Research Article

Effects of Atorvastatin and Rosuvastatin on glycemic parameters of dyslipidemic patients: A prospective study

Shamshi Azmi[1], Jameel Ahmad[1]*, Farida Ahmad[1], Anjum M. Chughtai[2]

[1]*Department of Pharmacology, JNMC AMU Aligarh (U.P.) India*
[2]*Department of Pharmacology and Medicine, JNMC AMU Aligarh (U.P.) India*

Received: 25 September 2019 Revised: 10 December 2019 Accepted: 25 December 2019

Abstract

Objective: In the recent past, there were several reports of increased risk of type 2 Diabetes Mellitus with the use of statins. Therefore randomized, prospective, parallel group, open labeled, 24 weeks study of Atorvastatin and Rosuvastatin was done on newly diagnosed cases of dyslipidemia. **Methods:** This pre-specified analysis was conducted after the last patient completed 24 weeks. Eligible patients were randomized into two groups Group-1 (Atorvastatin) and Group-2 (Rosuvastatin). The two groups were further divided into subgroups based on different doses. At week 24, statistically significant increase in fasting plasma glucose, 2 hour post prandial plasma glucose and haemoglobin A1c was observed with Atorvastatin 10 and 20 mg, and Rosuvastatin 5 and 10 mg. **Results:** Statins were well tolerated with no evidence of any severe adverse event. Atorvastatin and Rosuvastatin showed an increase in all glycemic parameters (FPG, 2hours PPG, HbA1c); yet none of the subjects entered into overt diabetic range during our study period. **Conclusion:** Atorvastatin and Rosuvastatin showed an increase in all glycemic parameters (FPG, 2 hours PPG, HbA1c).

***Keywords*:** Atorvastatin, rosuvastatin, glycemic parameters, HbA1C, dyslipidemia

Introduction

Abnormalities in the plasma lipoproteins and derangements in lipid metabolism rank among the most firmly established and best understood risk factors for atherosclerosis (Libby, 2015). Atherosclerosis may lead to coronary heart disease (CHD) (Yusuf et al., 2004). Obesity and nsulin resistance frequently accompany dyslipidemia which may lead to metabolic syndrome (Khan et al., 2018). Indians have a tendency for greater elevation in non-HDL cholesterol (NHDL-C) by virtue of high triglycerides and low HDL-C, which is common to this population (Enas et al., 2015). Lipid lowering therapies have been shown to lower the risk of CHD events by 30-40% (Brunton et al., 2011). Drugs that are generally used to treat dyslipidemia include statins, fibric acid derivatives, nicotinic acid and ezetimibe etc. Statins have proven mortality and morbidity benefit in both primary and secondary prevention of coronary heart disease. This is the reason that statins are frequently used therapeutic agents for lowering cholesterol (Stone et al., 2014).

Address for Corresponding Author:
Jameel Ahmad
Department of pharmacology, JNMC AMU Aligarh (U.P.) India
Email: ahmad.drjameel@gmail.com

Diabetes mellitus is another established risk factor for cerebrovascular and peripheral arterial diseases (ADA guidelines 2017). Studies have shown that India has a potential epidemic of diabetes and by the year 2040, it will have maximum increase in the incidence of diabetes mellitus (Ogurtsova et al., 2017). Diabetes may also result from certain drugs eg; glucocorticoids, β-adrenergic agonists and thiazides etc. These drugs may precipitate diabetes in individuals with insulin resistance (Powers 2015). Dyslipidemia and diabetes mellitus are two independent known risk factors for atherosclerotic cardiovascular, peripheral arterial and cerebrovascular diseases (Libby 2015; ADA guidelines 2017).

In the recent past, there are several reports of increased risk of type 2 Diabetes mellitus with the use of statins. On February 28, 2012 the Food and Drug Administration (FDA) added new safety label changes for the statins regarding their potential to increaseHbA1c and fasting plasma glucose. TNT trial (Ho et al., 2009) and WHI study (Culver et al., 2012) suggested an increased risk of New Onset Diabetes Mellitus (NODM) with different statins. Whereas, WOSCOPS (West of Scotland Coronary Prevention Study) trial (Freeman et al., 2001) and J-PREDICT trial (Odawara et al., 2013) have shown a risk reduction of diabetes with pravastatin and

DOI: https://doi.org/10.31024/ajpp.2020.6.1.3

pitavastatin, respectively. Till date, number of studies done on glycemic effect of statins in Indian population is limited. Most of these studies have been conducted on diabetic subjects or on patients with impaired glucose profile.

Therefore, selection of a non-diabetic cohort is crucial for a clear understanding of statin's effect on blood glucose levels. Hence, this study was designed to determine the effects statins on normoglycemic patients who are newly diagnosed with dyslipidemia.

Materials and methods

This was a randomized, prospective, parallel group and open labeled study, conducted in the Department of Pharmacology and Department of Medicine on patients newly diagnosed with dyslipidemia attending out-patient department of J.N. Medical College & Hospital, A.M.U., Aligarh, India from May 2017 to September 2018. This pre-specified analysis was conducted after the last patient completed 24 weeks. Eligible patients were randomized into two groups, Group-1 (Atorvastatin) and Group-2 (Rosuvastatin). They were further divided into subgroups based on different doses (Figure 1). Non-diabetic dyslipidemic patients of age > 20 years with definite indication for starting statins were included in the study. Patients with an existing diagnosis of diabetes, statin exposure before enrollment and those on medications known to affect blood glucose parameters were excluded from the study. Diagnosis of dyslipidemia was made according to National Cholesterol Education Program-Adult Treatment Panel IV guidelines (Odawara et al., 2013). Patients were screened for Diabetes mellitus according to ADA 2017 guidelines. The patients were followed up at 12 and 24 weeks to assess the effects of Atorvastatin and Rosuvastatin on blood FPG, 2 hours PPG, HbA1c, lipid profile, RFT, LFT and adverse effects if any.

Written and informed consent was obtained from all patients before enrolling them in the study.

Ethical clearance for the study protocol was obtained from the Institutional Ethics Committee (IEC) of J.N. Medical College and Hospital, AMU, Aligarh on 18.05.2017 with registration number **626/FM.** The study was also registered with Clinical Trial Registry of India (CTRI Ref No: CTRI/2018/05/013991).

Patients were advised to remain on a stable diet as per NCEP ATP-IV guidelines, 2015. All adverse events experienced by the patients were recorded at each visit. Adverse drug reactions were assessed using Naranjo Adverse Drug Reaction Probability Scale (Naranjo et al., 1981) and severity was assessed using Modified Hartwig and Siegel scale (Hartwig et al., 1992).

Statistical analysis

Statistical analysis was done using SPSS-23 software and charts were prepared using Microsoft Excel 2013. For descriptive statistics; frequency, percentage and graphs were used to present the study results.Repeated Measure Analysis of variance (RM-ANOVA) followed by Bonferroni post-hoc test was used to analyze the change in parameters from baseline values at different time points during follow up. All the values were expressed as mean ±S.E. $P<0.05$ was considered to be statistically significant.

Results

A total of 100 patients were enrolled, out of which 18 patients (7 patients of Group 1 and 11 patients of Group 2) failed to complete the study (Figure1). Finally 82 patients were left in the two groups, group 1 (44 patients) and group 2 (38 patients).

The baseline parameters in all the four groups were similar in respect to age distribution, mean age and gender.

Safety assessment

A total of 7 patients in Atorvastatin group experienced adverse events. Number of patients experiencing adverse events in Group 1A and 1B were three and four. A total of fivepatients in Rosuvastatin group experienced adverse events. Number of patients experiencing adverse events in

Table 1. Effect of Atorvastatin (10 mg, 20 mg) and Rosuvastatin (5 mg, 10 mg) on FPG

Groups	Baseline (mg/dL) Mean±SE	12 weeks (mg/dL) Mean±SE	24 weeks (mg/dL) Mean±SE	P value (0-12 weeks)	P value (0-24 weeks)
1A	94.53 ±2.45	98.00 ±2.37	99.92 ±2.33	<0.05*	<0.05*
1B	94.50 ±3.60	96.47 ±3.75	98.11 ±3.72	<0.05*	<0.05*
2A	90.66 ±3.31	93.60 ±3.41	95.50 ±3.36	<0.05*	<0.05*
2B	92.00 ±3.56	95.54 ±3.99	97.07 ±4.02	<0.05*	<0.05*

The increase in mean values of FPG, when compared to baseline values was found to be significant ($p<0.05$) at both the time points (12 and 24 weeks) in groups 1A, 1B, 2A and 2B (Intragroup comparison).

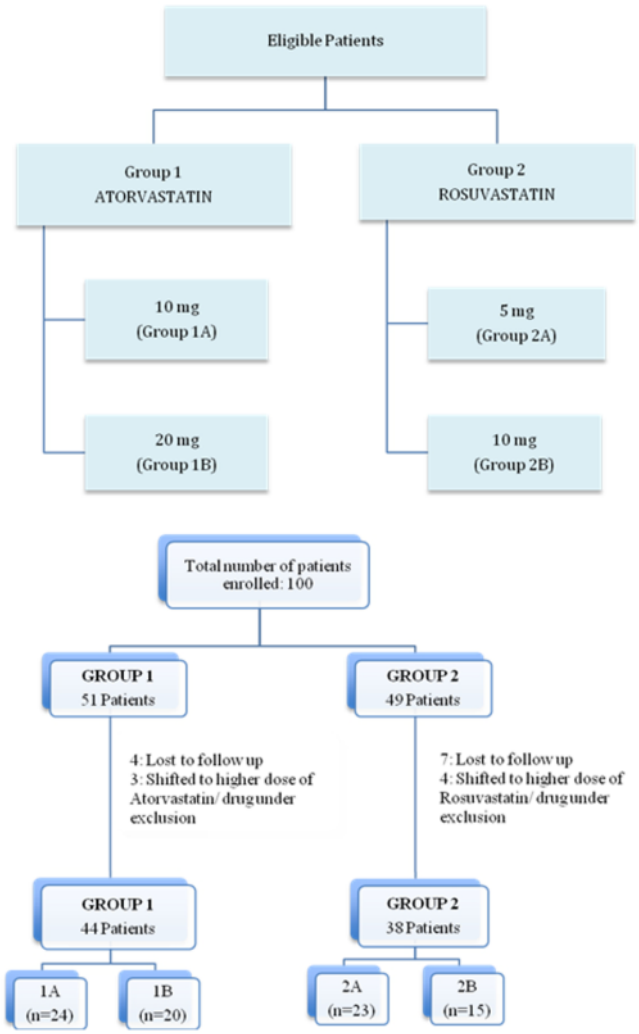

Figure 1. Drug distribution

Group 2A and 2B were two and three. The most commonly observed adverse event was mild gastrointestinal upset, followed by nausea. Other adverse events observed were dyspepsia, fatigue and body pain. No adverse event required discontinuation of therapy.

On Naranjo's ADR Probability Scale, events were possible in three and four cases of Group 1A and 1B respectively. Number of cases in possible category in Group 2A, and 2B were two and one. The events were probable in one case of Group 1A and 1B each.

Discussion

Recent epidemiological evidence suggests a rising trend of Diabetes mellitus epidemic across both the affluent as well as poor classes in India (Tripathy et al., 2017). Studies in India have shown that dyslipidemia is prevalent in 25-30% of urban and 15-20% of rural population. Statins are generally used to treat dyslipidemia. Statins have a proven mortality and morbidity benefit in cardiovascular diseases[6]. The most common adverse effect with the use of statins is myalgia, with documented rates from 1-10% and associated with a rise in creatine kinase (Ramkumar et al., 2016). Rhabdomyolysis is another rarely occurring (<1%) adverse effect of statin (Pedro-Botet et al., 2015).

Parida et al in (2017) studied that Atorvastatin at the dose of 10 and 20 mg increases mean FPG at the end of 24 weeks in normoglycemic patients ($p<0.05$). These findings are consistent with the results of our study in which Atorvastatin at the dose of 10 mg and 20 mg showed statistically significant increase in FPG ($p<0.05$) at 12 and 24 weeks. Kostapanos et al. (2009) reported a trend towards an increase in FPG by 2.9% in Rosuvastatin 10 mg group over a period of 12.4 weeks ($p=0.09$). Similarly, we observed that Rosuvastatin at the dose of 5 mg and 10 mg showed statistically significant ($p<0.05$) increase in mean FPG at 12 and 24 weeks.

The increase in mean values of 2 hours PPG, when compared to baseline values was found to be insignificant ($p>0.05$) in both Atorvastatin and Rosuvastatin groups at 12 weeks. However, at 24 weeks, Atorvastatin at the doses of 10 mg and 20 mg; and Rosuvastatin at thedose of 10 mg

Table 2. Effect of Atorvastatin (10 mg, 20 mg) and Rosuvastatin (5 mg, 10 mg) on 2H PPG levels

Groups	Baseline (mg/dL) Mean±SE	12 weeks (mg/dL) Mean±SE	24 weeks (mg/dL) Mean±SE	P value	
				(0-12 weeks)	(0-24 weeks)
1A	126.70 ±4.77	129.85 ±4.31	131.27 ±4.23	>0.05#	<0.05*
1B	118.93 ±3.80	119.29 ±3.75	122.84 ±3.69	>0.05#	<0.05*
2A	113.79 ±4.97	114.07 ±5.04	114.76±5.00	>0.05#	>0.05#
2B	119.05 ±4.49	120.51 ±4.47	126.59 ±4.25	>0.05#	<0.05*

The increase in mean values of 2 hours PPG, when compared to baseline values was found to be insignificant ($p>0.05$) in all groups at 12 weeks. However, the increase in 2 hours PPG in Groups 1A, 1B and 2B when compared with their baseline values was found to be statistically significant ($p<0.05$) at 24 weeks.

Table 3. Effect of Atorvastatin (10 mg, 20 mg) and Rosuvastatin (5 mg, 10 mg) on HbA1c

Groups	Baseline (%) Mean±SE	12 weeks (%) Mean±SE	24 weeks (%) Mean±SE	P value	
				(0-12 weeks)	(0-24 weeks)
1A	5.38 ±0.08	5.41 ±0.07	5.50 ±0.07	>0.05#	<0.05*
1B	5.23 ±0.05	5.29 ±0.05	5.41 ±0.04	>0.05#	<0.05*
2A	5.38 ±0.07	5.40 ±0.06	5.58 ±0.07	>0.05#	<0.05*
2B	5.13 ±0.06	5.14 ±0.04	5.36 ±0.06	>0.05#	<0.05*

The increase in mean values of HbA1c, when compared to baseline, was insignificant (p>0.05) at 12 weeks in all the groups (p>0.05). However, the increase in HbA1cwhen compared with baseline was found to be statistically significant (p<0.05) at 24 weeks in Groups 1A, 1B, 2A and 2B.

showed statistically significant (p<0.05) increase in 2 hours PPG when compared with their baseline values. Rosuvastatin at the dose of 5 mg showed statistically insignificant (p>0.05) increase in 2 hours PPG at both time points, i.e. 12 and 24 weeks. Similar results were reported in studies done by Endo et al; 2004, who found no change in HbA1c levels by Atorvastatin (10 mg/day) over a period of 12 weeks and 16 weeks, respectively.

At 24 weeks, Atorvastatin and Rosuvastatin at both the doses showed statistically significant (p<0.05) increase in HbA1c levels when compared with their baseline values.Atorvastatin at the dose of 10 mg and 20 mg led to an increase of 0.12% and 0.18% in mean HbA1c levels, respectively. The increase in mean HbA1c by Rosuvastatin 5 mg and 10 mg was 0.20% and 0.23%, respectively. Parida et al. (2017) have also reported statistically significant (p<0.05) increase in HbA1c levels by Atorvastatin 10 and 20 mg doses at the end of 24 weeks in normoglycemic patients.

ADA recommends measurement of HbA1c or fasting plasma glucose levels in patients at elevated risk of diabetes mellitus. In such patients glucose profile should be assessed before initiation of statin therapy and thereafter for early screening of diabetes mellitus (Maki et al., 2014).

Conclusion

Atorvastatin and Rosuvastatin showed an increase in all glycemic parameters (FPG, 2 hours PPG, HbA1c); yet none of the subjects entered into overt diabetic range during our study period of 24 weeks. This study was limited by a small cohort of patients and single centre design. More such prospective studies are needed with a large cohort to elucidate the glycemic effects of different statins.

Conflicts of interest: Not declared.

References

American Diabetes Association. 2017Classification and diagnosis of diabetes. Diabetes care, 40(Supplement 1):S11-24.

Brunton LL, Chabner BA, Knollmann BC. Goodman & Gilman's, The Pharmacological Basis of Therapeutics: Drug Therapy for Hypercholesterolemia and Dyslipidemia .12th ed. New York: McGraw-Hill; 2011. p. 877.

Culver AL, Ockene IS, Balasubramanian R, Olendzki BC, Sepavich DM, Wactawski-Wende J, Manson JE, Qiao Y, Liu S, Merriam PA, Rahilly-Tierny C, Thomas F, Berger JS, Ockene JK, Curb JD, Ma Y. 2012. Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative. Archives of Internal Medicine, 172 (2):144-52.

Enas E, Dharmarajan T, Varkey B. 2015. Consensus statement on the management of dyslipidemia in Indian subjects: A different perspective. Indian Heart Journal, 67(2):95–102.

Endo K, Miyashita Y, Saiki A, Oyama T, Koide N, Ozaki H, Otsuka M, Ito Y, Shirai K. 2004. Atorvastatin and pravastatin elevated pre-heparin lipoprotein lipase mass of type 2 diabetes with hypercholesterolemia. Journal of Atherosclerosis and Thrombosis, 11:341-47.

Freeman DJ, Norrie J, Sattar N, Neely RD, Cobbe SM, Ford I, Isles C, Lorimer AR, Macfarlane PW, McKillop JH, Packard CJ, Shepherd J, Gaw A. 2001. Pravastatin and the development of diabetes mellitus: Evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. Circulation, 103(3):357-62.

Hartwig SC, Siegel J, Schneider PJ. 1992. Preventability and severity assessment in reporting adverse drug reactions. American Journal of Health-System Pharmacy, 49(9):2229-32.

Ho JE, Waters DD, Colhoun H, DeMicco DA, Breazna A, Shepherd J. 2009. Predictors of Incident Diabetes in the TNT Trial. Circulation, 120(18): S397.

Khan Y, Lalchandani A, Gupta AC, Khadanga S, Kumar S. 2018. Prevalence of metabolic syndrome crossing 40% in Northern India: Time to act fast before it runs out of proportions. Journal of Family Medicine and Primary Care, 7(1):118.

Kostapanos MS, Milionis HJ, Agouridis AD, Rizos CV, Elisaf MS. 2009. Rosuvastatin treatment is associated with an increase in insulin resistance in hyperlipidaemic patients

with impaired fasting glucose. International Journal of Clinical Practice, 63(9):1308-13.

Libby P. The Pathogenesis, Prevention, and Treatment of Atherosclerosis. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. Harrison's principles of internal medicine. 19th ed. New York: Mc Graw Hills; 2015. p .291e-4.

Maki KC, Ridker PM, Brown WV, Grundy SM, Sattar N. 2014. An assessment by the statin diabetes safety task force: 2014 update. Journal of Clinical Lipidology, 8(3):S17-29.

Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ. 1981. A method for estimating the probability of adverse drug reactions. Clinical Pharmacology & Therapeutics, 30(2):239-45.

National Cholesterol Education Program Adult Treatment Panel III. Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. Circulation. 2002; 106:3143-421.

Odawara M, Yamazaki T, Kishimoto J, Ito C, Noda M, Terauchi Y, Shiba T, Kitazato H, Maemura K, Tobe K, Iwamoto Y. 2013. Effect of pitavastatin on the incidence of diabetes in Japanese individuals with impaired glucose tolerance. Diabetologia, 56: S59-S59.

Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, Cavan D, Shaw JE, Makaroff LE. 2017. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Research and Clinical Practice, 128:40-50.

Parida S, Swain TR, Routray SN, Maiti R. 2017. Effect of atorvastatin on glycaemic parameters in normoglycaemic and prediabetic subjects: a prospective, panel study. Journal of Clinical and Diagnostic Research, 11(2):FC04.

Pedro-Botet J, Núñez-Cortés JM, Flores JA, Rius J. 2015. Muscle symptoms related with statin therapy in general practice. Atherosclerosis, 241(1):e197.

Powers AC. Diabetes Mellitus: Diagnosis, Classification, and Pathophysiology.In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. Harrison's principles of internal medicine. 19th ed. New York: Mc Graw Hill; 2015. p. 2404.

Ramkumar S, Raghunath A, Raghunath S. 2016. Statin therapy: review of safety and potential side effects. Acta Cardiologica Sinica, 32(6):631.

Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ. 2008. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. New England Journal of Medicine, 359(21):2195-207.

Stone NJ, Robinson JG, Lichtenstein AH, Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology, 63(25 Part B):2889-934.

Tripathy JP, Thakur JS, Jeet G, Chawla S, Jain S, Pal A, Prasad R, Saran R. 2017. Prevalence and risk factors of diabetes in a large community-based study in North India: results from a STEPS survey in Punjab, India. Diabetology & metabolic syndrome, 9(1):8.

Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L. 2004. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. The lancet, 364(9438):937-52.