Brief Communication:
Plasma Lipoprotein(a) Levels and LDL-Cholesterol Lowering Response to Statin Therapy in Patients with Heterozygous Familial Hypercholesterolemia

George Miltiadou,1 Vasilios Saougos,1 Marios Cariolou,2 and Moses S. Elisaf1
1Department of Internal Medicine, Medical School, University of Ioannina, Ioannina, Greece, and 2Molecular Genetics Department, Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus

Abstract. Familial hypercholesterolemia (FH) is characterised by elevated plasma LDL-cholesterol levels and premature ischemic heart disease. Statin therapy is mandatory in order to prevent atherosclerosis in patients with heterozygous FH. Both genetic and environmental factors affect the statin-induced LDL-cholesterol lowering effect in patients with heterozygous FH. Recently published data suggest that plasma lipoprotein(a) levels may affect the efficacy of statin therapy in patients with nephrotic syndrome. However, no data are available concerning the effect of lipoprotein(a) levels on the efficacy of statin therapy in patients with heterozygous FH. This report demonstrates negative correlation between plasma lipoprotein(a) levels and the LDL-cholesterol lowering effect of statin therapy in 49 patients with heterozygous FH.

Keywords: Lipoprotein(a), familial hypercholesterolemia, statins

Introduction
Familial hypercholesterolemia (FH), the most common human genetic disorder, is characterized by high plasma LDL-cholesterol (LDL-C) levels, tendon xanthomata, and ischemic heart disease early in life. Patients with heterozygous FH have significantly higher lipoprotein(a) [Lp(a)] levels than non-FH individuals, while FH homozygotes have about 2-fold higher Lp(a) than FH heterozygotes. This increase cannot be explained by differences in apolipoprotein(a) allele frequencies [1,2]. The underlying mechanisms are unclear, but they may be related to delayed Lp(a) catabolism through the LDL receptor (LDLR), as well as other poorly understood metabolic changes [3-5].

Untreated heterozygous FH patients carry a serious prognosis due to lifelong elevated LDL-C levels. Early diagnosis and treatment of FH patients are mandatory in order to prevent premature atherosclerosis and ischemic heart disease [5]. Statin therapy is the first choice in patients with heterozygous FH [6]. However, many factors affect the response to statin therapy in patients with heterozygous FH, including the type of LDLR gene mutations, baseline LDL-C levels, and apolipoprotein E gene polymorphisms [7].

Kronenberg et al [8] showed that the efficacy of statins in lowering LDL-C depends on the Lp(a) levels in patients with nephrotic syndrome. They deduced that in populations with high Lp(a) levels, such as patients with nephrotic syndrome, the elevated Lp(a) levels may be responsible for non-responders or poor-responders to statin treatment.

We have recently published data regarding the effect of genetic and environmental factors on the response to statin therapy in patients with heterozygous FH [7]. Specifically, the administration of 20 mg of atorvastatin daily resulted in a decrease in LDL-C levels by 37% in 49 patients with heterozygous FH. The effectiveness of the statin therapy was related to the baseline LDL-C levels and the
type of the LDLR gene mutations. Heterozygotes sharing a type V mutation of the LDLR gene showed a higher percentage decrement in LDL-C levels after atorvastatin administration compared to patients sharing type II mutations (49 ± 9% vs 34 ± 9%, p = 0.001).

Patients with type V mutations have receptors with normal apolipoprotein B binding activity, but these receptors fail to recycle to the cell membrane after LDL endocytosis [9]. On the other hand, type II mutations of the LDLR gene are characterized by a failure in transport of the receptor to the cell membrane [9].

As suggested by Miltiadous et al [7], statin therapy in patients with heterozygous FH carrying a type V mutation of the LDLR gene results in more functional receptors in the cell surface and consequently in a higher decrease of LDL-C levels than in heterozygotes with a type II mutation. Moreover, statins can enhance the LDLR recycling to the cell surface after LDL endocytosis, resulting in higher receptor-mediated decrease in LDL-C in patients with defective LDLR recycling to the cell membrane [7]. However, plasma Lp(a) levels were not taken into consideration in the statistical analysis used in the above study.

Materials and Methods

This study was designed to examine the effect of the baseline Lp(a) levels on the response to statin therapy in patients with heterozygous FH. The study population, the protocol used, and the statistical analysis were the same as in our recent report [7]. In brief, 20 mg/day of atorvastatin was prescribed for 12 weeks in 49 unrelated FH patients in whom the genetic defect of the LDLR gene was previously detected. In all cases, blood samples were obtained after a 14-hr overnight fast for the determination of lipid parameters before drug administration and after 12 weeks of drug administration. Plasma LDL-C concentration was calculated using Friedewald’s formula, provided that plasma triglyceride levels were lower than 400 mg/dl. Plasma Lp(a) level was measured with a Behring nephelometer (model BN100) using reagents...
(antibodies and calibrators) from Dade-Behring Holding GmbH (Liederbach, Germany). Pearson’s correlation coefficient was determined and multiple linear regression analysis was used to estimate the independent contributions of the LDLR type mutations and of the baseline LDL-C and Lp(a) levels to the LDL-C lowering effect of the drug. All participants gave informed consent for participation in the study, and the Ethics Committee of our university hospital reviewed and approved the study protocol.

Results and Discussion

Our previously published data showed that both the type of the LDLR gene mutations and the baseline LDL-C levels affect the response to statin therapy in patients with heterozygous FH [7]. However, the effect of the baseline plasma Lp(a) levels on the LDL-C drug’s lowering effect has not been examined. As shown in Fig. 1, plasma Lp(a) levels showed negative correlation with the percent decrease of plasma LDL-C after statin therapy. This correlation was statistically significant in a multivariate analysis model, which included the type of the LDL-receptor gene mutations and the baseline LDL-C levels as covariates (Table 1).

It was previously shown that plasma Lp(a) contains about 45% cholesterol and thus, in cases with high Lp(a) levels (such as in patients with nephrotic syndrome or FH), a considerable amount of LDL-C derives from Lp(a) [8]. Since plasma Lp(a) levels are not influenced by statin treatment, the drug’s lipid-lowering effect may be masked by the extremely elevated Lp(a) concentrations in patients with FH [8].

In summary, the plasma Lp(a) level appears to be an independent factor that affects the statin-induced lipid-lowering effect in patients with heterozygous FH.

Table 1. Multivariate analysis to estimate the independent contributions of the Lp(a) levels, the type of the LDL-receptor gene mutations, and the baseline LDL-C levels to the LDL-C lowering response to statin therapy in patients with heterozygous FH.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>beta</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of the LDL-receptor gene mutation (II vs V)</td>
<td>0.60</td>
<td>0.001</td>
</tr>
<tr>
<td>Lp(a) levels</td>
<td>0.71</td>
<td>0.001</td>
</tr>
<tr>
<td>Baseline values of LDL-C</td>
<td>0.69</td>
<td>0.001</td>
</tr>
</tbody>
</table>

References