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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Abstract---Dyslipidemia is one of the major risk factors for cardiovascular disease in diabetes mellitus. The lipid changes associated with diabetes mellitus are attributed to increased free fatty acid flux secondary to insulin resistance. 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 collaboration with Department of Pharmacology, Tertiary care teaching hospital over a period of month. Newly diagnosed 90 cases of patients of Type II Diabetes Mellitus well controlled on oral hypoglycemic drugs were randomly divided into 3 groups of 30 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. In Group 'A' the mean difference of Total Cholesterol between baseline versus after 6 months was 82.37 mg/dl, 64.92 mg/dl and 52.23 mg/dl in Group B and Group C respectively. The mean difference of Triglycerides between baseline versus after 6 months was 65.04 mg/dl in Group A, 39.99 mg/dl in Group B and 37.04 mg/dl in Group C. The mean difference of HDL between baseline versus after 6

months was 10.04 mg/dl in Group A, 10.26 mg/dl in Group B and 9.13 mg/dl in Group C. The mean difference of LDL between baseline versus after 6 months was 79.4 mg/dl in Group A, 67.6 mg/dl in Group B and 33.82 mg/dl in Group C. The mean difference of VLDL between baseline versus after 6 months was 13.01 mg/dl in Group A, 7.58 mg/dl in Group B and 7.41 mg/dl in Group C. 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---rosuvastatin, simvastatin, atorvastatin, type 2 diabetic patients, dyslipidaemia.

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. [1] 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. The lipid changes associated with diabetes mellitus are attributed to increased free fatty acid flux secondary to insulin resistance. [2]

The availability of multiple lipid-lowering drugs and supplements provides new opportunities for patients to achieve target lipid levels. However, the variety of therapeutic options poses a challenge in the prioritization of drug therapy. [3] The prevalence of hypercholesterolemia is not increased in patients with diabetes mellitus, but mortality from coronary heart disease increases exponentially as a function of serum cholesterol levels, and lowering of cholesterol with statins reduces diabetic patients' relative cardiovascular risk. [4] Although drug therapy for dyslipidemia must be individualized, most people with diabetes mellitus are candidates for statin therapy and often need treatment with multiple agents to achieve therapeutic goals. [5]

It is seen that Indian population is genetically more prone for atherogenic LDL particles along with the unhealthy lifestyle nowadays due to the factors like junk food, lack of exercise, obesity etc. which makes us more prone for the long-term complications of diabetes. [6] So this study was undertaken so as to assess the comparative safety and efficacy of the Atorvastatin, Simvastatin and Rosuvastatin in the patients of Type 2 diabetes mellitus with dyslipidemia.

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 collaboration with Department of Pharmacology, Tertiary care teaching hospital over a period of month. Newly diagnosed 90 cases of patients of Type II Diabetes Mellitus well controlled on oral hypoglycemic drugs were randomly divided into 3 groups of 30 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 90 patients were enrolled. Patients were randomly divided into three groups of 30 each.

Table 1: Distribution of Age of the subjects

Age in years	Group A	Group B	Group C
30-40	8	8	9
41-50	11	10	10
51-60	11	12	11

In table 1 depicts the age distribution of the subjects in all 3 groups under study. All the three groups consisted of 30 subjects each.

Table 2: Distribution of patients according to Gender

	Group A		Group B		Group C	
	No	Percentage	No	Percentage	No	Percentage
Male	18	60	17	56.6%	19	63.3%
Female	12	40%	13	43.4%	11	36.6%

Total	30	100%	30	100%	30	100%

In Table 2 shows the sex distribution of the subjects in 3 groups under study. Three groups consisted of 30 subjects each. Group A consisted of 18 male and 12 female patients. In Group B patients were 17 Male and female 13. In Group C patients were 19 Male and female 11.

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	304.80±49.56	307.49±48.47	304.80±49.22
	After 6 months	222.43±32.58	242.57±32.59	252.57±33.81
	p-value	<0.0001	<0.0001	<0.0001
Triglycerides (mg/dl)	Baseline	291.20±49.47	284.47±48.46	293.20±49.12
	After 6 months	226.16±41.75	244.48±32.58	256.16±46.75
	p-value	<0.0001	<0.0001	<0.0001
HDL (mg/dl)	Baseline	37.42 ± 4.68	36.23 ± 4.46	36.23 ± 4.54
	After 6 months	47.46 ± 5.64	46.49 ± 5.48	45.36 ± 5.68
	p-value	<0.0001	<0.0001	<0.0001
LDL (mg/dl)	Baseline	209.14 ± 35.06	214.79 ± 34.83	189.80 ± 34.86
	After 6 months	129.74 ± 18.59	147.19 ± 20.60	155.98 ± 18.78
	p-value	<0.0001	<0.0001	<0.0001
VLDL (mg/dl)	Baseline	58.24 ± 9.82	56.47 ± 9.69	58.64 ± 9.82
	After 6 months	45.23 ± 8.35	48.89 ± 6.51	51.23 ± 9.35
	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 Therap

Parameters	Group A	Group B	Group C
Total Cholesterol	82.37	64.92	52.23
Triglycerides	65.04	39.99	37.04
HDL	10.04	10.26	9.13
LDL	79.4	67.6	33.82
VLDL	13.01	7.58	7.41

In Group 'A' the mean difference of Total Cholesterol between baseline versus after 6 months was 82.37 mg/dl, 64.92 mg/dl and 52.23 mg/dl in Group B and Group C respectively. The mean difference of Triglycerides between baseline versus after 6 months was 65.04 mg/dl in Group A, 39.99 mg/dl in Group B and

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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 [7]. Importantly, there is strong and convincing evidence that cholesterol lowering therapy significantly reduces CHD in patients both with and without diabetes. [8] There also appears to be no threshold below which a further reduction in low-density lipoprotein (LDL) cholesterol might be beneficial. [9]

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. [10] 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. [11]

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 [12].

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. [14]

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. [15]

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. [16] 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. [17]

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 [18]. 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

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.

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