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Study on Lipid Abnormalities with High-Sensitivity C – reactive Protein (hs-CRP) in Patients Treated with Atorvastatin: A Teaching Hospital Based Study.

Atchuta Chytanya Paka[1], Kamal Rajesh Jampana[2]

[1]Assistant Professor, Department of General Medicine, NRI Academy of Sciences, Mangalagiri Road, Chinakakani, Guntur, Andhra Pradesh-522503.

[2]Associate Professor, Department of General Medicine, Nimra Institute of Medical Sciences, Nimra Nagar, Ibrahimpatnam, Jupudi, Vijayawada, Andhra Pradesh-521456.

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ABSTRACT

Background: The number of cases of cardiovascular disease, the leading causes of death at any age group in the world, is rising rapidly now-a-days. Disorder in lipid metabolism is one of the main determinants of cardiovascular risk. The primary target of lipid management is to achieve low-density lipoprotein cholesterol at goal. **Methods:** The study included total 70 cases, among which 40 were males and 30, were females. Sample size calculation was done according to the standard methods available. **Results:** On statistically analyzing the data, it is clearly indicated that atorvastatin has a significant effect on the lowering of hs-CRP levels (p=0.01), reducing LDL-C levels (p=0.006), elevating HDL-C levels (p=0.03) along with reducing TC (p=0.002) and TG (p=0.004) levels in obese T2DM patients. **Conclusion:** Treatment with Atorvastatin leads to a significant reduction in plasma Total cholesterol, LDL cholesterol and Triglyceride levels, lowering of plasma CRP and an improvement in endothelial dysfunction.

Keywords: Dyslipidemia, hs-CRP and Atorvastatin.

INTRODUCTION

The number of cases of cardiovascular disease, the leading causes of death at any age group in the world, is rising rapidly now-a-days.[1] Disorder in lipid metabolism is one of the main determinants of cardiovascular risk. The primary target of lipid management is to achieve low-density lipoprotein cholesterol at goal.[2] Statin therapy lowers the risk of cardiovascular events by reducing plasma cholesterol levels, and practice guidelines for patients with known cardiovascular disease emphasize the importance of reaching target goals for low density lipoprotein cholesterol.[3] For the management of dyslipidemia, statins or fibrates are commonly used. Statins (HMG~CoAreductase inhibitors) reduce cardiovascular diseases risk by approximately 23% per every 1 mmol/l (~39 mg/dl) of low-density lipoprotein cholesterol reduction.[4] Atorvastatin, at doses ranging from 2.5 mg to 80 mg daily, can reduce low-density lipoprotein cholesterol by 25% with the lowest dose and up to 60% with the maximal dose.[5] Beside lipid parameters, high sensitivity C-reactive protein– an inflammatory cytokine and an independent predictor of cardiovascular disease,[6-11] is claimed to be reduced by treatment with statins.[12-17] The US Food and Drug Administration approved a new use for statin therapy among those with elevated hs-CRP and one additional risk factor, and the Canadian Cardiovascular Society recently issued new national guidelines indicating that statin therapy should be offered to those at "intermediate risk" who have elevated levels of hs-CRP, even if low-density lipoprotein cholesterol levels are low.[18] Even though benefit of statins on cardiovascular disease risk has been proven, patients with dyslipidemia remains at high risk for cardiovascular events even after low-density lipoprotein cholesterol, blood pressure and HbA1c targets have been achieved.[19] Hence, this study has been undertaken to evaluate and compare the effects on high-sensitivity C-reactive protein (hs-CRP) levels and lipid profile in Patients Treated with Atorvastatin.

Name & Address of Corresponding Author
Dr. Kamal Rajesh Jampana,
Associate Professor,
Department of General Medicine,
Nimra Institute of Medical Sciences, Nimra Nagar,
Ibrahimpatnam,
Jupudi, Vijayawada, Andhra Pradesh-521456.

MATERIALS AND METHODS

This study was conducted in the Department of Medicine, Nimra Institute of Medical Sciences in

collaboration with the Department of Biochemistry, during the period of six months i.e., from September 2017 to March 2018. The study included total 70 cases, among which 40 were males and 30 were females. A Pilot study was conducted before starting the current study. Sample size calculation was done according to the standard methods available. Statistical analysis was done using SPSS18 software.

Inclusion criteria

Patients with Newly diagnosed dyslipidemia, not taking any medications which can alter the lipid profile (neither hypolipidemic drugs nor any other drugs like thiazide diuretics, glucocorticoids etc.) were included in the study.

Exclusion criteria

Patients with infection, stroke, myocardial infarction, major surgery, mal-absorption, severe allergy, cancer, severe illness, liver dysfunction, chronic kidney disease (CKD), pregnancy, edema, oral contraceptive users and steroid or Non-steroidal anti-inflammatory drugs (NSAID) users were excluded from the study.

Clinical measurements

Blood samples were obtained in the morning after an overnight fasting period, with the subject sitting comfortably in a chair, in a quiet room. The blood samples were drawn from the antecubital vein, and were transfused into vacuum tubes containing EDTA. After separation, blood samples were centrifuged for 10 minutes at 2500 rpm to obtain serum. Then serum was aliquoted into 2 microtubes, one preserved for lipid profile measurements and another was preserved at -200C for hs-CRP estimation until analysis.

Parameters to be measured

1. Total Cholesterol (TC) by enzymatic end point CHOD-POD methods.
2. Triglyceride (TG) by enzymatic glycerol phosphate oxidase/peroxidase methods.
3. HDL-Cholesterol by direct enzymatic end point method.
4. LDL-Cholesterol by Friedewald's formula.
   LDL cholesterol (mg/dL) = Total cholesterol – HDL cholesterol – (TG/5)
5. hs-CRP by sandwich ELISA technique using hs-CRP kit.

RESULTS

A total of 70 newly diagnosed dyslipidemic subjects were included in this study to explore residual lipid abnormalities and subclinical inflammation on statin therapy. All the subjects were treated with statin (Atrovastatin, 10 mg per day). Baseline clinical characteristics of the study subjects are shown in [Table1]. Dyslipidemia is a prominent risk factor among the traditional biochemical risk factors of CVDs. Elevated TG, total cholesterol, and LDL cholesterol as well as decreased HDL cholesterol has been implicated with a variably increased risk of CVDs both in cross-sectional and prospective studies.[20-22] The nature and extent of dyslipidemia, however, may vary depending on the ethnic, cultural and environmental background of a particular population. For the management of lipid abnormalities, statins and fibrates are commonly used in our population. Some studies have identified residual CVD risk on therapy in different population;[23] No study has yet been carried out to explore the prevalence of lipid abnormalities on stable statin therapy in this population. In the present teaching hospital based study on south Indian population, 70 statin treated subjects were included. Among the study subjects most of them (82.8%) were diabetic, 73% were hypertensive, 23 % were obese and 14% had a habit of smoking [Table1].

Table 1: Baseline clinical characteristics of study subjects

Parameters	Mean ± SD / Number
Age in years	52 ± 10.1
Male : Female ratio	1.33
Body mass index (Kg/m2)	26.7 ± 4.1
Hypertension (%)	51 (73%)
Systolic blood pressure (mm Hg)	126 ± 12
Diastolic blood pressure (mm Hg)	82 ± 7.1
Diabetes mellitus (%)	58 (82.8%)
Smoking (%)	10 (14.3%)

On statistically analyzing[Table 2], it is clearly indicated that atorvastatin has a significant effect on the lowering of hs-CRP levels (p=0.01), reducing LDL-C levels (p=0.006), elevating HDL-C levels (p=0.03) along with reducing TC (p=0.002) and TG (p=0.004) levels in obese T2DM patients.

Table 2: Effects of Atorvastatin on hs-CRP and lipid profile

Biochemical Parameters	Baseline (Mean ± S D)	Atorvastatin after treatment (Mean ± S D)
Total cholesterol	246.52 ± 44.12	192.74 ± 16.71
Triglycerides	174.22 ± 51.02	162.0 ± 54.36
HDL-c	41.7 ± 7.94	51.86 ± 9.12
LDL-c	164.86 ± 24.8	90.15 ± 18.37
hs-CRP	2.78 ± 0.5	1.76 ± 0.53

(Statistically Significant at p value <0.05) *NS: Statistically not Significant

This study showed a strong and significant positive correlation between the serum hs-CRP levels and total serum cholesterol (p<0.002, r=0.36) and significant positive correlation of triglycerides with hs-CRP (p=0.000, r=0.42). A statistically non-significant and weak negative correlation is seen between the serum hs-CRP levels and HDL-C (p=0.32, r= -0.12). On the other hand, LDL-C showed a statistically significant positive correlation with serum hs-CRP level (p=0.01, r=0.29).

Table 3: Correlation between lipid abnormalities with hs-CRP with the in dyslipidemic patients

Parameters	Correlation coefficient (r)	p-value
TC	0.36	0.002
TG	0.42	0.000
HDL-c	-0.12	0.32*
LDL-c	0.29	0.01

*Statistically significant (p<0.05); *NS: Statistically not Significant

Several mechanisms by which statins improve endothelial dysfunction have been investigated, and it has been shown that statins have pleiotropic properties that complement their cholesterol-lowering effects.[24] One of these pleiotropic properties is the anti-inflammatory effect of statins. Atorvastatin has a direct anti-inflammatory effect on the vessel wall in animal models,[25] and statin therapy has been shown to lower CRP levels in patients with hypercholesterolemia and combined hyperlipidemia.[26,27] We have shown, for the first time, that atorvastatin also reduces CRP levels in patients with type 2 diabetes, and the magnitude of reduction in CRP correlated with the degree of improvement in endothelium-dependent vasodilatation. This would support the hypothesis that the improvement in endothelium-dependent vasodilatation in our diabetic patients might be partly mediated by the anti-inflammatory effect of atorvastatin. We cannot exclude the possibility that other mechanisms might also be involved. There is both in vitro and in vivo evidence to show that the effect of statins on endothelial dysfunction is related not only to the lowering of LDL, but also to a direct effect on NO production. Statins have a direct effect on endothelial NO synthase (eNOS) expression and cause up regulation of eNOS with increased bioavailability of NO in vivo [28–30]. Statins can also reverse the inhibitory effect of oxidized LDL on eNOS [28]. In addition to the effect on NO, statins have been shown to reduce the synthesis of endothelin- 1, a potent vasoconstrictor, by endothelial cells.[31] The metabolites of atorvastatin have potent antioxidant activities on LDL in vitro, protect HDL against oxidation, and have a paraoxonase-sparing effect.[32] All these additional pleiotropic properties of statins are independent of their cholesterol-lowering effect, and this may explain why we did not find a significant correlation between the magnitude of LDL lowering and the degree of improvement in endothelium dependent vasodilatation.

CONCLUSION

In conclusion, treatment with Atorvastatin leads to a significant reduction in plasma Total cholesterol, LDL cholesterol and TG, a lowering of plasma CRP and an improvement in endothelial dysfunction. The screening of patients with elevated CRP levels may identify patients who have an increased risk for cardiovascular events, although the use of CRP levels as a predictor of cardiovascular events is not well defined for patients who already qualify for statin treatment because of lipid abnormalities. Thus, screening of patients with dyslipidemia for elevated blood hs-CRP levels may be done to identify those patients with an increased risk for future development of atherosclerosis as well as bad cardiovascular events at earlier stages so that they can change their life style, food habits etc. to resist further aggravation of dyslipidemic status as well as catastrophic cardiovascular events.

REFERENCES

1. Miranda JJ, Kinra S, Casas JP, Davey Smith G, Ebrahim S. Noncommunicable diseases in low- and middle-income countries:Context, determinants and health policy. Trop Med Int Health 2008;13:1225-1234.
2. Carreiro-Lewandowski E (2004) Update on selected markers used in riskassessment for vascular disease. Clin Lab Sci 17: 43-49.
3. National Cholesterol Education Program (2001) Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2001; 285:2486-2497.
4. Pichandi S, Pasupathi P, Raoc YY, Farook J, Ambika A, et al. (2011) The role of statin drugs in combating cardiovascular diseases. Int. J. Cur. Sci. Res. 1: 47-56.
5. Nawrocki JW, Weiss SR, Davidson MH, Sprecher DL, Schwartz SL, et al. (1995) Reduction of LDL Cholesterol by 25% to 60% in Patients with Primary Hypercholesterolemia by Atorvastatin, a New HMG-CoA Reductase Inhibitor. Arteriosclerosis, Thrombosis, and Vascular Biology 15: 678-682.
6. Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, et al. (2010). Emerging Risk Factors Collaboration. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant metaanalysis. Lancet 375: 132-140.
7. Ridker PM, Brown NJ, Vaughan DE, Harrison DG, Mehta JL (2004) Established and emerging plasma biomarkers in the prediction of first atherothrombotic events. Circulation 109: IV6-19.
8. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon III RO, et al. (2003) Centers for Disease Control and Prevention; American Heart Association. Markers of inflammation and cardiovascular disease: application to clinical and public health practice. A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 107: 499-511.
9. Sabatine MS, Morrow DA, Jablonski KA, Rice MM, Warnica JW, et al. (2007) Prognostic significance of the Centers for Disease Control/American Heart Association high-sensitivity C-reactive protein cut points for cardiovascular and other outcomes in patients with stable coronary artery disease. Circulation 115: 1528-1536.
10. Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, et al. (2005) C-reactive protein levels and outcomes after statin therapy. N Engl J Med 352: 20-28.
11. Emerging Risk Factors Collaboration, Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, et al. (2010) C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet 375: 132-140.

12. Balk EM, Lau J, Goudas LC, Jordan HS, Kupelnick B, et al. (2003) Effects of statins on nonlipid serum markers associated with cardiovascular disease: a systematic review. Ann Intern Med 139: 670-682.
13. Ridker PM, Rifai N, Pfeffer MA (1998) Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events (CARE) Investigators. Circulation 98: 839-844.
14. Ridker PM, Rifai N, Clearfield M, Downs JR, Weis SE, et al. (2001) Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. N Engl J Med 344: 1959-1965.
15. Nissen SE, Tuzcu EM, Schoenhagen P (2005) Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) Investigators. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. N Engl J Med. 352: 29-38.
16. Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, et al. (2005) C-reactive protein levels and outcomes after statin therapy. N Engl J Med 352: 20-28.
17. Morrow DA, de Lemos JA, Sabatine MS, Wiviott SD, Blazing MA, et al. (2006) Clinical relevance of C-reactive protein during follow-up of patients with acute coronary syndromes in the Aggrastat-to-Zocor Trial. Circulation 114: 281-288.
18. Genest J, McPherson R, Frohlich J, Anderson T, Campbell N, et al. (2009) 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult - 2009 recommendations. Can J Cardiol 25: 567-579.
19. Fruchart JC, Sacks F, Hermans MP, Assmann G, Brown WV, et al. (2008) The Residual Risk Reduction Initiative: a call to action to reduce residual vascular risk in patients with dyslipidemia. Am. J. Cardiol. 102: 1K-34K.
20. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, et al. (1996) The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med 335: 1001-1009.
21. Verschuren WM, Jacobs DR, Bloemberg BP, Kromhout D, Menotti A, et al. (1995) Serum total cholesterol and long-term coronary heart disease mortality in different cultures. Twenty-five-year follow-up of the seven countries study. JAMA 274: 131-136.
22. Brewer HB Jr (2002) Rising to the challenge of the new NCEP ATP III guidelines: exceeding current therapeutic limitations. Am J Manag Care 8: S23-28.
23. Strang AC, Kaasjager HA, Basart DC, Stroes ES (2010) Prevalence of dyslipidaemia in patients treated with lipid-modifying drugs in the Netherlands. Part of the dyslipidaemia international survey. Neth J Med 68: 168-174.
24. Davignon J, Laaksonen R 1999 Low-density lipoprotein-independent effects of statins. CurrOpinLipidol 10:543–559.
25. Bustos C, Hernandez-Presa MA, Ortego M, Tunon J, Ortega L, Perez F, Diaz C, Hernandez G, Egido J 1998 HMG-CoA reductase inhibition by atorvastatin reduces neointimal inflammation in a rabbit model of atherosclerosis. J Am CollCardiol 32:2057–2064.
26. Ridker PM, Rifai N, Lowenthal SP 2001 Rapid reduction in C-reactive protein with cerivastatin among 785 patients with primary hypercholesterolemia. Circulation 103:1191–1193.
27. Jialal I, Stein D, Balis D, Grundy SM, Adams-Huet B, Devaraj S 2001 Effect of hydroxymethylglutaryl coenzyme a reductase inhibitor therapy on high sensitive C-reactive protein levels. Circulation 103:1933–1935.
28. Laufs U, La Fata V, Plutzky J, Liao JK 1998 Upregulation of endothelial nitric oxide synthase by HMG CoA reductase inhibitors. Circulation 97:1129–1135.
29. Kaesemeyer WH, Caldwell RB, Huang J, Caldwell RW 1999 Pravastatin sodium activates endothelial nitric oxide synthase independent of its cholesterol- lowering actions. J Am CollCardiol 33:234–241.
30. John S, Schlaich M, Langenfeld M, Weihprecht H, Schmitz G, Weidinger G, Schmieder RE 1998 Increased bioavailability of nitric oxide after lipidlowering therapy in hypercholesterolemic patients: a randomized, placebocontrolled, double-blind study. Circulation 98:211–216.
31. Hernandez-Perera O, Perez-Sala D, Navarro-Antolin J, Sanchez-Pascuala R, Hernandez G, Diaz C, Lamas S 1998 Effects of the 3-hydroxy-3-methylglutaryl- CoA reductase inhibitors, atorvastatin and simvastatin, on the expression of endothelin-1 and endothelial nitric oxide synthase in vascular endothelial cells. J Clin Invest 101:2711–2719.
32. Aviram M, Rosenblat M, Bisgaier CL, Newton RS 1998 Atorvastatin and gemfibrozil metabolites, but not the parent drugs, are potent antioxidants against lipoprotein oxidation. Atherosclerosis 138:271–280

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