Cognitive Function Assessment in Patients on Moderate- or High-Intensity Statin Therapy

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Abstract

Background: Cardiovascular diseases are the leading cause of death in the USA. Statin therapy reduces cardiovascular events significantly. Cognitive impairment has been reported with statin therapy but there is a lack of consensus. We analyzed the cognitive functions of adult patients who were on moderate-intensity statin therapy (MIST) or high-intensity statin therapy (HIST).

Methods: A total of 213 patients underwent cognitive assessment testing. Cognitive function scores were correlated with the durations of statin therapy, age, and level of education by using Pearson correlation. Independent *t*-test was used to compare the mean cognitive function score to the gender, race, type of statin therapy, and comorbid conditions.

Results: Mean age of all the patients was 55.4 years. Majority of the patients (66.2%) were on MIST while the rest (33.8%) were on HIST. Cognitive impairment was observed in 17.8% of the studied patients. A total of 41.7% of the patients in the HIST group and 5.7% in the MIST group had cognitive impairment (P < 0.001). There was no correlation between cognitive function score and age (r = -0.106), weakly positive correlation between the level of education and cognitive function score (r = 0.252), and weakly negative correlation between the duration of statin therapy and cognitive function score (r = -0.283). In the group of patients on HIST with cognitive impairment, the proportion of patients on atorvastatin 40 - 80 mg was significantly higher than the proportion of patients on rosuvastatin 20 - 40 mg (66.7% vs. 33.3%; P < 0.05). In the group of patients on MIST with

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cognitive impairment, atorvastatin 10 - 20 mg was the most commonly used statin therapy (50%), followed by rosuvastatin 10 mg (25%), simvastatin 20 - 40 mg (12.5%) and pravastatin 40 - 80 mg (12.5%).

Conclusions: We found a significantly higher association of cognitive impairment in patients who were on MIST or HIST compared to the general population. We found no correlation between cognitive function score and age, weakly positive correlation between the level of education and cognitive function score, and weakly negative correlation between the duration of statin therapy and cognitive function score. HIST was associated with a higher frequency of cognitive impairment compared to the MIST.

Keywords: Cognitive function; Cognitive impairment; Dementia; Statin therapy

Introduction

Atherosclerotic cardiovascular disease is the leading cause of death, both nationally and worldwide [1]. Overwhelming evidence supports that treatment with a statin (3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors) reduces cardiovascular events [2]. In the last decade, the number of adults on statin therapy has gradually increased [3]. This is in part due to inclusion of a substantial number of people who are qualified to be included in the statin benefit groups by following the 2013 American College of Cardiology/American Heart Association guidelines [4]. According to a cohort study, the use of statins has increased from 17.9% in 2002 - 2003 to 27.8% in 2012 - 2013 among adults aged 40 years and older [5]. It is, therefore, important to be aware of all of the potential benefits and risks associated with the use of statins.

In 2012, the US Food and Drug Administration (FDA) released a new warning regarding the use of statin therapy and cognitive impairment by stating "certain cognitive (brain-related) effects have been reported with statin use" [6]. The basis of the report was a review of the multiple studies and clinical trials on statins that included assessment of cognitive function [7-18]. In 2016, the FDA announced: "Memory loss and confusion have been reported with statin use. These reported events were generally not serious and went away once

the drug was no longer being taken" [19]. Human brain is the most cholesterol-rich organ which contains about 20% of the total cholesterol in the human body [20]. Cholesterol is an important constituent of the myelin sheaths and the plasma membranes of astrocytes and neurons. Cholesterol is imperative for signal transmission in synapses within the central nervous system [20]. Low levels of cholesterol may have a negative influence on the composition and functioning of the neurons.

Many studies have reported association between the use of statins to lower circulating cholesterol levels and decline in neurocognitive function [7-9, 20-23]. On the contrary, there are many studies that have shown either no association between the use of statins and cognitive changes [24-27], or a beneficial neuroprotective role attributable to the statin use [28-36].

It is clear that there has been a lack of consensus among the available studies evaluating the impact of statin use on the cognitive function. The aims and objectives of our study were to analyze the cognitive functions of adult patients who were on a moderate-intensity statin therapy (MIST) or a high-intensity statin therapy (HIST), and to compare the proportion of patients with cognitive impairment in this group with that of the general population in the USA in order to assess if there was a higher prevalence of cognitive impairment among persons on statin therapy.

Materials and Methods

Study selection

This was a prospective study which included single-arm assessment of cognitive function in patients who were on MIST or HIST. Patient enrollment started in January 2017 and completed in February 2020. The study was reviewed and approved by the Institutional Review Board of the Cooper University Health Care (CUHC), Camden, NJ, USA. This study was fully compliant with the ethical standards set forth by the CUHC institutional review board.

Adult patients aged 18 years and older who presented in our internal medicine offices and who were either on MIST or HIST were approached by the study investigators for enrollment during their scheduled routine office visits. All patients received a description of the study and they were informed about the purpose, risks, benefits, alternatives, and follow-ups. Informed consents were obtained from each patient who decided to participate in the study. A one-time in-office cognitive function was assessed on each patient as per the established assessment tool Modified Mini-Mental State Examination (3MS) [37], which is a questionnaire based cognitive assessment tool. The study investigators also reviewed the electronic medical records of the patients for data collection.

The inclusion criteria were English language speaking patients aged 18 years or older, who were taking a moderate-intensity or high-intensity statin, and who were willing to give consent to participate in the study. The exclusion criteria were patients with established diagnosis of dementia due to any cause, patients who were not self-administering medications, patients who could not communicate in English language, pa-

tients who had advanced comorbid medical condition(s) that could have affected their cognitive function, such as advanced neurological condition (e.g. cerebrovascular accident, Parkinson's disease, multiple sclerosis), advanced cardiac condition with poor performance state (e.g. New York Heart Association (NYHA) III or IV congestive heart failure, cardiomyopathy with left ventricular ejection fraction of less than 40%), advanced pulmonary disorder (e.g. chronic obstructive or restrictive airway disease requiring ambulatory oxygen therapy), end-stage renal disease on hemodialysis, end-stage liver disease (e.g. cirrhosis), hematological disorders leading to severe anemia (hemoglobin less than 9.0 g/dL), advanced uncontrolled rheumatological disorder (e.g. rheumatoid arthritis, systemic lupus erythematosus, osteoarthritis), advanced multisystem disorder (e.g. sarcoidosis), and patients with factors limiting their cognitive assessment (e.g. developmental disorders, mental retardation, and uncontrolled psychiatric disorders).

Data collection

After obtaining informed consents the study investigators administered the 3MS examination to the participating patients. The test was a 100-point cognitive scoring system. According to the test interpretation guidelines, normal cognitive function was defined as a 3MS score between 79 and 100, while a score under 79 was defined as cognitive impairment [37]. We collected the following data for each patient: age, gender, race, highest education level, duration of statin use, associated medical condition(s), blood pressure, serum lipid profile, name and the dose of statin, and 3MS score.

Statistical analysis

The patient data was entered in the Microsoft Excel (2013, Redmond, WA, USA) spreadsheet. Statistical analysis was done using SPSS (Statistical Package for the Social Sciences, version 15.01, IBM, Armonk, NY, USA). We analyzed the mean 3MS score based on age, gender and duration and type of statin use between the subgroups, and examined 3MS score with moderate-intensity or high-intensity statin use and other parameters. A descriptive analysis was used to provide information on the sample characteristics. Means (with standard deviations), medians (with IQR) and proportions were presented. Binomial tests were used to compare the sample proportion of cognitive impairment (as indicated by the 3MS score being 79 or under) to the percentage cognitive impairment in the USA (which is 5%). The sample size of 213 subjects was needed in order to ascertain adequate power for the study, given the inconclusive data results found in the literature and the lack of data concerning the proportion of cognitive impairment within the statin population, and the prevalence of cognitive impairment was based on professional opinion and observation. The patients' education levels and duration of statin use were considered in the statistical analysis through the use of Pearson correlation with the scores of 3MS scale. Independent t-test was used to compare the mean 3MS score to the gender

and Pearson correlation was used to examine the relationship between 3MS score with age. We used independent *t*-test to observe the difference between the 3MS score with moderate-intensity or high-intensity statin use, and race, gender and co-morbid conditions. In this study, significance was defined as a P < 0.05.

Results

Two hundred thirteen patients participated in the study. Cognitive impairment was observed in 17.8% of all patients who were either on MIST or on HIST. Subgroup analysis showed that eight patients (5.7%) in the MIST group and 30 patients (41.7%) in the HIST group had cognitive impairment (P < 0.001).

Baseline characteristics

About two-thirds of all the patients (141/213; 66.2%) were on MIST while the rest (72/213; 33.8%) were on HIST. The age range of all patients was between 26 and 96 years. The mean age of all the patients was 55.4 years. There were no statistically significant differences in the mean ages between the patients on MIST with normal cognitive function and patients on MIST with cognitive impairment; patients on HIST with normal cognitive function and patients on HIST with cognitive impairment; and patients on MIST with cognitive impairment and patients on HIST with cognitive impairment (Table 1). The majority of the patients with cognitive impairment were in the age group of 50 to 59 years (48.6%) (Fig. 1). There was no correlation between 3MS score and age (r = -0.106).

Our study had 58.2% male patients among all the patients who were on statin therapy. There was no statistically significant difference between the mean 3MS scores of all men and women (91.2 ± 9.5 vs. 91.3 ± 12.8; P = 0.98). In the group of patients on the MIST with cognitive impairment, there were more women than men (62.5% vs. 37.5%; P < 0.05). On the contrary, there were more men than women in the group of patients on the HIST with cognitive impairment (60% vs. 40%; P < 0.05) (Table 1).

Overall, the majority of all the patients were Caucasians (36.6%), while 35.5% were African-Americans, 14.1% were Hispanics, and 17.8% were of other races mainly Asians. There was no statistically significant difference between the mean 3MS scores among all the races (Caucasians 92.9 ± 9.4, African-Americans 89.9 ± 13.5, Hispanics 88.8 ± 10.4, and other races 91.9 ± 8.9; P = 0.207). The majority of the patients in the MIST with cognitive impairment group were Caucasians and African-Americans (37.5% each), followed by Hispanics and other races (12.5% each), while the majority of the patients in the HIST with cognitive impairment group were African-Americans (36.7%), followed by Hispanics (26.7%), Caucasians (23.3%) and other races (13.3%). There was no statistically significant difference in the race distribution between the patients on MIST with cognitive impairment group and the patients on HIST with cognitive impairment group (Table 1).

Level of education and cognitive function

There was a weakly positive relationship between the level of education and cognitive function score (r = 0.252). Although cognitive impairment was observed more in patients who had an education level beyond high school in both MIST group (87.5%) and HIST group (73.3%), the difference between the two groups was not significant (P = 0.650) (Table 1).

Duration of statin therapy and cognitive function

Our study showed that there were significantly greater proportion of patients (56.7%) in the HIST with cognitive impairment group who took statins for more than 10 years compared to 12.5% patients in the MIST with cognitive impairment group (P < 0.05) (Table 1). There was a negative but weak correlation between the duration of statin therapy and cognitive function score (r = -0.283) (Fig. 2).

Blood pressure and lipid parameters

We found no significant difference in the mean blood pressures, mean total cholesterol levels, mean high-density cholesterol (HDL) levels, and mean triglyceride levels between the patients on MIST with normal or impaired cognitive function, between the patients on HIST with normal or impaired cognitive function, and between the patients on MIST or HIST with cognitive impairment. The mean low-density cholesterol (LDL) levels were higher in the patients on MIST with cognitive impairment compared to the patients on MIST with normal cognitive function (P < 0.05), but there was no difference in the mean LDL levels between the patients on HIST with normal or impaired cognitive function, and between the patients on MIST or HIST with cognitive impairment (Table 1).
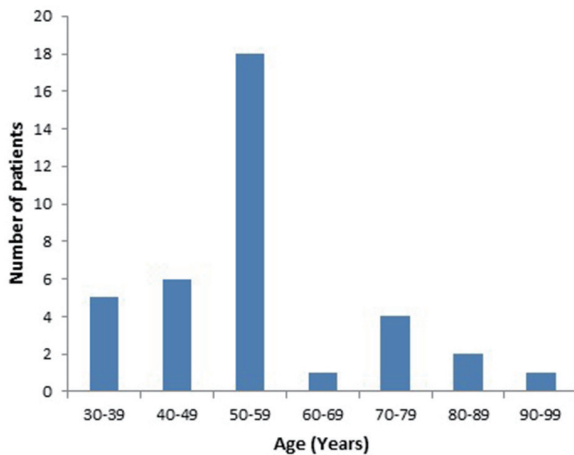
Comorbid medical conditions

We found that there was a significantly lower frequency of association of hypertension in the patients on MIST with cognitive impairment group compared to the patients on MIST with normal cognitive function group (P < 0.05), while there was no difference in the frequency of association of hypertension in the patients on HIST with cognitive impairment group compared to the patients on HIST with normal cognitive function group (Table 2). There was a significantly higher frequency of association of hypertension in the patients on HIST with cognitive impairment group compared to the patients on MIST with cognitive impairment group (P < 0.05) (Table 2). We also found that the frequency of association of diabetes mellitus was significantly higher in the patients on HIST with cognitive impairment group compared to the patients on HIST with normal cognitive function group (P < 0.05), while there was no difference in the frequency of association of diabetes mellitus in the patients on MIST with cognitive impairment group compared to the patients on MIST with normal cognitive function

Table 1. Baseline Characteristics

Variable	All patients (n = 213)	(A) Patients on MIST with normal cognitive function (n = 133)	(B) Patients on MIST with cognitive impairment (n = 8)	P (A vs. B)	(C) Patients on HIST with normal cognitive function (n = 42)	(D) Patients on HIST with cognitive impairment (n = 30)	P (C vs. D)	P (B vs. D)
Age, years, mean (SD)	55.4 (12.9)	53.9 (12.6)	47.3 (12.2)	0.150	59.7 (11.5)	53.4 (14.4)	0.655	0.053
Gender								
Male, n (%)	124 (58.2%)	74 (55.6%)	3 (37.5%)	0.468	29 (69%)	18 (60%)	0.461	0.426
Female, n (%)	89 (41.8%)	59 (55.6%)	5 (62.5%)		13 (31%)	12 (40%)		
Race								
Caucasian, n (%)	78 (36.6%)	49 (36.8%)	3 (37.5%)	0.889	19 (45.2%)	7 (23.3%)	0.214	0.796
African-American, n (%)	67 (31.5%)	44 (33.1%)	3 (37.5%)		9 (21.4%)	11 (36.7%)		
Hispanic, n (%)	30 (14.1%)	10 (7.5%)	1 (12.5%)		11 (26.2%)	8 (26.7%)		
Other/Asian, n (%)	38 (17.8%)	30 (22.6%)	1 (12.5%)		3 (7.1%)	4 (13.3%)		
Education								
Beyond high school (> 12)	104 (48.8%)	58 (43.6%)	7 (87.5%)	0.024	22 (52.4%)	22 (73.3%)	0.072	0.650
High school or less (0 - 12)	109 (51.2%)	75 (56.7%)	1 (12.5%)		20 (47.6%)	8 (26.7%)		
Duration of statin therapy								
Less than 5 years, n (%)	36 (16.9%)	21 (15.8%)	3 (37.5%)	0.272	11 (26.2%)	1 (3.3%)	0.032	0.008
5 - 10 years, n (%)	113 (53.1%)	82 (61.7%)	4 (50%)		15 (35.7%)	12 (40%)		
More than 10 years, n (%)	64 (30%)	30 (22.6%)	1 (12.5%)		16 (38.1%)	17 (56.7%)		
Vitals								
Systolic BP (mm Hg), mean (SD)	128 (13.9)	128.1 (13.4)	125.9 (14.4)	0.658	128.1 (14.3)	132.1 (13.8)	0.238	0.269
Diastolic BP (mm Hg), mean (SD)	77.9 (9.5)	78.2 (9.5)	74.9 (10)	0.325	77.3 (10.6)	78.2 (9.2)	0.715	0.383
Lipids								
Total cholesterol (mg/dL), mean (SD)	170.7 (38.6)	166.6 (36.8)	195.38 (29.8)	0.032	169.3 (41.5)	184.3 (41.3)	0.130	0.485
LDL (mg/dL), mean (SD)	88.2 (31.9)	84.1 (29.5)	114.5 (29.8)	0.005	90.9 (33.5)	96.2 (23.4)	0.528	0.203
HDL (mg/dL), mean (SD)	49.4 (12.3)	49.3 (11.9)	53.5 (11.3)	0.335	47 (13.5)	51.8 (14.4)	0.124	0.728
TG (mg/dL), mean (SD)	169.9 (91)	169.5 (90.7)	136.63 (49.1)	0.313	162.5 (75.9)	190.9 (114.4)	0.242	0.056

MIST: moderate-intensity statin therapy; HIST: high-intensity statin therapy; SD: standard deviation; LDL: low-density lipoprotein; HDL: high-density lipoprotein; TG: triglyceride; BP: blood pressure.
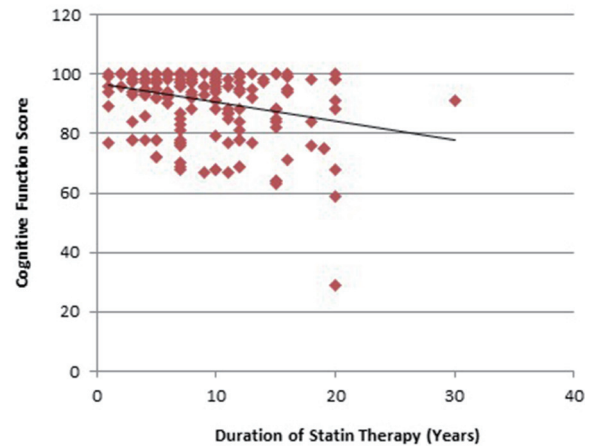
Figure 1. Age distribution of patients with cognitive impairment.

Figure 2. Correlation of duration of statin therapy and cognitive function score.

group, as well as between the patients on HIST with cognitive impairment group compared to the patients on MIST with cognitive impairment group (Table 2). There were no differences in the frequencies of association of other comorbid medical conditions across all the groups, such as hypothyroidism, depression, coronary artery disease, cerebrovascular accident, congestive heart failure, chronic obstructive pulmonary disease, chronic kidney disease, anemia, arthritis, malignancy, and obstructive sleep apnea (Table 2). The correlation of 3MS cognitive scores with and without the specific comorbid medical conditions showed no difference between the mean scores of all the groups of patients and in all categories of comorbid medical conditions.

Statin therapy

Our study showed that the majority of the patients in the HIST group were on atorvastatin 40 - 80 mg (71.4% in normal cognitive function group vs. 66.7% in cognitive impairment group) compared to the rest of the patients who were on rosuvastatin 20 - 40 mg (28.7% in normal cognitive function group vs. 33.3% in cognitive impairment group). In the patients on HIST with cognitive impairment group the proportion of patients on atorvastatin 40 - 80 mg was significantly higher than the proportion of patients on rosuvastatin 20 - 40 mg (66.7% vs. 33.3%; P < 0.05) (Table 3).

Among the patients who were on MIST with normal cognitive function, simvastatin 20 - 40 mg was the most commonly used statin therapy (29.3%) followed by atorvastatin 10 - 20 mg (27.1%), rosuvastatin 10 mg (15.8%), pravastatin 40 - 80 mg (9%), lovastatin 40 mg (6%), pitavastatin 2 - 4 mg (5.3%), fluvastatin XL 80 mg (4.5%), and fluvastatin 40 mg twice a day (3%). In the group of patients on MIST with cognitive impairment, atorvastatin 10 - 20 mg was the most commonly used statin therapy (50%) followed by rosuvastatin 10 mg (25%), simvastatin 20 - 40 mg (12.5%) and pravastatin 40 - 80 mg (12.5%) (Table 3). There was no significant difference in the proportion of patients on a specific statin type between the patients on MIST with normal cognitive function group and

the patients on MIST with cognitive impairment group, as well as between the patients on HIST with normal cognitive function group and the patients on HIST with cognitive impairment group (Table 3).

Discussion

Our study had three major findings: first, a significantly higher association of cognitive impairment in patients who were on HIST compared to the general population; second, a weakly negative correlation between the duration of statin therapy and cognitive function score; and third, cognitive impairment was most commonly associated with moderate- or high-intensity atorvastatin therapy.

Several studies have reported that the prevalence of cognitive impairment in the US population above the age of 65 years range between 10% and 37.4% [38-41]. Although the actual prevalence of cognitive impairment in the US population under the age of 60 years is not known, several studies with small sample size suggest prevalence rates of 0-13.7% in adults under 65 years of age [42-45]. In our study, the majority of the patients were under 65 years of age with a mean age of 55.4 years, and the prevalence of cognitive impairment was 17.8%, which was significantly higher compared to the general population as reported in the aforementioned studies. Also, in our study we did not find a correlation between the cognitive function score and age.

There are several prospective and retrospective cohort studies that have reported similar associations between statins and cognitive impairment and other psychological disorders, such as an increased risk of suicide [7-9, 21-23]. As early as in 1997, there have been implications of statin therapy with cognitive behavioral changes, such as increased violence [23]. Since then, there has been increasing data from case reports, various retrospective and prospective studies, which ultimately lead to the FDA formally recognizing that statins may cause cognitive impairment [7, 9, 11, 19, 23, 46]. Muldoon et al have done multiple studies that tested attention, reaction

Table 2. Comorbid Medical Conditions

Medical comorbidity	All patients (n = 213)	(A) Patients on MIST with normal cognitive function (n = 133)	(B) Patients on MIST with cognitive impairment (n = 8)	P (A vs. B)	(C) Patients on HIST with normal cognitive function (n = 42)	(D) Patients on HIST with cognitive impairment (n = 30)	P (C vs. D)	P (B vs. D)
Hypertension, n (%)	168 (79.2%)	106 (80.3%)	2 (25%)	0.002	34 (58.2%)	26 (86.7%)	0.750	0.002
Diabetes mellitus, n (%)	167 (78.44%)	110 (82.7%)	6 (75%)	0.632	25 (59.5%)	26 (86.7%)	0.012	0.587
Hypothyroidism, n (%)	29 (13.6%)	19 (14.3%)	0 (0%)	0.598	6 (14.3%)	4(13.3%)	1.000	0.560
Depression, n (%)	42 (19.8%)	25 (18.8%)	3 (37.5%)	0.195	9 (21.4%)	5(16.7%)	0.765	0.327
CAD, n (%)	31 (14.6%)	18 (13.4%)	0 (0%)	0.596	7 (16.7%)	6 (20%)	0.717	0.309
CVA, n (%)	18 (8.5%)	4 (3%)	0 (0%)	1.000	8 (19%)	6 (20%)	0.920	0.309
CHF, n (%)	8 (3.8%)	7 (5.3%)	0 (0%)	1.000	0 (0%)	1 (3.3%)	0.417	1.000
COPD, n (%)	13 (6.1%)	9 (6.8%)	0 (0%)	1.000	2 (4.8%)	2 (6.7%)	1.000	1.000
CKD, n (%)	17 (8%)	18 (6%)	0 (0%)	1.000	4 (9.5%)	5 (16.7%)	0.476	0.563
Anemia, n (%)	23 (10.8%)	12 (9%)	0 (0%)	1.000	8 (19%)	3 (10%)	0.341	1.000
Arthritis, n (%)	42 (19.9%)	23 (17.6%)	0 (0%)	0.352	9 (21.4%)	10 (33%)	0.258	0.082
Malignancy, n (%)	9 (4.2%)	7 (5.3%)	0 (0%)	1.000	1 (2.4%)	1 (3.3%)	1.000	1.000
OSA, n (%)	29 (13.6%)	18 (6%)	1 (12.5%)	1.000	5 (11.9%)	5(16.7%)	0.732	1.000

MIST: moderate-intensity statin therapy; HIST: high-intensity statin therapy; CAD: coronary artery disease; CVA: cerebrovascular accident; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; OSA: obstructive sleep apnea.

Table 3. Type and Intensity of Statin Therapy

Daily statin	All patients (n = 213)	(A) Patients on MIST with normal cognitive function (n = 133)	(B) Patients on MIST with cognitive impairment (n = 8)	P (A vs. B)	(C) Patients on HIST with normal cognitive function (n = 42)	(D) Patients on HIST with cognitive impairment (n = 30)	P (C vs. D)
Atorvastatin 40 - 80 mg, n (%)	50 (23.5%)				30 (71.3%)	20 (66.7%)	0.796
Rosuvastatin 20 - 40 mg, n (%)	22 (10.3%)				12 (28.7%)	10 (33.3%)	0.665
Atorvastatin 10 - 20 mg, n (%)	40 (18.8%)	36 (27.1%)	4 (50%)	0.217			
Rosuvastatin 10 mg, n (%)	23 (10.8%)	21 (15.8%)	2 (25%)	0.617			
Simvastatin 20 - 40 mg, n (%)	40 (18.8%)	39 (29.3%)	1 (12.5%)	0.440			
Pravastatin 40 - 80 mg, n (%)	13 (6.1%)	12 (9%)	1 (12.5%)	0.548			
Lovastatin 40 mg, n (%)	8 (3.8%)	8 (6%)	0 (0%)	1.000			
Fluvastatin XL 80 mg, n (%)	6 (2.8%)	6 (4.5%)	0 (0%)	1.000			
Fluvastatin 40 mg BID, n (%)	4 (1.9%)	4 (3%)	0 (0%)	1.000			
Pitavastatin 2 - 4 mg, n (%)	7 (3.3%)	7 (5.3%)	0 (0%)	1.000			

MIST: moderate-intensity statin therapy; HIST: high-intensity statin therapy; BID: twice a day.

time, and psychomotor speed of those on statins [7, 9]. Their study showed statistically significant decline in attention, psychomotor speed, and reaction time in those who were on statin therapy compared to placebo. In 2014, the FDA released a report via the Adverse Event Reporting System (AERS) which reported that the patients experienced ill-defined memory loss, confusion, and foggy thinking after statin exposure [6, 19]. A retrospective study of 3,500 patients found that patients on statin therapy had a significantly higher association of dementia or cognitive impairment compared to the patients who were not on statins (39.9% vs. 18.9%) [46]. A study by Wagstaff et al also observed cognitive impairment with statin therapy but could not determine the causal relationship [11]. Similarly, Glasser et al studied a national cohort of the US population and found 8.6% prevalence of cognitive impairment in statin users [47]. A significantly negative cognitive effect with statin use was reported in a study that found that the effects were directly related to the potency of the statins, and the statin therapy offered significantly negative impact in the quality of life of the study participants [8].

Additionally, we believe that although the muscle-related adverse effects are more commonly reported by the patients, the influence of statin on cognitive decline remains largely underreported. Golomb et al reported that patients commonly discussed muscle-related adverse effects with their physicians, and the cognitive status changes were rarely assessed or inquired by the physicians [48]. We believe that this phenomenon underestimates the actual prevalence of cognitive impairment associated with the statins. As such the voluntary reporting to the AERS by the physicians varies between 1% and 10%, which is considered as extremely low [49]. Extrapolation of the underreported data estimates that annually about 3,000 - 30,000 adverse effects of cognitive impairments due to statins, especially simvastatin and atorvastatin, were not reported to the AERS [21]. Hence, our finding of significantly higher association of cognitive impairment in patients who were on HIST compared to the general population highlights the importance of an inclusive approach in the adverse effect assessment in the form of periodic assessment of cognitive function of patients who are on statin therapy, especially in patients who are on HIST.

There have been several mechanisms that have been proposed as the possible pathogenesis of the association of cognitive impairment secondary to statins. One mechanism proposed by Ainiyet et al suggests a connection between low serum cholesterol and lower activity of central serotonergic release which influences mood, impulsive behavior, and cognition [22]. Experiments in animal models have shown that lowering the synaptosomal membrane cholesterol with statins results in a decline in the number of serotonin receptors, which leads to a reduction in the behavioral and cognitive responses [50]. Another mechanism proposed is that the adverse effects of statins on cognition could be related to the lipophilicity of the drug and its ability to cross the blood brain barrier.

In our study, we found a weakly negative correlation between the duration of statin therapy and cognitive function score, suggesting that longer duration of statin therapy was associated with declining cognitive function. More than half of our patients on HIST with cognitive impairment group were

on a statin for more than 10 years. The PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) study found no difference in cognitive impairment between patients on pravastatin or placebo within the 42-month follow-up [17]. In 2013, a meta-analysis found no significant short-term cognitive detriment and potentially beneficial role of statins in prevention of dementia with long-term use [28]. Our finding of negative correlation between the duration of statin therapy and cognitive function score is unique. Further studies are needed to explore the influence or association of both the dose and duration of statin therapy on cognitive function.

We found that the cognitive impairment was most commonly associated with moderate- or high intensity atorvastatin therapy. A retrospective review of 3,500 patients revealed that among patients on statin treatment with cognitive deficit, the majority of the patients were on atorvastatin (43.9%) or simvastatin (35.1%) [46]. The study also found that cognitive impairment was significantly higher in the patients who were on lipophilic statins, such as atorvastatin and simvastatin, compared to the hydrophilic statins, such as rosuvastatin and pravastatin [46]. The mechanism of such association has been proposed as the lipophilicity of the statin and its ability to cross the blood brain barrier. In the 2014 study that analyzed reports of cognitive dysfunction related to statin use within the FDA AERS found that hydrophilic statins (rosuvastatin and pravastatin) showed essentially no evidence of increased risk of cognitive dysfunction; however, among lipophilic statins (atorvastatin, simvastatin, fluvastatin, lovastatin, and pitavastatin), those with the highest degree of lipophilicity (atorvastatin, simvastatin) were associated with the highest reporting of associated cognitive impairment [6, 19]. Evans and Golomb found that the potency of statins had a greater negative effect on cognition [8].

There are several explanations to our findings. Hyperlipidemia inhibits intracellular cholesterol synthesis in the neurons and increases intracellular amyloid (Ab) production. This phenomenon facilitates cell lysis and subsequent inhibition of cholesterol synthesis. Atorvastatin and simvastatin, being lipophilic statins, inhibit neuronal cholesterol promoting neuronal degeneration and subsequent cognitive impairment [51]. Lipophilic statins also increase cerebral levels of interleukin-1 beta and tumor necrosis factor-alpha (TNF-alpha), enhancing neuronal inflammatory response, which results in alteration in the function of neurons [52]. Lipophilic statins also demonstrate passive diffusion and non-selective diffusion into hepatocytes and non-hepatocyte tissues [53-58], while the hydrophilic statins, such as rosuvastatin and pravastatin, are highly hepatoselective and enter into the hepatocytes via active transportation, which makes them less likely associated with non-hepatocytic adverse effects [51, 54]. Additionally, atorvastatin and simvastatin are metabolized through CY3PA4. Atorvastatin has a longer half-life (about 11 - 30 h), while simvastatin has a higher percentage of absorption (about 65-85%). Other lipophilic statins, such as fluvastatin, go through an extensive first-pass metabolism and protein binding. It appears to be the reason why atorvastatin and simvastatin have higher association with non-hepatocytic adverse effects, such as cognitive impairment, compared to all other lipophilic statins [51, 54]. Our findings of higher association of cognitive impairment

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