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# TO COMPARE ROSUVASTATIN WITH ATORVASTATIN IN TERMS OF MEAN CHANGE IN LDL-C IN PATIENT OF DIABETES MELLITUS.

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**ABSTRACT:** Diabetes Mellitus is a very common metabolic disorder characterized by hyperglycemia and altered metabolism of lipids, proteins and carbohydrates due to absolute or relative insulin deficiency or insulin resistance. There is a close association between complications of Diabetes and Diabetic Dyslipidemias. The lowering of LDL levels with statins varies from 20 to 60% and greatest effects are seen with the most potent statins such as Atorvastatin, and Rosuvastatin in higher doses. **Objectives:** The objective of the study was; to compare Rosuvastatin with Atorvastatin in terms of mean change in LDL-C in patients of Diabetes Mellitus. **Study Design:** Randomized Control Trail. **Setting:** Department of Medicine DHQ Hospital, Faisalabad. **Period:** Six months from 01/10/2018 to 31/03/2019. **Material & Methods: Results:** A total of 160 cases (80 in each group) fulfilling the inclusive/exclusive criteria were enrolled to compare Rosuvastatin with Atorvastatin in terms of mean change in LDL-C in patients of Diabetes Mellitus. Mean LDL-C levels at baseline was recorded as159.61+1.22 in Group-A and 159.51+1.21 in Group-B, p value was calculated as 0.603 showing insignificant difference. Mean LDL-C after 6 weeks of treatment was recorded as129.11p+1.50 in Group-A and 129.89+2.23 in Group-B, p value was calculated as 0.01 showing significant difference. Mean change in LDL-C level after 6 weeks of treatment was recorded as 30.5+1.88 in Group-A and 29.63+2.57 in Group-B, p value was calculated as 0.01 showing a significant difference. The data was stratified for Age, Gender, Duration of Diabetes Mellitus and control of Diabetes Mellitus. **Conclusion:** This study proves superiority of Rosuvastain over Atorvastatin in reducing LDL-C level in type 2 DM Patients.

**Key word:** Atorvastatin, Diabetes Mellitus, Hyperglycemia, Insulin Deficiency and Resistance, LDL-C, Rosuvastain.

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## INTRODUCTION

Diabetes, Smoking, Hypertension and Hypercholestremia are well established risk factors for the development of coronary artery disease.[1,2] Hypercholestremia is a major contributor of Cardio Vascular Disease in both developed and developing worlds. In patients with Diabetes lipid abnormalities play an important role in the development of Atherogenesis, therefore lowering serum cholesterol and LDL cholesterol concentration reduces the risk of Cardiovascular events including MI, Stroke, Coronary revascularization and Death.[3,4]

Therapeutic life style adjustment is very helpful in managing familial hypercholestremia.[5] Lifestyle modification includes modification in Diet, exercise, reduction in Alcohol consumption and withdrawal of tobacco products. Regarding pharmacological therapy, statins are the first line drugs in LDL- cholesterol reduction and their clinical use has significantly contributed to the prevention and treatment of Atherosclerosis in Cardiovascular diseases. However different statins have different effect in this regard and their doses also differ to reach same level of LDL-C. In patients of CAD use of synthetic statins such as Rosuvastatin and Atorvastatin is beneficial and they are prescribed commonly. In addition to this they also have other pleotropic effects

such as modification in endothelial funcation, inflammatory response, stability of plague and formation of the thrombus.

Rosuvastatin is an HMGR Antagonist which competes with endogenous substrate for the site of activity of the enzyme. Multiple clinical trials have demonstrated that both Rosuvastatin and Atorvastatin are effective & safe in reducing fatal and non-fatal CV events. Use of Rosuvastatin causes more reduction in LDL-C in Western population; however the response may be different in Asians as compared with Whites due to genetic differences. According to FDA recommendations Asian patients may be started with 5mg daily Rosuvastatin and 10mg daily Atorvastatin.

The STELLAR Trial by Jone PH et al, comparing Rosuvastatin with Atorvastatin, revealed that Rosuvastatin produced significant reduction in LDL-C levels[11] as compared to Atorvastatin. In the LISTEN trial by Arshad et al. 10mg of Atorvastatin was compared with 5mg Rosuvastatin.

The previous comparison between these two statins, in patients of raised LDL, shows 0.54 ± 0.88 reduction in LDL level with atorvastatin as compared to Rosuvastatin which shows 0.96 ± 0.96 reduction in LDL-C.

This study will further explore the reduction in LDL_C and its magnitude, in patients with Hypercholestremia by Rosuvastatin as compared with Atorvastatin, and it will help us in modifying our treatment regimes in such cases so that we may manage these patients more appropriately and cost effectively.

## MATERIAL & METHODS

Study Design it was a Randomized Control trail contucted at Department of Medicine DHQ Hospital, Faisalabad.

Total duration of study was 6 months from 01/10/2018 to 31/03/2019. Each patient was evaluated after 6 weeks of statin therapy.

### Sample Size

By using WHO sample calculator for two means:

- Anticipated population means = 0.54
- Test value of population mean =0.96
- Pooled standard deviation =0.92
- Power of study =80%
- Level of signification =5%
- Sample size =160(80 in each group)

Conservative Non-probability sampleing technique was used.

Inclusion Criteria

Diabetic out patients of either gender between 40 to 80 years of age.

Patients with the history of type 2 DM for two years.

Patients with raised LDL-C at single reading.

Exclusion Criteria

Subjects with significant Liver or Renal impairment.

Subjects with myopathy (pain and weakness of muscles, raised CPK level>200mcg/L).

Permission was taken from ethical committee of hospital before the start of study and informed consent was taken from all the participants of study. Randomization was done by computer generated number table to allocate patients in either Group-A(Rosuvastatin) or Group-B(Atorvastatin).patients were instructed to take study medication at the bed time with a glass of water for up to six weeks. Group A was given 10mg of Rosuvastatin and group B was given 20mg Atorvastatin daily.

Baseline LDL-C level was recorded at the start of the study and patients were advised to take medications for six weeks. After six weeks LDL-C levels were done in hospital lab and verified by pathologist. Patients were followed up by keeping telephonic contact. All data was entered in specially designed Performa by me.

All data was entered and analyzed according to SPSS (Statistical Package for social studies) version12.0.Mean and standard deviation was calculated for age, LDL-C level at baseline

and 6 weeks and change in levels. Frequency and percentages were calculated for gender. Independent test was used to compare mean change in LDL-C between two groups. A p-value of ≤ 0.05 was considered significant. Effect modifiers like Age, Gender, Duration of DM, Type and control of DM was stratified and post stratification t-test was applied.

## RESULTS

A total of 160 cases (80 in each group) fulfilling the Inclusive/Exclusive criteria were enrolled to compare Rosuvastatin with Atorvastatin in terms of mean change in LDL-C in patients of Diabetes Mellitus.

Regarding Age of the patients study shows that 32.5%(n=26) in group A and 35%(n=28) in group B were between 40 to 46 years of age while 67.5%(n=54) in group A and 65%(n=52) in group B was between 61 to 80 years of age mean difference was calculated as 54.3 ±7.54 in group A and 50 3.84±7.3 8 years in group B. (Table-I).

| Age (in years) | Group-A (n=80) | | Group-B (n=80) | |
|---|---|---|---|---|
| | No. of patients | % | No. of patients | % |
| 40-60 | 26 | 32.5 | 28 | 35 |
| 61-80 | 54 | 67.5 | 52 | 65 |
| Total | 80 | 100 | 80 | 100 |
| Mean+SD | 54.32+7.54 | | 53.84+7.38 | |

**Table-I. Age Distribution (N=160).**

According to Gender 57.5 %( n=46) in group A and 52.5%(n=42) in group B were Male while 42.5%(n=34) in group A and 47.5%(n=38) in group B were Female patients. (Table-II).

| Gender | Group-A (n=80) | | Group-B (n=80) | |
|---|---|---|---|---|
| | No. of patients | % | No. of patients | % |
| Male | 46 | 57.5 | 42 | 52.5 |
| Female | 34 | 42.5 | 38 | 47.5 |
| Total | 80 | 100 | 80 | 100 |

**Table-II. Gender Distribution. (N=160).**

Mean LDL-C levels at baseline was recorded as159.61+1.22 in Group-A and 159.51+1.21 in Group-B, p-value was calculated as 0.603 showing insignificant difference. (Table-III).

| LDL-C | Group-A (n=80) | | Group-B (n=80) | |
|---|---|---|---|---|
| | Mean | SD | Mean | SD |
| | 159.61 | 1.22 | 159.51 | 1.21 |

**Table-III. Mean LDL-C levels at baseline. (n=160). P value=0.603**

Mean LDL-C after 6 weeks of treatment was recorded as129.11p+1.50 in Group-A and 129.89+2.23 in Group-B, p value was calculated as 0.01 showing significant difference (Table-IV).

| LDL-C | Group-A (n=80) | | Group-B (n=80) | |
|---|---|---|---|---|
| | Mean | SD | Mean | SD |
| | 129.11 | 1.50 | 129.89 | 2.23 |

**Table-IV. Mean LDL-C levels after 6 weeks of treatment. (n=160). P value: 0.01**

Mean change in LDL-C level after 6 weeks of treatment was recorded as 30.5+1.88 in Group-A and 29.63+2.57 in Group-B, p-value was calculated as 0.01 showing a significant difference. (Table-V).

| LDL-C | Group-A (n=80) | | Group-B (n=80) | |
|---|---|---|---|---|
| | Mean | SD | Mean | SD |
| | 30.5 | 1.88 | 29.63 | 2.57 |

**Table-V. Mean change in LDL-C levels after 6 weeks of treatment. (n=160) P value: 0.01**

The data was stratified for age, gender, duration of diabetes mellitus and control of diabetes mellitus. (Table-VI to IX).

| | Group-A (n=80) | | Group-B (n=80) | |
|---|---|---|---|---|
| | Mean | SD | Mean | SD |
| LDL-C | 40-60 years | | | |
| | 29.56 | 1.27 | 29.97 | 2.34 |
| | 61-80 years | | | |
| | 30.3 | 1.52 | 29.41 | 2.11 |

**Table-VI. Stratification for mean change in LDL-C levels after 6 weeks of treatment with regards to age. (n=160) 40-60 years.**
**P-value: 0.01**

| | Group-A (n=80) | | Group-B (n=80) | |
|---|---|---|---|---|
| | Male | | | |
| LDL-C | Mean | SD | Mean | SD |
| | 28.99 | 1.04 | 29.44 | 2.09 |
| | Female | | | |
| | 29.55 | 1.47 | 30.48 | 2.16 |

**Table-VII. Stratification for mean change in LDL-C levels after 6 weeks of treatment with regards to gender. (n=160).**
**P value: 0.01, P value: 0.00**

| | Group-A (n=80) | | Group-B (n=80) | |
|---|---|---|---|---|
| | Mean | SD | Mean | SD |
| LDL-C | 0-1 Year | | | |
| | 29.41 | 1.19 | 30.51 | 2.14 |
| | 1-2 Year | | | |
| | 29.47 | 1.25 | 29.97 | 2.20 |

**Table-VIII. Stratification for mean change in ldl-c levels after 6 weeks of treatment with regards to duration of diabetes mellitus. (n=160).**
**P value: 0.00, P value: 0.02**

| | Group-A (n=80) | | Group-B (n=80) | |
|---|---|---|---|---|
| | Mean | SD | Mean | SD |
| LDL-C | Controlled | | | |
| | 28.41 | 1.06 | 29.49 | 2.23 |
| | Uncontrolled | | | |
| | 29.55 | 1.47 | 30.48 | 2.16 |

**TABLE-IX. Stratification for mean change in LDL-C levels after 6 weeks of treatment with regards to control of diabetes mellitus(n=160).**
**P value: 0.00, P value: 0.00**

## DISCUSSION

In Diabetes Mellitus relative deficiency, complete absence or resistance of insulin leads to hyperglycemia and certain changes in lipid, protein & carbohydrate metabolism. Due to this Diabetes Mellitus is considered to be a metabolic disorder.[8,12] Complications of Diabetes are closely associated with Dyslipidemias which are responsible for approximately 80% of Diabetic deaths.[13] Dose of different statins for treating dyslipidemias is variable[14,15], and the decrease in LDL-C levels varies between 20% and 60%. It is also suggested that statins such as Rosuvastatin & Atorvastatin are more potent but at high doses.

Evidence is lacking regarding their superiority over each other[16,17], This study was done with the objective that reduction in LDL-C in patients with Hypercholestremia with Rosuvastatin as compared with Atorvastatin may be explored as this may help us in modifying our treatment regimens for reducing the LDL-C.

The previous comparison of Rosuvastatin and Atorvastatin in patients of raised LDL shows 0.54 ± 0.88 reductions in LDL-C level with Atorvastatin as compared to Rosuvastatin which shows 0.96± 0.96 reductions in LDL-C from the base line.[8] These findings support results of our study that Rosuvastatin is more effective in decreasing LDL-C as compare to Atorvastatin. (0.87 with Rosuvastatin as compare to 0.42 with Atorvastatin).

Wolffen buttel BH et all[17] in their study compared the cholesterol lowering effect of, Rosuvastatin with Atorvastatin in type 2 Diabetics. They recorded that base line LDL-C in the RSV and ATV groups was 4.23 +/- 0.98 mmol and 4.43+/-0.99, whilst apoB/apoA1 was 0.86 +/- 0.22 and 0.92 +/-0.35, respectively. A greater reduction in apoB/apoA1 was seen with RSV(-34.9%,-39.2% and -40.5%) than with ATV(-32.4%,-34.7% and -35.8%,P<0.05 at weeks 12,16 and 18).According to American Diabetes Association(ADA) guidelines LDL-C goal of <2.6mmol/l(-1) was reached by 82%,84% and 92% of patients with RSV and 74%,79% and 81% with ATV. Reduction in Triglyceride was comparable in both groups of treatment and ranged between 16-24%.In addition to this both modes of treatment were well tolerated and only 9 and 11 patients respectively stopped treatment

due to side effects. Overall Wolffen buttel BH et al concluded that Rosuvastatin showed more improvement in lipid profile as compare & Atorvastatin.

Another study, URANUS[18] done by Berne A and Siewert-Delle, also compared the same effect of statins on lipid profile in patient with type 2 Diabetes Mellitus and they found that Rosuvastain had greater lowering effect on LDL-C level during fixed dose and titration periods ($p<0.0001$). In their study Berne A and Siewert-Delle demonstrated that more patients, 81% vs 65% ($p<0.001$) at 4 weeks of treatment and 94% vs 88% (p 0.05) at 10 weeks of treatment, achieved their LDL-C goal with Rosuvastatin as compared with Atorvastatin. Furthermore patients receiving Rosuvastatin showed a less dose titration and continued with their starting dose. Considering 2003-European LDL-C goal (2.5 mmol/L) more patients on Rosuvastatin than on Atorvastatin achieved this goal, i.e. 65% vs. 33% ($p<0.0001$).[18]

Moreover both drugs were well tolerated by the patients as there were no significant safety concerns and in view of all these facts was concluded that Rosuvastatin is more effective than Atorvastatin in achieving the LDL-C goal in type 2 Diabetic patients.

Peter H. Jones and others[11] compared Rosuvastain with Atorvastatin, Pravastatin and simvastatin across dose Ranges for reduction of LDL cholesterol and recorded that Rosuvastatin has greater effect in reduction of total cholesterol when compared with other competitors. Also it has more effect in reducing Triglyceride as compared to simvastatin and pravastatin. Besides this HDL-C was increased by 7.7%-9.6% with Rosuvastatin as compared with2.1-6.8% with Atorvastatin. Adult treatment panel 111 LDL cholesterol goals were achieved by 82%to 89% of patients treated with Rosuvastatin 10 to 40 mg compared with 69%to 85% of patients treated with atorvastatin 10 to 80 mg: the European LDL cholesterol goal of less than 3mmol/L was achieved by 79% to 92% in Rosuvastatin groups compared with 52% to 81% in Atorvastatin groups. Drug tolerability was similar across treatments.

In August 2003 the United States food and drug administration FDA approved Rosuvastatin calcium(Crestor; AstraZeneca Pharmaceutical ,Wilmington, DE) as an adjunct to diet in patients with primary Hypercholestremia, Mixed Dyslipidemia or Fredrickson type 4 for hypercholesterolemia. In addition to this Rosuvastatin is also proved for use as an adjunct to other lipids lowering treatments in patients with Homozygous or Heterozygous familial Hypercholesterolemia.

In light of the above discussion and comparison our hypothesis that, Rosuvastatin is better in reducing LDL-C as compared to Atorvastatin in patients of Type 2 Diabetes Mellitus, is justified. Although results of our study are quite clear and substantial helping us in modifying the treatment for reducing the LDL C however more trials are required to further validate these effects.

## CONCLUSION

Our study concludes that Rosuvastatin is significantly more effective in reducing LDL-C in patients of diabetes mellitus.



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## AUTHORSHIP AND CONTRIBUTION DECLARATION

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| 1 | Masood Javed | Study design, Manuscript writing, Integrity of data. | |
| 2 | Dilshad Mohammad | Editing and formatting the manuscript, literature reivew. | |
| 3 | Muzzammal Iftikhar | Interpretation of results, Editing & formatting the manuscirpt. | |
| 4 | Mohsin Jameel | Data collection,Statistical analysis, Literature review. | |
| 5 | Zain Masood | Manuscript drafting, Formulation of tables. | |
| 6 | Nazir Ahmed | Interpretation of results, Literature review. | |