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Pravastatin does not affect insulin sensitivity and adipocytokines levels in healthy nondiabetic patients☆

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Abstract

Background: The effect of statins on insulin resistance is controversial and poorly studied in nondiabetic subjects. In addition, the effect of statins on leptin and adiponectin has never been studied.

Methods: Forty healthy nondiabetic volunteers (22 men and 18 women) aged 28 to 72 were randomized either to placebo or pravastatin 40 mg daily for a 12-week period. Insulin resistance, assessed using the Quantitative Insulin Sensitivity Check Index (QUICKI), as well as serum leptin and adiponectin levels, was measured at baseline and at the end of therapy.

Results: Pravastatin treatment decreased total cholesterol, low-density lipoprotein cholesterol, and triglycerides levels by 24%, 32%, and 14%, respectively ($P < .05$ for all), but did not affect glucose and insulin levels, the QUICKI index, and adiponectin and leptin levels. When stratification was performed according to QUICKI index or sex, no significant differences were observed in the prevalues and postvalues of leptin, adiponectin, or QUICKI index in the pravastatin group. Adiponectin, leptin, and QUICKI index were statistically higher in women than in men ($P < .001$ for both variables). Adiponectin was negatively correlated with body mass index (BMI; $r = -0.39$, $P < .05$) and positively correlated with the QUICKI index ($r = 0.54$, $P < .001$) and with high-density lipoprotein cholesterol ($r = 0.50$, $P < .01$). The relation between adiponectin and QUICKI index remained significant after adjustment for sex and BMI ($P = .005$ and $P = .007$, respectively). Leptin was only related to BMI ($r = 0.57$, $P < .001$) and to sex ($P < .001$) with no significant correlations with lipid parameters or QUICKI index. Both sex and BMI are independent predictors of leptin ($P < .001$ and $P < .001$).

Conclusion: A 12-week treatment with pravastatin 40 mg/d does not change the QUICKI index and leptin and adiponectin levels in healthy volunteers. In addition, our results emphasize the importance of sex and BMI in the determination of both adiponectin and leptin. Adiponectin was also related to QUICKI index, whereas this relation was not found with leptin.

Several studies have previously shown that the beneficial effects of HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitors (statins) are not solely related to their lipid-lowering effect. Current knowledge of such pleiotropic effects is mainly related to the anti-inflammatory and endothelial effects of the drug class [1-4]. The effects of statins on glucose metabolism are, however, less well established and controversial, showing either a beneficial [5-7], a neutral [8-12], or a worsening effect [13] on insulin resistance. In addition, the effect of statins on new cytokines implicated in insulin resistance [14] such as leptin or adiponectin has never been studied.

The objective of this prospective randomized study was to analyze the effect of a short-term pravastatin treatment on an insulin sensitivity marker, the Quantitative Insulin Sensitivity Check Index (QUICKI), and on leptin and adiponectin. Because insulin resistance is a component of the metabolic syndrome [15] and is a risk factor for cardiovascular disease

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[16], a potential effect of pravastatin on these markers could explain part of the cardioprotective effect of the drug. Moreover, in the West of Scotland Coronary Prevention Study, a reduction in the development of diabetes mellitus was observed [17] suggesting that statins may improve insulin resistance.

1. Methods

1.1. Design

This study was a prospective, randomized, placebo-controlled, double-blind trial. Forty healthy volunteers were recruited and were instructed to follow a step 1 National Cholesterol Education Program diet. Study patients were then randomized to receive either pravastatin at the dose of 40 mg/d or placebo for a period of 12 weeks. Lipids, glucose, and insulin levels, as well as leptin and adiponectin levels, were measured at baseline and on the last day of therapy. Insulin sensitivity was assessed using the QUICKI index determined according to the equation QUICKI = 1/(log insulin [μIU/mL] + log glucose [mg/dL]) [18]. Low QUICKI index indicates low insulin sensitivity, whereas high QUICKI index indicates high insulin sensitivity.

Exclusion criteria were chronic or acute inflammatory diseases, known cardiovascular diseases, diabetes defined as fasting blood glucose above 126 mg/dL according to the last American Diabetes Association classification, elevation of alanine aminotransferase (serum glutamic-pyruvic transaminase), or creatine phosphokinase levels more than 1.5 the upper limit of normal. Volunteers who were on any kind of lipid-lowering therapy were also excluded. For each subject, body mass index (BMI) was calculated as weight (in kilograms)/height (in squared meters). Informed consent was obtained from all participants, and the study was approved by the institutional review board of the Hotel Dieu de France Hospital.

1.2. Blood sampling and laboratory methods

Blood samples were obtained after a12-hour fast. Dosages of total and high-density lipoprotein (HDL) cholesterol, triglycerides, glucose, creatinine, alanine aminotransferase (serum glutamic-pyruvic transaminase), and creatine phosphokinase were performed by Kodak automate. Low-density lipoprotein (LDL) was calculated using Friedewald equation. Insulin was measured by a chemiluminescent assay (DPC Immulite, Los Angeles, Calif). The sensitivity of the assay was of 2 μIU/mL. Leptin and adiponectin were measured by radioimmunoassays (Linco Research, St Charles, Mo). The sensitivities of the assays were 0.05 and 1 ng/mL, respectively. Interassay coefficients of var <9.5%.

1.3. Statistics

Prior to the study, a sample size estimate was obtained using means and SDs from our laboratory. We estimate that, to show a 20% reduction of adiponectin, leptin, glucose, insulin levels, and QUICKI index with a power of 80% and an α error of 5%, a sample size of 20 patients in each group (placebo or pravastatin) is sufficient to perform the study.

All quantitative variables were distributed normally. Data are represented as means ± SD. The Student *t* test was used to compare mean markers' values in the placebo and the pravastatin groups. The paired *t* test was used to compare mean values at baseline and after pravastatin or placebo treatments. Pearson coefficient of correlation was used to study the linear correlations between variables. Multilinear regression analysis were also performed to study the confounding factors that may affect adiponectin and leptin. A P value <.05 was considered significant. Statistical analysis was performed using SPSS software version 11.

2. Results

2.1. Baseline clinical and biologic characteristics

The study population consisted of 40 healthy subjects (22 men and 18 women) who were randomized to pravastatin 40 mg/d (n = 19) or to placebo (n = 21). Baseline demographics and risk factors were similar between the 2 groups (Table 1) as well as baseline lipid profile, QUICKI index, and leptin and adiponectin levels (Table 2). All subjects continued the study and took their assigned medication for a total of 12 weeks as specified by the protocol.

At baseline, men and women had nonsignificant differences in age and BMI. Plasma adiponectin (P < .001), plasma leptin (P < .001), and QUICKI index (P = .01) were significantly lower in men than in women (adiponectin, 5.31 ± 2.77 vs 9.79 ± 5.3 μg/mL; leptin, 7.41 ± 3.24 vs 11.77 ± 4.13 ng/mL; QUICKI index 0.338 ± 0.029 vs 0.361 ± 0.033).

2.2. Effect of treatment on lipid profile and on insulin sensitivity markers

Pravastatin treatment decreased total cholesterol, LDL cholesterol, and triglycerides levels by 24%, 32%, and 14%,

Table 1
Baseline patients characteristics

	Placebo (n = 21)	Pravastatin (n = 19)
Sex ratio (M/F)	12/9	10/9
Age (y)	46.3 ± 9.7	51.6 ± 13.0
Hypertension	1	4
Smoking	10	5
Hypercholesterolemia >200 mg/dL	17	14
HDL <40 mg/dL	7	8
Family history of CAD	4	4
BMI (kg/m^2)	26.1 ± 4.20	26.8 ± 4.28

Data are shown as mean ± SD or absolute number. P = not significant for all comparisons. CAD indicates coronary artery disease.

Table 2
Effect of pravastatin or placebo on lipid and insulin sensitivity markers

	Placebo group (n = 21)			Pravastatin group (n = 19)		
	Before	After	*P* value	Before	After	*P* value
Total cholesterol (mg/dL)	229.8 ± 48.9	207.7 ± 30.0	.003	234 ± 51.7	177.7 ± 33.4*	<.001
HDL cholesterol (mg/dL)	47.8 ± 13.5	42.2 ± 10.9	.002	44.1 ± 14.1	44.4 ± 12.2	NS
Triglycerides (mg/dL)	168.5 ± 100.7	162.4 ± 85.2	NS	146.6 ± 56.9	125.5 ± 67.5	.04
LDL cholesterol (mg/dL)	149.7 ± 43.8	132.2 ± 26.5	.01	159.6 ± 43.9	107.7 ± 24.1**	<.001
Glucose (mg/dL)	89.5 ± 9.2	88.8 ± 11.2	NS	92.8 ± 15.1	91.9 ± 12.5	NS
Insulin (μIU/mL)	9.48 ± 4.04	8.23 ± 3.15	NS	10.52 ± 6.94	10.34 ± 8.36	NS
QUICKI index	0.35 ± 0.028	0.35 ± 0.025	NS	0.35 ± 0.038	0.35 ± 0.041	NS
Leptin (ng/mL)	8.97 ± 4.56	7.67 ± 3.55	NS	9.83 ± 3.93	9.78 ± 4.58	NS
Adiponectin (μg/mL)	7.36 ± 3.59	7.46 ± 4.21	NS	7.30 ± 4.79	7.02 ± 4.09	NS

All other comparisons between pravastatin and placebo are not statistically significant. NS indicates not significant.
* $P = .005$, compared with placebo.
** $P = .004$, compared with placebo.

respectively ($P < .05$ for all; Table 2). HDL level remained unchanged. Patients on placebo had a reduction varying from 9% to 12% in their total cholesterol, LDL cholesterol, and HDL cholesterol levels ($P < .05$ for all; Table 2) which probably reflects the effect of diet and lifestyle modifications. Triglycerides level remained statistically unchanged. As a result of therapy, total and LDL-cholesterol levels were statistically lower in pravastatin patients compared to placebo ($P = .005$ and .004, respectively). BMI remained constant during the whole study period.

Markers of insulin sensitivity which constitute the end points of the study were not significantly affected by pravastatin therapy. Insulin levels, glucose, the QUICKI index, leptin, and adiponectin levels did not significantly change compared with baseline and were similar between the placebo and the pravastatin groups (Table 2).

We also performed, in the pravastatin group, stratification with respect to QUICKI index using a multitude of paired *t* tests that compare growing groups of subjects from the lower to the highest QUICKI levels. In all these comparisons, no significant changes of adiponectin, leptin, or QUICKI index were observed suggesting that the response to pravastatin is still nonsignificant in the more insulin-resistant subgroups. Moreover, stratification with respect to sex, using paired *t* test in men and women, did not show significant changes of adiponectin, leptin, or QUICKI index in both groups.

2.3. Baseline relations between QUICKI index, adipocytokines, and lipid parameters

Plasma adiponectin was related to BMI ($r = -0.39$, $P = .01$), to QUICKI index ($r = 0.54$, $P < .001$), to sex ($P < .001$), and to HDL cholesterol ($r = -0.50$, $P < .001$). The relation of adiponectin to QUICKI index remained significant after adjustment for sex ($P = .005$) and BMI ($P = .007$). Moreover, the relation of plasma adiponectin to HDL cholesterol remained significant after adjustment for BMI ($P = .003$) but not after adjustment for sex ($P = .08$).

Leptin was significantly related to BMI ($r = 0.57$, $P < .01$) and sex ($P < .01$). Both variables were independent predictors of leptin levels.

3. Discussion

This study shows that a 12-week treatment with pravastatin at a dose of 40 mg/d has no effects on markers of insulin sensitivity in healthy patients without diabetes mellitus and without evidence of cardiovascular disease. Despite reducing serum LDL-cholesterol level and improving total cholesterol/HDL ratio compared to placebo, pravastatin did not improve the QUICKI index or leptin and adiponectin levels. These results remained not significant after stratification with respect to QUICKI index, suggesting that even the more insulin-resistant patients of our population have a nonsignificant response to pravastatin.

The effects of statins administration on insulin sensitivity have been the subject of previous investigations, which were performed mainly on type 2 diabetic patients [5,6,10,11,13], as well as on dyslipidemic nondiabetic patients [7,8,12]. Unfortunately, there was a great discrepancy between the results, possibly because of the type or the dose of the statin used, the different techniques to evaluate insulin sensitivity, or because of the variability of the study groups (dyslipidemic [7,8], hypertensive [9], or diabetic [5,10,13]).

Our study is the first randomized trial using, as a statin, pravastatin to evaluate the effect of the drug on insulin sensitivity markers and is also the first randomized placebo-controlled study done in healthy subjects without diabetes mellitus. Prior studies were either nonrandomized, performed on a smaller number of patients, or randomized but performed in patients with diabetes mellitus. Similar to our results, most of them did not show any beneficial effects for statins on insulin resistance.

The only prospective, randomized, placebo-controlled trial testing the effect of statins on insulin sensitivity was the one performed by Paolisso et al [6] who reported that both atorvastatin and simvastatin improve the homeostatis model

assessment (HOMA) index (an indirect measurement of insulin resistance) in elderly patients with type 2 diabetes mellitus. In that study, the change in triglycerides level was positively correlated with the HOMA index suggesting that the beneficial effect of statins on insulin resistance may be the result of triglycerides lowering. In our trial, the effect of pravastatin on triglycerides was modest, and triglycerides levels were not significantly different between the 2 groups. In addition, our study population was composed by healthy nondiabetic patients who have a much lower degree of insulin resistance. These factors may explain the differences in the results between the 2 trials.

Our study is also, to the best of our knowledge, the first to test the effect of statin therapy on leptin and adiponectin serum levels. Recently, these adipocytokines have been the subject of intensive research because of their important relation with BMI, lipid parameters, and insulin resistance. Leptin is related to the amount of body fat [19], may contribute to platelets aggregation [20] and to inflammation [21], and was shown to be an independent risk factor for cardiovascular disease [22,23]. Conversely, adiponectin has protective effects: it exhibits anti-inflammatory activity [24] and inhibits metalloproteinase activity in human coronary plaques [25]. Low levels of this molecule are associated with obesity, type 2 diabetes mellitus, and coronary artery disease [26,27]. Similar to its effect on the QUICKI index, statin therapy did not significantly affect the plasma concentration of these 2 adipocytokines.

We have also shown that sex and BMI are determinants of both adiponectin and leptin levels. In addition, QUICKI index is significantly related to adiponectin, whereas leptin is not. These results are in agreement with previously published data. In a cohort of nondiabetic subjects, Baratta et al [28] found that plasma adiponectin and plasma leptin were statistically lower in men compared with women. They also found that plasma adiponectin, but not plasma leptin, correlates with insulin sensitivity and that this correlation remained statistically significant after adjustment for age and BMI. Similar results were found with adiponectin in patients with coronary artery disease [29].

The negative results of pravastatin therapy on insulin resistance and on leptin and adiponectin levels cannot explain the reduction in the incidence of newly diagnosed diabetes mellitus observed in the West of Scotland Coronary Prevention Study. Other explanatory factors such as the anti-inflammatory properties and endothelial effects of the drug may be implicated. However, in 2 more recent trials, the rate of new-onset diabetes did not differ among high-risk patients assigned to simvastatin or placebo in the Heart Protection Study [30] or among patients receiving atorvastatin compared with placebo in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm [31]. These findings are in agreement with our results, suggesting that statins do not affect insulin sensitivity.

The limitation of this study is mainly related to its small sample size. However, it is remarkable that the QUICKI index did not change at all (0.35 before and after therapy in both groups) and that the effect of therapy on both leptin and adiponectin levels was <5% in the pravastatin group. It is thus unlikely that a larger sample would have provided different results. In addition, our population was limited to "healthy" volunteers with normal QUICKI index. It is possible that patients with insulin resistance (lower QUICKI index) may have a better response to pravastatin.

In conclusion, a 12-week treatment with pravastatin 40 mg/d does not change markers of insulin resistance measured by the QUICKI index as well as leptin and adiponectin levels in healthy controls. In addition, our results emphasize the importance of sex and BMI as determinants of both adiponectin and leptin. QUICKI index is also related to adiponectin but not to leptin.

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