

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

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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~CoA reductase 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.

MATERIALS AND METHODS

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

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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	Atorvastatin after treatment
	(Mean ± S D)	(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.

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