ORIGINAL ARTICLE

EFFICACY OF 5MG AND 10MG ROSUVASTATIN IN TYPE 2 DIABETES MELLITUS WITH HYPERCHOLESTEROALEMIA

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Background: Coronary Heart Disease (CHD) is the most important complication and the leading cause of death in patients with type 2 diabetes mellitus (T2DM). Hypercholesterolemia is an important modifiable risk factor for CHD. Statins are the first line drugs for the treatment of hypercholesterolemia in DM. Comparative studies between different statins are available but different doses of the same statin have not been compared in our population. The objective of this study is to compare mean reduction in serum LDL-C level after using 5mg and 10mg of rosuvastatin among T2DM patients with hypercholesterolemia. This study will help finding lowest effective dose of rosuvastatin to achieve internationally set low density lipoprotein cholesterol (LDL-C) goals. **Methods:** A total of 82 patients with T2DM having fasting LDL-C levels equal or more than 100mg/dl were randomly allocated into two groups with 41 patients in each group. Baseline fasting serum LCL-C levels were obtained in all patients. Group A received 5mg while group B received 10mg of rosuvastatin daily at night. After 6 weeks, fasting LDL-C levels were obtained and analysed to compare the mean±SD reduction of LDL-C levels in both groups. **Results:** Baseline mean± SD LDL-C levels in group A and group B were 134.12±30.02 and 143.49±32.01 respectively (*p* 0.176). Follow up mean±SD LDL-C levels were 81.59±28.47 and 83.24±36.06respectively (p 0.818). Mean±SD reduction in LDL-C levels from baseline levels in group A and group B were 52.51±19.49 and 60.20±24.09 (*p* 0.116**). Conclusion:** Rosuvastatin 5mg is as effective as 10mg in reducing the LDL-C levels in type 2 diabetic patients with hypercholesterolemia.

Keywords: Diabetes Mellitus, hypercholesterolemia, rosuvastatin

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INTRODUCTION

Diabetes Mellitus (DM) is one of the leading causes of morbidity and mortality around the globe and is responsible for 3.8 million deaths per year.[1] Its prevalence has shown an exponential rise worldwide in the last two decades from 30 million cases in 1985 to 177 million in 2000.[2] The estimated numbers of diabetics worldwide in 2010 were 285 million which is projected to increase to 439 million by 2030[3]. The International Diabetes Federation ranks Pakistan 7th in the list of the prevalence of DM.[1]

Diabetes mellitus is associated with 10–30% decrease in life expectancy.[4] Cardiovascular diseases (CVD) are the leading cause of death in patients with T2DM; they suffer from other macrovascular complications and die at earlier ages than non-diabetics.[5] Hypercholesterolemia is a significant risk factor for CVD.[5] T2DM patients have decrease serum levels of high density lipoprotein cholesterol (HDL-C) and elevated serum triglycerides (TGs) levels with variable total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) levels ,but LDL-C particles are smaller, denser, and more atherogenic as a result lipid lowering guidelines are based mainly on plasma LDL-C levels.[5]

A large number of randomized controlled trials have shown that treatment with statins results in significant reduction in CVD related morbidity, mortality and total mortality in patients with DM.[6] In a meta-analysis of 18,686 diabetics who were taking statins it was found that there was 9% and 21% decrease in all-cause mortality and in major vascular events respectively with per mmol/L reduction in LDL-C levels compared with nondiabetics.[7]

Rosuvastatin decrease LDL-C more than any other statin approved for use in human beings. In a study it was found that more T2DM patients achieved their target LDL-C goal when given rosuvastatin compared with other statins ($p<0.05$).[8]

When given at the different doses rosuvastatin results in different mean % reduction in LDL-C levels. In a multicenter study conducted in Pakistan it was found that 5mgs of rosuvastatin when given for 6 weeks resulted in a mean reduction of 78.18±6.14 from baseline LDL-C (pre-treatment Mean 176.35±11.2 to post treatment mean of 98.2±8.95).[9] In another study mean reduction of 58±39 occurred from baseline LDL-C (pre-treatment mean 157±39 to post treatment mean of 99±30.3) with 10mg of rosuvastatin.[10]

It is shown in a study that Asians display higher plasma levels of rosuvastatin in comparison with Whites[11],as a result the Canadian Cardiovascular

Society and the US FDA recommend lower dose ranges of statins in Asian patients[12].

The current study is designed to compare the mean reduction in LDL-C levels using 5 mg and 10 mg rosuvastatin in our local population. As mentioned above, Asians have higher plasma levels of statins then Whites. To date no local study has been carried out comparing these two regimens. The objective of this study is to compare the mean reduction in serum low density lipoprotein-cholesterol level after using 5mg and 10mg of rosuvastatin among patients with T2DM and hypercholesterolemia This study will be first of its kind in our local population and if it shows that the mean reduction in LDL-C from baseline after 6 weeks is more in 5mg group than 10mg, we will share the results of this study and will also suggest the routine use of 5 mg of rosuvastatin in the management of patients with T2DM and hypercholesterolemia. Mean reduction in low density lipoprotein-cholesterol with 5mg of rosuvastatin is more than with 10mg of rosuvastatin for patients with diabetes mellitus and hypercholesterolemia.

MATERIAL AND METHODS

This randomized controlled trial was conducted in the Department of Medicine, Khyber Teaching Hospital Peshawar over a period of 7 months from 15thJanuary 2012 to 15th august 2012 including 82 patients (41 in each group using 78.18+6.14 mg/dl reduction in LDL-C level with 5mg rosuvastatin[9] and 58+39 mg/dl reduction in LDL-C level with 10mg rosuvastatin[10] among patients with DM with hypercholesterolemia, 95% confidence interval and 90% power of the test using non probability consecutive sampling technique.

All patients with T2DM with baseline fasting LDL-C level > 100 mg/dl, more than 35 years of age of either gender were included.

Patients with history of intake of lipid lowering drugs in past 6 month or any type of familial hypercholestrolemia based on family history were excluded. Patients with chronic kidney disease, hypothyroidism and history of alcohol intake were also excluded**.**

The study was conducted after approval from the hospital's ethical and the research committee. All patients with T2DM with baseline fasting serum LDL-C level of ≥100 mg/dl and met the inclusion criteria were included in the study (both OPD and admitted patients). The purpose and benefits of the study were explained to all patients and they were assured that the study was purely done for data publication and research purpose and written informed consent was obtained.

All patients were subjected to detailed history and clinical examinations. All patients were randomly allocated into two groups by lottery method. Patients in group A were given rosuvastatin (5mg/day) and patients in group B received rosuvastatin (10 mg/day).

All patients were followed up after 6 weeks and blood sample for fasting serum LDL-C level was obtained. All the laboratory investigations were performed from the single hospital laboratory under supervision of a single expert pathologist with a minimum of 5 years of experience. All the above mentioned information including name, age, gender and address were recorded in a predesigned *pro forma*. Strict exclusion criteria were followed to control confounding and bias in the study results.

Data were entered and analysed by SPSS version 14. Mean+SD was calculated for numerical variables like age, baseline fasting serum LDL-C and follow up fasting serum LDL-C level. Frequencies and percentages were calculated for categorical variables like gender. The student T test was used to compare the mean reduction of LDL-C in both groups while keeping *p*-value of <0.05 as significant. All results were presented in the form of tables and graphs.

RESULTS

A total of 82 patients with T2DM and LDL-C more than or equal to 100mg/dl were included in the study, 41 each in group A and group B. There were 18 (43.90) male and 23 (56.09%) females in group A while 17 (41.46%) males and 24 (58.53%) females and in group B. Mean±SD age of patients in group A was 55.46±9.76 years while in group B it was 57.46±11.36 years descriptive statistics of the study population are shown in table- while the distribution of age, gender, age groups, baseline line LDC-C levels and distribution of baseline LDL-C levels in both groups are shown in figure 1 and tables 2, 3 respectively. Baseline mean± SD fasting serum LDL-C levels in group A were 134.12±30.03 mg/dl while on follow up these were 81.59±28.47 mg/dl with mean± SD reduction in LDL-C levels from baseline level was 52.51±19.49 mg/dl (p<0.001). Baseline mean±SD fasting serum LDL-C levels in group B were 143.49±32.01 mg/dl while on follow up these were 83.24±36.06 mg/dl with mean±SD reduction in LDL-C levels from baseline levels was 60.20±24.09 mg/dl.(p<0.001).

Mean± SD reduction in fasting serum LDL-C levels from baseline levels in group A was 52.51±19.49 mg/dl while in group B was 60.20±24.09 mg/dl and this difference was statistically insignificant. (p-0.116)

Baseline and follow up mean±SD LDL-C levels and mean±SD reduction from baseline levels in LDL-C levels in both are shown in table 5 and 6 respectively

Table-1: Descriptive statistics of study population (n=82)

Age	56.46±10.57 years (min 35 max 80)		
Gender	**Male** 35 (42.68%)	**Female** 47 (57.31%)	
Age groups	**36–50** 28 (34.10%)	**51–65** 39 (47.56%)	**>65** 15 (18.29%)
Patients in each group	**Group A (5 mgs)** 41	**Group B (10 mgs)** 41	

Table-2: Distribution of age groups in both groups (n=82)

Age group	Treatment Groups of the Patients		Total
	A (n=41)	B (n=41)	
36–50 years	17	11	28
51–65 years	19	20	39
>65 years	5	10	15
Total	41	41	82

Table-3: Distribution of baseline LDL-C levels in both groups (n=82)

Baseline LDL-C levels	**Group A**	**Group B**	**Total**
100–130 mg/dl	22	17	39
131–160 mg/dl	10	9	19
>160 mg/dl	9	15	24
Total	41	41	82

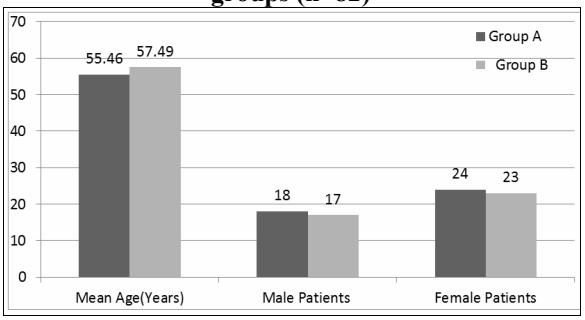
Table-4: Baseline and follow up LDL-C levels in each group (n=82)

	Baseline LDL-C levels	**Follow up LDL-C levels**	**Mean reduction in LDL-C levels**	***p*-valve**
Group A	134.12±30.03	81.59±28.47	52.51±19.49	<0.001
Group B	143.49±32.01	83.24±36.06	60.20±24.09	<0.001

Table-5: Baseline and follow up LDL-C levels in both groups (n=82)

	Group A (n=41)	**Group B (n=41)**	***p*-valve**
Baseline LDL-C levels	134.12±30.03	143.49±32.01	0.176
Follow up LDL-C levels	81.59±28.47	83.24±36.06	0.818
Mean reduction In LDL-C levels	52.51±19.49	60.20±24.09	0.116

Figure-1: Age and gender distribution in both groups (n=82)



DISCUSSION

Coronary heart disease is the most important complication of DM and is the leading cause of death in such patients. Many factors have proven role in predisposing diabetic patients to CAD related mortality. Important among them are uncontrolled hypertension, smoking, male gender, prolonged hyperglycaemia, hyperhomocysteinemia, lack of exercise and moderate alcohol consumption and hypercholesterolemia.

Type 1 diabetic patients usually have hypertriglyceridemia and low HDL-C concentrations while most common lipid abnormalities in T2DM are hypertriglyceridemia, low serum HDL-C concentrations and high serum LDL-C and lipoprotein (a) levels. Lipid lowering guidelines like NCEP ATP III and AHA/ACC are mainly based on plasma LDL-C levels, as LDL-C particles are smaller, denser, and more atherogenic.

Statin therapy has proven efficacy in lowering CHD related mortality and morbidity in patients with DM. Different statins available for clinical used have been shown to be effective in lowering plasma LDL-C levels, like atorvastatin, simvastatin, pravastatin and rosuvastatin.[13]

In this study mean±SD age of patients in group A was 55.46±9.76 years while in group B was 57.46±11.36 years. This is comparable to the prospective study to evaluate the Use of Low doses of the Statins Atorvastatin and Rosuvastatin (PULSAR) study, where the mean±SD age of group received 10 mg/d rosuvastatin was 60.2±10. 4 years. Male patients were 54.2% in the study population who received rosuvastatin 10 mg/d in PULSAR trail, while in this study 42.68% were males in group B.[14]

Mean±SD baseline fasting serum LDL-C in 10mg/d arm of this study was 134.12±30.02 mg/dl**,** while Khan S et al, reported it to be 176.35±11.2 mg/dl.[9] Brown WV *et al*, reported baseline levels of 187.3±17. 8 mg/dl.[15] This difference in baseline mean±SD LCD-C levels can be partially explained by the difference in lifestyles in study populations.

At 6 weeks Khan S, et al reported mean±SD reduction of 78.18±6.14mg/dl.[9] Follow up LDL-C levels were 98.2±8.95 mg/dl with 5 mg/d rosuvastatin while in this study 5mg/d rosuvastatin resulted in statistically significant 52.51±19.49 mg/dl reduction in mean±SD. Follow up fasting plasma levels of LDL-C were 81.59±28.47 mg/dl. Glueck CJ *et al,* reported a statistically significant mean±SD reduction of 75±34 mg/dl from baseline LDL-C level after a mean follow up of 16 weeks in patients who took rosuvastatin 5 mg/d.[16] More significant reduction in plasma LDL-C observed by Glueck CJ *et al,* compared to this study may be explained by the long duration between baseline and follow up, 16 weeks to 6 weeks in this study.

Mean± SD baseline fasting serum LDL-C was 143.49±32.01 in 10mg/d group in this study while *Viigimaa M et al,* reported it to be 124.2±16.7.[17] In CORALL study baseline serum LDL-C levels in 10mg/d arm were 163.6±37.9

mg/dl.[18] In Uranus study baseline levels were 179.9±32.9.[19]

At 12 weeks, DISCOVERY-Beta study reported a mean reduction of 73.5 mg/dl and follow up LDL-C levels were 109.4 mg/dl with 10 mg/d rosuvastatin.[20] In this study 10 mg/d rosuvastatin resulted in mean±SD reduction of 60.20±24.09 mg/dl and follow up levels were 83.24±36.06 mg/dl. In STELLAR Trial mean±SD baseline plasma LDL-C levels were 188±19 mg/dl in 10 mg/d arm of the study while follow up levels were 103.4 mg/dl with 83.5 mg/dl reduction from the baseline.[21]

Lipid lowering efficacy of rosuvastatin has been studied in detail in comparable doses with atorvastatin in CORALL study, URANUS study, PULSAR study and many others.[14,18,19] Rosuvastatin is found to be much more effective than others, resulting in a more effective reduction in mean±SD and per cent in LCL-C levels from baseline and high percentage of patients achieving target LDL-C levels. Rosuvastatin has been shown to be more effective than atorvastatin, simvastatin, and pravastatin across different doses in STELLAR Trial, than simvastatin in DISCOVERY-Beta study, than simvastatin, and atorvastatin in T2DM patients with dyslipidemia by Adsule SM *et al*.[20–22]

In different trails, different doses of rosuvastatin have been compared both with each other and with comparable doses of other statins. In this study 5 mg/d rosuvastatin group had mean±SD fasting serum baseline LDL-C 134.12±30.02 mg/dl and 10mg/d rosuvastatin group had 143.49±32.01 mg/dl (*p* 0.176). Brown WV *et al*, also used 5 mg/d and 10mg/d groups in their study along with simvastatin 20 mg/d and pravastatin 20 mg/d. Baseline mean± SD plasma LDL-C in 5 mg/d group was 187.3±17.8mg/dl, while in 10mg/d it was 187.0±20.4 and no statistical significance was observed in this study.[15] The difference in the baseline fasting plasma LDL-C levels can partially be explained by racial and environmental differences in two study populations. Treatment with rosuvastatin resulted statistically significant mean± SD reduction of 52.51±19.49 mg/dl in group A and 60.20±24.08 mg/dl in group B from baseline in this study, but statistically insignificant mean±SD reduction has occurred between the two groups at 6 weeks. Brown WV *et al,* reported 73.23 mg/dl reduction from baseline in 5 mg/d group and 88.63 mg/dl in 10mg/d group at 12 weeks. Mean±SD reductions in plasma LDL-C levels in both groups are comparatively more than this study. This difference can be explained by follow up duration of 6 weeks in this study versus 12 weeks in a study conducted by Brown *et al*.[15] The mean±SD reduction between rosuvastatin groups was statistically significant when compared to simvastatin 20mg and pravastatin 20mg groups, but the difference between two groups of rosuvastatin was not statistically significant.

Glueck CJ *et al,* found that after treatment with rosuvastatin 5 mg/d for 16 weeks, there was 75±34 mg/dl reduction in mean± SD from baseline in plasma LDL-C. After a follow up of 44 weeks, rosuvastatin 10 mg/d resulted in 79±49 mg/dl reduction in mean±SD from baseline LDL-C levels. No statistically significant difference was found in both groups as in this study

Blood glucose level is a major factor affecting plasma LDL-C as well as other lipoprotein levels in diabetic patients. In this study, glycaemic control before and during the study period was not taken into consideration and this might have affected the results. Secondly, in spite of proper education and reinforcement compliance with drug remained an issue during the study which again might have some impact on the results. Finally, with the limited sample size of 41 patients in each group, the results cannot generalize to the general population.

Rosuvastatin is a comparatively new drug in this class and has been shown to reduce CHD related mortality and morbidity in Type 2 DM in different studies. Doses from 5mg/d to 40mg/d have been studied in different populations. Asian population exhibit higher plasma level of rosuvastatin and it has shown that lower doses of this drug can be used effectively in Asian populations.

CONCLUSION

Coronary Heart Disease is one of the most important complications and the leading cause of death in patients with T2DM. Diabetic patients die at early age compared to non-diabetic patients mainly due to different complications associated with DM. Hypercholesterolemia is an important modifiable risk factor for CHD. Treatment with statin drug class has shown to reduce CHD related mortality in T2DM.

In this study 5 mg/d of rosuvastatin reduced LDL-C levels as effectively as 10mg/d, which suggest that in our local populations, 5 mg/d of rosuvastatin can be used instead of 10 mg/d. This will improve the compliance as lower dose will be cost effective and associated with fewer side effects. However, studies enrolling greater numbers of subjects confirming the same results should be conducted to help establish these findings further.

AUTHOR'S CONTRIBUTION

FU: Design and concept of study, contributed in data collection, writing results, introduction, data analysis and abstract writing, EAK: Contributed in main conception of study, contributed in writing introduction, discussion and data collection, FR:

Contributed in study design, data collection, references writing, SR: Final review and contributed in writing conclusion, MA: Contributed in formatting study design, data analysis, writing introduction.

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