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Effect of atorvastatin on inflammatory markers in hemodialysis patients

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Abstract

Background: Cardiovascular disease is the commonest cause of death in patients with end-stage renal disease (ESRD) under maintenance hemodialysis. Dyslipidemia, oxidative stress, and low-grade inflammation with increased circulating cytokines are factors that increase the cardiovascular risk in patients with chronic kidney disease, in addition to traditional risk factors, such as obesity, hypertension, and diabetes. We aimed to investigate the possible anti-inflammatory effects of atorvastatin in prevalent hemodialysis patients. Fifty-three stable adult hemodialysis patients were assigned into two groups (a drug group and a control group). Patients in the drug group received 20 mg of atorvastatin daily for 6 months. Serum levels of highly sensitive C-reactive protein (hs-CRP) and interleukin-6 (IL-6) were measured in both groups at baseline and at the end of the study period.

Results: Atorvastatin therapy caused a statistically significant decrease in levels of hs-CRP but no change in levels of IL-6 after 6 months of therapy.

Conclusions: In addition to its favorable effect on lipid profile parameters, atorvastatin therapy can be considered as an effective and safe modality to overcome the problem of chronic inflammation encountered in end-stage renal disease patients.

Keywords: C-reactive protein, Interleukin-6, End-stage renal disease, Inflammation

Background

Cardiovascular disease is still considered the most common cause of mortality and morbidity in end-stage renal disease (ESRD) patients undergoing maintenance hemodialysis. Cardiovascular mortality in this patient population is about 30 times higher than the general population [1].

In addition to the traditional risk factors such as diabetes, hypertension, and obesity, the crucial role of inflammation in the pathogenesis of cardiovascular disease recently began to emerge, with several studies highlighting the ominous role of inflammatory mediators in this setting [2].

Statins, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are used for the treatment of dyslipidemia. In addition to their lipid-lowering effects, they also have antioxidant, anti-inflammatory, and immunomodulatory effects, collectively known as "pleiotropic" effects [3]. These "pleiotropic" effects are achieved by inhibiting the synthesis of a variety of compounds, including isoprenoids derived from the mevalonate pathway which are involved in many important biological processes in all cell types [4].

The anti-inflammatory effects of statins and their favorable effects on cardiovascular risks have been well studied in the general population [5].

In this interventional randomized controlled trial, we evaluated the effects of atorvastatin treatment on the inflammatory markers (hs-CRP and IL-6) in prevalent hemodialysis patients.

Methods

Fifty-three adult stable patients with ESRD on maintenance hemodialysis for at least 6 months were included in this study. Exclusion criteria included patients with a history of previous or current malignancy, recent surgery, genetic dyslipidemia, myopathies, or signs of active inflammation; smokers; and those taking corticosteroids,

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antioxidants, and any hypolipidemic drugs for the preceding 2–3 months. Patients with three or more fold elevation of liver enzymes were also excluded. A detailed medical history was taken from each participant.

After eligibility was confirmed, patients were randomly assigned to one of the two groups. Randomization was done using sealed opaque envelops with random numbers. Each patient had an envelope once he/she agreed to participate in the study to be in one of the two groups:

- Group 1 (drug group) which included 33 patients who received oral atorvastatin 20 mg daily [6] for a period of 6 months
- Group 2 (control group) which included 20 patients who did not receive atorvastatin

In all patients, hemodialysis was performed three times a week for 4 h on average, using the same dialyzer. A bicarbonate dialysis solution was used during hemodialysis sessions with an average flow rate of 300 ml/h. All the selected patients had an adequate dialysis with urea reduction ratio > 65%. Periodic follow-up visits were done for patients in their dialysis units.

A written informed consent was obtained from all patients participating in the study after explaining the benefits of the given therapy, its implications on their health, and the expected side effects.

Measurements

Citrate samples of venous blood were collected in the morning and in the fasting state before the mid-week session. The serum was separated, and samples were either analyzed immediately or kept frozen at − 80 °C until the time of assay.

1. hs-CRP at baseline and after 6 months using a high-sensitivity C-reactive protein ELISA Kit (Chemux-BioScience Inc., CA, USA)
2. IL-6 at baseline and after 6 months using the Human Interleukin-6 ELISA Kit (Glory Science Co. Ltd., Del Rio, TX, USA)
3. Hemoglobin level
4. Lipid profile (total cholesterol, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), and serum triglyceride levels at baseline and after 6 months using standard kits)
5. Alanine transaminase (ALT), aspartate transaminase (AST), and total creatine kinase (CK-T) levels at baseline and at the end of the study period (after 6 months) using standard kits

Sample size calculation

After reviewing the literature [7], we used G*POWER statistical programming (version 3.1.9.4; Franz Faul, University of Kiel, Germany) to calculate the sample size per group. Using $a = 0.05$, a power of 85%, an effect size of 0.835, and an allocation ratio of 2:1 showed that a sample size of 60 (40 patients in the treatment group and 20 patients in the control group) was needed to avoid type II error. Seven patients were lost to follow-up from the drug group (2 underwent renal transplantation, 3 developed muscle pain with normal creatine kinase levels, 2 were non-compliant and asked to stop). So, there were 33 patients only in the drug group,

Statistical analysis

Data are presented as mean ± SD or N (%). The baseline characteristics of patients randomized to the drug or control groups were compared by chi-square (χ^2 test) or independent samples t test. Paired t tests were used to compare values obtained at baseline and after 6 months. P less than 0.05 is considered statistically significant, and P less than 0.001 is considered highly statistically significant. The statistical analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA).

Results

This study included 53 stable adult hemodialysis patients who were divided into two groups (Table 1):

1. Group 1 (drug group) which included 33 patients who received an oral daily dose of 20 mg of atorvastatin for a period of 6 months
2. Group 2 (control group) which included 20 patients who did not receive atorvastatin

There was no statistically significant difference in age, sex, duration of hemodialysis therapy, and presence of diabetes, hypertension, or hepatitis C between the two groups (Fig. 1).

Overall, the underlying cause of renal failure was hypertension ($n = 25$), obstructive uropathy ($n = 8$), diabetic nephropathy ($n = 6$), unknown cause ($n = 5$), chronic glomerulonephritis ($n = 3$), interstitial nephritis ($n = 3$), lupus nephritis ($n = 2$), and autosomal dominant polycystic kidney disease ($n = 1$).

Baseline biochemical characteristics of the drug and control groups showed no statistically significant difference regarding levels of inflammatory markers (hs-CRP and IL-6), lipid profile parameters, and liver or muscle enzymes. The mean LDL in the atorvastatin group was 106.18 ± 39.82 mg/dl prior to the treatment which means that some of these involved patients had baseline LDL ≈ 65 mg/dl; this was to detect the anti-inflammatory effect in patients with dyslipidemia and patients without dyslipidemia (Table 2).

Atorvastatin therapy for 6 months caused a statistically significant decrease in levels of hs-CRP ($P < 0.001$).

Table 1 Comparison between the drug and control groups as regards the demographic data of the enrolled patients at baseline

	Drug group (***n*** = 33)	Control group (***n*** = 20)	Test	***P*** value
Age (years)	52.03 ± 11.36	49.30 ± 10.86	$t = 0.743$*	0.393
Gender				
Male	15 (45.5%)	11 (55%)	$\chi^2 = 0.454$**	0.501
Female	18 (54.5%)	9 (45%)		
Duration of dialysis (years)	7.29 ± 5.69	7.55 ± 5.21	$t = 0.028$*	0.867
HCV-Ab positive	10 (30%)	9 (45%)	$\chi^2 = 1.170$**	0.279
Hypertension	19 (58%)	13 (65%)	$\chi^2 = 0.287$**	0.592
Diabetes mellitus	4 (12%)	6 (30%)	$\chi^2 = 2.600$**	0.107

Data are mean ± SD or *N* (%) for all variables
HCV-Ab hepatitis C virus antibody
*Independent sample *t* test
**Chi-square test

However, there was no significant change in levels of IL-6 at the end of the study period ($P = 0.918$). No change from baseline readings was demonstrable in the control group.

In the drug group, there was a statistically significant decrease in levels of total cholesterol ($P < 0.001$), LDL cholesterol ($P < 0.001$), and triglycerides ($P < 0.001$), in addition to a significant rise in levels of HDL cholesterol ($P = 0.021$) in response to atorvastatin therapy. No significant changes were observed in the control group.

Regarding the effect of atorvastatin therapy on liver and muscle enzymes, our results showed that there was no significant change in levels of liver transaminases as well as total creatine kinase after 6 months of atorvastatin therapy.

It shows a high statistically significant change in total cholesterol level (P value < 0.001), LDL (P value < 0.001), triglycerides (P value < 0.001), and in hs-CRP (P value < 0.001) in the drug group after 6 months of atorvastatin therapy. There was a significant change in HDL (P value < 0.021) in the same group. Also, there was a significant change in LDL level (P value < 0.051) in the control group. There was a statistically significant difference in total cholesterol level (P value < 0.001), LDL (P value < 0.001), triglycerides (P value < 0.001), and in hs-CRP (P value < 0.001) between the changes that occur in the

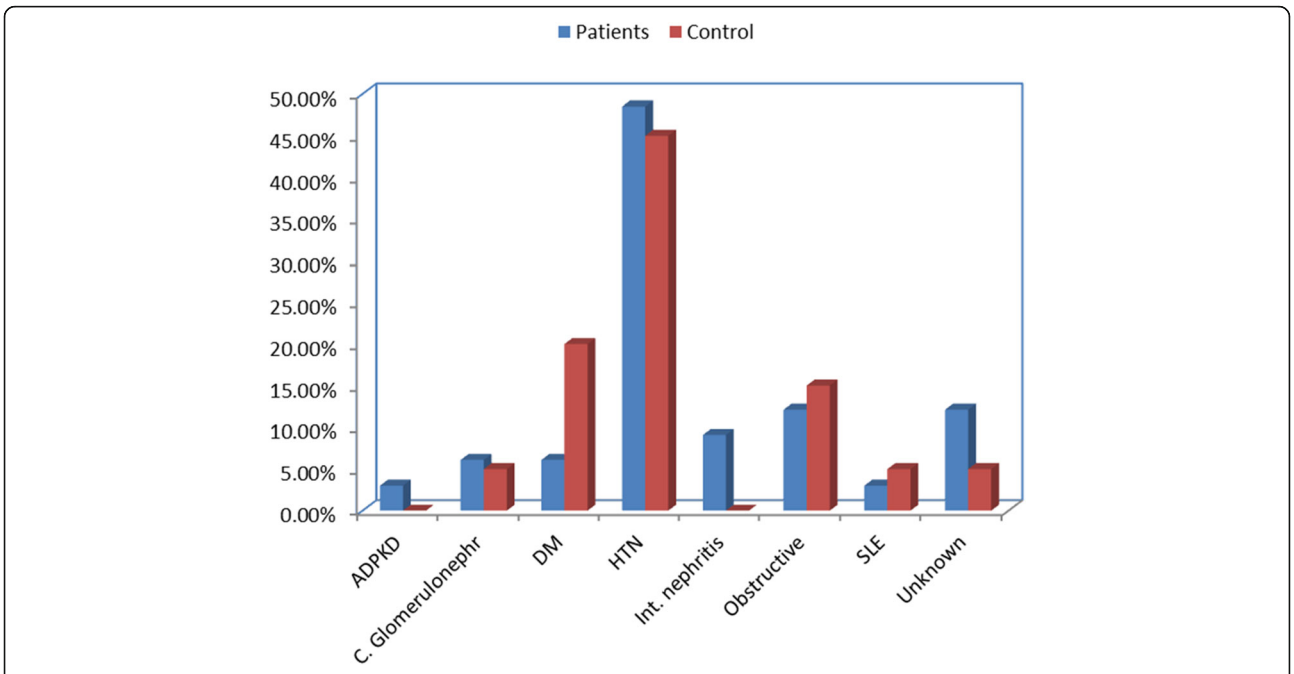

Fig. 1 Bar chart showing a comparison between the drug and control groups according to the etiology of renal failure

Table 2 Comparison between the drug and control groups as regards the biochemical data at baseline and after 6 months

		Groups		*t* test	
		Drug group, mean ± SD	Control group, mean ± SD	*t*	*P* value
AST	**Baseline**	17.879 ± 6.348	17.200 ± 6.469	0.375	0.709
	After 6 months	15.242 ± 5.831	15.550 ± 6.219	− 0.182	0.857
ALT	**Baseline**	15.727 ± 6.458	13.450 ± 5.799	1.292	0.202
	After 6 months	14.061 ± 4.115	13.550 ± 6.452	0.352	0.726
CK-T	**Baseline**	67.182 ± 32.520	71.350 ± 33.039	− 0.450	0.655
	After 6 months	69.242 ± 28.306	81.900 ± 33.176	− 1.478	0.145
T. cholesterol	**Baseline**	177.152 ± 43.952	164.650 ± 56.611	0.899	0.373
	After 6 months	122.667 ± 30.370	175.800 ± 60.845	− 4.237	< 0.001*
HDL	**Baseline**	35.030 ± 8.372	37.050 ± 9.827	− 0.797	0.429
	After 6 months	38.909 ± 8.364	37.150 ± 10.205	0.683	0.498
LDL	**Baseline**	106.182 ± 39.819	93.200 ± 43.397	1.112	0.271
	After 6 months	67.758 ± 22.240	110.000 ± 47.703	− 4.380	< 0.001*
Triglycerides	**Baseline**	179.939 ± 65.941	171.650 ± 73.992	0.424	0.674
	After 6 months	97.879 ± 39.478	155.800 ± 68.743	− 3.906	< 0.001*
IL-6, pg/ml	**Baseline**	6.543 ± 4.499	6.800 ± 4.295	− 0.205	0.838
	After 6 months	6.627 ± 4.214	7.085 ± 3.575	− 0.406	0.687
CRP, mg/l	**Baseline**	8.989 ± 5.223	9.688 ± 5.000	− 0.480	0.634
	After 6 months	4.850 ± 4.058	9.826 ± 4.746	− 4.058	< 0.001*

Data are mean ± SD for all variables
hs-CRP highly sensitive C-reactive protein, *IL-6* interleukin-6, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *ALT* alanine transaminase, *AST* aspartate transaminase, *CK-T* total creatine kinase
*Independent sample *t* test

case and control groups from baseline to 6 months after atorvastatin therapy in the drug group (Tables 3, 4, 5, 6, and 7).

Discussion

Persistent low-grade inflammation appears to be an important contender in the pathogenesis of cardiovascular disease and the ensuing morbidity and mortality in prevalent hemodialysis patients [8]. In this study, we investigate the possible anti-inflammatory effects of atorvastatin in ESRD patients undergoing hemodialysis.

The results of our study revealed that atorvastatin therapy caused a statistically significant decrease in levels of hs-CRP after 6 months of therapy; however, it

Table 3 Comparison between the drug and control groups as regards the change in the biochemical data at baseline and after 6 months

	Drug group, mean ± SD	Paired test, *P* value	Control group, mean ± SD	Paired test, *P* value	*t* test, *P* value
AST	2.636 ± 7.717	0.058	1.650 ± 6.507	0.271	0.635
ALT	1.667 ± 6.406	0.145	− 0.100 ± 8.169	0.957	0.385
CK-T	− 2.061 ± 28.402	0.680	− 10.550 ± 42.960	0.286	0.390
T. cholesterol	54.485 ± 46.438	< 0.001*	− 11.150 ± 40.547	0.234	< 0.001*
HDL	− 3.879 ± 9.215	0.021*	− 0.100 ± 6.617	0.947	0.116
LDL	38.424 ± 41.218	< 0.001*	− 16.800 ± 36.071	0.051*	< 0.001*
Triglycerides	82.061 ± 53.615	< 0.001*	15.850 ± 46.164	0.141	< 0.001*
IL-6, pg/ml	− 0.084 ± 4.641	0.918	− 0.285 ± 4.503	0.780	0.878
hs-CRP, mg/l	4.140 ± 4.530	< 0.001*	− 0.138 ± 4.782	0.899	0.002*

Data are mean ± SD for all variables
hs-CRP highly sensitive C-reactive protein, *IL-6* interleukin-6, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *ALT* alanine transaminase, *AST* aspartate transaminase, *CK-T* total creatine kinase
*Paired sample *t* test

Table 4 Linear regression analysis displaying independent predictors of IL-6 at baseline

	Unstandardized coefficients		Standardized coefficients	*t*	*P* value
	B	Std. error	Beta		
Age	0.046	0.079	0.117	0.586	0.563
HD duration (years)	0.028	0.178	0.035	0.157	0.876
AST	0.008	0.239	0.011	0.032	0.975
ALT	− 0.099	0.243	− 0.141	− 0.405	0.689
CK-T	0.015	0.028	0.109	0.536	0.597
HDL	0.017	0.115	0.033	0.152	0.880
LDL	0.032	0.025	0.280	1.257	0.221
Triglycerides	− 0.009	0.015	− 0.138	− 0.647	0.524

Dependent variable: IL-6, pg/ml, baseline
None of the studied variables is an independent predictor of IL-6 level at baseline
IL-6 interleukin-6, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *ALT* alanine transaminase, *AST* aspartate transaminase, *CK-T* total creatine kinase

failed to cause a significant change in levels of IL-6 when compared to baseline levels.

The results published by Dornbrook-Lavender et al. [9] and Vernaglione et al. [10] come in line with our results. In both studies, 10 mg of atorvastatin was administered to hemodialysis patients for 5 and 6 months, respectively. Despite the lower dose used, compared to our study, both studies showed a significant decrease in levels of hs-CRP. This decrease was statistically significant in the study by Vernaglione et al. [10], and sizeable but nonetheless insignificant in the study by Dornbrook-Lavender et al. [9].

Our results also agree to those by Tian et al. [11] where two groups of hemodialysis patients received either 20 mg of atorvastatin or 10 mg of rosuvastatin daily for 12 weeks. Both drugs significantly reduced the concentrations of hs-CRP; however, this effect was more pronounced in the atorvastatin group accompanied with improved nutritional status.

In the study by Kirmizis et al. [12], a daily dose of 10 mg of simvastatin for 6 months caused a significant decrease in levels of hs-CRP along with a significant decrease in levels of IL-6 in hemodialysis patients, which comes in partial agreement with our results.

A higher dose of simvastatin was evaluated in the studies by Chang et al. [7] and Shahbazian et al. [13]. In both trials, a daily dose of 20 mg of simvastatin was given to a group of hemodialysis patients, for a period of 8 weeks and 12 weeks, respectively. In accordance with our results, in both studies, levels of hs-CRP showed a significant decrease at the end of the study period. However, Shahbazian et al. [13] also reported a significant decrease in levels of IL-6. These similarities in the effect on levels of hs-CRP come despite the shorter duration of statin administration in both studies compared to our study (8 weeks and 12 weeks versus 24 weeks in our study). This may suggest that the anti-inflammatory effect exerted by statins can be elicited both in the short and long terms.

The shortest recorded duration evaluated, as far as our knowledge goes, for the effect of a statin on levels of inflammatory makers comes from the study by Tsirpanlis

Table 5 Linear regression analysis displaying independent predictors of hs-CRP at baseline

	Unstandardized coefficients		Standardized coefficients	*t*	*P* value
	B	Std. error	Beta		
Age	0.131	0.083	0.286	1.583	0.127
Duration (years)	− 0.154	0.187	− 0.168	− 0.822	0.419
AST	0.344	0.252	0.418	1.364	0.185
ALT	− 0.328	0.257	− 0.406	− 1.277	0.214
CK-T	0.018	0.030	0.113	0.609	0.548
HDL	0.068	0.121	0.109	0.561	0.580
LDL	0.004	0.027	0.032	0.156	0.877
Triglycerides	0.004	0.015	0.046	0.236	0.815

Dependent variable: hs-CRP, mg/l, baseline
None of the studied variables is an independent predictor of hs-CRP level at baseline
hs-CRP highly sensitive C-reactive protein, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *ALT* alanine transaminase, *AST* aspartate transaminase, *CK-T* total creatine kinase

Table 6 Linear regression analysis displaying independent predictors of IL-6 after 6 months

	Unstandardized coefficients		Standardized coefficients	*t*	*P* value
	B	Std. error	Beta		
Age	− 0.054	0.083	− 0.146	− 0.657	0.517
Duration (years)	0.196	0.149	0.264	1.312	0.202
AST	0.216	0.216	0.300	1.004	0.326
ALT	− 0.433	0.295	− 0.423	− 1.468	0.156
CK-T	− 0.005	0.030	− 0.033	− 0.161	0.873
T. cholesterol	0.048	0.107	0.344	0.444	0.661
HDL	0.131	0.153	0.259	0.856	0.401
LDL	− 0.102	0.127	− 0.538	− 0.805	0.429
Triglycerides	− 0.017	0.036	− 0.159	− 0.467	0.645

Dependent variable: IL-6, pg/ml, after 6 months
None of the studied variables is an independent predictor of IL-6 level after 6 months
IL-6 interleukin-6, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *ALT* alanine transaminase, *AST* aspartate transaminase, *CK-T* total creatine kinase

et al. [14], in which a daily dose of 40 mg of fluvastatin was administered for a period of 4 weeks only. In complete disagreement with our results, levels of IL-6 decreased significantly at the end of the study period, while CRP levels did not change.

As regards the effect of atorvastatin on different parameters of lipid profile, our results revealed that the drug caused a statistically significant decrease in levels of total cholesterol, LDL cholesterol, and serum triglycerides with a significant increase in levels of HDL cholesterol.

These results agree fully with the results reported by Tsirpanlis et al. [14] and Tian et al. [11]. However, the latter reported that levels of LDL cholesterol decreased more significantly with improved nutrition status in the rosuvastatin group compared with the atorvastatin group.

Although the results by Kirmizis et al. [12] showed a significant decrease in levels of total cholesterol, LDL cholesterol, and triglycerides, HDL levels remained unchanged from their baseline values, which does not agree with our results.

Regarding the safety of atorvastatin therapy in hemodialysis patients who are considered to be a vulnerable subset of the population, our results revealed that transaminase levels as well as total creatine kinase levels failed to show any significant change in the drug group after intake of the drug for 6 months when compared to the control group.

This comes in agreement with the results by Tsirpanlis et al. [14], who demonstrated that there was no significant rise in the levels of AST and creatine kinase associated with fluvastatin therapy.

Also, in accordance with our results, Vernaglione et al. [10] and Shahbazian et al. [13] failed to record any significant elevations in hepatic or muscle enzymes that may be interpreted as side effects related to atorvastatin and simvastatin use, respectively.

Table 7 Linear regression analysis displaying independent predictors of hs-CRP after 6 months

	Unstandardized coefficients		Standardized coefficients	*t*	*P* value
	B	Std. error	Beta		
Age	0.052	0.070	0.146	0.741	0.466
HD duration (years)	− 0.190	0.127	− 0.266	− 1.496	0.148
AST	− 0.308	0.184	− 0.443	− 1.679	0.107
ALT	0.346	0.251	0.351	1.378	0.181
CK-T	0.059	0.026	0.452	2.303	0.031*
T. cholesterol	0.036	0.091	0.270	0.395	0.697
HDL	− 0.141	0.130	− 0.291	− 1.088	0.288
LDL	− 0.049	0.108	− 0.269	− 0.456	0.653
Triglycerides	− 0.045	0.031	− 0.437	− 1.453	0.160

Dependent variable: CRP, mg/l, after 6 months
None of the studied variables is an independent predictor of hs-CRP level after 6 months except for CK-T (P value < 0.031)
hs-CRP highly sensitive C-reactive protein, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *ALT* alanine transaminase, *AST* aspartate transaminase, *CK-T* total creatine kinase

None of the patients in the drug group in the study by Shahbazian et al. [13] suffered any clinical side effects related to drug intake. In contrast, three patients who were originally allocated to the drug group in our study suffered from mild muscle pains nearly 1 month after starting atorvastatin therapy and chose to stop the drug, after which their symptoms readily improved. However, total creatine kinase levels performed for these patients at the time of complaint did not show any abnormalities. They were excluded from the statistical analysis.

Of special interest is the lack of correlation in our study between hs-CRP levels and total as well as LDL cholesterol levels after 6 months of atorvastatin therapy. This was also true for the results demonstrated by Vernaglione et al. [10], where hs-CRP levels did not correlate with levels of total cholesterol after 6 months of atorvastatin intake. Such scenarios suggest that the decrease in serum hs-CRP levels would be attributed to an effect of atorvastatin on hs-CRP, independent from the reduction in serum total or LDL cholesterol levels, entailing a different mechanism of action of statins on inflammatory markers.

This hypothesis is in disagreement with the results by Kirmizis et al. [12], which demonstrated a positive correlation between the decrease in levels of hs-CRP and the relative decrease in levels of total as well as LDL cholesterol, a finding that was not present in our study. However, in the same study, no similar correlation was found between changes in the lipid profile and IL-6 levels.

Linear regression analysis displaying independent predictors of IL-6 and hs-CRP at baseline and after 6 months showed that none of the studied variables is an independent predictor of IL-6 and hs-CRP except for CK-T (P value < 0.031) in hs-CRP level after 6 months.

The absence of a significant reduction in IL-6 by atorvastatin could be related to its greater diurnal variability [15] and shorter half-life (2 to 4 h) compared with CRP (20 h) [16]. Accordingly, it is likely that IL-6 was changing more rapidly than increasing its variance compared with CRP. Although the reductions in IL-6 with atorvastatin were not statistically significant, the trend observed for this marker agreed with the changes seen with CRP; this comes in agreement with Scott Kinlay et al. who studied the effect of high-dose atorvastatin (atorvastatin 80 mg/d) on the decline in inflammatory markers in patients with acute coronary syndromes in the MIRACL Study [17].

Conclusion

Atorvastatin therapy can be considered as an effective and safe modality to overcome the problem of chronic inflammation encountered in end-stage renal disease patients on maintenance hemodialysis. This is reflected by its effect on reducing levels of hs-CRP, evident after 6 months of therapy, in addition to its favorable effect on lipid profile parameters in this patient population.

Abbreviations

HCV: Hepatitis C virus; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ESRD: End-stage renal disease; SPSS: Statistical Package for Social Sciences; Hb: Hemoglobin; hs-CRP: Highly sensitive C-reactive protein; IL-6: Interleukin-6; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; CK-T: Total creatine kinase; HMG-CoA: 3-Hydroxy-3-methylglutaryl coenzyme A; ELISA: Enzyme-linked immunosorbent assay; MIRA CL: Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering

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Authors' contributions

NOA and NMT analyzed and interpreted the patient data. GEM, HSH, and SMS put the study design. NMT was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Ethics approval and consent to participate

This study was performed in accordance with the ethical standards of the Ain Shams University Research Committee (committees reference number 340/2015) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.
A written informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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