e-ISSN: 0975-1556, p-ISSN:2820-2643
Available online on www.ijpcr.com
International Journal of Pharmaceutical and Clinical Research 2024; 16(3); 796-802
Original Research Article

To Assess the Effects of Atorvastatin on C-Reactive Protein, Glycaemic Status, and Liver Enzymes in Non-Diabetic Patients

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Received: 15-01-2024 / Revised: 20-02-2024 / Accepted: 10-03-2024
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Conflict of interest: Nil

Abstract:

Background: To assess the effects of Atorvastatin on C - reactive protein, Glycaemic Status, and Liver Enzymes in non-diabetic patients.

Materials and Methods: The research involved 100 patients. Patients aged 28-72 years, who have not taken any drugs before, and are prescribed oral atorvastatin for dyslipidemia or for secondary prevention of cardiovascular or cerebrovascular illnesses were included in the research. All participants were receiving atorvastatin treatment and were monitored for one year, with a review of the mentioned parameters at the 1st, 6th, and 12th month marks. The study concluded after three follow-up visits. The main endpoint was the progression from normal blood sugar levels to prediabetes or diabetes, together with substantial alterations in CRP and hepatic enzyme levels.

Results: The baseline mean values of FBS, PPBS, and CRP were compared with the values from the 1st follow-up visit (after one month), and the differences were determined to be statistically insignificant. After comparing the initial mean hepatic enzyme levels with those obtained four weeks later, the changes in ALT, AST, and ALP values were determined to be statistically insignificant. Significant changes (p-value=0.03) were seen in baseline serum triglyceride, blood cholesterol, LDL, and VLDL levels after four weeks. The average PPBS value was 111.33±5.38 mg/dL at the beginning and 113.41±3.99 mg/dL during the 6-month follow-up appointment. The difference in PPBS value was statistically significant at a significance level of $p<0.05$. There were no statistically significant changes in the mean FBS and CRP values at six months compared to the baseline. The FBS, PPBS, and CRP values were acquired after one year. The changes were determined to be statistically significant compared to the baseline values ($p<0.05$). ALT, AST, and ALP levels were collected after one year. They are then compared to their corresponding average baseline values. There was a statistically significant modest rise in mean ALT and AST readings ($p<0.05$), although the changes in ALP were not significant at the conclusion of the trial.

Conclusion: HMG-CoA reductase inhibitors are widely used medications that have the ability to reduce negative cardiovascular outcomes. However, these cholesterol-lowering medications have been shown to negatively impact blood sugar management in individuals who had normal blood sugar levels at the start of treatment.

Keywords: HMG-CoA, ALT, AST, FBS, PPBS, CRP and ALP.

Introduction

Dyslipidemia is a significant known risk factor for cardiovascular disease. Statins, commonly known as HMG-CoA reductase inhibitors, effectively reduce LDL cholesterol levels in people with hypercholesterolemia [1, 2]. Several prospective studies have shown the cardio-protective and antioxidant properties of statins, which have been routinely used for this purpose for many years [3, 4]. LDL-cholesterol levels are the primary focus for lipid management and statin medication in order to reach the aim of lowering LDL cholesterol. Statins have been shown to be useful in preventing cardiovascular events by reducing LDL-cholesterol levels in people with or without diabetes, both in primary and secondary prevention [5]. CRP is a dependable and consistent laboratory marker of systemic inflammation and unfavourable cardiovascular outcomes in a healthy population, making it an independent predictor. Studies vary in their findings on the reduction of CRP by

atorvastatin, its correlation with regular and intensive statin treatment, and its connection with other risk factors such as blood glucose levels, LDL, triglycerides, and blood cholesterol levels [6, 7]. A decreased CRP level is linked to a reduced likelihood of recurring episodes in individuals with acute coronary syndrome. Due to the intricate nature of atherosclerosis, which involves several factors, it is challenging to understand how statins lower CRP levels and produce their anti-inflammatory impact. Statins, namely atorvastatin, have been shown to significantly reduce mortality from cardiovascular disease. However, many meta-analyses have indicated a connection between statins and negative effects on glycemic control. The FDA has added a safety label to statins due to their tendency to raise FBS levels. A research conducted by Koh KK et al. shown the occurrence of new-onset diabetes mellitus in individuals using atorvastatin [8, 9]. Various studies have shown the dose-dependent diabetogenic potential of statins. A research conducted by Preiss D et al. found a 12% greater incidence of New-Onset Diabetes Mellitus (NODM) associated with higher potency statins as compared to lower potency statins[10].Atorvastatin may impact the liver enzymes of individuals, especially when they are concurrently using drugs that can influence their metabolism. As per Motola D et al., 10.9% of 1245 adverse medication reaction reports from January 1950 to May 2005 had increased liver enzymes related to statin use [11]. Statins have a greater likelihood of increasing liver enzyme levels compared to antiplatelet and nonsteroidal anti-inflammatory medicines. This raises concerns about monitoring the effects of atorvastatin on liver enzymes during long-term treatment. Asymptomatic hepatic enzyme increases are the most prevalent hepatic adverse effects of atorvastatin usage. However, serious side effects such hepatocellular damage, cholestatic injury, autoimmune reactions, and fulminant liver failure may also occur [12, 13]. Hepatic dysfunction is a significant worry for adverse effects caused by statins, requiring close monitoring of liver enzymes after statin therapy, in addition to its impact on blood sugar levels. Insufficient clinical evidence on the impact of atorvastatin on biochemical parameters including FBS, PPBS, CRP, and hepatic enzymes in non-diabetic Indian individuals. An observational longitudinal research was undertaken on euglycemic patients in Eastern India who were taking statins to examine the impact on CRP levels, glycemic status, and hepatic enzymes. The study's hypothesis was that atorvastatin did not lead to substantial alterations in FBS, PPBS, CRP, and hepatic enzyme levels in non-diabetic individuals from the Indian population.

Aims and Objectives: To assess the effects of Atorvastatin on C-reactive protein, Glycaemic Status, and Liver Enzymes in non-diabetic patients

Materials and Methods

The present prospective cross-sectional study consisted of 100 patients of both genders. After receiving approval from the institutional ethical committee, the present study has been carried out in the Departments of Pharmacology at Nalanda Medical College & Hospital, Patna, Bihar, India, in collaboration with the Departments of General Medicine at Nalanda Medical College & Hospital, Patna, Bihar, India. The study was carried out over a one-year period, from January 2023 to December 2023. All gave their written consent to participate in the study. Data such as name, age, etc. was recorded.

Inclusion Criteria: Patients aged 28-72 years, who have not taken any drugs before, and are prescribed oral atorvastatin for dyslipidemia or for secondary prevention of cardiovascular or cerebrovascular illnesses were included in the research.

Exclusion Criteria: Patients with diabetes mellitus, abnormal fasting glucose levels, impaired glucose tolerance, or those taking medications such as corticosteroids, thiazide diuretics, or antipsychotics that affect blood sugar levels, as well as patients with known kidney, liver, or infectious diseases like tuberculosis, and terminally ill patients (e.g., cancer) were not included in the study. Pregnant and nursing moms were not included.

Methodology

Plasma glucose levels were assessed through FBS (normal range: 70-110 mg/dL) and PPBS (normal range: 80-140 mg/dL). Additionally, serum triglyceride level (normal range: 44-165 mg/dL), blood cholesterol level (normal range: desirable <200 mg/dL), LDL (normal range: <100 mg/dL), VLDL (normal range: 12-34 mg/dL), HDL (normal range: 40-59 mg/dL), CRP (normal range: <5 mg/L), ALT (normal range: <45 U/L), AST (normal range: <35 U/L), and ASP levels (normal range: 35-104 U/L) were measured as baseline parameters[14].

Anthropometric data, including height, weight, and Body Mass Index (BMI), were taken from all patients at the beginning of the study. BMI was classified based on the World Health Organization (WHO) Asia Pacific BMI guidelines [15]. All participants were receiving atorvastatin treatment and were monitored for one year, with a review of the mentioned parameters at the 1st, 6th, and 12th month marks. The study concluded after three follow-up visits. The main endpoint was the progression from normal blood sugar levels to prediabetes or diabetes, together with substantial alterations in CRP and hepatic enzyme levels.

Statistical analysis: The data were analyzed using SPSS version 22.0, Microsoft Excel, and Graph Pad Prism software. Analysis was conducted using a paired Student's t-test. Results were presented in terms of mean, frequencies, and percentages.

Results

The research aimed to determine the effects of atorvastatin on the CRP levels, glycemic status, and hepatic enzymes of the persons taking it.

Table 1: Gender and age of the Participants

Parameter	Number (n=100)	Percentage	P value
Genders			
Male	70	70	0.12
Female	30	30	
Age (years)			
Below 35	3	3	0.16
35-45	22	22	
46-55	48	48	
56-65	16	16	
Above 65	11	11	
Mean Age	55.34±5.38		0.14
Mean Weight	59.89±4.78		0.11

The majority of participants in the research were male (70%) with an average age of 55.34±5.38 years and an average weight of 59.89±4.78 kg [Table 1].

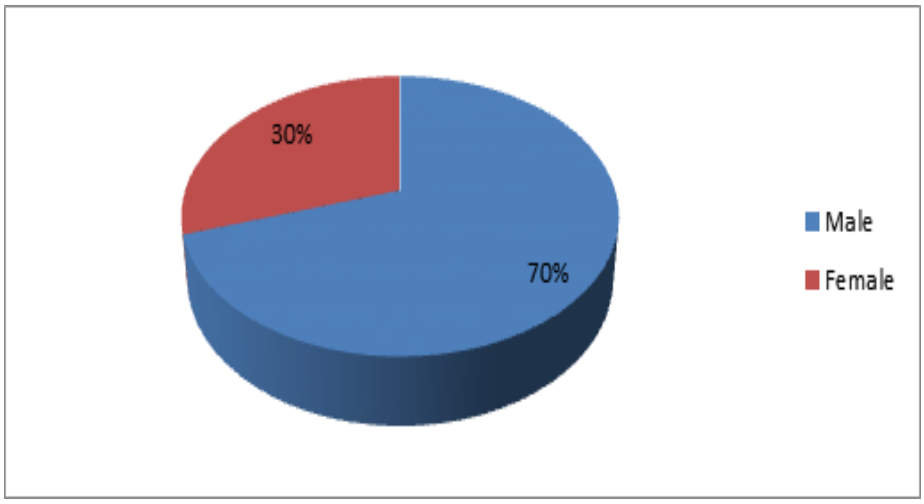

Figure 1: Gender wise distribution of patients

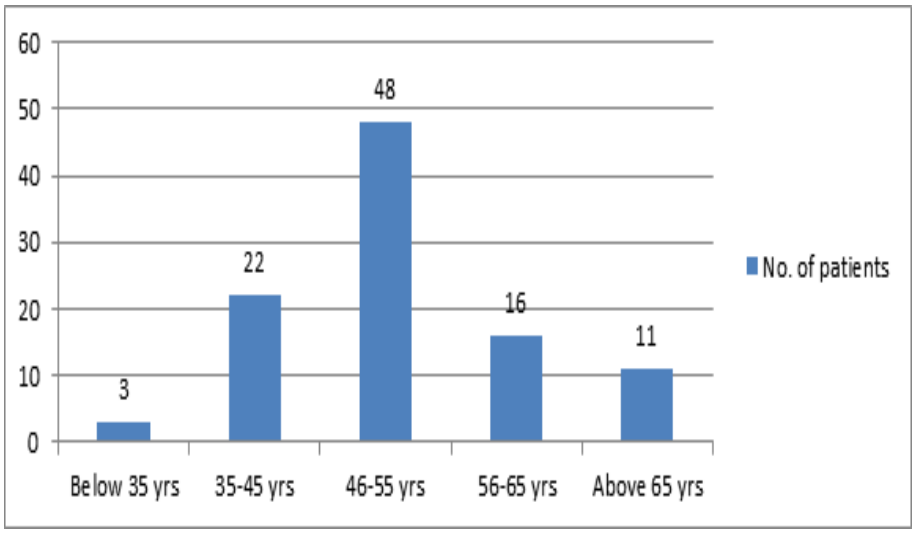

Figure 2: Age wise distribution of patients in years

Table 2: BMI of the participants

BMI	Number (n=100)	Percentage	P value
Underweight	2	2	0.15
Overweight	54	54	
Normal weight	24	24	
Obese	20	20	

Most participants (54%) were classified as overweight based on their BMI, with normal weight individuals making up 24% and obese individuals 20% [Table 2].

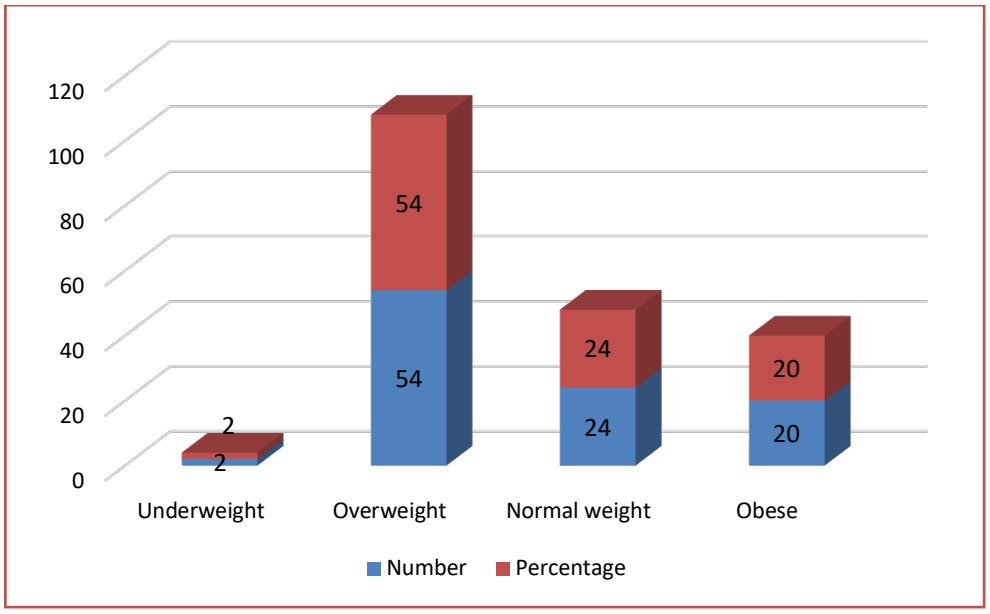

Figure 3: BMI of the participants

Table 3: Atorvastatin dose for the participants

Atorvastatin dose	Number (n=100)	Percentage
Atorvastatin 40 mg	61	61
Atorvastatin 20 mg	27	27
Atorvastatin 10 mg	12	12

61% of the patients were on atorvastatin 40 mg, 27% were on atorvastatin 20 mg, and 12% were taking atorvastatin 10 mg according to Table 3.

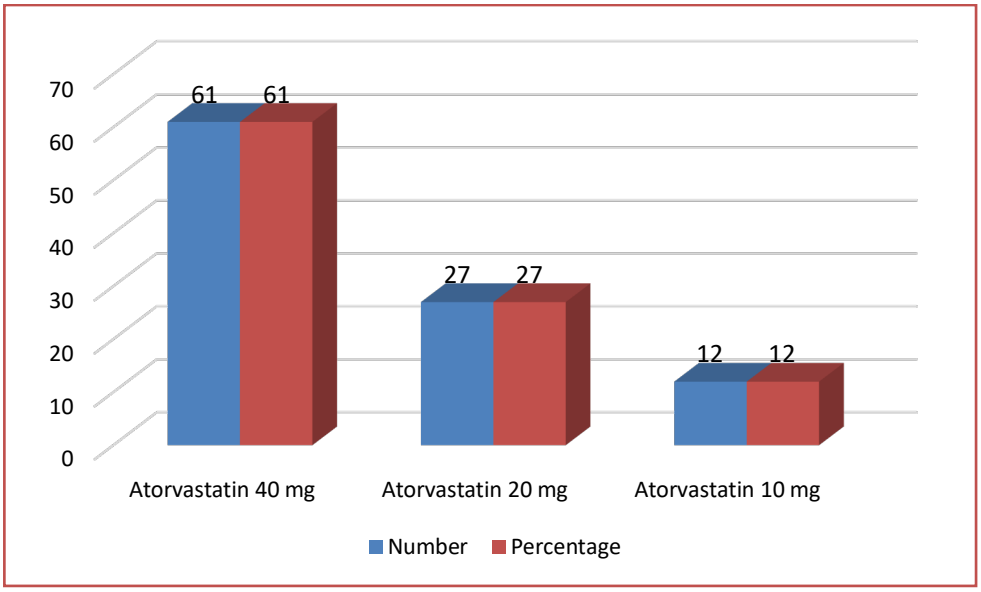

Figure 4: Atorvastatin dose for the participants

Table 4: Comparison of CRP, glycaemic status, liver enzymes and lipid profile values

Parameters	Baseline values	After one month	p-value	After 6 months	p-value	After one year	p-value
FBS (mg/dL)	85.50±6.45	85.07±5.23	0.13	84.50±4.57	0.08	85.42±5.33	0.03
PPBS (mg/dL)	111.33±5.38	110.68±5.64	0.11	113.41±3.99	0.03	114.47±4.27	<0.05
CRP	1.61±0.44	1.61±0.35	0.15	1.60±0.34	0.15	1.53±0.36	<0.05
ALT (U/L)	22.44±3.87	22.82±3.54	0.07	23.02±3.87	0.15	23.74±3.22	0.003
AST (U/L)	22.00±3.38	22.36±2.98	0.13	22.68±2.73	0.06	26.14±3.57	<0.05
ALP (U/L)	93.03±4.55	93.13±4.75	0.21	94.37±4.11	0.11	94.56±4.94	0.06
Serum triglyceride (mg/dL)	209.53±5.78	202.28±4.66	<0.05	187.66±5.69	<0.05	176.13±4.24	<0.05
Total blood cholesterol (mg/dL)	193.15±5.32	189.50±5.22	<0.05	179.52±4.87	<0.05	167.58±4.37	<0.05
LDL (mg/dL)	115.00±4.54	112.86±4.62	<0.05	105.73±3.48	<0.05	95.34±4.82	<0.05
HDL (mg/dL)	36.20±3.22	36.14±3.62	0.13	36.48±2.89	<0.05	34.53±3.62	<0.05
VLDL (mg/dL)	41.16±3.02	39.70± 3.74	<0.05	36.80±3.05	<0.05	36.91±3.12	<0.05

At the start of the trial, the average CRP level was 1.61±0.44 mg/dL, the average FBS level was 85.50±6.45 mg/dL, and the average PPBS level was 111.33±5.38 mg/dL. The serum lipid parameters were examined, revealing mean total blood cholesterol of 193.15±5.32 mg/dL and LDL of 115.00±4.54 mg/dL. The mean serum triglyceride at baseline was 209.53±5.78 mg/dL. After starting atorvastatin medication, the average ALT/SGPT, AST/SGOT, and ALP levels were 22.44±3.87 IU/L, 22.00±3.38 IU/L, and 93.03±4.55 IU/L, respectively. The patient's biochemical parameters were measured one month later. The baseline mean values of FBS, PPBS, and CRP were compared with the values from the 1st follow-up visit (after one month), and the differences were determined to be statistically insignificant. After comparing the initial mean hepatic enzyme levels with those obtained four weeks later, the changes in ALT, AST, and ALP values were determined to be statistically insignificant. Significant changes (p-value=0.03) were seen in baseline serum triglyceride, blood cholesterol, LDL, and VLDL levels after four weeks. However, the mean HDL value did not show statistical significance [Table 4].

The average PPBS value was 111.33±5.38 mg/dL at the beginning and 113.41±3.99 mg/dL during the 6-month follow-up appointment. The difference in PPBS value was statistically significant at a significance level of $p<0.05$. There were no statistically significant changes in the mean FBS and CRP values at six months compared to the baseline. There were no statistically significant changes in the mean ALT, AST, and ALP levels at 6 months compared to the baseline. The lipid profile values, including serum triglyceride, blood cholesterol, LDL, HDL, and VLDL, obtained after 24 weeks were compared to the initial levels. A statistically significant reduction was seen in serum triglyceride, blood cholesterol, LDL, and VLDL values, together with a modest rise in HDL value ($p<0.05$) [Table 4]. The FBS, PPBS, and CRP values were acquired after one year. The changes were determined to be statistically significant compared to the baseline values ($p<0.05$). ALT, AST, and ALP levels were collected after one year. They are then compared to their corresponding average baseline values. There was a statistically significant modest rise in mean ALT and AST readings ($p<0.05$), although the changes in ALP were not significant at the conclusion of the trial. The lipid profile values were collected after one year and compared with the initial levels. The mean serum triglyceride, blood cholesterol, LDL, and VLDL levels decreased, whereas the mean HDL level slightly increased. All the changes were determined to be statistically significant at a significance level of $p<0.05$ as shown in Table 4.

Discussion

Statins are the predominant medications used for both the primary and secondary prevention of cardiovascular diseases [16]. The study participants had an average age of 55.34±5.38 years, consistent with research by Sattar N et al. [17], indicating that those aged between 55 and 76 years were more susceptible to developing diabetes. Non-diabetic statin users in that age range had a 9% higher chance of developing diabetes. There was a male majority among statin users in this research sample, with 70% being men. Male participants outnumbered female participants in the JUPITER and LI-

PID trials, with 61.8% and 80% of the study population being men, respectively. The Collaborative Atorvastatin Diabetes Study (CARDS) experiment revealed that 84% of participants who used statins were hypertensive [18–20].

The current research demonstrates a 66% prevalence of hypertension in those who take statins. Atorvastatin therapy has been shown to impact not just cholesterol and lipoprotein levels but also hemostatic and inflammatory markers. The research demonstrated a significant decrease in all lipid markers, except HDL, after 12 months of using atorvastatin, which is likely due to the HMG-CoA inhibitory action of the atorvastatin molecule. The research shown that atorvastatin causes a temporary reduction in CRP levels after a few months of treatment, with a continued decline up to one year ($p<0.05$). The significant decrease in CRP levels after one year of atorvastatin medication ($p<0.05$) is noteworthy, especially in light of recent findings on statin early intervention in acute coronary syndrome [21]. Drug-induced liver damage is categorized as hepatocellular injury, cholestatic liver injury, and mixed liver injury based on blood levels of ALT and AST, as well as the ALT/ALP ratio [22]. The authors of the research discovered statistically significant variations in the mean ALT and AST readings after one year of follow-up. However, as the readings were within the normal range, they had minimal clinical importance. Although atorvastatin is often administered, cases of liver impairment generated by this statin are rare according to post-marketing data. Therefore, regular monitoring of liver function may be advantageous for individuals on prolonged statin treatment. This research highlighted the need of regularly monitoring Liver Function Test (LFT) to prevent serious atorvastatin-related liver damage, especially for individuals with numerous health conditions and on long-term statin treatment. Furthermore, there is a limited number of researches from India that have assessed the effect of statins on the glycemic status of patients. The research conducted in the Eastern part of India did not find any cases of new-onset diabetes mellitus (NODM) among individuals using statins. However, it did reveal a 5% prevalence of a prediabetic condition among statin users, indicating a potential influence of HMG-CoA reductase inhibitors on the blood sugar levels of patients. The research emphasized the need of regularly monitoring hepatic enzymes to prevent serious atorvastatin-related liver damage, particularly for individuals with various health conditions and on long-term statin treatment. It is recommended to utilize statin medication with caution in individuals who already have pre-existing diabetes or in the prediabetic population. The study's results may be influenced by regression to the mean owing to the absence of a placebo control group, a limitation imposed by ethical reasons. Genetic predisposition, dietary variables, sedentary lifestyle, and metabolic syndrome are additional factors that might influence the metabolic state of individuals. Additional research involving control groups is necessary to solidify the association.

Limitations of study: The sample size was small and duration of the study was small.

Conclusion

HMG-CoA reductase inhibitors are widely used medications that have the ability to reduce negative cardiovascular outcomes. However, these cholesterol-lowering medications have been shown to negatively impact blood sugar management in individuals who had normal blood sugar levels at the start of treatment.

Acknowledgment: The authors would like to acknowledge the entire faculty and staff of the Department of Pharmacology, Nalanda Medical College and Hospital, Patna, Bihar, India, for their valuable support and time- to- time suggestion in undertaking the present study. Special thanks to Dr. Asha Singh, Professor and Head of Department, Department of Pharmacology, Nalanda Medical College and Hospital, Patna, Bihar, India, for their valuable suggestions during the study.

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