Effect of *Atorvastatin* (10 mg/day) on Glucose Metabolism in Patients With the Metabolic Syndrome

Sebastian Huptas, MD, Hans-Christian Geiss, MD, Carsten Otto, MD, and Klaus Georg Parhofer, MD*

Large interventional studies have shown that statins may reduce the incidence of type 2 diabetes mellitus. However, it is uncertain whether short-term statin therapy can affect insulin sensitivity in patients with the metabolic syndrome. We evaluated the effect of atorvastatin (10 mg/day) in 10 insulin-resistant subjects (age 40 ± 12 years, body mass index 33.6 ± 5.2 kg/m^2, triglycerides 2.84 ± 1.99 mmol/L [249 ± 175 mg/dl], glucose 6.06 ± 0.67 mmol/L [109 ± 12 mg/dl)] using the homeostasis model assessment (HOMA) index (parameter of insulin resistance derived from fasting glucose and fasting insulin concentrations; 5.7 ± 2.6) in a randomized placebo-controlled, double-blind, crossover study. Subjects were randomized to receive placebo or atorvastatin, each given for 6 weeks separated by a 6-week wash-out period. At the beginning and end of each treatment phase, the patients underwent an oral glucose tolerance test, a 72-hour continuous glucose measurement, and a detailed lipid determination, including a standardized fat tolerance test. Compared with placebo, atorvastatin resulted in a significant ($p = 0.05$) reduction in the HOMA index (−21%), fasting C-peptides (−18%), glucose (area under the curve during the oral glucose tolerance test, −7%), and a borderline ($p = 0.08$) reduction of insulin (−18%). The parameters derived from the continuous 72-hour glucose monitoring did not change. A significant reduction also occurred in the total and low-density lipoprotein cholesterol concentrations, although the fasting and postprandial triglyceride concentrations did not change significantly. However, we found a significant correlation between atorvastatin-induced changes in the HOMA and baseline HOMA and between the atorvastatin-induced changes in triglycerides and insulin concentrations. The free-fatty acid, interleukin-6, and high sensitivity C-reactive protein concentrations did not change. Our data indicated that in insulin-resistant, nondiabetic subjects, 6 weeks of atorvastatin (10 mg/day) resulted in significant improvement in insulin sensitivity. **(Am J Cardiol 2006;98:66–69)**

Type 2 diabetes mellitus represents the final stage of a progressive disease that in many patients develops from the metabolic syndrome.[1] Insulin resistance is a central feature of the metabolic syndrome, which, in addition, is characterized by abdominal obesity, dyslipoproteinemia, and hypertension. The progression from metabolic syndrome to type 2 diabetes can be delayed or even prevented by a number of different modalities, such as lifestyle modification and acarbose, metformin, or glitazone therapy.[2–5] However, it was also shown that statin therapy, angiotensin-converting enzyme inhibition or angiotensin II receptor blockade can reduce the risk of diabetes, presumably by preventing patients with the metabolic syndrome from progressing to type 2 diabetes.[6] To address this issue further, we designed a randomized, placebo-controlled, double-blind, crossover study to evaluate the effects of atorvastatin (10 mg/day for 6 weeks) on glucose homoeostasis in insulin-resistant subjects.

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We included 10 subjects with the metabolic syndrome, which was defined by the presence of insulin resistance (homeostasis model assessment [HOMA] index ≥2.5) and overweight (body mass index ≥25 kg/m^2 or waist circumference >102 cm). Patients with diabetes mellitus or patients taking any regular medication were excluded. The study was performed as a randomized, placebo-controlled, double-blind, crossover study. The study was conducted in accordance with the guidelines of the Declaration of Helsinki and approved by the ethics committee of the Ludwig-Maximilians University Munich. All subjects gave written informed consent.

Subjects were randomized to first receive placebo or atorvastatin (10 mg/day) for 6 weeks. This was followed by a 6-week wash-out period. Then, patients received the other medication (placebo or atorvastatin) for another 6 weeks. Before the beginning and at the end of each treatment phase, the primary and secondary parameters were determined. The participating subjects were advised not to change their diet 4 weeks before and throughout the study.

Department of Internal Medicine II, Klinikum Grosshadern, Ludwig-Maximilians University, Munich, Germany. Manuscript received July 27, 2005; revised manuscript received and accepted January 17, 2006.

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* Corresponding author: Tel: 49-89-7095-3010; fax: 49-89-7095-8879.

E-mail address: Klaus.Parhofer@med.uni-muenchen.de (K.G. Parhofer).

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Table 1
Parameters of glucose metabolism during placebo and atorvastatin treatment

Parameter	Before Placebo	During Placebo	p Value*	Before Atorvastatin	During Atorvastatin	p Value*
Glucose fasting (mg/dl)	107 ± 15	106 ± 14	NS	111 ± 10	105 ± 11	NS
Glucose fasting (mmol/L)	5.94 ± 0.83	5.89 ± 0.78		6.17 ± 0.56	5.83 ± 0.61	
Glucose 2 h (mg/dl)†	119 ± 44	100 ± 47	NS	119 ± 35	102 ± 26	NS
Glucose 2 h (mmol/L)†	6.61 ± 2.44	5.56 ± 2.61		6.61 ± 1.94	5.67 ± 1.44	
Glucose AUC†	313 ± 56	287 ± 63	NS	295 ± 55	272 ± 40	<0.05
HbA1c (%)	5.59 ± 0.43	5.57 ± 0.37	NS	5.57 ± 0.48	5.49 ± 0.36	NS
Insulin 0 min (μU/ml)	17.8 ± 9.5	15.6 ± 6.9	NS	22.3 ± 9.9	16.2 ± 5.7	0.08
Insulin 30 min (μU/ml)†	101 ± 67	119 ± 63	NS	120 ± 78	103 ± 101	NS
C-peptide (ng/ml)	2.71 ± 1.35	2.64 ± 0.75	NS	3.16 ± 0.93	2.59 ± 1.02	<0.05
HOMA index	4.76 ± 2.38	4.23 ± 1.95	NS	6.31 ± 2.95	4.33 ± 1.70	<0.05
Insulinogenic index‡	1.44 ± 1.07	1.52 ± 1.03	NS	1.39 ± 1.18	2.01 ± 2.23	NS
3-d average glucose concentration (mg/dl)	100 ± 2.7	97 ± 3.4	NS	98 ± 3.4	100 ± 2.8	NS
(mmol/l)§	5.56 ± 0.15	5.39 ± 0.19		5.44 ± 0.19	5.56 ± 0.16	

* Change observed during placebo and atorvastatin phase (Wilcoxon test).
† Oral glucose tolerance test.
‡ $\Delta\text{insulin}_{(30-0)}/\Delta\text{glucose}_{(30-0)}$.
§ Continuous glucose concentration measurement.
AUC = area under the curve; HbA1c = hemoglobin A1c.

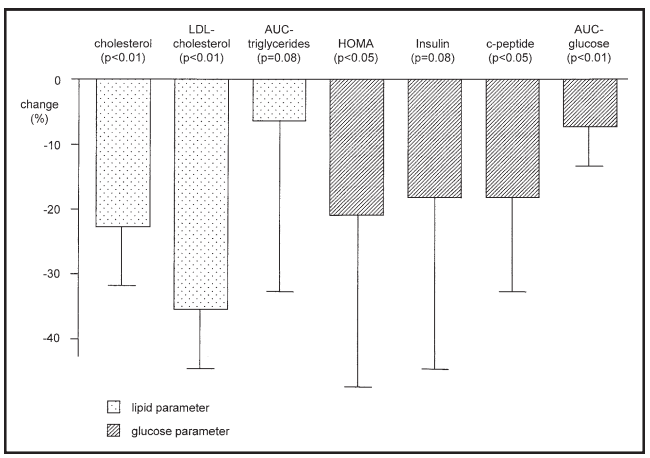

Figure 1. Relative changes of lipid and glucose parameters observed during atorvastatin therapy. Changes refer to comparison between before and during therapy. AUC = area under the curve; LDL = low-density lipoprotein.

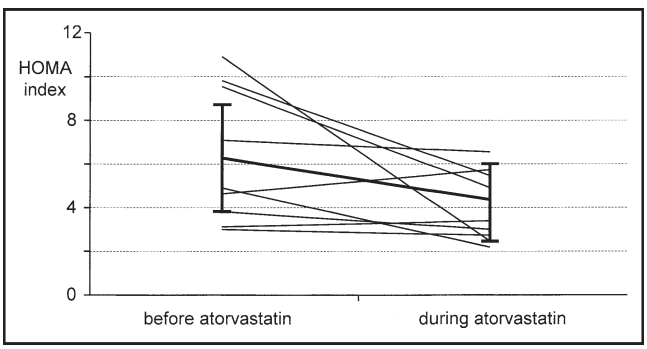

Figure 2. Patient changes in insulin resistance (HOMA index) during atorvastatin therapy.

Glucose metabolism was evaluated by fasting values, an oral glucose tolerance test, and a 3-day continuous glucose measurement (MiniMed, Medtronic, Northridge, California). The fasting values included glucose, insulin, and C-peptide concentrations. These parameters were also used to estimate insulin sensitivity (HOMA index).[7,8] The oral glucose tolerance test was performed using 75 g of glucose after a 12-hour fast and was evaluated for the 2-hour value and the area under the glucose curve, as defined by the glucose concentrations determined at 0, 30, 60, 90, and 120 minutes. The insulin concentration was also measured at 30 minutes to calculate the insulinogenic index. This index is defined by $\Delta\text{insulin}_{(30-0)}/\Delta\text{glucose}_{(30-0)}$ and represents an estimate of the first phase of the insulin response.[9] Continuous glucose monitoring was evaluated concerning the average glucose concentration during a 3-day period.

The triglyceride and cholesterol concentrations were measured using commercial kits (Roche, Mannheim, Germany). Preparative ultracentrifugation was performed to isolate very-low-density lipoprotein (supernatant); high-density lipoprotein cholesterol and low-density lipoprotein cholesterol were determined in the infranatant. Furthermore, postprandial lipoprotein metabolism was evaluated using a standardized oral fat tolerance test, as previously described.[10] In brief, after a 12-hour fast, a fatty meal was ingested within 5 minutes. After the fat load, samples were taken every 2 hours for 10 hours. The total triglycerides and triglycerides in the density range >1.006 g/ml (containing chylomicrons, chylomicron-remnants, and very-low-density lipoprotein) were determined. The postprandial triglyceride metabolism was evaluated by determining the total and incremental area under the triglyceride concentration curve. We also measured high-sensitivity C-reactive protein, interleukin-6 (IL-6), free-fatty acid concentrations, and safety parameters (liver function tests, creatine kinase).

The differences between the parameters obtained during atorvastatin and placebo therapy were evaluated by the

Table 2
Parameters of lipid metabolism and inflammatory parameters during placebo and atorvastatin therapy

Parameter	Before Placebo	During Placebo	p Value*	Before Atorvastatin	During Atorvastatin	p Value*
Cholesterol (mg/dl)	229 ± 64	208 ± 46	NS	213 ± 48	164 ± 41	<0.01
Cholesterol (mmol/L)	5.92 ± 1.66	5.38 ± 1.19		5.51 ± 1.24	4.24 ± 1.06	
Triglycerides (mg/dl)	218 ± 174	198 ± 122	NS	198 ± 142	192 ± 188	NS
Triglycerides (mmol/L)	2.49 ± 1.98	2.26 ± 1.39		2.26 ± 1.62	2.19 ± 2.14	
HDL cholesterol (mg/dl)	45.8 ± 13.4	45.0 ± 11.4	NS	47.9 ± 10.3	47.6 ± 10.5	NS
HDL cholesterol (mmol/L)	1.18 ± 0.35	1.16 ± 0.29		1.24 ± 0.27	1.23 ± 0.27	
LDL cholesterol (mg/dl)	130 ± 63	125 ± 43	NS	130 ± 37	85 ± 30	<0.01
LDL cholesterol (mmol/L)	3.36 ± 1.63	3.23 ± 1.11		3.36 ± 0.96	2.20 ± 0.78	
AUC triglycerides†	2,869 ± 1,440	3,506 ± 2,853	NS	2,277 ± 750	2,239 ± 1,160	0.08
Free fatty acids (mmo/L)	0.81 ± 0.31	0.96 ± 0.49	NS	0.54 ± 0.12	0.52 ± 017	NS
hs-CRP (mg/L)	3.6 ± 3.1	5.4 ± 6.8	NS	2.9 ± 2.7	3.1 ± 2.9	NS
IL-6 (pg/ml)	1.33 ± 1.05	1.29 ± 0.82	NS	1.18 ± 0.59	1.59 ± 0.9	NS
Fibrinogen (mg/dl)	406 ± 112	426 ± 107	NS	365 ± 382	388 ± 80	NS

* Change observed during placebo and atorvastatin phase (Wilcoxon test).
† Oral fat load.
HDL = high-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; other abbreviations as in Table 1.

Wilcoxon test for paired samples. All parameters were evaluated such that the data obtained before placebo were compared with those obtained during placebo, and those obtained before atorvastatin were compared with those during atorvastatin. The associations between variables were identified using the Spearman rho test. All statistical tests were performed using the Statistical Package for Social Sciences software (SPSS, Inc., Chicago, Illinois).

All subjects tolerated placebo and atorvastatin without side effects. However, 1 subject was identified as having secondary hypertriglyceridemia (alcohol abuse) and was therefore excluded from the analysis.

Compared with placebo, atorvastatin resulted in an improvement of several parameters of glucose metabolism (Table 1 and Figure 1), most notably a significant reduction in C-peptide and the HOMA index (Figure 2). The fasting, 2-hour glucose (oral glucose tolerance test), and average glucose concentration during 3 days of continuous monitoring remained unaffected. Atorvastatin therapy resulted in the expected changes in lipid metabolism (Table 2). We observed no significant changes in free-fatty acid concentrations, high-sensitivity C-reactive protein, IL-6, and fibrinogen.

Insulin concentration correlated positively with the triglyceride concentration and the area under the triglyceride curve during placebo and atorvastatin therapy ($r^2 = 0.44$, $p = 0.05$). Furthermore, the atorvastatin-induced changes in insulin concentration correlated with the atorvastatin-induced changes in the triglyceride concentration and changes in the area under the triglyceride curve after the oral fat load ($r^2 = 0.43$, $p = 0.05$).

When we compared the responders with the nonresponders concerning a decrease in the HOMA index, we observed that the nonresponders had lower baseline triglycerides (1.13 mmol/L [99 mg/dl] vs 2.00 mmol/L [175 mg/dl]), lower cholesterol (4.63 mmol/L [179 mg/dl] vs 5.61 mmol/L [217 mg/dl]), lower insulin concentrations (14.6 μU/ml vs 25.4 μU/ml), a lower HOMA index (4.23 vs 7.12), and lower IL-6 concentrations (0.91 vs 1.31 pg/ml). Furthermore, we observed a correlation between the atorvastatin-induced changes in the HOMA index with the baseline HOMA index ($r^2 = 0.49$, $p = 0.04$), as well as with the baseline insulin concentration ($r^2 = 0.51$, $p = 0.03$). However, changes in the HOMA index did not correlate with any of the lipid parameters.

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The major aim of the present study was to evaluate whether short-term low-dose atorvastatin therapy affects parameters of glucose metabolism in insulin-resistant subjects. Atorvastatin (10 mg/day) for 6 weeks resulted in a significant reduction in the HOMA index, fasting C-peptide concentrations, and area under the glucose curve after an oral glucose tolerance test. Other parameters, such as the fasting glucose concentration, hemoglobin A1c, 3-day average glucose concentration, and the insulinogenic index, did not change. Furthermore, we did not observe any change in the free-fatty acid concentration or inflammatory parameters.

This observation is consistent with large-scale interventional trials that showed that the incidence of type 2 diabetes can be decreased with statin therapy. Furthermore, a number of smaller studies have also shown that statin therapy can improve the parameters of glucose metabolism in diabetic and nondiabetic patients.[11–15] However, the results of these studies were ambiguous, with some studies showing an improvement and others not. This may have been related to the different patient groups studied and that the main focus was not glucose metabolism in some studies.[15] We therefore performed a detailed study of the effect of atorvastatin on glucose metabolism in a homogeneous sample of insulin-resistant subjects.

Although we observed some improvement in glucose metabolism, our study also included nonresponders. These nonresponders had a better lipid profile and more normal

baseline parameters. Thus, it seems that patients with more pronounced metabolic syndrome will benefit more than those with less pronounced changes. Furthermore, in subjects with such large stores of visceral adipose tissue, the low dose of atorvastatin may be sufficient to improve lipid parameters but not to improve insulin sensitivity. Higher doses may have had more effect on C-reactive protein, free-fatty acids, and, ultimately, insulin sensitivity.

The improvement in the HOMA index and area under the glucose curve indicates that insulin resistance improved. However, it is unclear whether this improvement was achieved by decreased gluconeogenesis or by increased uptake of glucose in muscle and fat, or both. Statins not only decrease low-density lipoprotein cholesterol but also affect the metabolism of triglyceride-rich lipoproteins in the fasting state and postprandially.[10,16] It is, therefore, conceivable that an altered metabolism of triglyceride-rich lipoproteins results in an altered flux of substrate (e.g., free fatty acids) to the liver, thereby decreasing gluconeogenesis. However, fibrates that can lower triglyceride-rich lipoproteins more than statins have no clear-cut effects on glucose metabolism.[15,17] In contrast, animal data have indicated that the flux and turnover of portal free-fatty acids is crucial for the development of insulin resistance.[18] It is, however, unclear how closely the metabolism of triglyceride-rich lipoproteins is linked to free-fatty acid metabolism and whether manipulations of triglyceride metabolism will affect portal free-fatty acid metabolism. In addition, we did not observe a change in free-fatty acid concentrations. However, changes in portal free-fatty acid concentrations may not necessarily result in changes in peripheral free-fatty acid concentrations. Finally, inflammation results in insulin resistance and statins have anti-inflammatory properties.[19,20] However, in our study, neither IL-6 nor high-sensitivity C-reactive protein changed during atorvastatin therapy. Again, more sophisticated methods may be necessary to detect small differences in the inflammatory status.

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