Simvastatin Improves Flow-Mediated Dilation, but Reduces Adiponectin Levels and Insulin Sensitivity In Hypercholesterolemic Patients

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Running Title: Simvastatin Reduces Adiponectin Levels and Insulin Sensitivity

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ABSTRACT

Objective: We hypothesized simvastatin may reduce adiponectin levels and insulin sensitivity in hypercholesterolemic patients.

Research Design and Methods: This was a randomized, double-blind, placebo-controlled, parallel study. Age, sex, and body mass index were matched. Thirty-two patients were given placebo and 30, 32, 31, and 31 patients were given daily simvastatin 10, 20, 40, and 80 mg, respectively during a 2 month treatment period.

Results: Simvastatin 10, 20, 40, and 80 mg significantly reduced total cholesterol (mean % changes; 27, 25, 37, and 38%), LDL cholesterol (39, 38, 52, and 54%) and apolipoprotein B levels (24, 30, 36, and 42%) and improved FMD (68, 40, 49, and 63%) after 2 months therapy when compared with baseline (\(P<0.001\) by paired \(t\)-test) or when compared with placebo (\(P<0.001\) by ANOVA). Simvastatin 10, 20, 40, and 80 mg significantly decreased plasma adiponectin levels (4, 12, 5, and 10%) and insulin sensitivity (determined by QUICKI) (5, 8, 6, and 6%) when compared with baseline (\(P<0.05\) by paired \(t\)-test) or compared with placebo (\(P=0.011\) for adiponectin and \(P=0.034\) for QUICKI by ANOVA). However, the magnitude of these percent changes (FMD, adiponectin, and QUICKI) were not significantly different among four different doses of simvastatin therapy despite dose-dependent changes in reduction of apolipoprotein B levels.

Conclusions: Simvastatin significantly improved endothelium-dependent dilation, but reduced adiponectin levels and insulin sensitivity in hypercholesterolemic patients independent of dosage and the extent of apolipoprotein B reduction.
Many patients on statin therapy have initial or recurrent coronary heart disease events despite reductions in LDL cholesterol. Coronary heart disease is characterized by endothelial dysfunction and frequently cluster with disorders of metabolic homeostasis including obesity and type 2 diabetes that are characterized by insulin resistance. These co-morbidities may be explained, in part, by reciprocal relationships between endothelial dysfunction and insulin resistance.

The effects of statins on insulin sensitivity are controversial. Simvastatin and atorvastatin improve insulin sensitivity in some diabetic patients. However, others have reported that simvastatin either does not change or worsens insulin sensitivity in patients with metabolic syndrome or type 2 diabetes. Lipophilic statins, particularly at high doses, may cause unfavorable pleiotropic effects such as reduction of insulin secretion and exacerbation of insulin resistance. Indeed, recent large scale clinical studies demonstrate that lipophilic statins, particularly at high dose, may increase the rate of onset of new diabetes.

Adiponectin is an adipocytokine secreted specifically by adipose cells. In humans, plasma levels of adiponectin are negatively correlated with adiposity and insulin resistance. We recently reported that fenofibrate, candesartan, or efonidipine increase adiponectin levels and insulin sensitivity in patients without changing body mass index. Thus, decreased levels of adiponectin may promote insulin resistance rather than simply serving as a biomarker for insulin sensitivity. Adiponectin may represent an important link between metabolic signals, inflammation, and atherosclerosis. We also reported that simvastatin 20 mg tended to reduce plasma levels of adiponectin and insulin sensitivity (although these changes did not achieve statistical significance).

Therefore, we hypothesized simvastatin may reduce plasma levels of adiponectin and insulin sensitivity in hypercholesterolemic patients.

METHODS

Study Population and Design. We used a randomized, double-blind, placebo-controlled, and parallel study design. Age, sex, and body mass index were matched among all subjects. Patients with hypercholesterolemia (low-density lipoprotein cholesterol levels ≥100 mg/dl and body mass index ≥23.0 kg/m²) participated in this study. We excluded patients with overt liver disease, chronic renal failure, hypothyroidism, myopathy, uncontrolled diabetes, severe hypertension, stroke, acute coronary events, 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. Before and during the study period a dietitian educated patients to maintain a low fat diet. Activity levels of the subjects were not monitored before or during the study. Clinical characteristics of these patients are summarized in Table 1. Each of 32 patients in 5 groups was given placebo or simvastatin 10, 20, 40, or 80 mg, respectively once daily during a 2 month treatment period. A research nurse counted pills at the end of treatment to monitor compliance. The patients were seen at least every 14-days during the study. To minimize side effects, we measured serum asparate aminotransferase, alanine aminotransferase, creatine kinase, blood urea nitrogen and creatinine before and after therapy. Two patients on simvastatin 10 mg withdrew from the study because they moved to other places and each one patient on simvastatin 40 and 80 mg, respectively experienced moderate elevations in serum liver enzyme or creatine kinase, respectively.
and they dropped out from the study. Thus, thirty-two patients on placebo and 30, 32, 31, and 31 patients on simvastatin 10, 20, 40, and 80 mg, respectively finished the study. None of the patients were diabetic. No additional medications including aspirin or nonsteroidal anti-inflammatory drugs were allowed during the study period to avoid confounding effects of other drugs. Calcium channel or beta adrenergic blockers were withheld for ≥48 hours before the study. The study was approved by the Gil Hospital Institute Review Board and all participants gave written, informed consent.

**Laboratory Assays and Vascular Studies.** Blood samples for laboratory assays were obtained at approximately 8:00 a.m. following overnight fasting before and at the end of each 2-month treatment period. These samples were immediately coded so that investigators performing laboratory assays were blinded to subject identity or study sequence.

Assays for lipids, glucose, and plasma adiponectin were performed in duplicate by ELISA (R & D Systems, Inc., Minneapolis, Minnesota), assays for high sensitivity C-reactive protein (CRP) levels by latex agglutination (CRP-Latex(II)®, Denka-Seiken, Tokyo, Japan), and assays for plasma insulin levels by immunoradiometric assay (INSULIN-RIABEAD® II, SRL, Inc, Tokyo, Japan) as previously described. The interassay and intraassay coefficients of variation were <6%. Quantitative Insulin-Sensitivity Check Index (QUICKI), a surrogate index of insulin sensitivity based on fasting glucose and insulin levels, was calculated as follows (insulin is expressed in microU/ml and glucose in mg/dl): QUICKI = 1/[log(insulin)+log(glucose)]. Imaging studies of the right brachial artery were performed using an ATL HDI 3000 ultrasound machine (Bothell, WA, USA) equipped with a 10 MHz linear-array transducer, based on a previously published technique.

**Statistical Analysis.** Data are expressed as mean±SEM or median (range:25%-75%). After testing data for normality, we used Student’s paired t or Wilcoxon Signed Rank test to compare values between baseline and treatment at 2 months, as reported in Table 2. We used one way analysis of variance (ANOVA) or Kruskal-Wallis ANOVA on Ranks to compare baseline or treatment effects among treatment groups. Post-hoc comparisons between different treatment pairs were made using the Student-Newman-Keuls multiple comparison procedures or Dunn’s method. Pearson or Spearman correlation coefficient analysis was used to assess associations between measured parameters. We calculated that 30 subjects would provide 80% power for detecting an absolute increase of 1.5% or greater in flow-mediated dilation of the brachial artery between baseline and simvastatin 20 mg, with α=0.05 based on our previous studies. The comparison of endothelium-dependent dilation was prospectively designated as the primary end-point of the study. All other endpoints and comparisons were considered secondary. A value of P<0.05 was considered to represent statistical significance.

**RESULTS**

Age, sex, and body mass index were matched in all groups of subjects. The baseline patient characteristics are reported in Table 1 and there were no significant differences between groups for any of the baseline measurements (Table 2). **Effects on Lipids.** Placebo significantly reduced total and low-density lipoprotein (LDL) cholesterol levels from baseline. Simvastatin 10, 20, 40, and 80 mg significantly reduced total cholesterol (mean % changes; 27, 25, 37, and 38%), LDL cholesterol (39, 38, 52, and 54%) and apolipoprotein B levels (24, 30, 36, and 42%) from baseline (all P<0.001 by paired t-test)
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after 2 months administration. These effects of four different doses of simvastatin were also significant when compared with placebo ($P<0.001$ by ANOVA; Fig. 1). No significant changes in other lipid profiles were noted with simvastatin therapy at any of the doses evaluated when compared with placebo.

Effects on Vasomotor Function and High Sensitivity C-reactive Protein. Placebo did not significantly improve flow-mediated dilator response to hyperemia (FMD) relative to baseline measurements. Simvastatin 10, 20, 40, and 80 mg significantly improved FMD (mean % changes; 68, 40, 49, and 63%) after 2 months therapy when compared with baseline ($P<0.001$ by paired $t$-test). All of these effects were also significant when compared with placebo ($P<0.001$ by ANOVA; Fig. 1). Brachial artery dilator responses to nitroglycerin were not significantly different between any of the therapies. In addition, no significant changes in high sensitivity CRP were noted with any of the therapies ($P=0.363$ by ANOVA on Ranks).

Effects on Adiponectin and Insulin Resistance. Placebo did not significantly change insulin or glucose levels from baseline. Simvastatin 80 mg significantly increased glucose levels (mean % changes; 7%) after 2 months administration when compared with baseline ($P=0.011$ by paired $t$-test). The effects of four different doses of simvastatin on glucose were not significant when compared with placebo ($P=0.501$ by ANOVA). Simvastatin 10, 20, 40, and 80 mg tended to increase insulin levels (mean % changes; 67, 160, 93, and 96%) after 2 months therapy when compared with baseline ($P=0.096$, $P=0.007$, $P=0.005$, and $P=0.268$ by paired $t$-test). The effects of four different doses of simvastatin to raise fasting insulin levels were significant when compared with placebo ($P=0.006$ by ANOVA on Ranks; Fig. 1). Post-hoc comparison demonstrated a significant difference between placebo and simvastatin 20 mg ($P<0.05$). We observed significant correlations between baseline high density lipoprotein cholesterol levels and baseline adiponectin levels ($r=0.354$ before placebo; $r=0.540$ before simvastatin 10 mg; $r=0.323$ before simvastatin 20 mg; $r=0.376$ before simvastatin 40 mg; $r=0.537$ before simvastatin 80 mg). Placebo did not significantly change plasma adiponectin levels and insulin sensitivity (determined by QUICKI) relative to baseline measurements. Simvastatin 10, 20, 40, and 80 mg significantly decreased plasma adiponectin levels (mean % changes; 4%, 12%, 5%, and 10%) and insulin sensitivity (mean % changes; 5%, 8%, 6%, and 6%) when compared with baseline (all $P<0.05$ by paired $t$-test). Moreover, these effects of all four doses of simvastatin were significant when compared with placebo ($P=0.011$ for adiponectin and $P=0.034$ for QUICKI by ANOVA; Fig. 1). The magnitude of percent changes in FMD, adiponectin, and QUICKI were not significantly different among the four different doses of simvastatin despite dose-dependent changes in reduction of apolipoprotein B levels.

We investigated whether changes in percent flow-mediated dilator response to hyperemia, plasma levels of adiponectin, or insulin resistance were related to changes in lipoprotein levels. There were no significant correlations between changes in these parameters and changes in lipoprotein levels following any of the simvastatin therapies. There were inverse correlations between percent changes in adiponectin levels and percent changes in insulin ($r=-0.414$, $P=0.018$ after placebo; $r=-0.273$, $P=0.152$ after simvastatin 10 mg; $r=-0.211$, $P=0.276$ after simvastatin 20 mg; $r=-0.263$, $P=0.152$ after simvastatin 40 mg; $r=-0.366$, $P=0.043$ after simvastatin 80 mg) following therapies. There were correlations between percent changes in adiponectin levels and percent changes in QUICKI ($r=0.543$, $P=0.001$ after
placebo; \( r = 0.366, P = 0.051 \) after simvastatin 10 mg; \( r = 0.441, P = 0.011 \) after simvastatin 20 mg; \( r = 0.234, P = 0.205 \) after simvastatin 40 mg; \( r = 0.380, P = 0.035 \) after simvastatin 80 mg) following therapies.

**DISCUSSION**

We observed that simvastatin significantly improved endothelium-dependent dilation, but reduced adiponectin levels and insulin sensitivity in hypercholesterolemic patients independent of dosage. Despite dose-dependent effects of simvastatin on apolipoprotein B reduction, the magnitude of these percent changes (FMD, adiponectin, and QUICKI) were not significantly different among four different doses of simvastatin.

Due to reciprocal relationships between endothelial dysfunction and insulin resistance,\(^2,3\) we hypothesized that improvements in endothelial dysfunction may be accompanied by simultaneous improvement in metabolic parameters. However, simvastatin significantly reduced adiponectin levels and insulin sensitivity despite improvement in endothelium-dependent dilation in hypercholesterolemic patients. Further, there were no significant correlations between endothelial dysfunction and metabolic parameters. By contrast, in previous studies with fenofibrate, ramipril, angiotensin II receptor blockers, or efonidipine, improvement in endothelial dysfunction was accompanied by simultaneous improvement in insulin sensitivity and increased adiponectin levels.\(^{15-19}\) Taken together, this suggests that not all mechanisms for improving endothelial dysfunction are tightly coupled to metabolic homeostasis. Alternatively, potential improvements in insulin sensitivity and adiponectin levels caused by improvement in endothelial function after simvastatin therapy may be masked by other endothelial-independent effects of simvastatin that worsen insulin resistance and lower adiponectin levels.

Adiponectin is an adipose-derived factor that augments and mimics metabolic and vascular actions of insulin.\(^4\) In our study, simvastatin therapy significantly decreased adiponectin levels without a corresponding change in body mass index. This is consistent with a recent paper describing the PIOSTAT study.\(^21\) Thus, it is possible that statin therapy is directly altering adiponectin levels independent of adiposity. In 3T3-L1 adipocytes pravastatin increases expression of adiponectin mRNA and enhances adiponectin secretion into conditioned media. This corresponds to increased plasma levels of adiponectin and enhanced insulin sensitivity in C57BL/6J mice without changes in body weight. By contrast, simvastatin does not increase production of adiponectin in 3T3L1 adipocytes.\(^22\) Thus, the lipophilic status of particular statins may determine, in part, beneficial or detrimental effects on adiponectin levels and insulin sensitivity. Decreasing adiponectin levels is predicted to worsen insulin sensitivity by multiple mechanisms.\(^4\) In the current study, there were correlations between percent changes in adiponectin levels and percent changes in insulin or QUICKI following simvastatin therapy.

There may be additional mechanisms to reduce insulin sensitivity and adiponectin levels following simvastatin therapy. Lipophilic statins particularly high dose may cause unfavorable pleiotropic effects such as reduction of insulin secretion and exacerbation of insulin resistance.\(^7,9\) Lipophilic statins inhibit the glucose-caused elevation of free Ca level in cytoplasm, leading to suppressed insulin secretion. Glucose-induced elevation in intracellular Ca\(^{2+}\) level is attributable to inflow of Ca\(^{2+}\) following activation of the L-type Ca\(^{2+}\) channel in β cells. Simvastatin suppresses glucose-induced elevation of intracellular Ca\(^{2+}\) level in a dose-dependent manner in an
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experiment using the patch clamp method. When the influence of statins on glucose-stimulated insulin secretion was evaluated by direct measurement, simvastatin exerted significant suppression. The possibility of lipophilic statins reducing sensitivity to insulin is suggested by an experiment using rats with streptozotocin-induced diabetes mellitus. Impaired glucose tolerance is observed after 6 weeks of treatment with atorvastatin when compared with the control group. Moreover, lovastatin treatment down-regulates expression of the insulin-responsive glucose transporter GLUT4 and up-regulates GLUT1 in 3T3-L1 adipocytes. This is associated with marked inhibition of insulin-stimulated glucose transport. Under these conditions, lovastatin had no effect on cell cholesterol levels but its metabolic effects were reversed by mevalonate. This suggests that inhibition of isoprenoid biosynthesis causes insulin resistance in 3T3-L1 adipocytes.

The effects of statins on adiponectin and insulin sensitivity in humans are controversial. Simvastatin and atorvastatin improve insulin sensitivity in some diabetic patients. However, others report that simvastatin either does not change or worsens insulin sensitivity in patients with metabolic syndrome or type 2 diabetes. We reported that simvastatin 20 mg tended to reduce plasma levels of adiponectin and insulin sensitivity. However, these effects were not statistically significant. Simvastatin 20 mg reduces plasma adiponectin levels from 4.5 (3.4-7.0) μg/ml to 4.5 (2.9-6.0) μg/ml (P=0.153) and QUICK from 0.475 to 0.458 (P=0.191) in hypercholesterolemic, hypertensive patients and reduces plasma adiponectin levels from 3.8 (2.7-5.2) μg/ml to 3.7 (2.2-5.1) μg/ml (P=0.247) and QUICKI from 0.367 to 0.360 (P=0.270) in patients with type 2 diabetes. In the current study, we observed that simvastatin significantly reduced adiponectin levels and insulin sensitivity in hypercholesterolemic patients independent of dosage. Despite dose-dependent effects of simvastatin on apolipoprotein B reduction, the magnitude of these percent changes on adiponectin and QUICKI were not significantly different among different doses of simvastatin. The effects of simvastatin on glucose were not significant when compared with placebo. However, the effects of simvastatin on insulin were significant when compared with placebo. In the current study, the average body mass index is larger than in our previous studies. Thus, the metabolic effects of simvastatin may differ depending on body mass index. Because measures of insulin resistance were considered secondary in the current study, we did not measure insulin sensitivity using the reference standard euglycemic glucose clamp technique. However, QUICKI, the surrogate measure of insulin sensitivity we employed is the most extensively validated and accurate surrogate index of insulin sensitivity currently available in humans. Indeed, QUICKI is the most appropriate surrogate measure of insulin sensitivity to use with our patient population and study design. Our current study evaluated 2 month therapy. However, others using longer durations of therapy have found similar results.

Simvastatin significantly increases serum insulin levels whereas a modified Mediterranean-type diet counteracts this effect of simvastatin. Indeed, recent large scale clinical studies have demonstrated that lipophilic statins may increase rather than decrease the rate of onset of new diabetes. In the sub-group analysis of diabetic patients in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA) study, atorvastatin 10 mg treatment group reduces the cumulative incidence of non-fatal myocardial infarction and fatal coronary heart disease. However, onset of diabetes mellitus was seen more frequently in the atorvastatin treatment group than in the placebo group.
Moreover, the onset of diabetes mellitus was seen more frequently in the simvastatin 40 mg treatment group than in the placebo group.\textsuperscript{11} A nested case-control study demonstrates an adjusted odds ratio for pravastatin use alone and simvastatin use alone compared with non-exposed of 0.7 and 1.0, respectively.\textsuperscript{10} Atorvastatin 80 mg is associated with a statistically significant increase in the risk of developing a HbA\textsubscript{1c}>6% both in non-diabetics (adjusted HR 1.78) and in diabetics (adjusted HR 2.36). The pooled adjusted HR was 1.84 (p<0.0001).\textsuperscript{13} These results emphasize the importance of combination therapy for patients at high risks or with diabetes. Such combinations may include the addition of thiazolidinediones\textsuperscript{21}, fenofibrate\textsuperscript{15}, angiotensin-converting enzyme inhibitors\textsuperscript{19}, or angiotensin II type-1 receptor blockers\textsuperscript{18}, in addition to therapeutic lifestyle changes\textsuperscript{25}. Indeed, combination therapies improve both insulin resistance and endothelial function by multiple independent and interdependent mechanisms that improve the overall cardiometabolic profile to a greater extent than monotherapy.\textsuperscript{2,3,26}

We and others report simvastatin lowers CRP in hyperlipidemic coronary patients.\textsuperscript{27,28} In the current study, we observed that simvastatin tended to lower CRP in hyperlipidemic patients. However, these results did not achieve statistical significance. This may be due, in part, to very low baseline CRP levels. Interestingly, the magnitude of percent changes in CRP levels were not significantly different among four different doses of simvastatin despite differential effects on apolipoprotein B reduction. Our observation is consistent with a previous study.\textsuperscript{28}

In summary, simvastatin significantly improved endothelium-dependent dilation, but reduced adiponectin levels and insulin sensitivity in hypercholesterolemic patients independent of dosage and the extent of apolipoprotein B reduction.

**ACKNOWLEDGMENTS**

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REFERENCES

5. Devaraj S, Siegel D, Jialal I: Simvastatin (40 mg/day), adiponectin levels, and insulin sensitivity in subjects with the metabolic syndrome. Am J Cardiol 100:1397-1399, 2007
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### TABLE 1. Baseline Characteristics of the Study Population

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<th>Placebo (n=32)</th>
<th>Simvastatin 10 (n=30)</th>
<th>Simvastatin 20 (n=32)</th>
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<td>6 (19)</td>
<td>5 (16)</td>
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TABLE 2. Effects of Placebo or Simvastatin on Lipids, Endothelium, and Endocrine Parameters in Hypercholesterolemic Patients

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<td>247±6†</td>
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<td>7.70±0.29†</td>
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</tr>
</tbody>
</table>
**Simvastatin Reduces Adiponectin Levels and Insulin Sensitivity**

<table>
<thead>
<tr>
<th>Insulin Resistance</th>
<th>ADP (μg/ml)</th>
<th>Insulin (μU/ml)</th>
<th>Glucose (mg/dl)</th>
<th>QUICKI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6.6±1.0</td>
<td>3.3±0.45</td>
<td>95±4</td>
<td>0.43±0.01</td>
</tr>
<tr>
<td></td>
<td>6.6±0.9</td>
<td>3.04±0.33</td>
<td>89±3</td>
<td>0.44±0.01</td>
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<tr>
<td></td>
<td>6.4±1.0</td>
<td>3.02±0.49</td>
<td>87±8</td>
<td>0.46±0.02</td>
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<tr>
<td></td>
<td>5.9±0.9*†</td>
<td>3.59±0.43</td>
<td>86±3</td>
<td>0.43±0.01*†</td>
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<tr>
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<td>6.0±1.0</td>
<td>2.95±0.44</td>
<td>84±3</td>
<td>0.46±0.02</td>
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<tr>
<td></td>
<td>5.3±1.0*†</td>
<td>5.01±0.70+</td>
<td>91±4</td>
<td>0.41±0.01+†</td>
</tr>
<tr>
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<td>6.2±0.8</td>
<td>2.98±0.31</td>
<td>91±5</td>
<td>0.44±0.02</td>
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<tr>
<td></td>
<td>5.7±0.7*†</td>
<td>4.27±0.48+</td>
<td>91±2</td>
<td>0.41±0.01*†</td>
</tr>
<tr>
<td></td>
<td>6.4±0.8</td>
<td>3.14±0.31</td>
<td>98±4*</td>
<td>0.44±0.02</td>
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<tr>
<td></td>
<td>5.7±0.7*†</td>
<td>3.56±0.32</td>
<td></td>
<td>0.41±0.01*†</td>
</tr>
</tbody>
</table>

Data are expressed as means ±SEM or median.
There were no significant differences among each baseline values.
*P<0.05, +P<0.01, ‡P<0.001 for comparison with each baseline value.
ADP=adiponectin
Quantitative Insulin-Sensitivity Check Index (QUICKI)=1/[log (insulin) + log (glucose)]
NS=not significant.
†P<0.05 for comparison with the value after therapy with placebo.
Simvastatin Reduces Adiponectin Levels and Insulin Sensitivity

FIGURE LEGEND

**Figure 1.** Simvastatin 10, 20, 40, and 80 mg significantly reduced LDL cholesterol (A) and apolipoprotein B levels (B) from baseline after 2 months daily therapy. Moreover, these effects of four different doses of simvastatin were significant when compared with placebo. Simvastatin 10, 20, 40, and 80 mg significantly improved flow-mediated dilator response to hyperemia after 2 months daily therapy when compared with baseline. Moreover, these effects of four different doses of simvastatins were significant when compared with placebo (C). Simvastatin 10, 20, 40, and 80 mg increased insulin levels after 2 months daily therapy when compared with baseline. The effects of four different doses of simvastatins on insulin were also significant when compared with placebo (D).

Simvastatin 10, 20, 40, and 80 mg significantly decreased plasma adiponectin levels (E) and insulin sensitivity (F) when compared with baseline. Moreover, these effects of four different doses of simvastatins were significant when compared with placebo. Pl=placebo, S10=simvastatin 10 mg, S20=simvastatin 20 mg, S40=simvastatin 40 mg, S80=simvastatin 80 mg. Standard error of the mean is identified by the bars. Median values are used in percent change in insulin.
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FIGURE 1

Koh et al, Fig 1-A, B

A

%Change in LDL Cholesterol

P<0.001 by ANOVA

All P<0.001 vs. Placebo

B

%Change in Apolipoprotein B

P<0.001 by ANOVA

All P<0.001 vs. Placebo
Koh et al, Fig 1–C,D

**C**

**%Change in FMD**

All *P*<0.001 vs. Placebo

**D**

**%Change in Insulin**

*P*<0.05

*P*=0.006 by ANOVA on Ranks
Simvastatin Reduces Adiponectin Levels and Insulin Sensitivity

Koh et al. Fig 1-E,F

**E**

%Change in Adiponectin

- PI: P = 0.016
- S10: P = 0.064
- S20: P = 0.011
- S40: P = 0.007
- S80: P = 0.104

**F**

%Change in QUICKI

- PI: p = 0.063
- S10: p = 0.071
- S20: p = 0.024
- S40: p = 0.026
- S80: P = 0.034