Original Article

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Role of Statins on Cognition and Memory: A Case-control Study

Pharmacology Section

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ABSTRACT

Introduction: Statins are a class of lipid lowering medications, which can effectively lower cardiovascular mortality and morbidity by the beneficial effects in atherosclerotic cardiovascular disease. Recently, there are increasing concerns over the relationship between statins and cognitive deficits. On the contrary, some studies have indicated an improvement in memory functions with the use of statins. However, the impact of statins on cognition is still unclear.

Aim: To analyse the effect of statins on cognition and memory using Mini-Mental Scale Examination (MMSE).

Materials and Methods: The case-control study was conducted in Department of Cardiology at PSG Institute of Medical Sciences and Research, Coimbatore, Tamil Nadu, India (tertiary care teaching hospital), from June 2019 to December 2019. Out of total 127 participants, case group included 63 adult patients of both genders, on statin therapy for at least 12 weeks duration and control group included 64 age and gender matched adults who were not on statin therapy. After obtaining a written informed consent, MMSE questionnaire was administered by a trained blinded interviewer to both groups. Pearson's correlation was performed to evaluate any significant correlation between duration of statin therapy with MMSE and individual domain scores. Data was analysed using Statistical Package for Social Sciences (SPSS) version 24.0, and p-value <0.05 was considered significant.

Results: The mean age of the cases was 61.1±7.90 years, and that of the control group was 60.6±7.68 years. Using the cut-off score of 23 to diagnose dementia, 21 (33.3%) cases and 24 (37.5%) control participants had cognitive deficits, with no statistically significant difference. The mean score of patients on statin therapy for more than one year (26.45±3.03) was higher compared to those with less than or equal to one year duration of therapy (24.48±4.11); however, it did not reach statistical significance. The statistically significant difference between mean scores of cases and controls was evident in cognitive domains like registration (p-value=0.01) and recall (p-value=0.04) in addition to a significant correlation (p-value=0.03) between the duration of statin therapy and orientation score.

Conclusion: This study refutes the possibility of an association of statin therapy with cognitive decline in the study population. In contrast, the results are illustrative of a potential cognitive benefit with the use of statins.

Keywords: Attention/calculation, Construction, Dementia, Duration, Language, Mini-mental scale examination, Orientation score, Recall, Registration

INTRODUCTION

Statins or 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors are a group of drugs commonly prescribed for their beneficial effects on lipid metabolism, reducing artherosclerosis, and lowering cardiovascular mortality and morbidity [1]. Statins are well tolerated and have a low propensity of causing adverse effects despite potent therapeutic benefits, which has rendered their current position in cardiovascular therapeutics [2]. An epidemiological study has revealed that within 3 months after diagnosis, 47%, 71%, and 78% of patients with diabetes, cardiovascular disease, and both conditions, respectively were prescribed lipid lowering therapy, predominantly statins [3]. Prescription prevalence has revealed a sharp rise from 1995 (2.36 per 1,000 person-years) to 2013 (128.03 per 1,000 person-years), especially in older age groups with men generally having a higher prevalence rate over time than women [4]. There are anecdotal reports of cognitive decline with statins, the recognition of which has led to increasing concerns over the relationship between statins and memory loss, forgetfulness, and confusion [5,6].

Cognitive impairment is a broad term that commonly describes a decline in cognitive functions with the severity of the impairment ranging from mild deficit to dementia. Dementia is a syndrome characterised by deterioration in memory, thinking, behaviour, and the ability to perform everyday activities and thus refers to global cognitive disability. According to the World Health Organisation, currently there are approximately 50 million dementia patients worldwide, and there are 10 million new cases annually contributing to a huge social and economic burden. Additionally, the number is expected to increase to 131 million in 2050 [7].

Statins have been implicated in causing cognitive decline in certain patient populations and hence Food and Drug Administration (FDA) has issued warnings on the potential cognitive impairment. Contradictorily, statins have been evaluated for potential therapeutic benefit in patients with dementia [8]. However, evidence also exists for statins not being effective in the prevention of cognitive decline or dementia in elderly individuals at risk of vascular disease [9,10]. Thus there are obvious gaps in knowledge on the cognition and memory effects of statins [11]. Also, the literature evidences are largely from the Western population and it remains largely unexplored whether the use of statins is associated with cognitive impairment in Asian population.

Hence, this study is focused on evaluation of cognition in patients on statin therapy in comparison to matched controls using the MMSE. MMSE is a tool that can be used systematically to assess the cognitive status. It is an 11-item questionnaire that tests five domains of cognitive functions namely orientation, registration, attention/calculation, recall, and language. The maximum score is 30. A score of 23 or lower is indicative of cognitive impairment. The MMSE has high test-retest reliability, internal consistency, and high inter-observer reliability with a sensitivity of 87% and specificity of 82%. The MMSE has been validated in both primary and specialist care settings with the advantage of having an administration time of less than 10 min [12].

The results of this study would help discerning the effects of statins on cognition and the magnitude of such changes in the Indian population. This evaluation will be significant as it would contribute to enhanced understanding on the cognition effects of statins especially

considering the huge proportion of patients being prescribed this class of hypolipidemic drugs in current clinical practice.

MATERIALS AND METHODS

The study was a hospital-based case-control study conducted in Department of Cardiology at PSG Institute of Medical Sciences and Research, Coimbatore, Tamil Nadu, India (tertiary care teaching hospital), from June 2019 to December 2019. Approval from the Institutional Human Ethics Committee (Approval number: 17/092) was obtained. Informed written consents were obtained from all the participants.

Inclusion criteria

Cases: All adult patients of both sexes, on statins for at least 12 weeks were recruited in the case group.

Control: Subjects who were not on statin therapy, matched for age, gender, and literacy in addition to smoking and alcoholic status were chosen as the control population.

Exclusion criteria: Patients with known history of any neurological illnesses including senile, vascular or Alzheimer's dementia, any psychiatric illness or unstable cardiac conditions, known case of liver or renal failure, hypothyroidism and metabolically unstable patients, morbid obesity, and neoplastic conditions were excluded from the study.

Sample size calculation: Sample size estimation using Epitools software revealed 67 participants per group for 80% power at 95% confidence interval, considering a prevalence rate of 2.7%, as reported in the national health portal of India (http://nhp.gov.in). A total of 127 participants were recruited for the study.

- Cases (n=63)
- Control (n=64)

Procedure

The MMSE questionnaire was administered by a trained interviewer who was blinded to the group to which the patient belonged [12].

The MMSE score of 23 or lower was considered as the cut-off for cognitive deficit, both in the cases and matched control group.

Seven MMSE domains were examined, namely:

- Orientation to time and place
- Registration
- Attention/calculation
- Recall
- Language
- Construction

Except for construction, which involved copying a pair of intersecting hexagons and scored at 1 or 0 depending on whether the participant was able to accomplish the task or not, the rest of the domain scores were categorised into good or poor performance based on the participants' responses. The definition of good performance was indicated by a score equal to or greater than the median score [13]. For example, if the possible score for the domain "orientation" ranged from 0 to 10, good performance on this variable was defined by a score equal to or greater than the median value of 9. Similarly, for the domains registration, attention/calculation, recall, and language, the median scores of 3,3,3, and 8, respectively were used as the cut-off values.

STATISTICAL ANALYSIS

The statistical significance of the difference in the proportion of participants with cognitive decline between cases and controls was analysed using Chi-square test. The frequency distribution of good and poor performances based on the component scores of the MMSE subscale domains were also analysed for statistical significance using Chi-square test. The association of duration of the statin therapy with the mean MMSE score and that of the subscale components was performed using student's t-test. Pearson's correlation was conducted to evaluate any significant correlation between duration of statin therapy with MMSE and individual domain scores. Data was analysed using SPSS version 24.0, and p-value <0.05 was considered significant.

RESULTS

The mean age of the cases was 61.1±7.90 years, and that of the control group was 60.6±7.68 years. In both groups, 34 (54%) participants were men, while the remaining 46% were women. Approximately 35% of the study population were illiterates, and 75% were literates. Overall, 9.5% individuals in both groups had smoking and/or alcoholic history, while the rest were non smokers and non alcoholics [Table/Fig-1].

Parameters	Cases (n, %)	Controls (n, %)	p-value
Age			
<60 years	28 (44.44%)	27 (42.19%)	0.797
≥60 years	35 (55.56%)	37 (57.81%)	
Gender			
Males	34 (53.97%)	33 (51.56%)	0.785
Females	29 (46.03%)	31 (48.44%)	
Education			
Illiterate	16 (25.40%)	22 (34.38%)	0.269
literate	47 (74.60%)	42 (65.63%)	
Habit history			
Smokers	7 (11.11%)	6 (9.38%)	0.746
Non smokers	56 (88.89%)	58 (90.62%)	
Alcoholics	4 (6.35%)	6 (9.37%)	0.526
Non alcoholics	59 (93.65%)	58 (90.63%)	
Duration of statin therapy (case)			
<1 year	19 (30.16%)	-	-
≥1 year	44 (69.84%)	-	-

[Table/Fig-1]: Demographic data of study participants.
n for cases=63, n for controls=64

A statistically significant difference between male and female cases in the mean MMSE scores was obtained. The mean scores of subscale cognitive constructs largely responsible for this difference were the domains "orientation" and "attention/calculation" whose differences were also statistically significant. Interestingly, the mean scores of cognition component "language" was also significantly higher in the male cases group whilst, the minor differences in the mean values of the remaining cognition parameters between males and females did not translate to statistical significance [Table/Fig-2].

Analysing the statistical significance for the mean difference in scores of the cases based on the literacy (considered as one of the important factors influencing the cognition scores in MMSE scale), it was found that the results paralleled gender differences with a significantly higher orientation, attention/calculation, and language scores in addition to the MMSE score attained by the literate compared to the illiterate population [Table/Fig-2].

Large proportion of participants belonged to the non-smoking and non alcoholic category, which precluded a between group analysis of the two groups with and without smoking and alcohol intake history.

Using the cut-off score of 23 to diagnose dementia, 21 (33.3%) subjects among the cases and 24 (37.5%) control participants had cognitive deficits. A Chi-square test revealed that there was no statistically significant difference between the two groups (p-value=0.62). Determining the frequencies of good and poor performers amongst cases (defined by the scores being equal to or greater than the median value), it was detected that the percentage of good performers in the registration and recall component scores

Groups	Literates (n=47) (Mean±SD)	Illiterates (n=16) (Mean±SD)	t-value	p-value	Males (n=34) (Mean±SD)	Females (n=29) (Mean±SD)	t-value	p-value
MMSE score	26.40±3.88	21.3±4.62	3.952	0.001*	27.14±3.24	22.72±4.89	4.283	<0.001*
Orientation score	8.78±1.65	6.37±1.52	3.568	0.002*	9.20±1.14	6.96±1.45	4.748	<0.001*
Registration score	2.97±0.14	3.00±0.00	1.000	0.323	2.97±0.17	3.00±0.00	0.922	0.360
Attention/Calculation score	3.48±1.76	1.37±1.99	3.765	0.001*	3.76±1.63	2.00±1.07	3.780	<0.001*
Recall score	2.72±0.64	2.62±0.80	0.442	0.663	2.76±0.60	2.62±0.77	0.827	0.411
Language score	7.74±0.53	7.31±0.60	2.554	0.018*	7.79±0.47	7.44±0.63	2.469	0.016*

[Table/Fig-2]: Comparison of mean MMSE scores and subscale domain scores of cases between the gender and literacy groups.
*p-value <0.05 was considered as statistically significant; SD: Standard deviation; Median values for individual component scores of orientation, registration, attention, recall, language, and construction were 9,3,3,3,8, and 1, repsectively. MMSE: Mini-mental state examination

were distinctively higher. This apparently resulted in a statistically significant difference in the proportion of good performers among the cases in the registration (χ^2=5.963, p-value=0.01) and recall (χ^2=3.970, p-value=0.04) domains compared to the control population using Chi-square test [Table/Fig-3]. Also, the mean score of cases (25.10±4.62) was higher than that of the controls (24.64±4.08) though the difference was not statistically significant using independent samples t-test (p-value=0.54).

The mean duration of statin therapy in cases was 1.68±0.94 years. A total of 58 (92.06%) cases were on atorvastatin, with 40 mg and 80 mg being the doses prescribed in 31 (49.20%) and 25 (39.68%), respectively. A small percentage, that is, 2 (3.17%) and 5 (7.94%) of patients were on atorvastatin 20 mg and rosuvastatin 15 mg, respectively.

A higher but not statistically significant mean MMSE score was obtained in patients on statin therapy for more than 1 year compared to those with less than or equal to one year duration of therapy. A higher score was likewise evident in orientation and attention/calculation cognitive constructs in patients with longer duration of statin treatment, though only the difference in mean orientation scores achieved statistical significance using independent samples t-test [Table/Fig-4]. This result was mirrored in Pearson's correlation test, which demonstrated a significant correlation (r-value=0.269) between the duration of statin therapy and orientation score [Table/Fig-5].

DISCUSSION

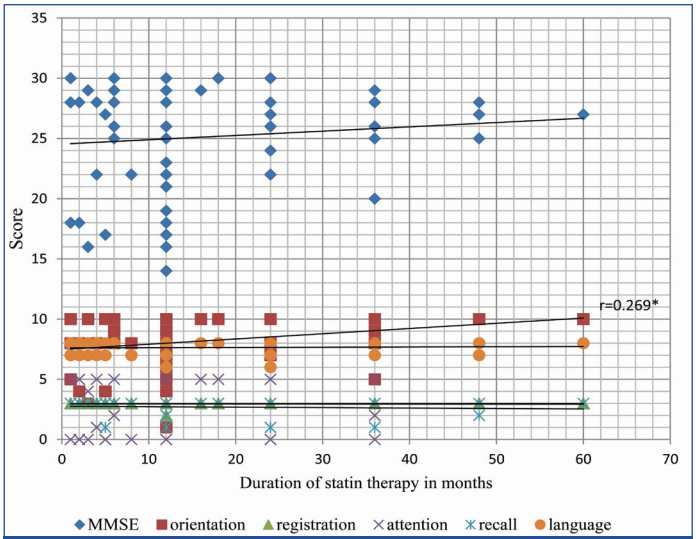
In this case-control study involving 127 participants of which 63 subjects were cases who were on statin treatment and the rest were

Good performer	MMSE score >23	Orientation score	Registration	Attention/Calculation	Recall	Language	Construction
Cases	21 (33.33%)	32 (50.79%)	60 (95.23%)	38 (60.32%)	52 (82.54%)	43 (68.25%)	40 (63.49%)
Controls	24 (37.50%)	41 (64.06%)	52 (81.25%)	25 (39.06%)	43 (67.19%)	41 (64.06%)	38 (59.38%)
Chi-square statistic	0.240	2.287	5.963	0.411	3.970	0.249	0.227
p-value	0.62	0.13	0.01*	0.52	0.04*	0.61	0.63

[Table/Fig-3]: Comparison of mean MMSE scores and subscale domain scores between cases and controls.
*p-value <0.05 was considered as statistically significant; Median values for individual component scores of orientation, registration, attention, recall, language, and construction were 9,3,3,3,8, and 1, MMSE: Mini-mental state examination

Duration of statin therapy	MMSE score#	Orientation	Registration	Attention and calculation	Recall	Language	Construction
≤1 year	24.48±4.11	7.69	2.97	2.79	2.72	7.60	0.67
>1 year	26.45±3.03	9.20	3.00	3.30	2.65	7.70	0.55
p-value	0.12	0.009*	0.500	0.359	0.706	0.545	0.348

[Table/Fig-4]: Comparison of mean score of cases based on duration of statin therapy.
#Expressed as mean±SD; *p-value <0.05 was considered as statistically significant



[Table/Fig-5]: Correlation of mean MMSE scores and subscale domain scores with duration of therapy.
*Pearson's correlation for orientation, r-value=0.269 was statistically significant with p-value=0.03 while in case of MMSE score, the r-value was 0.103 (p-value=0.42) and the r value for the other domains were less than 0.05 indicating no evidence of correlation; MMSE: Mini-mental state examination

matched controls not on statins, the mean age was approximately 60 years. It has been established that MMSE, which is one of the widely used screening tools for general cognitive functioning both in clinical and research settings, the mean scores are fairly similar at each decade of age before 70 years. However, from 70 years onwards, the variation with age is larger, indicating greater age differences in MMSE scores at older ages. Evidences are suggestive that this could be attributed to the fact that respective contributions of the different cognitive components to the MMSE score differed as a function of age [14,15].

The mean age of the present study population was relatively lesser, which consequentially explains the lower proportion of participants who scored below the cut-off value for dementia. The current research indicated a significantly higher mean MMSE score in males on statin therapy compared to the female cases. Amongst the MMSE subscale, the mean orientation, attention/calculation, and language scores were significantly lower in female cases compared to their male counterparts. Various studies have corroborated that sex differences influenced cognitive assessments with women scoring lesser in addition to a greater decline in MMSE scores with age than men [16,17].

A birth cohort study of 13,004 individuals has proved that small mean difference in cognitive score at 65 years between the gender

groups widened further with ageing [17]. A similar study analysing the underlying reasons for the gender differences has brought out that such gender differences in the MMSE scores were more pronounced in the low educated group indicating the interplay of education and gender contributory to the evidence and that no differences were detectable in the gender groups with higher level of schooling [17-19]. The close parallelism between the domains, which demonstrated significant differences for the gender and literacy groups in this study signifies the complex interaction between gender and literacy parameters playing a seminal role in cognitive task performances.

It has been well established that education or literacy is considered as one of the most important variables in determining the performance in cognitive tests like MMSE [20]. In this research too there was a significant difference in the mean score between the literate and illiterate population. However, literature evidence suggests that years of education may not be a comprehensive measure of literacy status of an individual reflecting the potential ability in performing cognitive tests [21]. In contrast, the content of education, actual school grades, unique educational experiences and especially reading skills are said to play a major role in contributing to differences in MMSE cognition score emphasising on the need to validate a composite measure to assess the effects of literacy on cognitive performance tasks [19,21].

This investigation has revealed that approximately one-third of the cases were diagnosed with cognitive deficits using MMSE scale, which was not significantly different from the proportion of controls. Yet, within the sample population of cases studied, the percentages of good performers were higher than that of poor performers in all cognitive constructs including the overall MMSE score with a significant percentage difference evident in the recall and registration domains in addition to a definite correlation between the orientation score and duration of statin therapy despite the mean MMSE score failing to demonstrate a statistically significant increase compared to the control population. Cumulatively, we found that the results were illustrative of potentially beneficial changes in cognitive functions with statin therapy in the study population.

Scrutinising the underlying causative mechanisms for the impact of statins on cognition, it was apparent that various hypotheses have been proposed in literature. Cholesterol is considered a key determinant of the lipid microviscosity of the neuronal membranes, which is important for neurotransmitter synthesis, synaptic binding and uptake in addition to myelin sheath formation in the neurons [22]. Hence, the administration of high doses of lipophilic statins and the ensuing reduction in brain cholesterol synthesis can occur due to the concentration gradient and the lipid soluble property [23,24]. Though this could lead to high concentrations of the statins in the Central Nervous System and potentially affect the neuronal function, it remains unclear whether the translation to an actual reduced cholesterol level in the brain happens as there are plenty of intervening factors like cytochrome P450 enzymes, mitochondrial enzymes, influx and efflux transporters, hepatocyte selectivity of the drug which could alter the brain exposure to statins [24,25]. In addition, statins exert a dose dependent lowering effect on coenzyme Q10 levels, which in turn can affect mitochondrial function and energy metabolism. This has also been proposed as a likely mechanism for cognitive deficits with statin use [26].

On the contrary, the ability to reduce brain ischemic events by improving endothelial cell function and blood flow, decreasing low density lipoprotein oxidation, enhancing the stability of atherosclerotic plaques, inhibiting vascular smooth muscle proliferation and platelet aggregation apart from reducing vascular inflammation are mechanisms envisioned as being contributory to the beneficial effect of statin on cognition [10,27]. Additionally, animal studies have shown that atorvastatin attenuates the beta-amyloid pathology and ameliorates neuroinflammation in Alzheimer's disease [28,29]. Statins, by virtue of HMG CoA reductase inhibition, reduce the amount of mevalonate, a precursor to isoprenoids. Increasing age in mice has been found to be associated with specific changes in mevalonate downstream products including rise in short-chain isoprenoids Farnesyl Pyrophosphate and Geranylgeranyl Pyrophosphate, which impacts protein prenylation contributing to the neuronal dysfunction observed in aging and certain neurodegenerative diseases [30]. Thus, reduction in mevolanate derived isoprenoids and favourable modification of the protein prenylation, secondary to changes in isoprenoid regulation, might explain the potentially beneficial effects of statins on cognition, independent of its direct cholesterol lowering effect [31].

Limitation(s)

The study adds to the limited evidence currently available supporting the potentially protective effect of statins against dementia. However, the major study limitation is the utilisation of a single cognitive assessment tool as replication of results using other tools would enable further confirmation of the evidence. Moreover, the results require validation in large clinical trials with prospective randomised study design to overcome the inherent deficits in a cross-sectional study design before the results could be generalised.

CONCLUSION(S)

This study enlightens that the statin group of hypolipidemic drugs could potentially improve few cognitive domains like orientation, registration, and recall. This research enhances our understanding on a highly important facet of action of statins when used in therapy. Considering the wide usage of statins in cardiovascular therapeutics, the study has effectively indicated the lack of detrimental cognitive effects even though the beneficial effects may not be explicitly significant.

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