Atorvastatin Reduces Fibrinogen Levels in Patients with Severe Hypercholesterolemia: Additional Evidence to Support the Anti-Inflammatory Effects of Statins

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Key words: fibrinogen, hypercholesterolemia, atherosclerosis, inflammation

Abstract

Background: Elevated fibrinogen levels are considered a risk factor for the development of atherosclerosis and might be used as a predictor of risk for the development of atherothrombotic events. Several studies have reached equivocal conclusions regarding the effect of statins on fibrinogen.

Objectives: To evaluate the effect of atorvastatin on plasma fibrinogen levels in patients with severe hypercholesterolemia and no other risk factors.

Methods: Twenty-two patients with low density lipoprotein-cholesterol levels above 170 mg/dl (4.40 mmol/L) and with no other risk factors were included in the study. None of the patients had ever received hypolipidemic medication. Patients were followed for 24 weeks (6 office visits 4 weeks apart). During office visits, lipid profile, complete blood count, fibrinogen and C-reactive protein levels were measured.

Results: After 24 weeks of follow-up, total cholesterol decreased by 33% (287 $\pm$ 10 to 192 $\pm$ 8 mg/dl, $P < 0.001$), LDL-C by 45% (198 $\pm$ 8 to 111 $\pm$ 7 mg/dl, $P < 0.001$) and triglycerides by 21% (189 $\pm$ 26 to 138 $\pm$ 15 mg/dl, $P < 0.001$). Fibrinogen levels dropped by 18% (355 $\pm$ 26 to 275 $\pm$ 7 mg/dl, $P = 0.01$). CRP levels decreased from 0.51 $\pm$ 0.15 to 0.28 $\pm$ 0.10 mg/dl, but the difference was not statistically significant ($P = 0.09$). High density lipoprotein, hemoglobin, white blood cell and platelet counts did not change.

Conclusions: We found that atorvastatin reduces plasma fibrinogen in patients with hypercholesterolemia.

IMAJ 2004;6:456–459

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It is established that atherosclerosis is an inflammatory process of the arterial wall and that oxidation of low density lipoprotein particles is one of the triggering events of the immune/inflammatory cascade. This process results in the development of foam cells and atherosclerotic plaques [1]. There are many inflammatory markers that are risk factors for atherosclerosis and vascular events [2]. Among the inflammatory markers, C-reactive protein is the most known, with significant correlations to vascular events and mortality [2]. Another marker that is elevated in active inflammatory processes is fibrinogen, and high levels of fibrinogen were proven to be an independent risk factor for atherosclerotic events [3–5]. The role for fibrinogen is unknown, and whether it plays a role as an inflammatory marker alone or affects blood rheology and increases the risk for thrombus formation is not fully established [5].

Statins are commonly prescribed to lower cholesterol, prevent the development of atherosclerosis, and reduce the incidence of atherosclerotic events. Recent studies have shown that statins have additional effects in preventing atherosclerosis [6,7] by affecting non-lipid serum markers associated with cardiovascular disease. Although the effect of statins on plasma fibrinogen levels has been studied, different conclusions were drawn. Pravastatin was shown to reduce the levels of fibrinogen in one study [8], but another study did not show the same effect [9]. Simvastatin was shown to reduce the levels of fibrinogen if combined with HELP treatment [10], but simvastatin alone did not affect plasma fibrinogen levels [11–13]. Fluvastatin was shown to increase the levels of fibrinogen [14,15], despite reduction of plasma lipid levels. The effect of atorvastatin on plasma fibrinogen has been much investigated and debated [7,10,16–20]. Several studies found that treatment with atorvastatin causes an increase in fibrinogen levels [7,10,11,14], while others demonstrated a reduction [15–17].

The purpose of the present study was to examine the effect of atorvastatin on plasma levels of fibrinogen and CRP in patients with severe dyslipidemia.

Patients and Methods

Patients with severe hypercholesterolemia (LDL-C above 170 mg/dl) were included in the study. All patients were naive to hypolipidemic treatment. The patients signed an informed consent upon entry to the study, and the local Helsinki committee approved the study. We excluded those with additional risk factors for atherosclerosis (smoking, diabetes, hypertension, or positive family history for early ischemic heart disease) or any signs or symptoms of atherosclerotic vascular

LDL-C = low density lipoprotein-cholesterol
CRP = C-reactive protein

Table 1. Changes in parameters according to visit number.

	1	2	3	4	5	6	*P* value
Cholesterol (mg/dl)	283±6	191±6	192±5	190±6	187±5	192±8	<0.001
LDL (mg/dl)	198±5	114±5	114±5	110±5	106±4	111±7	<0.001
Triglycerides (mg/dl)	167±16	129±12	128±10	139±12	147±17	138±15	<0.001
HDL (mg/dl)	52±3	52±3	52±3	51±3	51±3	51±4	NS
Body mass index (kg/m^2)	26.5±0.8	26.6±0.8	26.5±0.8	26.7±0.8	26.8±1	26.7±1.1	NS
Hemoglobin (g/dl)	13.8±0.3	13.7±0.3	13.5±0.3	13.7±0.3	13±0.3	13.8±0.3	NS
White blood cells (cm/m^3)	6.1±0.3	5.9±0.3	6.0±0.3	6.5±0.3	6.0±0.3	6.1±0.5	NS

Lipid profile improved significantly. No difference was noted for the other parameters. *P* indicates the results of paired *t*-test between visit 1 and visit 6.

disease, as well as patients who were pregnant and those with liver enzyme elevation and known sensitivity for statin therapy. We also excluded patients with any sign of febrile or infectious illnesses before or during the follow-up period.

Patients were enrolled from December 1999 to August 2000, mostly during the spring (April–June 2000). Patients were screened after undergoing routine laboratory testing that revealed a high LDL-C level (above 170 mg/dl). After signing the consent form, patients received atorvastatin at a starting dose of 10 mg/day and were followed every 4 weeks for 24 weeks. At each visit body mass index was evaluated and the patients underwent laboratory tests, including lipid profile (cholesterol, LDL-C, HDL-C and triglycerides), fibrinogen, CRP, liver funtion tests and a complete blood count. At each visit the atorvastatin dose was adjusted to reach a target LDL-C below 100 mg/dl. Fibrinogen levels were determined by enzyme-linked immunosorbent assay. CRP levels were determined by immunoturbidometric assay (Roche Diagnostics GmbH, Mannheim, Germany).

Statistical anaysis

We used paired *t*-test to examine the effect of treatment on the different laboratory parameters, and independent sample *t*-test to examine the differences between males and females.

Results

Twenty-two patients (10 males and 12 females; mean age 53.9 ± 1.9 years, range 32–70) were included in the study. Patients' characteristics are shown in Table 1. To reach LDL-C target levels, atorvastatin doses were up-titrated at each visit, from 12.5 mg/day (1.1 mg SE) at visit 1 to 14.3 mg/day (1.4 mg SE) at visit 6 (median 10 mg/day, range 10–20 mg/day).

Atorvastatin treatment improved the lipid profile as expected. After 24 weeks of follow-up, total cholesterol levels were reduced by 33% (from 287 ± 10 to 192 ± 8 mg/dl, $P < 0.001$), LDL-C by 45% (from 198 ± 8 to 111 ± 7 mg/dl, $P < 0.001$) and triglycerides by 21% (from 189 ± 26 to 138 ± 15 mg/dl, $P < 0.001$). HDL-C levels did not change significantly [Table 1].

Fibrinogen levels dropped by 18% (355 ± 26 to 275 ± 7 mg/dl, $P = 0.01$). This reduction in fibrinogen levels was significant in both males and females (17% and 20%, respectively; $P = 0.85$ between the sexes). CRP tended to decrease, but was not statistically significant (0.51 ± 0.15 to 0.25 ± 0.11 mg/dl, $P = 0.09$). Although CRP levels did not decrease significantly, undetectable levels of CRP were measured in 8 patients (36%) at the beginning of the study, as compared to 11 (50%) patients at the end of the study [Figure 1]. Body mass index, hemoglobin, white blood cell count and platelet count did not change during follow-up [Table 1].

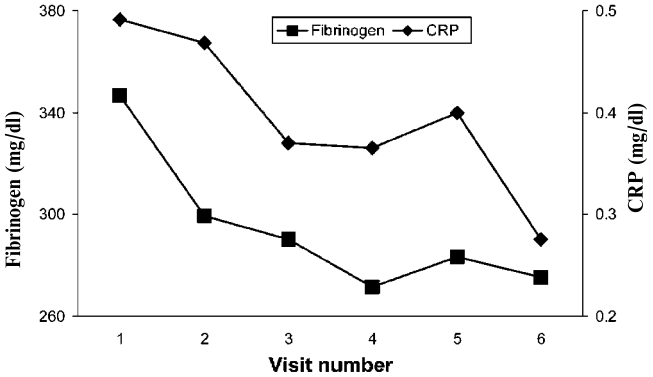

Figure 1. Changes in fibrinogen and CRP levels according to visit number. Fibrinogen changes were statisticaly significant

We found that baseline LDL levels correlated with baseline fibrinogen levels ($r = 0.62$, $P = 0.002$). We also found that the reduction in LDL levels between visit 1 and visit 6 correlated with the reduction in fibrinogen between those levels ($r = 0.58$, $P = 0.01$). Baseline CRP levels did not correlate with baseline LDL levels ($r = -0.27$, $P = 0.22$), nor did the reduction in CRP correlate with the reduction in LDL ($r = -0.18$, $P = 0.57$).

Discussion

Statins are the mainstay of hyperlipidemia treatment, especially in patients with clinically evident atherosclerotic vascular disease. Their beneficial effect on the lipid profile and their ability to reduce atherothrombotic events has been proven many times. Recent studies suggest that statins can reduce morbidity and mortality of atherosclerotic vascular disease by means other than the reduction of cholesterol [7].

Many studies have shown that high levels of inflammatory markers (such as CRP and fibrinogen) are predictors of atherosclerotic disease and atherothrombotic events [1–4]. Different interventions that affect inflammatory parameters were performed,

HDL-C = high density lipoprotein-cholesterol

and the reduction of fibrinogen levels with HELP treatment (heparin-mediated extracorporeal LDL/fibrinogen precipitation) yielded good results, both in the pathogenesis of atherosclerotic plaques in graft vessel disease [9] and in the morbidity and mortality of patients with coronary and cerebral ischemia [10]. Several studies also proved a beneficial effect of statins on different inflammatory markers like CRP [22,23] and leukocyte adhesion molecules [23], however the effects of statins on the levels of fibrinogen yielded equivocal results [7,10,11,14–17].

We wished to determine whether atorvastatin reduces the levels of fibrinogen and CRP. Since many conditions and factors influence fibrinogen (infection, inflammatory diseases, stress, environmental factors, etc.), we aimed at a very specific group of patients, excluding other illnesses, behavioral risk factors and procedures that might affect its levels. By choosing this specific group of patients we tried to isolate dyslipidemia, and perhaps the oxidized LDL particles, as the reason for increased levels of inflammatory markers.

We showed that baseline levels of fibrinogen are correlated to the levels of LDL among hyperlipidemic patients. This is suggestive of the pro-coagulant pro-inflammatory state in hyperlipidemic patients. We also found that atorvastatin significantly reduces the levels of fibrinogen, and that the reduction in fibrinogen was correlated to the LDL reduction. The mechanism of action of statins on fibrinogen is not clear. Our data suggest that the fibrinogen reduction is dependent upon lipid and lipoprotein reduction. These results are concordant with the results of Marais et al. [16]; however, several other studies did not find any association between LDL and fibrinogen [14]. It is possible that this correlation is due to the observed effect of statins on platelet-dependent thrombin formation [24]. This effect on thrombin and fibrinogen is established in some statins, mainly atorvastatin and pravastatin, and is not considered a group effect [25].

It is not clear whether this reduction of fibrinogen is a sign of decreased inflammatory activity because of decreased levels of inflammation of the arteries, or is caused by statins with no relation to their lipid-lowering effect. It is also not clear whether this reduction of fibrinogen levels might have a clinical significance; clearly, additional studies are needed to investigate this issue.

Our results show an expected reduction in CRP levels, although the reduction was not statisticaly significant. We believe that the small study size and possibly the small dose of atorvastatin given were the reasons for this lack of significance. It is likely that the effect of statins on CRP is dose related and can be demonstarted in patients with high baseline levels of CRP.

Our study has several limitations. The most pronounced limitation is the fact that we did not have a control group. Despite the lack of a control group, we believe our homogenous group of patients might prove our findings valid. Another limitation of our study is related to the fact that fibrinogen levels vary because of seasonal variations, i.e., many patients have higher fibrinogen levels during winter. This possibility was considered but found to be irrevelant since our subjects were recruited throughout the year (from January to October 1999), and most of them (65%) were recruited in the summer (May–August). Seasonal variations dictate that mean fibrinogen levels are higher in the winter and lower in the summer. Despite the expected increase in fibrinogen levels (from summer to winter), our results show a significant decrease in fibrinogen. It is thought that the equivocal effects of statins on fibrinogen were partially due to the fact that seasonal variations were not taken into consideration. It is possible that the effect of statins is too weak to be noticeable among patients with other conditions that are associated with increased levels of plasma fibrinogen (i.e., infections) [25].

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Three may keep a secret, if two of them are dead

Benjamin Franklin (1706-90), American diplomat, scientist and author

Capsule

Haemophilus influenza vaccines

The benefits of recombinant protein and DNA-based vaccines exist to a large extent in the relative ease and low cost of their production. Similarly, chemical synthesis could allow cheap and large-scale production of carbohydrate-based vaccines for bacterial infections. Verez-Bencomo et al. generated and tested a synthetic oligosaccharide vaccine against *Haemophilus influenza* type b (Hib), one of the causes of bacterial meningitis. Oligomers of specific length were first produced by using a derivative of the repeating monosaccharide unit of capsular polysaccharide of Hib. These oligosaccharides were covalently attached to tetanus toxoid, which acts as a protein carrier to generate efficient T cell help during the immune response. In clinical trials, the synthetic vaccine provided levels of immunity to Hib infection that were equivalent to the existing vaccine.

Science 2004;305:522

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Capsule

Epithelial-mesenchymal transitions and metastasis

Epithelial-mesenchymal transitions (EMTs) are processes in which normally immotile epithelial cells are converted into cells that are capable of migrating. EMTs have more recently been implicated in tumor progression and metastasis, events that likewise involve tissue remodeling and cell migration. Exciting new evidence illustrating the importance of EMTs in tumorigenesis is provided by Yang et al., who report that a transcriptional regulator of embryonic morphogenesis called Twist is required for tumor metastasis in a mouse model of breast cancer. Overexpression of Twist caused tumor epithelial cells to lose their adherent properties, become motile, and express markers of mesenchymal cells: all characteristic features of EMTs. Conversely, suppression of Twist expression by RNA interference produced a marked decline in the numbers of circulating tumor cells and lung metastases in the mice. In support of the clinical relevance of these observations, Twist expression levels in human breast cancer specimens were found to be highest in the most invasive tumors. Further studies of the mechanisms driving EMTs may help identify new drug targets for cancer.

Cell 2004;117:927

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