Original Research Article

To Evaluate the efficacy and safety profile of Rosuvastatin, Simvastatin and Atorvastatin in Newly Diagnosed Type 2 Diabetic patients with Dyslipidaemia

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Received: 03-05-2021 / Revised: 13-06-2021 / Accepted: 19-07-2021

Abstract

Introduction: The dyslipidemia of type 2 diabetes is characterized by high triglyceride levels and decreased high-density lipoprotein (HDL) cholesterol, changes observed many years before the onset of clinically relevant hyperglycemia. Dyslipidemia is common in diabetes and there is strong evidence that cholesterol lowering improves cardiovascular outcomes, even in patients with apparently unremarkable lipid profiles.

Materials and Methods: This is prospective, comparative, open label, randomized and parallel group. The subjects enrolled for this study were selected from the Out-Patient Department of Medicine at Tertiary care teaching hospital over a period of month. Newly diagnosed 120 cases of patients of Type II Diabetes Mellitus with Dyslipidaemia were randomly divided into 3 groups of 40 each. Group A was received Rosuvastain 10 mg O.D for 3 months, Group B: Simvastatin 10 mg O.D and Group C was received Atrovastatin 10 mg O.D.**Results:** In Group 'A' the mean difference of Total Cholesterol between baseline versus after 6 months was 78.84 mg/dl, 61.20 mg/dl and 60.22 mg/dl in Group B and Group C respectively. The mean difference of Triglycerides between baseline versus after 6 months was 74.82 mg/dl in Group A, 41.11 mg/dl in Group B and 37.61 mg/dl in Group C. The mean difference of HDL between baseline versus after 6 months was 10.95 mg/dl in Group A, 9.57 mg/dl in Group B and 8.01 mg/dl in Group C. The mean difference of LDL between baseline versus after 6 months was 74.89 mg/dl in Group A, 63.25 mg/dl in Group B and 60.01 mg/dl in Group C. The mean difference of VLDL between baseline versus after 6 months was 14.90 mg/dl in Group A, 7.52 mg/dl in Group B and 8.22 mg/dl in Group C.**Conclusion:** Finally using Rosuvastatin seems high for the patients but the result obtained by reducing the lipid parameters by given therapy is beneficial to the patients in long term control of lipid profile and thus helps in the overall reduction of morbidity and mortality in patients with type 2 diabetes mellitus with dyslipidaemia.

Keywords: Diabetes, Dyslipidemia, Lipoproteins, Low density lipoprotein cholesterol

Introduction

The dyslipidemia of type 2 diabetes is characterized by high triglyceride levels and decreased high-density lipoprotein (HDL) cholesterol, changes observed many years before the onset of clinically relevant hyperglycemia [1]. Recent evidence suggests that low HDL cholesterol is an independent factor not only for cardiovascular disease but also for the development of diabetes itself [2]. These changes, and the presence of small dense LDL particles, probably contribute to accelerated atherosclerosis even before diabetes is formally diagnosed[3].In type 1 diabetes, hyper-triglyceridemia may occur, but HDL cholesterol levels are often normal or even high unless glycemic control is poor or nephropathy is present [4]. In addition, patients with diabetes show qualitative and kinetic abnormalities for all lipoproteins [5].

A number of factors may contribute to the alterations in lipid metabolism observed in patients with diabetes, including insulin deficiency or resistance, adipocytokines, and hyperglycemia [5]. Many aspects of the pathophysiology and consequences of diabetes dyslipidemia remain unclear, but the mechanism by which hypertriglyceridemia arises is fairly well understood [6]. Insulin deficiency or resistance activates intracellular hormone-sensitive lipase which increases the release of non-esterified fatty acids (NEFA) from triglycerides stored in the more metabolically active centrally distributed adipose tissue [7]. High circulating levels of NEFA increase hepatic triglyceride production. Increased hepatic triglyceride synthesis is associated with increased secretion of apolipoprotein B (apoB) [8].

Furthermore, the normal inhibitory effect of insulin on hepatic apoB production and triglyceride secretion in VLDL is lost, and the VLDL secreted is larger and more triglyceride-rich [9]. The tendency to hypertriglyceridemia is further augmented by reduced VLDL catabolism [10]. Lipoprotein lipase located on vascular endothelium largely determines the rate of removal of triglycerides from the circulation. In contrast to intracellular hormone-sensitive lipase this lipoprotein lipase may be downregulated in states of insulin resistance or deficiency [11].

Statin therapy is recommended as the initial pharmacological treatment for lowering LDL-C levels in patients with type 2 diabetes who either have overt CVD or are over 40 years old and have increased CVD risk [12]; however, even with adequate LDL-C lowering via statin therapy, CVD risk remains high in many patients [13]. The beneficial effects of statin treatment are thought to be mediated predominantly via lowering of LDL-C levels, although effects on HDL-C and other lipoproteins may also play a role [14]. Statin treatment lowers non-HDL-C more than apoB [15], and

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reaching the apoB target usually requires more intensive therapy than that required to achieve the non-HDL-C goal [16]. Common adverse events associated with statin use include gastrointestinal upset and muscle aches, although dose-related hepatoxicity and myotoxicity are the most clinically significant adverse events [17].

Materials and Methods

This is prospective, comparative, open label, randomized and parallel group. The subjects enrolled for this study were selected from the Out-Patient Department of Medicine at Tertiary care teaching hospital over a period of month. Newly diagnosed 120 cases of patients of Type II Diabetes Mellitus with Dyslipidaemia well controlled on oral hypoglycemic drugs were randomly divided into 3 groups of 40 each. Group A was received Rosuvastain 10 mg O.D for 3 months, Group B: Simvastatin 10 mg O.D and Group C was received Atrovastatin 10 mg O.D.

Inclusion Criteria

Patients 30 to 60 years of either gender newly diagnosed Type-2 Diabetes Mellitus with Dyslipidaemia. Type 2 Diabetes Mellitus patients well controlled on oral hypoglycemic drugs.

Exclusion Criteria

Patients with a history of Type 1 diabetes mellitus.
Patients with a history of cardiovascular diseases, renal diseases
Patients with a history liver disease.
Pregnant or lactating women.
Smokers and alcoholic patients.

Statistical Analysis: UnPaired T test was used to measure the differences among the group and for the comparison while using SPSS 25th version.

Results

The present study was carried out in collaboration with the Department of Medicine, and Department of Pharmacology, Tertiary Care Teaching Hospital. A total 120 patients were enrolled. Patients were randomly divided into three groups of 40 each.

Table 1: Distribution of Age of the subjects

Age in years	Group A	Group B	Group C
30-40	11	10	11
41-50	14	16	15
51-60	15	14	14

In table 1 depicts the age distribution of the subjects in all 3 groups under study. All the three groups consisted of 40 subjects each.

Table 2: Distribution of patients according to Gender

	Group A		Group B		Group C	
	No	Percentage	No	Percentage	No	Percentage
Male	23	57.5	21	52.5	22	55.0
Female	17	42.5	19	47.5	18	45%
Total	40	100%	40	100%	40	100%

In Table 2 shows the sex distribution of the subjects in 3 groups under study. Three groups consisted of 40 subjects each. Group A consisted of 23 males and 17 female patients. In Group B patients were 21 Male and female 19. In Group C patients were 22 Male and female 18.

Table 3: Comparison of Mean Lipid profile in three Groups at baseline versus 6 months of treatment by unpaired "t" test

Parameters		Group A Mean±SD	Group B Mean±SD	Group C Mean±SD
Total Cholesterol (mg/dl)	Baseline	309.47±52.83	298.57±58.29	293.48±53.38
	After 6 months	249.25±39.72	237.37±38.33	214.64±39.53
	p-value	<0.0001	<0.0001	<0.0001
Triglycerides (mg/dl)	Baseline	289.35±41.63	287.53±48.51	273.36±47.63
	After 6 months	214.53±33.73	246.42±42.75	235.75±30.74
	p-value	<0.0001	<0.0001	<0.0001
HDL(mg/dl)	Baseline	38.64 ± 5.75	37.86 ± 5.86	38.85 ± 5.36
	After 6 months	49.59 ± 6.43	47.43 ± 6.23	46.86 ± 6.86
	p-value	<0.0001	<0.0001	<0.0001
LDL(mg/dl)	Baseline	197.04.94 ± 35.06	206.04 ± 34.83	213.12 ± 34.86
	After 6 months	122.15 ± 18.59	142.79 ± 20.60	153.11 ± 18.78
	p-value	<0.0001	<0.0001	<0.0001
VLDL(mg/dl)	Baseline	57.80 ± 8.32	54.67 ± 9.52	57.50 ± 9.70
	After 6 months	42.90 ± 6.74	47.15 ± 6.14	49.28 ± 6.68
	p-value	<0.0001	<0.0001	<0.0001

P value < 0.05 is significant & P value > 0.05 is not significant

Table 4: Overview of Mean Differences between Baseline Vs after 6 months of the Therapy

Parameters	Group A	Group B	Group C
Total Cholesterol	78.84	61.20	60.22
Triglycerides	74.82	41.11	37.61
HDL	-10.95	-9.57	-8.01
LDL	74.89	63.25	60.01
VLDL	14.90	7.52	8.22

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Discussion

Dyslipidaemia is a common feature of diabetes. There is an association between atherosclerotic cardiovascular disease and serum cholesterol and triglyceride levels in both type 1 and type 2 diabetes. The risk of CHD is greater at any given level of serum cholesterol in patients with diabetes and its association with hypertriglyceridemia is stronger than in the general population. Importantly, there is strong and convincing evidence that cholesterol lowering therapy significantly reduces CHD in patients both with and without diabetes. [18] There also appears to be no threshold below which a further reduction in low-density lipoprotein (LDL) cholesterol might be beneficial. [19]

Improved glycemic control generally has favorable effects on lipoprotein levels in diabetes, with a reduction in cholesterol and triglyceride levels through decreased circulating very-low-density lipoprotein (VLDL) and by increased catabolism of LDL through reduced glycation and upregulation of LDL receptors. [20] It is certainly possible that any cardiovascular benefit which might be derived from intensive glucose lowering is related to effects on lipoprotein metabolism rather than directly through altered glycemia. [21]

In our present study, we found out that Rosuvastatin significantly decreased the levels of Serum Cholesterol, Serum triglycerides, L.D.L. and V.L.D.L. and increased the levels of H.D.L. after 12 weeks of therapy. The difference in the parameters studied was highly significant (P< 0.001). These results are comparable to the studies conducted by Gleuk *et al*, which was conducted at The Cholesterol Centre, Jewish Hospital, Cincinati, USA [22].

Atorvastatin and Simvastatin also decreased the levels of Serum Cholesterol, Serum triglycerides, L.D.L. and V.L.D.L. and increased the levels of H.D.L. after 6 months of therapy. The difference in the studied groups in the lipid parameters after therapy was also found to be significant but less when compared with the Rosuvastatin. These results correlate with the studies conducted by Goudevenos *et al*, for the efficacy of Atorvastatin and Simvastatin in dyslipidemia respectively. [23, 24]In the comparison of L.D.L. reduction it is seen that reduction in the Rosuvastatin group was statistically significant when compared with Atorvastatin and Simvastatin group. In the group of Atorvastatin, the values were not statistically significant in decreasing the L.D.L. values. This is comparable to the studies done by Bullano*et al* which concluded that Rosuvastatin was more effective than both Atorvastatin and Simvastatin in decreasing the L.D.L. levels significantly. [25]The rise in the H.D.L. levels in Rosuvastatin group after the therapy was statistically significant when compared with atorvastatin group and highly significant when compared with the simvastatin group. This is in contrast with the study done by Hunning*et al* which concluded that simvastatin produced more increase in the H.D.L. levels. [26]The COMETS study (A comparative study of Rosuvastatin in subjects of metabolic syndrome) concluded that Rosuvastatin increased High density lipoprotein as compared to atorvastatin which is in correlation with our study. [27]The comparison of serum cholesterol reduction in Rosuvastatin group when compared with serum cholesterol of simvastatin and atorvastatin group has revealed that reduction in serum cholesterol levels of rosuvastatin group were statistically significant when compared with the simvastatin group but not significant when compared with the Atorvastatin group.

The dyslipidemia of type 2 diabetes is characterized by high triglyceride levels and decreased high-density lipoprotein (HDL) cholesterol, changes observed many years before the onset of clinically relevant hyperglycemia[28]. Recent evidence suggests that low HDL cholesterol is an independent factor not only for cardiovascular disease but also for the development of diabetes itself [29]. These changes, and the presence of small dense LDL particles, probably contribute to accelerated atherosclerosis even before diabetes is formally diagnosed [30]. In type 1 diabetes, hypertriglyceridemia may occur, but HDL cholesterol levels are often normal or even high unless glycemic control is poor or nephropathy is present [31]. In addition, patients with diabetes show qualitative and kinetic abnormalities for all lipoproteins [32].

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Furthermore, the normal inhibitory effect of insulin on hepatic apoB production and triglyceride secretion in VLDL is lost, and the VLDL secreted is larger and more triglyceride-rich [37]. The tendency to hypertriglyceridemia is further augmented by reduced VLDL catabolism [38]. Lipoprotein lipase located on vascular endothelium largely determines the rate of removal of triglycerides from the circulation. In contrast to intracellular hormone-sensitive lipase this lipoprotein lipase may be downregulated in states of insulin resistance or deficiency [39]. This reduction in lipoprotein lipase activity also contributes to postprandial lipemia[40].

Conclusion

In summary, after 6 months of treatment with three groups caused reduction in Sr. Cholesterol, Sr. triglycerides, LDL and VLDL and increased HDL values in group A, B and C. The advantage of using Rosuvastatin 10 mg OD can be clearly seen as it reduced Sr. Cholesterol, Sr. triglycerides, LDL and VLDL and increased HDL values in group to a great extent. Finally using Rosuvastatin seems high for the patients but the result obtained by reducing the lipid parameters by given therapy is beneficial to the patients in long term control of lipid profile and thus helps in the overall reduction of morbidity and mortality in patients with type 2 diabetes mellitus with dyslipidaemia. We conclude that all the 3 groups i.e. those who were administered Atorvastatin, Simvastatin and Rosuvastatin therapy elicited a clinically meaningful decrease in Sr. Cholesterol, Sr. triglycerides, LDL and VLDL and increased HDL values sustained throughout 12 weeks of treatment in drug-naïve patients of Type 2 DM with Dyslipidaemia.

References

1. Jellinger PS, Smith DA, Mehta AE, Ganda O, Handelsman Y, Rodbard HW *et al*. American association of clinical endocrinologists' guidelines for management of Dyslipidemia and prevention of atherosclerosis. EndocrPract. 2012; 18 Suppl1:1-78.
2. Chen G, McAlister FA, Walker RL,Hemmelgarn BR, Campbell NR. Cardiovascular outcomes in framingham participants with diabetes: the importance of blood pressure. Hypertension. 2011;57(5):891-7.
3. Bobby D, Vinodha R. Dyslipidemia in type 2 diabetes mellitus – a major risk factor for cardiovascular morbidity. Int J Med Res Rev. 2016;4(8):1387-1391.
4. Osuji CU, Nzerem BA, Dioka CE. Metabolic syndrome in newly diagnosed type 2 diabetes mellitus using NCEP-ATPIII, the Nnewi experience. Niger J ClinPract. 2012;15(4):475–480.

5. Unnikrishnan R, Anjana RM, Mohan V. Diabetes mellitus and its complications in India. Nat Rev Endocrinol. 2016; 12(6):357–370.
6. Jayarama N, Reddy M, Lakshmaiah V. Prevalence and pattern of dyslipidemia in type 2 diabetes mellitus patients in a rural tertiary care centre, southern India. Glob J Med Public Health. 2012;1:24-8.
7. Mohan V,Sandeep S,Deepa R,Shah B,Varghese C. Epidemiology of type 2 diabetes: Indian scenario. Indian J Med Res. 2007;125:217-30.
8. Anjana RM, Pradeepa R, Deepa M, Datta M, Sudha V, Unnikrishnan R. ICMR–INDIAB Collaborative Study Group. Prevalence of diabetes and prediabetes (impaired fasting glucose and/or impaired glucose tolerance) in urban and rural India: Phase I results of the Indian Council of Medical Research India Diabetes (ICMR INDIAB) study. Diabetologia. 2011;54:3022-7.
9. Taylor HA Jr, Akylbekova EL, Garrison RJ, Sarpong D, Joe J, Walker E, Wyatt SB, Steffes MW. Dyslipidemia and the treatment of lipid disorders in African Americans. Am J Med. 2009;122(5):454-63.
10. Keech A, Colquhoun D, Best J, Kirby A, Simes RJ, Hunt D, Hague W, Beller E, Arulchelvam M, Baker J, Tonkin A. LIPID Study Group. Secondary prevention of cardiovascular events with long-term pravastatin in patients with diabetes or impaired fasting glucose: results from the LIPID trial. Diabetes Care. 2003;26(10):2713-21.
11. Farmer JA. Diabetic dyslipidemia and atherosclerosis: Evidence from clinical trials. CurrDiab Rep. 2008;8:71-7.
12. Misra A, Pandey RM, Devi JR, Sharma R, Vikram NK, Khanna N. High prevalence of diabetes, obesity and dyslipidaemia in urban slum population in northern India. Int J Obes Relat Metab Disord. 2001;25:1722-9.
13. Masram SW, Bimanpalli MV, Ghangle, S. Study of lipid profile and glycatedhemoglobin in Diabetes mellitus. Indian Medical Gazette. 2012, 257-65.
14. Parikh RM, Joshi SR, Menon PS, Shash NS. Prevalence and Pattern of Diabetic Dyslipidemia in Indian type 2 Diabetic patients. Diabetes and Metabolic Syndrome. Clinical Research and Review. 2010;4(1):10-12.
15. Smith S, Lall AM. A Study on Lipid Profile Levels of Diabetics and Non-Diabetics AmongNaini Region of Allahabad, India. Turk J Biochem. 2008;33(4):138-41.
16. Rani HS, Madhavi G, Rao VR, Sahay BK, Jyothy A. Risk factors for coronary heart disease in type II diabetes mellitus. Indian J ClinBiochem. 2005;20(2):75-80.
17. Keech A, Colquhoun D, Best J, Kirby A, Simes RJ, Hunt D. LIPID Study Group. Secondary prevention of cardiovascular events with long-term pravastatin in patients with diabetes or impaired fasting glucose: results from the LIPID trial. Diabetes care. 2003;26(10):2713-21.
18. Pandya H, Lakhani JD, Dadhania J, Trivedi A. The prevalence and pattern of dyslipidemia among type 2 diabetic patients at rural based hospital in Gujarat, India. J Clin Prac. 2012;22 (12): 36-44.
19. Samatha P, Venkateswarlu M, Siva Prabodh V. Lipid profile levels in type 2 diabetes mellitus from tribal population of Adilabad in Andhra Pradesh, India. J Clin Diagnostic Res. 2012;6(4):590-2.
20. Krauss RM. Lipids and lipoproteins in patients with type 2 diabetes. Diabet Care. 2004;27:1496-504.
21. Mahato RV, Gyawali P, Raut PP, Regmi P, Singh PK, Pandey DR et al. Association between glycaemic control and serum lipid profile in type 2 diabetic patients: glycated haemoglobin as a dual biomarker. Biomed Res. 2011;22(3):375-80.
22. Firdous S, Khan MZ. Comparison of patterns of lipid profile in type-2 diabetics and nonraised diabetics. Ann King Edward Med Coll. 2007;3(1):84-7.
23. Dixit AK, Dey R, Suresh A, Chaudhuri S, Panda AK, Mitra A, et al. The prevalence of dyslipidemia in patients with diabetes mellitus of ayurveda Hospital. J DiabetMetabol Disorders. 2014;13:58.
24. Uttra KM, Devrajani BR, Shah SZA, Devrajani T, Das T, Raza S, et al. Lipid Profile of Patients with Diabetes mellitus. World Appl Sci. 2011;J12(9):1382-4.
25. Kengne AP, Limen SN, Sobngwi E. Metabolic syndrome in type 2 diabetes: comparative prevalence according to two sets of diagnostic criteria in sub-Saharan Africans. Diabetol Metab Syndr. 2012;4(1):22.
26. Selvin E, Coresh J, Golden SH, Boland LL, Brancati FL, Steffes MW. Atherosclerosis risk in communities study. Glycemic control, atherosclerosis, and risk factors for cardiovascular disease in individuals with diabetes: the atherosclerosis risk in communities study. Diabetes Care. 2005; 28(8):1965-73.
27. Gavin JR 3rd. Reducing global cardiovascular risk in patients with type 2 diabetes mellitus. J Am Osteopath Assoc. 2008;108 (5 Suppl 3):S14-9.
28. Marjani A, Shirafkan A. The metabolic syndrome in type 2 diabetic patients in Gorgan: according to NCEP ATPIII and IDF definitions. Diabetes Metabol Syndr: Clin Res Rev. 2011; 5(4): 207–210.
29. Janghorbani M, Amini M. Incidence of metabolic syndrome and its risk factors among type 2 diabetes clinic attenders in Isfahan, Iran. ISRN Endocrinol. 2012;2012:167318.
30. Gokcel A, Karakose H, Ertorer EM, Tanaci N, Tutuncu NB, Guvener N. Effects of sibutramine in obese female subjects with type 2 diabetes and poor blood glucose control. Diabetes Care. 2001;24(11):1957-60.
31. Milicevic Z, Raz I, Beattie SD, Campaigne BN, Sarwat S, Gromniak E et al. Natural history of cardiovascular disease in patients with diabetes: role of hyperglycemia. Diabetes Care. 2008;31 Suppl 2:S155–160.
32. Regensteiner JG, Golden S, Huebschmann AG, Barrett-Connor E, Chang AY, Chyun D et al. Sex Differences in the Cardiovascular Consequences of Diabetes Mellitus: A Scientific Statement From the American Heart Association. Circulation. 2015;132:2424–2447.
33. Fox CS, Golden SH, Anderson C, Bray GA, Burke LE, de Boer IH et al. Update on Prevention of Cardiovascular Disease in Adults With Type 2 Diabetes Mellitus in Light of Recent Evidence: A Scientific Statement From the American Heart Association and the American Diabetes Association. Diabetes Care. 2015;38:1777–1803.
34. Lind M, Svensson AM, Kosiborod M, Gudbjornsdottir S, Pivodic A, Wedel H, Dahlqvist S, Clements M, Rosengren A. Glycemic control and excess mortality in type 1 diabetes. N Engl J Med. 2014;371:1972–1982.
35. de Ferranti SD, de Boer IH, Fonseca V, Fox CS, Golden SH, Lavie CJ, Magge SN, Marx N, McGuire DK, Orchard TJ, Zinman B, Eckel RH. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. Diabetes Care. 2014;37:2843–2863.
36. Maahs DM, Daniels SR, de Ferranti SD, Dichek HL, Flynn J, Goldstein BI, Kelly AS, Nadeau KJ, Martyn-Nemeth P, Osganian SK, Quinn L, Shah AS, Urbina E. Cardiovascular disease risk factors in youth with diabetes mellitus: a scientific statement from the American Heart Association. Circulation. 2014;130:1532–1558.
37. Huxley RR, Peters SA, Mishra GD, Woodward M. Risk of all-cause mortality and vascular events in women versus men with

type 1 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2015;3:198–206.
38. Rawshani A, Sattar N, Franzen S, Rawshani A, Hattersley AT, Svensson AM, Eliasson B, Gudbjornsdottir S. Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study. Lancet. 2018;392:477–486.
39. Chillaron JJ, Flores Le-Roux JA, Benaiges D, Pedro-Botet J. Type 1 diabetes, metabolic syndrome and cardiovascular risk. Metabolism. 2014;63:181–187.
40. Constantino MI, Molyneaux L, Limacher-Gisler F, Al-Saeed A, Luo C, Wu T, Twigg SM, Yue DK, Wong J. Long-term complications and mortality in young-onset diabetes: type 2 diabetes is more hazardous and lethal than type 1 diabetes. Diabetes Care. 2013;36:3863–3869.

Conflict of Interest: Nil
Source of support:Nil