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# Fluvastatin Improves Insulin Resistance in Nondiabetic Dyslpidemic Patients

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**Statins have multiple actions, independent of their classical effects on lipoproteins. The data about the effects of statins on insulin resistance is controversial. This study was designed to search the statin effects on nondiabetic dyslipidemic patients. Thirty-five (17 male, 18 female) consecutive dyslipidemic patients 54.25 ± 8.81 yr were enrolled in the study. After a standard follow-up period of lifestyle modification, the patients were given fluvastatin 40 mg/d for 8 wk. Serum analyses were done both before and after treatment. Insulin resistance was assessed by homeostasis assessment model (HOMA). Fasting plasma triglyceride, total and LDL cholesterol, fasting insulin, and HOMA index were significantly reduced and HDL cholesterol was improved after fluvastatin treatment. HOMA-IR was not correlated with triglycerides, LDL, HDL, or total cholesterol levels. The same situation was present for both fasting plasma insulin and fasting plasma glucose levels. Also age was not associated with HOMA-IR and fasting plasma insulin levels. As a conclusion, the present study indicates that fluvastatin treatment improves insulin resistance in dyslipidemic patients who do not have diabetes or impaired fasting glucose. Also, the effect of fluvastatin on insulin resistance is not associated with the lowering of triglycerides. The latter finding indicates that the effect of statins on insulin sensitivity may not be related with the lowering of triglycerides in dyslipidemic patients.**

**Key Words:** Insulin resistance; fluvastatin; dyslipidemia.

## Introduction

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) reduce cardiovascular disease risks and events *(1–3).* However, statins have multiple actions that are independent of their classical effects on lipoproteins. Among these actions are the modulation of endothelial function, plaque stabilization, attenuation of atherogenesis, and anti-inflammatory and antithrombotic actions. The reduction of the development of diabetes as observed in the West of Scotland Coronary Prevention Study (WOSCOPS) implies that statins may also improve insulin sensitivity *(4).*

Insulin resistance is a component of a metabolic syndrome *(5).* Several studies revealed that the presence of insulin resistance increases the risk of coronary heart disease *(6–9).* However, the data about the effects of statins on insulin resistance are controversial *(10–14).* Some reports indicate that statins worsen the insulin action *(13),* whereas some reports indicate that statins have no effects on plasma insulin levels *(14).* There are also reports which indicate that statins improve the insulin sensitivity *(10–12).* Performing different methods in the assessment of insulin resistance is a possible reason for the discrepancies of these results. Moreover, the group profiles are not similar in those studies. The former study populations had diabetes mellitus or impaired fasting glucose. There are no data about the effect of statins on insulin sensitivity in dyslipidemic patients who have no diabetes or impaired fasting glucose. The aim of the current study is to investigate the effect of fluvastatin on insulin resistance in a selected group of patients who have only dyslipidemia.

## Results

No difference of body mass index, mean arterial blood pressure, and fasting plasma glucose was present in the end of treatment. Fasting plasma triglyceride, total cholesterol, LDL cholesterol, fasting insulin, and HOMA index were significantly reduced after fluvastatin treatment. Fasting plasma HDL cholesterol was improved significantly (Table 1).

The HOMA-IR was not correlated with triglycerides, LDL, HDL, and total cholesterol levels. The same situation was present for both fasting plasma insulin and fasting plasma glucose levels. Also, age was not associated with HOMA-IR and fasting plasma insulin levels (Table 2).

## Discussion

Clinical trials and animal studies have shown that statins reduce cardiovascular disease risks and events *(1–3).* Cardiovascular benefits of statins have conventionally been attributed to reduction of LDL-cholesterol. However, the benefits of statins seem to go beyond lipid lowering alone. For

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**Table 1**
Clinical Characteristics of the Study Group

| | Before treatment ($n$ = 35) | After treatment ($n$ = 35) | $p$ [a] |
|---|---|---|---|
| Age yr (yr) | 54.25 ± 8.81 | | |
| Gender | 17M/18F | | |
| Body mass index ($kg/m^2$) | 26.37 ± 3.14 | 25.86 ± 2.62 | >0.05 |
| MABP (mmHg) | 136.24 ± 10.32 | 133.37 ± 9.31 | >0.05 |
| FP glucose (mg/dL) | 90.74 ± 10.81 | 87.68 ± 10.64 | >0.05 |
| FP insulin (μU/mL) | 11.57 ± 2.56 | 5.95 ± 1.54 | <0.0001 |
| FP triglycerides (mg/dL) | 161.97 ± 41.91 | 123.17 ± 51.78 | <0.0001 |
| FP total cholesterol (mg/dL) | 277.65 ± 88.03 | 209.08 ± 45.08 | 0.003 |
| FP LDL-cholesterol (mg/dL) | 203.54 ± 89.29 | 133.97 ± 41.09 | <0.0001 |
| FP HDL-cholesterol (mg/dL) | 45.88 ± 4.87 | 50.40 ± 5.85 | <0.001 |
| HOMA-IR | 2.60 ± 0.71 | 1.29 ± 0.39 | <0.0001 |

[a]Paired $t$-test; MABP: mean arterial blood pressure; FP: fasting plasma; M: male; F: female.

**Table 2**
Correlation of Indicators in Patients

| | Insulin | FPG | HOMA-IR | Age |
|---|---|---|---|---|
| Total cholesterol (mg/dL) | $r$ =–0.163 $p$ = 0.349 | $r$ = 0.023 $p$ = 0.896 | $r$ =–0.131 $p$ = 0.452 | $r$ = 0.137 $p$ = 0.434 |
| Triglyceride (mg/dL) | $r$ =–0.235 $p$ = 0.175 | $r$ =–0.034 $p$ = 0.848 | $r$ =–0.205 $p$ = 0.238 | $r$ = 0.237 $p$ = 0.170 |
| HDL cholesterol (mg/dL) | $r$ = 0.019 $p$ = 0.913 | $r$ =–0.203 $p$ = 0.242 | $r$ =–0.059 $p$ = 0.736 | $r$ =–0.070 $p$ = 0.691 |
| LDL cholesterol (mg/dL) | $r$ =–0.143 $p$ = 0.411 | $r$ = 0.041 $p$ = 0.813 | $r$ =–0.106 $p$ = 0.546 | $r$ = 0.097 $p$ = 0.580 |

example, in WOSCOPS *(3),* the time-to-event curves began to diverge within 6 mo of initiating therapy, an effect that is earlier than predicted from cholesterol lowering alone. Potential mechanisms that may mediate these effects include modulation of endothelial function, plaque stabilization, attenuated atherogenesis, and anti-inflammatory and antithrombotic action. Moreover, the potential reduction in the development of diabetes as observed in WOSCOPS implies that statins may also improve the insulin resistance *(4).*

The effects of statin administration on insulin action and metabolic control were investigated mostly on diabetics or on people with impaired fasting glucose *(10–13).* The results of these trials have great discrepancies, possibly because of the different techniques on the evaluation of insulin sensitivity and the variability of the study populations. Ohrvall et al. *(13)* compared the efficacy of gemfibrozil with simvastatin in NIDDM patients. According to the results, simvastatin had no effect on plasma triglyceride concentrations. And insulin action, measured by the intravenous glucose tolerance test, was deteriorated after statin treatment. However, half of the patients of the later study were hypertensive, and were taking various drugs that might affect insulin sensitivity. Paolisso et al. *(12)* reported that both simvastatin and atorvastatin improve insulin resistance, measured by the indirect HOMA index technique, on elderly patients with NIDDM. There are no data about the effects of statins on people without diabetes mellitus and without impaired fasting glucose. Thus, the present study, which shows that fluvastatin improves insulin resistance in patients without diabetes and impaired fasting glucose, gives additional information on the effects of statins.

Recent advances in understanding the cellular actions of statins may explain mechanisms that mediate the statin effect on insulin sensitivity. Statins may affect substrate delivery to insulin-sensitive tissues or modulate insulin-activated signaling cascades that mediate glucose uptake. Insulin increases skeletal muscle perfusion and substrate delivery by enhancing eNOS activity. Statins also increase eNOS expression, which may result in increased capillary recruitment and glucose disposal *(15).* Insulin activates a series of kinase cascades that involve PI3K and Akt, resulting in the translocation of glucose transporters to cell membrane and enhanced glucose uptake *(15).* This cascade is inhibited by circulating cytokines (TNF-α and IL-6) *(15).* Statins, like insulin, activate PI3K and Akt, which may play a role in glucose uptake. It is widely accepted that elevated plasma triglyceride concentrations may impair insulin action *(16,17)* probably through an overactivity of the Randle cycle *(18).* Some authors believe that the decrement in plasma triglyceride concentration is associated with an improvement of insulin-mediated glucose uptake. Paolisso et al. reported that the HOMA index and triglyceride levels were correlated in their patients and the statin effect on the insulin resistance is the result of triglyceride lowering *(12).* However, in our study group there was no correlation between the triglyceride levels and HOMA indexes. The retrospective analysis of the WOSCOPS revealed that the prevention in the onset of diabetes was associated with significant reduction in triglyceride levels. But the reduction in triglycerides did not account for the effect of statins on the development of diabetes *(4).* Thus, it may be inferred that the improvement of insulin resistance may not be related with the lowering of triglyceride levels.

However, there are several implications of the present study. The lack of randomization and placebo control group are the shortcomings and prevent us from making reasonable conclusions. Furthermore, all patients in the study were encouraged to perform therapeutic lifestyle modifications. Thus, it is not completely possible to attribute the improvement of insulin resistance to the distinctive effect of fluva-

statin. Lifestyle modifications that were begun before the beginning of fluvastatin treatment and continued to the end of the study may also contribute to the improvement of insulin sensitivity.

In conclusion, the present study shows that fluvastatin treatment improves insulin resistance in dyslipidemic patients who perform therapeutic lifestyle modifications and who have no diabetes or impaired fasting glucose. Also, the effect of fluvastatin on insulin resistance is not related with the lowering of triglycerides.

## Methods

Thirty-five (17 male, 18 female) consecutive dyslipidemic patients were enrolled in the study. All were outpatients of our Department of Internal medicine. Eligibility criteria included (a) age < 60 yr; (b) BMI <29.0 kg/m$^2$; (c) fasting blood glucose <107mg/dL; (d) fasting plasma triglyceride concentrations ranging between 150 and 350 mg/dL; (e) fasting plasma LDL-cholesterol concentrations >160 mg/dL; (f) no evidence of hypertension or renal, hepatic, endocrine, or cancer diseases or severe allergies as determined by medical history, physical examination, and routine laboratory tests**.** The blood pressures were measured on each visit for at least three times for each patient. Levels under 140/90 mmHg were eligible for the study. All patients had a stable body weight in the 3 mo before the study and were not taking any medicine up to the time of the study. The purpose and nature of the study were explained to all patients and voluntary consent was obtained before they were enrolled.

Before the beginning of the treatment, all patients were encouraged to perform therapeutic lifestyle modifications according to the Adult Treatment Panel III *(19).* Six weeks after the lifestyle modifications, the patients were given fluvastatin 40 mg/d for additional 8 wk. Patients continued to perform lifestyle modifications during the study period. The serum analyses were done both before and after the treatment.

### *Blood Chemistry*

Fasting blood samples were collected from hypercholesterolemic and control patients between 08:00 and 08:30 AM after a 12 h fasting. The tubes were promptly centrifuged; plasma was separated and stored at –70ºC for measurement of glucose, total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL) cholesterol. All plasma samples were run in a single assay. Glucose, total cholesterol, TG, and HDL cholesterol were measured by the enzymatic colorimetric method with Olympus AU 600 autoanalyzer using reagents from Olympus Diagnostics, GmbH (Hamburg, Germany). LDL cholesterol was calculated by Friedewald's formula *(20).* The serum basal insulin value was determined in duplicate by the coated tube method (DPC-USA). The intraassay coefficient of variation was 22% ($n$ = 35).

### *Assessment of Insulin Resistance*

In particular, an insulin resistance score (HOMA-IR) was computed with the formula: (HOMA-IR) = [FPG (mg/dL) × immunoreactive insulin (IRI) (μU/mL)]/405 *(21–24)*. Low HOMA-IR values indicate high insulin sensitivity, whereas high HOMA-IR values indicate low insulin sensitivity (insulin resistance).

### *Statistical Analysis*

The serum total, HDL and LDL cholesterol, triglycerides, insulin, fasting blood glucoses, and HOMA indexes were compared with each other by paired $t$-test both before and after treatment. The association between HOMA indexes and the lipid parameters were investigated by Pearson correlation test. All values were expressed as mean ± SD.

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