The effect of atorvastatin treatment duration on oxidative stress markers and lipid profile in patients with coronary artery diseases: A case series study

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Original Article

Abstract

BACKGROUND: The major aim of this study was evaluating the effect of atorvastatin treatment on thiobarbituric acid reactive substances (TBARS), ferric reducing the ability of plasma (FRAP), small dense low-density lipoprotein cholesterol (sdLDL) and lipid profile in coronary artery disease (CAD) patients.

METHODS: This study was carried out on 83 patients with angiographically proven coronary artery stenosis (52 men and 31 women) at Shahid Madani Hospital, Khorramabad, Iran, in 2015. The patients were divided into the 3 groups. 27 patients were classified statins consumption less than 6 days, 28 patients for 6 to 90 days, and 28 patients for more than 90 days. The level of sdLDL, lipid profile, TBARS and FRAP were assayed.

RESULTS: FRAP levels of patients that received atorvastatin for more than 90 days (832 ± 101) were significantly elevated (P = 0.01) compared to the patients received atorvastatin less than 6 days (688 ± 75), whereas the levels of TBARS diminished significantly (P = 0.04). Also, the levels of total cholesterol (TC) and LDL-C were significantly decreased after 3 months of atorvastatin receiving (158 as compared to patients that consumed atorvastatin less than 6 days), (P = 0.02 and 0.03, respectively). The level of sdLDL was slightly increased with long-time consumption of atorvastatin (37 ± 14) in patients in comparison with patients that received atorvastatin less than 6 days (32 ± 15) (P = 0.06), but was not significant.

CONCLUSION: The serum level of TBARS decreased and the serum level of FRAP increased in patients with long-time receiving atorvastatin. Therefore, atorvastatin contributes to the lowering oxidative stress in these patients.

Keywords: Atorvastatin, Coronary Artery Disease, Oxidative Stress

Introduction

Coronary artery disease (CAD) is the consequence of atherosclerosis, a vascular disorder. CAD is the first cause of mortality and debility in the developed countries.[1] Atherosclerosis, the primary cause of CAD, is a heterogeneous disorder and a multifactorial disease. Oxidative stress is known to be involved in a number of human disorders including atherosclerosis.[2-4] Elevation of oxidants and reduction of antioxidants play the main role in the incidence and development of atherosclerosis. Hydroxymethylglutaryl-CoA reductase inhibitors (statins) promote reductions in plasma levels of low-density lipoprotein cholesterol (LDL-C), a primary risk factor for CAD. Statins raise a considerable study interest due to their pleiotropic effects such as antioxidative, anti-inflammatory and endothelium protective capabilities.[5,6]

LDL-C particles have two phenotypes: phenotype A consisting of large buoyant LDL-C, and phenotype B which contains small dense LDL-C (sdLDL).[5] sdLDL is a subfraction of LDL-C with smaller particle size and higher density that is strongly associated with the development of CAD. In addition, sdLDL has prolonged plasma residence time compared to native LDL-C, and had a lower affinity for the LDL-C receptor. On the other hand, sdLDL particles are highly susceptible to oxidation

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than large buoyant LDL-C. Their oxidation concept is related to the atherogenic potential of sdLDL particles and is associated with incident atherosclerosis.[6,7] Several studies found that sdLDL particles had lower affinity for the LDL-C receptor, and therefore have a longer residence time in plasma, which affects them to oxidative alteration and their increased affinity to bind to intimal proteoglycan.[8,9] In addition, other studies have highlighted that people with sdLDL particles are prone to the formation and development of atherosclerosis and sdLDL is more atherogenic than native LDL.

People with a predominance of sdLDL have a 3 fold increased risk of myocardial infarction. Relative risk is 4.5 fold for CAD and 7 fold for myocardial infarction when sdLDL > 100 mg/dl.[10,11] sdLDL was also found to be elevated in patients with diabetes, metabolic syndrome and other disorders such as preeclampsia. There is also an association between sdLDL and early atherosclerosis in menopausal women.[12-15]

Although atorvastatin clearly decreases total LDL-C particle level, it is unclear whether it can affect the concentration of sdLDL. Also, several studies have reported that statin treatment results in a reduction of malondialdehyde (MDA) and or lipid peroxidation products as oxidative stress-related markers.[16-18] However, there are several questions about the duration of intake, required dose of statin and response to the therapy in atorvastatin treatment of CAD. The main aim of this study was evaluating the serum levels of sdLDL, thiobarbituric acid reactive substances (TBARS) and ferric reducing the ability of plasma (FRAP) as total antioxidant capacity index after 20 mg/day consumption of atorvastatin in atherosclerosis patients.

Materials and Methods

This study was carried out on 83 subjects considered as CAD patients (52 men and 31 women, aged 60 ± 11 years) diagnosed with positive angiography as the golden standard at Shahid Madani Hospital, Khoramabad, Iran, in 2015.

All subjects were given written informed consents. The research protocol was approved by the Ethics Committee of Lorestan University of Medical Sciences, Lorestan, Iran, (Ethics Committee registration number was 200/72425).

Inclusion criterion was coronary heart disease (CHD) patients diagnosed by coronary angiography. Exclusion criteria were diabetic patients, patients with any concurrent illness like chronic liver disease,

hypothyroidism and active rheumatologic disease, and patients on drugs like diuretics, steroids, oral contraceptives and beta blockers.

Fasting blood samples were collected into tubes. Serum was recovered after centrifugation at 3500 rpm for 10 minutes at 4 °C and stored at -80 °C until analysis. Atherosclerosis patients were divided into 3 groups on the basis of 20 mg/day consumption of atorvastatin. 27 patients were classified as atorvastatin consumption less than 6 days, 28 patients consumed 6 to 90 days and 28 patients received for more than 90 days.

Serum TBARS were measured by a modified spectrophotometric (Shimadzu Corp, Kyoto, Japan) method by using tetramethoxypropane as a standard and a standard curve was constructed using solutions of 0-100 μM. All measurements were carried out in duplicate. TBARS are expressed in terms of MDA equivalents.[19]

The level of FRAP was measured according to previously published methods.[20] In brief, three reagents were used including sodium acetate in acetic acid buffer (pH = 3.6), 10 mM solution of 2,4,6-tripyridyl-s-triazine in a 40 mM solution of hydrochloric acid, and 20 mM solution of ferric chloride. The FRAP reagent was prepared daily with 25 ml of reagent 1, and 2.5 ml reagent 2 and 3.

Serum FRAP was measured by adding FRAP reagent to serum and the absorbance at 540 nm was measured in a microplate reader. All measurements were carried out in duplicate. FRAP concentrations were calculated with a calibration curve of iron (II) sulfate ($FeSO_4$) (100-1000 μmol/l).

Serum sdLDL was measured by using a precipitate method described previously.[21] The precipitation reagent (0.1 ml) containing 150 U/ml heparin-sodium salt and 90 mM $MgCl_2$ was added to each serum sample (0.1 ml), mixed, and incubated for 10 minutes at 37 °C. Then, each sample was placed in an ice bath for 15 minutes. After centrifugation at 15000 rpm for 15 minutes at 4 °C, the precipitate was packed at the bottom of the tube and the clear supernatant consisted of sdLDL.

The serum levels of fasting blood sugar (FBS), triglyceride (TG), total cholesterol (TC), LDL and high-density lipoprotein cholesterol (HDL-C) were analyzed. FBS, TC and TG concentrations were measured by biochemical analyzer using commercial kits (Olympus AU-600, Tokyo, Japan).

HDL-C was analyzed by a Pars Azmoon kit (Iran). All measurements were carried out in duplicate. LDL-C was determined by a calculation, according to our previous study.[22]

Table 1. Difference of baseline characteristics among three various durations of atorvastatin (20 mg/day) consumption in coronary artery stenosis patients

Variable	Groups of patients according to consumption of atorvastatin			P*
	< 6 days (n = 27)	6-90 days (n = 28)	> 90 days (n = 28)	
Sex (man)	17 (63.0)	20 (67.8)	18 (64.3)	0.20
Smoking	15 (55.6)	14 (50.0)	15 (54.0)	0.14

Data are shown as number (%); *Chi-square test

The data were analyzed by SPSS software (version 20, IBM Corporation, Armonk, NY, USA). Continuous variables were mentioned as mean ± standard deviation (SD) and categorical variables as number and percentage. Normality of the variables was confirmed by Kolmogorov-Smirnov test. Hence, comparison of mean values between studied groups was performed using analysis of variance (ANOVA) followed by post-hoc pairwise comparisons by Tukey's test. Discontinuous variables were analyzed with the chi-square test. P less than 0.05 was considered statically significant.

Results

The difference of baseline characteristics among three various durations of 20 mg/day atorvastatin consumption in coronary artery stenosis patients is shown in tables 1 and 2.

There was no significant difference in age (P = 0.12), sex (P = 0.20), body mass index (BMI) (P = 0.51) and smoking (P = 0.14) between three groups (Tables 1 and 2). Also, There was no significant difference in levels of FBS (P = 0.39), TG (P = 0.17), HDL-C (P = 0.48), erythrocyte sedimentation rate (ESR) (P = 0.24) and sdLDL (P = 0.24) among three groups (Table 3).

The levels of TC and LDL-C in patient groups with long-time receiving atorvastatin was significantly decreased compared to the group that consumed less than 90 days (P = 0.04 and P = 0.02, respectively), while TG levels were moderately decreased (P = 0.17). The levels of HDL-C were not significantly increased after 90 days of treatment compared to atorvastatin consumption less than 6 days (P = 0.48). There was not a significant

difference in ESR levels among three groups. These differences were not significant (P = 0.24) (Table 2).

The serum FRAP index in patients received atorvastatin for more than 90 days was significantly elevated compared to the patients received atorvastatin less than 6 days (P = 0.04). While the levels of TBARS, an index of lipid peroxidation and oxidative stress, in atherosclerosis patients that consumed atorvastatin for more than 90 compared to patients taking atorvastatin less than 6 days showed a significant decrease (P = 0.04). The serum levels of sdLDL in patients that received atorvastatin for more than 90 were slightly increased compared to the patients that received less than 6 days. These differences were not significant (P = 0.24) (Table 3).

Discussion

In this study, atherosclerosis patients that received 20 mg/day atorvastatin for long-term had significantly decreased levels of cholesterol and LDL-C as compared to the patients that received atorvastatin less than 6 days. There was not any significant difference in HDL-C and TG levels among three groups. Oxidative environment develops oxidative stress because of the disparity between oxidative reactants, such as reactive oxygen species (ROS), and antioxidants.[23] Biological samples have a mixture of TBARS, including lipid hydroperoxides and aldehydes, which are an index of lipid peroxidation and oxidative stress.[24] In the present study, treatment with 20 mg/day atorvastatin for long-term in atherosclerosis patients with coronary artery stenosis led to a significant decrease in the levels of TBARS and a significant increase of serum FRAP index as total antioxidant capacity.

Table 2. Difference of baseline characteristics among three various durations of atorvastatin (20 mg/day) consumption in coronary artery stenosis patients

Variable	Groups of patients according to consumption of atorvastatin			P*
	< 6 days (n = 27)	6-90 days (n = 28)	> 90 days (n = 28)	
Age (year)	62 ± 11	58 ± 10	60 ± 11	0.12
BMI (kg/m²)	27 ± 3	26 ± 3	27 ± 2	0.51

Data are shown as mean ± standard deviation (SD); *Analysis of variance (ANOVA)
BMI: Body mass index

Table 3. Difference of fasting blood sugar (FBS), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), erythrocyte sedimentation rate (ESR), small dense LDL-C (sdLDL), ferric reducing the ability of plasma (FRAP) and thiobarbituric acid reactive substances (TBARS) among three various durations of atorvastatin (20 mg/day) consumption in coronary artery disease (CAD) patients

Variable	< 6 days (n = 27)	6-90 days (n = 28)	> 90 days (n = 28)	P*	P†	P‡	P§
FBS (mg/dl)	93 ± 22	96 ± 23	99 ± 25	0.39	0.90	0.53	0.92
TG (mg/dl)	161 ± 72	156 ± 50	141 ± 57	0.17	0.62	0.11	0.32
TC (mg/dl)	184 ± 43	178 ± 49	158 ± 26	0.04	0.39	0.03	0.08
LDL-C (mg/dl)	128 ± 33	109 ± 41	104 ± 25	0.02	0.06	0.02	0.84
HDL-C (mg/dl)	37 ± 8	39 ± 10	41 ± 7	0.48	0.79	0.38	0.79
ESR (mm/h)	17 ± 15	16 ± 9	12 ± 8	0.24	0.80	0.36	0.27
sdLDL (mg/dl)	32 ± 15	33 ± 16	37 ± 14	0.24	0.87	0.06	0.16
FRAP (µmol/l)	688 ± 75	760 ± 175	832 ± 101	0.04	0.12	0.01	0.13
TBARS (µmol/l)	2 ± 1	2 ± 1	2 ± 1	0.04	0.21	0.04	0.15

Data are shown as mean ± standard deviation (SD); * Analysis of variance (ANOVA); † Post-hoc pairwise comparisons (Tukey's test) (difference between subjects who received 20 mg/day atorvastatin less than 6 days and someone who used it 6 to 90 days); ‡ Post-hoc pairwise comparisons (Tukey's test) (difference between subjects who received 20 mg/day atorvastatin less than 6 days and someone who used it more than 90 days); § Post-hoc pairwise comparisons (Tukey's test) (difference between subjects who received 20 mg/day atorvastatin 6 to 90 days and someone who used it more than 90 days)
FBS: Fasting blood sugar; TG: Triglycerides; TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; ESR: Erythrocyte sedimentation rate; sdLDL: Small dense LDL-C; FRAP: Ferric reducing the ability of plasma; TBARS: Thiobarbituric acid reactive substances

FRAP concentrations consider the cumulative action of all the antioxidants present in plasma and body fluids and provide an integrated parameter rather than the simple sum of measurable antioxidants.[25] Our results indicated that with long-time treatment with atorvastatin oxidative stress decreased in the patients. Moreover, ESR values were decreased with increasing duration of atorvastatin use that represents a relative decrease inflammation in patients under treatment.

The results of this study are similar to the findings of the studies conducted by other researchers.[17,26,27] Some studies performed on the duration of statins intake indicated a significant decrease in the serum levels of MDA as lipid peroxidation marker in patients treated with high-dose simvastatin for at least 6 months.[28] The results of the present study suggest that a daily dose of 20 mg/day atorvastatin taking for at least three months in patients with CAD has significant effects on improving the indices of oxidative stress compared to higher doses of the drug, along with the fewer side effects.

Among LDL-C particles, the sdLDLs are believed to be atherogenic since these particles are taken up more easily by arterial wall. They are highly susceptible to oxidation and have reduced affinity for LDL-C receptor and higher affinity for arterial proteoglycans.[5-7] In our study, we showed that sdLDL was slightly increased with long-time atorvastatin consumption in patients. The results of this study are similar to the results of other studies

in terms of higher serum levels of sdLDL in patients with CAD treated with statins. These studies have shown no effect of statins in reducing serum levels of sdLDL.[29,30] However, despite the finding of the present study, other studies indicated that statins reduce sdLDL levels. Several studies conducted on the effect of statins on serum levels of sdLDL represent conflicting results on the decreased levels of sdLDL and increased size of LDL-C particles with statin therapy. Furthermore, the results of some studies suggest that the treatment with statins alters the size of LDL-C particles and, on the other hand, reduces the amount of sdLDL.[31,32] In this study, sdLDL cholesterol had a positive correlation with LDL-C, TG and TC and negative correlation with HDL-C. LDL-C, TG and TC are considered as major risk factors for coronary stenosis in atherosclerosis patients. Our findings are in agreement with previously reported outcomes demonstrating that patients with CAD had sdLDL particles and sdLDL was positively correlated to LDL-C, TG and cholesterol while was negatively correlated with HDL-C.[33]

Previous studies have shown that C-reactive protein (CRP), BMI, and metabolic syndrome can affect the level of sdLDL.[34,35] In the present study, there were no significant differences in CRP, BMI and metabolic syndrome among all groups. As increased BMI and metabolic syndrome are of factors effective in raising serum levels of sdLDL, and with respect to the fact that these variables have no significant differences in all the study groups, it

can be inferred that mild increase in serum sdLDL levels in the groups with increased duration of treatment with atorvastatin represents a negligible effect on the metabolism of sdLDL. The proposed possible mechanism may be that more than 90% of Apolipoprotein B (ApoB) is found in the LDL-C particles, and patients with sdLDL develop lower levels of ApoB.[36] Treatment with statin reduces sdLDL removal by the receptor, because statins increase LDL-C receptor activity, and other LDL particles are better ligands for LDL-C receptor than sdLDL. Therefore, a long-term treatment with statins may cause a slight increase in the levels of sdLDL.[37]

Conclusion

This study showed that atorvastatin has beneficial effects in reducing the elevated serum TBARS, as lipid peroxidation indicator, TC and LDL-C in coronary artery stenosis patients. Also, this study revealed that atorvastatin has beneficial effects in increasing the reduced serum level of FRAP as a total antioxidant capacity index in patients. Also, this study showed that sdLDL was negatively correlated with HDL-C and positively with LDL-C, TG and cholesterol. Hence, attenuation of total antioxidant capacity, TBARS, lipid profile and atherogenic index can decrease the risk of CAD and its complication such as inflammation, atherogenic process and myocardial infarction in coronary artery stenosis patients.

Acknowledgments

Conflict of Interests

Authors have no conflict of interests.

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