

## Pravastatin Improves Insulin Resistance in Dyslipidemic Patients

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**To evaluate the effect of pravastatin on both lipid and glucose metabolism, twenty-two consecutive dyslipidemic patients treated with pravastatin at 10 mg/day for one year were enrolled in this study. The meal test, which consisted of 115 g of cookies (energy 560 kcal; glucose 75 g; protein 7 g; fat 24 g), was conducted before and after one year of treatment. Insulin resistance was assessed by the homeostasis model assessment of insulin resistance (HOMA-IR), by the area under the IRI curve (AUC-IRI), and by the formula  $AUC-IRI \times AUC-PG$ . After one year of treatment with pravastatin, the plasma glucose (PG), immunoreactive insulin (IRI) and C-peptide levels were unchanged after fasting and at 120 minutes after the meal test; however, PG, IRI and C-peptide levels at 60 minutes after the meal were all significantly decreased from baseline ( $p < 0.05$ ). AUC-IRI and  $AUC-IRI \times AUC-PG$  were also significantly decreased ( $p < 0.05$ ). HOMA-IR was reduced by 26.8%, but the reduction was not significant. The triglyceride (TG) level was decreased after fasting and increased at 60 and 120 minutes after the meal test, but not significantly. This study demonstrated that pravastatin not only reduced serum lipids, but also improved the glucose metabolism, including insulin resistance, of dyslipidemic patients. *J Atheroscler Thromb*, 2005; 12: 322–329.**

**Key words: Statin, meal test, Postprandial change, Area under the IRI curve (AUC-IRI)**

### Introduction

Metabolic syndrome is a disorder in which insulin resistance is the main component of the etiology. In 1988, Reaven (1) defined syndrome X, which consists of insulin resistance, hyperinsulinemia, glucose intolerance, hypertriglycemia, decreased HDL-C and hypertension. He suggested that the major feature of the syndrome is insulin resistance, and that all other changes are likely to follow this abnormality. He also suggested that such a state might increase the risk of coronary artery disease (CAD). Several subsequent studies also revealed that insulin resistance increases the risk of CAD (2–4). There-

fore, it is important to know whether or not the drugs used to treat these diseases have a secondary effect, either favorable or unfavorable, on insulin resistance.

Statins have multiple actions, independent of their classical effects on serum lipids. These actions include the modulation of endothelial function, the stabilization of plaques, an attenuation of atherogenesis, and anti-inflammatory and antithrombotic effects. However, research into the effect of statins on insulin resistance is inconclusive. Some reports indicate that statins worsen the insulin action (5), or have no effect on the plasma insulin level (6). Other reports indicate that statins improve insulin sensitivity (7–10). In the West of Scotland Coronary Prevention Study (WOSCOPS) (10), the incidence of type 2 diabetes mellitus was found to be thirty percent lower in pravastatin-treated patients than in controls, suggesting that the anti-inflammatory and endothelial effects of pravastatin, in addition to the lipid lowering effect, may have been a factor. This also implies that pravastatin

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might improve insulin sensitivity. To our knowledge, no previous reports have compared the effect of statins using a meal test to reveal postprandial change in both glucose and lipids.

The purpose of this study was to evaluate the effect of pravastatin on insulin resistance in a selected group of dyslipidemic patients.

## Methods

### Subjects and study design

The study included 32 (12 male, 20 female) consecutive dyslipidemic patients at the outpatient clinic of the Department of General Medicine, Kyushu University, between September 2001 and April 2002. The examination consisted of a general physical examination, a questionnaire, carotid ultrasound, and a meal test. Eligibility criteria included (a) 40 to 75 years; (b) BMI (body mass index) < 30 kg/m<sup>2</sup>; (c) fasting total cholesterol (TC) ≥ 220 mg/dl and/ or fasting triglyceride levels between 150 and 350 mg/dl; (d) fasting plasma glucose (PG) < 126 mg/dl (e) plasma glucose < 200 mg/dl at 2 hours after the meal test; (f) no evidence of hypertension (systolic blood pressure < 140 mmHg, diastolic blood pressure < 90 mmHg, and no treatment with antihypertensive medications), and no renal, hepatic, endocrine, or cancer diseases or severe allergies as determined by medical history, physical examination, and routine laboratory tests; and (g) no history of taking any medicine known to affect glucose and lipid metabolism. The purpose, nature, and potential risk of the study were explained to all patients and written informed consent was obtained before enrollment. Of the potential subjects, ten were omitted because of withdrawal of consent, or ineligibility, leaving 22 patients (7 male, 15 female) who were followed up for one year.

After the baseline measurements were taken, the administration of pravastatin at 10 mg per day was begun. Monitoring visits were scheduled 4 weeks after the baseline data was gathered and every 2 months thereafter. At each visit, a brief physical examination was conducted and drug compliance was confirmed.

### Meal test

After a 10- to-14- hour overnight fast, a meal test, similar to that conducted in numerous recent studies (11, 12), was done by all the patients between 8:30 and 9:30 AM. Ingested within 15 minutes, the test meal was a cookie (Abitil co., Ltd, Osaka, Japan) consisting of the following: energy 560 kcal; carbohydrate 75 g; protein 7 g; fat 24 g (13). The amount of carbohydrate in this "cookie test" is equivalent to that (75 g) in the standard oral glucose tolerance test (OGTT) (Trelan- G, Shimizu Pharmaceutical, Shimizu, Japan). Patients were asked not to do any unusual exercise or drink alcohol the day before the test. Water was allowed, but no other beverages or foods

were permitted during the test. Walking, but no strenuous exercise or smoking, was allowed. Blood samples were taken at 0, 60, and 120 minutes for the measurement of PG, immunoreactive insulin (IRI), C-peptide, and TG, at 0 and 120 minutes for TC and HDL-C, and in a fasting state for hs CRP and hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>).

### Biochemical measurements

PG was measured by the glucose oxidase method and immunoreactive insulin (IRI) and C-peptide were measured by radioimmunoassay at a commercial laboratory (MBC Laboratories, Inc., Tokyo, Japan). TC, HDL-C, TG, and HbA<sub>1c</sub> were measured by standard laboratory techniques at the above laboratory. High-sensitivity CRP (hs CRP) was measured by high-sensitivity latex-enhanced immunonephelometrics. LDL-C was calculated according to the Friedewald formula.

### Assessment of insulin resistance

Homeostasis model assessment of insulin resistance (HOMA-IR), a widely advocated index that reflects insulin resistance, was calculated with the formula: HOMA-IR = [fasting PG (mg/dl) × fasting IRI (μU/ml)]/405 (14). The area under the PG and IRI curves (AUC) during the meal test were estimated by the linear trapezoidal method. AUC-IRI, and AUC-IRI × AUC-PG are recommended for determining possible insulin resistance in non-diabetic subjects (15, 16), so, in addition to HOMA-IR, these two factors were used to evaluate insulin resistance.

### Carotid ultrasound measurements

Both carotid arteries scanned with high-resolution B-mode ultrasound using a 7.5 MHz mechanical sector transducer on the Aloka SSD-2000 (Aloka co., Ltd., Tokyo, Japan) by four trained physicians as described previously (17–20). The maximum IMT was measured 2 to 3 cm proximal to the flow divider on the far wall of the right and left common carotid arteries at the end of the diastolic phase. All assessments of the carotid arteries were done blinded to a knowledge of the clinical history or risk factor profile.

An analysis of within- and between-reader (reading of a duplicate set of 25 scans) and -observer (duplicate mean IMT measurements of five subjects) variability was done (20). The Spearman correlation coefficients for intra-observer and intra-reader measurements were > 0.95, and the mean differences (± 2 SD) were < 1% (10%). The Spearman correlation coefficients for between-observer and between-reader variability were > 0.95 and > 0.95, respectively, and the mean differences (± 2 SD) were < 5% (15%).

### Statistical analysis

All data were reported in standardized forms, which were

then entered into a database. Categorical variables among the groups were assessed using the chi-square test or Fisher's exact test. The mean levels of variables between two groups were compared with the unpaired *t*-test or Mann-Whitney *U*-test. Comparisons between more than two groups were made using the Kruskal-Wallis test. Differences in BMI, HbA<sub>1c</sub>, blood pressure, serum lipids, hs CRP, max IMT, PG, IRI, C-peptide, AUC-IRI, AUC-IRI × AUC-PG, and HOMA-IR between baseline and after 12 months were compared using the paired *t*-test or Wilcoxon's signed-ranks test. Between-group changes in each variable from 0 to 60 min and from 0 to 120 min from baseline to 12 months were compared using the Bonferroni correction method. Percent change was calculated with the following formula: % change = (value at 12 months – baseline value) / baseline value × 100. *P* values < 0.05 were considered statistically significant in all analyses.

## Results

### Baseline characteristics

The baseline characteristics of the study subjects are shown in Table 1. The mean age ± S.D. of the patients was 58.0 ± 9.2 years. Of the 22 patients, 10 were men (45.5%). The average BMI was 25.4 ± 2.4 kg/m<sup>2</sup>. The average systolic and diastolic blood pressures were 119.8 ± 8.1 and 70.2 ± 8.2 mmHg, respectively. Of the 22 patients (*n* = 1, 4.5%) had a history of cardiovascular disease, and none had a history of hypertension, diabetes mellitus, or cerebrovascular disease.

### Change in variables from baseline to the 12 month follow-up

The changes in BMI, HbA<sub>1c</sub>, blood pressure, serum lipids, high-sensitivity CRP, and maximum IMT are shown in Table 2.

No significant change in BMI, HbA<sub>1c</sub>, blood pressure, TG, or maximum IMT was found from baseline to the 12 month follow-up. TC levels decreased after 12 months, falling by 13.6% in a fasting state (*p* < 0.001) and 12.7% (*p* < 0.001) at 120 minutes after the meal test. LDL-C levels also decreased after 12 months, falling by 23.3% in a fasting state (*p* < 0.001) and 26.4% (*p* < 0.001) at 120 minutes after the meal test. HDL-C levels significantly increased, by 8.5% in a fasting state (*p* = 0.030) and 8.9% at 120 minutes (*p* = 0.033). A significant decrease (46.1%) in the fasting state hs CRP was found after 12 months (*p* = 0.048).

### Change in glucose metabolism and insulin sensitivity from baseline to the 12 month follow-up

PG, IRI, and C-peptide levels in response to the "cookie test" at baseline and after 12 months of pravastatin treatment are shown in Table 3. These results showed that

**Table 1.** Baseline characteristics of the 22 study subjects

Characteristic	
Age (years)	58.0 ± 9.2
Sex (males/females)	10 /12
Body mass index (kg/m <sup>2</sup> )	25.4 ± 2.4
Blood pressure (mmHg)	
Systolic	119.8 ± 8.1
Diastolic	70.2 ± 8.2
Medical history (%)	
Hypertension	0 (0)
Diabetes mellitus	0 (0)
Cardiovascular disease	1 (4.5)
Cerebrovascular disease	0 (0)

Data represents the mean value ± S.D. or number (%) of subjects.

the fasting PG, IRI, and C-peptide levels did not change, even after the patients were treated with pravastatin. However, the PG, IRI, and C-peptide levels at 60 minutes in response to the cookie test were all significantly decreased after treatment: PG, from 171.1 mg/dl to 152.6 mg/dl (– 10.8%), *p* = 0.017; IRI, from 66.8 mg/dl to 50.3 mg/dl (– 24.7%), *p* < 0.035; and C-peptide, from 8.52 mg/dl to 7.10 mg/dl (– 16.7%), *p* = 0.019. PG, IRI, and C-peptide levels at 120 minutes in response to the test were decreased after treatment, but not significantly. The change in PG levels from 0 to 60 min was significantly greater at baseline than at 12 months (72.2 mg/dl vs. 49.6 mg/dl, *p* = 0.004), but the change from 0 to 120 min did not differ between baseline and the 12 month follow up. The change in IRI levels from 0 to 60 min was significantly greater at baseline than at 12 months (55.5 mg/dl vs. 41.6 mg/dl, *p* = 0.098), but again that from 0 to 120 min did not differ between baseline and 12 months. The change in C-peptide levels from 0 to 60 min was significantly greater at baseline than at 12 months (6.0 mg/dl vs. 4.7 mg/dl, *p* = 0.019), but once again the change from 0 to 120 min did not differ significantly between baseline and 12 months.

Insulin resistance, as indicated by HOMA-IR, was reduced after 12 months of pravastatin treatment, from 2.88 to 2.11 (– 26.7%), although the reduction was not significant (Fig. 1). AUC-IRI was significantly decreased after the treatment, from 99.5 to 77.9 (– 21.7%) (*p* = 0.020) (Fig. 2). AUC-IRI × AUC-PG was also significantly decreased after 12 months of pravastatin treatment, from 29215.5 to 21478.6 (– 26.5%) (*p* = 0.018) (Fig. 2).

## Discussion

This study evaluated the effect of pravastatin on both

**Table 2.** Changes in the tested variables from baseline to 12 months of follow-up.

	Baseline mean $\pm$ S.D.	12 months mean $\pm$ S.D.	Percentage change (%)	<i>p</i> -value
BMI (kg/m <sup>2</sup> )	25.4 $\pm$ 2.4	25.5 $\pm$ 2.7	0.3	0.189
HbA <sub>1c</sub> (%)	5.15 $\pm$ 0.37	5.27 $\pm$ 0.46	2.3	0.383
Blood pressure				
Systolic	119.8 $\pm$ 8.1	128.4 $\pm$ 15.4	7.2	0.188
Diastolic	70.2 $\pm$ 8.2	75.2 $\pm$ 8.5	7.1	0.250
Serum lipids				
TC (mg/dl)				
0 min	226.3 $\pm$ 30.1	195.5 $\pm$ 26.5	- 13.6	< 0.001
120 min	221.6 $\pm$ 33.0	193.5 $\pm$ 25.3	- 12.7	<0.001
change from 0 to 120 min	- 4.7 $\pm$ 7.1	- 2.4 $\pm$ 5.0		0.101
LDL-C (mg/dl)				
0 min	144.5 $\pm$ 28.0	110.8 $\pm$ 20.3	- 23.3	< 0.001
120 min	135.2 $\pm$ 26.0	99.5 $\pm$ 18.9	- 26.4	< 0.001
change from 0 to 120 min	- 9.3 $\pm$ 7.3	- 11.6 $\pm$ 8.5		0.318
HDL-C (mg/dl)				
0 min	56.2 $\pm$ 10.5	61.0 $\pm$ 13.1	8.5	0.030
120 min	54.0 $\pm$ 10.4	58.8 $\pm$ 12.3	8.9	0.033
change from 0 to 120 min	- 2.3 $\pm$ 2.2	- 2.4 $\pm$ 2.7		0.881
TG (mg/dl)				
0 min	127.8 $\pm$ 65.7	118.5 $\pm$ 56.0	- 7.3	0.494
60 min	151.0 $\pm$ 63.4	145.0 $\pm$ 69.7	- 4	0.540
change from 0 to 60 min	23.3 $\pm$ 45.1	27.0 $\pm$ 34.5		0.680
120 min	162.4 $\pm$ 58.5	175.8 $\pm$ 72.6	8.3	0.293
change from 0 to 120 min	34.6 $\pm$ 48.5	57.8 $\pm$ 39.0		0.063
high-sensitivity CRP (mg/dl)	0.13 $\pm$ 0.15	0.07 $\pm$ 0.06	- 46.1	0.048
maximum IMT (mm)	1.47 $\pm$ 0.92	1.42 $\pm$ 0.83	- 3.4	0.220

BMI: body mass index, HbA<sub>1c</sub>: hemoglobin A<sub>1c</sub>, TC: total cholesterol, LDL-C: LDL- cholesterol, HDL-C: HDL-cholesterol, TG: triglyceride, CRP: C-reactive protein, IMT: intima-media thickness.

lipid and glucose metabolism in dyslipidemic patients. We used a new meal test that provides a natural source of carbohydrates and lipids that is more similar to our daily food intake than the regular OGTT (13). This test, using the same criteria as OGTT, can evaluate glucose tolerance in subjects without endocrine pancreatic diseases, and also reveals hyperinsulinemia, insulin resistance and postprandial dyslipidemia more effectively than an OGTT or fat loading test. In addition, while 30% of the healthy subjects tested showed reactive hypoglycemia

(2h PG below 80 mg/dl) in response to OGTT, none showed hypoglycemia or adverse effects to this meal test (13). Our study demonstrated that pravastatin can improve both lipid and glucose metabolism.

Large-population studies of the effect of statin administration on glucose metabolism have produced conflicting results (10, 21). In the WOSCOPS report (10), the incidence of type 2 diabetes mellitus was found to be thirty percent lower in pravastatin-treated patients than in controls; by contrast, the Anglo-Scandinavian Cardiac Out-

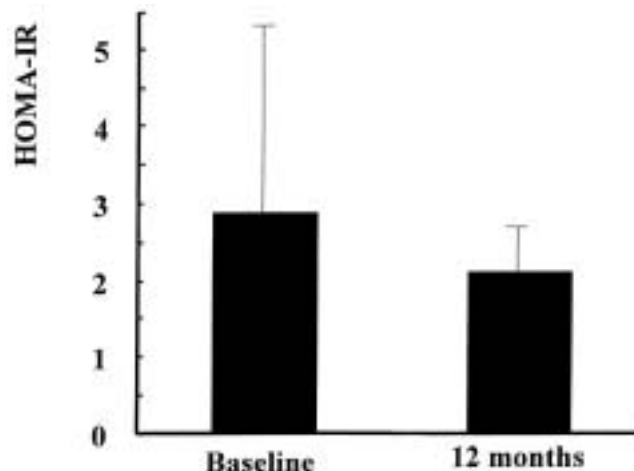
**Table 3.** Change in glucose metabolism from baseline to 12 months of follow-up.

	Baseline mean $\pm$ S.D.	12 months mean $\pm$ S.D.	Percentage change (%)	<i>p</i> -value
PG (mg/dl)				
0 min	98.9 $\pm$ 11.3	101.6 $\pm$ 13.3	2.7	0.137
60 min	171.1 $\pm$ 47.3	152.6 $\pm$ 41.6	- 10.8	0.017
change from 0 to 60 min	72.2 $\pm$ 39.5	49.6 $\pm$ 30.9		0.004
120 min	137.9 $\pm$ 42.0	139.0 $\pm$ 36.9	0.8	0.654
change from 0 to 120 min	39.0 $\pm$ 34.6	36.2 $\pm$ 27.7		0.775
IRI (mg/dl)				
0 min	11.3 $\pm$ 12.3	8.3 $\pm$ 4.7	- 26.5	0.291
60 min	66.8 $\pm$ 37.2	50.3 $\pm$ 26.3	- 24.7	0.035
change from 0 to 60 min	55.5 $\pm$ 37.9	41.6 $\pm$ 22.3		0.098
120 min	54.2 $\pm$ 27.7	46.8 $\pm$ 30.8	- 13.7	0.235
change from 0 to 120 min	42.8 $\pm$ 26.6	37.9 $\pm$ 27.7		0.487
C-peptide (mg/dl)				
0 min	2.6 $\pm$ 0.8	2.4 $\pm$ 0.9	- 7.8	0.230
60 min	8.5 $\pm$ 2.2	7.1 $\pm$ 3.0	- 16.7	0.019
change from 0 to 60 min	6.0 $\pm$ 2.1	4.7 $\pm$ 2.5		0.026
120 min	8.7 $\pm$ 2.1	7.9 $\pm$ 2.4	- 9.5	0.124
change from 0 to 120 min	6.2 $\pm$ 2.3	5.5 $\pm$ 2.0		0.253

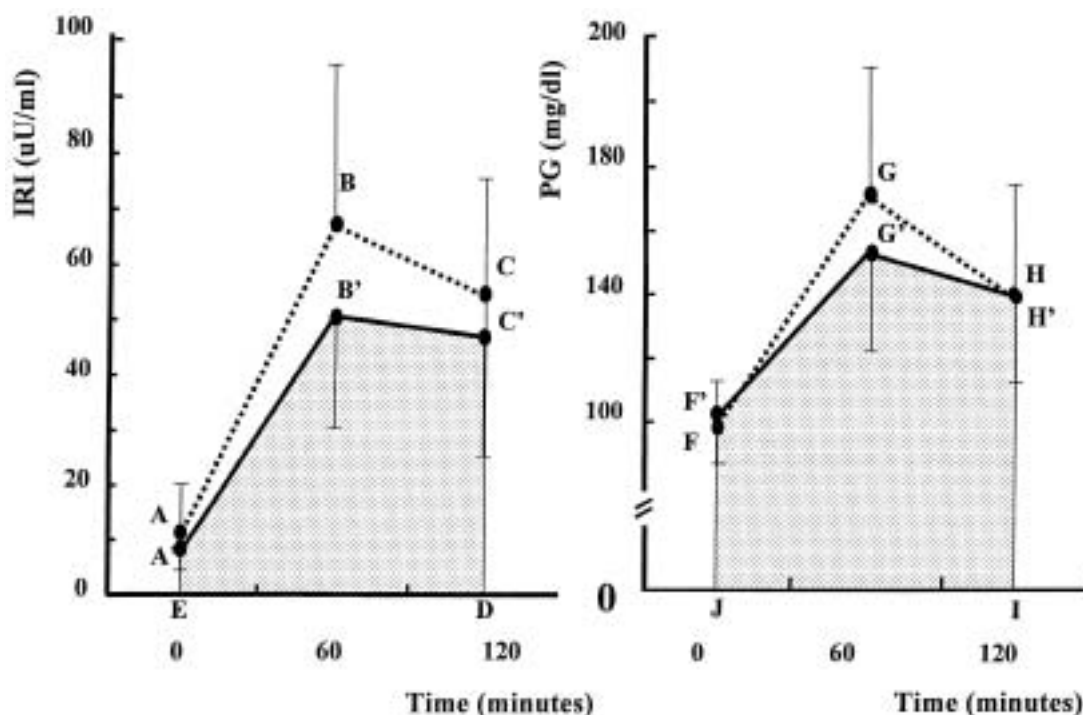
PG: plasma glucose, IRI: immunoreactive insulin

comes Trial-Lipid Lowering Arm (ASCOT-LLA) (21) revealed the incidence of diabetes to be significantly higher in an atorvastatin group than in a placebo group.

An important effect of statins on glucose metabolism is the anti-inflammatory effect. Pravastatin has been shown to reduce circulating levels of interleukin-6 (IL-6) and TNF- $\alpha$  (22). It has been assumed that these cytokines, derived in part from adipose tissue, may be responsible for the metabolic syndrome associated with insulin resistance (23). Hs CRP, an inflammatory marker, has been reported to be a strong independent predictor of risk of future myocardial infarction (24). A nested, case-control study in the secondary-prevention Cholesterol and Recurrent Events (CARE) trial (25) showed that the relative risk of recurrent events was reduced to a greater degree in pravastatin versus placebo-administered patients who had elevated levels of hs CRP than in pravastatin versus placebo-administered patients with normal hs CRP levels. These results support the idea that statins have an inflammatory effect which results in a reduction in the incidence of cardiovascular events. In our study, a significant decrease in hs CRP, by 46.1%, was found after 12 months of pravastatin treatment. This decrease may have been the cause of the reduction in insulin resis-



**Fig. 1.** Change in HOMA-IR over the 12 months of pravastatin treatment.



**Fig. 2.** PG levels and IRI levels in response to the “cookie test” at baseline and after 12 months of pravastatin treatment. The broken line indicates the baseline values and the thick line indicates the values at 12 months.

AUC-IRI at baseline = the area of ABCDE=  $99.6 \pm 46.6 \mu\text{U}\cdot\text{Eh}/\text{ml}$

AUC-IRI at 12months = the area of A'B'C'DE=  $77.9 \pm 39.8 \mu\text{U}\cdot\text{Eh}/\text{ml}$ .

\* $p < 0.05$  vs. baseline.

AUC-IRI  $\times$  AUC-PG at baseline = the area of ABCDE  $\times$  the area of FGHIJ =  $29215.5 \pm 15736.1 (\mu\text{U}\cdot\text{Ehr}/\text{ml})$  (mg·Eh/dl)

AUC-IRI  $\times$  AUC-PG at 12 months = the area of A'B'C'DE  $\times$  the area of F'G'H'IJ  $21478.6 \pm 12389.8 (\mu\text{U}\cdot\text{Ehr}/\text{ml})$  (mg·Eh/dl).

\* $p < 0.05$  vs. baseline.

tance, which may be attributed to the inhibition of proinflammatory cytokines.

Some statins, especially lipophilic statins, have been reported to have an unfavorable effect on glucose metabolism. Yada *et al.* (26) found that simvastatin, a lipophilic statin, inhibited glucose-induced cytosolic  $\text{Ca}^{2+}$  signaling and insulin secretion due to a blockade of L-type  $\text{Ca}^{2+}$  channels in rat islet  $\beta$ -cells; however, pravastatin, a hydrophilic statin, caused no such inhibition. Kanda *et al.* (27) reported that atorvastatin, also a lipophilic statin, significantly increased blood glucose at several time points during OGTT, however, pravastatin did not. It seems reasonable to suppose that this hydrophobic statin, pravastatin, is processed only in the liver, whereas the lipophilic statins are processed in other organs, such as the pancreas, adipose tissue, and muscle, causing a decrease in insulin secretion and exacerbation of insulin resistance.

There are potential limitations regarding the interpretation of our results. First, the small number of patients that were eligible for the analysis makes it difficult to generalize the results. Second, there is no control group that would allow us to more properly evaluate the effect of pravastatin. Further study will be required to clarify the effect of pravastatin on insulin resistance.

In conclusion, our study indicated that pravastatin improves insulin resistance in addition to reducing the serum cholesterol level and that the “cookie test”, AUC-IRI, and the formula AUC-IRI  $\times$  AUC-PG, were useful for evaluating glucose and lipid metabolism.

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