Decreasing Triglyceride by Gemfibrozil Therapy Does Not Affect the Glucoregulatory or Antilipolytic Effect of Insulin in Nondiabetic Subjects With Mild Hypertriglyceridemia

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We studied the effects of gemfibrozil on glucose and fatty acid metabolism in subjects with mild endogenous hypertriglyceridemia. Twenty subjects (serum triglycerides, 3.2 ± 1.4 mmol/L; age, 52 ± 7 years; body mass index, 27.8 ± 1.8 kg/m^2) were randomly allocated to receive either placebo or gemfibrozil 1,200 mg daily for 12 weeks in a double-blind study. Gemfibrozil decreased serum total and very-low-density lipoprotein (VLDL) triglycerides by 53% and 57%, respectively, and serum apolipoprotein (apo) B concentration by 21%. Gemfibrozil had no effect on the diurnal concentration of free fatty acids (FFA). Neither did gemfibrozil change diurnal blood glucose or serum insulin concentrations. The endogenous glucose production rate remained unchanged in both groups during the treatment period, and was similarly suppressed by hyperinsulinemia. The rate of insulin-induced whole-body glucose disposal increased similarly both before (basal 10.8 ± 1.8, low-dose insulin 10.5 ± 2.1, and high-dose insulin 20.9 ± 11.9 μmol · kg^{-1} · min^{-1}) and after (11.1 ± 1.7, 10.7 ± 1.2, and 18.6 ± 7.9, respectively) gemfibrozil treatment. Rates of oxidative and nonoxidative glucose metabolism remained unchanged during gemfibrozil treatment. Basal pretreatment and posttreatment FFA turnover rates were similar in both study groups, as were the rates of substrate oxidation. In summary, gemfibrozil proved to be an effective serum triglyceride-lowering agent in patients with mild hypertriglyceridemia, but had no effect on the insulin sensitivity of glucose metabolism or of antilipolysis. These data support the idea that triglycerides per se do not cause insulin resistance, and that the triglyceride-lowering effect of gemfibrozil is not mediated via antilipolytic action.

HYPERTRIGLYCERIDEMIA is closely associated with hyperinsulinemia and insulin resistance.[1-5] A significant inverse correlation between insulin-stimulated glucose disposal and serum triglycerides has also been observed in healthy normolipidemic subjects.[6] Recent epidemiologic data suggest that impaired insulin sensitivity precedes the development of hypertriglyceridemia.[7] It has been proposed that the elevation of serum triglycerides is a consequence rather than a cause of insulin resistance and hyperinsulinemia.[1,8,9] Theoretically, increased plasma levels of free fatty acids (FFA) and impaired suppression of FFA by insulin, which have been observed in nondiabetic patients with endogenous hypertriglyceridemia, may decrease oxidative glucose metabolism due to substrate competition.[8,10] This concept can be tested by decreasing serum triglycerides using hypolipidemic agents. Acute suppression of basal FFA and lipid oxidation with an antilipolytic agent has indeed been shown to improve both oxidative and nonoxidative glucose metabolism in hypertriglyceridemic individuals.[11] In contrast, a marked decrease of serum triglycerides with bezafibrate did not influence the insulin sensitivity of hypertriglyceridemic subjects regardless of whether they had diabetes.[12,13]

Gemfibrozil, a fibric acid derivative, is another potent triglyceride-lowering agent commonly used to treat hyperlipidemic patients.[14] Gemfibrozil decreases hepatic synthesis and secretion of triglyceride-enriched lipoproteins and enhances their degradation by increasing the activity of lipoprotein lipase.[15,16] Gemfibrozil is also proposed to have an antilipolytic effect that could contribute to its hypolipidemic effect.[17] We have recently shown that gemfibrozil did not change glucose or FFA metabolism in non–insulin-dependent diabetes mellitus (NIDDM) patients with hypertriglyceridemia.[18] However, one may postulate that NIDDM represents an advanced state of metabolic abnormalities where defects cannot be corrected. To exclude this possibility, we studied whether insulin sensitivity could be improved by decreasing serum triglycerides with gemfibrozil in nondiabetic subjects with mild hypertriglyceridemia and insulin resistance as evidenced by hyperinsulinemia.

SUBJECTS AND METHODS

Patients

Twenty subjects with a mild to moderate elevation of serum triglycerides and hyperinsulinemia participated in the study. Their clinical data are listed in Table 1. Patients with serum triglyceride levels between 1.5 and 4.5 mmol/L, measured on two occasions during a screening phase, were eligible for the study. Furthermore, all subjects had to have a normal fasting blood glucose concentration and a fasting serum insulin concentration in excess of 10 mU/L, indicating insulin resistance.[19] Secondary causes of hypertriglyceridemia were excluded by history, physical examination, and normal liver, kidney, and thyroid function tests. None of the subjects used hypolipidemic drugs before the study. Drug therapies for coronary heart disease (n = 8), hypertension (n = 2), or bronchial asthma (n = 1) were continued unchanged throughout the study period. Four patients in the gemfibrozil group and three in the placebo group used β-blocking agents during the study. Written consent including information on the nature and risks of the study was obtained from each participant before the study. The study protocol was approved by the Ethical Committee of Helsinki University Hospital.

Study Design

During a 6-week run-in period, two placebo capsules were given to each patient twice a day (single-blind). Serum lipid levels were

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Table 1. Clinical Characteristics of the Study Subjects

	Gemfibrozil Group		Placebo Group	
	Week 0	Week 12	Week 0	Week 12
Sex (male/female)	9/1		10/0	
Age (years)	52 ± 7		53 ± 7	
Body mass index (kg/m^2)	28.6 ± 1.5*		26.9 ± 1.6	
Body weight (kg)	86.5 ± 13.1	86.5 ± 13.8	83.9 ± 8.8	85.3 ± 9.1†
Hemoglobin$_{1c}$ (%)	5.4 ± 0.4	5.3 ± 0.3	5.4 ± 0.4	5.3 ± 0.4
Blood glucose (mmol/L)	5.1 ± 0.4	5.0 ± 0.5	4.9 ± 0.7	4.9 ± 0.6
Serum insulin (pmol/L)	81 ± 32	96 ± 47	96 ± 47	123 ± 14
Blood pressure (mm Hg)				
Systolic	134 ± 14	130 ± 18	131 ± 14	128 ± 14
Diastolic	83 ± 9	81 ± 11	84 ± 4	83 ± 6

*$P < .05$ for comparison between groups.

†$P < .05$ for comparison between pretreatment and posttreatment values.

measured at 3 and 6 weeks during the run-in period. Patients were advised to continue normal dietary habits during this period. There were no significant changes in serum triglycerides during the run-in period (data not shown). Patients were admitted to the hospital for metabolic tests (week 0), randomly allocated (double-blind) to receive either placebo (two tablets twice per day) or gemfibrozil (600 mg twice per day), and discharged from the hospital for an outpatient follow-up period of 12 weeks. The patients visited the outpatient clinic at 4 and 8 weeks and were readmitted to the ward for final metabolic tests (week 12).

Laboratory Tests

At each visit, blood samples were taken for measurement of serum lipid levels. In addition, serum lipids, lipoproteins, and apolipoproteins were analyzed at weeks 0 and 12.

Metabolic Tests at 0 and 12 Weeks

On the day of admission, blood glucose, serum insulin, triglycerides, and plasma FFA concentrations were determined in blood samples taken at 7:30 and 11:30 AM, 2:00, 4:00, and 8:00 PM, 12 midnight, and 4:00 and 8:00 AM. During diurnal curves, patients were on an isocaloric hospital diet (35% of energy as fat, 50% as carbohydrate, and 15% as protein). On day 2, after an overnight fast, whole-body glucose uptake, hepatic insulin sensitivity, and FFA kinetics and oxidation were determined between 8:00 AM and 1:00 PM as shown in Fig 1. During the clamp study, patients were kept in a fasting state and were served lunch at 1:00 PM. Each study consisted of a basal period (from −60 to 0 minutes) and two hyperinsulinemic periods (0 to 120 minutes, low-dose insulin infusion; and 120 to 240 minutes, high-dose insulin infusion). Rates

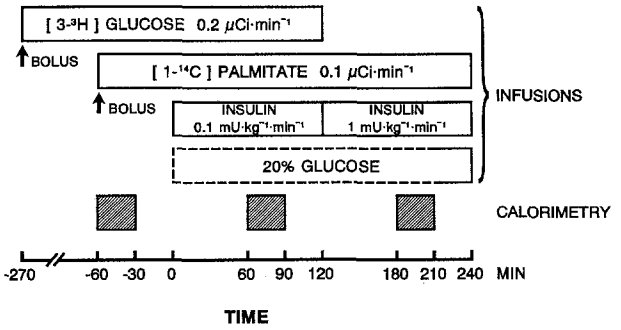

Fig 1. Study design for determination of insulin sensitivity of glucose and FFA kinetics. (▨) Period of indirect calorimetry measurements.

of glucose appearance (R_a) and disappearance (R_d) were calculated using an infusion of (3-^{3} H)glucose, and plasma FFA kinetics were determined using (1-^{14}C)palmitate-labeled albumin. During hyperinsulinemia, plasma glucose was maintained constant using the insulin clamp technique as previously described.[20,21] These measurements were combined with indirect calorimetry to determine substrate oxidation rates.

Whole-Body Glucose Disposal

For measurement of glucose R_a and R_d in the basal state and during low-dose insulin infusion, a primed continuous (0.2 μCi/min) infusion of (3-^{3}H)glucose (Amersham International, Amersham, Bucks, UK) was started at 4:30 AM and continued until 11:00 AM (from −270 to 120 minutes). Glucose specific activity[22] was measured at −60, −30, 0, 90, and 120 minutes. At 0 minutes, a primed continuous infusion of insulin (0.1 mU · kg^{-1} · min^{-1}, ActrapidHM; Novo-Nordisk Pharma, Copenhagen, Denmark) was started to increase and maintain serum insulin at approximately 90 pmol/L.[20] Plasma glucose level was measured every 5 to 10 minutes in blood samples taken from arterialized venous blood, and 20% glucose was infused to maintain blood glucose at the fasting level. At 120 minutes, serum insulin concentration was increased and maintained at approximately 500 pmol/L (insulin infusion rate, 1.0 mU · kg^{-1} · min^{-1}). Glucose was infused to maintain normoglycemia. Serum free-insulin concentrations were measured at −60, 0, 30, 90, 120, 150, 210, and 240 minutes. It is well established that glucose uptake increases continuously as a factor of time, insulin sensitivity, and insulin concentration.[23] Thus, although achievement of a steady state for insulin-stimulated glucose uptake may not be possible, reliable estimates of insulin action can be obtained if one compares studies of equal duration both between and within individuals.

Glucose R_a and R_d were calculated according to the non–steady-state equation of Steele,[22] assuming a glucose distribution volume of 200 mL/kg and a pool fraction of 0.65. To avoid underestimation of glucose R_a and R_d,[24] the basal period lasted 270 minutes instead of the usual 120 to 150 minutes.[25]

Respiratory Exchange

Indirect calorimetry measurements were performed with a computerized flow-through canopy gas analyser system (Deltatrac Metabolic Monitor, Datex, Helsinki, Finland) as shown in Fig 1 and previously described.[26] Nonoxidative glucose R_d was defined as the difference between total R_d and oxidative R_d. Rates of protein, lipid, and carbohydrate oxidation were calculated as described previously.[26]

FFA Turnover

(1-^{14}C)palmitate (New England Nuclear, Boston, MA) complexed to albumin (SPR, Helsinki, Finland) was used for measurement of plasma FFA turnover. A priming dose of 6 μCi (1-^{14}C)palmitate-albumin was administered at 0 minutes, and 0.1 μCi/min of (1-^{14}C)palmitate-albumin solution was infused from −60 to 240 minutes. With these isotope doses, constant FFA specific activity is obtained within 30 minutes.[27,28] Serum triglycerides, plasma glycerol,[29] and FFA concentrations[30] and FFA specific activity[30] were measured in blood samples taken at −60, −30, 30, 90, 120, 210, and 240 minutes.

Analytical Procedures

Blood glucose level was measured by the glucose dehydrogenase method (Gluc-DH, Merck Oy, Darmstadt, Germany). During the clamp on day 2, glucose level was measured in plasma by the glucose oxidase method[31] using the Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA). Serum insulin concentration was determined by radioimmunoassay (RIA)[32] using a Phadeseph insulin RIA kit (Pharmacia, Uppsala, Sweden), and free insulin concentration was measured using the same method after precipitation with polyethylene glycol. Serum C-peptide level was measured by RIA[33] using the RIA-mat C-Peptid II kit (BYK-Sangtec Diagnostica, Frankfurt, Germany). Hemoglobin A_{1c} (reference range, 4.0% to 6.0%) was determined using ion-exchange high-performance liquid chromatography[34] (Bio-Rad, Richmond, CA). Serum and lipoprotein cholesterol and triglyceride concentrations were measured enzymatically using commercial kits (no. 0722138 for cholesterol and no. 0715166 for triglycerides, Hoffman-La Roche, Basel, Switzerland) with an automated Cobas Mira analyzer (Hoffman-La Roche). Very–low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) were separated by ultracentrifugation (Beckman L7-70) as previously described in detailed.[35] Apolipoprotein (apo) B concentrations were determined by radial immunoturbidometry using commercially available kits (Orion Diagnostica, Espoo, Finland). ApoA-I and apoA-II were determined by immunoturbidometry using commercially available antisera (no. 726 478 and 726 486, respectively; Boehringer).

Statistical Analysis

Data were analyzed using BMDP software (BMDP Statistical Software, Los Angeles, CA). Comparison between measurements at 0 and 12 weeks was made using two-way ANOVA for repeated measures, followed by a paired *t* test (BMDP program 7D). Comparison between study groups was made using BMDP program 3D. All results are given as the mean ± SD.

RESULTS

Serum Lipid Concentrations

At 0 weeks, there were no differences in serum total or VLDL triglycerides between gemfibrozil and placebo groups (Table 2). Gemfibrozil decreased the mean concentration of total and VLDL triglycerides by 53% and 57%, respectively (Table 2). Gemfibrozil significantly decreased the mean concentration of serum total and VLDL cholesterol. The slight increases of serum LDL and HDL cholesterol were not significant. Serum triglycerides were significantly lower at each time point of the 24-hour period after gemfibrozil than after placebo (Fig 2). The mean 24-hour concentration of serum triglycerides decreased from 3.34 ± 1.12 to 2.26 ± 0.53 mmol/L ($P < .01$). The mean 24-hour concentration of serum triglycerides in the placebo group increased from 2.71 ± 1.16 to 3.40 ± 1.49 mmol/L (NS; Fig 2). We also calculated the area under the curve for triglycerides before and after the treatment period in both the gemfibrozil (80.6 ± 27.2 *v* 46.2 ± 10.5 mmol · h, $P < .01$) and placebo (64.8 ± 28.2 *v* 72.4 ± 33.6, NS) groups. Neither gemfibrozil nor placebo had any effect on the mean 24-hour FFA concentration (Fig 2).

Serum Apolipoproteins

Gemfibrozil increased serum apoA-II concentration from 35 ± 2 to 39 ± 2 mg/dL ($P < .01$) and decreased serum apo B concentration from 141 ± 28 to 111 ± 20 mg/dL ($P < .01$), but had no effect on serum apoA-I concentration (125 ± 6 *v* 124 ± 5 mg/dL). No changes occurred in serum apo A-I (123 ± 5 *v* 132 ± 6 mg/dL), serum apoA-II (37 ± 2 *v* 40 ± 3 mg/dL), or serum apo B (123 ± 28 *v* 119 ± 30 mg/dL) concentrations during placebo treatment.

Blood Glucose and Serum Insulin Concentrations

There were no differences in fasting blood glucose, serum insulin, or hemoglobin A_{1c} concentrations between the groups at randomization (Table 1). As shown in Fig 3, neither gemfibrozil nor placebo treatment influenced the mean 24-hour blood glucose concentration. Pretreatment and posttreatment values were 5.0 ± 0.4 and 5.1 ± 0.2 mmol/L (NS) in the gemfibrozil group and 5.0 ± 0.2 and 5.0 ± 0.2 mmol/L (NS) in the placebo group, respectively. The mean 24-hour serum insulin concentration averaged 246 ± 100 versus 268 ± 79 pmol/L (NS) and 185 ± 100

Table 2. Fasting Concentrations of Serum Lipids and Lipoprotein Lipids (mmol/L)

	Gemfibrozil Group		Placebo Group	
	Week 0	Week 12	Week 0	Week 12
Triglycerides	3.34 ± 1.13	1.58 ± 0.20‡	3.08 ± 1.65	4.22 ± 2.10
VLDL triglycerides	2.39 ± 0.96	1.03 ± 0.35‡	2.00 ± 0.97	2.70 ± 1.61
Cholesterol	6.58 ± 1.45	5.74 ± 0.82*	5.87 ± 1.35	6.35 ± 1.35
VLDL	1.55 ± 0.98	0.53 ± 0.22†	0.87 ± 0.34	1.32 ± 1.05
LDL	3.47 ± 0.97	3.73 ± 0.67	3.65 ± 0.89	3.66 ± 0.67
HDL	0.99 ± 0.19	1.10 ± 0.20	1.00 ± 0.17	0.99 ± 0.20

NOTE. Results are the mean ± SD.

*$P < .05$, †$P < .01$, ‡$P < .001$: difference between pretreatment and posttreatment values.

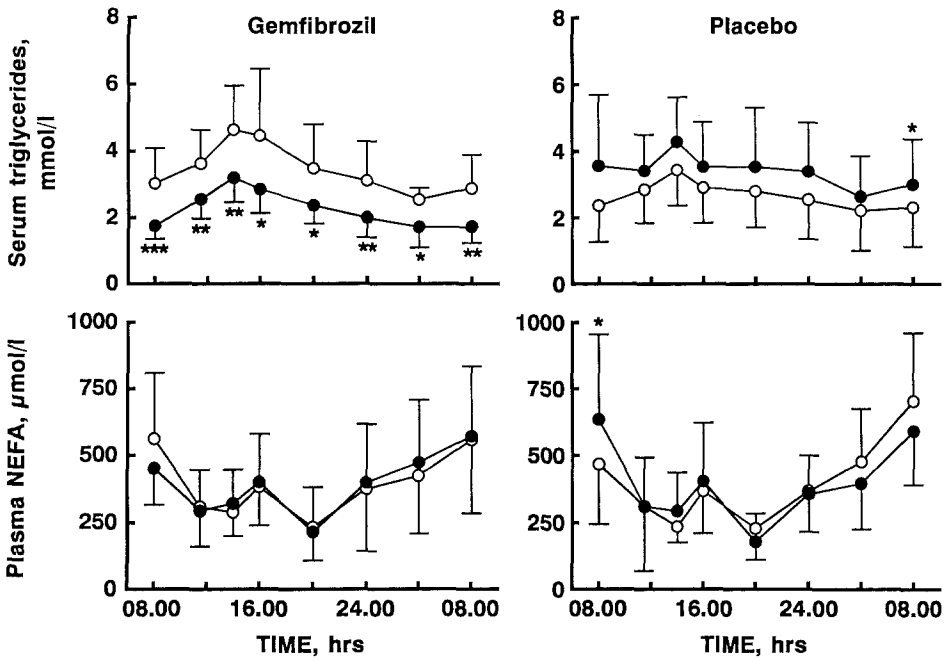

Fig 2. Diurnal profiles of serum triglyceride and plasma FFA concentrations (NEFA) before and after (●) gemfibrozil and placebo. *$P < .05$, **$P < .01$, ***$P < .001$: before *v* after gemfibrozil or placebo therapy.

versus 171 ± 85 pmol/L (NS) before versus after gemfibrozil and placebo treatment, respectively (Fig 3).

Plasma Glucose and Serum Free-Insulin Concentrations During the Metabolic Tests

Plasma glucose concentrations during the insulin clamp were similar before and after gemfibrozil and placebo treatments (Fig 4). Serum free-insulin concentrations during insulin infusions were also similar on both study occasions in both study groups (Fig 4).

Glucose Metabolism

Before treatment, the rate of hepatic glucose production (glucose R_a) in the basal state was similar in gemfibrozil and placebo groups (10.4 ± 1.6 *v* 10.7 ± 1.1 μmol · kg^{-1} · min^{-1}, NS) and remained unchanged in both groups during the therapy (11.2 ± 1.6 *v* 11.3 ± 1.7, respectively). During low-dose insulin infusion, glucose R_a was suppressed by 18% ($P < .05$) before and by 24% ($P < .01$) after gemfibrozil therapy as compared with the basal state. Similar suppression of glucose R_a was also observed before and after

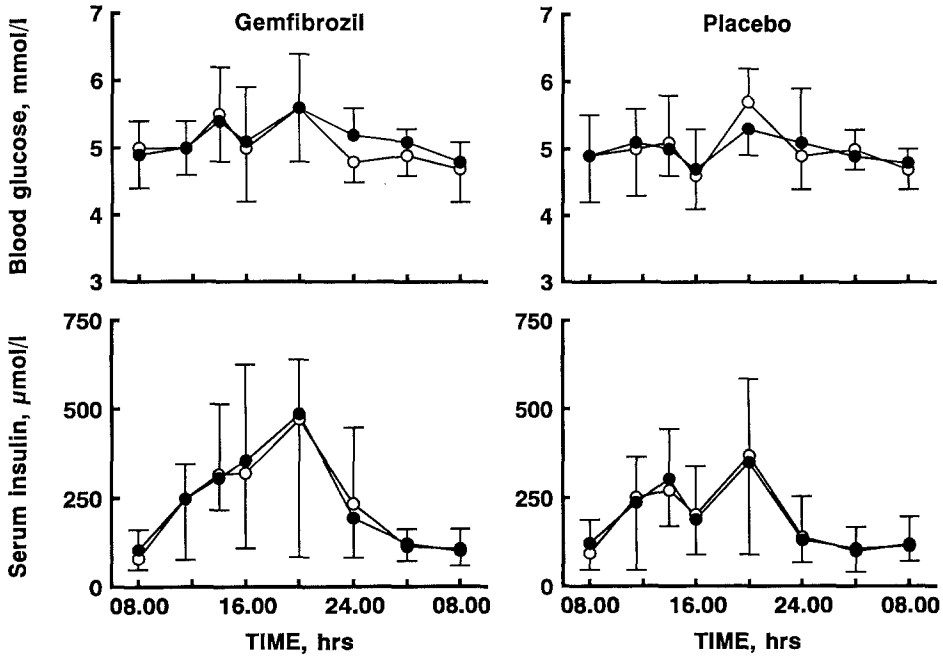

Fig 3. Diurnal blood glucose and serum insulin concentrations before (○) and after (●) gemfibrozil and placebo.

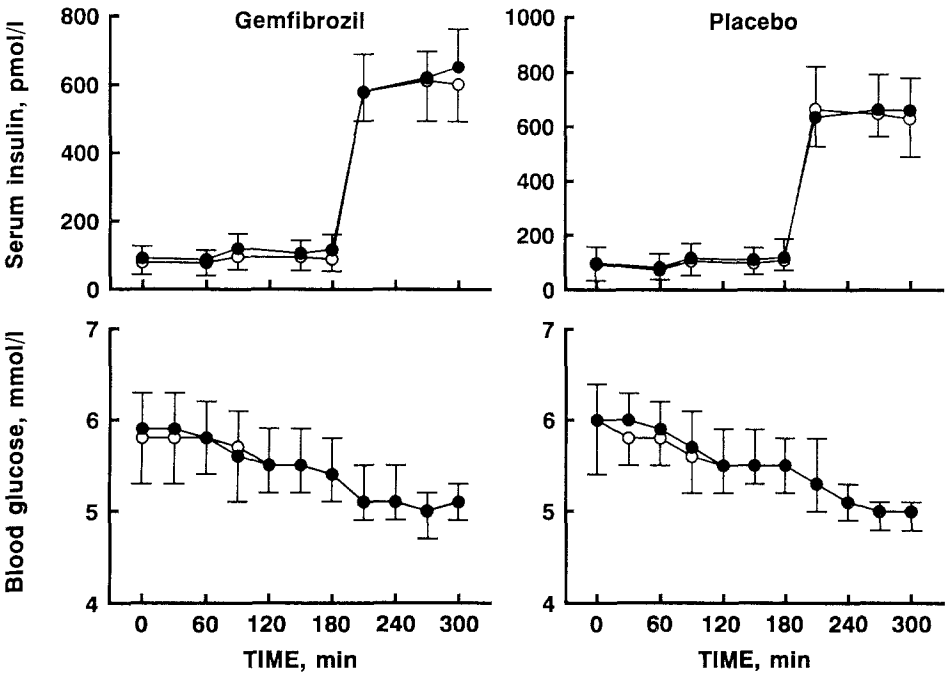

Fig 4. Plasma glucose and serum insulin concentrations during the 6-hour periods of the metabolic test in gemfibrozil- and placebo-treated patients before (○) and after (●) the treatment period.

placebo treatment (18% *v* 18%, $P < .05$) during low-dose insulin infusion. As shown in Table 3, there was no difference in pretreatment and posttreatment rates of total glucose disposal in the basal state or during low- or high-dose insulin infusions between the study groups. Moreover, oxidative and nonoxidative glucose metabolism in the basal state or during the low- or high-dose insulin infusion did not change during gemfibrozil or placebo therapy (Table 3).

FFA Metabolism

Gemfibrozil had no effect on plasma FFA or the FFA turnover rate in the basal state or during the low- or high-dose insulin infusion (Fig 5). Low- and high-dose insulin infusions caused stepwise suppression of the serum FFA concentration and transport rate. No differences were observed between plasma FFA concentrations or FFA turnover rates between gemfibrozil and placebo groups in the basal state or during insulin infusions (data not shown). Total lipid oxidation in the basal state was similar before and after gemfibrozil treatment (3.1 ± 0.8 *v* 3.2 ± 1.0 $\mu mol \cdot kg^{-1} \cdot min^{-1}$). During high-dose insulin infusion, total lipid oxidation was suppressed by 9% ($P < .01$) both before and after gemfibrozil therapy. Similar suppression of lipid oxidation was also observed before and after placebo treatment (data not shown).

DISCUSSION

Gemfibrozil decreased serum triglycerides effectively in patients with moderate hypertriglyceridemia. The magnitude of this reduction was comparable to that observed in previous studies, where nondiabetic hypertriglyceridemic subjects were treated with gemfibrozil.[14,36-37] In the present

Table 3. Glucose Metabolism in the Basal State and During Low- and High-Dose Insulin Stimulation

	Gemfibrozil Group		Placebo Group	
	Week 0	Week 12	Week 0	Week 12
Glucose R_d ($\mu mol \cdot kg^{-1} \cdot min^{-1}$)				
Basal	10.8 ± 1.8	11.1 ± 1.7	10.8 ± 1.2	11.5 ± 1.8
Low-dose insulin	10.5 ± 2.1	10.7 ± 1.2	10.1 ± 1.2	11.1 ± 1.9
High-dose insulin	20.9 ± 11.9	18.6 ± 7.9	17.2 ± 7.7	16.1 ± 5.2
Oxidative glucose R_d ($\mu mol \cdot kg^{-1} \cdot min^{-1}$)				
Basal	5.7 ± 1.8	6.1 ± 2.6	5.4 ± 2.2	5.2 ± 1.7
Low-dose insulin	5.1 ± 2.7	5.3 ± 2.6	4.0 ± 1.8	5.1 ± 2.4
High-dose insulin	7.8 ± 3.4	7.8 ± 4.0	6.6 ± 2.2	6.9 ± 1.6
Nonoxidative glucose R_d ($\mu mol \cdot kg^{-1} \cdot min^{-1}$)				
Basal	5.2 ± 2.9	5.1 ± 2.1	5.5 ± 2.4	6.6 ± 2.4
Low-dose insulin	5.4 ± 2.2	5.3 ± 2.2	6.1 ± 2.0	5.9 ± 2.9
High-dose insulin	13.2 ± 9.4	10.8 ± 4.2	10.6 ± 6.3	8.9 ± 5.1

NOTE. Results are the mean ± SD.

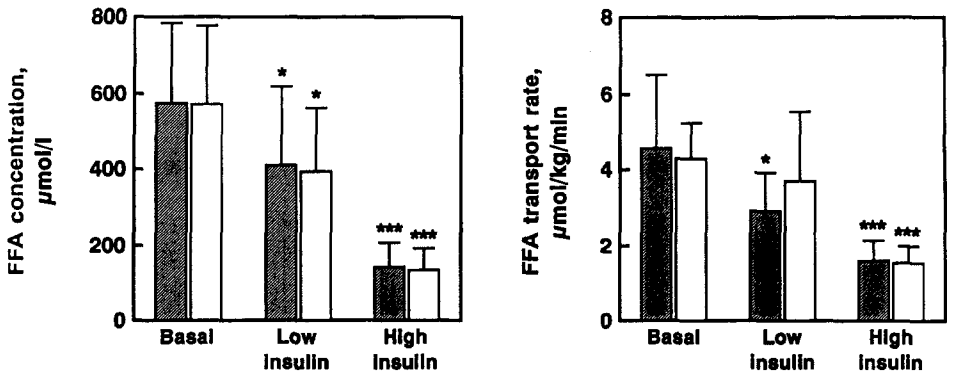

Fig 5. FFA concentration and FFA transport rate in the basal state and during low- and high-dose insulin infusions before (▨) and after (□) gemfibrozil treatment. *$P < .05$, ***$P < .001$: *v* basal state.

study, the effect of gemfibrozil on serum HDL cholesterol was modest (+10%, NS), but was comparable to that observed, eg, in the Helsinki Heart Study.[14] We also found a slight but nonsignificant increase of serum LDL cholesterol during gemfibrozil therapy. We recently reported that in NIDDM patients, gemfibrozil produces a shift in LDL density distribution toward less-dense LDL particles.[38] Similar fibrate-induced density changes of LDL particles have previously been found in both hypertriglyceridemic[39] and hypercholesterolemic patients.[40] These data suggest that the fibrate-induced decrease in VLDL concentration may be associated with restoration of a less-atherogenic LDL subclass pattern.

The major aim of this study was to evaluate whether insulin sensitivity could be improved by decreasing serum triglycerides with gemfibrozil. It is well established that insulin resistance is closely associated with hypertriglyceridemia, but the underlying mechanisms are complex.[1-5] The study subjects were selected based on fasting hyperinsulinemia, which is a reliable marker of insulin resistance in nondiabetic subjects.[19] The mean fasting serum insulin concentration in the study subjects was higher than in healthy controls and similar to that reported previously in nondiabetic hypertriglyceridemic subjects.[8,11] Also, at baseline the study subjects showed a decrease in insulin-stimulated glucose disposal as compared with age-matched normolipidemic subjects previously studied in our laboratory.[8,11] Despite a 50% decrease in triglycerides, we did not observe any improvement in total, oxidative, or nonoxidative glucose metabolism basally or during insulin stimulation in either the placebo or gemfibrozil group. However, we cannot totally exclude the possibility that the window of serum insulin concentrations left between low-dose and high-dose insulin infusions was too wide to demonstrate any gemfibrozil-induced changes of glucose metabolism and insulin sensitivity. These results agree with our previous observation that gemfibrozil also does not alter these parameters in NIDDM patients with mild hypertriglyceridemia.[18] Similar data have also been reported in hypertriglyceridemic nondiabetic subjects and NIDDM patients with hypertriglyceridemia treated with bezafibrate.[12,13] Thus, in either nondiabetic subjects or patients with NIDDM, decreasing serum triglycerides by fibrates does not improve insulin sensitivity. On the other hand, Steiner has reported that decreasing serum triglycerides with gemfibrozil decreases the insulin response to an oral glucose load, but this effect appeared to be mainly explained by changes observed in three subjects with severe hypertriglyceridemia.[41] Therefore, we cannot exclude the possibility that correction of severe hypertriglyceridemia may favorably influence glucose metabolism.

Increased serum concentrations of FFA are frequently observed in hypertriglyceridemic subjects.[11,42,43] The elevation of FFA has been proposed to be the consequence of resistance to the antilipolytic action of insulin.[8] The resulting increased flux of FFA to the liver stimulates VLDL synthesis and secretion in hypertriglyceridemic subjects.[44] According to the hypothesis of Randle et al,[10] increased FFA turnover impairs insulin-stimulated glucose utilization. Indeed, an acute elevation of serum FFA concentration induced by a lipid infusion increases lipid oxidation and decreases glucose disposal.[45-47] Recent data reported by Saloranta et al[11] suggest that the acute inhibition of lipolysis by acipimox decreased serum FFA concentrations and lipid oxidation and improved insulin-stimulated glucose uptake, predominantly the nonoxidative pathway.[11] Previous data from studies in experimental animals, as well as in humans, have suggested that gemfibrozil may have an antilipolytic effect.[17] However, in the present study gemfibrozil therapy decreased neither serum FFA concentrations nor FFA transport rates. Lipid oxidation also remained unchanged during gemfibrozil therapy. Our data therefore do not support the idea that gemfibrozil might decrease triglycerides via an antilipolytic effect.

In conclusion, gemfibrozil effectively reduced serum triglycerides in mild hypertriglyceridemic nondiabetic subjects. However, it had no effect on FFA metabolism and did not improve glucose metabolism. We therefore propose that hypertriglyceridemia per se does not cause insulin resistance, but is a consequence of insulin resistance or factors clustering with it.

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