RESEARCH PAPER

Effects of Statin Therapy on Cognitive Function and Glycemic Status: A Prospective Observational Study.

Dr Shantanu Kamboj[1], Dr Dinesh K Badyal[2]

[1]Medical Safety Lead, CRM, Novartis, Healthcare Private limited, Hyderabad, India.
[2]Professor & Head, Department of Pharmacology, Christian Medical College & Hospital, Ludhiana

ABSTRACT

Background: Statins are widely prescribed for the prevention and management of atherosclerotic cardiovascular disease. However, concerns regarding their potential effects on cognition and glycemic control have emerged following safety warnings issued by regulatory authorities.

Objectives: To evaluate the effects of statin therapy on cognitive function and glycemic status in statin-naïve patients.

Methods: This was a prospective, open-label study conducted in 100 patients aged 35–65 years attending the cardiology outpatient department of a tertiary care hospital. Cognitive function was assessed using the General Practitioner Assessment of Cognition (GPCOG), Mini-Mental State Examination (MMSE), Digit Symbol Substitution Test (DSST), and Six Letter Cancellation Test (SCT) at baseline, 3 months, and 6 months. Glycemic parameters including random blood sugar (RBS) and glycosylated hemoglobin (HbA1c) were measured at the same intervals. Adverse drug reactions were recorded and assessed using the Naranjo scale. Statistical analysis was performed using Student's t-test and repeated measures ANOVA.

Results: No statistically significant changes were observed in cognitive scores (GPCOG, MMSE, DSST, SCT) across the study period. Similarly, no significant changes were noted in RBS and HbA1c levels at 3 and 6 months compared to baseline. Adverse drug reactions were reported in 12% of patients, with dyspepsia being the most common. No serious adverse events were observed.

Conclusion: Short-term statin therapy did not result in significant cognitive impairment or deterioration in glycemic control. Statins were well tolerated, supporting their safety with respect to cognitive and glycemic outcomes over a six-month period

Keywords: Statins, Cognitive function, Glycemic control, Adverse drug reactions, Atherosclerotic cardiovascular disease, HbA1c, Random blood sugar

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INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) like coronary heart disease, peripheral vascular disease and ischemic cerebrovascular disease are major contributors to global morbidity and mortality especially in middle age group.[1] The incidence and prevalence of coronary heart disease and cerebrovascular diseases increased rapidly owing to changes in lifestyle due to rapid development and urbanization in last two decades.[2] Raised levels of low density lipoproteins (LDL) and low levels of high density lipoproteins (HDL) are implicated in increased risk of atherosclerosis.[3] Statins are one of the most efficacious drugs which achieve a significant reduction in the total serum cholesterol and LDL. Statins achieve about 35-45% reduction in the levels of low-density lipoproteins (LDL-C) and also reduces the levels of triglycerides approximately by same amount.[4]

Statins are important group of drugs which are used in myocardial infarction, stroke, angina and revascularization in patients with established coronary heart disease.[5] Statin therapy is associated with mild adverse reactions such as nausea, vomiting, anorexia, diarrhoea, dyspepsia, abdominal pain, headache which occurs during the course of treatment. Myopathy and hepatotoxicity are two serious adverse reactions associated with statin therapy which necessitates to stop the treatment. Elevation of hepatic transaminases were found to be associated with statin therapy and risk increases with higher doses.[6] Drug safety alert issued by USFDA in March 2012, warned about two new adverse drug reactions which include increase in blood sugar levels, increased glycosylated haemoglobin (HbA1c) levels along with risk of development of diabetes and cognitive impairment. Drug Controller General of India (DCGI) in November 2012 also issued directive to make sure the induction of label carrying the warning related to cognitive impairment and worsening of glycemic control.[7,8]

Cognitive impairment associated with statins have variable onset and is reversible on discontinuation of drug and can occur within 2 months of initiating the statin therapy.[9-11] Cognitive problems associated with statins may have a direct relation to statins potency and a significant negative impact on quality-of-life.[11] Improvement in cognition with discontinuation of statins and deterioration on rechallenge with the same or different drug of statins group was found in a pilot study.[12] On the other hand secondary analysis of Ginkgo Evaluation of Memory study (GEMS) conclude that statins use is associated with slowing in cognitive decline and delay onset of dementia and Alzheimer disease.[13] There are other studies which also suggests that statins do not

**Author for Correspondence: Dr Shantanu Kamboj*

influence cognitive performance in individual with normal cognition.[14]

Various observational studies, randomised controlled trials (RCT's) and meta- analysis shows that there is increased risk of impairment of glycemic control and risk of development of incident diabetes. The results of the Pravastatin in Elderly Individuals at Risk of Vascular Disease (PROSPER) study and findings of the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, showed that use of statins were significantly associated with increased risk of diabetes.[15,16] There is also risk of worsening of glycemic control in patients already diagnosed with diabetes.[17] The duration of treatment after which the change in glycemic status will appear have also added to the confusion. Some of the studies suggest that changes in fasting blood levels were seen as early as 3 months of initiation of therapy.[17,18] Statin therapy is also associated with increased levels of blood glucose and HbA1c among patients with hypertension.[19] Other RCTs and observational studies showed that statins may reduce the risk of diabetes. A majority of the results of the studies showing protective effects of statins were, however, not statistically significant.[20]

In the light of these new concerns raised by USFDA and DCGI, this study was designed to evaluate the effects of statins on cognition and glycemic status.

MATERIAL AND METHODS

This was a prospective, open-label, study designed to evaluate the effect of statins on cognition and glycemic status. This study was conducted in hundred patients visiting the outpatient department of department of cardiology of Christian Medical College and Hospital, Ludhiana from 1st December, 2014 to 31st July, 2016. The patients in whom statins were intended to be prescribed were enrolled. The patients were provided patient information sheet before they sign written informed consent form.

Patients of either gender between 35-65 years of age who were going to be prescribed statin therapy were included in the study. Patients with secondary hyperlipidaemia (lipid disorders attributable to chronic hepatitis, renal failure, or untreated hypothyroidism), severe hypertriglyceridemia (fasting serum triglyceride level ≥350 mg/dL), stroke, untreated hypertension (diastolic blood pressure ≥95 mm Hg), cancer and liver diseases, type-2 diabetes mellitus and major neuropsychiatric conditions (e.g., schizophrenia, seizures, dementia) were excluded from the study. The patients who were on current treatment with any lipid-lowering supplements, psychotropic medications, glucocorticoids, opiate analgesics and sexually active premenopausal women were excluded unless they were using birth control measures were also excluded from the study.

The effect of statins on cognition was evaluated by using General Practitioner Assessment of Cognition (GPCOG), Mini Mental State examination (MMSE) and Pencil and Paper test.[111-113] GPCOG screening test include questions about time orientation, clock drawing and memory recall.[111] On the basis of these questions scoring is done (score out of total 9). Patient having total score of 9 shows no significant cognitive impairment; 5-8 is doubtful and informant interview is required and with a score between 0-4 cognitive impairment is indicated. The Mini Mental State Examination is a 30-point scale consisting of questions about orientation (10 points), a registration and recall task (6 point), a task for attention (5 point), a multistep command task (3 point), two naming task (2 point), a repetition task (1 point), a reading comprehension task (1 point), a written sentence (1 point) and a visual construction task (1 point).[112] Pencil and Paper Test contains the Digit Symbol Substitution Test (DSST) (Annexure V) and the Six Letter Cancellation Test (SCT).[113] In DSST patients will be presented with sheets of paper with 200 randomized digit (0-9) arranged in 10 row. They were then instructed to substitute in the space beside each digit. A corresponding symbol according to code was printed at the top of the page. Time allotted for this test was 2 minutes and number of correct substitutions are scored. In SCT patients were presented with sheets in which 1200 randomized letters are arranged in 40 columns. Each sheet has 6 target letters printed at the top. Patients were given 5 minutes and instructed to cancel as many target letters as possible and marking the point up to which cancellations had been attempted. The number of correct cancellations were scored. The scales were applied at 0, 3 and 6 months for evaluation of cognition. Primary outcome measures also included observation of effect of statins on random blood sugar levels (RBS) and glycosylated haemoglobin (HbA1c). Blood samples were taken at 0, 3 and 6 months for measurement of blood glucose and HbA1c. Adverse drug reactions associated with statins were also recorded using a check list and spontaneous reporting. In case adverse event was reported Naranjo score as applied to see its causation to statins.

The ADR Probability Scale was developed in 1991 by Naranjo. It consists of a series of 10 questions with responses of "yes," "no," and "don't know," where different point values (−1, 0, +1 or +2) are assigned to each answer. The reaction is deemed definite if the score is 9 or above, probable if it is 5–8, possible if it is 1–4, and doubtful if it is 0 or lower. The total scores
range from −4 to +13.[21]

If the adverse event reported was found to be associated with statins, then the drug was withdrawn on physician advice. The patient data was included in the analysis, if the patient was on statins for more than one month. The World Health Organization defines ADR's as "a response to a medication that is noxious and unintended and occurs at doses normally used in man."[22].

STATISTICAL ANALYSIS:

Student's t-test and repeated measures ANOVA were used for analysis. P value less than 0.05 were considered as statistically significant. The values are expressed as mean ± SE (Standard Error).

RESULTS

Of the 135 patients screened for the study, 100 patients completed the follow-up for minimum of 6 months and

were included in the analysis. Most of the patients were prescribed atorvastatin (10-40 mg/ day) or rosuvastatin (10-40 mg/ day).

The demographic profile of the patients in this study is given in table 1. Among 100 patient who were enrolled in this study, 21 were females and 79 were males. The mean age of patients was 51.60±8.90 years. The mean age for males was 51.46 ±9.02 years for females was 52.14±8.61 years. Among all of the patients, 26 (26%) were alcoholic and smokers, however rest were non-alcoholic and non-smokers. All patients enrolled in the study had mean blood pressure 122.46±1.806/84.36±0.834 mm Hg, mean pulse rate 74.36±0.62 beat/minute and the mean weight 64.20±1.22 kilograms. Baseline characters are shown in table 2

Table 1: Demographic profiles of patients at the baseline

Characteristics	Value
Total no. of patients	100
Age in years	51.60±8.90
Sex (M: F)	79:21
Employed	59%
Unemployed	41%

Table 2: Clinical characteristics of the patients at baseline

Characteristics	Value (mean ± S.E.)
Pulse rate (Beat/minute)	74.36± 0.62
Weight (Kilogram)	64.20±1.22
Systolic BP mmHg	122.46±1.806
Diastolic BP mmHg	84.36±0.834

Effect of statins on General Practitioner assessment of Cognition (GPCOG)

The cognitive function was noted using General Practitioner assessment of Cognition (GPCOG) questionnaire at baseline and subsequent visit and the results are given in table 3 and figure 1 expressed as mean ± standard error (SE). The mean score of GPCOG at baseline was 8.89±0.314 that increased to 8.92±0.273 at 3 months and further to 8.93±0.256 at 6 months. However, change in the trend at various intervals was not statistically significant

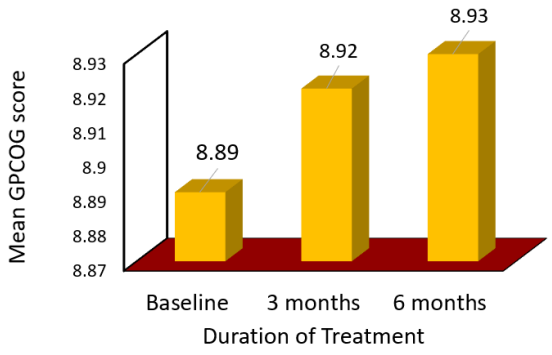
Table 3: Effect of statins on GPCOG score at various time intervals

Characteristic	Baseline	3 months	6 months
GPCOG score	8.89±0.314	8.92±0.273	8.93±0.256

Value expressed as mean ± SE (Standard Error).

Changes in the mean score at various time interval were not statistically significant.

GPCOG: General practitioner assessment of cognition



GPCOG: General practitioner assessment of cognition

Figure 1: Effect of statins on GPCOG scale

Effect of statins on mini-mental state examination (MMSE)

The cognitive changes were noted using mini mental state examination (MMSE) questionnaire and the results are given in table 4 and figure 2 expressed as mean ± standard error (SE). The mean score of MMSE at baseline was 26.74±0.799 that was reduced to 26.40±2.792 at 3 months which further reduced to 26.33±2.756 at 6 months. However, change in the trend of MMSE score at various intervals was not statistically significant

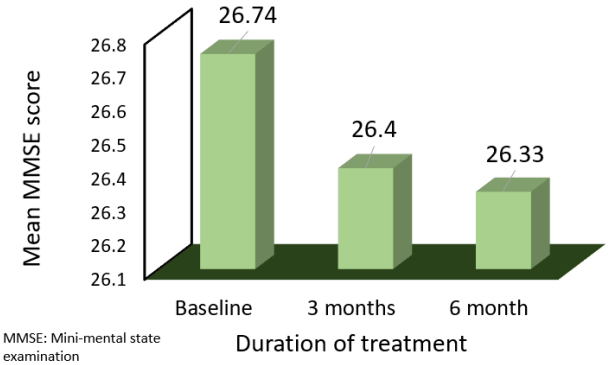
Table 4: Effect of statins on MMSE score at various time intervals

Characteristic	Baseline	3 months	6 months
MMSE score	26.74±0.799	26.40±2.792	26.33±2.756

Value expressed as mean ± SE (Standard Error).

Changes in the mean score at various time interval were not statistically significant.

MMSE: Mini-mental state examination



MMSE: Mini-mental state examination

Figure 2: Effect of statins on MMSE score

<u>Effect on various components of cognition according to MMSE</u>

Table 5 and figure 3 is showing effects on various components of cognition according to MMSE. The variation in trends in the mean scores of orientation, registration, language, calculation and attention were not statistically significant at various time intervals. The mean orientation score was 9.53±0.599 at baseline which slightly decreased to 9.52±0.608 at 3 months but further declined to

9.42±0.554 at 6 months. The mean registration score at baseline was 2.69±0.0465, which increased to 2.71±0.0465 at the end of 3 months but remained the same at the end of 6 months. The mean score was 6.10±0.859 at the baseline which reduced to 6.08±0.849 at the end of 3 months but remained at 6.08±0.748 at 6 months. The mean language score of patients at baseline was 8.39±0.510, which slightly decreased to 8.36±0.503 at 3 months but later returned to 8.40±0.512 at the end of 6 months

Table 5: Effect of statins on different components of MMSE score at various time intervals

Characteristic	Baseline	3 months	6 months
Orientation	9.53±0.599	9.52±0.608	9.42±0.554
Registration	2.69±0.465	2.71±0.0.456	2.71±0.456
Calculation and attention	6.10±0.859	6.08±0.849	6.08±0.748
Language	5.93±0.162	8.36±0.503	8.40±0.512

Value expressed as mean ± SE (Standard Error).
Changes in the mean score at various time interval were not statistically significant.
MMSE: Mini-mental state examination

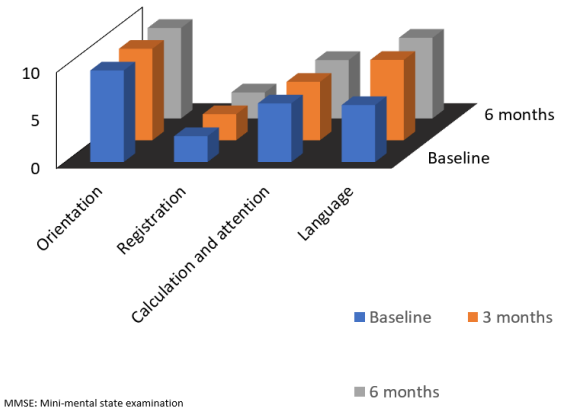


Figure 3: Effect of statin on various components of MMSE

Effect of statins on paper and pencil test

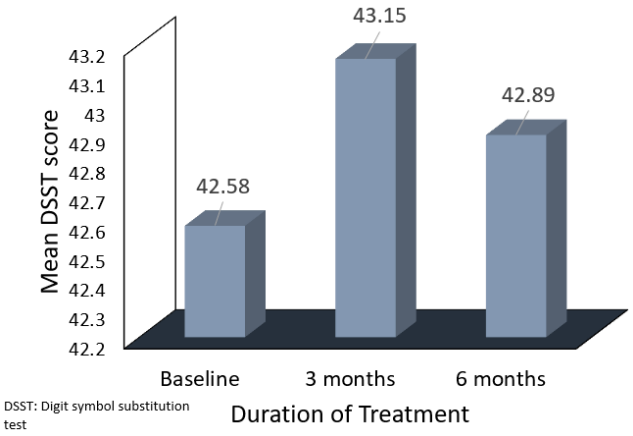
a). Effect on digit symbol substitution test (DSST)

Table 6 and figure 4 shows values of DSST scores expressed as mean ± SE of patients at baseline and at subsequent follow up visits. The mean DSST score was 42.58±3.156 at baseline which was increased to 43.15±2.185 at 3 months but later returned to 42.89±2.774 at 6 months. There was no statistically significant variation in trends among the three measures which were evaluated at different time interval

Table 6: Effect of statins on DSST at various time intervals

Characteristic	Baseline	3 months	6 months
DSST score	42.58±3.156	43.15±2.185	42.89±2.774

Value expressed as mean ± SE (Standard Error).
Changes in the mean score at various time interval were not statistically significant.
DSST: Digit-symbol substitution test



Figue 4: Effect of statins on DSST score

b). Effect on six-letter cancellation test (SCT)

Table 7 and figure 5 compares mean SCT scores of patients from baseline, 3 months and 6 months. The mean SCT score at baseline was 137.41±8.105 which was reduced to 136.94±7.460 at 3 months which was further reduced to 136.42±7.080. The reduction in the mean SCT score at various time intervals were not statistically significant.

Table 7: Effect of statins on SCT at various time intervals

Characteristic	Baseline	3 months	6 months
SCT score	137.41±8.105	136.94±7.460	136.42±7.080

Value expressed as mean ± SE (Standard Error).
Changes in the mean score at various time interval were not statistically significant.
SCT: Six letter cancellation test

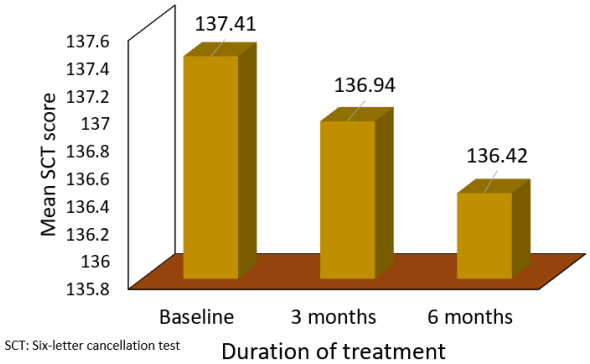


Figure 5: Effect of statins on SCT score

Sub- group analysis

Gender wise analysis of effect of statins on cognitive function test

The mean scores for different cognitive function tests in males and females are given in tables 8 and 9 respectively.

The mean MMSE score was 26.77±0.800 at baseline which was reduced to 26.38±3.114 at 3 months which was further reduced to 26.20±3.078 at 6 months in males. The changes in trends of MMSE score were not statistically significant. The mean DSST score in males increased from 42.33±3.201 at baseline to 43.14±2.118 at 3 months which was further increased to 42.25±3.2.907 at 6 months but changes in trends of DSST score at various follow up were not statistically significant. Similarly, mean SCT score was 137.44±8.076 at baseline which was reduced to 136.24±7.463 at 3 months but marginally increased to 136.48±7.168 at 6 months. The variation in mean SCT scores in males at various intervals was not found to be statistically significant.

Similarly, in females mean MMSE score was 26.62±0.805 at baseline which was reduced to 26.48±0.873 at 3 months which increased marginally to 26.81±0.602 at 6 months. Variation in trends of MMSE score was not found to be statistically significant in females. The mean DSST score decreased in females from 43.52±2.857 at baseline to 43.19±2.228 at 3 months which was further reduced to 42.68±31.632 at 6 months but reduction in mean DSST score at various follow up was not statistically significant. Mean SCT score, which was 137.29±7.476 at baseline which was increased to 139.57±7.004 at 3 months but reduced below the baseline value to 136.48±7.168 at 6 months. The variation in mean SCT scores in females at various intervals was not found to be statistically significant.

Table 8: Effect on different cognitive function tests in males at various time intervals

Characteristic	Baseline	3 months	6 months
MMSE score	26.77±0.800	26.38±3.114	26.20±3.078
DSST score	42.33±3.201	43.14±2.188	43.25±2.907
SCT score	137.44±8.076	136.24±7.463	136.48±7.168

Table 9: Effect on different cognitive function tests in females at various time intervals

Characteristic	Baseline	3 months	6 months
MMSE score	26.62±0.805	26.48±0.873	26.81±0.602
DSST score	43.52±2.857	43.19±2.228	42.68±1.632
SCT score	137.29±7.476	139.57±7.004	136.19±6.904

Value expressed as mean ± SE (Standard Error).
Changes in the mean score at various time interval were not statistically significant.
MMSE: Mini-mental state examination
DSST: Digit-symbol substitution test
SCT: Six letter cancellation test

Effect of statins on random blood sugar

The mean RBS value at baseline was 116.51±17.923 mg/dl, which decreased to 113.41±15.250 mg/dl at 3 months and returned to 114.62±15.698 mg/dl at 6 months. These changes in trend of the mean RBS levels at various time intervals were not statistically significant. Change in RBS levels of patients from baseline, 3 months and 6 months are shown in figure 6 and table 10 and values are expressed as mean ± SE

Table 10: Effect of statins on RBS at various time intervals

Characteristic	Baseline	3 months	6 months
RBS (mg/dl)	116.51±17.923	113.41±15.250	114.62±15.698

Value expressed as mean ± SE (Standard Error).
Changes in the mean score at various time interval were not statistically significant.
RBS: Random blood sugar

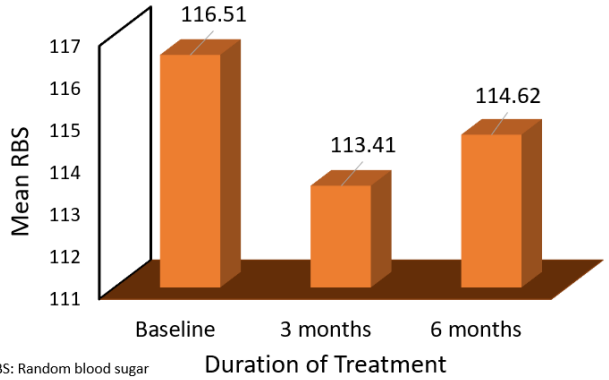


Figure 6: Effect of statins on RBS

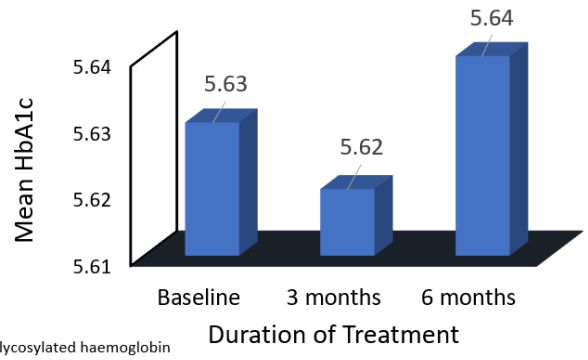
Effect of statins on glycosylated hemoglobin

The mean $HbA1_c$ at baseline was 5.635±0.5389% which was decreased to 5.622±0.4896% at 3 months which was later on returned back to 5.643±0.5958% at 6 months. These changing trends in the mean $HbA1_c$ levels were evaluated, which were found to be non-statistically significant. Table 11 and figure 7 shows mean $HbA1_c$ at baseline and at subsequent follow ups

Table 11: Effect of statins on $HbA1_c$ at various time intervals

Characteristic	Baseline	3 months	6 months
$HbA1_c$ (%)	5.635±0.5389	5.622±0.4896	5.643±0.5958

Value expressed as mean ± SE (Standard Error).
Changes in the mean score at various time interval were not statistically significant.
$HbA1_c$: Glycosylated haemoglobin



$HbA1_c$: Glycosylated haemoglobin

Figure 7: Effect of statins on HbA1c

Gender wise analysis of effect on random blood sugar and glycosylated hemoglobin

Mean RBS in male patients at baseline was 115.52±17.289 mg/dl which decreased to 113.15±15.697 mg/dl at 3 months but returned to 114.19±15.773 at 6 months. Mean $HbA1_c$ at baseline was 5.639±0.5121 % which reduced to 5.591±0.4896 % at 3 months and later returned back to 5.670±0.6043% at 6 months. These variations in mean RBS and $HbA1_c$ levels in males were evaluated, which were not found to be statistically significant.

In females mean RBS value at baseline was noted to be 120.24±20.147 mg/dl which decreased to 114.38±13.749 mg/dl at 3 months but returned to 115.71±15.733 at 6 months. The mean $HbA1_c$ was 5.618±0.6431 % at baseline which was increased to 5.738±0.4958 % at 3 months but was further reduced below the baseline levels to 5.542±0.65674 % at 6 months. The variation in levels of mean RBS and changes in trends of $HbA1_c$ in females was not statistically significant at various intervals. Gender wise analysis of mean levels of RBS and $HbA1_c$ are depicted in tables 12 and 13

Table 12: Effect of statins on RBS and $HbA1_c$ at various time intervals in males

Characteristic	Baseline	3 months	6 months
RBS (mg/dl)	115.52±17.289	113.15±15.697	114.19±15.773
$HbA1_c$ (%)	5.639±0.5121	5.591±0.4862	5.670±0.6043

Value expressed as mean ± SE (Standard Error).

Changes in the mean score at various time interval were not statistically significant.

RBS: Random blood sugar $HbA1_c$: Glycosylated haemoglobin

Table 6: Effect of statins on RBS and $HbA1_c$ at various time intervals in females

Characteristic	Baseline	3 months	6 months
RBS (mg/dl)	120.24±20.147	114.38±13.749	115.71±15.573
$HbA1_c$ (%)	5.618±0.6431	5.738±0.4958	5.542±0.5674

Value expressed as mean ± SE (Standard Error).

Changes in the mean score at various time interval were not statistically significant.

RBS: Random blood sugar $HbA1_c$: Glycosylated haemoglobin

Reported adverse drug reactions

Out of 100 patients, only 12 patients experienced side effects as reported through adverse drug reaction checklist and through spontaneous reporting. The most common adverse effect was dyspepsia and epigastric pain reported by 11 patients out of the total of 12 patients (91.67%) and 1/12 patients reported muscle ache (8.33%). There was no serious adverse effect noted in any patients.

DISCUSSION

This study was conducted to evaluate the cognitive changes as primary outcome parameters after warning was inducted in label about possible cognitive impairment in Indian population. Patients who were prescribed statins for the first time following any cardiovascular event were enrolled in the study.

Baseline demographic characteristics such as age and gender of patients were comparable to other studies.[21] Most of the patients enrolled in our study were in 6th decade of their life as premature mortality due to cardiovascular diseases is high in middle age group.[1] Ratio of males in the study was high as compared to females because it has been noted that males are at greater risk for development of ASCVD.[22] Patients were prescribed atorvastatin for minimum period of six months and average dose of 20 mg per day which is statin therapy of moderate intensity.[23]

The changes in cognition were assessed using three GPCOG, MMSE and pencil and paper tests. These tests are sensitive in assessing the cognitive function and can be performed with semi-literate patients.[24] The tests were conducted at baseline, three months and six months to see any changing trend in cognition after starting statin therapy. GPCOG is a simple, reliable and fast to perform in clinical settings. Cognitive function can be assessed by scoring the questionnaire and score above 8 indicates normal cognition.[25] The patients enrolled in the study had normal cognitive function at the time of the enrolment i.e. >8 score on GPCOG. The use of moderate intensity statin therapy did not show any decline in cognition as interpreted form GPCOG scale at subsequent follow-up done at various intervals within six months of starting the therapy. The mean values of GPCOG score increased marginally from the baseline but that was clinically insignificant. However, no cognitive decline was recorded in either treatment or placebo group.[26] Extensive search did not yield any study which evaluated the changes in cognition using GPCOG scale.

Various components of cognition such as orientation, registration and language skills, attention and calculation are usually assessed by using MMSE questionnaire and a score of less than 25 (out of 30) clinically indicates cognitive impairment.[27] The patients enrolled in this study were having normal cognitive function according to MMSE at the baseline i.e. >25. The patients did not show any clinically evident problem in orientation, registration and language skill and attention and calculation parameters at

baseline. Assessment of cognitive function according to MMSE which done at various intervals of study period did not show any significant decline with the use of statins. However, there was minor decrease in MMSE score at various interval which did not have any clinical significance.

There are also some studies and randomised control trials which showed a significant impairment in cognitive function.[10] However no such effect on cognition was observed in patients after six months of statin therapy in our study. This may be due to short follow up period while statins are prescribed for longer durations. Results from the more recent PROSPER study however, report that pravastatin use does not improve cognitive function in patients with dementia and Alzheimer's disease.[28]

Some studies claimed that cognitive impairment can happen as early 3 weeks after start of therapy. For instance, some case reports and randomized clinical trials have reported significant decrease in neuropsychological tests of attention and psychomotor speed with use of statin therapy.[10,11] A comparative, prospective open label study evaluating the effect of atorvastatin on memory and psychomotor functions (DSST & SCT scores) in hypertensive patients after three months of therapy did not report any significant improvement in scores with use of statin. But it also showed a significant difference between the scores of hypertensive patients and normotensive patients.[29]

In our study, no changes in short term memory, visual motor co-ordination, attention and psychomotor speed were noted in patients as assessed by SCT and DSST score at various intervals when compared with the baseline values. Swiger et al (2013) conducted a meta-analysis in which it was observed that there was no significant difference in the mean DSST score at various follow-up between the statin and placebo groups.[30]

We did not find any significant changes in the cognition within six months of initiation of statin therapy which is corroborated by results from various studies discussed above. However, non-significant findings in this study may be due to short observation period or due to exclusion of patients with liver disease, neuropsychiatric illness, severe hypertension and diabetes where interactions with concomitant medication can affect the bioavailability of the drugs and disease progression may interfere with normal cognitive function. Also, in our study moderate dose statin therapy was prescribed to the patients. The dose and bioavailability of statin can affect cognition as is shown in a phase one study which was conducted to understand the pharmacokinetics of atorvastatin reported mild transient restlessness, euphoria, and mental confusion in one volunteer at high doses of 120 mg per day which were considered to be dose-limiting side effects.[31]

Although the findings of our study suggest the safety of statin in patients as far as cognitive changes are concerned, similar findings should be replicated in studies with larger number of patients which should be carried out for longer duration.

The patients enrolled in this study did not have diabetes at the commencement of the study. There were no significant changes seen in the levels of RBS and $HbA1_c$ in patients at different intervals when compared to the baseline levels. A randomized controlled double-blinded study by Shepherd et al (1995) concluded that use of statin is not associated with significant increase in odds of incident diabetes and does not cause impairment of glycemic control.[32] However, there was a reduction in both mean RBS and $HbA1_c$ values at 3 months which may be due to improvement of lipid metabolism. West of Scotland Coronary Prevention Study (WOSCOPS) concluded that pravastatin therapy may have preventive action in the development of diabetes by reducing plasma TG levels.[20]

There was an increase seen in the levels of $HbA1_c$ at end of six months when compared to baseline, but none of the patient enrolled in the study did not have $HbA1_c$ levels above 6.5 %, the cut-off for diagnosis of diabetes. This finding is corroborated by an observational study which found that statin therapy does not have any protective effect against development of diabetes mellitus.[32]

However, data from recent clinical trials such as JUPITER and PROSPER has shown that there is significant risk of development of new onset diabetes mellitus with the use of statins.[18,19] But in all these studies and trials, the period of observation was more than one year. The non-significant changes which are seen in RBS and $HbA1_c$ levels could be due to a smaller number of patients or short observation period. Other side effects which were reported were non-serious and did not require any intervention. Few patients reported dyspepsia and heartburn after initiation of therapy which was resolved within few days while one patient reported muscle ache after which drug was stopped. A meta-analysis conducted to analyse the overall incidence of different adverse reaction in various trials showed incidence of myopathy about 1-3 %.[33,34] The incidence of side effects in our study were similar to other studies.

It has been noted that as the incidence of myopathy associated with statins varies significantly among different races and it is lower in Asian population.[33] It is important to evaluate the effect of statins in Indian population as the incidence of diabetes mellitus and cognitive impairment may vary in different population.

Although the findings of our study suggest the safety of statin in patients as far as glycemic changes are concerned, similar findings should be replicated in studies with larger number of patients which should be carried out for longer duration. Thus, it was found that use of statins did not have any significant effect on levels of RBS and $HbA1_c$ also did not show any significant variation at various time intervals in this study.

Limitations

This study has certain limitations that should be considered while interpreting the findings. The relatively small sample size and single-center design may limit the generalizability of the results. The duration of follow-up was restricted to six months, which may not be sufficient to detect delayed or cumulative effects of statins on cognitive function and glycemic control. The open-label nature of the study could have introduced observer or reporting bias. Additionally, exclusion of patients with diabetes mellitus, neuropsychiatric disorders, liver disease, and severe hypertension limits the applicability of the findings to these

high-risk groups. The use of screening-based cognitive assessment tools, although practical, may not detect subtle cognitive changes that could be identified through advanced neuropsychological testing or neuroimaging.

Future Directions

Future research should focus on large-scale, multicenter, randomized controlled trials with longer follow-up periods to better evaluate the long-term cognitive and metabolic effects of statins. Studies involving higher-intensity statin therapy, varied dosing regimens, and different statin molecules would help clarify potential dose- and drug-specific effects. Inclusion of elderly individuals, patients with diabetes, and those with baseline cognitive vulnerability would enhance the clinical relevance of future studies. Additionally, incorporating advanced cognitive assessment tools, biomarkers, and pharmacogenomic analyses may provide deeper insights into individual variability in statin response, particularly within the Indian population.

CONCLUSION

This prospective study demonstrates that moderate-intensity statin therapy over a six-month period does not significantly affect cognitive function or glycemic status in statin-naïve patients. The findings support the cognitive and metabolic safety of statins in the short term. Given the widespread use of statins and existing regulatory concerns, further long-term studies are essential to conclusively establish their safety profile across diverse patient populations

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