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Original Article

Pharmacology Section

Impact of Atorvastatin on C-reactive Protein, Glycaemic Status and Liver Enzymes among Non Diabetic Patients: A Prospective Study

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ABSTRACT

Introduction: Atorvastatin is one of the common drugs used for primary and secondary prevention of atherosclerotic cardiovascular diseases. Various studies have suggested variation in C-reactive Protein (CRP) value, glycaemic status and liver enzymes of patients following statin therapy. However, the adequate and exact data regarding the impact of atorvastatin on the above parameters in the population of Eastern India is still limited.

Aim: To estimate the effect of atorvastatin on CRP, glycaemic status and haepatic enzymes of non diabetic patients.

Materials and Methods: A prospective longitudinal observational study was conducted in the Outpatient Department (OPD) of Internal Medicine at Midnapore Medical College and Hospital, Paschim Medinipur, West Bengal, India. The duration of the study was one year six months, from June 2020- December 2021. A total of 150 non diabetic patients aged between 30-75 years receiving atorvastatin were enrolled in the present study. Patients with known Diabetes Mellitus (DM), impaired fasting glucose, impaired glucose tolerance, pregnancy and lactation were excluded. CRP, Fasting Blood Sugar (FBS), Postprandial Blood Sugar (PPBS), haepatic enzymes and lipid profile of participants were monitored at baseline, at the end of one month, six months and 12 months. The data was analysed using Statistical Package for Social Sciences (SPSS) version 22.0, Microsoft Excel and GraphPad Prism.

Results: The study population were predominantly males (69.6%), with mean age of 54±8.88 years and mean weight of 60±5.86 kg. Majority of the patients were on atorvastatin 40 mg (60.86%) followed by atorvastatin 20 mg (26.8%) and atorvastatin 10 mg (12.3%). There were statistical significant changes of mean CRP (1.502 mg/L), mean FBS (86.52 mg/dL), mean PPBS (113.57 mg/dL), mean Serum Glutamic-oxaloacetic Transaminase (SGOT) (22.84 IU/L), mean Serum Glutamic Pyruvic Transaminase (SGPT) (25.24 IU/L) and lipid profile levels at the end of one year. None of the patients developed new onset DM at the end of one year. A 5% of patients developed prediabetes at the end of 3rd follow-up.

Conclusion: Atorvastatin usage showed that, there was a significant increase in blood glucose and haepatic enzymes level in non diabetic population. Hence, strict monitoring of blood glucose levels along with periodic monitoring of haepatic enzyme levels should be done in regular intervals.

Keywords: Cardiovascular disease, Diabetes mellitus, Statin

INTRODUCTION

The Hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors are one of the most commonly used drugs now a days, for their major role in prevention of atherosclerotic cardiovascular diseases. Acute coronary syndromes typically arise from disruption of atherosclerotic plaques that leads to local thrombus formation, which contain numerous inflammatory cells. Inflammation plays a major role in plaque destabilisation. Inflammatory markers like CRP, reduces the production of nitric oxide by endothelial cells, causing increasing susceptibility of endothelial cells to destruction by cell lysis, thereby, participating in vascular inflammation and plaque destabilisation [1,2]. CRP is an independent predictor and the most stable and reliable laboratory measure of systemic inflammation and adverse cardiovascular outcome in healthy population [3]. Studies differ regarding the extent of CRP lowered by atorvastatin, its relation with standard and intensive statin therapy and its association with several other risk factors specifically like blood glucose levels, Low-density Lipoprotein (LDL), triglyceride and blood cholesterol levels [4,5]. A lower CRP level is associated with a lower risk of recurrent events in patients with acute coronary syndromes. But, as atherosclerosis is a disease of high complexity, involving multifactorial relationship, it is therefore, difficult to elucidate the mechanisms by which statin reduces CRP concentrations and exert their anti-inflammatory effect.

Though, statins (atorvastatin) causes significant reduction of cardiovascular disease mortality, various meta-analysis showed an association of statin with adverse glycaemic control [6]. A safety label has been added by Food and Drug Administration (FDA) to statins, because of its propensity to increase FBS levels. A study done by Koh KK et al., showed incidence of new onset DM among patients taking atorvastatin [7]. Dose dependent diabetogenic potential of statins was shown in various studies. Another study by Preiss D et al., shows 12% increased risk of New-Onset Diabetes Mellitus (NODM) with higher potency statins compared to lower potency statins [8]. Use of atorvastatin has been seen to affect liver enzymes of patients particularly, when patients are taking some other medications, which may affect its metabolism. According to Motola D et al., statin associated elevated liver enzymes hold 10.9% in a total of 1245 adverse drug reaction reports from January 1950 to May 2005 [9]. Statins are among those with the highest rate of causing elevation of liver enzymes, higher than anti-platelet and non steroidal anti-inflammatory drugs, raising a potential concern to monitor atorvastatin associated effects on liver enzymes on its long term use. Though, asymptomatic haepatic enzyme elevations are the most common forms of haepatic side effects following atorvastatin use, several forms of severe side effects such as hepatocellular injury, cholestatic injury, autoimmune type reaction and fulmitant liver failure also do occur [10]. Consequently, haepatic dysfunction is a major concern for statin induced side effects, which thereby, necessitates for strict monitoring of liver enzymes following statin use, besides its effects on glycaemic status.

Lack of adequate clinical data regarding the effect of atorvastatin on the following biochemical paremeters such as FBS, PPBS, CRP and haepatic enzymes on non diabetic Indian population. Hence, an observational longitudinal study was conducted on euglycaemic

patients of Eastern India receiving statins to see its effect on CRP, glycaemic status and haepatic enzymes of individuals receiving it. Atorvastatin does not cause significant changes in FBS, PPBS, CRP and haepatic enzymes levels of non diabetic Indian population.

MATERIALS AND METHODS

A prospective longitudinal observational study was conducted in the OPD of Internal Medicine at Midnapore Medical College and Hospital, Paschim Medinipur, West Bengal, India. The duration of the study was one year six months, from June 2020- December 2021. The study was initiated after approval of the Instituitional Ethics Committee ((MMC/IEC-2020/309). Informed consent was taken from each of the study participants.

Inclusion criteria: Patients aged between 30-75 years, who are drug naive, and to be receiving oral atorvastatin for dyslipidemia or for secondary prevention of cardiovascular or cerebrovascular diseases were enrolled as study subjects.

Exclusion criteria: Patients with pre-existing DM, impaired fasting glucose, impaired glucose tolerance or those receiving drugs like corticosteroids, thiazide diuretics, anti-psychotics which have an effect on glycaemic status, patients with known renal, haepatic disease, infective diseases like tuberculosis etc., terminally ill patients (e.g., cancer) were excluded from the study. Pregnant and lactating mothers were also excluded.

Sample size calculation: The sample size for the present study was 150. The sample size was calculated based on the equation 4PQ/L2, where P=Prevalance of prediabetes in normal Indian population (p=10.3%), Q=100-P, L=absolute allowable error. Here, L is considered to be 5% [11]. Simple random sampling technique was used for recruitment of study population.

Study Procedure

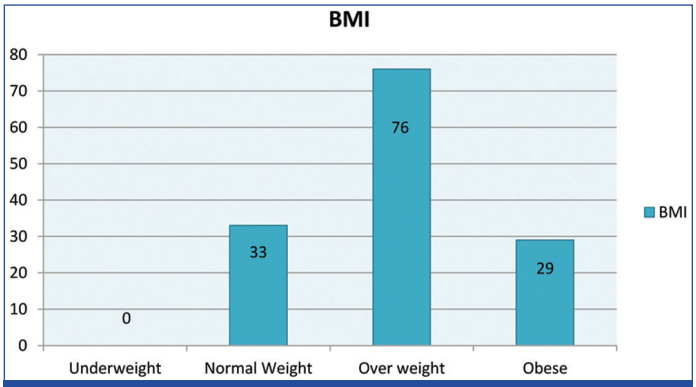
At the OPD, all the subjects were screened for conditions mentioned above. Assessment of plasma glucose levels- FBS (normal range:70-110 mg/dL) and PPBS (normal range:80-140 mg/dL), serum triglyceride level (normal range:44-165 mg/dL), blood cholesterol level (normal range: desirable <200 mg/dL), LDL (normal range:<100 mg/dL), Very Low-density Lipoprotein (VLDL) (normal range12-34 mg/dL), High-density Lipoprotein (HDL) (normal range 40-59 mg/dL) CRP (normal range:<5 mg/L), Alanine Transaminase (ALT) (normal range:<45 U/L) and Aspartate Aminotransferase (AST) (normal range:<35 U/L), Alkaline Phosphatise (ASP) levels (normal range:35-104 U/L) as baseline parameters were done [12]. Anthropometric measurements such as height, weight and Body Mass Index (BMI) of all the patients were measured at the baseline. BMI was categorised according to World Health Organization (WHO) Asia pacific BMI [13]. All the subjects were on atorvastatin therapy and were followed-up for 12 months with reassessment of the above parameters at the end of 1st, 6th and 12th month intervals. Study ended after three follow-up visits. Progression of normoglycaemic to prediabetes or diabetes, significant changes in CRP and haepatic enzymes levels were considered as primary end point.

STATISTICAL ANALYSIS

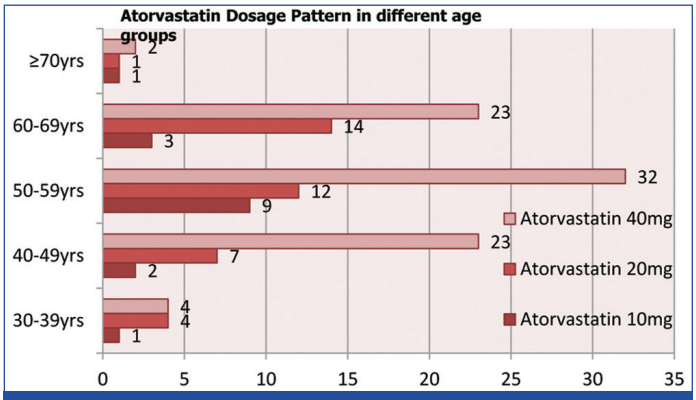
The data were analysed using SPSS version 22.0, Microsoft Excel and GraphPad Prism software. Analysis was done by paired Student's t-test. Results were expressed in terms of mean, frequencies and percentages.

RESULTS

The study was conducted to find out the impact of atorvastatin on the CRP, glycaemic status and haepatic enzymes of the individuals receiving it. Among the patients, aged between 30-75 years, attending general medicine OPD of Midnapore Medical College, 150 patients met the inclusion criteria and got enrolled in the study. A total of 12 patients were loss to follow-up. A total of 138 patients completed the study and were analysed accordingly. Most of the study subjects were males (69.6%) with mean age of 54±8.88 years and mean weight of 60±5.86 kg. Majority of the participants (55%) were from the overweight category according to their BMI, followed by normal weight (23.9%), and obese category (21%). 60.86% of their patients were on atorvastatin 40 mg, followed by atorvastatin 20 mg (26.8%) and atorvastatin 10 mg (12.3%) [Table/Fig-1]. A 50-59 years age group population had highest usage of tab. atorvastatin. Atorvastatin tablets of 40 mg strength were the most commonly used dosage formulation in this group of population (50-59 years). [Table/Fig-2] shows atorvastatin dosage usage pattern in different age groups of study population.



[Table/Fig-1]: BMI category-wise distribution of study population {WHO Asia pacific guideline of Body Mass Index (BMI)}.



[Table/Fig-2]: Atorvastatin dosage pattern in different age groups of study population.

The mean CRP, FBS level and the mean PPBS level at the beginning of the study were 84.60 mg/dL, 110.43 mg/dL and 5.3%, respectively. When they measured the serum lipid parameters, it was found that, the mean total blood cholesterol was 191.25 mg/dL and LDL was 114.007 mg/dL, whereas, the mean serum triglyceride was 207.63 mg/dL at the baseline. The mean ALT/SGPT, AST/SGOT and ALP values were 21.54 IU/L, 21.101 IU/L and 92.13 IU/L respectively after initiation of atorvastatin therapy, patient's biochemical parameters were obtained after four weeks (Ist follow-up). On comparing the baseline mean FBS, PPBS and CRP with the Ist follow-up visit values, the changes were found to be statistically non significant (p >0.05). On comparing the baseline mean haepatic enzymes values with that obtained after four weeks, the differences in the ALT, AST and ALP values were found to be statistically non significant (p >0.05) There were statistically significant differences (p<0.05) between baseline serum triglyceride, blood cholesterol, LDL, and VLDL values with that obtained after four weeks, whereas, mean HDL value was found to be statistically non significant [Table/Fig-3].

The mean PPBS value at baseline and at 2nd follow-up visit was 110.43 mg/dL and 112.51 mg/dL respectively. The change in PPBS value was statistically significant (p<0.05). Whereas, there were statistically non significant changes in the mean FBS and CRP value at the end of six months, when compared with the baseline. The changes in mean ALT, AST and ALP values were statistically non significant (p>0.05) at

Parameters	Baseline values	1st follow-up (after 4 weeks)	p-value
FBS (mg/dL)	84.60±10.44	84.17±9.20	0.305
PPBS (mg/dL)	110.43±16.30	109.78±14.81	0.397
CRP	1.58±0.67	1.581±0.67	0.452
ALT (U/L)	21.54±8.24	21.92±7.41	0.087
AST (U/L)	21.10±6.70	21.46±6.50	0.208
ALP (U/L)	92.13±18.14	92.23±21.74	0.552
Serum triglyceride (mg/dL)	207.63±42.21	200.38±40.71	<0.05
Total blood cholesterol (mg/dL)	191.25±17.21	187.60±16.60	<0.05
LDL (mg/dL)	114.00±12.78	111.96±12.23	<0.05
HDL (mg/dL)	36.10±6.41	36.04±6.34	0.342
VLDL (mg/dL)	41.06±8.45	39.60± 8.15	<0.05

[Table/Fig-3]: Comparison of CRP, glycaemic status, liver enzymes and lipid profile values of study population obtained at the end of four weeks with the baseline. (Paired t-test).
FBS: Fasting blood sugar (normal range: 70-110 mg/dL); PPBS: Post prandial blood sugar (normal range: 80-140 mg/dL); Serum Triglyceride level (normal range: 44-165 mg/dL), Blood Cholesterol level (normal range: Desirable <200 mg/dL), LDL: Low-density lipoprotein (normal range: <100 mg/dL); VLDL: Very low-density lipoprotein (normal range12-34 mg/dL);
HDL: High-density lipoprotein (normal range 40-59 mg/dL); CRP: C-reactive protein (normal range: <5 mg/L); ALT: Alanine transaminase (normal range: <45 U/L); and AST: Aspartate aminotransferase (Normal range: <35 U/L); ALP: Alkaline phosphatise levels (normal range:35-104 U/L) [10]

the end of 2nd follow-up when compared with baseline. The lipid profile values: serum triglyceride, blood cholesterol, LDL, HDL and VLDL obtained at the end of 24 weeks were compared with the baseline. There was a decrease in serum triglyceride, blood cholesterol, LDL, and VLDL value and slight increase in HDL value, which were all found to be statistically significant (p<0.05) [Table/Fig-4] [10].

Parameters	Baseline values	2nd follow-up	p-value
FBS (mg/dL)	84.60± 10.44	83.60±9.94	0.090
PPBS (mg/dL)	110.43±16.30	112.51±14.23	0.029
CRP	1.58±0.67	1.57±0.67	0.298
ALT (U/L)	21.54±8.24	22.02±6.90	0.120
AST (U/L)	21.10±6.70	21.78±6.02	0.077
ALP (U/L)	92.13±18.14	93.47±21.13	0.141
Serum triglyceride (mg/dL)	207.63±42.21	185.76±36.24	< 0.05
Blood cholesterol (mg/dL)	191.25±17.21	177.62±15.34	< 0.05
LDL (mg/dL)	114.00±12.78	104.83±10.80	<0.05
HDL (mg/dL)	36.10±6.41	36.38±6.18	<0.05
VLDL (mg/dL)	41.06±8.45	36.70±7.26	<0.05

[Table/Fig-4]: Comparison of CRP, glycaemic status, liver enzymes, and lipid profile values of total study population obtained at the end of six months (2nd follow-up) with the baseline value (paired t-test).
FBS: Fasting blood sugar (normal range: 70-110 mg/dL); PPBS: Post prandial blood sugar (normal range: 80-140 mg/dL); Serum triglyceride level (normal range: 44-165 mg/dL); Blood cholesterol level (normal range: Desirable <200 mg/dL); LDL: Low-density lipoprotein (normal range: <100 mg/dL); VLDL: Very low-density lipoprotein (normal range12-34 mg/dL); HDL: High-density lipoprotein (normal range: 40-59 mg/dL); CRP: C-reactive protein (normal range: <5 mg/L); ALT: Alanine transaminase (normal range: <45 U/L); and AST: Aspartate aminotransferase (normal range: <35 U/L); ALP: Alkaline phosphatise levels (normal range: 35-104 U/L)[10]

The FBS, PPBS and CRP value were obtained at the end of 3rd follow-up. On comparing with the baseline values, the changes were found to be statistically significant (p<0.05). A total of seven out of 138 patients were found to be prediabetic at the end of one year (3rd follow-up). The ALT, AST and ALP values were also obtained at the end of one year (3rd follow-up). They are then compared with their respective mean baseline values. There was slight increase in mean ALT and AST values which was found to be statistically significant (p<0.05), whereas, the differences in ALP was found to be non significant at the end of the study. Finally, the lipid profile values were obtained at the end of one year and were compared with the baseline values. There were decrease in mean serum triglyceride, blood cholesterol, LDL, VLDL levels and slight increase in mean HDL level. However, all the changes were found to be statistically significant (p<0.05) [Table/Fig-5] [10].

Parameters	Baseline values	3rd follow-up	p-value
FBS (mg/dL)	84.60±10.44	86.52±10.94	0.024
PPBS (mg/dL)	110.43±16.30	113.57±15.09	<0.05
CRP	1.58±0.67	1.50±0.62	<0.05
ALT (U/L)	21.54±8.24	22.84±7.58	0.004
AST (U/L)	21.10±6.70	25.24±7.41	<0.05
ALP (U/L)	92.13±18.14	93.66±20.70	0.071
Serum triglyceride (mg/dL)	207.63±42.21	174.23±31.27	<0.05
Blood cholesterol (mg/dL)	191.25±17.21	165.68±12.73	<0.05
LDL (mg/dL)	114.00±12.78	94.44±9.13	<0.05
VLDL (mg/dL)	41.06±8.45	34.43±6.25	<0.05
HDL (mg/dL)	36.10±6.41	36.81±5.81	<0.05

[Table/Fig-5]: Comparison of CRP, glycaemic status, liver enzymes and lipid profile values of total study population obtained at the end of one year (3rd follow-up) with the baseline values (paired t-test).
FBS: Fasting blood sugar (normal range: 70-110 mg/dL); PPBS: Post prandial blood sugar (normal range: 80-140 mg/dL); Serum triglyceride level (normal range:44-165 mg/dL); Blood cholesterol level (normal range: Desirable <200 mg/dL); LDL: Low-density lipoprotein (normal range: <100 mg/dL); VLDL: Very low-density lipoprotein (normal range 12-34 mg/dL); HDL: High-density lipoprotein (normal range 40-59 mg/dL); CRP: C-reactive protein (normal range: <5 mg/L), ALT: Alanine transaminase (normal range: <45 U/L); AST: Aspartate aminotransferase (normal range: <35 U/L); and ALP: Alkaline phosphatise levels (normal range:35-104 U/L) [10]

DISCUSSION

Statins are the most common drugs used for primary and secondary prevention of cardiovascular diseases [14]. The study subjects had a mean age of 54±8 years which collaborates with studies conducted by Sattar N et al., which also showed patients on age group between 55-76 years were at more risk of development of diabetes. They also showed a 9% increased risk of diabetes among non diabetic statin users of the above age group [15]. Male predominance among statin users were seen in this study group where 69.6% are males. Similar male predominance were seen in Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial [16] and Long term Intervention with Pravastatin in Ischaemic Diseases trial (LIPID trial) where, 61.8% and 80% of study population were males [17] Collaborative Atorvastatin Diabetes study (CARDS) trial shows 84% patients were hypertensive among statin users [18]. The present study shows 65.9% incidence of hypertension among statin users. Therapy with atorvastatin has been shown not only to affect lipid and lipoprotein levels but also, haemostatic and inflammatory molecules. The study showed significant lowering of all lipid parameters except HDL with usage of atorvastatin over 12 months, which can be attributed to HMG-CoA inhibitory activity of atorvastatin molecule. The present study showed that, atorvastatin induces a transient decrease in CRP levels within few months of therapy with further decrease up to one year (p<0.05). The observation that, CRP levels are extensively reduced through treatment with atorvastatin for one year (p<0.05) may be of particular interest in view of new data on early intervention with statins in acute coronary syndrome [19].

Drug induced liver injury includes hepatocellular injury, cholestatic liver injury and mixed liver injury which are defined on the basis of serum levels of ALT and AST and the ratio of ALT/ALP [20]. In the present study, authors found the statistical significant differences in mean ALT and AST values at the end of 3rd follow-up. But, as the values were within the respective normal range, they bring about limited clinical significance. However, though being one of the most commonly prescribed statin, atorvastatin induced liver injury is not common based on the post-marketing experience. Hence, frequent liver function evaluation may be beneficial for the patients on long term statin therapy. The present study emphasised the importance of periodical careful monitoring of Liver Function Test (LFT) to avoid severe atorvastatin -associated hepatotoxicity which may be beneficial for the patients on multiple co-morbidities and on long term statin therapy. Moreover, there are only a few studies from India, which evaluated the impact of statin on glycaemic status

of patients. Though, the present study from eastern part of India did not show any incidence of NODM among statin users, but the 5% incidence of prediabetic state among statin users definitely enlightens the suspicious impact of HMG-CoA reductase inhibitors on the glycaemic status of patients.

The study also enlightened the importance of periodical monitoring of haepatic enzymes to avoid severe atorvastatin-associated hepatotoxicity which may be beneficial for the patients on multiple co-morbidities and on long term statin therapy. It is also suggested to use statin therapy cautiously on the patients, who already had pre-existing diabetes or on the prediabetic population.

Limitation(s)

Theoretically, it cannot be completely ruled out that the findings in the study represent a regression to the mean since, it lacked a placebo control group, which is due to ethical considerations. Genetic predisposition, dietary factors, sedentary lifestyle, metabolic syndrome are the other factors which might also have an impact on metabolic status of the patients. Further studies with control groups needs to be done to further establish the relationship.

CONCLUSION(S)

The HMG-CoA reductase inhibitors are one of 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 cause impaired glycaemic control in patients, who were euglycaemic at the beginning of therapy. So, strict monitoring of blood glucose levels of patients on atorvastatin therapy for longer periods will be beneficial for preventing development of overt diabetes in near future.

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- Manual Googling: Mar 30, 2023
- iThenticate Software: Apr 19, 2023 (6%)

ETYMOLOGY: Author Origin

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