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IMPACT OF HMG COA REDUCTASE INHIBITORS ON THE GLYCEMIC STATUS OF NORMOGLYCEMIC INDIVIDUALS: A PROSPECTIVE, LONGITUIDINAL, OBSERVATIONAL STUDY

Subhayan Das, Dipan Saha*, Ram Narayan Maiti, Swarnali Paul, Sekhar Mandal

[1]Department of Pharmacology, Midnapore Medical College.

***Corresponding Author: Dipan Saha**

Department of Pharmacology, Midnapore Medical College.

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ABSTRACT

Background: HMG CoA reductase inhibitors (statins) are the most common drugs used for primary and secondary prevention of cardiovascular diseases. Various Clinical studies have suggested usage of long term statin therapy may lead to significant rise in the blood glucose levels of the patients. However the adequate and exact data regarding the impact of HMG CoA reductase inhibitors on glycemic status of Eastern Indian Population is still limited. **Objective**: To estimate the impact of HMG CoA reductase inhibitors on the glycemic status of euglycemic patients. **Methods and Materials**: An observational longitudinal study was carried out over 24 weeks at an Internal Medicine Outpatient Department of a tertiary care Hospital in Eastern India. Non diabetic Patients aged 30-65 years receiving HMG CoA reductase inhibitors were enrolled in our study. Patients with impaired fasting glucose and/or impaired glucose tolerance were excluded. FBS, PPBS, HbA1C and lipid profile of participants were monitored at baseline, at 12thweek and at 24th week. The data were analyzed accordingly by SPSS for the result. **Result**: The study population was predominantly male (64%), with mean age of 50.46± 9.65 years and mean weight of 70± 5.07kg. Majority of the patients were on Atorvastatin 20 mg. There were statistically significant rise of Mean FBS, Mean PPBS and Mean HbA1C at the end of 24 weeks. But since the values were within the normal clinical range, hence they were clinically insignificant. None of the patients developed New Onset Diabetes Mellitus at the end of 24 weeks. 3 out of 50 patients (6%) developed impaired blood glucose levels. **Conclusion**: Though Statins are the most common drugs used nowadays to prevent cardiovascular diseases, strict monitoring of blood glucose levels of the patients on statin therapy should be done at regular intervals.

KEYWORDS: Statins, Dyslipidemia, Diabetes.

INTRODUCTION

HMG-CoA Reductase Inhibitors are one of the most commonly used drugs nowadays for their major role in prevention of atherosclerotic cardiovascular diseases.[1] Evidence from many randomised controlled trials and long term observational studies indicates a major variability in glycemic status of individuals[2], with even a shift from prediabetic state to emergence of new onset diabetes following statin treatment.[3] A large, randomised ,placebo controlled, primary prevention trial called Justification for use of statins in Prevention of CVD(JUPITER) shows benefits of Rosuvastatin in subjects of intermediate CVD risk with 26% higher incidence of diabetes in the rosuvastatin study population.[4] Although meta-analysis of various primary prevention showed a significant 15% reduction in CVD mortality following statin use,[5] the major concern still lies with the gycemic status variability of the patients following longterm statin use.[6]

The mechanism underlying the disarrangements of glucose metabolism following statin use still remained unclear,[7] but there are evidences showing impaired insulin sensitivity and compromised beta cell function, due to increased intracellular uptake, following inhibition of intracellular cholesterol synthesis by statins.[8] Statins causes increased mitochondrial oxidation stress, following inhibition of ubiquinone(CoQ10) and also activates inflammasome NLRP3 from macrophages, under certain conditions which leads to Interleukin 1b mediated insulin resistance and beta cell apoptosis.[9] People taking statins showed increased uptake of fat and calorie intake in their diet and therefore gained weight over time, which causes lifestyle induced worsening in insulin sensitivity and loss of glycemic control.[10]

Hence, an observational longitudinal study was conducted on euglycemic patients of Eastern India receiving statins to see its effect on glycemic status of those individuals over time.

MATERIAL AND METHOD

This was an observational longitudinal study conducted at Midnapore medical college and hospital, Midnapore,

West Bengal. The study period was approximately 24 weeks. Patients aged 30-65 attending the Internal Medicine outpatient department was considered as study subjects. Among the patients who are drug naïve, and to be receiving HMG COA reductase inhibitors (Atorvastatin or Rosuvastain) for dyslipidemia, or for secondary prevention of cardiovascular or cerebrovascular diseases were enrolled as study subjects. Informed consent was taken from each of the participants. Patients with preexisting diabetes mellitus, impaired glycemic status or those receiving drugs like corticosteroid, thiazide diuretics which have an effect on glycemic status, patients with known renal, hepatic disease, infected disease like tuberculosis etc, and cancer were excluded from the study. Pregnant and lactating women were also excluded.

At the outpatient department all the subjects were screened for conditions mentioned above. Venous blood sample were sent and fasting, post prandial blood glucose, liver function test, urea and creatinine values at the baseline were obtained. All the subjects were on statin therapy and were followed up for total 6 months. After every 3 months from the baseline glycemic parameters i.e FBS, PPBS, HbA1c were evaluated. Study ended after 2 follow ups. Progression of normoglycemic state to prediabetes or diabetes was considered as the primary end point.

STATISTICAL ANALYSIS

Descriptive Statistics like Mean and percentages were used for the Analysis and interpretation of the results. Comparison of the groups was done by t tests. Statistical analysis was performed using SPSS version 21.

RESULTS

The Study was conducted to find out the impact of HMG-CoA Reductase inhibitors (statins) on the glycemic status of individuals receiving it. Among the patients, aged 30-65 yrs, attending General Medicine Outpatient department of Midnapore Medical College, 50 met the inclusion criteria and got enrolled in our study. Most of the study subjects were male (64%) as shown in fig 1, with Mean age of 50.46+-9.65 yrs (fig 2) and Mean weight of 70+-5.07 kg. Majority of the patients were on Atorvastatin 20mg (46%) followed by Atorvastatin10 mg (18%) and Atorvastatin 40mg (16%) respectively where as 12% of patients were on Rosuvastatin 10 mg and 8% of patients were on Rosuvastatin 20 mg (fig 3). The Mean Fasting Blood Sugar level (FBS) and the Mean Post prandial Blood sugar level (PPBS) of the study subjects at the beginning of the study were 86.620 mg/dl and 111.26 mg/dl respectively. At the end of 12 weeks the mean FBS was 92.04 mg/dl and the mean PPBS was 114.04 mg/dl, both were significant statistically when compared with the baseline values (table 1). Again after 24 weeks we assessed the glycemic status of the subjects, and then we observed there was significant rise in both the FBS as well as PPBS values compared to the baseline (table 2). However though the results were statistically significant, both Mean FBS and Mean PPBS were under clinically normal Blood Sugar range, hence clinically insignificant. There was also rise in Mean HbA1c levels in both groups of pts taking Atorvastatin and Rosuvastatin at end of 24 weeks (fig 4). If compared to baseline HbA1c this change after 24 weeks was significant (table 2), but still they were all within normal parameters. None of the patients developed new onset Diabetes mellitus at the end of 24 weeks. 3 out of 50 subjects (6%) developed prediabetes (impaired blood glucose level) at the end of the study. Further analysis showed that those patients who were on Atorvastatin 40 mg developed prediabetic state. None of the patients on Rosuvastatin developed IGT. Among the 50 subjects, 33 of them (66%) were hypertensive. 6% of the subjects had a past history of cerebrovascular accident whereas 10% known to have suffered from cardiovascular accident in the past. The changes in lipid Profile were noted in the 1st follow up and 2nd follow up when compared to the baseline values of the patients (fig 5).

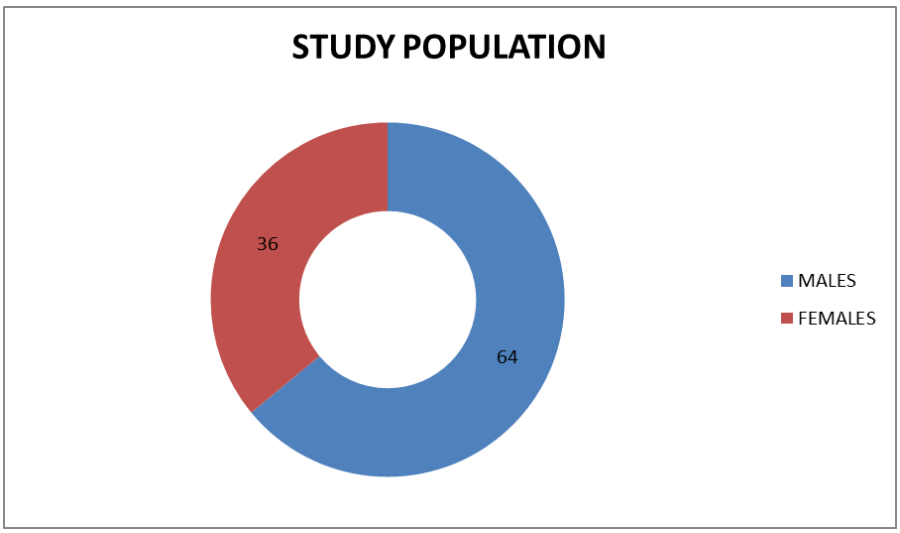

Figure 1: Gender wise distribution of the subjects.

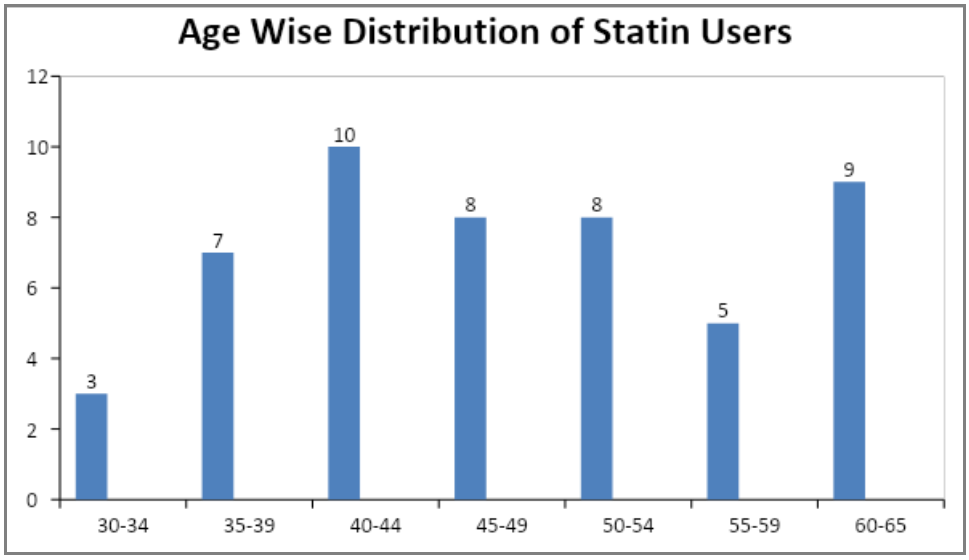

Figure 2: Age category wise distribution of study subjects.

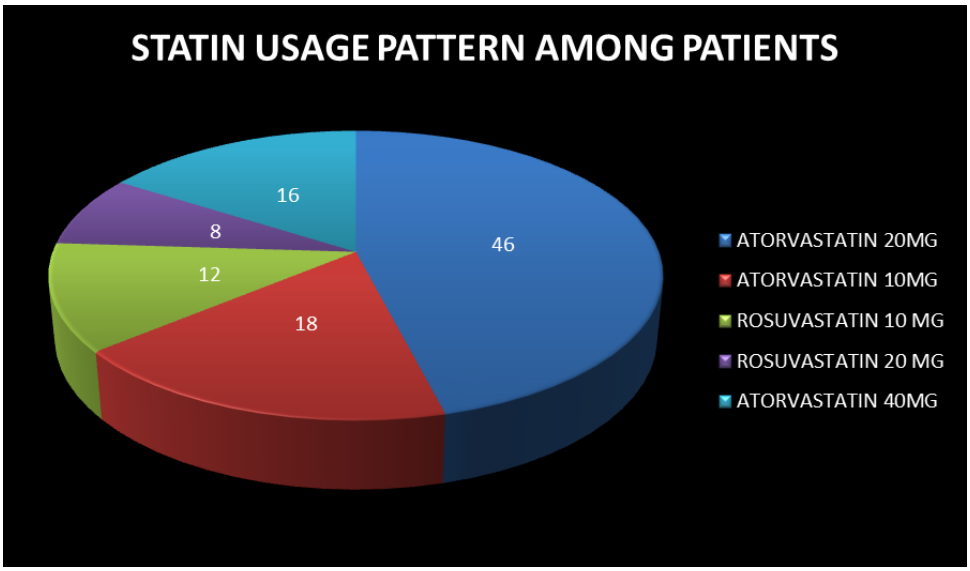

Figure 3: Statin usage pattern among subjects (values showed in %).

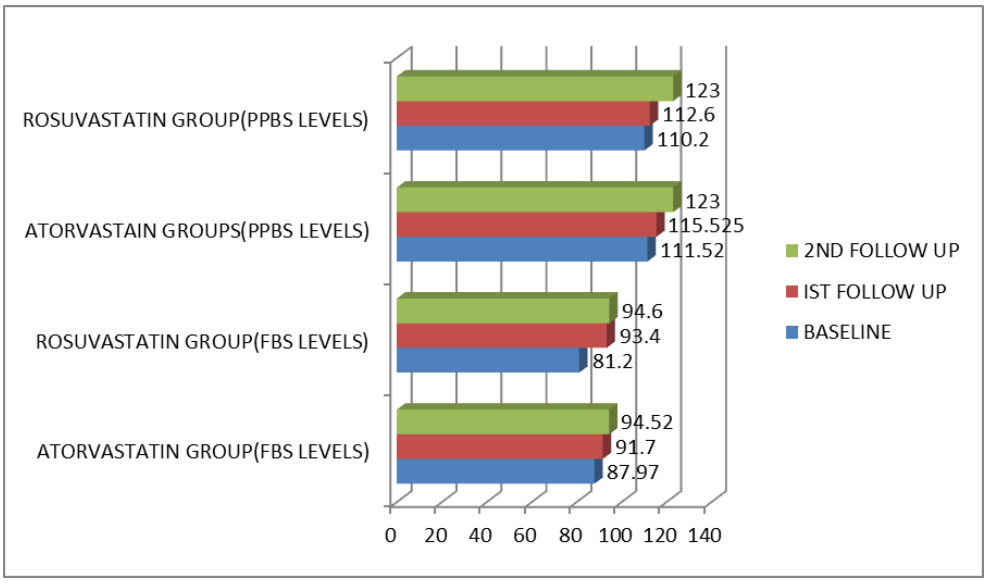

Figure 3: Comparison of mean FBS, PPBS levels of the subjects after 12 and 24 weeks with the baseline levels.

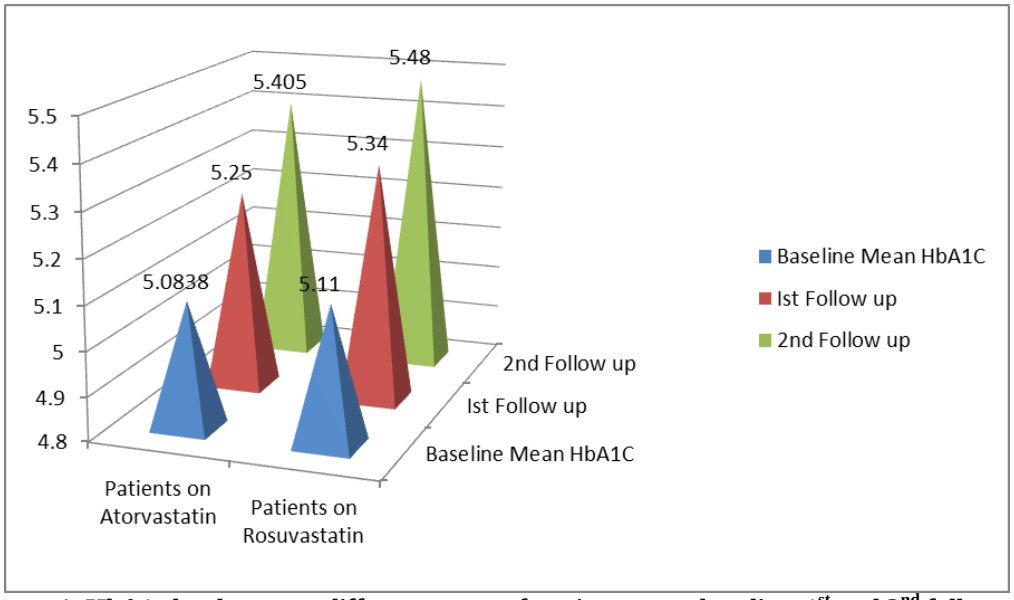

Figure 4: HbA1c levels among different group of statin users at baseline, 1st and 2nd follow up.

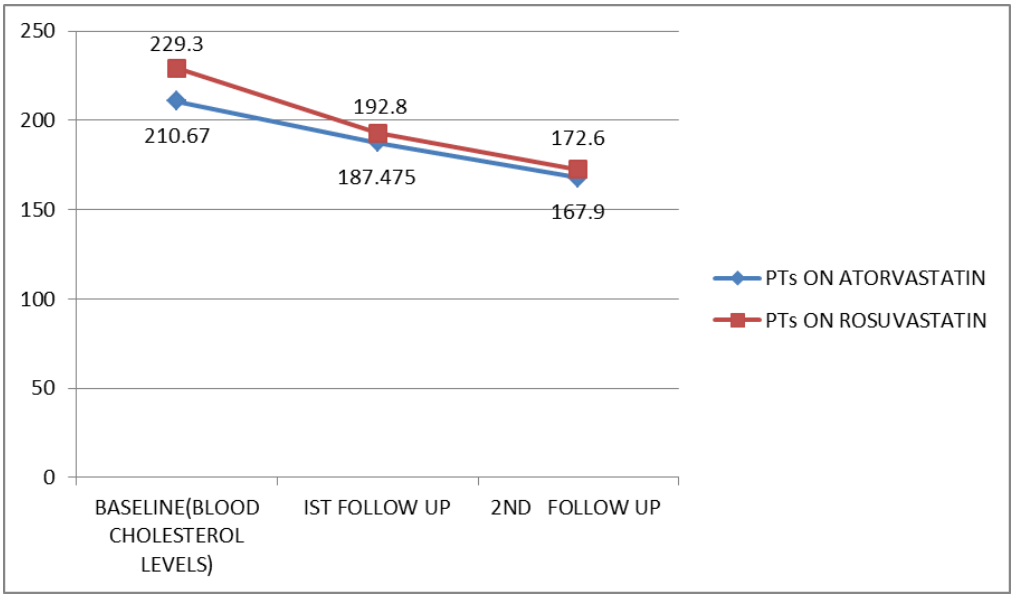

Figure 5: Comparison of serum cholesterol levels between Atorvasatain and Rosuvastatin users.

Table 1: Comparison of glycemic status and lipid parameters of total study population obtained after 3 months with the baseline values.

Parameters	Baseline	1st follow up	P value (t test)
FBS (mg/dl)	86.62	92.04	< 0.001
PPBS (mg/dl)	111.26	114.94	0.017
HbA1C %	5.08	5.26	<0.001
Total cholesterol (mg/dl)	211.90	188.5	<0.001
LDL (mg/dl)	148.66	139.62	<0.001

Table 2: Comparison of glycemic status and lipid parameters of total study population obtained after 6 months with the baseline values.

Parameters	Baseline	2nd follow up	P value (t test)
FBS (mg/dl)	86.62	94.54	0.002
PPBS (mg/dl)	111.26	123	<0.001
HbA1C %	5.08	5.42	<0.001
Total Cholesterol	211.90	168.84	<0.001
LDL	148.66	128.56	<0.001

DISCUSSION

Statins are the most common drugs used for primary and secondary prevention of Cardiovascular Diseases.[1] Concerned has been raised by several meta-analysis which shows an association of statin with impaired glycemic control of patients receiving it.[11] Meta-analysis by Preiss et al in 2011, showed 12% increased risk of New Onset Diabetes with higher potency statins compared to lower potency statins.[12] Our Study subjects had a mean age of 50+-9.65yrs.Studies conducted by Sattar et al showed patients on age group between 55-76 yrs were at more risk of development of diabetes. They also showed a 9% increase risk of diabetes among non diabetic statin users among the above age group.[13] Male predominance among Statin users were seen in our study group where 64% were males. Simillar Male Predominance were seen in JUPITER trail[14] and LIPID trial (Long term Intervention with Pravastatin In Ischaemic Diseases) where 61.8% and 80% of study population were males.[15] The most common Statin used in our study subjects were Atorvastatin. Various Drug utilization studies also showed Atorvastatin as the most commonly used statin.[16] Dose dependent diabetogenic potential of Statins were shown in various studies. Meta-analysis by Navarese et al showed the incidence of diabetes mellitus with Atorvastatin 80mg, Rosuvastatin 20mg, and Pravastatin 40mg were 15%, 25% and 7% respectively.[17] Studies by Koh et al also showed association of higher incidence of diabetes with Atorvastatin 80mg.[18] Though our study did not show any incidence of NODM, but 3 patients on Atorvastatin 40mg developed prediabetic state at the end of 24 weeks. However Demographic parameters like older age, weight gain, metabolic syndrome, dietary habits and genetic predisposition may be the other factors that may play an associated role in onset of prediabetic state in those subjects. The Canadian Network of Drug Administration reveals the incidence of diabetes to be seen highest in first 4 months after starting statin therapy, which justifies the 6% incidence of prediabetic state among Statin users in our study. Collaborative Atorvastatin Diabetes Study (CARDS) trial shows 84% patients were hypertensive among statin users.[19] Our study shows 66% incidence of hypertension among statin users. There are only a few studies from India which evaluated the impact of statins on glycemic status of patients. Though our study from eastern part of India did not show any incidence of NODM among statin users, but the 6% incidence of prediabetic state among statin users definitely enlightens the suspicious impact of HMG-CoA Reductase inhibitors on the glycemic status of patients.

CONCLUSION

HMG CoA reductase inhibitors are the most common drugs used in today's world for their potential benefit to prevent adverse cardiovascular events. But these cholesterol lowering agents also have showed to increase the risk of NODM and impaired glycemic control in patients who already had diabetes. So, we recommend to monitor blood glucose levels of the patients on statin therapy for longer periods. It is also suggested to use statin therapy cautiously on the patients who already had pre existing diabetes or on the pre-diabetic population. Further studies with control groups need to be done to further establish the relationship. However, Genetic predisposition, dietary factors, sedentary lifestyle, metabolic syndrome are the other factors which might also have an impact on glycemic status of the patients.

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Conflicts of Interest: There are no conflicts of interest.

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