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Additive Beneficial Effects of Fenofibrate Combined With Atorvastatin in the Treatment of Combined Hyperlipidemia

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OBJECTIVES We compared vascular and metabolic responses (and adverse responses) to statin and fibrate therapies alone or in combination in patients with combined hyperlipidemia.

BACKGROUND The mechanisms of action for statins and fibrates are distinct.

METHODS Fifty-six patients were given atorvastatin 10 mg and placebo, atorvastatin 10 mg and fenofibrate 200 mg, or fenofibrate 200 mg and placebo daily during each two-month treatment period of a randomized, double-blind, placebo-controlled crossover trial with two washout periods of two months' each.

RESULTS Lipoproteins were changed to a greater extent with combined therapy when compared with atorvastatin or fenofibrate alone. Flow-mediated dilator response to hyperemia and plasma high-sensitivity C-reactive protein and fibrinogen levels were changed to a greater extent with combined therapy when compared with atorvastatin or fenofibrate alone ($p < 0.001$, $p = 0.182$, and $p = 0.015$ by analysis of variance [ANOVA], respectively). The effects of combined therapy or fenofibrate alone on plasma adiponectin levels and insulin sensitivity (determined by the Quantitative Insulin-Sensitivity Check Index [QUICKI]) were significantly greater than those of atorvastatin alone ($p = 0.022$ for adiponectin and $p = 0.049$ for QUICKI by ANOVA). No patients were withdrawn from the study as the result of serious adverse effects.

CONCLUSIONS Combination therapy is safe and has beneficial additive effects on endothelial function in patients with combined hyperlipidemia. (J Am Coll Cardiol 2005;45:1649–53) © 2005 by the American College of Cardiology Foundation

High serum cholesterol and elevated low-density lipoprotein (LDL) cholesterol are important risk factors for coronary heart disease. Many patients on statin therapy have initial or recurrent coronary heart disease events despite reductions in LDL cholesterol (1). Interestingly, fibrate therapy, which significantly decreases triglycerides and increases high-density lipoprotein (HDL) cholesterol without reducing LDL cholesterol, is associated with significant decreases in coronary events (2). Moreover, combined therapy with statins and fibrates is more effective in controlling atherogenic dyslipidemia in patients with combined hyperlipidemia than the administration of either drug alone (3). Of concern is the fact that the combination of statins and fibrates is more likely to be accompanied by severe myopathy (4). This limitation is not observed with fenofibrate, and no significant side effects have been reported with combined statin and fenofibrate treatment (3–5).

Coronary heart disease frequently is associated with insulin resistance and metabolic disorders, such as obesity and combined hyperlipidemia. Endothelial dysfunction associated with cardiovascular diseases may contribute to insulin resistance (6). The effects of statins on insulin resistance are controversial (7,8). Peroxisome proliferator-activated receptor-alpha activators improve insulin sensitivity in rodents (9). The impact of atovastatin and fenofibrate therapies on endothelial homeostasis and insulin resistance may differ because the mechanisms underlying the biological actions of these drugs are distinct. Therefore, we investigated whether combined therapy has additive beneficial effects greater than atovastatin or fenofibrate alone in patients with combined hyperlipidemia.

METHODS

Study population and design. Fifty-six patients with combined hyperlipidemia (total cholesterol ≥200 mg/dl and triglycerides ranging from 200 mg/dl to 800 mg/dl) 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 three months, or evidence of alcohol abuse. Clinical characteristics of the study patients are summarized in Table 1. We administered atorvastatin 10 mg and placebo, atorvastatin 10 mg and fenofibrate 200 mg, or fenofibrate 200 mg and placebo daily during two months in a randomized, double-blind, placebo-controlled crossover trial with three treatment arms (each two months in duration) and two

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Abbreviations and Acronyms

ANOVA = analysis of variance
FMD = flow-mediated dilation
HDL = high-density lipoprotein
LDL = low-density lipoprotein
QUICKI = Quantitative Insulin-Sensitivity Check Index

washout periods (each two months in duration). Patients were observed at 14-day intervals (or more frequently) during the study. To avoid side effects, we measured serum asparate aminotransferase, alanine aminotransferase, creatine kinase, blood urea nitrogen, and creatinine before and after therapy. Calcium channel or beta adrenergic blockers were withheld for ≥48 h before the study. The study was approved by the Gil Hospital Institute Review Board, and all participants gave written, informed consent.

Laboratory assays. Blood samples were obtained at 8:00 AM after an overnight fast before and after each two-month treatment period. 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 enzyme-linked immunosorbent assay (R & D Systems, Inc., Minneapolis, Minnesota), assays for high-sensitivity C-reactive protein levels by latex agglutination (CRP-Latex(II), Denka-Seiken, Japan), and assays for plasma insulin levels by immunoradiometric assay (INSULIN-RIABEAD II, Abbott Japan, Japan) as described previously (10,11). The Quantitative Insulin-Sensitivity Check Index (QUICKI), a surrogate index of insulin sensitivity, was calculated as follows: QUICKI = 1/[log(insulin) + log(glucose)] (12).

Vascular studies. Imaging studies of the right brachial artery were performed using an ATL HDI 3000 ultrasound machine (Bothell, Washington) equipped with a 10-MHz linear-array transducer, on the basis of a published technique (10,11).

Statistical analysis. Data are expressed as mean ± SEM or median (range, 25% to 75%). After testing data for normality, we used the Student paired *t* or Wilcoxon signed rank test to compare values before and after each treatment (Tables 2 and 3). The effects of the three therapies were

Table 1. Baseline Characteristics of the Study Population

Variables	n = 56
Age	56 ± 1
Gender, M:F	23:33
Body mass index, kg/m^2	25.5 ± 0.3
Risk factors	
Current smoking	12 (21)
Ischemic heart disease	12 (21)
Hypertension	38 (68)
Diabetes	9 (16)
Medications	
Beta-adrenergic blockers	23 (41)
Calcium channel blockers	21 (38)

Values are expressed as means ± SEM or n (%).

Table 2. Effects of Atorvastatin, Combined Therapy, and Fenofibrate on Lipid Levels and Endothelial Function in Patients With Combined Hyperlipidemia

	Atorvastatin (A)		Atorvastatin + Fenofibrate (C)		Fenofibrate (F)					
Variables	Baseline 1	Treatment	Baseline 2	Treatment	Baseline 3	Treatment	ANOVA	A/C	A/F	C/F
Body mass index	25.46 ± 0.34	25.47 ± 0.34	25.45 ± 0.34	25.46 ± 0.33	25.47 ± 0.34	25.46 ± 0.35				
Lipids (mg/dl)										
Total cholesterol	243 ± 7	173 ± 5†	240 ± 6	171 ± 4†	234 ± 6	203 ± 5†	<0.001	NS	<0.05	<0.05
Triglycerides	301 ± 23	226 ± 17†	322 ± 19	138 ± 12†	337 ± 24	150 ± 10†	<0.001	<0.05	<0.05	NS
LDL cholesterol	134 ± 7	81 ± 5†	128 ± 6	90 ± 4†	130 ± 7	122 ± 4	<0.001	NS	<0.05	<0.05
Apo B	132 ± 4	92 ± 3†	127 ± 4	89 ± 3†	128 ± 4	101 ± 3†	0.004	NS	<0.05	<0.05
HDL cholesterol	46 ± 1	46 ± 2	46 ± 1	53 ± 2†	44 ± 1	54 ± 2†	<0.001	<0.05	<0.05	NS
Apo A-I	160 ± 3	163 ± 3	162 ± 3	178 ± 4†	154 ± 3	169 ± 4†	0.005	<0.05	<0.05	NS
Vasomotor (%)										
FMD (%)	4.70 ± 0.18	6.38 ± 0.21†	4.56 ± 0.19	7.44 ± 0.22†	4.73 ± 0.19	6.51 ± 0.19†	<0.001	<0.05	NS	<0.05
NTG dilation (%)	13.76 ± 0.50	14.36 ± 0.57	14.16 ± 0.55	14.69 ± 0.53	12.93 ± 0.46	13.77 ± 0.51	0.762			
CRP (mg/l)	1.20 (0.65–2.20)	0.75 (0.40–1.45)*	1.20 (0.70–2.35)	0.60 (0.40–1.10)†	0.80 (0.53–2.03)	0.70 (0.40–1.20)*	0.182			
Fibrinogen (mg/dl)	287 ± 9	264 ± 11	297 ± 7	235 ± 8†	282 ± 9	233 ± 9†	0.015	<0.05	NS	NS

Data are expressed as means ± SEM or median (25th percentile to 75th percentile). There were no significant differences among baseline values. *$p < 0.01$, †$p < 0.001$ for comparison with each baseline value.
A/C = atorvastatin vs. combined therapy; A/F = atorvastatin vs. fenofibrate; ANOVA = analysis of variance; C/F = combined therapy vs. fenofibrate; CRP = C-reactive protein; FMD = flow-mediated dilation; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NS = not significant; NTG = nitroglycerin.

Table 3. Effects of Atorvastatin, Combined Therapy, and Fenofibrate on Adiponectin Levels and Insulin Resistance in Patients With Combined Hyperlipidemia

	Atorvastatin (A)		Atorvastatin + Fenofibrate (C)		Fenofibrate (F)					
Variables	Baseline 1	Treatment	Baseline 2	Treatment	Baseline 3	Treatment	ANOVA	A/C	A/F	C/F
ADP (μg/ml)	3.5 (2.6–5.0)	3.4 (2.6–4.7)	3.4 (2.3–4.7)	3.5 (2.7–5.1)‡	3.2 (2.5–5.1)	3.6 (2.6–5.3)†	0.022	<0.05	<0.05	NS
Insulin (μU/ml)	4.34 ± 0.45	4.57 ± 0.58	4.66 ± 0.42	3.54 ± 0.36‡	4.31 ± 0.45	3.40 ± 0.41*	0.012	<0.05	NS	NS
Glucose (mg/dl)	92 ± 3	95 ± 5	91 ± 4	92 ± 3	89 ± 3	89 ± 3	0.896			
QUICKI	0.411 ± 0.008	0.412 ± 0.008	0.403 ± 0.007	0.430 ± 0.010†	0.419 ± 0.010	0.437 ± 0.009*	0.049	<0.05	NS	NS

Data are expressed as means ± SEM or median (25th percentile to 75th percentile). There were no significant differences among baseline values. *$p < 0.05$, †$p < 0.01$, ‡$p < 0.001$ for comparison with each baseline value.
ADP = adiponectin; QUICK = Quantitative Insulin-Sensitivity Check Index = 1/[log (insulin) + log (glucose)]; other abbreviations as in Table 2.

Figure 1. Fenofibrate alone or combined therapy significantly lowered triglycerides and increased high-density lipoprotein cholesterol levels when compared with atorvastatin alone. ANOVA = analysis of variance.

analyzed by one-way repeated measures analysis of variance (ANOVA) or Friedman's repeated ANOVA on ranks by comparing the relative changes in values in response to treatment. Post hoc comparisons between treatment pairs were made with the Student-Newman-Keuls multiple comparison procedure. Pearson or Spearman correlation coefficient analysis was used to assess associations between measured parameters. Comparisons between endothelium-dependent dilation among the three treatment schemes were prospectively designated as the primary study end point. All other comparisons were considered secondary. A value of $p < 0.05$ was considered to be statistically significant.

RESULTS

No significant differences among baseline values before each treatment period or carryover effects were noted (Tables 2 and 3).

Effects on lipids. Fenofibrate alone or combined therapy significantly lowered triglycerides and increased HDL cholesterol and apolipoprotein A-I levels when compared with atorvastatin alone (Fig. 1, Table 2).

Effects on vasomotor function. Atorvastatin, combined therapy, or fenofibrate significantly improved the percent flow-mediated dilator response to hyperemia relative to baseline measurements by 46 ± 9%, 81 ± 12%, and 45 ± 5%, respectively (all $p < 0.001$). Of note, combined therapy significantly improved this response more than atorvastatin or fenofibrate alone ($p < 0.001$ by ANOVA) (Fig. 2, Table 2). Brachial artery dilator response to nitroglycerin was not significantly changed from respective baseline values. After combined therapy, improvement in flow-mediated dilation (FMD) correlated with changes in total cholesterol ($r = -0.373$ and $p = 0.005$), triglycerides ($r = -0.288$ and $p = 0.032$), and apolipoprotein B levels ($r = -0.341$, $p = 0.010$).

Effects on acute-phase reactants. Atorvastatin, combined therapy, or fenofibrate significantly lowered plasma high-sensitivity C-reactive protein levels relative to baseline measurements from 1.20 to 0.75 ($p = 0.006$), 1.20 to 0.60

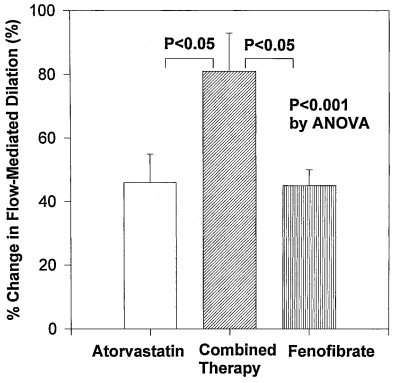

Figure 2. Percent change in flow-mediated dilation from respective pretreatment values after treatment with atorvastatin alone, combined therapy, and fenofibrate alone. ANOVA = analysis of variance.

($p < 0.001$), and 0.80 to 0.70 mg/l ($p = 0.002$), respectively. However, the magnitude of reduction among the three therapies was similar ($p = 0.182$ by ANOVA). Fenofibrate alone or combined therapy significantly lowered plasma fibrinogen levels relative to baseline measurements (both $p < 0.001$). Of note, combined therapy significantly reduced this more than atorvastatin alone ($p = 0.015$ by ANOVA) (Fig. 3, Table 2).

Effects on adiponectin and insulin resistance. There were significant inverse correlations between baseline adiponectin and baseline triglycerides ($r = -0.277$, $p = 0.039$ before atorvastatin; $r = -0.335$, $p = 0.012$ before combined therapy; and $r = -0.288$, $p = 0.032$ before fenofibrate). There were significant correlations between baseline adiponectin and baseline HDL cholesterol ($r = 0.284$, $p = 0.034$ before atorvastatin; $r = 0.258$, $p = 0.049$ before combined therapy; and $r = 0.353$, $p = 0.008$ before fenofibrate). However, there were no significant correlations between baseline adiponectin and baseline insulin or QUICKI.

Combined therapy or fenofibrate alone significantly increased plasma adiponectin levels relative to baseline measurements from 3.4 to 3.5 ($p = 0.001$) and 3.2 to 3.6 ($p = 0.004$), respectively. These increases were significantly

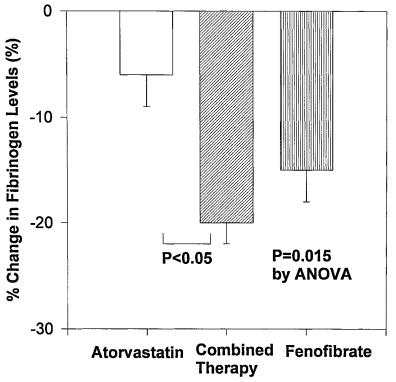

Figure 3. Fenofibrate alone or combined therapy significantly lowered plasma fibrinogen levels relative to baseline measurements. Combined therapy significantly reduced levels more than atorvastatin alone. ANOVA = analysis of variance.

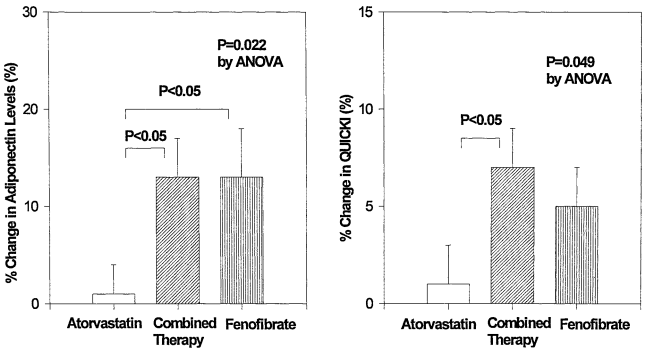

Figure 4. Percent change in adiponectin levels **(left)** and in Quantitative Insulin-Sensitivity Check Index (QUICKI) **(right)** from respective pretreatment values after treatment with atorvastatin alone, combined therapy, and fenofibrate alone. ANOVA = analysis of variance.

greater than those observed with atorvastatin alone ($p = 0.022$ by ANOVA) (Fig. 4, Table 3). The three therapies did not have significantly different baseline insulin and glucose levels. However, the magnitude of reduction of insulin with combined therapy was significantly greater than with atorvastatin alone ($p = 0.012$ by ANOVA) (Table 3). Combined therapy or fenofibrate alone significantly increased QUICKI relative to baseline measurements by 7 ± 2% ($p = 0.003$) and 5 ± 2% ($p = 0.043$), respectively. These increases with combined therapy were significantly greater than those observed with atorvastatin alone ($p = 0.049$ by ANOVA) (Fig. 4, Table 3). There were significant correlations between percent changes in adiponectin and percent changes in QUICKI ($r = 0.283$, $p = 0.034$) or apolipoprotein A-I ($r = 0.351$, $p = 0.008$), and there were significant inverse correlations between percent changes in adiponectin and percent changes in insulin ($r = -0.332$, $p = 0.013$) after combined therapy. However, there were no significant correlations between percent changes in adiponectin levels and percent changes in triglycerides ($r = 0.085$) or HDL cholesterol levels ($r = -0.048$).

Safety and adverse effects. No patients were withdrawn from the study because of serious adverse effects (Table 4). Elevations in liver and muscle enzymes and gastrointestinal upset were mainly transient and resolved spontaneously after patients finished the study.

Table 4. Adverse Effects of Atorvastatin, Combined Therapy, and Fenofibrate in Patients With Combined Hyperlipidemia

	Atorvastatin (%)	Combined Therapy (%)	Fenofibrate (%)
Liver enzymes 41–120 IU	4 (7)	8 (14)	4 (7)
Liver enzymes 121–136 IU	1 (2)	1 (2)	2 (4)
Creatine kinase 201–629 IU	1 (2)	4 (7)	2 (4)
Gastrointestinal upset	2 (4)	5 (9)	4 (7)

Upper limits of normal of liver enzymes (serum aminotransferases: alanine and aspartate) and creatine kinase are 40 IU and 200 IU, respectively.

DISCUSSION

In patients with combined hyperlipidemia, atorvastatin and fenofibrate therapy alone changed the lipoprotein profiles as expected. We reasoned that distinct biological actions of atorvastatin and fenofibrate therapies on lipoproteins, fibrinogen, adiponectin, and insulin sensitivity may improve endothelium-dependent vascular function by different mechanisms. Indeed, although monotherapy with atorvastatin or fenofibrate significantly improved lipid profiles, endothelial function, inflammatory markers, and insulin sensitivity, combined therapy had additional substantial and significant beneficial effects on these parameters over those seen with monotherapy for either drug. The enhanced vascular reactivity we observed with combination therapy may be the result of both changes in lipoprotein profiles as well as other effects, including pleiotropic actions of statins and actions of fenofibrate to increase nitric oxide production (13). Importantly, no patients were withdrawn from our study as the result of serious adverse effects.

Fenofibrate therapy alone resulted in significant elevation of adiponectin levels, decreased insulin levels, and increased insulin sensitivity (assessed by QUICKI). The present study is the first report demonstrating that fenofibrate therapy can increase adiponectin levels. Adiponectin is an adipose-derived factor that augments and mimics metabolic actions of insulin. Moreover, adiponectin can directly stimulate nitric oxide production from endothelium (14). Therefore, increasing adiponectin levels would be predicted to improve both insulin sensitivity and endothelial function by multiple mechanisms. Interestingly, in contrast to effects of combination therapy on FMD, the beneficial effects of fenofibrate therapy on adiponectin levels, insulin levels, and insulin sensitivity did not increase further with combination therapy. Thus, the benefits with respect to insulin resistance are predominantly the result of fibrate therapy rather than statin therapy, which suggests that improving endothelial function per se (as reflected by FMD) may not completely explain effects of fenofibrate or combined therapy to improve insulin sensitivity. However, combined therapy may reduce insulin resistance by multiple mechanisms such as lipoprotein changes and peroxisome proliferator-activated receptor-alpha activators. Fenofibrate or combined therapy for two months increased adiponectin levels without a change in body weight or body mass index, which raises the possibility that drug therapy is directly altering adiponectin levels independent of adiposity. It is possible that monotherapy with doses of statins higher than those used in our present study may have additional benefits similar to those we observed with our combined fibrate/statin therapy. However, caution is indicated because recent clinical studies suggest high doses of statins may increase the onset of new diabetes (15). In summary, our study suggests that combined atorvastatin/fenofibrate therapy is safe and has beneficial additive effects, supporting the updated National Cholesterol Education Program Adult Treatment Panel III guidelines (16).

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