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Atorvastatin Causes Insulin Resistance and Increases Ambient Glycemia in Hypercholesterolemic Patients

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Objectives We investigated whether atorvastatin might decrease insulin sensitivity and increase ambient glycemia in hypercholesterolemic patients.

Background Clinical trials suggest that some statin treatments might increase the incidence of diabetes despite reductions in low-density lipoprotein (LDL) cholesterol and improvement in endothelial dysfunction.

Methods A randomized, single-blind, placebo-controlled parallel study was conducted in 44 patients taking placebo and in 42, 44, 43, and 40 patients given daily atorvastatin 10, 20, 40, and 80 mg, respectively, during a 2-month treatment period.

Results Atorvastatin 10, 20, 40, and 80 mg significantly reduced LDL cholesterol (39%, 47%, 52%, and 56%, respectively) and apolipoprotein B levels (33%, 37%, 42%, and 46%, respectively) after 2 months of therapy when compared with either baseline (all $p < 0.001$ by paired *t* test) or placebo ($p < 0.001$ by analysis of variance [ANOVA]). Atorvastatin 10, 20, 40, and 80 mg significantly increased fasting plasma insulin (mean changes: 25%, 42%, 31%, and 45%, respectively) and glycated hemoglobin levels (2%, 5%, 5%, and 5%, respectively) when compared with either baseline (all $p < 0.05$ by paired *t* test) or placebo ($p = 0.009$ for insulin and $p = 0.008$ for glycated hemoglobin by ANOVA). Atorvastatin 10, 20, 40, and 80 mg decreased insulin sensitivity (1%, 3%, 3%, and 4%, respectively) when compared with either baseline ($p = 0.312$, $p = 0.008$, $p < 0.001$, and $p = 0.008$, respectively, by paired *t* test) or placebo ($p = 0.033$ by ANOVA).

Conclusions Despite beneficial reductions in LDL cholesterol and apolipoprotein B, atorvastatin treatment resulted in significant increases in fasting insulin and glycated hemoglobin levels consistent with insulin resistance and increased ambient glycemia in hypercholesterolemic patients. (Effects of Atorvastatin on Adiponectin Levels and Insulin Sensitivity In Hypercholesterolemic Patients; NCT00745836) (J Am Coll Cardiol 2010;55:1209–16) © 2010 by the American College of Cardiology Foundation

Coronary heart disease is characterized by endothelial dysfunction and insulin resistance (1,2). Statins have beneficial effects on atherosclerosis mediated by decreased low-density lipoprotein (LDL) cholesterol and improving endothelial function (3). Nevertheless, the effects of statins on insulin sensitivity are not clear.

Lipophilic statins have pleiotropic actions that might cause unfavorable metabolic effects such as reduction of insulin secretion and exacerbation of insulin resistance (4–6). Recent large-scale, randomized controlled clinical trials have raised the possibility that lipophilic statins might increase the rate of new onset diabetes (7–9). Specifically, in the HPS (Heart Protection Study), in the simvastatin group 335 subjects developed diabetes, whereas in the placebo group 293 subjects developed diabetes (hazard ratio: 1.15, 95% confidence interval [CI]: 0.98 to 1.35, $p = 0.10$) (7). In the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial), the atorvastatin group developed diabetes with a hazard ratio of 1.15 (95% CI: 0.91 to 1.44) (8). In both studies, there were no significant differences between the treatment group and placebo group; however, both studies showed a trend toward an increase in new onset diabetes. In JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), rosuvastatin 20 mg

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Abbreviations andAcronyms

ANOVA = analysis of variance

CI = confidence interval

HbA1C = glycated hemoglobin A1C

hsCRP = high-sensitivity C-reactive protein

LDL = low-density lipoprotein

QUICKI = Quantitative Insulin-Sensitivity Check Index

significantly increased the rate of onset of new diabetes (3.0% vs. 2.4%, p = 0.01) with significant increase in glycated hemoglobin (HbA1C) (5.9% vs. 5.8%, p = 0.001) (9). Meta-analysis of randomized controlled trials suggested potential differences between individual statins, with pravastatin showing a trend toward a reduction in risk (risk ratio: 0.84; 95% CI: 0.86 to 1.49) and atorvastatin, rosuvastatin, and simvastatin together demonstrating a significant increase in risk (risk ratio: 1.14; 95% CI: 1.02 to 1.28) versus placebo (10). We hypothesized that atorvastatin, particularly at high dose, might decrease insulin sensitivity and increase ambient glycemia, HbA1C in hypercholesterolemic patients.

Methods

Study population. Our study was a randomized, single-blind, placebo-controlled, parallel trial in patients with hypercholesterolemia (LDL cholesterol levels ≥100 mg/dl). We recruited patients from a primary care setting in the Cardiology Department, Gil Hospital, Gachon University. Metabolic syndrome was defined according to the definition of the National Cholesterol Education Program Adult Treatment Panel III (11). Most patients were hypertensive and/or hyperlipidemic. There were some patients (n < 5) with stable angina in each group. We performed 64 multislice computed tomography scan or heart scan to help evaluate angina. We excluded patients with overt liver disease, chronic renal failure, hypothyroidism, myopathy, uncontrolled diabetes, severe hypertension, stroke, unstable angina, acute myocardial infarction, coronary revascularization within the preceding 3 months, or alcohol abuse. No patient had taken any lipid-lowering agent, hormone replacement therapy, or antioxidant vitamin supplements during the 2 months preceding our study. Activity levels of the subjects were not monitored. Clinical characteristics of these patients are summarized in Table 1. Each of 44 patients in 5 groups was randomly assigned to either placebo or atorvastatin 10, 20, 40, or 80 mg, respectively, once daily during a 2-month treatment period. Allocation concealment was achieved by using envelopes with the collaboration of a statistician. Forty-four patients taking placebo and 42, 44, 43, and 40 patients taking atorvastatin 10, 20, 40, and 80 mg, respectively, finished the study (Fig. 1). Nineteen patients taking placebo and 18, 18, 20, and 18 patients taking atorvastatin 10, 20, 40, and 80 mg, respectively, had metabolic syndrome or type 2 diabetes.

Laboratory assays. Assays for lipids, glucose, adiponectin, high-sensitivity C-reactive protein (hsCRP), and insulin were performed as previously described (12–14), and assays for HbA1C by high-performance liquid chromatography assay (VARIANT II TURBO, BIO-RAD, Inc., Hercules, California) were performed as well. Quantitative Insulin-Sensitivity Check Index (QUICKI) was calculated as follows: QUICKI = 1/[log(insulin)+log(glucose)] (15).

Statistical analysis. Data are expressed as mean ± SD or median (range 25% to 75%). We used Student paired *t* or Wilcoxon signed rank test to compare values between baseline and treatment at 2 months. We used 1-way analysis of variance (ANOVA) or Kruskal-Wallis ANOVA on ranks to compare baseline or treatment effects among treatment groups. Student-Newman-Keuls multiple comparison procedures for post-hoc pair-wise comparisons were routinely used when the omnibus test was significant. An ANOVA indicates group differences, and post hoc analysis shows drug different from placebo. We calculated that 35 subjects/group would provide 80% power for detecting an absolute increase of 0.15% or greater in HbA1C between baseline and atorvastatin 10 mg, with $\alpha = 0.05$ on the basis of previous studies (14). The comparison of HbA1C was prospectively designated as the primary end point of the study. A value of p < 0.05 was considered to represent statistical significance. All other end points were considered secondary. Results for secondary end points were not considered definitive, and p values for secondary end points were presented unadjusted for multiple comparisons.

Results

All patients. There were no significant differences between treatment groups for any of the baseline parameters measured (Table 2).

Table 1 Baseline Characteristics of the Study Population

	Placebo (n = 44)	Atorvastatin 10 mg (n = 42)	Atorvastatin 20 mg (n = 44)	Atorvastatin 40 mg (n = 43)	Atorvastatin 80 mg (n = 40)
Risk factors					
Current smoking	7 (16)	7 (17)	7 (16)	8 (19)	7 (18)
Metabolic syndrome	10 (23)	8 (19)	9 (21)	10 (23)	10 (25)
Diabetes	9 (21)	10 (24)	9 (21)	10 (23)	8 (20)
Medications					
Beta-adrenergic blockers	10 (23)	12 (29)	12 (27)	13 (30)	11 (28)
Calcium-channel blockers	5 (16)	6 (14)	8 (18)	7 (16)	6 (15)

Values are n (%).