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A comparative evaluation of safety and efficacy of Rosuvastatin, Simvastatin, and Atorvastatin in patients of type 2 diabetes mellitus with dyslipidemia

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Abstract---Introduction: Type 2 diabetes mellitus consists of an array of dysfunctions characterized by hyperglycaemia and resulting from the combination of resistance to insulin action, inadequate insulin secretion, and excessive or inappropriate glucagon secretion. Dyslipidemia is one of the major risk factors for cardiovascular disease in diabetes mellitus. The characteristic features of diabetic dyslipidemia are a high plasma triglyceride concentration, low HDL cholesterol concentration and increased concentration of small dense LDL-cholesterol particles. To evaluate and compare the safety and efficacy of Rosuvastatin, simvastatin, and atorvastatin in patients of type 2 diabetes mellitus with dyslipidemia. Material and Method: This is prospective, comparative, open label, randomized and parallel group. The subjects enrolled for this study were selected from the Out-Patient Department of General Medicine collaboration with Department of Biochemistry, Tertiary care teaching hospital over a period of 1 month. Newly diagnosed 120 cases of patients of Type II Diabetes Mellitus well controlled on oral hypoglycemic drugs were

randomly divided into 3 groups of 40 each. Group A: Simvastatin 10 mg O.D and Group B received Atorvastatin 10 mg O.D and Group C received Rosuvastatin 10 mg O.D for 6 months. Results: In Group 'A' the mean difference of Total Cholesterol between baselines versus after 6 months was 61.14 mg/dl, 78.55 mg/dl and 91.41 mg/dl in Group B and Group C respectively. The mean difference of Triglycerides between baselines versus after 6 months was 53.82 mg/dl in Group A, 61.07 mg/dl in Group B and 76.21 mg/dl in Group C. The mean difference of HDL between baselines versus after 6 months was 9.04 mg/dl in Group A, 11.89.62 mg/dl in Group B and 12.01 mg/dl in Group C increases. The mean difference of LDL between baselines versus after 6 months was 59.41 mg/dl in Group A, 78.24 mg/dl in Group B and 88.32 mg/dl in Group C. The mean difference of VLDL between baselines versus after 6 months was 15.24 mg/dl in Group A, 12.20 mg/dl in Group B and 15.24 mg/dl in Group C. Conclusion: The results obtained in the current study have shown that Rosuvastatin is the most effective statin at reducing total cholesterol, triglycerides, LDL-C and VLDL-C at the Moreover, Rosuvastatin was more efficacious than both atorvastatin and simvastatin in increasing HDL levels. Thus, in the diabetic dyslipidemia population it appears to be the most effective statin. In addition, this study provides a good base for future large-scale prospective studies to be conducted on the topic.

Keywords--Atorvastatin, dyslipidemia, Rosuvastatin, simvastatin, type-2 diabetes mellitus.

Introduction

Diabetes mellitus is a very commonly occurring metabolic disorder characterized by hyperglycaemia and altered metabolism of lipids, proteins, and carbohydrates which is due to absolute or relative deficiency of insulin or insulin resistance. [1] Diabetes mellitus is associated with increased oxidative stress due to hyperglycaemia. The oxidative damage plays a role in development of micro and macro vascular complications, leading to a significant impact on quality of life. Long-term complications involve almost all vital organs such as heart, eyes, kidney, blood vessels, and nervous system. These complications lead to the development of obesity, hypertension, dyslipidaemia, and insulin resistance. [2]

There is a close association between complications of diabetes and diabetic dyslipidaemia. Diabetic dyslipidaemia accounts for around 80 percent diabetic deaths due to cardiovascular complications. There is a growing body of evidence to show that hyperglycaemia and dyslipidaemia are associated with excess of cardiovascular risk. [3]

Treatment of type 2 diabetes requires the agents that act beyond their blood glucose effect. Drug therapy that not only has an effect on blood glucose level but also has a beneficial effect on dyslipidaemia, hypertension, obesity,

hyperinsulinemia, and insulin resistance is likely to be the most useful therapy in treating type-2 diabetes. ^[4]

Diabetic patients tend to have a higher concentration of small dense LDL particles, which are associated with higher CHD risk. Lowering LDL levels is the first priority in treating diabetic dyslipidaemia. Statins are the first drug of choice, followed by resins or ezetimibe, then fenofibrate, or niacin. Current evidence and guidelines mandate that diabetic dyslipidaemia should be treated aggressively, and lipid goals can be achieved in most patients with diabetes when all available products are considered and, if necessary, used in combination. ^[5]

Different statins require different dosing to reach the same LDL level. The lowering of LDL levels with statins varies from 22 to 58%. Therefore, the greatest effects are seen with the most potent statins such as simvastatin, atorvastatin, and rosuvastatin in the higher doses. Besides, majority of diabetic patients are at risk of coronary heart disease and deserve LDL cholesterol lowering to the currently recommended targets. ^[6]

The diabetes atorvastatin lipid intervention (DALI) study concluded that either 10 or 80 mg of atorvastatin is equally effective in the treatment of diabetic dyslipidaemia. ^[7] Intensive lowering of LDL-C with high dose atorvastatin does not result in a significant reduction in the primary outcome of major coronary events, but reduces the risk of other composite secondary end points and nonfatal acute MI. ^[8] Atorvastatin is more effective than simvastatin-based therapies in achieving treatment targets in patients with familial hypercholesterolemia. ^[9] Rosuvastatin 10 and 20 mg tablet improves the overall lipid profile of hypercholesterolemia patients better than does milligram equivalent doses of atorvastatin. ^[10]

Considering the above-mentioned facts, it seems that prevention of cardiovascular complications of diabetes must be considered as a national public health goal in the light of the increasing prevalence of the disease and the high frequency and seriousness of its complications.

The present study was thus planned to primarily evaluate and then to compare the efficacy and safety of newer emerging and promising statin rosuvastatin *vs* existing commonly used statins such as simvastatin and atorvastatin in patients with type-2 diabetes mellitus with dyslipidaemia, so as to guide the present treatment strategies in the management of diabetes with dyslipidaemia in Indian population.

Material 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 General Medicine collaboration with Department of Biochemistry, Tertiary care teaching hospital over a period of 1 month. Newly diagnosed 120 cases of patients of Type II Diabetes Mellitus well controlled on oral hypoglycemic drugs were randomly divided into 3 groups of 40 each. Group A: Simvastatin 10 mg O.D and Group B received Atorvastatin 10 mg O.D and Group C received Rosuvastatin 10 mg O.D for 6 months,

Inclusion criteria

Patients 30 to 60 years of either gender newly diagnosed Type-2 Diabetes Mellitus with Dyslipidemia. 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.

Result

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	12	12	13
41-50	14	13	13
51-60	14	15	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%	22	55%	24	60%
Female	17	42.5%	18	45%	16	40%
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 22 Male and female 18. In Group C patients were 24 Male and female 16.

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	285.40±31.23	293.23±39.61	273.23±37.70
	After 6 months	224.26±23.50	214.68±24.38	181.68±24.18
	p-value	<0.0001	<0.0001	<0.0001
Triglycerides (mg/dl)	Baseline	301.10±39.71	295.34±39.26	303.42±30.35
	After 6 months	247.28±22.66	234.28±22.85	227.21±26.85
	p-value	<0.0001	<0.0001	<0.0001
HDL (mg/dl)	Baseline	37.58 ± 3.86	36.32 ± 3.64	37.32 ± 3.64
	After 6 months	46.62 ± 3.87	48.21 ± 4.82	49.33 ± 4.71
	p-value	<0.0001	<0.0001	<0.0001
LDL (mg/dl)	Baseline	187.60 ± 16.27	197.86 ± 15.38	175.23 ± 15.61
	After 6 months	128.19 ± 28.96	119.62 ± 31.54	86.91 ± 28.69
	p-value	<0.0001	<0.0001	<0.0001
VLDL (mg/dl)	Baseline	60.22 ± 7.94	59.05 ± 7.85	60.68 ± 6.07
	After 6 months	49.45 ± 9.57	46.85 ± 7.87	45.44 ± 10.97
	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 (Decreases)	61.14	78.55	91.41
Triglycerides (Decreases)	53.82	61.07	76.21
HDL (Increases)	9.04	11.89	12.01
LDL (Decreases)	59.41	78.24	88.32
VLDL (Decreases)	15.24	12.20	15.24

In Group 'A' the mean difference of Total Cholesterol between baselines versus after 6 months was 61.14 mg/dl, 78.55 mg/dl and 91.41 mg/dl in Group B and Group C respectively. The mean difference of Triglycerides between baselines versus after 6 months was 53.82 mg/dl in Group A, 61.07 mg/dl in Group B and 76.21 mg/dl in Group C. The mean difference of HDL between baselines versus

after 6 months was 9.04 mg/dl in Group A, 11.89.62 mg/dl in Group B and 12.01 mg/dl in Group C increases. The mean difference of LDL between baselines versus after 6 months was 59.41 mg/dl in Group A, 78.24 mg/dl in Group B and 88.32 mg/dl in Group C. The mean difference of VLDL between baselines versus after 6 months was 15.24 mg/dl in Group A, 12.20 mg/dl in Group B and 15.24 mg/dl in Group C.

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 [11]. Importantly, there is strong and convincing evidence that cholesterol lowering therapy significantly reduces CHD in patients both with and without diabetes. [12] There also appears to be no threshold below which a further reduction in low-density lipoprotein (LDL) cholesterol might be beneficial. [13]

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. [14] 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. [15]

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 6 months 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, Cincinnati, USA [16].

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. [17] 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. [18]

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 [19]. Recent evidence suggests that low HDL cholesterol is an independent factor not only for cardiovascular disease but also for the development of diabetes itself [19]. These changes, and the presence of small dense LDL particles, probably contribute to accelerated atherosclerosis even before diabetes is formally diagnosed [20]. 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 [21]. In addition, patients with diabetes show qualitative and kinetic abnormalities for all lipoproteins [22].

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 [23]. Many aspects of the pathophysiology and consequences of diabetes dyslipidemia remain unclear, but the mechanism by which hypertriglyceridemia arises is fairly well understood [24]. 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 [25]. High circulating levels of NEFA increase hepatic triglyceride production. Increased hepatic triglyceride synthesis is associated with increased secretion of apolipoprotein B (apoB) [26].

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 [27]. The tendency to hypertriglyceridemia is further augmented by reduced VLDL catabolism [28]. 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 [29]. This reduction in lipoprotein lipase activity also contributes to postprandial lipemia [30].

Conclusion

The results obtained in the current study have shown that Rosuvastatin is the most effective statin at reducing total cholesterol, triglycerides, LDL-C and VLDL-C at the Moreover, Rosuvastatin was more efficacious than both atorvastatin and simvastatin in increasing HDL levels. Thus, in the diabetic dyslipidemia population it appears to be the most effective statin. In addition, this study provides a good base for future large-scale prospective studies to be conducted on the topic.

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