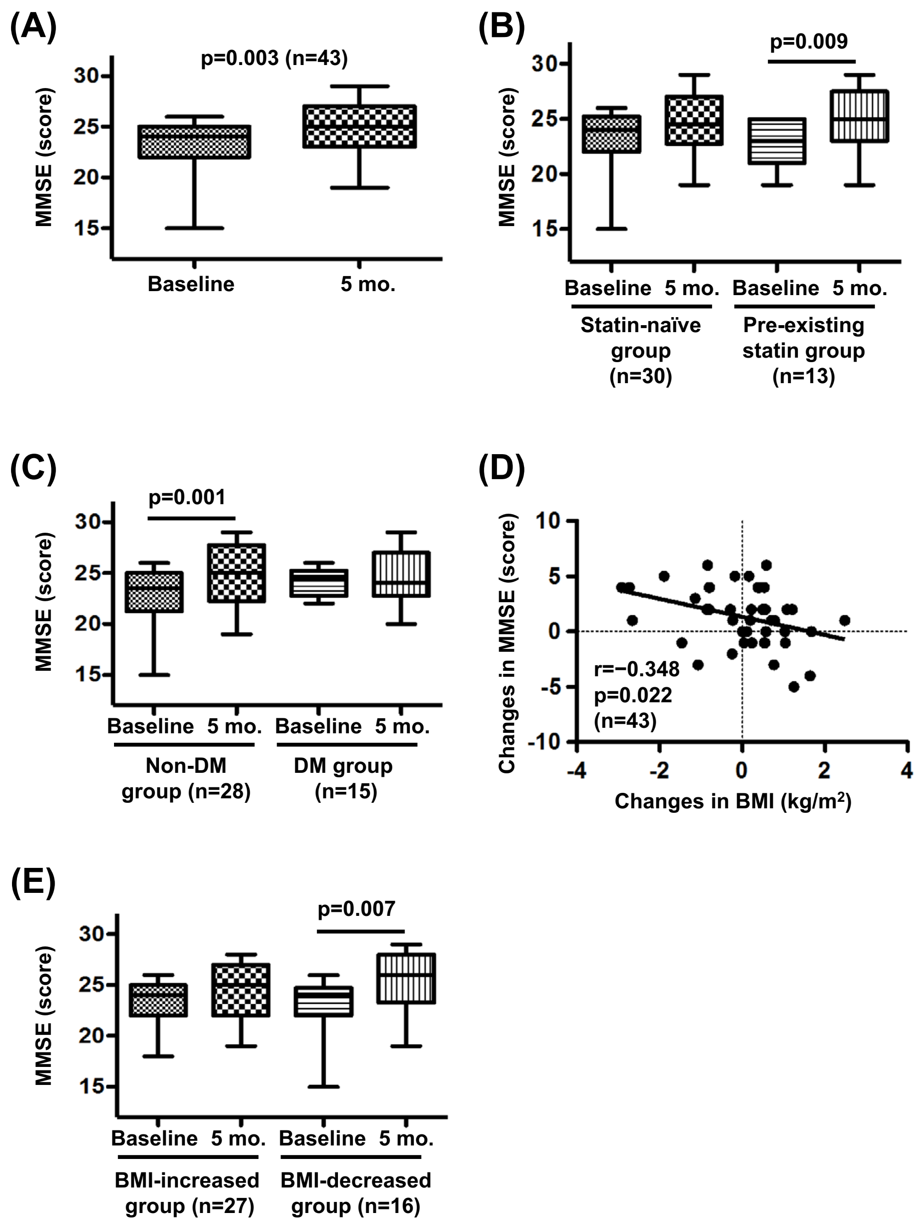

Figure. The effect of statin-exercise therapy on cognition in CAD patients with mild cognitive decline. (A) Box-and-whisker plot showing the effect of combined exercise and statin treatment for 5 months on the cognitive function using the MMSE test. (B) Box-and-whisker plot showing the effect of statin-exercise therapy on the MMSE score between the statin-naïve group and pre-existing statin groups. (C) Box-and-whisker plot showing the effect of combined exercise and statin therapy for 5 months on the MMSE scores between patients without DM (non-DM) and those with DM. (D) A regression analysis showing the correlation between changes in the BMI and changes in the MMSE score. (E) Box-and-whisker plot showing the effect of statin-exercise therapy on the MMSE score between the BMI-increased and BMI-decreased groups. (A, B, C, and E) In these box-and-whisker plots, the lines within the boxes represent the median values, the upper and lower lines of the boxes represent the 25th and 75th percentiles, respectively, and the upper and lower bars outside the boxes represent the 90th and 10th percentiles, respectively. MMSE: mini mental state examination, BMI: body mass index, 5 mo: 5 months, n: number of patients in each group

inversely correlated with changes in the MMSE (Figure D, Table 4). After adjusting for age, sex, and the presence of hypertension, DM, and cerebral stroke, a multivariate linear regression analysis showed that changes in the BMI were still significantly associated with changes in the MMSE (Table 5). Furthermore, there was a significant inter-subgroup difference in changes in the BMI between the MMSE-increased (ΔMMSE >1.0) and the MMSE-decreased groups (ΔMMSE ≤1.0) (Table 6).

The MMSE in the BMI-decreased group (ΔBMI = [BMI after 5 months] - [baseline BMI]; ΔBMI <0.0) was significantly elevated after treatment compared with before treat-

Table 2. Effects of Statin-exercise Treatment on Various Parameters.

All patients (n=43)	Baseline	5 months	p value
Systolic blood pressure, mmHg	120 ± 14	122 ± 15	0.298
Diastolic blood pressure, mmHg	69 ± 9	70 ± 10	0.451
Body mass index, kg/m^2	24.3 ± 3.6	24.3 ± 3.5	0.966
Abdominal circumference, cm	88 (84 to 94)	87 (81 to 93)	0.070
Anaerobic threshold, mL/min/kg	10.3 ± 2.0	10.7 ± 2.0	0.238
Peak oxygen uptake, mL/min/kg	15.7 ± 3.9	16.4 ± 3.0	0.067
Maximum work load, max Watts	77 (53 to 95)	82 (63 to 97)	0.003
Left ventricular ejection fraction, %	59.1 ± 11.8	61.8 ± 7.8	0.086
Hemoglobin, g/dL	13.7 ± 1.5	13.7 ± 1.5	0.719
Albumin, g/dL	3.9 (3.5 to 4.1)	4.2 (4.0 to 4.6)	< 0.001
Estimated glomerular filtration rate, mL/min/1.73 m^2	58.9 (53.4 to 66.4)	59.7 (51.3 to 67.9)	0.915
Total cholesterol, mg/dL	185 (153 to 204)	145 (126 to 156)	< 0.001
High-density lipoprotein cholesterol, mg/dL	45 (39 to 56)	47 (42 to 57)	0.199
Low-density lipoprotein cholesterol, mg/dL	115 (91 to 127)	69 (57 to 82)	< 0.001
Triglycerides, mg/dL	116 (76 to 163)	108 (66 to 152)	0.343
HbA1c, %	5.7 (5.5 to 6.4)	5.8 (5.5 to 6.3)	0.819

Data are mean ± SD, or median (25-75%).

Table 3. Logistic Regression Analysis for Elevation of Mini Mental State Examination Scores among Baseline Parameters.

All patients (n=43)	Univariate		Multivariate (Hosmer–Lemeshow test; p=0.204)	
	OR (95% CI)	p value	OR (95% CI)	p value
Age, years	1.04 (0.96 to 1.13)	0.311		
≥65 years old, yes	1.98 (0.48 to 8.13)	0.342	1.54 (0.32 to 7.49)	0.593
Sex, male	1.77 (0.36 to 8.55)	0.480	2.20 (0.32 to 15.0)	0.422
Systolic blood pressure, mmHg	1.01 (0.96 to 1.05)	0.769		
Diastolic blood pressure, mmHg	0.99 (0.93 to 1.07)	0.873		
Body mass index, kg/m^2	0.99 (0.84 to 1.17)	0.897		
Decrease in body mass index, yes	3.74 (1.01 to 13.9)	0.049	4.57 (1.05 to 20.0)	0.043
Abdominal circumference, cm	0.98 (0.91 to 1.06)	0.602		
Decrease in Abdominal circumference, yes	1.63 (0.48 to 5.47)	0.433		
Anaerobic threshold, mL/min/kg	1.01 (0.75 to 1.37)	0.935		
Peak oxygen uptake, mL/min/kg	0.98 (0.84 to 1.15)	0.789		
Maximum work load, max Watts	1.00 (0.98 to 1.02)	0.896		
Left ventricular ejection fraction, %	1.00 (0.95 to 1.06)	0.944		
Hemoglobin, g/dL	0.92 (0.65 to 1.32)	0.668		
Albumin, g/dL	1.05 (0.19 to 5.63)	0.959		
Estimated glomerular filtration rate, mL/min/1.73 m^2	1.03 (0.97 to 1.08)	0.359		
Total cholesterol, mg/dL	0.99 (0.98 to 1.01)	0.262		
High-density lipoprotein cholesterol, mg/dL	1.00 (0.95 to 1.05)	0.913		
Low-density lipoprotein cholesterol, mg/dL	0.99 (0.98 to 1.01)	0.459		
Triglycerides, mg/dL	1.00 (0.99 to 1.00)	0.246		
Fasting blood glucose, mg/dL	0.99 (0.96 to 1.01)	0.280		
HbA1c, %	0.79 (0.40 to 1.57)	0.505		
Mini Mental State Examination score	0.75 (0.55 to 1.03)	0.076		
Risk factors				
Hypertension, yes	1.20 (0.30 to 4.74)	0.795		
Diabetes mellitus, yes	0.24 (0.06 to 0.93)	0.039	0.25 (0.06 to 1.15)	0.075
Dyslipidemia, yes	0.71 (0.16 to 3.12)	0.651		
Chronic kidney disease, yes	0.51 (0.15 to 1.73)	0.282		
Cerebral stroke, yes	0.50 (0.04 to 5.97)	0.584		
Current smoking, yes	0.23 (0.02 to 2.20)	0.200		
Medical therapies				
Aspirin, yes	0.00 (0.00 to)	1.000		
Anticoagulant, yes	5.00 (0.90 to 27.7)	0.066		
Angiotensin II receptor blocker, yes	0.86 (0.23 to 3.16)	0.817		
Angiotensin-converting enzyme inhibitor, yes	0.92 (0.28 to 3.04)	0.887		
Diuretic, yes	1.70 (0.44 to 6.55)	0.440		
Calcium channel blockers, yes	0.75 (0.23 to 2.50)	0.639		
β-blockers, yes	0.52 (0.15 to 1.76)	0.293		
Nitrate, yes	1.41 (0.32 to 6.16)	0.651		
Oral hypoglycemic agent, yes	1.06 (0.19 to 5.93)	0.951		
Insulin, yes	1.05 (0.13 to 8.24)	0.961		

Table 4. Correlations between Changes in the Mini Mental State Examination Score and Each Parameter.

All patients (n=43)	r	p value
Change in systolic blood pressure, mmHg	−0.165	0.290
Change in diastolic blood pressure, mmHg	−0.269	0.082
Change in body mass index, kg/m^2	−0.348	0.022
Change in abdominal circumference, cm	−0.046	0.770
Change in anaerobic threshold, mL/min/kg	−0.144	0.357
Change in peak oxygen uptake, mL/min/kg	−0.088	0.573
Change in maximum work load, max Watts	−0.050	0.748
Change in left ventricular ejection fraction, %	0.053	0.738
Change in hemoglobin, g/dL	−0.198	0.203
Change in albumin, g/dL	−0.233	0.133
Change in estimated glomerular filtration rate, mL/min/1.73 m^2	−0.012	0.939
Change in total cholesterol, mg/dL	−0.010	0.951
Change in high-density lipoprotein cholesterol, mg/dL	0.131	0.404
Change in low-density lipoprotein cholesterol, mg/dL	−0.111	0.479
Change in triglycerides, mg/dL	0.166	0.288
Change in HbA1c, %	0.220	0.179

Table 5. Multiple Regression Analysis of Changes in the Mini Mental State Examination.

Variable	Regression coefficient (β)	95% CI	p value
Age, years	0.014	−0.11 to 0.12	0.926
Sex, male	0.079	−1.53 to 2.60	0.601
Hypertension, yes	0.247	−0.36 to 3.35	0.111
Diabetes mellitus, yes	−0.254	−3.09 to 0.29	0.101
Cerebral stroke, yes	0.100	−2.14 to 4.21	0.513
Changes in body mass index, kg/m^2	−0.347	−1.51 to −0.08	0.030

$r^2 = 0.274$.

ment, while there was no marked MMSE change in the BMI-increased group (ΔBMI ≥0.0) (Figure E). On examining other patient characteristics (shown in Table 7), while the abdominal circumference in the BMI-increased group did not change markedly, that of the BMI-decreased group decreased significantly (Table 7). However, univariate logistic regression and linear regression analyses showed that the abdominal circumference was not associated with the MMSE score improvement (Table 3, 4). Additionally, while the average baseline renal function and left ventricular ejection fraction in the BMI-increased patients were significantly lower than in the BMI-decreased patients, a univariate logistic regression analysis showed no association between these variables and the MMSE score (Table 3). Finally, an analysis showed that both a decrease in the BMI, and the absence of baseline DM were significantly correlated with an elevation in the MMSE score in response to statin-exercise therapy (BMI, odds ratio: 3.74, p<0.05; DM, 0.24, p<0.05, Table 3). In multivariate logistic regression analysis adjusted for age >65 years of age, sex, and the presence of DM, a decrease in the BMI with statin-exercise therapy remained significantly correlated with an elevation in the MMSE score (odds ratio: 4.57, p<0.05, Table 3).

Discussion

The major finding of the present pilot study is that a combination of statins and regular exercise therapy appeared to significantly ameliorate cognitive dysfunction in patients already displaying mild cognitive dysfunction. This beneficial effect correlated with treatment-associated decrease in the BMI in CAD patients with mild cognitive decline as well as in those with pre-existing statin therapy.

Statins are an established therapy for reducing the risk of cardiovascular events. We previously reported the beneficial effects of statin-exercise treatment on CAD (9-11). Recently, perhaps because dietary control in statin users has been less emphasized as a therapeutic approach, high calorie and fat intake has been observed in many statin users, accompanied by higher BMI (vs. non-statin users) (12). High-calorie diets (and to a lesser extent fat intake) have a well-established role in the development of obesity and diabetes, which in-turn are risk factors associated with the pathogenesis of cognitive decline (13). The potential adverse effects of statins on the cognitive function are a concerning issue. Notably, some of the beneficial effects of exercise on the MMSE in our cohort were absent in the cohort that started taking a statin *de novo*.

Exercise is known to exert beneficial effects on cognition (14, 15); indeed, a very recent meta-analysis showed that aerobic exercise had a significant protective effect on cognitive dysfunction in older adults with mild cognitive impairment (16). However, weight loss per se is often seen in the course of dementia, particularly in Alzheimer's dis-

Table 6. Effects of Statin-exercise Treatment on Various Parameters in the Mini Mental State Examination Score-decreased and -increased Groups.

	Mini Mental State Examination Score -decreased Group (n = 22)		Mini Mental State Examination Score -increased Group (n = 21)	
	Baseline	5 months	Baseline	5 months
Systolic blood pressure, mmHg	119 ± 15	123 ± 15	120 ± 13	122 ± 15
Change in systolic blood pressure		+ 4 ± 19		+ 2 ± 16
Diastolic blood pressure, mmHg	69 ± 10	73 ± 10	69 ± 8	68 ± 9
Change in diastolic blood pressure		+ 3 ± 13		- 1 ± 11
Body mass index, kg/m^2	24.3 ± 3.4	24.7 ± 3.3	24.2 ± 3.9	23.8 ± 3.7
Change in body mass index		+ 0.4 ± 1.1		- 0.4 ± 1.1 ‡
Abdominal circumference, cm	88.8 (83.5 to 94.9)	86.3 (81.8 to 92.9)	88.0 (84.0 to 89.5)	87.0 (80.3 to 92.5)
Change in abdominal circumference		- 1.5 ± 5.6		- 1.4 ± 4.1
Anaerobic threshold, mL/min/kg	10.3 ± 1.9	10.7 ± 2.0	10.4 ± 2.2	10.7 ± 2.0
Change in anaerobic threshold		+ 0.4 ± 1.8		+ 0.4 ± 2.4
Peak oxygen uptake, mL/min/kg	15.9 ± 3.6	16.4 ± 3.0	15.5 ± 4.2	16.3 ± 3.1
Change in peak oxygen uptake		+ 0.6 ± 2.3		+ 0.8 ± 2.6
Maximum work load, max Watts	77.0 ± 23.9	81.0 ± 23.8 *	75.9 ± 29.6	79.1 ± 23.1
Change in maximum work load		+ 4 ± 7		+ 3 ± 17
Left ventricular ejection fraction, %	59.0 ± 11.8	61.8 ± 8.2	59.2 ± 12.0	61.9 ± 7.6
Change in left ventricular ejection fraction		+ 2.8 ± 10.8		+ 2.7 ± 9.7
Hemoglobin, g/dL	13.8 ± 2.0	13.9 ± 1.8	13.5 ± 1.3	13.6 ± 1.2
Change in hemoglobin		+ 0.1 ± 1.3		+ 0.0 ± 1.5
Albumin, g/dL	3.9 (3.6 to 4.1)	4.3 (4.0 to 4.6) †	3.8 (3.5 to 4.2)	4.2 (4.0 to 4.5) †
Change in albumin		+ 0.4 ± 0.5		+ 0.3 ± 0.4
Estimated glomerular filtration rate, mL/min/1.73 m^2	58.8 (46.4 to 64.1)	58.2 (48.3 to 66.7)	59.1 (54.1 to 68.9)	60.6 (50.0 to 71.5)
Change in estimated glomerular filtration rate		-0.2 ± 7.0		-0.1 ± 8.9
Total cholesterol, mg/dL	187 (168 to 203)	148 (134 to 156) †	180 (142 to 209)	145 (119 to 157) †
Change in total cholesterol		- 48 ± 45		- 43 ± 44
High-density lipoprotein cholesterol, mg/dL	45 (40 to 57)	46 (41 to 54)	46 (38 to 55)	50 (44 to 59)
Change in high-density lipoprotein cholesterol		- 0.5 ± 11.5		+ 3.0 ± 9.1
Low-density lipoprotein cholesterol, mg/dL	116 (93 to 128)	76 (67 to 84) †	115 (77 to 128)	61 (56 to 79) †
Change in low-density lipoprotein cholesterol		- 45 ± 38		- 46 ± 34
Triglycerides, mg/dL	133 (87 to 176)	113 (84 to 152)	92 (62 to 134)	88 (61 to 159)
Change in triglycerides		- 24 ± 78		- 3 ± 101
Mini Mental State Examination score	24 (23 to 25)	23 (22 to 25)	23 (22 to 25)	27 (25 to 28) †
Change in Mini Mental State Examination score		- 0.8 ± 1.7		+ 3.5 ± 1.4 ‡

Data are mean ± SD, or median (25% to 75%). Mini Mental State Examination Score-decreased (ΔMMSE ≤1.0) and -increased (ΔMMSE >1.0) Groups *$p < 0.05$, †$p < 0.01$ compared with the respective baseline values; ‡ $p < 0.05$ compared with the Mini Mental State Examination Score-decreased Group.

ease (17). In fact, low BMI as well as weight-loss were the predominant risk factors for mild cognitive impairment-to-dementia conversion in aged subjects with cognitive decline (18). This likely relates to a diminished appetite and not increased physical activity. To prevent further progression of dementia in CAD patients with cognitive decline, we suspect that body weight management through exercise during statin therapy may be crucial in order for patients to experience maximal benefit.

The findings of this study could lead to novel and practical therapeutic approaches to prevent development and/or limit progression of cognitive decline in CAD patients. However, to confirm the importance of combined statin-exercise therapy, further large prospective clinical studies are required; for example, comparing the cognitive outcomes among independent groups receiving exercise or statin, a statin-exercise combination group, and a non-exercise (control) group. Standardization of statin dosing and type are also crucial, as the present pilot study suggests that the effects of the combination of certain statin therapy types with exercise in CAD patients should be evaluated. The MMSE score in lipophilic statins users increased significantly over the study period, while hydrophilic statin users saw no marked change. Hydrophilic statins are less permeable across the blood-brain barrier than lipophilic statins in model systems (19), raising the question of what impact the hydrophilicity of a given statin might have on brain disorders and/or healthy brain. Interestingly, Rojas-Fernandez et al. concluded in a systemic review that hydrophilic statins (pravastatin and rosuvastatin) might be less likely to contribute to cognitive impairment, due to their limited penetration across the blood-brain barrier (20). These elements should be assessed in combination with exercise in future investigations of the cognitive function.

Our study has several limitations. First, our study design prevented effective confirmation of which element of the in-

Table 7. Effects of Statin-exercise Treatment on Various Parameters in the Body Mass Index-decreased and -increased Groups.

	Body Mass Index-decreased Group (n =16)		Body Mass Index-increased Group (n =27)	
	Baseline	5 months	Baseline	5 months
Systolic blood pressure, mmHg	120 ± 14	123 ± 16	119 ± 14	122 ± 15
Change in systolic blood pressure		+ 2 ± 14		+ 3 ± 20
Diastolic blood pressure, mmHg	68 ± 8	68 ± 8	70 ± 9	72 ± 10
Change in diastolic blood pressure		- 1 ± 10		+ 3 ± 13
Body mass index, kg/m^2	25.0 ± 4.4	23.8 ± 4.1 †	23.8 ± 3.1	24.5 ± 3.1 †
Change in body mass index		- 1.2 ± 0.9		+ 0.7 ± 0.6 ‡
Abdominal circumference, cm	89.0 (84.1 to 94.6)	85.3 (79.4 to 92.4)*	87.0 (83.5 to 94.0)	87.0 (84.0 to 94.0)
Change in abdominal circumference		- 3.5 ± 5.4		- 0.4 ± 3.9
Anaerobic threshold, mL/min/kg	10.9 ± 2.0	11.0 ± 2.0	10.0 ± 2.0	10.5 ± 1.9
Change in anaerobic threshold		+ 0.2 ± 2.7		+ 0.5 ± 1.6
Peak oxygen uptake, mL/min/kg	16.4 ± 3.8	17.0 ± 2.3	15.3 ± 3.9	16.0 ± 3.4
Change in peak oxygen uptake		+ 0.6 ± 2.9		+ 0.8 ± 2.1
Maximum work load, max Watts	79.4 ± 27.2	79.3 ± 18.2	74.7 ± 26.5	80.5 ± 26.0 †
Change in maximum work load		0 ± 17		+ 6 ± 9
Left ventricular ejection fraction, %	63.7 ± 11.2	63.2 ± 6.7	56.4 ± 11.4 ‡	61.0 ± 8.4 *
Change in left ventricular ejection fraction		- 0.5 ± 9.7		+ 4.6 ± 10.1
Hemoglobin, g/dL	13.7 ± 1.6	13.6 ± 1.3	13.6 ± 1.8	13.8 ± 1.6
Change in hemoglobin		- 0.8 ± 1.2		+ 0.2 ± 1.4
Albumin, g/dL	3.8 (3.6 to 4.1)	4.2 (4.0 to 4.5) *	3.9 (3.5 to 4.1)	4.3 (4.0 to 4.6) †
Change in albumin		+ 0.3 ± 0.4		+ 0.4 ± 0.5
Estimated glomerular filtration rate, mL/min/1.73 m^2	59.8 (58.9 to 70.6)	65.1 (55.1 to 73.8)	56.8 (45.8 to 66.0)‡	55.1 (40.0 to 65.8)
Change in estimated glomerular filtration rate		+ 2.0 ± 8.1		- 1.5 ± 7.6
Total cholesterol, mg/dL	188 (166 to 234)	143 (116 to 155) †	180 (152 to 199)	151 (131 to 157) †
Change in total cholesterol		- 61 ± 50		- 37 ± 39
High-density lipoprotein cholesterol, mg/dL	49 (38 to 60)	48 (43 to 60)	44 (39 to 53)	47 (41 to 53)
Change in high-density lipoprotein cholesterol		+ 0.3 ± 11.2		+ 1.7 ± 10.1
Low-density lipoprotein cholesterol, mg/dL	116 (96 to 140)	64 (56 to 81) †	114 (87 to 127)	73 (61 to 82) †
Change in low-density lipoprotein cholesterol		- 56 ± 46		- 39 ± 26
Triglycerides, mg/dL	98 (67 to 142)	68 (52 to 124)	126 (81 to 169)	121 (88 to 172)
Change in triglycerides		- 35 ± 79		- 2 ± 94
Mini Mental State Examination score	24 (22 to 25)	26 (23 to 28) †	24 (22 to 25)	25 (22 to 27)
Change in Mini Mental State Examination score		+ 2.3 ± 2.6		+ 0.7 ± 2.6

Data are mean ± SD, or median (25% to 75%). Body Mass Index-decreased (ΔBMI <0.0) and -increased (ΔBMI ≥0.0) Groups
*p < 0.05, †p < 0.01 compared with the respective baseline values; ‡ p < 0.05 compared with the Body Mass Index -decreased Group.

tervention improved cognitive function in these CAD patients, although subgroup analyses suggested that exercise might be more crucial. Second, the study included only a small number of patients from a single center.

In conclusion, the combination of statins and exercise appears to be associated with significant improvement in the cognition of CAD patients with mild pre-existing cognitive dysfunction. A decrease in the BMI during therapy was an independent factor associated with improving cognition.

Author's disclosure of potential Conflicts of Interest (COI).

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