

Effect of Rosuvastatin Therapy on High-Sensitivity C-reactive Protein Values and Lipid Profile in Hyperlipidemic Patients: A prospective Study

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ABSTRACT

Background/Aims: Although many studies show statins' C-reactive protein (CRP) lowering effect, results are often inconsistent. To clarify this issue, we investigated the effect of rosuvastatin treatment on serum hs-CRP levels and the possible relationships between lipid profile and hs-CRP levels in hyperlipidemic patients before and after treatment.

Methods: A total of 123 patients diagnosed with hyperlipidemia were analyzed in this prospective study. All patients were administered oral 20 mg/day rosuvastatin for 12 weeks. The hs-CRP levels and lipid profile changes at baseline and the end of 12 weeks of treatment were evaluated.

Results: Seventy-five female and 48 male patients were included in our study, and the mean age was 53.91 ± 8.08 years. We found that post-treatment total cholesterol, triglyceride, low-density lipoprotein cholesterol, hs-CRP levels and total cholesterol / high-density lipoprotein cholesterol ratio were significantly lower than baseline. In contrast, HDL-C levels were significantly higher ($p=0.001$ for all parameters).

Conclusion: Considering the established prognostic effects of dyslipidemia, the increasingly definite effects of hs-CRP in cardiovascular diseases, and our results, which were in agreement with previous studies, it is evident that statins reduce inflammation as improving cholesterol levels in patients with hyperlipidemia.

Keywords: Rosuvastatin, high-sensitivity C-reactive protein, lipid profile, hyperlipidemia

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INTRODUCTION

Statins are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors and are widely used in treating dyslipidemia in patients with cardiovascular diseases (CVDs).¹ They are effective in treating not only atherosclerosis, in which dyslipidemia and inflammation are important factors, but also many other diseases in which inflammation contributes to pathophysiology.^{1,2} They can do this thanks to their proven "pleiotropic" effects concerning their anti-inflammatory effects, dependent and/or independent of their effect on lipid metabolism.³ The pleiotropic immunomodulatory effect of statins is demonstrated by lowered C-reactive protein (CRP) levels,^{1,3} which may result from their anti-inflammatory and anti-oxidant effects concerning cholesterol fractions,⁴

oxysterols,⁵ and lipid peroxidation.⁶

C-reactive protein (CRP) is a well-known acute-phase reactant and nonspecific marker of inflammation produced due to regulating various cytokines.^{1,3,7} Atherosclerotic lesions can increase synthesis by vascular smooth muscle cells and macrophages.^{3,8} High-sensitivity CRP (hs-CRP) level is an independent risk factor in CVDs. It is a reliable parameter for predicting atherosclerotic diseases in healthy individuals and recurrent cardiovascular events in patients with known atherosclerotic vascular disease.⁹⁻¹² These associations have led to the idea that interventions to reduce

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CRP levels can ameliorate inflammatory diseases. Various exploratory studies have been carried out^{13,14} showing that statins could minimize serum CRP levels through multiple mechanisms.^{1,3,14} Rosuvastatin is a high-potency statin, meaning that it has been found to decrease low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG) levels and increase high-density lipoprotein cholesterol (HDL-C) levels at a greater degree compared to other statins.^{15,16} Rosuvastatin (20 mg) was shown to reduce LDL-C levels by 50% and hs-CRP by 37% in a prospective study which suggested that CRP reduction was an indicator of statin therapy efficacy, as well as LDL-C reduction.⁸

Although many studies on the subject, results are inconsistent and demonstrate extreme heterogeneity.^{1,17,18} To clarify this issue, we investigated the effects of rosuvastatin treatment on serum hs-CRP levels and the relationships between lipid profile and hs-CRP levels before and after treatment in hyperlipidemic patients.

METHODS

Study design and population

This prospective observational study was conducted between February 2007 and January 2008 at the Department of Internal Medicine, Sisli Etfal Training and Research Hospital, Istanbul, Turkey. Ethics committee approval was obtained for this study from the Clinical Research Ethics Committee of Sisli Etfal Training and Research Hospital (decision no: 2007/01). Furthermore, the ethical standards specified in the Declaration of Helsinki and its amendments were strictly followed. Written informed consent was acquired from each participant included in the study.

A total of 124 patients were admitted to our outpatient clinic and were diagnosed with hyperlipidemia and who had an indication for drug treatment according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) 19 criteria, despite four weeks of first-line diet and lifestyle changes, were included in the study. The exclusion criteria were determined as follows: Refusing treatment, having known hypersensitivity to HMG-CoA reductase inhibitors, having a fasting TG level of ≥ 400 mg/dl, pregnant or breastfeeding, history of stroke or acute coronary syndrome within the last three months, receiving lipid-lowering therapy within the previous three months, change in antidiabetic treatment in the past three months,

history of trauma or surgery in the prior month, acute or chronic liver disease, liver and/or kidney failure, and subjects with secondary causes of hyperlipidemia (such as uncontrolled hypothyroidism, nephrotic syndrome, severe renal failure, alcohol dependence, hepatobiliary diseases). Additionally, patients with muscle disease, those who were found to have ≥ 3 times the upper reference range for creatine phosphokinase (CPK), those with acute infection, malignancy, autoimmune disease and/or immunosuppressive therapy, rheumatic disease, and subjects reporting use of drugs that would increase the risk of rhabdomyolysis when taken together with HMG-CoA reductase inhibitors (such as warfarin, cyclosporine, amiodarone, nicotinic acid, erythromycin, itraconazole, antihistamine, fibrate) were excluded. In addition, patients with the following conditions identified after treatment initiation were excluded from the analyses: non-adherence to treatment, detection of an increase of ≥ 2.5 times normal transaminase levels, severe myalgia or ≥ 10 -fold increase in CPK, and development of acute coronary syndrome or cerebrovascular event while under treatment.

Data collection and laboratory measurements

Initially, clinic demographic characteristics of the participants such as age, gender, comorbidity, and smoking status were recorded, detailed physical examinations were performed, and electrocardiogram records were obtained.

Patients' lipid profiles [total cholesterol (TC, mg/dl), TG (mg/dl), LDL-C (mg/dl), HDL-C (mg/dl) and TC/HDL-C ratio], liver enzymes [aspartate aminotransferase (AST), alanine aminotransferase (ALT)], CPK, and hs-CRP (mg/L) values before treatment were recorded.

All patients were started on 20 mg/day rosuvastatin tablets. On the 10th day of the treatment, the patients were called for a control assessment. Myalgia symptoms were questioned, and AST, ALT, and CPK levels were measured. Since one patient had diffuse myalgia (CPK value within normal limits) during follow-up, they could not continue the study, and the study was completed with a total of 123 patients. At the 4th, 8th and 12th weeks of the treatment, the patients were called for pre-scheduled follow-up studies and evaluated in terms of treatment adherence and complications. At the 12th-week assessment, the patients' serum lipid profiles and hs-CRP values were measured and recorded. Patients were grouped according to their hs-CRP values, taking into

account relevant guidelines for cardiovascular disease risk, as follows: "Low" (0-1 mg/L), "Moderate" (1.1-2.9 mg/L) and "High" (≥ 3 mg/L).²⁰

All blood samples were taken from the antecubital vein into standard serum separator tubes in the morning after at least 12 hours of fasting. The enzymatic colourimetric method measured TC, TG, and HDL-C levels. The enzymatic kinetic method measured AST, ALT, and CPK levels using an Abbott Aero set autoanalyzer with Abbott kits (Abbott Aeroset™, Abbott Laboratories, Illinois, USA). Hs-CRP values were studied by the nephelometric method using a Beckman Coulter IMMAGE® 800 Immunochemistry System (Beckman Coulter, California, USA). LDL-C was calculated using the Friedewald formula as follows: $LDL-C = TC [HDL-C + (TG/5)]$.²¹

Statistical Analysis

All analyses were performed on NCSS 2007 & PASS 2008 Statistical Software (Utah, USA). Data are summarized as mean $\pm$ standard deviation for continuous variables and frequency (percentage) for categorical variables. Normality of distribution was assessed with the Shapiro-Wilk test. Repeated measurements were analyzed with the paired t-test. Analysis of the variables between the hs-CRP groups was performed with the one-way analysis of variances or the Kruskal-Wallis test, depending on the normality of distribution. Analysis of variables between sex and diabetes mellitus (DM) groups was performed with the independent samples t-test or the Mann-Whitney U test, depending on the normality of distribution. The statistical significance value was accepted as $p < 0.05$.

RESULTS

Seventy-five female and 48 male patients were included in our study, and the mean age of the patients was 53.91 ± 8.08 (range 29 - 72) years. Post-treatment mean TC, TG, LDL-C, hs-CRP levels and TC/HDL-C ratio were significantly lower and HDL-C levels significantly higher before treatment ($p=0.001$ for all parameters). Of the patients, 34.1% were smokers, 55.3% had hypertension, 21.1% had coronary artery disease, and 20.3% had diabetes mellitus. (Table 1).

According to the pre-treatment hs-CRP classification, pre-treatment mean LDL-C level ($p=0.478$), HDL-C ($p=0.178$) level and TC/HDL-C ratio ($p=0.178$) were similar between groups. Likewise, post-treatment LDL-C level ($p=0.190$),

Table 1. Summary of patient characteristics and laboratory measurements	
Age	—
Sex	
Female	75 (61.0%)
Male	48 (39.0%)
Smoking	42 (34.1%)
Hypertension	68 (55.3%)
Coronary artery disease	26 (21.1%)
Diabetes mellitus	25 (20.3%)
Pre- and post-treatment laboratory differences, p-values	
Total cholesterol	0.001
Triglyceride	0.001
LDL-C	0.001
HDL-C	0.001
Total cholesterol/HDL-C ratio	0.001
hs-CRP	0.001
Total cholesterol, mg/dl	
Before treatment	271.04 ± 29.25
After treatment	161.55 ± 22.55
Triglyceride, mg/dl	
Before treatment	208.86 ± 74.42
After treatment	135.39 ± 49.12
LDL-C, mg/dl	
Before treatment	185.91 ± 24.86
After treatment	88.62 ± 17.64
HDL-C, mg/dl	
Before treatment	43.20 ± 11.20
After treatment	45.59 ± 10.33
Total cholesterol/HDL-C ratio	
Before treatment	6.15 ± 1.81
After treatment	3.17 ± 0.93
hs-CRP	
Before treatment	2.44 ± 1.50
After treatment	1.21 ± 0.88
Data are given as mean $\pm$ standard deviation for continuous variables and as frequency (percentage) for categorical variables. p values were obtained by paired t test.	
Abbreviates: LDL -C: Low -density lipoprotein cholesterol, HDL -C: High-density lipoprotein cholesterol, hs -CRP: High-sensitivity C - reactive protein	

HDL-C ($p=0.571$) level, and TC/HDL-C ratio ($p=0.291$) were similar when compared between groups formed according to post-treatment hs-CRP level (Table 2).

There was no significant difference between males and females regarding hs-CRP levels, neither before treatment ($p=0.977$) nor after treatment ($p=0.138$). Relative changes in hs-CRP levels from baseline to post-treatment were similar in the two groups ($p=0.084$). There was no significant difference between the mean hs-CRP levels of patients with and without DM, both before treatment ($p=0.474$) and after treatment ($p=0.552$). Relative changes

Table 2. Summary of laboratory measurements with regard to hs-CRP groups				
	hs-CRP, before treatment			
	Low (n=24)	Moderate (n=55)	High (n=44)	p ⁽¹⁾
LDL-C, before treatment, mg/dl	182.58 ± 19.23	184.52 ± 23.78	189.45 ± 28.71	0.478
HDL-C, before treatment, mg/dl	46.79 ± 12.54	43.00 ± 11.88	41.50 ± 9.40	0.178
Total cholesterol/HDL-C ratio, before treatment	5.66 ± 1.88	6.20 ± 1.95	6.36 ± 1.55	0.178
	hs-CRP, after treatment			
	Low (n=52)	Moderate (n=66)	High (n=5)	p ⁽²⁾
LDL-C, after treatment, mg/dl	85.48 ± 15.32	91.60 ± 18.97	82.00 ± 17.79	0.190
HDL-C, after treatment, mg/dl	45.92 ± 10.95	45.65 ± 9.74	41.40 ± 12.75	0.571
Total cholesterol/HDL-C ratio, after treatment	3.17 ± 0.89	3.22 ± 0.85	3.20 ± 0.23	0.291
Data are given as mean ± standard deviation. (1) One-way analysis of variances, (2) Kruskal Wallis test. Abbreviates: LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, hs-CRP: High-sensitivity C-reactive protein				

Table 3. Summary of hs-CRP levels with regard to sex and diabetes mellitus comorbidity				
	Sex			
	Female (n=75)	Male (n=48)	p ⁽¹⁾	p ⁽²⁾
hs-CRP				
Before treatment	2.44 ± 1.51	2.44 ± 1.51	0.977	0.084
After treatment	1.12 ± 0.89	1.36 ± 0.85	0.138	
	Diabetes mellitus			
	Yes (n=25)	No (n=98)	p ⁽¹⁾	p ⁽²⁾
hs-CRP				
Before treatment	2.83 ± 1.50	2.58 ± 1.48	0.474	0.488
After treatment	1.20 ± 0.66	1.33 ± 0.99	0.552	
Data are given as mean ± standard deviation. (1) Between groups analysis of measurements with independent samples t test, (2) Between groups analysis of change in measurements (%) with Mann Whitney U test				
Abbreviates: hs-CRP: High-sensitivity C-reactive protein				

in hs-CRP from baseline to post-treatment in patients with and without DM were also similar (p=0.488) (Table 3).

DISCUSSION

Based on the importance of reducing hs-CRP levels in CVD, we planned this study to assess the success of statins in lowering hs-CRP levels as claimed in several studies.^{22,23}

We examined the changes in hs-CRP levels and lipid profiles after 12 weeks of 20 mg rosuvastatin treatment in patients with hyperlipidemia. We found that Rosuvastatin significantly decreased TC, TG, LDL-C, hs-CRP levels and TC/HDL-C ratio and significantly increased HDL-C levels, regardless of sex and DM comorbidity.

As the role of hs-CRP in the formation and prognosis of many CVDs has become more evident, many researchers have explored the prognostic impact of lowering hs-CRP levels. Several clinical studies have attempted to demonstrate that statins are essential in preventing CVDs and cardiovascular events by reducing CRP levels.^{24,25} The results of our study were consistent with previous studies. We showed that 12 weeks of 20 mg rosuvastatin treatment

significantly decreased hs-CRP levels and beneficial changes in lipid values in patients with hyperlipidemia. In addition, the Cholesterol and Recurrent Events (CARE) study and Air Force / Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) showed that CVD risk reduction is associated with statin therapy was more pronounced in those with high hs-CRP levels.^{24,25} The ACT FAST study demonstrated that atorvastatin significantly reduced serum concentrations of hs-CRP regardless of previous statin use or the presence of metabolic syndrome and/or DM.

Moreover, it was shown that patients with lower hs-CRP levels after statin treatment had better clinical outcomes than those with higher levels.²² In a study examining the relationship between statin and hs-CRP in stroke patients, it was concluded that statin therapy decreased hs-CRP levels during follow-up and could predict vascular events, including stroke recurrence.²³ Different mechanisms have been described for statins to reduce CRP levels. Cytokines such as IL-6, IL-1 and TNF-alpha stimulate CRP

production, whereas statins suppress IL-6 production and consequently prevent CRP production.^{1,7} Statins may decrease CRP production through ApoA-I upregulation.²⁶ HMG-CoA reductase inhibition lowers protein isoprenylation levels, causes alterations in lipid fractions and prevention of lipid peroxidation.^{6,18,27} Statins suppress Rac-1, a guanosine triphosphate binding protein, geranylgeranylation, preventing elevation of CRP expression.^{3,28,29} It is known that statins indirectly reduce CRP by reducing inflammation in the arteries and contributing to plaque stabilization.^{3,30} One study analyzed the effect of atorvastatin on CRP kinetics in humans using stable isotope methodology and showed that the CRP fractional catabolism rate was increased by 39.9%.³¹ A recent *in silico* study suggests that there may be a direct interaction between statins and CRP. In this study, it was shown that Rosuvastatin had the most substantial effect on CRP.³² Taking into account our results and prior research; it appears that statins confer positive alterations in lipid profile and hs-CRP, supporting their importance in preventing CVD complications in dyslipidemic patients.

How hs-CRP is involved in lipid metabolism and how it influences the pathogenesis of CVD through impaired lipid metabolism has not yet been clarified.³³ It has been suggested that the accumulation of blood lipids in the blood vessel wall caused by dyslipidemia may lead to chronic inflammation, producing inflammatory proteins that enter the bloodstream.^{33,34} Lipid oxidation creates endothelial dysfunction, activates inflammation, increases monocyte adhesion and migration, and contributes to the development of atherosclerotic plaques. It is thought that hs-CRP binds to LDL in atherosclerotic plaques and causes complement activation, leading to increased inflammation.^{33,35} The results of a recent case-control study suggested an independent correlation between hs-CRP and dyslipidemia and that hs-CRP levels partially mediate the relationship between dyslipidemia and CAD.³³ In a cross-sectional study, hs-CRP was found to demonstrate a positive correlation with TC, LDL-C and TG levels, while there was a negative correlation with HDL-C.³⁶ We separately examined the relationship between three categories of hs-CRP level and lipid parameters before and after treatment. As a result, we did not find any significant association between pre- or post-treatment hs-CRP categories and

LDL-C, HDL-C, and TC/HDL-C ratio values. These results suggest similar mechanisms that alter hs-CRP levels and lipid levels. However, more specific studies are needed to understand how hs-CRP and lipids affect each other.

DM is accepted as a "coronary heart disease risk equivalent". This is mainly due to the high rates of dyslipidemia among patients, believed to be one of the main factors responsible for the high percentage of CVD-related deaths in diabetic patients. Studies have shown that differences in lipid profile between diabetics and non-diabetics are responsible for the increased CVD risk. The typical type 2 DM lipid profile is as follows: TG levels are high, HDL-C is low, LDL-C levels are often normal, but LDL particles are denser and more minor. This lipid profile is thought to increase atherogenic potential. Statins constitute the first-line treatment of dyslipidemia in patients with DM.^{16, 37} It was shown that Rosuvastatin was the most effective statin in decreasing LDL-C, TG, and TC in dyslipidemic diabetic patients.¹⁶ It is also important to note that DM is considered a low-grade inflammatory disease, and several inflammatory markers in the blood, including CRP, appear to be significantly elevated in the DM population. Therefore, CRP may be an independent risk marker for CVD risk, especially in DM.³⁶ In a case-control study, the mean hs-CRP levels in T2DM patients were significantly higher compared to healthy individuals.³⁶ Another study showed that atorvastatin and Rosuvastatin significantly lowered hs-CRP, LDL-C, TC, and TG levels and increased HDL-C levels in obese T2DM patients.³⁸ The results in our study were not compatible with these results. We did not see a significant difference between the pre-and post-treatment hs-CRP levels of patients with and without DM. This result may be because the number of patients with DM was deficient compared to those without DM, thereby limiting analyses from this perspective.³⁹

Our study has some limitations. First, the fact that it was a single-centre study limited the generalizability of the findings. In addition, the analyses concerning DM may not be generalizable to the DM population since the study's primary objective was not to assess hs-CRP levels in patients with DM. Therefore, our results concerning this analysis should be interpreted with caution. Also, as this was a clinical study, the possible mechanisms by which Rosuvastatin lowers hs-CRP were not investigated;

however, potential implications regarding this matter were inferred from the available literature. Finally, patients were evaluated for laboratory values only after 12 weeks of treatment which cannot be used to assess the effect of Rosuvastatin on disease-related outcomes.

CONCLUSION

In conclusion, with 12 weeks of 20 mg rosuvastatin treatment, TC, TG, LDL-C, hs-CRP levels and TC/HDL-C ratio were significantly decreased, and HDL-C levels were significantly increased in patients with hyperlipidemia. Our findings support the increasing body of evidence concerning the beneficial effects of statins on CVD-related prognostic parameters, including hs-CRP and lipid profile. However, more comprehensive, multicenter studies are needed to clarify the relationships between statins and hs-CRP, dyslipidemia, and CVD prognosis.

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Ethics Committee Approval: Ethics committee approval was obtained for this study from Clinical Research Ethics Committee of Sisli Etfal Training and Research Hospital (decision no: 2007/01). The ethical standards specified in the Declaration of Helsinki and its amendments were strictly followed. Written informed consent was acquired from each of the participants included in the study.

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