

Effect of Hydroxymethylglutaryl-CoA Reductase Inhibitors on Low-density Lipoprotein Cholesterol, Interleukin-6, and High-Sensitivity C-Reactive Protein in End-stage Renal Disease

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Keywords.

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Introduction. This study was conducted to determine the effect of statins on the serum levels of interleukin-6 (IL-6), low-density lipoprotein cholesterol (LDLC), and high-sensitivity C-reactive protein (HSCRP).

Materials and Methods. This randomized clinical trial was carried out on 95 hemodialysis patients divided into three groups of atorvastatin, 10 mg; simvastatin, 20 mg; and lovastatin, 40 mg, daily, administered for 2 months. Levels of serum HSCRP, IL-6, and LDLC were all measured before and after the study period.

Results. At baseline, 59% of the hemodialysis patients presented with elevated HSCRP, 46.3% them had increased IL-6, and 26.3% had an increased LDLC level. The three drugs were capable to lower the level of HSCRP, among which atorvastatin had the highest effect size (41.8% reduction, $P = .001$). Lovastatin stood in the next (37.6% reduction, $P = .02$), while HSCRP reduction was not significant in the simvastatin group (25% reduction, $P = .14$). Neither of the drugs significantly reduced IL-6 levels. Effects of atorvastatin and simvastatin on the LDLC levels were significant, while lovastatin had a marginal effect.

Conclusions. Use of statins resulted in CRP reduction in patients on hemodialysis. Atorvastatin was much more effective than lovastatin, while CRP reduction was not significant by simvastatin. However, simvastatin had the greatest impact on LDLC. None of these drugs could reduce IL-6 levels within 2 months.

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INTRODUCTION

Interleukin-6 (IL-6) and high-sensitivity C-reactive protein (HSCRP) are two inflammatory markers or mediators which are prone to an increased serum level in end-stage renal disease (ESRD), infections, cerebrovascular accidents, myocardial infarction, malignancies, and rheumatic diseases.^{1,2} Their serum levels also decrease where medicines like nonsteroidal anti-inflammatory drugs (NSAIDs), cyclosporine, and corticosteroids are used. In chronic renal insufficiency and particularly ESRD, micro-inflammation commonly mediates

the increased levels of IL-6 and HSCRP,² which may be attributed to the low clearance of pro-inflammatory cytokines, body's incompatibility with dialysis solution, accelerated atherosclerosis, higher prevalence of diabetes, hypertension, infections, and complications of uremia.

High IL-6 and CRP levels were both reported in 20% to 60% of the hemodialysis patients,³ which likewise a high levels of serum low-density lipoprotein cholesterol (LDLC) do intensify atherosclerosis and are consequently influential in the incidence of cardiovascular events such as

myocardial infarction.⁴ In fact, the CRP produced in the liver acts in much far places; that is, the atheromatous plaque, and leads to both the stimulation of the area macrophages and secretion of other inflammatory mediators, such as IL-6, tissue factor, and the platelet aggregating factor. It is of interest that the increased serum level of IL-6 also acts as a stimulant for secretion of HSCRP by the liver. Since mortality of most of the hemodialysis patients is due to the vascular events,⁵ if CRP and IL-6 are lowered by means of medical therapy, a major contribution has been made to prevent cardiovascular events, decrease mortality, and improve the patients' survival.

In a great majority of the recent studies, the effect of hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors, namely, statins, on CRP and IL-6 has been well reported.⁶ However, some studies demonstrated that statins were ineffective on the inflammatory mediators.⁷ There is uncertainty about the effect of statins on HSCRP and IL-6 levels in hemodialysis patients. This study was aimed to investigate whether statins could decrease IL-6, HSCRP, and LDLC among ESRD patients on hemodialysis.

MATERIALS AND METHODS

In this randomized double-blinded controlled trial, we recruited 95 hemodialysis patients in Akhavan Hospital of Kashan, in 2009. Patients were eligible only if they were younger than 70 years. The exclusion criteria were infectious, inflammatory, or rheumatic diseases during the past 2 months (based on the physician's records); myocardial infarction, cerebrovascular accident, or any indisposition during the past 3 months; and having been receiving statins, nonsteroid anti-inflammatory drugs, corticosteroids, or other immunological inhibitors like cyclosporine within the past 3 months. The eligible patients provided written informed consent.

The participants were divided randomly (block randomization) into 3 equally arranged groups to receive atorvastatin, 10 mg; simvastatin, 20 mg; or lovastatin, 40 mg, daily for 2 months. All of the drugs were manufactured by Sobhan Drug Company (Tehran, Iran). Variations in the doses for each drug are because of their identical efficacy on lowering LDLC in the dyslipidemic patients.⁸ The drugs were given to the patients as 60-tablet

packages by a person in the dialysis care team who was not involved with the research project, and the physician, the research team, and the patients were blinded to the drug administered to each patient. During the study period, no changes in dialysis dose or other treatment properties were administered. Hemodialysis process was done 3 times in a week for 4 hours through arteriovenous fistulas or permanent catheters, using polysulfone filters. The dialysis fluid flow rate was 700 mL/min and the blood flow rate was dependent on the dry weight of each patient. During the study period, the patients were monitored in terms of the adverse effects, such as hepatitis or myopathy.

Before the intervention started, a 3-mL blood sample of each patient was taken to measure HSCRP and IL-6. Blood samplings were repeated at the end of the treatment period (2 month). Serum level of HSCRP was measured quantitatively using the Minineph human CRP kit (ZK044.L.R, Binding Site Ltd, Birmingham, UK). It was evaluated using the nephelometry technique, based on the rate of both light dispersion targeted at the patient's serum and anti-CRP antibiotic added on the kit. Levels of CRP doses less than 3.8 mg/L, 3.8 mg/L to 9.9 mg/L, 10 mg/L to 40 mg/L, and more than 40 mg/L were considered respectively as normal, mild, moderate, and severe, according to manufacturer. The Human IL-6 BMS 213/2 kit (Bender Medsystems GmbH, Vienna, Austria) was used to measure IL-6 levels, which acts based on the enzyme-linked immunosorbent assay technique. According to the manufacturer, IL-6 doses less than or equal to 1.3 pg/mL, 1.31 pg/mL to 3 pg/mL, 3.1 pg/mL to 5 pg/mL, and more than 5 pg/mL were considered as normal, mild, moderate, and severe, respectively. The LDLC serum level was measured by the enzymatic nephelometry technique.

The data were analyzed using the paired *t* test by the SPSS software (Statistical Package for the Social Sciences, version 13.0, SPSS Inc, Chicago, Ill, USA). Continuous variables were demonstrated as mean standard deviation. A *P* value less than .05 was considered significant.

RESULTS

Of the 136 hemodialysis patients, 37 were excluded (6 with recent intake of statins, 7 due to sepsis in the past month, 3 with cyclosporine intake,

13 with recent use of nonsteroid anti-inflammatory drugs, 5 due to cardiovascular events during the past 3 months, and 3 who refused to take part in the study). Also, 2 patients died and 2 underwent kidney transplantation during the study period, and consequently, 95 patients remained in the data analysis. There were 31 patients in the atorvastatin group (21 men and 10 women), 32 in the simvastatin group (19 men and 13 women), and 32 in the lovastatin group (22 men and 10 women). The mean values for age were 49.8 ± 12.3 years, 47.2 ± 9.4 years, and 51.6 ± 14.2 years in the atorvastatin, simvastatin, and lovastatin groups, respectively. The underlying disease was diabetes mellitus in 54 patients (57.8%) and hypertension in 22 (23.1%).

The HSCRP levels were higher than normal in 59.0% of the patients before treatment and in 49.4% after treatment (Table 1). Also, a high level of IL-6 was seen in 46.3% and 39% of the participants, respectively, before and after the treatment (Table 2). The three drugs were capable to lower the level of HSCRP, among which atorvastatin had the highest effect size (41.8% reduction, $P = .001$). Lovastatin stood in the next (37.6% reduction, $P = .02$), while CRP reduction was not significant in the simvastatin group (25% reduction, $P = .14$; Table 3). With regards to IL-6 levels, neither of the drugs was effective. Reduced of the level of IL-6 was seen in the three groups, but it was not significant (Table 3).

Effects of atorvastatin and simvastatin on the LDLC levels were significant, while lovastatin had

Table 3. Mean Level and the Reduction Percentage of Interleukin-6 (IL-6) and High-Sensitivity C-Reactive Protein (CRP) Before and After Treatment With Atorvastatin, Simvastatin, and Lovastatin in Patients on Hemodialysis

Parameter	Before	After	Reduction, %	P
IL-6, pg/mL				
Atorvastatin	2.74	2.66	2	.18
Simvastatin	2.76	2.52	8	.22
Lovastatin	2.73	2.58	5	.18
All	2.74	2.58	5	.30
CRP, mg/L				
Atorvastatin	24.4	14.2	42	.001
Simvastatin	13.6	10.2	25	.14
Lovastatin	14.6	9.1	38	.02
All	17.5	11.1	35	.02

a marginal effect (Figures 1 to 3). Unexpectedly, the three drugs reduced the HDLC as well. The three drugs were capable to reduce total cholesterol, of which simvastatin was the most effective one (19.5% reduction). Simvastatin was the only drug that decreased triglyceride to a significant level (Figure 2).

Throughout the study, no known side effects, such as headache, nausea, myalgia, abdominal pain, myositis, and clinical hepatitis, were noticed in any of the patients. A 3-fold increase in the levels of hepatic enzymes was seen in 2 of the participants receiving atorvastatin and 1 receiving simvastatin. The drugs were discontinued and started again after their when the enzyme levels were normalized. Treatment with lovastatin was completely safe as compared to the other two drugs.

Table 1. High-Sensitivity C-Reactive Protein (CRP) Levels Before and After Treatment With Atorvastatin, Simvastatin, and Lovastatin in Patients on Hemodialysis*

CRP Elevation	Atorvastatin		Simvastatin		Lovastatin		All	
	Before	After	Before	After	Before	After	Before	After
No	13 (42.0)	19 (61.3)	12 (37.5)	12 (37.5)	14 (43.8)	17 (53.2)	39 (41.1)	38 (40.0)
Mild	10 (32.2)	8 (25.9)	12 (37.5)	3 (9.3)	9 (28.1)	8 (25.0)	31 (32.6)	19 (20.0)
Moderate	4 (12.9)	2 (6.4)	7 (21.8)	16 (50.0)	7 (21.9)	5 (15.6)	18 (19.0)	23 (24.2)
Severe	4 (12.9)	2 (6.4)	1 (3.1)	1 (3.1)	2 (6.2)	2 (6.2)	7 (7.4)	5 (5.2)

*Values in parentheses are percents.

Table 2. Interleukin-6 (IL-6) Levels Before and After Treatment With Atorvastatin, Simvastatin, and Lovastatin in Patients on Hemodialysis*

IL-6 Elevation	Atorvastatin		Simvastatin		Lovastatin		All	
	Before	After	Before	After	Before	After	Before	After
No	14 (45.0)	16 (51.7)	16 (50.0)	19 (59.5)	21 (65.7)	23 (71.9)	51 (53.6)	58 (61)
Mild	11 (35.6)	11 (35.3)	10 (31.3)	11 (34.3)	6 (18.5)	5 (15.7)	27 (28.4)	27 (28.3)
Moderate	3 (9.7)	0	2 (6.2)	2 (6.2)	3 (9.6)	2 (6.2)	8 (8.4)	4 (4.2)
Severe	3 (9.7)	4 (13)	4 (12.5)	0	2 (6.2)	2 (6.2)	9 (9.5)	6 (6.3)

*Values in parentheses are percents.

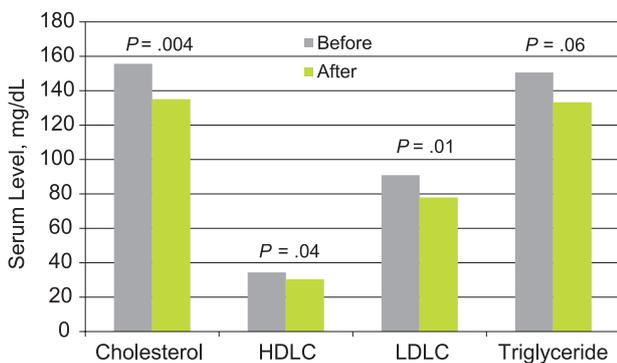


Figure 1. Serum lipid levels before and after treatment with atorvastatin in patients on hemodialysis. LDLC indicates low-density lipoprotein cholesterol and HDLC, high-density lipoprotein cholesterol.

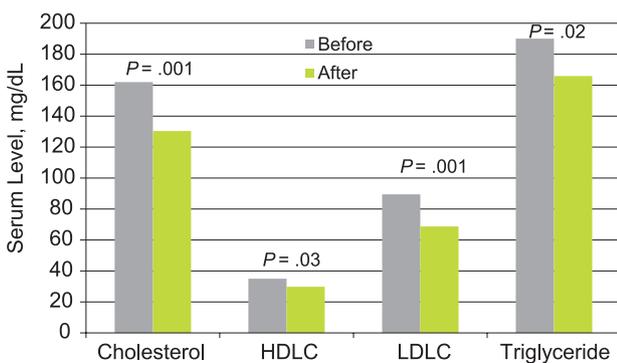


Figure 2. Serum lipid levels before and after treatment with simvastatin in patients on hemodialysis. LDLC indicates low-density lipoprotein cholesterol and HDLC, high-density lipoprotein cholesterol.

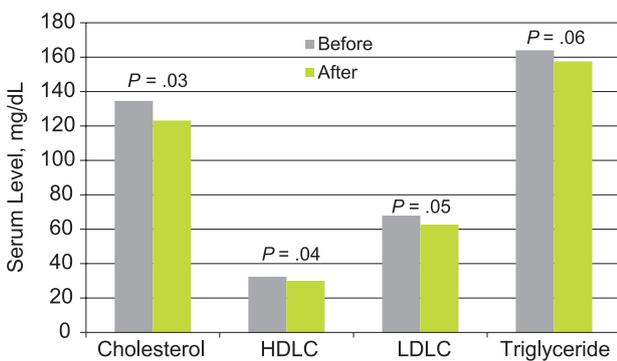


Figure 3. Serum lipid levels before and after treatment with lovastatin in patients on hemodialysis. LDLC indicates low-density lipoprotein cholesterol and HDLC, high-density lipoprotein cholesterol.

DISCUSSION

This study aimed to assess the effect of HMG-CoA reductase inhibitors on the level of IL-6, HSCRP, and LDLC in the ESRD patients. In 49.4% of our patients, the HSCRP level was still high after the treatment (Table 1). The three drugs were

capable to lower the level of HSCRP to varying degrees, but CRP reduction was not significant in the simvastatin group (Table 3). None of the statins used were able to lower the IL-6 levels to a meaningful extent (Table 3). It seems the drugs needed more time to show their effects completely.

Effects of atorvastatin and simvastatin, in particular, on LDLC and HDLC were significant, where HDLC reduction was unexpected because generally statins can increase and not decrease plasma HDLC levels. Some researchers also found the contradictory effect of statins on HDLC level (5% reduction to 10% increase).⁹ Furthermore, we found that lovastatin had no significant effect on LDLC, which was counter the current knowledge.^{8,10} The three drugs, however, were capable to reduce total cholesterol levels. Triglyceride was significantly reduced only by simvastatin. It seems our finding about the effects of statins on lipid profiles of ESRD patients are differ from those effects on other patients with hyperlipidemia without ESRD.

In hemodialysis patients given simvastatin, 40 mg/d, Panichi and colleagues⁶ noticed that IL-6 and CRP were lowered from 5.1 pg/mL to 3.5 pg/mL and from 2.6 mg/L to 2 mg/L, respectively, after 3 months. The LDLC level was also reduced from 139 mg/dL to 104 mg/dL (25.2% reduction). However, Dronbrook-Lavender and associates⁷ reported that atorvastatin, 10 mg/d, was ineffective on the CRP of 19 hemodialysis patients within a 20-week period, although the effect was significant on LDLC (29% reduction). In a study by Athyros and colleagues,¹¹ conducted on patients with chronic kidney disease, administration of atorvastatin, 10 mg/d, for 3 months contributed to a significant reduction in LDLC, total cholesterol, serum creatinine, CRP, and IL-6. These findings except for the creatinine and IL-6 were present in our study as well. Ikejiri and coworkers¹² found that administration of atorvastatin, 10 mg/d, to 35 hemodialysis patients for 3 months, lowered CRP and LDLC in a way that the level of HSCRP was decreased by 4 mg/L from 8 mg/L. Also a 32% reduction in LDLC was reported. In a study¹³ on the effect of atorvastatin, 10 mg/d, and simvastatin, 20 mg/d, on CRP in 13 and 20 hemodialysis patients, respectively, during a 3-month period, van den Akker and colleagues noticed no effect contributable to both drugs, which may be probably due to either short duration of the trial or its small sample size.

Minimal effectiveness of the drugs on IL-6 and

CRP in our study even after a 3-month period may also be more likely because of short duration of simvastatin administration. This is logical because according to Panichi and colleagues, the effect of simvastatin on IL-6 and CRP was not significant even after 3 months of administration, and only after a 6-month administration of the drug, the effect grew significant. In a study carried out by Goicoechea and colleagues¹⁴ and colleagues, administration of atorvastatin, 20 mg, to 44 patients with stages 2 to 4 of chronic kidney disease for 6 months, as compared with the control group (without kidney disease) led to a significant reduction in total cholesterol, LDLC, HSCRP, and IL-6. Goicoechea and colleagues' study, like ours, revealed no meaningful correlation between the serum levels of the two inflammatory factors. The same findings were gained from the hemodialysis patients. Thus, the use of statins will be recommended for the patients with chronic kidney disease to prevent cardiovascular events even if LDLC is normal. As mentioned above, however, discrepancies are seen between several researches' findings about the effect of statins on lipid profile, CRP, and IL-6 in ESRD patients. Thus, more research with more participants and longer follow-ups is required to draw a solid conclusion on the use of statins in this population of patients.

CONCLUSIONS

The effects of statins on lipid profile were somewhat different from their effects on lipid profile in other patients with hyperlipidemia. Atorvastatin and then lovastatin were able to reduce inflammation by lowering HSCRP, while simvastatin had no significant effect on HSCRP. These drugs cannot reduce IL-6, although atorvastatin showed a nonsignificant reducing effect in this respect. Despite the ineffectiveness of simvastatin on inflammation, it was found to be the most effective drug on the serum lipids such as LDLC in ESRD patients.

CONFLICT OF INTEREST

None declared.

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