Effects of atorvastatin and rosuvastatin on high-sensitivity C-reactive protein and lipid profile in obese type 2 diabetes mellitus patients

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ABSTRACT

Objective: To evaluate and compare the effects on high-sensitivity C-reactive protein (hs-CRP) levels and lipid profile of atorvastatin and rosuvastatin in obese type 2 diabetes mellitus (T2DM) patients. **Materials and Methods:** A total of 40 subjects with 20 in each group were randomly allocated to two groups. Group 1 patients received atorvastatin and that of Group 2 rosuvastatin treatment for 6 months. The patients were administered atorvastatin (40-80 mg) and rosuvastatin(10-40 mg) in accordance to their LDL-C status as per NCEP-ATP III guidelines. The parameters studied were, hs-CRP and lipid profile comprising LDL-C, HDL-C, TG and TC. **Results:** Results obtained from the study, clearly indicate that atorvastatin (A) as well as rosuvastatin(R) have significant effect on lowering of hs-CRP levels (for A P=0.001; for R P=0.002), reducing LDL-C levels (for A P=0.008; for R P=0.001), elevating HDL-C levels (for A P=0.02; for R P=0.001) along with reducing TC (for A P=0.003; for R P=0.002) and TG (for A P=0.000; for R P=0.000) levels in obese T2DM patients. It is also seen that there is no significant (P>0.05) difference in effect of atorvastatin and rosuvastatin in lowering of hs-CRP levels, elevating HDL-C levels and reducing TG levels in obese T2DM patients. However, percentage lowering of LDL-C (P=0.000) and TC (P=0.001) by rosuvastatin is to a greater extent than that caused by atorvastatin in these patients. **Conclusions:** Thus this study throws light on the fact that rosuvastatin should be preferred over atorvastatin in obese T2DM patients in whom LDL-C and TC levels are deviated from normal reference values. In rest of obese T2DM either of atorvastatin or rosuvastatin can be employed to lower hs-CRP levels, to elevate HDL-C levels or to reduce TG levels.

Key words: Diabetes mellitus, hs-CRP, obese, statins

INTRODUCTION

The diabetes prevalence for 2010 has risen to 285 million, representing 6.6% of the world's adult population, with a prediction that by 2030 the number of people with diabetes will have risen to 438 million.[1] Increasing numbers of patients with diabetic complications will impose an enormous burden on the healthcare system.[2,3] It is characterised by clustered metabolic abnormalities including hyperglycemia, elevated triglycerides (TG) and total cholesterol (TC), low high-density lipoprotein cholesterol (HDL-C) and central obesity.[4] Cardiovascular diseases (CVD), account for the majority of deaths in these patients. Low-grade inflammation has a pivotal role in atherosclerosis, an important risk factor for CVDs. The inflammatory marker high-sensitivity C-reactive protein (hs-CRP) has emerged as a strong predictor for cardiovascular events.[5] Elevated baseline concentrations of hs-CRP are

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associated with the risk of atherosclerotic events and show a predictive value in terms of secondary prevention of CVD.

The global epidemic of DM is in large part due to obesity and sedentary lifestyle. Serum hs-CRP levels have also been correlated positively with adipocyte size[6] as well as body mass index (BMI).[7]

By previous studies[8-11] statins, the most widely used drugs for the lipid management have also been found to cause significant reduction in CRP concentrations, unrelated to the magnitude of low-density lipoprotein cholesterol (LDL-C) reduction.

Keeping these points in mind along with the facts that obesity is strongly associated with elevated plasma lipid levels and that actually 60-90% of cases of type 2 DM (T2DM) now appear to be related to obesity, it was thought worthwhile to evaluate and compare the effects on hs-CRP levels and lipid profile of various statins in obese T2DM patients.

According to the studies done previously[12-14] atorvastatin and rosuvastatin are two potent statins which can efficiently lower hs-CRP levels. So, in the present study effects of atorvastatin and rosuvastatin were evaluated and compared on the basis of the effects on hs-CRP levels and lipid profile in obese T2DM patients. Such study is hoped to be useful in choosing a statin out of plethora of statins available, suitable for lowering risk of atherosclerosis and hence chances of CVD specifically in obese T2DM patients. To best of our knowledge, no other study has been taken up as yet so as to evaluate and compare effects on hs-CRP levels and lipid profile of atorvastatin and rosuvastatin in obese T2DM patients.

MATERIALS AND METHODS

The present study was planned as prospective randomized open-labelled, parallel group, comparative study of 6-months duration held from August 2010 to February 2011. Study subjects were allocated randomly to two groups as follows:

Group 1: Obese T2DM patients administered atorvastatin (40-80 mg) in accordance to their LDL-C status as per NCEP-ATP III guidelines.

Group 2: Obese T2DM patients administered rosuvastatin (10-40 mg) in accordance to their LDL-C status as per NCEP-ATP III guidelines.

A total of 40 subjects with 20 in each group were enrolled. Inclusion and exclusion criteria, treatment allocation and follow-up of patients in the study are shown in Figure 1. The study subjects were randomized into respective groups by block permuted randomization. Approval of the Institutional

Ethics Committee was taken prior to the start of the study. Forty patients were enrolled in the study after satisfying the inclusion and exclusion criteria. Included patients were explained in detail about the study protocol and related hazards. Informed written consent was obtained from all the patients.

Lipid profile was measured using standard methods. Serum hs-CRP levels were measured by ELISA using commercial kit (Accu-Bind Elisa Microwells, Monobind Inc., USA). Lipid profile comprised of LDL-C, HDL-C, TG and TC.

Each patient in the respective group was provided with the drug supplies for 15 days and was asked to visit the diabetic clinic for follow-up and for collection of drugs. As suggested by previous studies,[15] pill-count method was utilised to measure medication adherence by patient. Pill counts were calculated as the number of pills taken (the number of pills dispensed – the number of pills counted). The number of pills expected to have been taken was calculated by multiplying the daily dose (1/2, 1 or 2 tablets) by the number of days since the date dispensed. Pill count was 85–100% for all patients in our study. So, in accordance with previous studies[16] there was successful adherence of the medication. At each follow-up visit, patients were also assessed for glycemic control, and history pertaining to adverse drug effects was asked. All patients were given advice about diet and exercise.

Statistical methods

Sample size was calculated taking into consideration the mean values and standard deviation from study done by Lam *et al.*[17] Power of study = 80%, $\alpha = 0.05$ and $\beta = 0.20$. The data obtained at day 0 and after 6 months were entered into Case Record form and analyzed statistically. To analyze the results, paired *t*-test was used to assess within–subjects change across all study variables. Independent samples *t*-test was employed for analyzing inter-group variation across all study variables. Normal distribution of data was checked before applying statistical tests. Skewness and Kurtosis values were found to be between −2 and +2. All statistical analysis was done using SPSS 17.0 software. *P*-value <0.05 was taken as significant.

RESULTS

All variables in the study were equally distributed (*P*>0.05) in both groups before starting drug treatment. During the study no adverse drug reaction was encountered in any of the study subjects. In group 1 and in group 2, two and three patients were lost to follow-up, respectively. The results obtained following analysis are shown in Tables 1 and 2.

On statistically analyzing the tables, it is clearly indicated that atorvastatin (A) as well as rosuvastatin (R) have significant effect on lowering of hs-CRP levels (for A *P*=0.001; for R *P*=0.002),
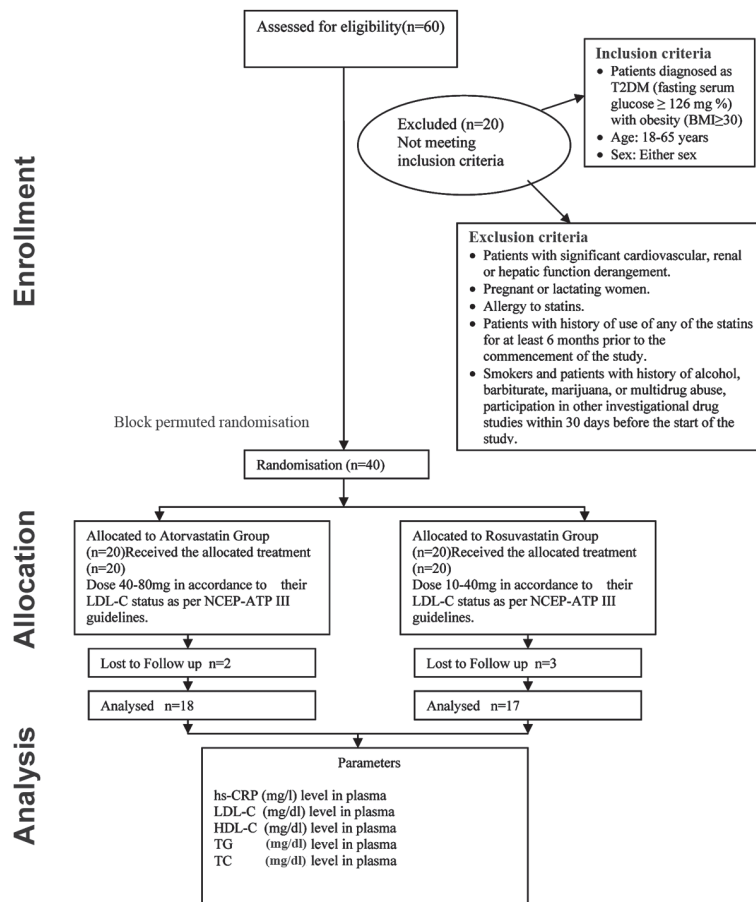
Figure 1: CONSORT statement of the study (Prospective randomized open-labeled parallel study)

Table 1: Baseline characteristics of patients in the atorvastatin and rosuvastatin groups

	Atorvastatin (*n*=20)	Rosuvastatin (*n*=20)
Age (yrs)	49 ± 8.99	49.1 ± 6.82
BMI, kg/m^2	32.15 ± 1.40	32.1 ± 1.72
Female, number (%)	7	7
Plasma glucose, mg%	183.3 ± 31.42	181.6 ± 52.6
hs-CRP (mg/l)	1.85 ± 0.48	1.75 ± 0.49
LDL-C (mg/dl)	94.68 ± 19.56	84.33 ± 29.30
HDL-C (mg/dl)	49.17 ± 9.8	51.77 ± 9.41
TG (mg/dl)	180.20 ± 62.92	183.12 ± 51.07
TC (mg/dl)	208.61 ± 52.18	179.95 ± 60.95

Data are given as means ± SD, or frequency, as appropriate. There were no significant differences between atorvastatin and rosuvastatin groups

reducing LDL-C levels (for A *P*=0.008; for R *P*=0.001), elevating HDL-C levels (for A *P*=0.02; for R *P*=0.001) along with reducing TC (for A *P*=0.003; for R *P*=0.002) and TG (for A *P*=0.000; for R *P*=0.000) levels in obese T2DM patients. It is also seen that there is no significant (*P*>0.05) difference in effect of atorvastatin and rosuvastatin in lowering of hs-CRP levels, elevating HDL-C levels and reducing TG levels in obese T2DM patients. However, percentage lowering of LDL-C (*P*=0.000 confidence interval 6.75-19.44) and TC (*P*=0.001 confidence

interval 7.07 to 24.42) by rosuvastatin is to a greater extent than that caused by atorvastatin in obese T2DM patients.

DISCUSSION

In the present study, the study subjects were obese type 2 diabetic patients. The criteria for evaluation were serum hs-CRP levels and lipid profile parameters, namely, LDL-C, HDL-C, TG and TC. The present study shows that both atorvastatin and rosuvastatin have significant effect on lowering of hs-CRP levels, reducing LDL-C levels, elevating HDL-C levels along with reducing TC and TG levels in obese T2DM patients.

Further both these agents are equally effective in lowering of hs-CRP levels, elevating HDL-C levels and reducing TG levels in obese T2DM patients. However, rosuvastatin lowers LDL-C and TC levels to a greater extent than atorvastatin in these patients. Atorvastatin reduced LDL-C levels from 163.98 ± 25.88 to 91.05 ± 19.39 whereas rosuvastatin reduced LDL-C from 173.72 ± 27.80 to 74.66 ± 18.48. Similarly, atorvastatin lowered TC from 243.56 ± 45.15 to 194.77 ± 40.80 and rosuvastatin lowered TC from 245.93 ± 48.15 to 158.40 ± 40.80.

Table 2: Analysis of effects of atorvastatin and rosuvastatin on hs-CRP and lipid profile

Biochemical parameters	Atorvastatin			Rosuvastatin			Confidence limits for the difference between % change
	Baseline Mean ± S.D.	After treatment Mean ± S.D.	% Change ± S.D.	Baseline Mean ± S.D.	After treatment Mean ± S.D.	% Change ± S.D.	
hs-CRP	2.78 ± 0.55	1.80 ± 0.52*	35.36 ± 13.79	2.89 ± 0.66	1.69 ± 0.43*	41 ± 10.43	–3.39, 14.67
LDL-C	163.98 ± 25.88	91.05 ± 19.39*	44.12 ± 10.13	173.72 ± 27.80	74.66 ± 18.48*	57.22 ± 6.66†	6.75, 19.44
HDL-C	42.73 ± 7.95	51.92 ± 9.10*	23.18 ± 21.92	44.11 ± 8.31	52.23 ± 8.88*	19.42 ± 13.62	–9.75, 17.29
TG	173.16 ± 52.0	162.00 ± 55.26*	7.99 ± 7.6	182.07 ± 38.33	164.16 ± 32.36*	9.26 ± 7.58	–4.31, 6.85
TC	243.56 ± 45.15	194.77 ± 40.80*	19.84 ± 12.98	245.93 ± 45.15	158.40 ± 40.80*	35.58 ± 10.38†	7.07, 24.42

hs-CRP: High-sensitivity C-reactive protein; LDL-C: Low density lipoprotein cholesterol; HDL-C: High density lipoprotein cholesterol, TG: Total triglycerides; TC: Total cholesterol. *$P<0.05$ significantly different when compared to respective baseline values, †$P<0.05$ significantly different when compared to %change induced by atorvastatin

The results of this study are similar to other studies where in patients with T2 DM, statin therapy has been shown to significantly reduce LDL -C, reduce elevated triglycerides, and modestly increase HDL cholesterol.[18,19-22]

Similar to present study, in the Use of Rosuvastatin Versus Atorvastatin in T2DM study, rosuvastatin reduced lipid and lipoprotein fractions compared with atorvastatin during, including LDL -C, non-HDL cholesterol, and apolipoprotein (apo) B to a significantly ($P<0.0001$) greater extent.[21]

Both rosuvastatin and atorvastatin significantly reduced LDL-C, non-HDL cholesterol, and the apoB/apoA1 ratio (all, $P<0.001$ vs. placebo) in the compare rosuvastatin with atorvastatin on ApoB/ApoA1 Ratio in Patients with T2DM and dyslipidemia study.[22]

Differing from interpretation of present study, a study carried out in T2DM patients with dyslipidemia had shown that atorvastatin and rosuvastatin are equally effective in reducing LDL-C levels along with reducing TC and TG levels but rosuvastatin elevated HDL-cholesterol levels more significantly.[23]

In general, LDL cholesterol levels in people with diabetes are not higher than those in people without diabetes who are matched for age, sex and body weight.[24] In fact, the most common LDL cholesterol level in diabetes is "borderline high" (130-159 mg/dl).[24] Moreover, high LDL cholesterol levels (≥160 mg/dl) do not occur at higher-than-average rates in people with diabetes. Nonetheless, LDL cholesterol does not play less of a role in cardiovascular risk in people with T2DM. In fact, LDL cholesterol levels may underestimate cardiovascular risk in diabetes.[25] Small, dense LDL particles are considered more atherogenic than the larger, buoyant LDL particles because they are more readily oxidized and glycated, which make them more likely to invade the arterial wall.[26,27] This can initiate atherosclerosis or lead to increased migration and apoptosis of vascular smooth muscle cells in existing atherosclerotic lesions.[26,27] As a consequence, elevated or "normal" LDL cholesterol may be more pathogenic in people with diabetes. The strong association between increased small, dense LDL particles and elevated triglycerides, for example,

appears to be linked to the altered insulin sensitivity common in the metabolic syndrome and T2DM.[28,29]

Limitation of study

This study was carried with the aim to evaluate effects of two commonly used statins, namely atorvastatin and rosuvaststin, on hs-CRP and lipid profile in obese T2DM. Such study is expected to guide physicians to choose a statin from plethora of statins available which can prevent or cure atherosclerosis and thus CVDs in T2DM patients particularly in those who are obese. The present study gives results of only 6-month treatment and that too only of two statins. Further, only surrogate markers have been studied. Hence, studies of longer duration and involving study of greater number of statins and those involving primary end points like prevention of CVDs as well as secondary end points like prevention of atherosclerosis need to done to strengthen clinical implications of the present study.

CONCLUSIONS

This study throws light on the fact that rosuvastatin should be preferred over atorvastatin in obese type 2 diabetic patients in whom LDL-C and TC levels are deviated from normal reference values. In rest of obese T2DM either of atorvastatin or rosuvastatin can be employed to lower hs-CRP levels, to elevate HDL-C levels or to reduce TG and TC levels. More elaborate research is required to study the pathophysiology in obese T2DM patients along with attempt to understand the pharmacological aspect of statin therapy in such patients.

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