

C-Reactive Protein Level Following Treatment and Withdrawal of Lovastatin in Diabetic Nephropathy

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Keywords. C-reactive protein, diabetic nephropathies, inflammation, cholesterol, hydroxymethylglutaryl-CoA reductase inhibitors, lovastatin

Introduction. We aimed to evaluate the high-sensitivity C-reactive protein (HS-CRP) level changes at the beginning and after withdrawal of lovastatin therapy in patients with diabetic nephropathy.

Materials and Methods. Thirty male patients with type 2 diabetes mellitus and diabetic nephropathy were enrolled in the study. Lovastatin, 20 mg/d, was administered for 90 days. Afterwards, Lovastatin was withdrawn for the next 30 days. Blood samples were obtained before the intervention, on the 90th day, and days 1, 7, and 30 after withdrawal of Lovastatin. Serum level of HS-CRP was determined by enzyme-linked immunosorbent assay. Alterations in lipid profile was assessed, as well, and compared with that of HS-CRP.

Results. Serum level of HS-CRP was significantly reduced after 90 days of lovastatin therapy ($P < .001$). Then, the HS-CRP reached the pretreatment baseline level on the 7th day after lovastatin withdrawal and maintained until the 30th day ($P < .001$). Serum HS-CRP changes showed no significant association with lipid profile except for serum total cholesterol level ($r = 0.9$, $P = .006$) after 3 months of lovastatin therapy. Their association was re-evaluated after 7 days and 1 month of treatment withdrawal and no significant correlations were found.

Conclusions. Our findings suggest that lovastatin decreases serum CRP level in patients with diabetic nephropathy, and 7 days after lovastatin cessation, CRP level increases again.

IJKD 2009;3:93-8
www.ijkd.org

INTRODUCTION

Diabetic nephropathy (DN) is the major complication of diabetes mellitus and is most commonly associated with cardiovascular and renal comorbidities.¹ Hypertension, smoking, and poor glycemic and lipid control are among the main factors which enhance the risk of DN development.² It seems that sophisticated multiple approach including intensive lifestyle modification in addition with aggressive management of blood

pressure, blood glucose, and lipid control may reduce the progression rate of DN and accompanied cardiovascular diseases.³

Diabetic nephropathy begins with damage of the glomerular and tubular cells.² Recent studies have indicated that inflammation plays a significant role in the pathogenesis of DN.^{4,5} Some studies have also shown that patients with diabetic mellitus and overt DN have high levels of various acute-phase markers of inflammation,

including C-reactive protein (CRP).^{5,6} On the other hand, statins that are potent inhibitors of cholesterol biosynthesis used widely in the treatment of patients with hypercholesterolemia, are shown to reduce inflammatory factors as well.⁷ Moreover, subsequent studies reported that abrupt withdrawal of statins might result in rapid loss of its protective effect against atherosclerotic.⁸⁻¹² Thus, we can speculate that administration of statins in diabetic patients may slow down progression of the inflammatory process that leads to DN.

The aim of the present study was to determine the antilipidemic and anti-inflammatory effect of lovastatin therapy and its withdrawal effect on lipid profile and C-reactive protein level in patients with type 2 diabetes mellitus and diabetic nephropathy.

MATERIALS AND METHODS

Patients

The present study was conducted in Sheikholraees clinic in Tabriz, Iran, from February 2006 to March 2008. After initial clinical and laboratory evaluations, 38 men with clinically documented DN were consecutively enrolled. To eliminate potential confounding factors on the serum level of CRP, we included only patients with type 2 diabetes mellitus and proteinuria lower than the nephrotic range (ie, < 3 g/d) whose estimated creatinine clearance was higher than 30 mL/min (calculated by the Cockcroft-Gault formula). Since female sexual hormones can affect biochemical and acute-phase markers of inflammation, we did not enroll women.¹³ All of the participants provided informed consent, and the ethics committee of Tabriz University of Medical Sciences reviewed and approved the study protocol.

Fasting blood glucose of the participants was controlled by insulin injection and/or administration of oral sulfonylurea. Blood pressure was maintained less than 130/75 mm Hg with treatment by angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers with α -blockers and diuretics, whenever needed. All of the patients were under their own regular restricted protein diet (≤ 0.8 g/kg/d), prescribed by a nutrition consultant. Any major changes in blood pressure, protein intake, and physical activity during the study period was

considered as the withdrawal criteria. Exclusion criteria were the use of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) antagonists, fibrates, aspirin, β -blockers, vitamins, pentoxifylline, fish oil, or other antioxidant drugs during the past 3 months, active smoking, chronic inflammation (such as diabetic foot, hepatitis, infection, etc), active coronary artery disease (diagnosed by symptoms and electrocardiography) during the past 3 months, and poorly controlled diabetes mellitus (Hb-A1c > 7.5%).

Study Protocol

Lovastatin (Ghazal Co, Tehran, Iran), 20 mg/d, was administered in the patients for 90 days. At the end of the 3rd month, the patients were stopped lovastatin intake from the 91st day until the 120th day. To determine the trend of lipid profile and high-sensitivity CRP (HS-CRP) level, blood samples were obtained at 5 times according to the following schedule: (1) before of lovastatin therapy (baseline), (2) after 3 months of lovastatin therapy, (3) one day after withdrawal of lovastatin therapy, (4) seven days after withdrawal of lovastatin therapy, and (5) thirty days after withdrawal of lovastatin therapy.

Biochemical Analyses

The patients were asked to be fasted for 12 hours. Blood samples were taken before breakfast in the morning and collected in sterile tubes, centrifuged at 3000 rpm for 10 minutes at 4°C, and then stored at -79°C until assayed. High-sensitivity CRP was measured using an ultrasensitive solid-phase enzyme-linked immunosorbent assay (DRG instruments GmbH, Marburg, Germany; Lot No: RN-28874). Serum levels of fasting blood glucose (FBS), total cholesterol (TC), high-density lipoprotein cholesterol (HDL), and triglyceride (TG) were determined using commercial reagents with an automated chemical analyzer (Abbott analyzer, Abbott Laboratories, Abbott Park, Chicago, Illinois, USA). Low-density lipoprotein cholesterol (LDL) was calculated using the Friedewald equation.¹⁴

Statistical Analyses

Statistical analyses were performed using the SPSS software (Statistical Package for the Social Sciences, version 13.0, SPSS Inc, Chicago,

Ill, USA). The results are presented as mean \pm standard deviation. One-way repeated-measures analysis of variance, paired *t* test and Wilcoxon signed rank test were used to assess the differences between each of the two stages, as appropriate. A *P* value less than .05 was considered significant.

RESULTS

Data of 30 patients with DN were analyzed in this study, while 8 were excluded from the study because of the following reasons: uncooperativeness (2 patients), vitamin C intake during the intervention period (1 patient), life style change during the intervention period (1 patient), smoking during intervention period (1 patient), travel to another region (1 patient), change of lovastatin to atorvastatin by an endocrinologist (1 patient), and development of end-stage renal disease (1 patient). The mean age of the eligible participants was 54.5 ± 6.1 years (range, 43 to 66 years). The mean duration of diabetes mellitus was 9.8 ± 3.1 years (range, 5 to 15 years). Thirteen participants (43.3%) had mild to moderate hypertension for 3.1 ± 4.0 years. The mean systolic and diastolic blood pressures at the beginning of study were 124.6 ± 11.8 mm Hg and 72.9 ± 5.8 mm Hg, respectively.

The measured values of FBS and lipid profile are shown in the Table. These results demonstrated the mean values of TC and LDLC levels were significantly reduced following 3 months of lovastatin therapy. Additionally, lovastatin therapy resulted in increased HDLC level at the end of the 3rd month of treatment. In contrast, the mean TC, TG, LDLC, and HDLC levels on the 90th day after lovastatin therapy were not significantly different from those on the 7th day after withdrawal of lovastatin. Thirty days after

withdrawal of lovastatin, the mean levels of TC, TG, and LDLC (but not HDLC) were significantly increased in comparison with the measured levels on the 90th day of lovastatin therapy.

One-way repeated-measures analysis of variance was conducted to compare HS-CRP levels measured before the intervention, after 90 days of lovastatin therapy, and on the 1st, 7th, and 30th days of lovastatin withdrawal, which showed significant changes in its levels during the studied period ($P < 0.001$; Figure). The mean serum level of HS-CRP was significantly reduced from 3.52 ± 4.16 mg/dL (95% confidence interval [CI], 1.96 to 5.08) to 2.84 ± 3.06 mg/dL (95% CI, 1.69 to 3.98) after 90 days of lovastatin therapy ($P < .001$). Although the HS-CRP level did not significantly change at the first day after lovastatin withdrawal (2.99 ± 3.41 mg/dL; 95% CI, 1.71 to 4.26; $P = .19$), it increased significantly and returned to the baseline level on the 7th day (3.55 ± 3.68 mg/dL; 95% CI, 2.17 to 4.61; $P < .001$). The HS-CRP level on the 30th day after termination of lovastatin was not significantly different from that on the 7th day of withdrawal (3.55 ± 3.68 mg/dL; 95% CI, 2.17 to 4.61 versus 3.31 ± 3.51 mg/dL; 95% CI, 2.67 to 3.81; $P = .10$), and finally, the serum level of HS-CRP on the 30th day after lovastatin withdrawal was not significantly different from that of the baseline ($P = .88$).

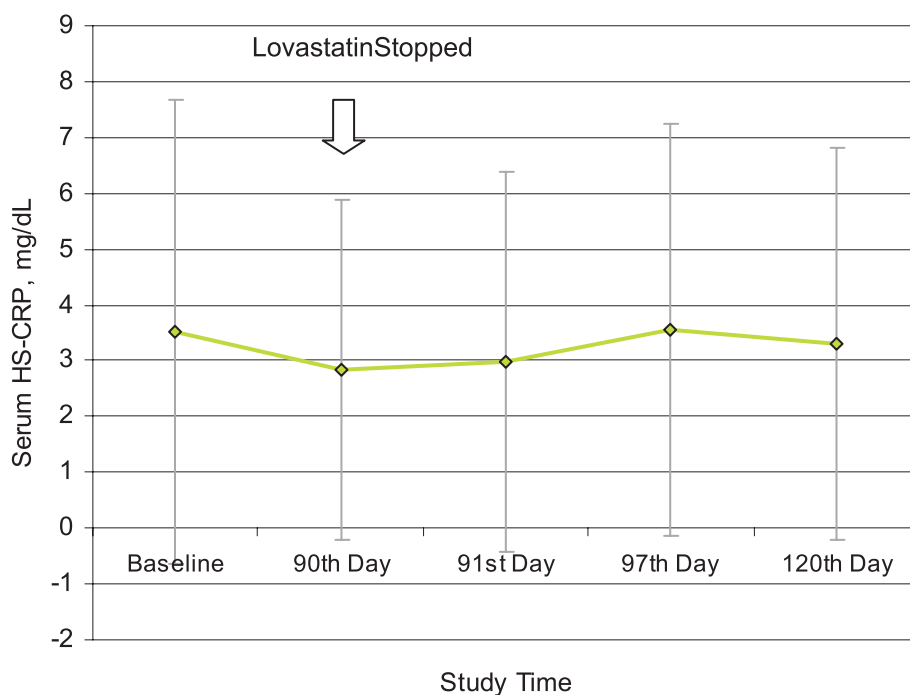
The relationship of serum HS-CRP changes with lipid profiles changes were assessed which showed no significant association except for TC ($r = 0.2$, $P = .20$ for TG; $r = 0.2$, $P = .10$ for HDLC; $r = 0.09$, $P = .60$ for LDLC; and $r = 0.9$, $P = .006$ for TC) after 3 months of lovastatin therapy. The above parameters after 7 days and 1 month of treatment withdrawal were repeated and again no significant correlations were found.

Changes in Fasting Blood Glucose and Lipid Profile of Patients With Diabetic Nephropathy Following Lovastatin Therapy for 3 Months and Its Cessation*

| Parameter | Study Time | | | | P† | | |
|-------------|--------------------|--------------------|--------------------|--------------------|--------|-----|--------|
| | Baseline | 90th day | 97th Day | 120th Day | 1st | 2nd | 3rd |
| FBG, mg/dL | 157.8 \pm 66.8 | 151.5 \pm 57.6 | 165.9 \pm 61.0 | 156.6 \pm 57.2 | .50 | .10 | .40 |
| TC, mg/dL | 199.00 \pm 43.33 | 164.66 \pm 35.19 | 165.43 \pm 40.41 | 198.40 \pm 48.18 | < .001 | .85 | < .001 |
| LDLC, mg/dL | 123.92 \pm 45.18 | 91.45 \pm 31.36 | 91.18 \pm 37.72 | 116.5 \pm 38.78 | < .001 | .47 | < .001 |
| HDLC, mg/dL | 40.00 \pm 5.30 | 42.80 \pm 5.14 | 42.47 \pm 4.33 | 40.60 \pm 4.49 | .006 | .65 | .08 |
| TG, mg/dL | 175.4 \pm 95.0 | 152.1 \pm 94.7 | 158.9 \pm 95.2 | 206.5 \pm 141.0 | .19 | .44 | .007 |

*Values are presented as mean standard deviation. FBG indicates fasting blood glucose; TC, total cholesterol; LDLC, Low-density lipoprotein cholesterol; HDLC, high-density lipoprotein cholesterol; and TG, Triglyceride.

†The 1st *P* values are related to the comparisons between the baseline and 90th day (end of lovastatin therapy); the 2nd, to those between the 90th day and the 97th day; and the 3rd, to those between the 97th day and the 120th day.



The serial levels of high-sensitivity C-reactive protein (HS-CRP) in patients with diabetic nephropathy before and after lovastatin therapy (3 months), and during the 1st, 7th, and 30th days after withdrawal of lovastatin therapy. The serum level of HS-CRP was significantly reduced following therapy and elevated on the 7th day of withdrawal of lovastatin therapy.

DISCUSSION

Results of the present study showed that the serum levels of HS-CRP, TC, TG, and LDLC in patients with DN significantly decreased following 3 months of lovastatin therapy. More importantly, despite the insignificant changes of lipid profile, the HS-CRP level elevated rapidly on the 7th day after withdrawal of lovastatin therapy.

Diabetic nephropathy is a common complication of type 1 and type 2 diabetes mellitus, and it remains the single most common cause of kidney failure in the world.¹⁵ Renal involvement was reported in 25% to 40% of type 1 and type 2 diabetic patients.¹⁶ It is demonstrated that diabetes mellitus is not only a metabolic disorder and that diverse molecules related to inflammation play a significant role in the development of diabetes mellitus and its complications.¹⁷ Study of inflammatory parameters in diabetic patients showed that these patients had elevated levels of CRP, tumor necrosis factor- α , and interleukin-6, compared with nondiabetic control subjects.^{18,19} Recent studies suggest that CRP is not only an inflammatory marker of atherosclerosis and coronary events, but also a mediator of these diseases, because it contributes to the underlying lesion formation, plaque rupture, and coronary

thrombosis through interaction with and alteration of the vascular phenotype.²⁰ Also, CRP has been shown to correlate with markers of endothelial dysfunction.²¹

Statins are potent inhibitors of cholesterol biosynthesis. However, the overall clinical benefits observed with statins therapy appear to be greater than what might be expected from changes in lipid profile alone, suggesting that the beneficial effects of statins may extend beyond their effects on serum cholesterol levels (pleiotropic effects).²² The HMG-CoA reductase inhibitors may prove to be key inhibitors of low-grade inflammation and endothelial dysfunction by reducing inflammatory cell signaling. In a recent study, atorvastatin was found to improve endothelial-dependent vasodilatation in diabetic patients, and this improvement correlated with significant decrease in CRP levels.²³ In case of statins effects on CRP, Plenge and colleagues performed a double-blind study on patients with elevated LDLC and demonstrated that 14 days of simvastatin therapy reduced TC and CRP levels.²⁴ They concluded that HS-CRP lowering effect of simvastatin in 14 days is independent of its effect on LDLC. Huang and coworkers also reported that discontinuation of

chronic simvastatin treatment led to a significant rebound effect on HS-CRP.²⁵ Similarly, in 20 patients with hypercholesterolemia, termination of atorvastatin therapy resulted in a rapid increase of HS-CRP levels, but not TC and LDLC, within 2 days.⁹ In the present study, the serum levels of HS-CRP in association with the TC, TG, and LDLC were significantly reduced following 3 months of lovastatin therapy; however, after 7 days of lovastatin withdrawal, despite the increased level of HS-CRP, serum levels of TC, TG, and LDLC did not significantly change.

The CRP lowering mechanism of statin therapy is not clearly known. The main part of CRP is synthesized by hepatocytes in response to interleukin-6,^{27,28} which promotes transcription of CRP by means of signal transducer and activator of transcription 3.²⁷ When hepatocytes are exposed to interleukin-6, the consequent serine phosphorylation of signal transducer and activator of transcription 3 is mediated by a signal transduction pathway in which the G protein Rac-1 plays an obligatory role. Statins inhibit the HMG-CoA reductase in cholesterol biosynthesis cycle, and on the other hand, they inhibit mevalonate and its resultant isoprenoids.²⁹ Isoprenoid products are needed for posttranslational modification of a variety of proteins including Rac family.^{30,31} Therefore, by inhibiting mevalonate synthesis pathway, Rac-1 remains unmodified and inactivated.

In addition to these HS-CRP reducing effects of statins, recent experimental studies have demonstrated that statins may confer renoprotection in a variety of glomerular diseases including DN through their lipid-lowering properties or pleiotropic effects.^{32,33} Human studies have also had mixed success in demonstrating attenuated progression of DN with statins.³⁴⁻³⁶ In support of a beneficial effect of statins in ameliorating the progression of DN, Lam and colleagues reported a preserved glomerular filtration rate and serum creatinine in diabetic patients with proteinuria treated with lovastatin.³⁵ Other studies of diabetics with chronic renal insufficiency and hyperlipidemia also found decreased progression of DN in patients allocated to statin therapy.³⁷

Our data indicated that lovastatin therapy for 3 months resulted in decreased levels of HS-CRP, as well as TC, TG, and LDLC. Despite the unchanged levels of TC, TG, LDLC, and HDLC

early after withdrawal of lovastatin, the HS-CRP level increased to the baseline level after 7 days. Hence, further renoprotective effect of statins in patients with DN might be due to prevention of cardiovascular events in these patients by reducing the CRP level.

CONCLUSIONS

We conclude that lovastatin has anti-inflammatory effect in diabetic patients that reduces CRP level. Although both of the antilipidemic and anti-inflammatory effects could have protective effect on progression of atherosclerosis, their pathways seem to be separate and independent. However, since this study only included male participants and the study population was of a low number, further studies with long-term evaluation after withdrawal of the drug are warranted.

FINANIAL SUPPORT

The present study was conducted in Sheikhholraees Clinic of Tabriz University of Medical Sciences, in Tabriz, Iran. The Applied Research Center of Tabriz University of Medical Sciences was the sponsor of the present research, and all the reagents, kits, and drugs were provided by the grant of this center.

CONFLICT OF INTEREST

None declared.

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Received November 2008
Revised February 2009
Accepted February 2009