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Effect of Lovastatin on Lipid peroxidation and total antioxidant concentrations in hemodialysis patients

Hassan Argani*[1,2], Amir Ghorbani[2], Nadereh Rashtchizade[2] and Mohammad Rahbaninobar[2]

Address: [1]Hemodialysis and Nephrology Division of Emam Hospital, Tabriz University of medical Sciences, Tabriz, Iran and [2]Biochemistry lab. Drug Applied Research Center, Tabriz University of medical sciences. Tabiz, Iran

Email: Hassan Argani* - hassanargani@hotmail.com; Amir Ghorbani - ghorbaniamir@hotmail.com; Nadereh Rashtchizade - Rashtcizadeh@hotmail.com; Mohammad Rahbaninobar - Rahbanim@hotmail.com

* Corresponding author

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Abstract

Background: Atherosclerosis is the main cause of mortality and morbidity in end stage renal diseases (ESRD), especially in hemodialysis (HD) patients. In addition the classic risk factors for atherosclerosis, non classical risk factors, such as high lipid peroxidation and low antioxidants, also, are culprit in the pathogenesis.

Method: We tested lipid peroxidation and total antioxidant levels in forty five stable hyperlipidemic HD males (age range 40–60 years) before, after 45 and 90 days of prescription of 20 mg/day Lovastatin for three months. Malondialdehyde (MDA), as prototype of lipid peroxidation, and total antioxidants (TA) were measured by flourimetric and spectrophotometric assays, respectively.

Results: Serum triglyceride (Tg) (213.7 ± 112.4 mg/dl vs. 153.4 ± 54.8 mg/dl p = 0.003), serum cholesterol (C) (185.8 ± 48.3 mg/dl vs. 149.3 ± 37.8 mg/dl, p = 0.014), LDL-C (120.1 mg/dl ± 48.9 vs. 84.8 ± 43.7 mg/d, p = 0.001), VLDL-C (40.7 ± 18.9 mg/dl vs. 30.7 ± 10.9 mg/dl, p = 0.025), MDA (13.1 ± 3.5 nmol/ml vs. 1.27 ± 1 nmol/ml, p = 0.00), TA (0.98 ± 0.17 mmol/l vs. 1.28 ± 0.27 mmol/l, p = 0.001) and HDL (24.9+11.1 mg/dl vs. 31.4 ± 7.7 mg/dl, p = 0.007) significantly were changed by 3 months of Lovastatin therapy. These changes for HDL, VLDL and Tg after the 3 months were more obvious than 45 days of Lovastatin therapy.

Conclusion: In HD patients serum lipids and their oxidations are increased. Both of them, quantitatively and qualitatively, are improved by using of Lovastatin. The later would be due to enhance of TA activity.

Introduction

End stage renal diseases (ESRD), despite of the different etiologies, show a common hyperatherogenic state [1]. This may be due to existence of classic and nonclassic risk factors. Hypertension, hyperlipidemia, diabetes mellitus and cardiovascular hypertrophy as the first group, and

Table 1: Serum lipoproteins, MDA and total antioxidants before and after beginning of Lovastatin at the end of 1.5 and 3 months.

markers time	Cholesterol (mg/dl)	LDL-C (mg/dl)	VLDL-C (mg/dl)	HDL-C (mg/dl)	TG (mg/dl)	MDA (nmol/ml)	Total Antioxidant (mmol/ml)
Pre Lovastatin	185.8 ± 48.3	120.1 ± 48.9	40.7 ± 18.9	24.9 ± 11.1	213.7 ± 112.4	13.1 ± 3.5	0.98 ± 0.17
45 days after Lovastatin	150.9 ± 32	83.9 ± 38.3	36.6 ± 15.6	29.0 ± 12.2	183.3 ± 78.1	3.68 ± 2.6	1.16 ± 0.29
90 day after Lovastatin	149.3 ± 37.8	84.8 ± 43.7	30.7 ± 10.9	31.4 ± 7.7	153.4 ± 54.8	1.27 ± 1.0	1.28 ± 0.27

hyperhemocycteinemia, increased Lpa, inflammation, hyperfibrinogenemia and oxidative stresses, as the later, are usually seen in ESRD. Higher levels of triglyceride (Tg) and cholesterol (C) are observed in 33%–70% and 20%, respectively [2]. Higher melvalonate level (due to its retention in ESRD) [3], lower serum albumin concentration [4], lower lipoprotein lipase enzyme [5] and lower Lecithin cholesterol acetyl transferase (LCAT) enzyme [6] are responsible for dyslipidemia. Although hyperlipidemia due to the above causes is a main factor for atherosclerosis in ESRD, lipid peroxidation has an important role, also [7]. Malondialdehyde (MDA), a prototype of lipid peroxidation metabolite, is accumulated in ESRD. Higher concentration of MDA may be due to defective antioxidant defense in ESRD [8]. Statins by their inhibitory actions on HMG-CoA enzyme and decrement of liver Apo-B100 synthesis, and also by lowering of LDL susceptibility to oxidation, are well known drugs for treatment of hyperlipidemia of ESRD [9]. But their effect on total antioxidant (TA) and their relationship with MDA need more studies in HD patients.

Subjects and methods

In this study we selected 45 male HD patients. All of them were dialyzing 3 times per week by cuprophane membrane and acetate solution for 4 hours at each session. Drug schedules did not change during the study. They had negative history of hypolipidemic drug consumption at least during the two months prior the study. The age range was between 40 to 60 years. General conditions were stable in all of them, i.e. no active infection, no myocardial infarction and no malnutrition were present. Lipoproteins, MDA and total antioxidant capacity were measured by enzymatic, flourimetric and spectrophotometric assays, respectively, at the time of zero, 1.5 and 3 months after using of 20 mg/day of Lovastatin. Results of the above data were analyzed by SPSS 10.05. ANOVA and paired t test were used to comparison of parametric variables after Lovastatin therapy. Pearson's coefficient relation and linear regression analysis were used for any possible correlations between the variables. $P < 0.05$ was considered significant.

Results

At the beginning of the study the mean levels of total C, Tg, LDL-C, VLDL-C, HDL-C, were 185.8 ± 48.3 mg/dl, 213.7 ± 112.4 mg/dl, 120.1 ± 48.9 mg/dl, 40.7 ± 18.9 mg/dl and 24.9 ± 11.1 mg/dl, respectively. MDA level and TA activity were 13.1 ± 3.5 nmol/ml and 0.98 ± 0.17 mmol/l, respectively (Table 1). 45 days after treatment by Lovastatin significant decrease in levels of total C (150.9 ± 32 mg/dl, $p = 0.002$), LDL-C (83.9 ± 38.3, $p = 0.001$), VLDL-C (36.6 ± 15.6 mg/dl, $p = 0.001$) and MDA (3.68 ± 2.6 mg/dl, $p = 0.000$) were observed. But serum levels of Tg (183.3 ± 78.1 mg/dl, $p = 0.064$) and HDL-C (29 ± 12.2 mg/dl, $p = 0.17$) did not change significantly. It was also a significant increase in TA level after this period of Lovastatin therapy (1.16 ± 0.29 mmol/l, $p = 0.022$) (fig. 1).

After 3 months of Lovastatin therapy the hypolipidemic effect on total C, LDL-C, VLDL-C was maintained, even more than before. In addition serum levels of HDL-C increased (31.4 ± 7.7 mg/dl, $p = 0.007$) and Tg decreased (153.4 ± 54.8 mg/dl, $p = 0.003$), significantly. At that time more obvious decrease in serum MDA (1.27 ± 1 nmol/ml, $p = 0.00$) and increase in TA activity (1.28 ± 0.27 mmol/l, $p = 0.001$) was observed, also (fig. 2). Although it was not a significant at the base It was an inverse linear correlations between TA activity and serum level of MDA during Lovastatin therapy, especially at the 90th day of Lovastatin administration ($r = -0.7$, $p < 0.05$), Although, such a significant correlation was not present at the pretreatment period.

Discussion

In this study we showed that hyperlipidemia, especially hypertryglyceridemia, is common in HD patients. In other studies its prevalence has been reported up to 70% in ESRD [2]. Despite of hyperlipidemia quantitatively, as a main factor of atherosclerosis, changes of lipid qualities, also, are among the important risk factors [10]. The later is not improved after beginning of dialysis, even it may becomes more severe [11].

Reactive oxygen species (ROS), contributory to mitochondrial electron transport and superoxide formation, affect lipids and eventually leads to lipid peroxidation in HD

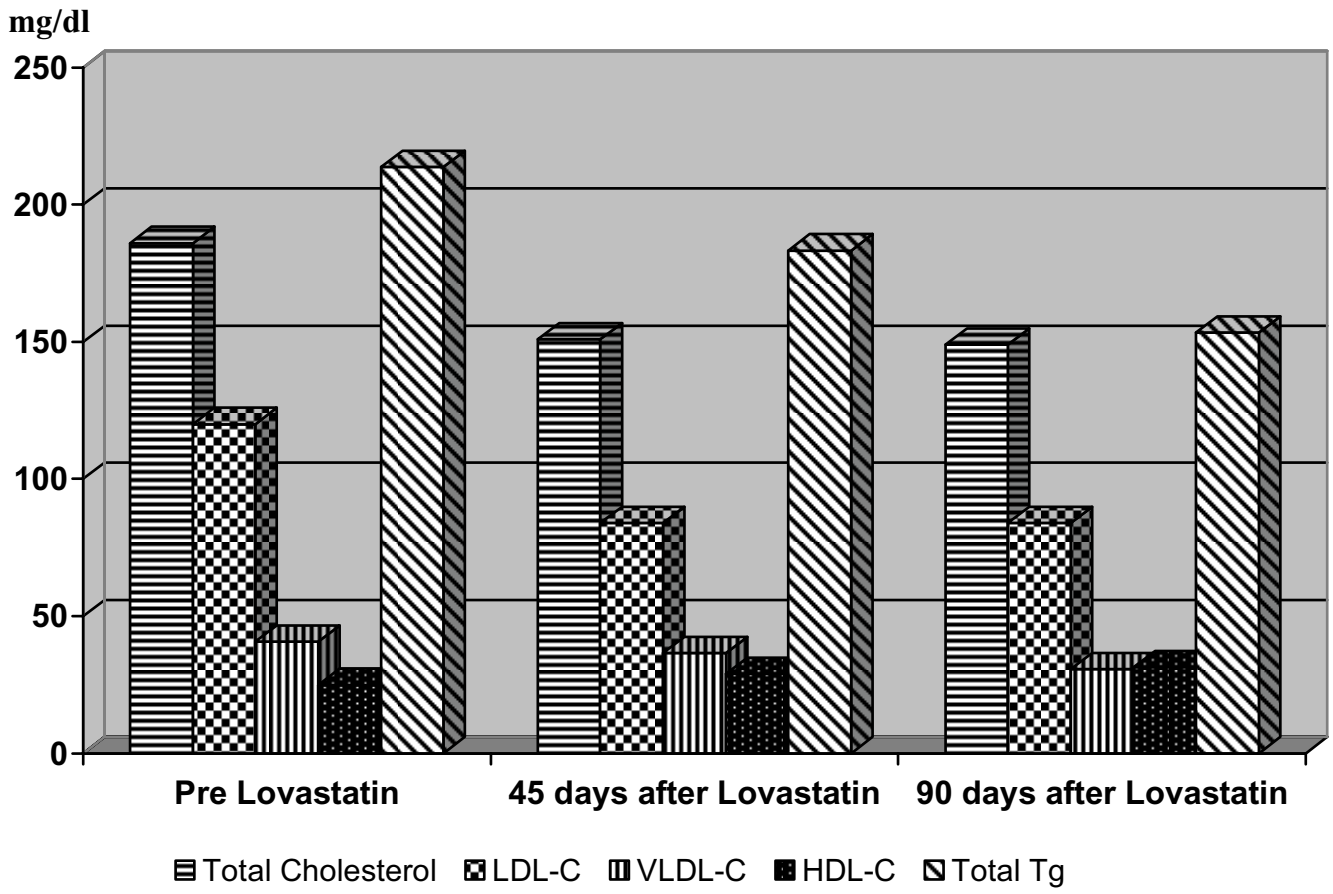

Figure 1
Serum lipoproteins before and after beginning of Lovastatin at the end of 1.5 and 3 months

patients. Recent studies have demonstrated that this lipid peroxidation even has more important relationship with atherosclerosis than hyperlipidemia alone [12]. The effect may be reversible after adding of Lovastatin on the culture medium of endothelial cells. Oxidized LDL results to aggravate of atherosclerotic process by accumulation of intracellular Ca++, recruitment of macrophages, to induce cytokines and proliferation of endothelial cells. On the other hand superoxide desmotase (SOD), catalaze and glutathione peroxidase (GSHPX) are among the main defensive antioxidant agents, which scavenge oxygen free radicals in HD [13]. So they have a protective role to development of atherosclerosis by ROS and their products, i.e. oxidized lipids.

Lovastatin, as a prototype of HMG-CoA inhibitors, is used as an anti atherosclerotic drug in clinic. Although the protective role on atherosclerosis may be partially due to its lowering effect on lipid level by inhibition of HMG-CoA enzyme, the full story is not complete. It inhibits expression of scavenging receptors on macrophages [14], inhibits super oxide anion production, preserves intracellular SOD, prevents of ROS permeation in to the lipoproteins [9] and eventually has a preventive role on inflammation [15]. The above assumption of anti oxidant properties of Lovastatin was demonstrated by our study, although it was not observed at the short term, i.e. during 45 days of treatment. But after 3 months of Lovastatin therapy it was an inverse linear relationship between decrement of MDA and increased total anti oxidant activity. Our result confirms the previous study, which has demonstrated that Lovastatin causes to block LDL-C oxidation of WBC in rabbits at concentration of 10 micro mol/l [16]. This blockage had an inverse correlation with SOD, also. On the other hand we showed that VLDL-C and LDL-C lipoproteins are reduced significantly after Lovastatin consumption. HDL-C, the protective lipoprotein against of atherosclerosis, was increased significantly only after longer time (3 months) of Lovastatin consumption. Hypolipoproteinemic effect of Lovastatin in 54 diabetic

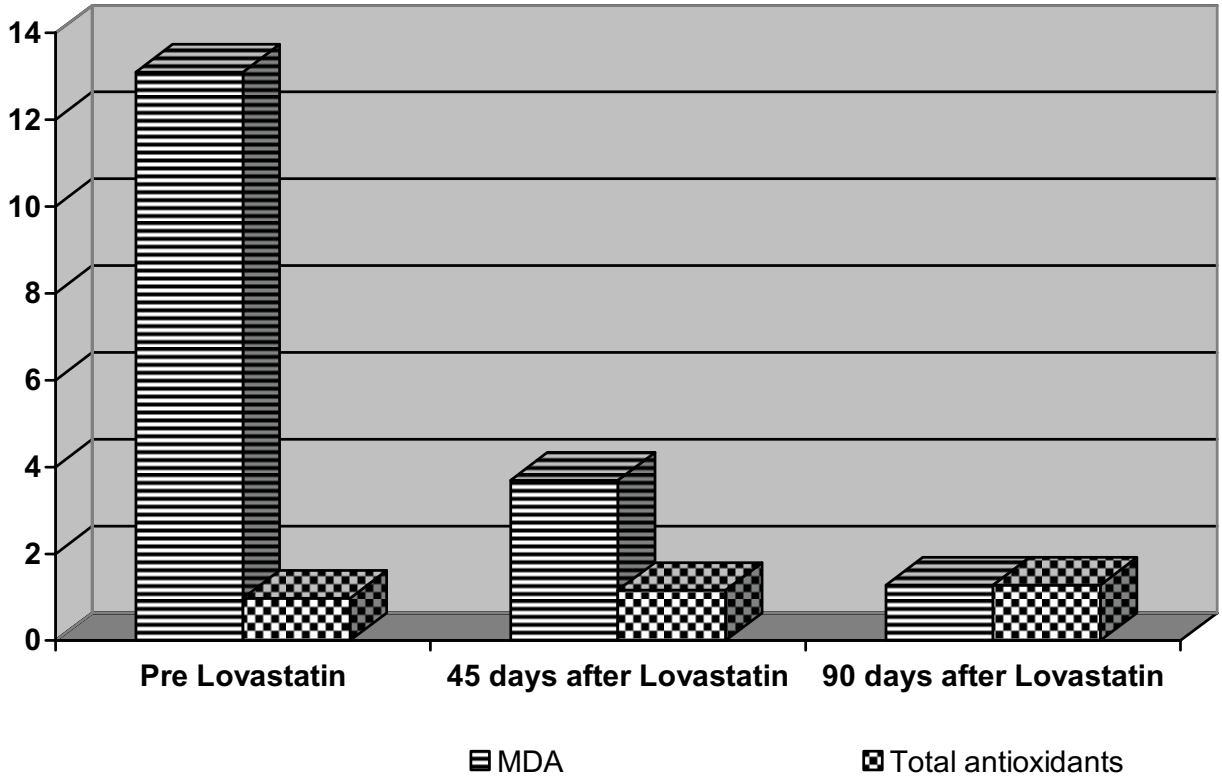

Figure 2
Serum MDA (nmol/ml) and Total antioxidants (mmol/L) before and after beginning of Lovastatin at the end of 1.5 and 3 months.

hamsters has been shown by Swefy etal study, also. They found that Lovastatin and vitamin E have anti oxidant property and decrease lipoprotein concentration after 12.5 weeks of therapy [17].

In summary we showed that dyslipoproteinemia, as a main risk factor of atherosclerosis in ESRD, is common in HD patients. Changes of lipoproteins in HD patients are quantitatively (higher lipids) and qualitatively (higher oxidized lipids) are reversible by prescription of Lovastatin in these high risk patients.

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