Comparison in Patients With Type 2 Diabetes of Fibric Acid Versus Hepatic Hydroxymethyl Glutaryl-Coenzyme A Reductase Inhibitor Treatment of Combined Dyslipidemia

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Patients with combined dyslipidemia are at greatly increased coronary heart disease (CHD) risk. The threat of rhabdomyolysis with dual pharmacologic treatment (hepatic hydroxymethyl glutaryl coenzyme A [HMG-CoA] reductase inhibitors plus fibric acid derivatives) has tended to limit therapy in patients with combined dyslipidemia to a choice of one or the other drug. Judgment of the potential benefits of either agent has rarely taken into account their effect on the postprandial accumulation of highly atherogenic, triglyceride (TG)-rich, remnant lipoprotein particles (RLPs). Because this information could be of substantial clinical relevance, we addressed this question in patients with type 2 diabetes and combined dyslipidemia by comparing the effects of gemfibrozil versus HMG-CoA reductase inhibitors (statins) on both fasting and postprandial lipid and lipoprotein concentrations. For this purpose, 22 patients with type 2 diabetes and combined dyslipidemia were randomized to treatment with either a statin or gemfibrozil for 3 months. Glycemic control was similar in both groups at baseline and did not change in response to treatment. Baseline lipid and lipoprotein concentrations were also similar in the 2 treatment groups, but the responses to therapy were quite different. Statin-treated patients had a statistically significant decrease in low-density lipoprotein (LDL) cholesterol concentration (156 mg/dL to 96 mg/dL, $P < .001$), whereas there was no change in patients treated with gemfibrozil. In contrast, there was a statistically significant decrease ($P < .05$) in plasma TG concentrations (116 mg/dL) in gemfibrozil-treated individuals, without any change in subjects treated with statins. However, the decrease in total integrated postprandial plasma RLP response measured hourly from 8 AM to 4 PM was not different in patients treated with either gemfibrozil (-43%) or statins (-34%). These results indicate that statin treatment, in addition to its beneficial effect on hypercholesterolemia, was as effective as gemfibrozil in reducing postprandial accumulation of triglyceride-rich, atherogenic RLPs in patients with type 2 diabetes and combined dyslipidemia. As such, the clinical utility of statin monotherapy in the treatment of combined dyslipidemia may have been underestimated.
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CORONARY HEART DISEASE (CHD) is the major cause of morbidity and mortality in patients with type 2 diabetes, and it is apparent that hyperglycemia is not the only CHD risk factor present in these individuals.[1] Hypertriglyceridemia is the characteristic lipoprotein abnormality in patients with type 2 diabetes,[2,3] and this metabolic defect has been identified as an independent predictor of CHD in this population.[4] Although low-density lipoprotein (LDL) cholesterol concentrations are no higher in patients with type 2 diabetes than in the population at large,[3] patients with type 2 diabetes can also have increased LDL cholesterol concentrations, and lowering LDL cholesterol concentrations with hepatic hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) has been shown to reduce CHD in these patients.[5,6] The pharmacologic approach to treatment of combined dyslipidemia in patients with type 2 diabetes has been somewhat confounded by concern that there is an increased likelihood of myopathy in patients treated with both a fibric acid derivative and a statin.[7] Although this problem may be less common than was originally suggested,[8,9] questions remain as to the most appropriate pharmacologic approach to reduce CHD in this high-risk population, type 2 diabetes with combined dyslipidemia.

In general, questions as to whether a fibric acid derivative or a statin should be used to treat combined dyslipidemia in patients with type 2 diabetes have focused on the anticipated changes in fasting triglyceride (TG) and LDL cholesterol concentrations that would occur with either approach. However, it is now apparent that the postprandial accumulation of TG-rich lipoproteins significantly increases CHD risk,[10-14] a possibility that was first advanced 23 years ago.[15] Thus, efforts to treat dyslipidemia in patients with type 2 diabetes should be evaluated in terms of their efficacy in improving both fasting and postprandial lipoprotein metabolism. In this context, there is evidence that the magnitude of postprandial lipemia is significantly correlated with the size of fasting TG-pool size.[16,17] Because fibric acid derivatives lower fasting plasma TG concentrations to a greater degree than do statins,[8,9] it would be anticipated that they also would be more effective in decreasing the postprandial accumulation of TG-rich atherogenic, remnant lipoprotein (RLP) cholesterol. On the other hand, statins upregulate the hepatic LDL receptor,[18,19] which also binds TG-rich chylomicron and very–low-density lipoprotein (VLDL) remnants, and it has been suggested that statins may decrease CHD risk, in part, by lowering plasma remnant concentrations.[19] Thus, it is certainly possible that the decrease in postprandial, TG-rich, RLP particles would be much greater in statin-treated patients than the decrease in fasting TG concentration. As a corollary, simply measuring fasting LDL cholesterol and TG concentrations would underestimate the clinical benefits of statin therapy in patients with type 2 diabetes and combined dyslipidemia.

The study to be presented was initiated to test the hypothesis that the postprandial accumulation of RLPs would, as expected, decrease in gemfibrozil-treated patients with combined dyslip-

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idemia in proportion to the treatment-associated decrease in fasting plasma TG concentration, whereas the decline in postprandial RLPs would exceed the decrease in fasting plasma TG concentrations in similar patients treated with a statin.

MATERIALS AND METHODS

Subjects

The study population consisted of 22 patients with type 2 diabetes who volunteered in response to newspaper advertisements. To qualify, participants had to be in good general health, with a fasting plasma cholesterol concentration greater than 200 mg/dL and a fasting plasma TG concentration between 200 to 400 mg/dL. All subjects had been on a stable program of diet or diet plus an oral antihyperglycemic agent for at least 4 weeks. Patients taking either a thiazolidenedione compound or a lipid-lowering drug were excluded.

Screening

The Stanford Human Subjects Committee approved the study protocol, and all subjects provided written, informed consent. Subjects were screened in the Stanford General Clinical Research Center (GCRC) with history, physical examination, red blood cell blood count, chemical screening battery, and fasting TG and cholesterol measurements. Those meeting the requirements outlined above returned for a repeat fasting lipid panel the following week. The average of the 2 lipid determinations was considered for study eligibility. If highly discrepant, a third fasting lipid measurement was made, and the 2 most similar values used to determine study eligibility.

Protocol

Before drug randomization, subjects underwent an 8-hour meal profile, designed to evaluate postprandial excursions of TG and RLP concentrations. Blood was drawn before the first meal, given at 8:00 AM and hourly thereafter for 8 hours. A second meal was given at noon. Both meals contained as percent of total calories, 15% protein, 43% carbohydrate, and 42% fat, with breakfast comprising 20% and lunch comprising 40% of estimated daily caloric requirement. Subjects were then randomized to gemfibrozil (600 mg, twice a day) or either pravastatin (20 mg/d) or simvastatin (10 mg/d). Six subjects received simvastatin and 6 received pravastatin in an effort to see if the statin-induced changes varied as a function of the drug used. After the initiation of drug treatment, subjects were seen weekly in the GCRC during the first month for evaluation of symptoms, vital signs, and diabetic control. At week 4, liver function tests were performed. If liver function tests were normal, the doses of simvastatin or pravastatin were doubled for the duration of the study, whereas the dose of gemfibrozil remained the same. Liver function tests remained normal in all 22 volunteers throughout the study. Patients were seen every other week for an additional 2 months of treatment before being admitted to the GCRC to repeat the 8-hour meal profile.

Plasma TG, cholesterol, LDL cholesterol, and HDL cholesterol concentrations were determined as described previously.[20,21] RLPs were isolated by an immunoseparation method[22,23] based on the use of monoclonal antibodies to human apolipoproteins (apo) B-100 and A-1 to remove most of the apo B-100 and apo A-1 containing lipoproteins; leaving behind a fraction of TG-rich lipoproteins containing very–low-density and chylomicron remnants enriched in apo E. This unbound fraction is designated RLP and quantified by determining the cholesterol concentration with a highly sensitive enzymatic assay.[22,23]

Subjects were urged not to make changes in their dietary or exercise habits during the study, and the antihyperglycemic treatment was kept constant. At the end of the treatment period, the 8-hour meal profile was repeated in the same manner as at baseline and the 2 data sets compared.

Statistical Analysis

The decision to use 2 different statins was based on the assumption that the effects on all of the measurements being made would be "class" effects and would not differ substantially as a function of a specific drug. This was the case, and there were no differences in the results with each statin. Because there were no differences between the results of the 2 statin-treated groups, they were combined for statistical analyses. All data are expressed as mean ± SEM. Student's paired *t* test was used to assess statistical significance of differences in fasting glucose, lipid, and lipoprotein concentrations. Total integrated postprandial responses of TG and RLP cholesterol were quantified by the trapezoidal method and used to compare the response to the treatment intervention. In addition, 2-way analysis of variance (ANOVA) was used to compare the effect of gemfibrozil versus statins on the daylong changes in TG and RLP cholesterol concentrations.

RESULTS

Baseline characteristics of the 2 treatment groups are shown in Table 1. It can be seen that the 2 groups were quite similar in terms of age, gender distribution, and body weight. Furthermore, baseline plasma glucose, lipid, and lipoprotein concentrations were comparable in the 2 groups. None of the small mean differences in any of these variables reached statistical significance. Furthermore, neither weight nor fasting plasma glucose concentration varied significantly with either treatment.

The changes in fasting lipid and lipoprotein concentrations after treatment are given in Table 2. Fasting plasma TG concentrations decreased by 44% in gemfibrozil-treated patients ($P = .04$), associated with a quantitatively comparable change (-39%, $P = .07$) in fasting RLP cholesterol concentration. However, fasting total cholesterol, LDL cholesterol, and non-HDL cholesterol concentrations did not change significantly in gemfibrozil-treated patients. In contrast, both fasting total (-28%) and LDL cholesterol concentrations (-38%) decreased significantly ($P < .001$) in statin-treated patients, as did the non-HDL cholesterol concentration (-28%, $P < .001$). In contrast to treatment with gemfibrozil, neither fasting TG (-10%) nor RLP cholesterol (-17%) concentrations were significantly lower after statin treatment.

Postprandial TG and RLP cholesterol concentrations from 8 AM to 4 PM before and after the 2 treatments are seen in Figs 1 and 2. The results in Fig 1 show that daylong plasma TG concentrations ($P < .001$) were significantly lower after gemfibrozil treatment, as were the RLP cholesterol concentrations ($P < .001$). Statin treatment (Fig 2) was also associated with

Table 1. Baseline Characteristics

Variable	Gemfibrozil (n = 10)	Statin (n = 12)
Age (yr)	56 ± 2	57 ± 3
Male/female	7/3	9/3
Weight (kg)	91.6 ± 5.6	84.4 ± 4.8
Fasting glucose (mg/dL)	171 ± 16	157 ± 8
Total cholesterol (mg/dL)	225 ± 10	237 ± 8
Triglyceride (mg/dL)	263 ± 37	268 ± 28
LDL cholesterol (mg/dL)	138 ± 6	156 ± 8
HDL cholesterol (mg/dL)	35 ± 4	33 ± 2
RLP cholesterol (mg/dL)	18 ± 3	18 ± 3
Non-HDL cholesterol (mg/dL)	190 ± 10	204 ± 9

NOTE. Values are mean ± SEM.

Table 2. Treatment-Associated Changes in Fasting Lipid and Lipoprotein Concentrations

Variable	Gemfibrozil (N = 10)		Statin (N = 12)	
	Change (%)	*P*	Change (%)	*P*
Cholesterol	−1 mg/dL (<1%)	NS	−66 mg/dL (−28%)	<.001
LDL cholesterol	+5 mg/dL (+4%)	NS	−60 mg/dL (−38%)	<.001
Triglyceride	−116 mg/dL (−44%)	.04	−28 mg/dL (−10%)	NS
HDL cholesterol	+3 mg/dL (+9%)	NS	−2 mg/dL (−6%)	NS
RLP cholesterol	−7 mg/dL (−39%)	.07	−3 mg/dL (−17%)	NS
Non-HDL cholesterol	−22 mg/dL (−12%)	.87	−57 mg/dL (−28%)	<.001

significantly lower daylong TG ($P = .001$) and RLP cholesterol ($P < .001$) concentrations.

Although the data in Figs 1 and 2 indicate that daylong postprandial TG and RLP cholesterol concentrations were lower after either treatment, they do not permit a quantitative comparison. To provide such information, the total integrated TG and RLP cholesterol responses over the 8-hour period were quantified. These results appear in Table 3, and, in conjunction with those in Table 2, highlight some important differences in the postprandial TG and RLP cholesterol responses to the 2 treatments. For example, the changes in the integrated postprandial TG (-37%) and RLP cholesterol (-43%) responses after gemfibrozil treatment (Table 3) are essentially identical to the changes in fasting plasma TG concentration (Table 2, -44%). In contrast, the relationship between these 3 variables is quite different in statin-treated patients. Thus, the results in Table 3 show that the decrease in the postprandial integrated RLP cholesterol response was essentially twice the change in postprandial TG response (-34% *v* –18%, $P < .002$), and 3 times the decrease in fasting plasma TG concentration (-34% *v* –10%, $P = .001$) as shown in Table 2. Finally, despite the differences in the change in fasting plasma TG concentration (Table 2) and the total integrated postprandial TG response (Table 3) between the 2 treatments, it can be seen that the decline in the total integrated postprandial plasma RLP cholesterol response was similar (-43% ± 7% *v* -34% ± 8%), irrespective of treatment with gemfibrozil or with a statin.

DISCUSSION

The changes in fasting total cholesterol (and LDL cholesterol) and TG concentrations after either gemfibrozil or statin treatment in type 2 diabetes patients with combined dyslipidemia were similar to those of many previously reported studies.[8,9] Specifically, both total (-28%) and LDL (-38%) cholesterol concentrations declined significantly ($P < .001$) in statin-treated patients, associated with a modest decrease in triglyceride concentrations (-10%). In contrast, plasma TG concentrations decreased by 44% in gemfibrozil-treated patients, with essentially no change in total or LDL cholesterol concentration. As such, these results reinforce the dilemma in selecting the appropriate pharmacologic approach to patients with combined dyslipidemia.

Less predictable were the treatment-related changes in postprandial TG and RLP cholesterol concentrations. Although postprandial plasma TG concentrations decreased significantly in both treatment groups, the 37% decline in the total integrated TG response in gemfibrozil-treated patients was greater ($P = .06$) than that in the statin-treated group (-18%). The relative changes in postprandial RLP cholesterol concentrations were even more divergent as a function of treatment group. Specifically, the decrease in the total integrated postprandial RLP cholesterol response of the gemfibrozil-treated patients was no different than the decrease in either fasting TG (-43% *v* –44%, P = not significant [NS]) or postprandial TG (-43% *v* –37%, P = NS) concentrations. In contrast, the decrease in postpran-

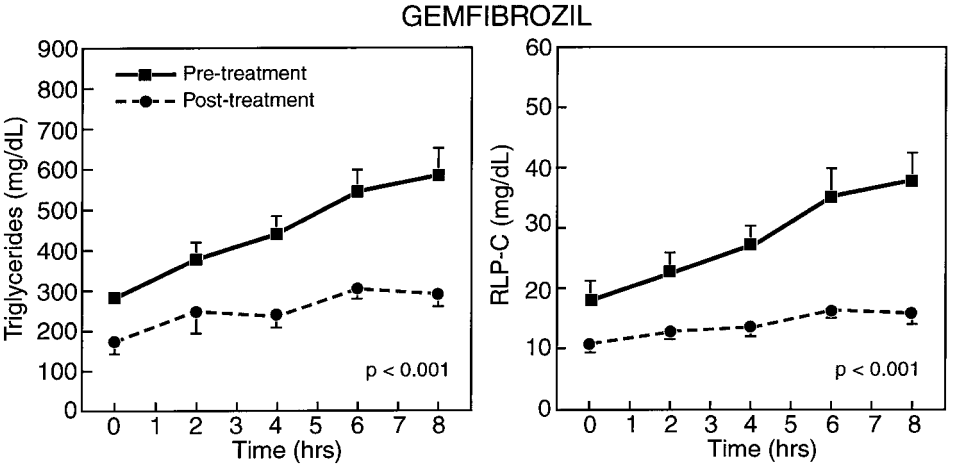

Fig 1. Plasma TG and RLP cholesterol concentrations measured at hourly intervals from 8 AM to 4 PM before and after gemfibrozil treatment. Subjects ate breakfast at 8 AM (20% of daily caloric requirement) and lunch at noon (40% of daily caloric requirement).

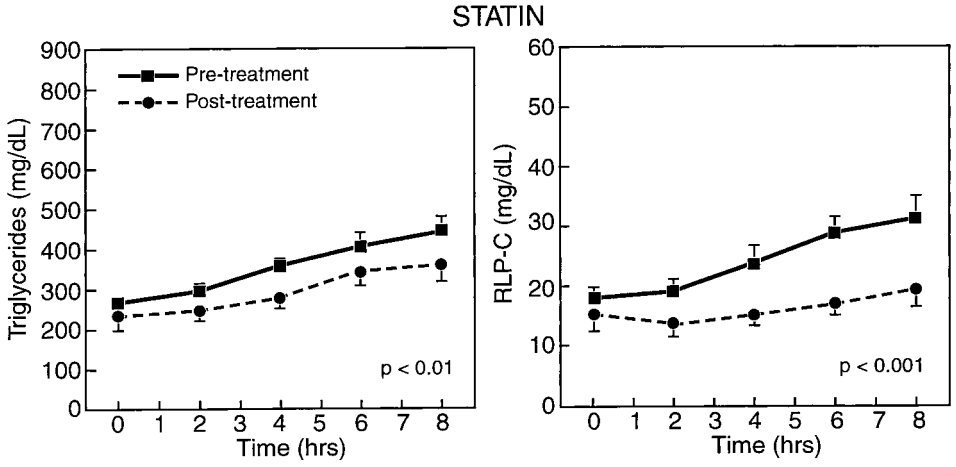

Fig 2. Plasma TG and RLP cholesterol concentration measured at hourly intervals from 8 AM to 4 PM, before and after statin treatment. Subjects ate breakfast at 8 AM (20% of daily caloric requirement) and lunch at noon (40% of daily caloric requirement).

dial RLP-cholesterol response (−34%) in statin-treated patients was more than 3-fold greater than the decline in fasting TG concentration (−10%, $P = .001$) and double that of postprandial TG concentrations (−18%, $P = .002$). These data indicate that the decrease in postprandial RLP cholesterol response was divergent from the associated decrease in fasting and postprandial TG concentrations in statin-treated, but not in gemfibrozil-treated patients.

The observation that the total integrated postprandial TG and RLP cholesterol responses decreased to a similar degree in gemfibrozil-treated patients, and proportionate to the decrease in fasting plasma TG concentration, is consistent with the general belief that the postprandial accumulation of TG-rich lipoprotein is directly related to the degree of fasting hypertriglyceridemia.[16,17] Mechanistically, the decline in both fasting and postprandial TG concentrations in response to fibrate administration is generally assumed to be due to an increase in the catabolic rate of TG-rich lipoproteins, with the decrease in postprandial concentrations being secondary to a decrease in the competition for removal of TG-rich lipoproteins of endogenous origin. Although this is likely to be the case in the gemfibrozil-treated patients, it is apparent that this mechanism cannot explain the exaggerated decrease in postprandial RLP concentrations in statin-treated patients. Based on the results of previous studies,[18,19] the simplest interpretation of our findings could be that the upregulation of the LDL receptor that occurs in statin-treated patients, coupled with greater affinity of the postprandial apo E-enriched remnant population for the LDL receptor, is responsible for the decrease in plasma RLP cholesterol concentrations in excess of the associated decrease in plasma TG concentration in statin-treated patients.

Although questions may be raised as to the explanation of our results, the clinical message seems quite clear. The degree of decline in postprandial RLP cholesterol response in statin-treated patients would be expected to mirror the decrease in either fasting or postprandial TG response if competition for TG-rich lipoprotein removal were the sole mechanism regulating postprandial RLP-cholesterol concentrations. In fact, the decrease in plasma TG concentration in statin-treated patients in our study was only one fourth of that seen in patients treated with gemfibrozil, whereas the decline in postprandial RLP cholesterol concentration was comparable to that seen in the gemfibrozil-treated group. Whether or not elevated RLP concentrations account for the atherogenicity associated with increases in TG-rich lipoproteins remains to be seen. However, if postprandial RLPs are as atherogenic as they appears to be,[10-15] our results suggest that the benefits of statin treatment in decreasing CHD risk in patients with combined dyslipidemia is substantially underestimated if only fasting LDL cholesterol and TG concentrations are determined.

In conclusion, our results demonstrate that statin treatment of combined dyslipidemia in patients with type 2 diabetes leads to the anticipated decrease in total, LDL, and non-LDL cholesterol concentrations, but a significantly greater decline in postprandial accumulation of RLPs than would have been anticipated by their effect on fasting TG concentration. Indeed, the postprandial decline in RLP response after treatment with either statin approximates the decrease seen after treatment with

Table 3. Treatment-Associated Changes in Total Integrated Postprandial Triglyceride And RLP Cholesterol Responses

Gemfibrozil	Pre	Post	% Change	*P*
Triglyceride (mg/dL × 8 h)	3,384 ± 369	2,040 ± 221	−37 ± 7*	.01
RLP-C (mg/dL × 8 h)	212 ± 27	113 ± 9	−43 ± 7†	.009
Statin				
Triglyceride (mg/dL × 8 h)	2,850 ± 216	2,311 ± 227	−18 ± 6	.10
RLP-C (mg/dL × 8 h)	201 ± 20	127 ± 15	−34 ± 8	.01

NOTE. Values are mean ± SEM.

*Refers to percent change *v* statin-treated group, $P = .06$.

†Refers to percent change *v* statin-treated group, $P = .38$.

gemfibrozil. Given the atherogenicity of RLPs and the greatly increased risk of CHD in patients with type 2 diabetes and combined dyslipidemia, our results suggest that pharmacologic therapy in patients with type 2 diabetes and combined dyslipidemia might appropriately be initiated with a statin. Finally, because that results were similar with both lovostatin and pravastatin, the beneficial effect on RLP metabolism seemed to be independent of the specific drug used.

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