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TO EVALUATE THE EFFICACY AND SAFETY PROFILE OF ROSUVASTATIN, SIMVASTATIN AND ATORVASTATIN IN NEWLY DIAGNOSED TYPE 2 DIABETIC PATIENTS WITH DYSLIPIDEMIA

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ABSTRACT

Introduction: Diabetes mellitus is an metabolic disorder characterized by hyperglycemia and altered metabolism of lipid, protein and carbohydrate metabolism. **Method:** A total of 60 diagnosed cases of patients of Type II Diabetes Mellitus well controlled on oral hypoglycemic drugs in age group of 30-65 years who have satisfied inclusion and exclusion criteria and have consented to participate in study were enrolled. Each enrolled subjects Type 2 Diabetes Mellitus patients well controlled on oral hypoglycemic drugs. All patients had fasting samples of blood sent for evaluation of lipid profile. They were randomly allocated into 3 groups of 20 each. Group I received Atrovastatin 10 mg O.D. Group II Simvastatin 10 mg O.D. Group III Rosuvastain 10 mg O.D. for 3 months. **Result:** The results of our study are comparable to the Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER). JUPITER Trial provides yet more evidence about the effectiveness of statin therapy in reducing cardiovascular risk, even among persons who would not currently be considered for pharmacotherapy.

KEYWORDS: Diabetes Mellitus, Rosuvastatin, Simvastatin, Atorvastatin, dyslipidemia.

INTRODUCTION

Diabetes Mellitus (DM) is a metabolic disorder of multiple aetiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both.[1] Diabetes mellitus is linked with increased oxidative stress due to hyperglycemia. This damage plays an important role in the long term complications such as microvascular and macrovascular complications. Thus in long term they are responsible for the morbidities such as dyslipidemia, obesity, insulin resistance and hypertension.[2]

The most common pattern of abnormality in patients with type 2 diabetes mellitus is increased triglyceride levels, decreased HDL levels and increased concentration of low density lipoproteins (LDL) particles. These LDL particles have been identified as a major risk factor for CHD by the National Cholesterol Education Programme (NCEP) Adult Treatment panel (ATP) III. The treatment of diabetes requires not only adequate control of blood glucose but also drugs which have a beneficial effect on the dyslipidemia, hypertension, obesity and insulin resistance in the patients with type 2 diabetes mellitus.

Statins are the most powerful drugs for lowering LDL cholesterol. They are considered as the first line of treatment for dyslipidemia. Statins are competitive inhibitors of HMG-CoA reductase, the rate limiting step in cholesterol synthesis. In response to decreased cholesterol production, the number and activity of LDL receptors are up regulated, stimulating removal of circulating LDL. Intermediate density and very low-density lipoprotein (VLDL) are removed as well, contributing to lowering triglyceride-rich lipoprotein levels. Statins also have modest effect on HDL levels. Statins have been shown to reduce total mortality, major coronary events, progression of atherosclerosis.[3] Statins have been to have other benefits other than the effects on the lipid metabolism .these effects include the pleiotropic effects on vascular smooth muscle proliferation, decreasing the fibrinogen levels, decreasing highly sensitive C-Reactive proteins (HSCRP) and also possessing some antioxidant properties.[4] It is seen that Indian population is genetically more prone for atherogenic L.D.L. 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.[5]

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 2diabetes mellitus with dyslipidemia.

MATERIAL AND METHOD

Study Design: Open label, randomized, parallel group, and comparative, prospective study. 60 diagnosed cases of patients of Type II Diabetes Mellitus well controlled on oral hypoglycemic drugs. Informed written consent were obtained from all the patients. They were randomly allocated into 3 groups of 20 each.Group I received Atrovastatin 10 mg O.D. Group II Simvastatin 10 mg O.D. Group III Rosuvastain 10 mg O.D. for 12 weeks.

Dyslipidemia was defined according to our laboratory ranges as.

- Total cholesterol 240 mg/dl, Total triglycerides 200-399 mg/dl, LDL cholesterol 100 -129 mg/dl, HDL cholesterol < 40 mg/dl

Method: Inclusion criteria were 1) male or female patients aged 30 to 65 years with Type-2 Diabetes Mellitus. 2) Type 2 Diabetes Mellitus patients well controlled on oral hypoglycemic drugs. 3) All patients had fasting samples of blood sent for evaluation of lipid profile. Exclusion criteria were 1) A history of: 1) Type 1 diabetes, 2)Clinically significant cardiovascular diseases, including h/o CCF, Angina pectoris within 1 year and h/o MI with in 1 year, 3) Convulsive disorder, 4) Clinically significant G.I disease, including active peptic ulcer with in the preceding 5 years, 5) Renal disease,6) Hepatic disease, hematological disease and insulin dependent diabetes mellitus, 7) Known infection human immunodeficiency virus, 8) Pregnant or lactating female, 9) Smokers, alcoholic patients. Institutional ethical clearance was obtained.

Lipid Profile[6],[7]

Biochemical assays: All biochemical assays were carried out with Automated Random access clinical chemistry analyzer ERBA Chem 7 with ERBA TEST REAGENT (Transasia Bio-medicals Ltd., india).

Blood Sugar[8]

Fasting and Postprandial done on semi auto analyzer by glucose oxidase /peroxidase [GOD / POD] method.

Statistical analysis: Paired T test was used to measure the differences among the group and for the comparison.[version SPSS 17.1]

RESULTS AND DISCUSSION

A total 60 patients that have satisfied the inclusion and exclusion criteria were enrolled and evaluated for 3 months. Patients were randomly divided into three groups of 20 each. Group I Atorvastatin 10 Mg O.D. Group II Simvastatin 10 Mg O. D. Group III Rosuvastatin 10 Mg O.D.

Table No.1: Age and sex wise distribution of the subjects under study.

Age in years	Group 1		Group 2		Group 3	
Gender	M	F	M	F	M	F
30- 40	4	3	3	4	2	2
40-50	7	3	4	4	5	5
50-65	1	2	1	4	3	3
Total	60%	40 %	40%	60%	50%	50%

Table No. 1 shows the age and sex wise distribution of the subjects in all 3 groups under study. All the three groups consisted of 20 subjects each.

Table No.2: Baseline and after 12 weeks value of lipid parameters in all 3 groups

parameter	Group I mean		Group II mean		Group III mean	
Sr. cholesterol	before	301.7 ± 46.30	before	306.4 ± 7.21	before	308.5 ± 62.24
	after	272.9 ± 43.91	after	268.7 ± 47.96	after	242.4 ± 62.52
	t-value	5.205	t-value	90.32	t-value	63.83
	p-value	<0.0001	p-value	<0.0001	p-value	<0.0001
Sr. triglycerides	Before	283.3 ± 45.81	Before	276.1 ± 45.46	Before	287.8 ± 50.57
	after	242.4 ± 47.99	after	233.7 ± 40.18	after	210.9 ± 46.22
	t-value	14.45	t-value	9.498	t-value	15.41
	p-value	<0.0001	p-value	<0.0001	p-value	<0.0001
H.D.L.	before	38.15 ± 4.344	Before	36.80 ± 3.915	Before	37.00 ± 4.437
	after	43.40 ± 4.728	After	40.65 ± 3.392	After	43.05 ± 4.729
	t-value	15.13	t-value	6.725	t-value	24.62
	p-value	<0.0001	p-value	<0.0001	p-value	<0.0001
L.D.L.	Before	204.3 ± 38.89	Before	214.2± 43.07	Before	222.8 ± 64.22
	After	187.3 ± 64.20	After	181.4 ±44.71	After	160.2 ± 59.78
	t-value	1.264	t-value	25.98	t-value	6.800
	p-value	>0.0001	p-value	<0.0001	p-value	<0.0001
V.L.D.L.	Before	59.24 ± 9.387	Before	55.23 ± 9.092	Before	57.17 ± 9.609
	After	49.03 ± 9.122	After	46.64 ± 9.259	After	41.68 ± 8.749
	t-value	7.090	t-value	8.652	t-value	14.92
	p-value	<0.0001	p-value	<0.0001	p-value	<0.0001

(if $p > 0.05$ Not Significant, $p < 0.05$ Significant)

Table No. 2 shows the baseline and after 12 weeks value of lipid parameters and their significance in all 3 groups under study. All the three groups consisted of 20 subjects each.

Table No.3: Overview of the total changes in lipid parameters after the therapy.

Lipid Parameters (mgs %)	Group 1 (in %)	Group 2 (in %)	Group 3 (in %)
Sr. Cholesterol	↓ 9.6 %	↓ 12.4 %	↓ 21.4 %
Sr. Triglycerides	↓ 14.4 %	↓ 15.5 %	↓ 26.7 %
Sr. H.D.L.	↑ 13.8 %	↑ 10.3 %	↑ 16.2 %
Sr. L.D.L.	↓ 8.3 %	↓ 15.4 %	↓ 28.2 %
Sr.V.L.D.L.	↓ 17.2 %	↓ 15.6 %	↓ 27.1 %

DISSCUSSION

Diabetes mellitus induces a state of dyslipidemia with abnormality in all classes of lipids. The importance of lipid disorders in diabetes is due to an increased risk of accelerated atherosclerosis in patients with diabetes. Type 2 diabetes mellitus is emerging as a silent killer. The central pathological mechanism is the process of atherosclerosis, which leads to narrowing of arterial walls throughout the body. There is considerable evidence that the lipid lowering therapy with statins reduces the macrovascular complications as well as micro vascular complications in the patients of type 2 diabetes. 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.[9]

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 12 weeks 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.[10]

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.

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.[11] 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.[12]

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.

In our study we have found that Rosuvastatin decreased the L.D.L. values by 28.2%, Simvastatin decreased the L.D.L. values by 15.4% and atorvastatin decreased the L.D.L. values by 17.2 %. These are inconsistent with the STELLAR TRIAL where Rosuvastatin, Simvastatin, Atorvastatin reduced L.D.L. levels by 45.8%, 28.3 & 36.8% respectively.

CONCLUSION

In summary, after 12 weeks of treatment The advantage of using Rosuvastatin 10 mg OD can be clearly seen in last group as it reduced Sr. Cholesterol, Sr. triglycerides, LDL and VLDL and increased HDL values in group to a great extent. Finally the cost of 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.

The results of our study are comparable to the Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER). JUPITER Trial

provides yet more evidence about the effectiveness of statin therapy in reducing cardiovascular risk, even among persons who would not currently be considered for pharmacotherapy.

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