The Effects of Atorvastatin Treatment on the Fibrinolytic System in Dyslipidemic Patients

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SUMMARY

Statins have pleiotrophic effects related to the pathogenesis of atherosclerosis and thrombogenicity of the vessel wall beyond lipid lowering. The aim of the present study was to examine the effect of atorvastatin treatment on the fibrinolytic system in patients with dyslipidemia.

The investigation was carried out on 41 dyslipidemic patients (21 males and 20 females) with a mean age of 53.8 years (range, 30-76). The patients were divided into subgroups according to their cholesterol and triglyceride levels as hypercholesterolemic (n = 26) and mixed-type hyperlipidemic (n = 15) and their risk factors for coronary heart disease including age, sex, hypertension, obesity, smoking, and family history. The patients were started on atorvastatin 10 mg/day, and evaluated within 6-12 weeks to assess the changes in fibrinolytic parameters including global fibrinolytic capacity, plasminogen activator inhibitor type-1 and tissue plasminogen activator, and lipids.

After successful lipid-lowering therapy, global fibrinolytic capacity (P = 0.003) and tissue plasminogen activator levels (P = 0.04) were found to be increased and plasminogen activator inhibitor type-1 levels (P = 0.02) decreased in dyslipidemic patients. Global fibrinolytic capacity levels increased (P < 0.001) and plasminogen activator inhibitor type-1 levels decreased (P = 0.01) in patients with hypercholesterolemia (n = 26). However, no significant changes were observed in fibrinolytic parameters in patients with mixed-type hyperlipidemia (n = 15). When the patients were separately evaluated according to risk factors, significant beneficial effects on the fibrinolytic system were observed, especially in patients without obesity and hypertension as well as in older patients and males.

These findings suggest that atorvastatin treatment has a beneficial effect on the fibrinolytic system in patients with hypercholesterolemia, but not in patients with mixed-type hyperlipidemia. Further studies are needed to show whether higher doses and longer periods of lipid lowering treatment have beneficial effects in patients with mixed type hyperlipidemia and some risk factors. (Jpn Heart J 2004; 45: 977-987)

Key words: Atorvastatin, Dyslipidemia, Global fibrinolytic capacity, Fibrinolytic system

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DYSLIPIDEMIA has been shown to be one of the major risk factors of atherosclerosis.[1,2] Clinical trials of statin therapy have demonstrated an improvement in cardiovascular end points and coronary stenosis.[3-5] However, improvement in cardiovascular endpoints and coronary stenosis is incompletely explained by the baseline or treated low density lipoprotein cholesterol (LDL-C) level,[6] as evaluated in several clinical trials.[3,7] These analyses suggest that the beneficial effects of statins on clinical events may involve a nonlipid mechanism.[8] In particular, changes in thrombus formation and degradation, alteration of inflammatory response, atherosclerotic plaque stabilization, and endothelial cell function have been correlated to therapy with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors.[9-11]

Local activation of platelets and thrombus formation adjacent to atheromatous plaques, especially where ruptured or eroded, are now recognized to be of pathophysiological importance in the acute and chronic clinical expression of coronary heart disease (CHD).[12] Thrombus formation is regulated by a complex enzyme cascade, known as the fibrinolytic system, which, when activated, breaks down fibrin. Naturally occurring tissue plasminogen activator (t-PA) and the major inhibitor of fibrinolysis, plasminogen activator inhibitor type-1 (PAI-1), are critical components of the fibrinolytic system.[13] Several studies have reported an association between increased plasma levels of PAI-1 and risk for atherosclerosis and its ischemic manifestations.[14,15] Lipoprotein (a) [Lp (a)] interferes with fibrinolysis by competing with plasminogen because of apolipoprotein (a), which has a structural homology with plasminogen. In addition to these factors, there is a new technique called global fibrinolytic capacity (GFC) which is used to evaluate the entire fibrinolytic system.[16] GFC is sensitive to all of the factors involved in the process of fibrinolysis.

The aim of the present study was to examine the effects of atorvastatin treatment on the fibrinolytic system in dyslipidemic patients by measuring of GFC, t-PA, PAI-1, and Lp (a). The relationships between the changes in the fibrinolytic system with lipids and risk factors for CHD were also investigated.

METHODS

Patients: Dyslipidemic patients were recruited via the Cardiology Department of the Medical Faculty at Karadeniz Technical University in Turkey. The investigation was carried out on 41 dyslipidemic patients (21 males and 20 females) with a mean age of 53.8 (range, 30-76) randomly selected from outpatients who visited the Cardiology Department. These subjects were classified according to their serum cholesterol levels as 26 hypercholesterolemic patients (with cholesterol levels above 240 mg/dL) and their serum cholesterol and triglyceride levels as 15

mixed type hyperlipidemic patients (with cholesterol and triglycerides above 240 and 200 mg/dL, respectively). The patients were then divided into subgroups according to their risk factors for CHD (age, sex, hypertension, obesity, smoking, family history of CHD). Age as a coronary risk factor was considered to be above 45 years old in men and above 55 years old or premature menopause in women. Hypertension at baseline was defined as systolic blood pressure greater than or equal to 140 mmHg, diastolic blood pressure greater than or equal to 90 mmHg, or current treatment with an antihypertensive medication. Obesity was defined as a body mass index greater than 30 kg/m^2. CHD in a male first-degree relative with onset at age 55 or less or a female first-degree relative with onset at age 65 or less was defined as a family history of CHD.

The patients were eligible for entry if they met the criteria of the National Cholesterol Education Program-Adult Treatment Panel (NCEP-ATP) 2 and were not receiving lipid lowering therapy before entry into the study. All underwent a screening program consisting of a medical history, medication use, habits, including current smoking, and examination and full hematologic and biochemical profiles (measurement of serum electrolytes, liver function, uric acid, creatine phosphokinase, and serum lipids). Patients with any of the following conditions were excluded: hypothyroidism, diabetes mellitus, nephrotic syndrome, renal insufficiency, hepatic dysfunction, malignant diseases, immune disorders, major surgery or infections, CHD, and anti-inflammatory or anticoagulant medication. Eighteen patients had hypertension. Twelve of the hypertensive patients were on calcium channel blockers at the time of the study, nine of whom were taking an angiotensin converting enzyme inhibitor or angiotensin I receptor antagonist. The medications were unchanged during the study.

The patients were started on atorvastatin 10 mg/day, and were evaluated within 6-12 weeks to assess the changes in fibrinolytic parameters and lipids. Fasting blood samples were drawn in the morning between 8:00 AM and 10:00 AM at baseline and after treatment. The patients were also assigned to a hypolipidemic diet regimen according to the National Cholesterol Expert Panel step 1 diet during the treatment. This diet limits dietary cholesterol to < 300 mg/day and total fats to < 30% of total calories, with < 10% of total calories from saturated fats, 10% from polyunsaturated fats, and 10% to 15% from monounsaturated fats. Successful lipid lowering treatment was defined as LDL-C levels below 130 mg/dL in patients with ≥ 2 risk factors and LDL-C levels below 160 mg/dL in patients with 0-1 risk factor (according to ATP 2 criteria).

Determination of fibrinolytic parameters and lipids and lipoproteins: Blood samples were taken after a 12 hour-overnight fast and sera were separated by low speed centrifugation for 15 minutes and stored at -20°C. Blood samples were also collected in tubes with 1 volume of 0.109 M trisodium citrate solution for evalu-

ation of GFC levels. Evaluation of GFC in the plasma by measurement of D-dimer generated from a standardized fibrin amount in the presence of a constant and limited amount of exogeneous t-PA. The assay is influenced by t-PA levels, urokinase-plasminogen activator (u-PA), single-chain urokinase plasminogen activator (scu-PA), activated protein C (APC), factor 7, plasminogen, PAI-1, and alpha-2 antiplasmin, and therefore, reflects the effectiveness of the entire fibrinolytic system.[17] GFC was measured by the semiquantitative macrotex agglutination technique (Diagnostice Stago, Asnieres-sur-Seine, France).

The enzyme immunoassay procedure was designed to determine human t-PA antigen [American Diagnostica Inc. (Greenwich, USA) as an IMUBIND t-PA ELISA kit (product no. 860)] and PAI-1 antigen [American Diagnostica Inc. as an IMUBIND PAI-1 ELISA kit (product no. 822)]. Plasma levels of Lp (a) were determined by enzyme-linked immunosorbent assay using a commercially available test kit (Biopool, Umea, Sweden) according to the procedures described by the manufacturer. Levels of total cholesterols (Cat no: 1491458) and triglycerides (Cat no: 1730711) were determined by enzymatic methods using a Hitachi 917 autoanalyzer (Hitach Corp., Japan) with Boehringer Mannheim (Roche Diagnostic, Mannheim, Germany) original reagents. High density lipoprotein cholesterol (HDL-C) was measured by the dextran sulfate-Mg^{2+} precipitation method. LDL-C was calculated by the Friedewald formula.

Statistical analysis: The results are expressed as the mean ± standard deviation. The paired *t*-test for normally distributed data or Wilcoxon's signed-rank test for nonnormally distributed data were used to compare the parameters, including GFC, t-PA, and PAI-1 lipids between baseline and after lipid lowering therapy. The chi-square test was used to compare the risk factors between hypercholesterolemic and mixed-type hyperlipidemic groups. The unpaired *t*-test or Mann-Whitney U test was used to compare parameters between the patient subgroups. Relationships among variables were assessed by the Pearson and Spearman rank-order test. A P value < 0.05 was considered to be significant. Multiple regression analysis was used to evaluate the associations of changes in fibrinolytic parameters with risk factors and also the changes in GFC levels with the changes in LDL-C, HDL-C, and triglyceride levels. Because the percent changes in variables including GFC, t-PA, and PAI-1 levels have both negative and positive numbers, they have an abnormal distribution. Therefore, the percent changes in these variables were squared and then logarithmically transformed for regression analysis.

Table I. GFC, t-PA, PAI-1, Lp (a), Lipid, and Lipoproteins Levels in Patients With Dyslipidemia at Baseline and After Lipid Lowering Therapy (n = 41)

	At Baseline	After Treatment	P
GFC, μg/mL	34.6 ± 17.4	45.1 ± 17.5	*0.003
t-PA, ng/mL	10.8 ± 4.8	13 ± 5	*0.04
PAI-1, ng/mL	54.8 ± 14	49.4 ± 13.4	*0.02
Lp (a), mg/dL	18.4 ± 26.3	18.6 ± 27	0.53
Total cholesterol, mg/dL	283.8 ± 28.7	205.2 ± 36	*0.0001
Triglycerides, mg/dL	196.7 ± 104.6	143.6 ± 70.7	*0.0001
HDL-C, mg/dL	40.7 ± 7.2	44.3 ± 8	*0.0001
LDL-C, mg/dL	201.3 ± 30.6	131.6 ± 36	*0.0001

*P < 0.05, According to paired t test and Wilcoxon's signed-rank test.
GFC = global fibrinolytic capacity; t-PA = tissue plasminogen activator; PAI-1 = plasminogen activator inhibitor type-1; Lp (a) = lipoprotein (a); HDL-C = high density lipoprotein-cholesterol; LDL-C = low density lipoprotein-cholesterol.

RESULTS

The serum GFC, PAI-1, t-PA, Lp (a), and other lipid levels in patients with dyslipidemia at baseline and after atorvastatin treatment are presented in Table I. GFC levels were found to be significantly increased after treatment (P = 0.003). Regression analysis showed that the percent change in GFC levels was not significantly associated with the percent changes in the LDL-C, HDL-C, and triglyceride levels (B = 4, Std. Error 0.63, P = 0.37). While t-PA levels increased, PAI-1 levels decreased after treatment (P = 0.04, P = 0.02, respectively). As is expected, total cholesterol (P < 0.0001), LDL-C (P < 0.0001), and triglyceride levels decreased, while the HDL-C (P < 0.0001) levels increased. No significant change was observed in Lp (a) level (P = 0.53). No significant correlations were observed among GFC, t-PA, and PAI-1 levels at baseline or after treatment. We only found a significant negative correlation between HDL-C and PAI-1 levels after treatment (r = -0.31, P = 0.04).

Patients were divided into two groups as hypercholesterolemic (n = 26) and mixed-type hyperlipidemic (n = 15). Baseline characteristics, including risk factors, treatment duration, and dosage in the hypercholesterolemic and mixed-type hyperlipidemic groups are shown in Table II. The biochemical parameters in these groups are shown in Table III. As is seen in this table, while GFC levels significantly increased (P < 0.0001), PAI-1 levels decreased (P = 0.01) in patients with hypercholesterolemia after treatment. The t-PA levels increased after treatment, but this change was not significant (P = 0.08). Also, all of the changes in the lipid parameters related to the hypercholesterolemic and mixed-type hyperlipidemic patients appeared to have changes similar to those of the total dyslipi-

Table II. Baseline Characteristics in Hypercholesterolemic and Mixed-type Hyperlipidemic Groups

	Hypercholesterolemic group (n = 26)	Mixed-type hyperlipidemic group (n = 15)	P
Age	54 ± 12	53.4 ± 9.2	0.8
Sex, Women (%)	38.5	66.7	0.08
Men (%)	61.5	33.3	0.08
Hypertension (%)	38.5	53.3	0.35
Smoker (%)	30.8	20	0.45
Obesity (%)	15.4	26.7	0.38
Family history of CHD (%)	30.8	20	0.45
Treatment dosage (mg/day)	10	10	-
Treatment duration (weeks)	7.62 ± 1.9	8 ± 2.2	0.5

$P < 0.05$, According to paired t test and chi-square test.
CHD = coronary heart disease.

Table III. GFC, t-PA, PAI-1, Lp (a), Lipids and Lipoproteins Levels in Patients With Hypercholesterolemia and Mixed-type Hyperlipidemia at Baseline and After Lipid Lowering Therapy

	In patients with hypercholesterolemia (n = 26)			In patients with mixed-type hyperlipidemia (n = 25)		
	At baseline	After treatment	P	At baseline	After treatment	P
GFC, mg/mL	32 ± 16	47 ± 19.7	*0.0001	39.2 ± 19	42 ± 13.2	0.6
t-PA	10.4 ± 4.2	13 ± 4.7	0.08	11.5 ± 5.8	13.4 ± 5.9	0.3
PAI-1	53.2 ± 15	45.7 ± 12.8	*0.01	57.4 ± 12.4	55.7 ± 12.5	0.6
Lp(a), mg/dL	17.6 ± 29.2	18.7 ± 29.7	0.6	19.8 ± 21.4	18.4 ± 23	0.7
Total cholesterol, mg/dL	280.5 ± 30	202.8 ± 36.4	*0.0001	289.6 ± 26	209.4 ± 36.3	*0.0001
Triglycerides, mg/dL	131 ± 36.6	111.8 ± 40.2	*0.002	310.5 ± 84	199 ± 79.4	*0.0001
HDL-C, mg/dL	42.3 ± 8	46.2 ± 8.6	*0.0001	37.8 ± 4.7	41.3 ± 5.8	*0.002
LDL-C, mg/dL	208.4 ± 27.4	132.8 ± 34.7	*0.0001	189 ± 32.9	129.5 ± 39.4	*0.0001

*$P < 0.05$, According to paired t test.
GFC = global fibrinolytic capacity; t-PA = tissue plasminogen activator; PAI-1 = plasminogen activator inhibitor-1; Lp (a) = lipoprotein (a); HDL-C = high density lipoprotein-cholesterol.

demic subjects (Table III). In patients with mixed-type hyperlipidemia, no significant changes were observed in the fibrinolytic parameters. No significant correlations were observed in fibrinolytic parameters between the hypercholesterolemic and mixed-type hyperlipidemic groups. The levels of fibrinolytic parameters at baseline were also compared between these two dyslipidemic groups and no significant differences were observed.

The patients were divided into subgroups according to their risk factors for CHD (age, sex, hypertension, obesity, smoking, family history). The changes in the GFC, t-PA, and PAI-1 levels in these subgroups are shown in Table IV. It was found that there were different responses to atorvastatin treatment in patients with

Table IV. Percent Changes in Fibrinolytic Parameters With Risk Factors for Coronary Heart Disease

		GFC			t-PA			PAI-1		
		At baseline	After treatment	*P*	At baseline	After treatment	*P*	At baseline	After treatment	*P*
Age	+ (n = 27)	31.8 ± 15.5	45.9 ± 16.5	*0.002	10.8 ± 5	14.3 ± 5.6	*0.02	53.7 ± 15	48.5 ± 13	0.08
	- (n = 14)	40 ± 20	43.7 ± 20	0.5	10.8 ± 4.4	10.8 ± 3.2	0.9	56.8 ± 12.6	51.2 ± 14.5	0.2
Sex	Women (n = 20)	39.6 ± 17	40 ± 12.9	0.9	10.4 ± 5.2	11.6 ± 4.3	0.4	51.3 ± 14.6	48.5 ± 15	0.45
	Men (n = 21)	29.9 ± 16.9	50 ± 20	*0.0001	11.2 ± 4.5	14.5 ± 5.5	0.07	58 ± 13	50.2 ± 12	*0.01
Hyper-tension	+ (n = 18)	32.8 ± 13.9	39.5 ± 12.7	0.08	11.2 ± 5.5	12.6 ± 5	0.4	49.4 ± 14.4	49.7 ± 14.5	0.9
	- (n = 23)	36 ± 19.9	49.5 ± 19.7	*0.01	10.4 ± 4.3	13.4 ± 5.3	*0.04	59 ± 12.6	49.5 ± 19.7	*0.001
Smoker	+ (n = 11)	24.3 ± 16.6	40.8 ± 15.6	*0.02	13 ± 6	9.8 ± 3.2	0.1	61.3 ± 16.8	50.7 ± 10.9	*0.02
	- (n = 30)	34.7 ± 20.2	44.2 ± 21.2	*0.02	12.2 ± 5	12 ± 5.4	0.8	52.7 ± 12.3	48.8 ± 14	0.14
Obesity	+ (n = 8)	31.5 ± 16	41.4 ± 15.6	0.3	9 ± 3.2	15.2 ± 5.9	0.08	55.7 ± 7.8	58.3 ± 8.4	0.5
	- (n = 33)	35.5 ± 17.9	46 ± 18	*0.006	11.2 ± 5.1	12.6 ± 4.9	0.2	54.5 ± 15.3	47.2 ± 13.6	*0.009
Family history of CHD	+ (n = 11)	29.3 ± 13.6	42.9 ± 11.8	*0.04	8.9 ± 2.9	14 ± 5	*0.02	60.8 ± 16.9	50.9 ± 11.5	0.06
	- (n = 30)	36.5 ± 18.4	46 ± 19.3	*0.02	11.5 ± 5.2	12.7 ± 5.2	0.3	52.5 ± 12.5	48.8 ± 14.2	0.1

*$P < 0.05$, statistically significant difference from baseline according to paired t test.

and without several risk factors. When the patients were separately evaluated according to the risk factors, significant positive responses in the fibrinolytic system were observed, especially in patients without obesity and hypertension as well as in elderly and male patients (Table IV). In addition, significant changes in GFC levels in patients with and without smoking ($P = 0.02$, $P = 0.02$ respectively) and family history ($P = 0.04$, $P = 0.02$, respectively) were also found. Multiple regression analysis showed that the changes in fibrinolytic parameters were not significantly associated with risk factors for CHD ($P > 0.05$).

DISCUSSION

GFC is a new parameter that examines the effectiveness of the entire fibrinolytic system. Also, this assay provides a sensitive and reliable parameter with which to evaluate the fibrinolytic potency of plasma *in vitro*.[18] In the present study, a positive effect on the fibrinolytic system, including GFC, t-PA, and PAI-1, in patients with dyslipidemia without CHD by short-term atorvastatin treatment was demonstrated.

In previous studies, the effects of atorvastatin on the hemostatic system, including various parameters, were investigated separately. In a recent study, Ata-

lar, *et al* showed that GFC was significantly increased in 36 patients with CHD and hyperlipidemia who received atorvastatin 10 mg/day for 12 weeks.[17] Also, Seljeflot, *et al* showed that the levels of t-PA activity ($P = 0.024$) and global fibrinolytic activity ($P = 0.001$) were increased, whereas the levels of t-PA antigen were decreased in patients with CHD with atorvastatin (20-40 mg) after a 1-year treatment.[19] They also found that PAI-1 activity levels were numerically reduced, although not statistically significantly.[19] The two studies mentioned above were performed in patients with CHD. The present study is a primary prevention study. In the present study, global fibrinolytic activity as demonstrated by the levels of GFC was found to be increased by atorvastatin treatment. This observed positive effect may be associated with preventing thrombus formation or enhancing clot lysis, and reducing the risk of symptomatic coronary events upon plaque rupture. It is well-known that the atherosclerotic process is closely associated with an impaired hemostatic system. Therefore, monitoring the fibrinolytic system during primary prevention may be helpful to evaluate the risk of development of the atherosclerotic process. Our results showed that GFC may be a beneficial parameter with which to determine the effectiveness of the entire fibrinolytic system.

Our results related to PAI-1 and Lp (a) agree with those of previous studies. Bertolotto, *et al* showed that treatment with atorvastatin 40 mg/day in twelve patients with hypercholesterolemia for 6 months reduced the levels of PAI-1.[20] Most controlled studies that have measured Lp (a) levels in patients receiving atorvastatin 10 to 20 mg/day for up to 1 year demonstrated no significant changes in this parameter.[21,22] On the contrary, Gonbert, *et al* showed that Lp (a) levels were significantly decreased by atorvastatin (10 mg/day) after a 6-week treatment.[23]

The increased coronary risk associated with high levels of triglycerides may be assumed to be due to alterations within the hemostatic system.[24] In the present study, no significant differences were observed in the levels of fibrinolytic parameters at baseline between the hypercholesterolemic and mixed-type hyperlipidemic patients. The positive effect of atorvastatin treatment on fibrinolytic parameters such as GFC and PAI-1 levels were significant in hypercholesterolemic patients, but not in mixed-type hyperlipidemic patients. It was suggested that the mixed-type hyperlipidemic patients were insensitive to atorvastatin treatment with respect to changes in fibrinolytic parameters. This may be associated with the trygliceride and HDL-C levels. The mean triglyceride levels (199 ± 79.4 mg/dL) after treatment in patients with mixed-type hyperlipidemia were still higher than the baseline triglyceride levels (131 ± 36.6 mg/dL) in those with hypercholesterolemia. The goal of lipid lowering therapy is to maintain triglyceride levels below 150 mg/dL according to ATP III. Also, the mean HDL-C levels

(41.3 ± 5.8) in patients with mixed-type hyperlipidemia after treatment were lower than the baseline HDL-C levels (42.3 ± 8) in those with hypercholesterolemia. It has recently been demonstrated that HDL improves endothelial function by different mechanisms.[25)]

The response to the statin treatment of the patients could be affected by several risk factors. In the present study, the patients with the age risk factor had significant changes in the levels of GFC and t-PA, but no significant changes were observed in any fibrinolytic parameter in patients without the age risk factor. Also, significant changes were observed in the fibrinolytic parameters, except t-PA in men, whereas no significant changes were observed in any fibrinolytic parameter in women. No significant differences were found in the levels of any biochemical parameter at baseline between women and men. Sex differences in the response to statin treatment have not been studied extensively. Several studies have suggested that the systemic hemostatic and/or fibrinolytic profiles of women differ from those of men, possibly due to the female hormonal status.[26,27)] In another study, although PAI-1 levels were significantly decreased in both men and women at 3 and 6 months of follow-up, the percent change in PAI-1 was more predominant in men than in women: by 18.8% and 23.5%, respectively, in men, and 12.6% and 18.7%, respectively, in women.[28)] In the study, t-PA was significantly decreased at 6 months compared with baseline and D-dimer did not change with therapy between the genders.

In the present study, significant changes were observed in fibrinolytic parameters, except t-PA in nonobese patients. No significant differences were found in the levels of any biochemical parameters at baseline between the obese and nonobese patients. The response to the statin treatment of obese patients is unknown. In a previous study, it was shown that fibrinolytic activity was lower in obese than in lean patients and fibrinolytic compensation for hypercoagulation is incomplete in obese patients with type 2 diabetes, partly because of the elevated PAI-1 in the blood.[29)]

Essential hypertension is often accompanied by abnormalities of the coagulation/fibrinolytic system, predisposing to a procoagulant state.[30)] In the present study, significant changes in fibrinolytic parameters were observed in patients without hypertension, whereas no significant changes were observed in any fibrinolytic parameter in patients with hypertension. No significant differences were found in the levels of any biochemical parameter at baseline in patients with and without hypertension.

Significant changes were observed in fibrinolytic parameters, except PAI-1, in patients with a family history of CHD, whereas significant changes were observed only in GFC levels in patients without a family history of CHD. In both smokers and nonsmokers, significant changes were only observed in GFC levels.

Lp (a) levels did not change significantly in any group. Multiple regression analysis showed there were no significant relationships between the changes in fibrinolytic parameters and risk factors for CHD. This result may have resulted from the small number of patients.

It was shown that 1) GFC and t-PA levels were significantly increased, whereas PAI-1 levels were decreased, after short term treatment by 10 mg/day atorvastatin in patients with dyslipidemia, 2) In patients with the mixed-type hyperlipidemia, no significant changes in fibrinolytic parameters were observed, and 3) When the patients were separately evaluated according to the risk factors, no significant changes in fibrinolytic parameters were observed in those who had obesity and hypertension as risk factors or in young and female patients.

These findings suggest that atorvastatin treatment has a positive effect on the fibrinolytic system in hypercholesterolemic patients but not in mixed-type hyperlipidemic patients. In addition, we suggest that mixed-type hyperlipidemic, hypertensive, and obese patients may require more aggressive lipid lowering treatment. Further studies to confirm the above findings are needed.

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