Effects of Atorvastatin on Coagulation Parameters and Homocysteine in Patients with Primary Hypercholesterolemia

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Background: The mechanism of the antithrombotic action of statins is unclear. We evaluated the effects of atorvastatin on the coagulation parameters and homocysteine levels of patients with primary hypercholesterolemia.

Materials and Methods: Forty-four patients with primary hypercholesterolemia were treated with atorvastatin 10 mg/d for 24 weeks at Adnan Menderes University Medical Faculty, Division of Hematology, Aydin, Turkey. We evaluated the effects of atorvastatin on homocysteine; lipid parameters such as total cholesterol, low-density-lipoprotein (LDL) cholesterol, very-low-density-lipoprotein (VLDL) cholesterol, triglycerides, high-density-lipoprotein (HDL) cholesterol, lipoprotein (a), apolipoprotein AI and apolipoprotein B; and coagulation parameters such as fibrinogen, antithrombin-III, protein C, protein S, von Willebrand factor, D-dimer, partial thromboplastin time and prothrombin time; and hematological parameters such as hemoglobin, white blood cell and platelet counts, vitamin B_{12} and folic acid.

Results: Atorvastatin significantly decreased the levels of total cholesterol, LDL cholesterol ($p<0.001$), VLDL cholesterol, triglycerides and apo B ($p<0.001$). The level of HDL cholesterol significantly increased with atorvastatin treatment ($p<0.001$). Atorvastatin significantly increased the levels of fibrinogen ($p<0.001$), but it had no effect on other coagulation factors and homocysteine ($p>0.05$). After treatment, while vitamin B_{12} levels significantly increased ($p<0.05$), other hematological parameters were not changed with atorvastatin ($p>0.05$).

Conclusion: Although there were beneficial effects of atorvastatin on lipid parameters, atorvastatin did not significantly change the level of homocysteine and hematological, and coagulation parameters, with the exception of fibrinogen and vitamin B_{12} levels.

Key words: atorvastatin ■ hypercholesterolemia ■ homocysteine ■ coagulation

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INTRODUCTION

Hypercholesterolemia is a major risk factor for the development of coronary heart disease (CHD).[1] Recently, authors have focused on the role of hypercoagulability in patients with hypercholesterolemia, and a relation has been suggested between blood lipids and hemostatic activation.[2,3] The deficiencies of antithrombin-III (AT-III), protein C and protein S, which are inhibitory factors of coagulation, may increase the risk of thrombosis.[4] Increasing the levels of fibrinogen and von Willebrand factor may contribute to the development of thrombosis.[5,6] All these factors are risk factors for the occurrence of cardiovascular diseases and stroke.[4-6] In addition, elevated plasma levels of homocysteine, apoproteins and lipoprotein (a) are associated with higher prevalence of occlusive arterial disease.[7] Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) improved prognosis in patients with CHD.[8] Moreover, statins decreased the incidence of vascular events in patients with hypercholesterolemia and CHD.[8,9] They have favorable effects, including antithrombotic, improving endothelial functions, changing thrombus formation, altering platelet aggregation and enhancing fibrinolysis.[10-12] Statins may decrease thrombin generation and change the levels of these coagulation inhibitors, fibrinogen and homocysteine.[3,10,13,14]

In this study, which was conducted at Adnan Menderes University Medical Faculty, Division of Hematology, Aydin, Turkey, we evaluated the effects of atorvastatin treatment on particular coagulation parameters and homocysteine levels in patients with primary hypercholesterolemia.

MATERIALS AND METHODS

Design and Patients

This study was one blind and prospective and lasted 24 weeks.

Risk factors and treatment goals were evaluated in patients with primary hypercholesterolemia according to the Third Report of National Cholesterol Education Program (NCEP-III).[15] These risk factors include: smoking, hypertension (blood pressure ≥140/90 mmHg or taking antihypertensive drugs), low high-density lipoprotein (HDL) cholesterol <40 mg/dl), family history of premature CHD (male and female first-degree relatives <55 years and <65 years, respectively), age (men >45 years and women >55 years). All patients had ≥2 coronary risk factors and elevated levels of low-density lipoprotein (LDL) cholesterol >130 mg/dl). Patients with any of the following conditions were excluded: a family history of hypercholesterolemia compatible with a monogenic disease; pregnancy; lactation; malignancy; CHD; type-1 or type-2 diabetes mellitus; triglyceride concentrations >500 mg/dl; body mass index (BMI) >35 kg/m^2; taking lipid-lowering drugs within eight weeks; elevated serum creatine phosphokinase and liver enzyme levels above the upper limit of normal; thrombocytopenia (platelet count <100 x 10^3/mm^3); thrombocytosis (platelet count >400 x 10^3/mm^3); history of hemorrhagic diathesis; acute and chronic hepatitis; chronic renal failure; alcohol abuse; hypersensitivity to statins; current usage of drugs such as erythromycin, oral contraceptive, thiazide diuretics, systemic steroids, heparins, oral anticoagulants and immunosuppressive agents; secondary hypothyroidism (thyroid-stimulating hormone >10 IU/ml); obstructive liver disease, renal failure (plasma creatinine >176 μmol/l); and nephrotic syndrome. Before treatment, all patients were instructed to follow the step-1 diet for four weeks.[16] This diet was also continued during this study. The step-1 diet is defined as ≤30% of total calories from fat, ≤10% of calories from saturated fat and daily dietary cholesterol <300 mg.

Patients were treated with atorvastatin 10 mg/d. Before treatment, physical examination, biochemical and hematological tests, electrocardiograms were done.

Table 1. Patients' characteristics

	Total (n=44)	Female (n=37)	Male (n=7)
Age (years)			
Mean	55 ± 10	56 ± 10	48 ± 9
Range	33–79	33–79	33–58
Hypertension (BP ≥140/90 mmHg)	14 (32%)	12 (32%)	2 (29%)
BMI (kg/m^2)	27 ± 4	27 ± 4	28 ± 4
<27	21 (32%)	19 (51%)	2 (29%)
27–30	14 (48%)	10 (27%)	4 (57%)
>30	9 (20%)	8 (22%)	1 (14%)

At the 12th and 24th weeks, these procedures were repeated. When the target level of LDL cholesterol was not reached in the patients at 12 weeks according to ATP-III, the dosage was increased to 20 mg/d. All patients received a detailed description of this study and signed consent prior to enrollment.

Laboratory Methods

Venous blood samples were obtained from the antecubital vein after an overnight fast of 12 hours. Biochemical tests such as total cholesterol, HDL cholesterol, very-low-density-lipoprotein (VLDL) cholesterol, triglycerides, glucose, liver enzymes such as aspartate and alanine aminotransferase (ALT), alkaline phosphatase and creatine phosphokinase were measured with photometric method using ILAB-1800 instrument and kits (Instrumentation Laboratory, Milan, Italy). LDL cholesterol levels were calculated by Friedewald formula: LDL cholesterol = total cholesterol – HDL cholesterol – triglycerides / 5.[17] Fibrinogen, prothrombin time (PT) and partial thromboplastin time (PTT) were measured with immunonephelometric centrifugal method using ACL Futur instruments (ACL Advanced Chemistry, Atlanta, GA). AT-III and protein C were measured with chromogenic assay D-dimer. Von Willebrand factor and protein S were measured with immunological assay using ACL Futur instruments and kits. Apolipoprotein AI, apolipoprotein B and lipoprotein (a) were measured with immunoturbidimetry method using Syncron LX (Beckman Coulter Fullerton, Fullerton, CA) instrument and kits. Homocysteine was measured with the competitive immunoassay method using Immulate (Immulate Diagnostic Products, Los Angeles, CA) hormone instrument. Vitamin-B_{12} and folic acid levels were measured with electrochemiluminescent using Elecsys 2010 instrument and kits (Hoffman La-Roche, Basel, Switzerland). Whole blood counts were performed using Coulter Gene-S instrument (Beckman Coulter, California).

Safety

Adverse effects were recorded at 12 and 24 weeks. Atorvastatin therapy was discontinued if the level of creatine phosphokinase increased >5 times of normal or if ALT level increased >3 times of normal for two consecutive visits.

Statistical Analysis

Continuous variables were displayed as means ± standard deviation. The data were analyzed using SPSS 10.0 for Windows.® Two-paired Student's t test was used in the comparison of the levels of vitamin B_{12}, folic acid and homocysteine; and coagulation, lipid and hematological parameters in between pre- and posttreatments. The differences of values between females and males were analyzed using Mann-Whitney U test. P values <0.05 were accepted as significant.

RESULTS

Thirty-seven females and seven males with primary hypercholesterolemia were enrolled in this study. Mean age was 55 ± 10 years (range 33–79). Hypertension was detected in 32% of the patients. Nine (20%) patients were obese (BMI >30 kg/m^2). Patients' characteristics are shown in Table 1. At 12 weeks, the dose of atorvastatin was increased to 20 mg in 21 of 44 (47%) patients.

At the 24th week, while atorvastatin treatment significantly decreased the levels of total cholesterol, LDL cholesterol, VLDL cholesterol, triglycerides and apolipoprotein B ($p<0.001$), it significantly increased the levels of HDL cholesterol and fibrinogen ($p<0.001$). Although vitamin-B_{12} levels were not higher than normal (>900 pg/ml), these levels significantly increased after atorvastatin treatment ($p<0.05$). However, atorvastatin had no effects on homocysteine, folic acid and other hematological, lipid and coagulation parameters ($p>0.05$). In Table 2, the results of all parameters are shown in pre- and posttreatments.

While the levels of triglycerides in females were decreased more than those of males ($p<0.001$ vs. $p<0.05$), HDL cholesterol levels in males were increased more than females after the treatment ($p<0.001$ vs. $p<0.01$). Atorvastatin significantly decreased apolipoprotein-B levels in only female patients ($p<0.001$ vs. $p>0.05$). Fibrinogen levels significantly increased in only female patients ($p<0.001$ vs. $p>0.05$). Vitamin-B_{12} levels significantly increased in only male patients ($p<0.05$ vs. $p>0.05$). There were no differences for other parameters between two groups ($p>0.05$). Any difference was not found for all values between hypertensive and normotensive patients ($p>0.05$).

Adverse Effects

Adverse effects were seen in four patients (9%) treated with atorvastatin. There was headache in two patients. Constipation and anxiety were detected in one patient. Increase in ALT >3 times and creatine phosphokinase >3 times the upper limit of normal did not occur in any patient. In one of the patients, ALT level increased to two times of normal at the eighth week of treatment. But atorvastatin was not discontinued in any of the patients because of adverse effects.

DISCUSSION

In our study, while atorvastatin had favorable effects on lipid parameters, it did not change any of the coagulation parameters, with the exception of fibrinogen levels.

Atorvastatin significantly decreased the levels of total cholesterol, LDL cholesterol, VLDL cholesterol, triglyc-

Table 2. The values initially and at 24th weeks after atorvastatin treatment

	Total (n=44)		Female (n=37)		Male (n=7)	
Parameters	**Pretreat.**	**Posttreat.**	**Pretreat.**	**Posttreat.**	**Pretreat.**	**Posttreat.**
Total cholesterol (mg/dl)	299 ± 35	214 ± 45***	296 ± 30**	217 ± 47***	315 ± 53	201 ± 34***
Triglyceride (mg/dl)	201 ± 110	149 ± 73***	183 ± 73	179 ± 74***	282 ± 118	186 ± 78*
LDL cholesterol (mg/dl)	205 ± 31	128 ± 35***	207 ± 28	111 ± 22***	214 ± 44	120 ± 30***
VLDL cholesterol (mg/dl)	40 ± 18	28 ± 11***	37 ± 15	26 ± 9***	56 ± 24	37 ± 17***
HDL cholesterol (mg/dl)	53 ± 13	61 ± 16***	56± 14	58 ± 18**	44 ± 9	50 ± 10***
Lipoprotein (a) (mg/dl)	19 ± 41	28 ± 76	17 ± 38	27 ± 77	34 ± 57	37 ± 78
Apolipoprotein AI (g/l)	1.5 ± 0.3	1.5 ± 0.3	1.5 ± 0.3	1.6 ± 0.3	1.4 ± 0.2	1.4 ± 0.2
Apolipoprotein B (g/l)	1.6 ± 0.3	1.2 ± 0.5***	1.6 ± 0.3	1.2 ± 0.5***	1.1 ± 0.4	1.1 ± 0.5
Prothrombin time (sec)	12.1 ± 0.9	12.7 ± 1	12 ± 0.9	13 ± 1	12.7 ± 0.9	12.3 ± 0.9
Partial thromboplastin time (sec)	22.5 ± 2.1	22.9 ± 1.9	22.4 ± 2.2	23 ± 2	23.3 ± 1.3	22.7 ± 1.5
D-dimer (ng/ml)	195 ± 73	197 ± 85	189 ± 75	195 ± 85	229 ± 53	209 ± 91
von Willebrand factor (%)	119 ± 31	118 ± 30	119 ± 32	115 ± 31	120 ± 28	133 ± 25
Fibrinogen (mg/dl)	328 ± 91	403 ± 81***	325 ± 86	408 ± 80***	346 ± 121	376 ± 88
Protein C (%)	101 ± 20	100 ± 20	102 ± 20	101 ± 21	96 ± 20	94 ± 7
Protein S (%)	83 ± 18	82 ± 11	82 ± 16	83 ± 11	88 ± 27	78 ± 11
Antithrombin-III (%)	109 ± 18	117 ± 17	110 ± 19	115 ± 15	107 ± 18	116 ± 16
Hemoglobin (g/dl)	13.3 ± 1.3	13.2 ± 1.3	13.1 ± 1	12.9 ± 1	14.6 ± 1.9	14.6 ± 1.5
White blood cell count (x10^6/mm^3)	6.9 ± 1.5	7.3 ± 1.3	6.7 ± 1.4	7.3 ± 1.4	8 ± 2.1	7.6 ± 1.1
Platelet count (x10^6/mm^3)	297 ± 68	289 ± 61	295 ± 69	287 ± 60	309 ± 69	300 ± 67
Homocysteine (mmol/l)	14.5 ± 8.8	16 ± 9	13.5 ± 7.4	14.4 ± 7.2	19.9 ± 13.5	24.7 ± 12.5
Vitamin B12 (pg/ml)	319 ± 143	370 ± 137*	334 ± 147	378 ± 137	242 ± 88	331 ± 143*
Folic acid (ng/ml)	9.5 ± 3.3	9.8 ± 3.7	9.8 ± 3.3	10 ± 3.8	7.8 ± 2.6	9.2 ± 3.6

* $p<0.05$, ** $p<0.01$, *** $p<0.001$

erides and apolipoprotein B. Moreover, HDL cholesterol levels increased with atorvastatin. The effects of atorvastatin on lipid parameters, with the exception of HDL cholesterol, were more in females than males. It may be due to the number difference between the male and female groups. Although atorvastatin significantly decreased apolipoprotein-B level, it nonsignificantly increased lipoprotein (a) and apolipoprotein-AI levels in our study. The reduction in the level of apolipoprotein B was 22%. It might be related to a decrease in the levels of LDL cholesterol and VLDL cholesterol, because apolipoprotein B, which is the main protein, composes VLDL cholesterol, LDL cholesterol and intermediate-density lipoprotein cholesterol.[18]

Apolipoprotein-AI deficiency, elevated plasma apolipoprotein-B and lipoprotein (a) levels are risk factors for atherosclerosis.[19-21] The effects of atorvastatin on apolipoproteins are favorable. In previous studies, atorvastatin increased the levels of apolipoprotein AI and lipoprotein (a), and it decreased apolipoprotein-B levels.[19,20,22]

Atorvastatin reduces total cholesterol and LDL cholesterol levels in patients with hypercholesterolemia and CHD. But whether decreasing morbidity and mortality is the result of the lipid-lowering properties of statins or is due to their effects on hemostasis is controversial.[23,24] Colli et al.[25] stated that antithrombotic effects of statins are not only related to lipid-lowering effects. Lipophilic statins interfere with tissue factor biosynthesis by human macrophages through inhibition of the synthesis of the isoprenoid, which is also involved in the posttranslational modification of other proteins.[25] Tissue factor, a membrane-bound glycoprotein, plays a role in the extrinsic coagulation pathway and fibrin deposition.[26]

In our study, fibrinogen level significantly increased by 23% after 24 weeks. But this increase was more significant in female patients. Serum fibrinogen levels, which are also a cardiovascular risk factor, are directly correlated with plasma viscosity. Fibrinogen levels may be increased or decreased with atorvastatin treatment.[5,17] In some studies, atorvastatin (10–80 mg/d) significantly increased fibrinogen levels by 12–44%.[27,28] In our study, atorvastatin treatment did not significantly change the levels of D-dimer, von Willebrand factor, protein C, protein S and AT-III.

In some reports, it was detected that statins have no effects on D-dimer, von Willebrand factor, homocysteine, protein C, protein S and AT-III.[10,29,30] There were conflicting results in recent reports. Tousoulis et al.[31] reported that the levels of protein C and AT-III significantly decreased, but protein S, von Willebrand factor did not change after atorvastatin treatment. Broncel et al.[32] detected that AT-III increased with atorvastatin. In two studies, von Willebrand factor significantly decreased with atorvastatin.[13,33]

Atorvastatin treatment prolonged PT and PTT in one study.[28] This effect of atorvastatin may be evaluated as a useful marker on the coagulation system in patients with hypercholesterolemia. However, atorvastatin had no significant effect on PT and PTT in our study.

We detected that vitamin-B_{12} levels significantly increased after atorvastatin treatment, but other hematological parameters did not change. This increase was significant only in male patients. In a few studies, the effects of atorvastatin on hematological parameters, vitamin B_{12} and folic acid had not been found.[14,28,34] In the literature, there is no report to explain this increase in vitamin-B_{12} levels.

Homocysteine levels increased by 10.9% in our study, But this increase was statistically nonsignificant. Homocysteine causes endothelial dysfunction and is an independent risk factor for cardiovascular disease.[35,36] Homocysteine is toxic to endothelium. It causes lipid peroxidation and inhibits nitric oxide synthase.[37] The activation of factors XII and V, and tissue factor, the increments in platelet aggregation, adhesion and LDL oxidation, the inhibition of activated protein C, thrombomodulin, heparin sulphate, and the proliferation of smooth-muscle cell are other possible mechanisms to contribute to endothelial dysfunction and atherosclerosis in hyperhomocysteinemia.[37,38] In several studies, atorvastatin treatment did not affect homocysteine levels and vitamin-B_{12} levels. However, fibrates increased homocysteine levels.[14,39-41] In our study, homocysteine levels did not change with atorvastatin treatment. The limitation of our study was the difference in the number of male and female patients.

In conclusion, atorvastatin significantly improved lipid parameters, but it did not significantly change the level of homocysteine and hematological and coagulation parameters with the exception of fibrinogen and vitamin-B_{12} levels.

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