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
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 \(P=0.002\),...
Table 1: Baseline characteristics of patients in the atorvastatin and rosuvastatin groups

| Parameters       | Atorvastatin (n=20) | Rosuvastatin (n=20) |
|------------------|---------------------|---------------------|
| Age (yrs)        | 49 ± 8.99           | 49.1 ± 6.82         |
| BMI, kg/m²       | 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.
The results of this study are similar to other studies where
in patients with T2DM, 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]

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

| Biochemical parameters | Baseline Mean ± S.D. | After treatment Mean ± S.D. | Change ± S.D. | Baseline Mean ± S.D. | After treatment Mean ± S.D. | Change ± S.D. | Confidence limits for the difference between % change % |
|------------------------|----------------------|-----------------------------|--------------|----------------------|-----------------------------|--------------|---------------------------------|
| 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       | 74.68 ± 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.

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 rosuvastatin,
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
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.

REFERENCES
1. International diabetes federation. Available from: http://www.idf.org. [Last
   assessed on 2011 May 20].
2. Alberti G, Zimmet P, Shaw J, Bloomgarden Z, Kaufman F, Silink M. Type 2
diabetes in the young: The evolving epidemic: The international diabetes
federation consensus workshop. Diabetes Care 2004;27:1798-811.
3. Booth FW, Chakravarthy MV, Gordon SE, Spangenburg EE. Waging
   war on physical inactivity: Using modern molecular ammunition against an
   ancient enemy. J Appl Physiol 2002;93:3-30.
4. Belalcazar LM, Reboussin DM, Haffner SM, Hoogeveen RC, Krisa AM,
   Schwenke DC, et al. A One-Year Lifestyle Intervention for Weight Loss in
Persons with Type 2 Diabetes Reduces High C-Reactive Protein Levels and Identifies Metabolic Predictors of Change, from the Look AHEAD Action for Health in Diabetes Study. Diabetes Care 2010;33:2297-303.

5. Ridker PM, Rifai N, Bose L, Burning JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med 2002;347:1557-65.

6. Bahceci M, Gokalp D, Bahceci S, Tuzcu A, Atmaca S, Arikan S. The correlation between adiposity and adiponectin, tumor necrosis factor alpha, interleukin-6 and high sensitivity C-reactive protein levels. Is adipocyte size associated with inflammation in adults? J Endocrinol Invest 2007;30:210-4.

7. Lajunen T, Vikman S, Ploiju A, Ilonen T, Le pantalo M, Pussinen PJ, et al. Chlamydial LPS and high sensitivity CRP levels in serum are associated with an elevated body mass index in patients with cardiovascular disease. Innate Immun 2008;14:375-82.

8. Ridker PM, Rifai N, Cellafield M, Downs JR, Weiss SE, Miles JS, et al. Air Force/Texas Coronary Atherosclerosis Prevention Study Investigators. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. N Engl J Med 2001;344:1939-65.

9. Ridker PM, Rifai N, Pfeffer MA. Inflammation, pravastatin, and the prediction of first cardiovascular events. N Engl J Med 2002;347:1557-65.

10. Ridker PM, Morrow DA, Rose LM, Rifai N, Cannon CP, Braunwald E. Long-term effects of pravastatin and atorvastatin in patients at high risk of cardiovascular disease. Circulation 2005;112:2739-46.

11. Woffenden BH, Franken AA, Vincent HH; Dutch CORALL Study Group. Primary Prevention of cardiovascular disease with atorvastatin in patients with type 2 diabetes: Results from the URANUS study. Cardiovasc Diabetol 2005;4:7.

12. Wolffenbuttel BH, Franken AA, Vincent HH; Dutch CORALL Study Group. Cholesterol-lowering effects of rosuvastatin compared with atorvastatin in patients with type 2 diabetes: CORALL study. J Intern Med 2005;257:331-9.

13. Adsule SM, Baig MS, Gade PR, Khandelwal PN. A comparative evaluation of safety and efficacy of rosuvastatin, simvastatin, and atorvastatin in patients of type 2 diabetes with dyslipidemia. Int J Diabetes Dev Ctries 2009;29:74-9.

14. The Expert Panel. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III): Final report. Circulation 2002;106:3143-421.

15. Buse JB, Ginsberg HN, Bakris GL, Clark NG, Costa F, Eckel R. Primary prevention of cardiovascular diseases in people with diabetes mellitus. Diabetes Care 2007;30:162-72.

16. Krentz AJ. Lipoprotein abnormalities and their consequences for patients with type 2 diabetes. Diabetes Obes Metab 2003;5 (Suppl 1): S19-27.

17. Goldberg IJ. Diabetic dyslipidemia: Causes and consequences. J Clin Endocrinol Metab 2001;86:965-71.

18. Kruger KP, Felkey BG, Berger BA. Improving adherence and persistence: A review and assessment of interventions and description of steps toward a national adherence initiative. J Am Pharm Assoc (Wash DC) 2003;43:683-690.

19. Lam HC, Chu CH, Wei MC, Keng HM, Lu CC, Sun CC, et al. The effects of different doses of Atorvastatin on plasma endothelin-1 levels in type 2 diabetic patients with dyslipidemia. Exp Biol Med 2006;231:1010-5.

20. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Niel HA, Livingstone SJ, et al. and CARDS investigators. Primary Prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetic Study (CARDS): Multicentre randomized placebo-controlled trial. Lancet 2004;364:685-96.

21. Ridker PM, Rifai N, Bose L, Burning JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med 2002;347:1557-65.

22. Bahceci M, Gokalp D, Bahceci S, Tuzcu A, Atmaca S, Arikan S. The correlation between adiposity and adiponectin, tumor necrosis factor alpha, interleukin-6 and high sensitivity C-reactive protein levels. Is adipocyte size associated with inflammation in adults? J Endocrinol Invest 2007;30:210-4.

23. Lajunen T, Vikman S, Ploiju A, Ilonen T, Le pantalo M, Pussinen PJ, et al. Chlamydial LPS and high sensitivity CRP levels in serum are associated with an elevated body mass index in patients with cardiovascular disease. Innate Immun 2008;14:375-82.