COMPARISON OF LIPID LOWERING EFFECTS OF ROSUVASTATIN AND ATORVASTATIN IN TYPE 2 DIABETIC PATIENTS WITH PRIMARY HYPERLIPIDEMIA

Safina Shabbir, Zill-e-Humayun, Muhammad Adnan Manzar*, Muhammad Javad Yousaf*, Shabana Mushtaq*, Maria Yousaf*

Pakistan Naval Ship (PNS) Shifa Hospital, Karachi/National University of Medical Sciences (NUMS) Pakistan, *Pak Emirates Military Hospital/National University of Medical Sciences (NUMS) Rawalpindi Pakistan, **Army Medical College/National University of Medical Sciences (NUMS) Rawalpindi Pakistan

ABSTRACT

Objective: To evaluate & compare the mean change in fasting serum total cholesterol and LDL-C levels from baseline, after 12 weeks of oral treatment with oral Rosuvastatin and with Atorvastatin in type 2 diabetic patients with primary hyperlipidemia.

Study Design: Cross sectional comparative study.

Place and Duration of Study: The present study was conducted in the Medicine Department, Pakistan Naval Ship, Shifa Hospital, Karachi, from Mar to Sep 2016.

Methodology: The sample was collected by non- probability convenient sampling. The total of 114 DM type 2 patients were randomly divided into two equal groups. Group A was given Rosuvastatin whereas group B was given Atorvastatin orally daily for 12 weeks along with oral treatment for diabetes. After 12 weeks, Fasting Serum Total Cholesterol and Serum LDL-C were estimated, and noted as final levels.

Results: There was greater reduction in terms of mean change in serum total cholesterol levels and low-density lipoprotein – cholesterol (LDL-C) levels with Rosuvastatin as compared to Atorvastatin in type 2 diabetic patients with hyperlipidemia.

Conclusion: Rosuvastatin can significantly improve lipid profile as compared to Atorvastatin in type 2 diabetic patients with hyperlipidemia.

Keywords: Atorvastatin, Diabetes mellitus, Hyperlipidemia, Rosuvastatin.

INTRODUCTION

Diabetes mellitus is an intricate metabolic disorder characterized by the hyperglycemia due to impaired insulin secretion, defective insulin action or both[1]. The number of people suffering from diabetes mellitus has elevated rapidly in the past three decades, Asia being a major area of the rapidly evolving type 2 DM global epidemic[2]. According to International Diabetic Federation (IDF) 415 million people were suffering from type 2 DM[6] and the number is expected to rise to 642 million by the year 2040[3]. The prevalence of DM in Pakistan is 26.3% as documented by the freshly published National Diabetes Survey of Pakistan (NDSP)[4]. Approximately five million direct deaths occurred due to DM in 2015; implying that in every six seconds a patient dies because of the impediments of Type 2 DM.

Cardiovascular disease (CVD) is a chief source of mortality and disability in type-2 diabetics[5]. The CVD affects approximately 32.2% of all patients suffering from type 2 DM[6] with 68% mortality[7]. Among middle-age individuals with type 2 DM living in mediocre financial conditions, up to 27 individuals out of 1,000 die from CVD every year; one 3rd of them die from stroke, and one fourth expire from coronary artery disease[8].

DM aggravates core mechanisms responsible for atherosclerosis and heart failure[9]. Long standing hyperglycemia and insulin resistance play an vital role in the initiation and progression of macro and micro vascular impediments of DM. Number of mechanisms including; increased glucose flux to polyol pathway; increased formation

Correspondence: Dr Zill-e-Humayun, Classified Medical Specialist & Pulmonologist, PEMH, Rawalpindi Pakistan
Received: 01 Jan 2019; revised received: 01 Oct 2019; accepted: 10 Oct 2019

of advanced glycation end products (AGEs); stimulation of the receptor for advanced glycation end products (RAGE); oxidative stress; excited inflammation and immune responses and micro RNAs are held responsible for the diabetic vasculopathy. Which is exhibited as endothelial dysfunction, vascular inflammation, arterial remodeling, atherosclerosis and dyslipidemia via increased lipid peroxidation[10]. There is well established positive correlation between the incidence of CVD and levels of low-density lipoprotein cholesterol (LDL-C) concentration[11].

Decreasing atherosclerotic cardiovascular disease (ASCVD) prevalence in diabetes mellitus is a foremost clinical imperative that should be lined up to prevent premature death, improve quality of life, and reduce individual and economic burdens of concomitant morbidities, diminished work efficiency, and extraordinary cost of medical care provision[9]. Unfortunately, these mechanisms are not effectively restrained by therapeutic approaches aiming solely on ideal glycemic control with available drugs or treatment options at present. Multi dimensional CVD threats, with statins and other lipid-lowering drugs, antihypertensive therapies, life style modifications and anti-hyperglycemic treatment approaches, cardiovascular impediment rates are dropping, yet remain greater for patients with diabetes mellitus as compared to non-diabetics[12], hence proving the significance of more research in this direction.

Statins are widely used safer Lipid-lowering therapy (LLT) which escalates the clearance of atherogenic lipoproteins and hence reduces plasma cholesterol levels, primarily through decrease in LDL cholesterol[13]. The lowered LDL levels results in a significantly reduced risk of ASCVD with the comparative advantage associated to the total reduction in LDL cholesterol[14]. They are also known to significantly prevent cardiovascular complications of different disease. Statins have a significant role in preventing the long term complications in type 2 diabetic patients[15,16]. Different drugs from statins group are widely used for treating hyperlipidemia in high risk patients like diabetes, hypertension, stroke and myocardial infarction[16]. Atorvastatin and Rosuvastatin are commonly used statins for this purpose[17]. Multiple studies have compared their efficacy in wide variety of medical conditions[18-21]. As the genetic and ethnic diversity has great influence the effectiveness of treatment options among certain population, it is essential to carry out the comparison among various treatment options and their efficacy in our diabetic population, in order to evaluate/compare the benefits of these drugs. The objective of this study was to compare the mean change in fasting Serum Total Cholesterol and LDL-C levels from baseline, after 12 weeks of oral treatment with oral Rosuvastatin from Atorvastatin in type 2 diabetic patients with primary hyperlipidemia. This study will also be beneficial in suggesting new protocol for management of hyperlipidemia in diabetic population.

METHODOLOGY

This randomized control trial study was conducted in the Medicine Department, Pakistan Naval Ship (PNS) Shifa Hospital Karachi, from March 2016 to September 2016. After approval by the ethics committee, PNS Shifa Hospital, written informed consent was taken from the patient's prior to inclusion in the study. Subjects fulfilling the inclusion criteria, underwent complete systemic examination, along with confirmation of type 2 diabetes mellitus by fasting blood sugar levels. Fasting Serum Total Cholesterol and Serum LDL-C were advised, and noted as baseline. All examination and analysis of labs were done by same researcher to exclude observer bias. The sample size was calculated using World Health Organization sample size calculator by using 5% error, 95% confidence interval and anticipated population 8%[11]. Hence the sample size, n=114 (57 in each group). Sample was collected by non-probability convenient sampling.

The total 114 patients were randomly divided in two groups by lottery method. Group A was the Rosuvastatin group, prescribed with oral Rosuvastatin, 5mg at bed time, daily for 12 weeks along with oral treatment for diabetes. Group B

was Atorvastatin group, prescribed with oral Atorvastatin, 10 mg at bed time, daily for 12 weeks along with oral treatment for diabetes. After 12 weeks, Fasting Serum Total Cholesterol and Serum LDL-C were advised, and noted as final levels.

Statistical Analysis

Data was evaluated and analyzed using SPSS version 17.0. Mean and Standard deviation was reported for continuous variables (Age, Serum Blood sugar fasting, Fasting Total Serum Cholesterol, Fasting Serum LDL-C) while frequency and percentage for nominal/ordinal data like gender. Mean reductions in Serum Cholesterol and Serum LDL-C in two treatment groups over 12 weeks were calculated and compared using Independent sample t-test. A $p<0.05$ was considered as statistically significant.

RESULTS

Total 114 patients were included were randomly divided into two equal groups. Group A was given Rosuvastatin whereas group B was given Atorvastatin. Mean age (years) in the study was 49.61 ± 6.39, there were 79 (63.9) male and 41 (36.3) female patients. Mean serum total cholesterol fasting (mmol/L) was 4.85 ± 0.47 in the study whereas mean serum total LDL-C fasting (mmol/L) was 4.08 ± 0.49 in the study (fig-1). Mean change in serum total cholesterol fasting (mmol/L) in group A was 0.88 ± 0.51 and in group B it was 0.05 ± 0.08 which was statistically significant (*p*-value 0.000) whereas mean change in serum total LDL-C fasting (mmol/L) in both the groups was 1.42+0.92 and 0.94+0.54 which was again statistically significant (*p*-value 0.001) (table-I).

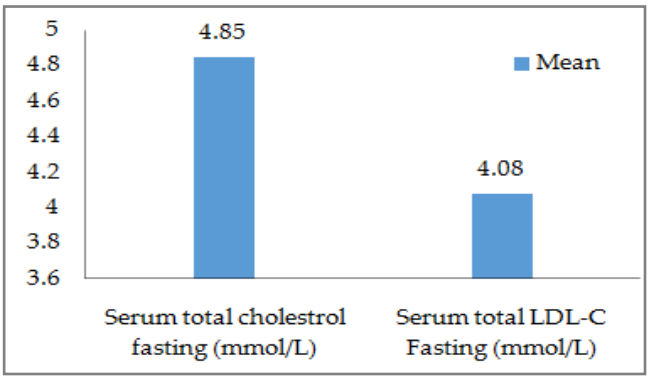

Figure-1: Serum total cholesterol fasting (mmol/L) & serum total LDL-C fasting (mmol/L) of both groups.

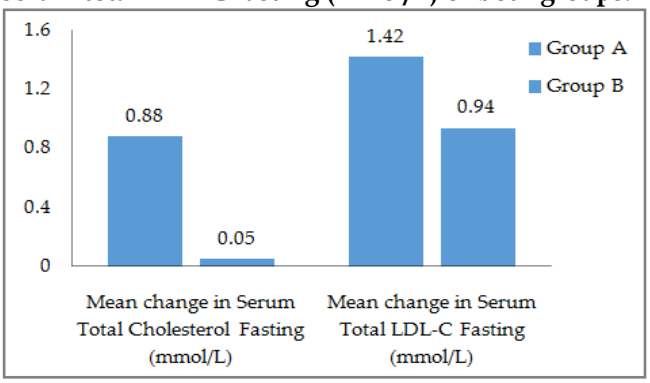

Figure-2: Bar graph exhibiting the comparison of serum TC and serum LDL-C after 12 weeks of treatment among the two groups.

DISCUSSION

Dyslipidemia is a well-recognized risk reason for the development & progress of diseases associated with atherosclerosis, including ischemic heart disease (IHD) and stroke. It has been estimated that in USA the prevalence of abnormal raised serum cholesterol is very high and about every 3rd adult person has raised serum LDL-C levels[22]. The lipid lowering is the most powerful intervention in primary prevention of these diseases. For treating high lipid levels,

Table: Comparison of mean change in fasting serum total cholesterol & LDC-C after 12 weeks in both the groups.

Lipid Profile Parameter	Groups (n=57)	Mean ± SD	*p*-value
Mean change in Serum Total Cholesterol Fasting (mmol/L)	Group A (Rosuvastatin)	0.88 ± 0.51	<0.001*
	Group B (Atorvastatin)	0.05 ± 0.03	
Mean change in Serum Total LDL-C Fasting (mmol/L)	Group A (Rosuvastatin)	1.42 ± 0.92	0.001*
	Group B (Atorvastatin)	0.94 ± 0.54	

p-value ≤0.05 was taken as significant, hence both the p-values were statistically significant.

Statins drugs are the first-line of therapy used all over the world[23].

The statin drugs in addition to the numeric decrease of lipid profile, they expressively decrease vascular events and all-cause mortality through their pleiotropic properties. It has already been verified & proved that statins drugs have anti-inflammatory, antioxidant properties and anti-thrombotic effects, which further increase their clinical utility. Statin drugs improve endothelial dysfunction and diminish the growth & development of atherosclerotic plaque. Available data & evidence does not powerfully propose clear clinical benefit of other lipid-lowering agents & drugs in such situations[24].

All of the currently available statins drugs in market have small differences & variation in terms of pharmacodynamic & pharmacokinetics; hence in clinical efficiency, efficacy and side effects profile. Atorvastatin & Simvastatin are the most commonly used statin drugs. It has been evidenced from the Western countries research in dyslipidemia patients that rosuvastatin attains greater reductions & drops in LDL-C and has a higher rate of attaining therapeutic milestones than other statins drugs used currently in market. However, such data from our country Pakistan is inadequate and it is well known that Asians population may respond in a different way from western population because of genetic differences in drug metabolism at the hepatic enzyme and drug transporter level[25].

In a study conducted in 2014, total serum cholesterol was 0.77 ± 0.85 mmol/L in Atorvastatin group and 1.09 ± 1.010 mmol/L in Rosuvastatin group[17]. Similarly, in our study, mean change in serum total cholesterol fasting (mmol/L) was 0.88 ± 0.51 and 0.05 ± 0.08 in Rosuvastatin and Atorvastatin groups respectively. In our study, mean change in serum total LDL-C fasting (mmol /L) was 1.42 ± 0.92 & 0.94 ± 0.54 in Rosuvastatin and Atorvastatin groups respectively. Whereas, in a study carried out by Arshad AR observed that the mean Low Density Lipoprotein – Cholesterol (LDL-C) levels with Rosuvastatin as compared to Atorvastatin were 0.96 and 0.54 mg/dL respectively[17].

The findings in the present study are consistent with those reported by Tsutomu Yamazak *et al*. (2009), by comparing the effects of Rosuvastatin and Atorvastatin in Japanese hypercholesterolemic patients[24]. Momin *et al* (2015), studied the effects of these two drugs on type-2 DM stroke patient and concluded that lipid lowering effects of Rosuvastatin is better than Atorvastatin[23].

CONCLUSION

The study concludes that there was a greater reduction in terms of mean change in serum total cholesterol levels and low-density lipoprotein–cholesterol (LDL-C) levels with rosuvastatin 5mg daily as compared to atorvastatin 10 mg daily in type 2 diabetic patients with primary hyperlipidemia.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

REFERENCES

1. Punthakee Z, Goldenberg R, Katz P. Definition, classification and diagnosis of diabetes, prediabetes and metabolic syndrome. Can J Diabetes 2018; 42(1): S10-S5.
2. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nature Rev Endocrinol 2018; 14(2): 88.
3. Shah SH, Hameed T, Bokhari AF, Khan Z, Ahmed BH, Yousaf M, et al. Configuration of dyslipidemia in patients with type 2 diabetes mellitus visiting tertiary care hospital Quetta-Pakistan. Pure App Bio 2019; 8(1): 288-94.
4. Basit A, Fawwad A, Siddiqui SA, Baqa K. Current management strategies to target the increasing incidence of diabetes within Pakistan. Diabetes Metab Syndr Obes 2019; 12(1): 85-90.
5. Haas AV, McDonnell ME. Pathogenesis of cardiovascular disease in diabetes. Endocrinol Metab Clin 2018; 47(1): 51-63.
6. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017. Cardiovascular Diabet 2018; 17(1): 83.
7. Srivastava RAK. Dysfunctional HDL in diabetes mellitus and its role in the pathogenesis of cardiovascular disease. Molecular Cellul Biochem 2018; 440(1-2): 167-87.
8. Imamura F, O'connor L, Ye Z, Mursu J, Hayashino Y, Bhupathiraju SN, et al. Consumption of sugar sweetened beverages, artificially sweetened beverages, and fruit juice and incidence of type 2 diabetes: systematic review, meta-analysis, and estimation of population attributable fraction. Br J Sports Med 2016; 50(8): 496-504.

9. Wang LCC, Hess CN, Hiatt WR, Goldfine AB. Clinical update: cardiovascular disease in diabetes mellitus: atherosclerotic cardiovascular disease and heart failure in type 2 diabetes mellitus–mechanisms, management, and clinical considerations. Circulation 2016; 133(24): 2459-502.
10. Petrie JR, Guzik TJ, Touyz RM. Diabetes, hypertension, and cardiovascular disease: clinical insights and vascular mechanisms. Canad J Cardiol 2018; 34(5): 575-84.
11. Akyea RK, Kai J, Qureshi N, Iyen B, Weng SF. Sub-optimal cholesterol response to initiation of statins and future risk of cardiovascular disease. Heart 2019; 18(1): 3142-53.
12. Okuyama H, Langsjoen PH, Ohara N, Hashimoto Y, Hamazaki T. Medicines and vegetable oils as hidden causes of cardiovascular disease and diabetes. Pharmacology 2016; 98(3-4): 134-70.
13. Ray KK, Leiter LA, Wieland DM, Cariou B, Colhoun HM, Henry RR, et al. Alirocumab vs usual lipid lowering care as add on to statin therapy in individuals with type 2 diabetes and mixed dyslipidaemia: the odyssey dm dyslipidemia randomized trial. Diab Obesit Metabol 2018; 20(6): 1479-89.
14. de Boer IH, Bakris G, Cannon CP. Individualizing blood pressure targets for people with diabetes and hypertension: Comparing the ADA and the ACC/AHA recommendations. J Am Med Assoc 2018; 319(13): 1319-20.
15. Subedi BH, Tota-Maharaj R, Silverman MG, Minder CM, Martin SS, Ashen MD, et al. The role of statins in diabetes treatment. Diab Spectr 2013; 26(3): 156-64.
16. Chogtu B, Magazine R, Bairy K. Statin use and risk of diabetes mellitus. World J Diabetes 2015; 6(2): 352.
17. Arshad AR. Comparison of low-dose rosuvastatin with atorvastatin in lipid-lowering efficacy and safety in a high-risk pakistani cohort: an open-label randomized trial. J Lipid 2014; 2014.
18. Berne C, Siewert-Delle A. Comparison of rosuvastatin and atorvastatin for lipid lowering in patients with type 2 diabetes mellitus: results from the URANUS study. Cardiovascular Diabet 2005; 4(1): 7-11.
19. Clearfield MB, Amerena J, Bassand JP, García HRH, Miller SS, Sosef FF, et al. Comparison of the efficacy and safety of rosuvastatin 10 mg and atorvastatin 20 mg in high-risk patients with hypercholesterolemia Prospective study to evaluate the use of Low doses of the Statins Atorvastatin and Rosuvastatin (PULSAR). Trials 2006; 7(1): 35-40.
20. de Zeeuw D, Anzalone DA, Cain VA, Cressman MD, Heerspink HJL, Molitoris BA, et al. Renal effects of atorvastatin and rosuvastatin in patients with diabetes who have progressive renal disease (PLANET I): a randomised clinical trial. Lancet Diabet Endocrinol 2015; 3(3): 181-90.
21. Marenzi G, Cosentino N, Werba JP, Tedesco CC, Veglia F, Bartorelli AL. A meta-analysis of randomized controlled trials on statins for the prevention of contrast-induced acute kidney injury in patients with and without acute coronary syndromes. Int J Cardiol 2015; 183: 47-53.
22. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics - 2016 update: a report from the American Heart Association. Circulation 2015: CIR. 0000000000000350.
23. Mujeeb MM, Mutha AS. Comparative efficacy and safety of atorvastatin versus low dose rosuvastatin in the management of dyslipidaemia. Benefits 2018; 2: 3-10.
24. Last AR, Ference JD, Falleroni J. Pharmacologic treatment of hyperlipidemia. Am Fam Physician 2011; 84(5): 1-5.
25. Liao JK. Safety and efficacy of statins in Asians. Am J Cardiol 2007; 99(3): 410-14.