Bezafibrate Therapy in Patients With Isolated Low High-Density Lipoprotein Cholesterol Levels May Have a Beneficial Effect in Prevention of Atherosclerosis

Moshe S. Weintraub, Itamar Grosskopf, Gideon Charach, Ronit Mor, Ardon Rubinstein, Yoram Wollman, Rachel Judevices, and Adrian Iaina

Although a low plasma high-density lipoprotein cholesterol (HDL-C) level is a well-accepted risk factor for coronary artery disease (CAD), it is unclear whether pharmacologic agents can effectively increase HDL-C levels and/or reduce the incidence of CAD in patients with isolated low HDL-C levels. An important determinant of HDL levels is the efficiency of postprandial lipoprotein catabolism. The purpose of the present study was to evaluate the efficacy of bezafibrate therapy in increasing HDL-C levels in these patients and to examine its effect on postprandial lipoprotein levels. Fasting and postprandial lipid and lipoprotein levels were studied in 23 patients with isolated low HDL-C levels before and during 3 and 6 months of bezafibrate treatment. Postprandial lipoprotein levels were evaluated using the vitamin A–fat loading test, in which these intestinally derived lipoproteins are specifically labeled with retinyl palmitate (RP). Patients with isolated low HDL had significantly higher levels of chylomicron RP than a control group of 19 normolipidemic subjects. The area below the chylomicron RP curve was 17,773 ± 6,821 versus 13,936 ± 6,217 μg/L · h, respectively ($P < .005$). No differences were found in chylomicron remnant levels between the groups. Bezafibrate therapy reduced the chylomicron RP area by 27%, from 17,773 ± 6,821 to 12,895 ± 2,576, and the nonchylomicron RP area by 25%, from 6,059 ± 3,310 to 4,430 ± 1,963 ($P < .0001$). It increased fasting HDL-C levels from 35 ± 3 to 38 ± 1.4 mg/dL after 3 months ($P < .001$) and to 40 ± 2.2 mg/dL after 6 months ($P < .001$). A highly significant inverse correlation ($r = .8885$, $P < .001$) was found between fasting HDL-C and postprandial chylomicron RP levels. The patients did not respond to therapy as a homogenous group. That is, eight patients did not respond to bezafibrate either by reducing postprandial lipoprotein levels or by increasing HDL-C levels. bezafibrate in these patients did significantly reduce low-density lipoprotein cholesterol (LDL-C) levels from 138 ± 4.8 to 125 ± 5.9 mg/dL ($P < .0001$) while the patients were on a strict low-fat, low-cholesterol diet. In conclusion, most patients with isolated low HDL-C levels also have a defect in postprandial lipoprotein metabolism. Bezafibrate therapy has a dual effect: it reduces the level of these possibly atherogenic lipoproteins and increases HDL-C levels. These findings support the use of bezafibrate therapy in high-risk patients with isolated low HDL-C levels.

THE INVERSE ASSOCIATION between incidence of coronary artery disease (CAD) and high-density lipoprotein cholesterol (HDL-C) levels in many populations has been used as evidence that HDL "protects" against atherosclerosis.[1-3] Low levels of HDL-C are well accepted as a risk factor for CAD. Yet, specific therapeutic regimens aimed at increasing HDL-C levels are recommended only in patients with concomitant hyperlipidemia. It remains unclear whether pharmacologic agents can effectively increase HDL-C levels in patients with isolated low HDL-C, in whom total cholesterol (TC) and triglyceride (TG) levels are within the normal range. In one study of patients with isolated low HDL-C, neither lovastatin nor gemfibrozil increased HDL-C levels,[4] whereas in another study, a significant increase was demonstrated with gemfibrozil.[5] Moreover, it is not known if such an effect, if it exists, would reduce the incidence of CAD. Only one study—the Helsinki Heart Study—showed an inverse correlation between reduced incidence of CAD and a gemfibrozil-induced increase in HDL-C levels.[6]

The generally accepted mechanism for the beneficial effect of HDL particles is a reverse cholesterol transport pathway mediated by HDL.[7] However, according to an alternative suggestion, HDL particles do not have a direct effect on atherosclerosis; their plasma level only reflects the presence of an excess of other lipoproteins with possible atherogenic properties, ie, very-low-density lipoproteins, intermediate-density lipoproteins, and postprandial lipoproteins (chylomicrons and chylomicron remnants).[8-14] Since there is a negative correlation between postprandial lipoprotein and fasting HDL-C levels,[8,15] the presence of low HDL-C levels may express a defect in postprandial lipoprotein clearance. Catabolism of postprandial lipoproteins is enhanced by fibric acid derivatives.[16,17]

The objective of the present study was to examine the effect of therapy with bezafibrate, a fibric acid derivative, on HDL-C and postprandial lipoprotein levels in patients with isolated low HDL-C. Demonstration of an increase in the former and a decrease in the latter would support the use of this group of drugs in patients with isolated low HDL-C levels, especially in those at high risk for CAD. To study postprandial lipoprotein metabolism, we used the vitamin A–fat loading test, which specifically labels chylomicrons and chylomicron remnants with retinyl palmitate (RP) and has been found to be efficient in evaluating their metabolism.[18-26]

SUBJECTS AND METHODS

Patients

Twenty-three men with isolated low HDL-C levels on at least three blood tests were recruited from a lipid clinic using the following criteria: TC less than 200 mg/dL, TG less than 170 mg/dL, low-density lipoprotein cholesterol (LDL-C) less than 150 mg/dL, and HDL-C less than 40 mg/dL. The patients were evaluated in the lipid clinic. All had CAD or were at high risk for CAD. None had diabetes or hepatic, renal, or other endocrine

From the Departments of Medicine C and Nephrology, Tel Aviv Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

Submitted July 9, 1994; accepted March 6, 1995.

Address reprint requests to Moshe S. Weintraub, MD, Department of Medicine C, Tel Aviv Medical Center, 6 Weizman St, Tel Aviv, Israel.

0026-0495/95/4411-0006$03.00/0

disease, and none were obese (body mass index [BMI] <26.4 kg/m^2). No changes were made in the medications they were taking for hypertension or CAD. Since β-blockers can affect lipid and lipoprotein levels, separate analysis of patients with and without β-blockers was performed. Patients were required to give informed consent before commencing treatment. Results obtained in 19 healthy normolipidemic subjects who had participated in an earlier study in our laboratory investigating postprandial lipoprotein metabolism were used for comparison.[27]

Study Design

The study consisted of a baseline phase and a treatment phase. Patients were asked not to make changes in diet or physical activity. All of them were on diets prescribed by clinical dietitians.

In the baseline phase, patients underwent a vitamin A–fat loading test, and three blood samples were drawn for fasting lipid and lipoprotein determinations. Treatment with bezafibrate retard 400 mg/d was started once daily in the evening before dinner. After 3 months of treatment, the vitamin A–fat loading test was repeated, and blood was drawn for fasting lipid and lipoprotein determinations. The latter were repeated after 6 months of treatment.

Vitamin A–Fat Loading Test

The vitamin A–fat loading test was performed as previously described.[24] After an overnight 12-hour fast, subjects were given a fatty meal plus aqueous vitamin A 60,000 U/m^2 body surface area. The fatty meal contained fat 50 g/m^2 body surface area, with 65% of calories as fat, 20% as carbohydrate, and 15% as protein. It contained cholesterol 600 mg/1,000 cal. The polyunsaturated to saturated ratio was 0.3. The meal was given as a milkshake, scrambled eggs, bread, and cheese, and was eaten within 10 minutes. Vitamin A was added to the milkshake. After the meal, subjects fasted for 10 hours, but drinking water was allowed ad libitum. To measure levels of RP, blood samples were drawn before the meal and every hour after the meal for 8 hours, and at 10 hours. Subjects tolerated the meal well, and none had diarrhea or other symptoms of malabsorption.

Analysis of Samples

Venous blood was drawn from the forearm and transferred to a tube containing sodium EDTA. Samples were immediately centrifuged at 1,500 × *g* for 15 minutes, and 1 mL plasma was stored wrapped in foil at −20°C for retinyl ester assay. Another 0.5 mL was stored at 4°C for TG determination. An aliquot of 2.5 mL plasma was transferred to a 2-in cellulose nitrate tube and overlayered with 2.5 mL sodium chloride solution (d = 1.006 g/mL). Tubes were subjected to preparative ultracentrifugation for 1.6×10^6 *g*-min in a rotor (SW-55; Beckman Instruments, Fullerton, CA) to float chylomicron particles of Sf greater than 1,000.[28-30] The chylomicron-containing supernatant was removed and brought to total vol 2 mL with saline. The infranatant was brought to vol 5 mL with saline, 0.5-mL aliquots of supernatant were brought to vol 5 mL with saline, and 0.5-mL aliquots of supernatant and infranatant were wrapped in foil and assayed for retinyl ester. Additional aliquots were assayed for TG. This procedure separates a predominantly chylomicron population from a predominantly remnant population.[24,28]

Retinyl Ester Assay

The assays were performed in subdued light with high-performance liquid chromatography–grade solvents. Retinyl acetate was added to the samples as an internal standard. The samples were then mixed with ethanol 4 mL, hexane 5 mL, and water 4 mL, with vortexing between each addition. Two phases were formed, and 4 mL of the upper (hexane) phase was removed and evaporated under nitrogen.[31] The residue was dissolved in a small volume of benzene, and an aliquot was injected into a 5-μm high-performance liquid chromatography ODS-18 radial compression column; 100% methanol was used as the mobile phase at a flow rate of 2 mL/min. The effluent was monitored at 340 nm, and the RP peak was identified by comparison to the retention time of purified standard (Sigma Chemical, St Louis, MO). In agreement with previous reports,[23] it was found that 75% to 80% of total plasma retinyl esters were accounted for by RP. In addition, distribution of retinyl esters remained constant throughout the study. RP levels in plasma and lipoprotein fractions were quantified by the area ratio method[32] using retinyl acetate as a reference.[22]

Lipid and Lipoprotein Determinations

Cholesterol and TG levels were measured enzymatically using the reagents cholesterol 236991 and triglyceride 126012 (Boehringer Mannheim, Indianapolis, IN). HDL-C was determined after precipitation of whole plasma with dextran sulfate–magnesium.

Statistical Analysis

Differences between the groups with regard to clinical characteristics, fasting lipids, and lipoprotein metabolic responses after the fatty meal and correlations between the different variables were analyzed for significance using the χ^2 test, two-sample *t* tests, multivariate analysis with repeated measures, and Pearson's correlation, respectively.

RESULTS

Subject Characteristics

Clinical characteristics of the study participants are shown in Table 1. Mean age and mean BMI were 53 ± 6 years and 24.2 ± 1.7 kg/m^2 in the patients and 55 ± 7 years and 23.9 ± 1.8 kg/m^2 in the controls and were not significantly different. Significant differences were found between the groups in HDL-C level (35 ± 3 in patients *v* 49 ± 2 mg/dL in controls, $P < .0001$) and fasting TG level (130 ± 26 *v* 109 ± 28 mg/dL, $P < .001$), although the latter values were within the normal range. In addition, the control group consisted of only healthy subjects who were not receiving medication, whereas the study group included eight patients with CAD and 10 with hypertension. Six patients were taking β-blockers (atenolol) or calcium antagonists and/or angiotensin-converting enzyme (ACE) inhibitors, as shown in Table 1.

Plasma and lipoprotein RP and plasma TG responses to the fat loading test before and during Bezafibrate therapy, postprandial plasma and lipoprotein RP and plasma TG levels for both groups, and levels before and during 3 months of bezafibrate therapy for the patients are shown in Table 2 and Fig 1. The chylomicron RP fraction, as measured by the area below the RP curve, was significantly higher in patients before therapy than in controls (17,773 ± 6,821 *v* 13,936 ± 6,217 μg/L · h, respectively, $P < .005$). No significant differences between the groups

Table 1. Clinical Characteristics of Study Participants

Subject No.	Age (yr)	BMI (kg/m²)	Fasting Lipids/Lipoproteins (mg/dL)				Smoker	CAD	Hyper-tension	Positive Family History	AHA Diet			Medication		
			TC	TG	LDL-C	HDL-C					1	2	3	BB	ACE-I	CA
1	46	24.8	188	135	131	34	+		+	++	+					+
2	61	26.0	200	146	135	36			+		+				+	
3	54	20.9	189	133	128	31		+				+				+
4	48	26.4	175	165	108	34		+			+					
5	58	24.5	198	134	136	38	+				+					
6	56	21.7	167	168	105	29			+		+			+	+	
7	45	24.7	200	127	144	35			+	++	+					+
8	66	22.6	197	136	134	36				++	+					
9	49	25.0	193	138	128	37					+					
10	53	23.3	189	157	121	37		+			+			+	+	
11	49	26.2	178	141	118	32		+			+			+		
12	60	24.3	196	166	131	32		+	+	++		+		+		
13	56	22.4	197	152	133	34				++	+					
14	52	26.3	194	148	132	32				+	+					
15	50	20.5	183	163	120	31			+	+			+		+	+
16	52	25.5	191	92	136	37			+	++			+			
17	46	23.4	198	88	143	38			+				+			
18	58	24.8	198	104	140	37		+					+			
19	62	23.4	190	95	130	39		+	+	+			+			+
20	46	25.2	197	105	135	38		+	+				+	+		
21	52	26.1	200	105	140	37	+			++			+			
22	54	23.4	192	100	136	37				++			+			
23	59	24.6	193	102	145	39				++			+	+		
Mean ± SD	53 ± 6	24.2 ± 1.7	188 ± 14	130 ± 26	130 ± 10	35 ± 3	3	8	9	12	12	2	9	6	4	5
Range	45-66	20.5-26.2	167-200	88-168	105-145	29-39										
Controls (n = 19)																
Mean ± SD	55 ± 7	23.9 ± 1.8	208 ± 34	109 ± 28	136 ± 30	49 ± 2	6	–	–	––	––	–	–	–	–	–
Range	39-60	20.7-25.8	130-244	60-145	79-165	30-64										
P	NS	NS	NS	<.001	NS	<.0001										

Abbreviations: BB, β-blockers; ACE-I, ACE inhibitors; CA, calcium antagonists.

were found in the areas of the nonchylomicron fractions (which contain predominantly chylomicron remnants) or in the areas below the TG curves. Bezafibrate treatment reduced chylomicron levels by 27% (from 17,773 ± 6,821 to 12,895 ± 2,576 μg/L · h, $P < .0001$). The nonchylomicron fraction was also reduced by the same amount (from 6,059 ± 3,310 to 4,430 ± 1,963 μg/L · h, $P < .0001$). The area below the plasma TG curve was reduced on bezafibrate treatment by 15% (from 1,457 ± 412 to 1,245 ± 219 mg/dL · h, $P < .0001$). A separate analysis of these results after excluding patients on β-blockers did not change the significance of the results (Table 2).

Individual responses, ie, postprandial lipoprotein levels, to bezafibrate treatment are shown in Fig 2. Based on each patient's response to the drug, it became possible to divide the patients into two groups: 15 responders and eight nonresponders. Table 3 and Fig 3 demonstrate these differences in postprandial RP and TG responses to bezafi-

Table 2. Postprandial Lipoprotein Levels of All Patients (N = 23), of Patients After Excluding Those on β-Blockers (n = 17), and of Controls (no treatment, n = 19), and Effect of Bezafibrate on Patient Lipoprotein Levels

Group	Area Below RP Curves (μg/L · h)			Area Below Plasma TG Curves (mg/dL · h)
	Plasma	Chylomicron Fraction	Nonchylomicron Fraction	
Patients (N = 23)				
Before treatment	23,720 ± 8,722	17,773 ± 6,821	6,059 ± 3,310	1,457 ± 412
On 3 mo bezafibrate	17,218 ± 3,036	12,895 ± 2,576	4,430 ± 1,963	1,245 ± 219
P pretherapy *v* posttherapy	<.0001	<.0001	<.0001	<.0001
Controls	20,192 ± 7,063	13,936 ± 6,217	6,162 ± 2,863	1,406 ± 280
P pretherapy patients *v* controls	<.01	<.005	NS	NS
Patients (n = 17)				
Before treatment	23,189 ± 8,162	17,721 ± 6,848	5,722 ± 3,020	1,484 ± 455
On 3 mo bezafibrate	17,122 ± 3,075	13,087 ± 2,489	4,227 ± 1,886	1,257 ± 239
P pretherapy *v* posttherapy	<.001	<.002	<.001	<.002

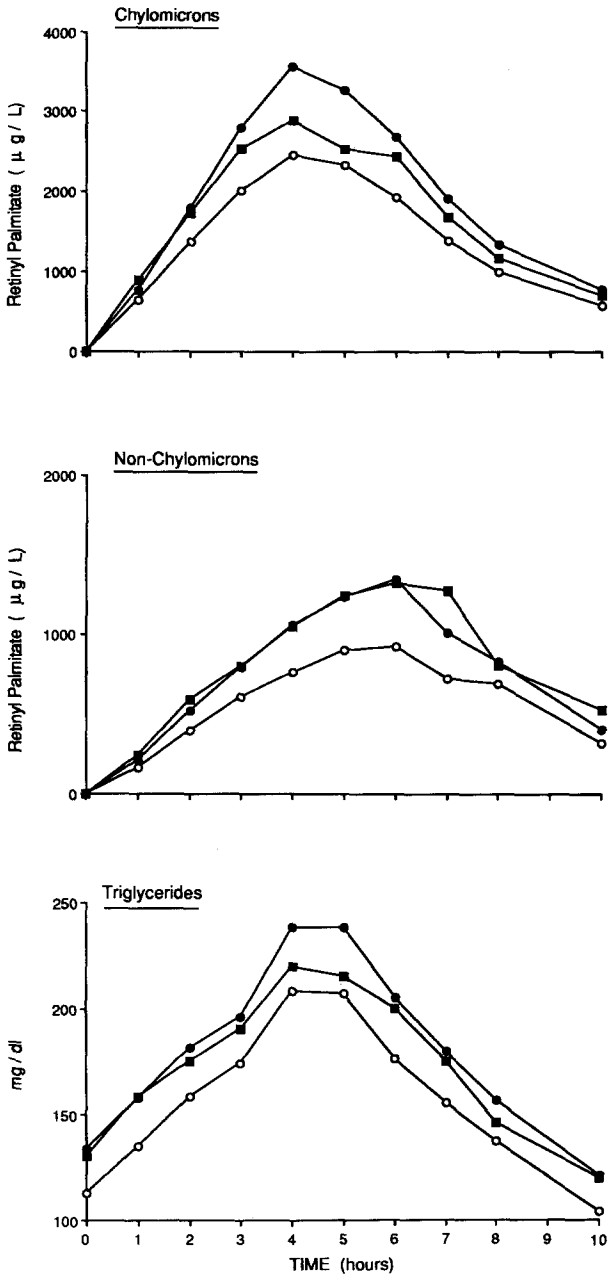

Fig 1. RP and TG concentration curves in patients with isolated low HDL-C and controls, and the effect of bezafibrate treatment in the patients. Chylomicron RP, nonchylomicron RP, and plasma TG responses in 23 patients with isolated low HDL before drug therapy (●), 19 normolipidemic controls (■), and the patient group on bezafibrate (○). For each group, levels at each time point were averaged.

brate. Responders had significantly higher levels of chylomicrons and nonchylomicrons before drug therapy than nonresponders. Areas below chylomicron RP curves were 21,041 ± 5,972 versus 11,646 ± 3,019 μg/L · h ($P < .0001$), and those below nonchylomicron RP curves were 7,307 ± 3,315 versus 3,218 ± 1,694 μg/L · h ($P < .002$); areas below TG curves were 1,571 ± 464 versus 1,242 ± 150 mg/dL · h ($P < .02$), respectively. Bezafibrate reduced chylomicron and nonchylomicron areas by 35% and 34%, respectively, in the responder group ($P < .0001$), but caused no significant change in these areas in the nonresponder group. Areas under RP curves of the two postprandial lipoprotein fractions and those under TG curves in the two patient subgroups on therapy were similar (Table 3).

Fasting Lipids and Lipoproteins Before and During Bezafibrate Therapy

Table 4 shows differences in clinical characteristics between patient subgroups. Responders had significantly higher fasting TG levels and lower HDL-C levels than nonresponders (147 ± 14 *v* 98 ± 6.4 and 34 ± 2.6 *v* 38 ± mg/dL, respectively, $P < .0001$). Nonresponders had significantly higher levels of LDL-C than responders (138 ± 5 *v* 126 ± 10 mg/dL, $P < .002$). No significant differences were found between the two subgroups in the presence of CAD or hypertension or in the medications they were taking. However, a careful examination of the patients' dietary intake showed that all nonresponders were on a strict low-fat, low-cholesterol diet, ie, the American Heart Association (AHA) diet phase 3. Thirteen responders were on AHA diet phase 1 and two on AHA diet phase 2 (Tables 1 and 4).

The effects of 3 and 6 months of bezafibrate 400 mg/d on fasting lipids and lipoproteins are shown in Table 5. Three months of therapy significantly reduced mean fasting TG levels in the entire group of patients (N = 23), from 130 ± 26 to 107 ± 10 mg/dL ($P < .0001$). An additional significant reduction was found at 6 months of therapy (107 ± 9 *v* 102 ± 9, $P < .01$). Mean fasting HDL-C levels increased from 35 ± 3 to 38 ± 1.4 mg/dL after 3 months of therapy ($P < .0001$) and to 40 + 2.0 mg/dL at 6 months of therapy ($P < .001$). No significant changes were found in fasting LDL-C levels with bezafibrate. When patients were divided into responders and nonresponders, it was noted that Bezafibrate had a highly significant effect on the former. It led to a reduction in TG levels from 147 ± 13 to 107 ± 9 mg/dL after 3 months ($P < .0001$) and to 99 ± 8 mg/dL at 6 months ($P < .001$), and to an increase in HDL-C levels from 34 ± 2.6 to 38 ± 1.6 mg/dL after 3 months ($P < .0001$) and to 40 ± 2.2 mg/dL after 6 months ($P < .001$). No significant effect of the drug was found on either TG or HDL-C levels in nonresponders. A significant decrease in LDL-C levels was found in nonresponders (from 138 ± 4.8 to 128 ± 5.6 mg/dL after 3 months, $P < .0001$), with an additional decrease to 125 ± 5.9 mg/dL at 6 months (NS).

Correlations Between Fasting Lipids and Lipoproteins and Postprandial Lipoprotein Fraction

To better understand the metabolic relationship between fasting lipids and lipoproteins and postprandial lipoproteins, correlations were sought between chylomicron, nonchylomicron RP, and plasma TG responses to fasting cholesterol, TG, LDL-C, and HDL-C levels (Table 6 and Fig 4). Highly significant inverse correlations were found in the responders subgroup between fasting HDL-C levels and both chylomicron fractions and TG areas ($r = -.8277$ and $-.7845$, respectively, $P < .001$). Significant positive

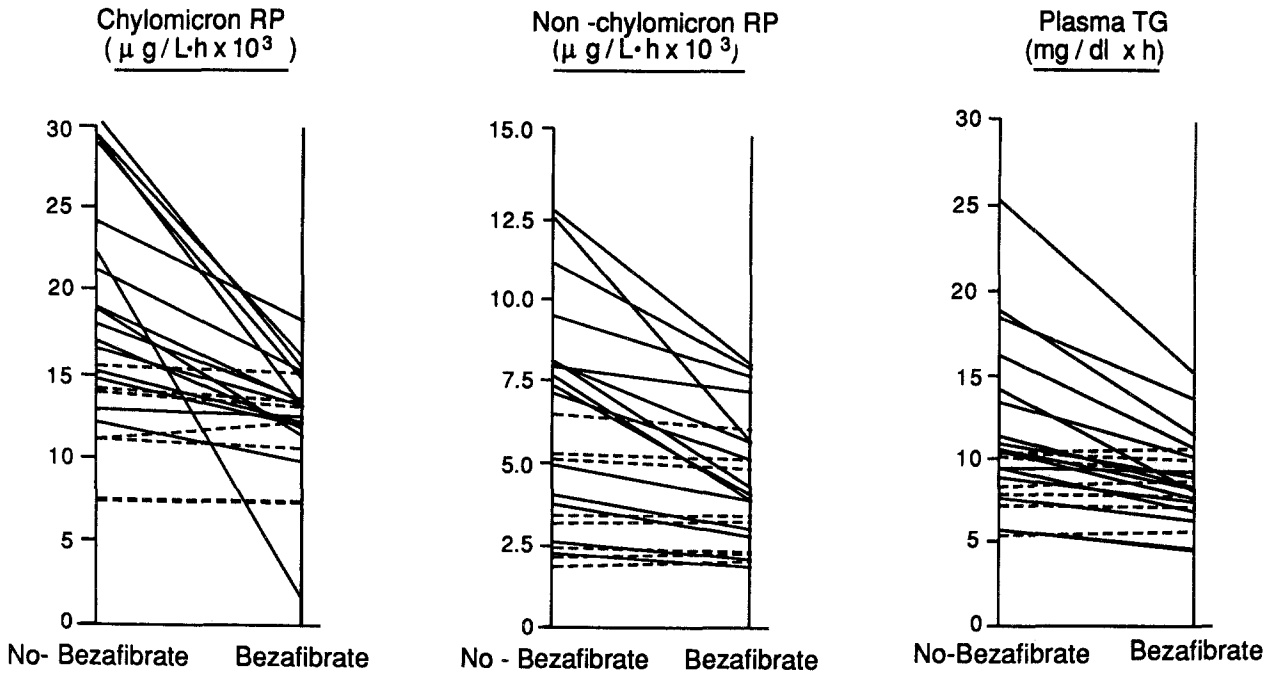

Fig 2. Individual response to bezafibrate treatment. Chylomicron RP, nonchylomicron RP, and plasma TG areas for each of 23 patients: 15 responders (—) and 8 nonresponders (---) are shown before and during bezafibrate therapy.

correlations were found between fasting TG and chylomicron fractions ($r = +.7876, P < .001$). No significant correlations were found between these variables in nonresponders.

DISCUSSION

The main question raised by this study was whether pharmaceutical treatment should be used in patients with isolated low HDL-C levels. Our results clearly demonstrate that most patients with so-called isolated low HDL-C levels have more than one isolated defect in lipoprotein metabolism: they also have an accompanying defect in postprandial lipoprotein metabolism, with an accumulation of these atherogenic lipoproteins in the circulation. This lipoprotein abnormality cannot be detected when lipids and lipoproteins are examined in the fasting state only. Bezafibrate therapy decreased postprandial lipoprotein levels and increased HDL-C levels in most of these patients.

Postprandial lipoprotein metabolism occurs in two stages. Initially, the chylomicrons that carry most of the dietary fat absorbed in the intestine interact with lipoprotein lipase, resulting in TG hydrolysis and delivery of free fatty acids to the tissues.[33-35] After most of the TG are hydrolyzed, chylomicron remnant particles are formed.[36,37] In the second stage, these particles are removed from the circulation by hepatocyte receptors that recognize apolipoprotein E.[38,39] The exact stage at which chylomicrons become remnants is not known, and there are no methods currently available to physically separate the two. In the present investigation, we used a centrifugation step to separate larger and less dense chylomicrons of Sf greater than 1,000 from smaller and more dense ones.[28] As shown in previous studies,[24-26] this

Table 3. Postprandial Lipoprotein Levels in Responders (n = 15) and Nonresponders (n = 8) Before and During Bezafibrate Therapy

Group	Area Below RP Curves (μg/L · h)			Area Below TG Curves (mg/dL · h)
	Plasma	Chylomicron Fraction	Nonchylomicron Fraction	Plasma
Responders				
Pretherapy	28,216 ± 7,110	21,041 ± 5,972	7,307 ± 3,315	1,571 ± 464
On therapy	18,321 ± 2,202	13,637 ± 5,972	4,849 ± 2,090	1,254 ± 256
Nonresponders				
Pretherapy	15,289 ± 3,667	11,646 ± 3,014	3,218 ± 1,694	1,242 ± 150
On therapy	15,150 ± 3,433	11,503 ± 2,839	3,644 ± 1,513	1,228 ± 138
P				
Between groups pretherapy	<.0001	<.0001	<.002	<.021
Between groups on therapy	<.039	NS	NS	NS

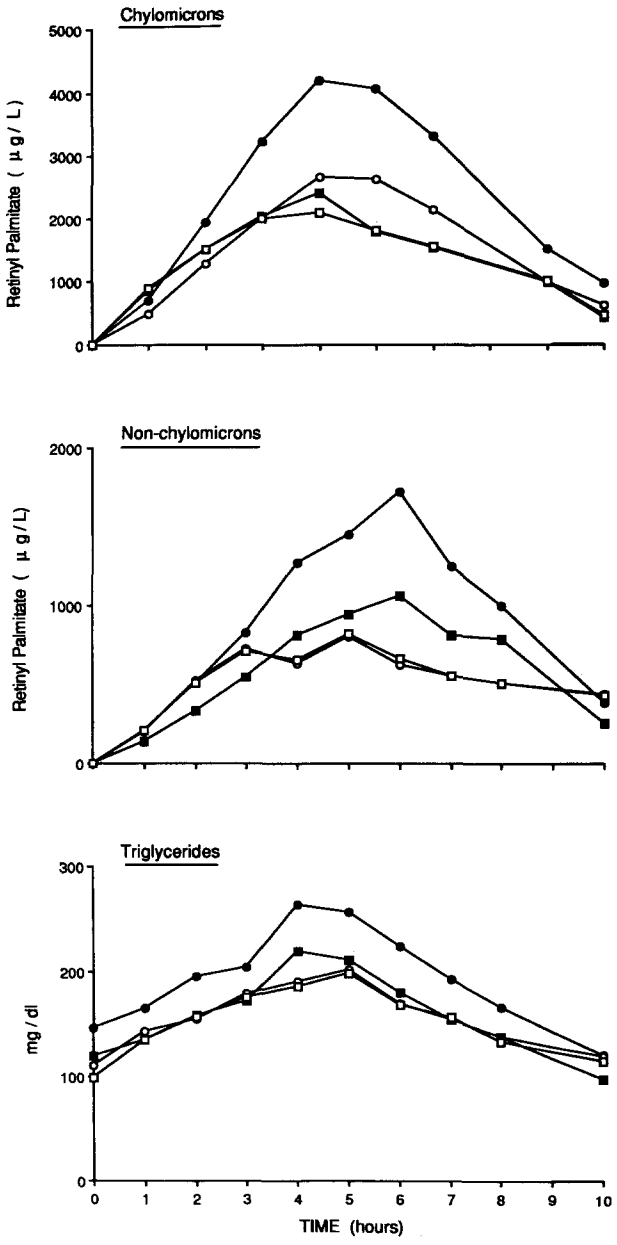

Fig 3. Effect of bezafibrate treatment on RP and TG concentrations in responder and nonresponder groups. Chylomicron RP, nonchylomicron RP, and plasma TG responses in 15 responders before (●) and during (○) bezafibrate therapy and in 8 nonresponders before (■) and during (□) bezafibrate therapy. For each group, levels at each time point were averaged.

method successfully separates a predominantly chylomicron population from a predominantly remnant (nonchylomicron fraction) population.

Fifteen of 23 patients with isolated low HDL-C levels who participated in the study demonstrated a significant accumulation of chylomicrons in the circulation that was inversely correlated with fasting plasma HDL-C levels. No differences in the chylomicron remnant fraction were found between patients and controls. Thus, accumulation of postprandial lipoproteins in these patients was the result of a defect in the first stage of postprandial lipoprotein catabolism—chylomicron lipolysis—and not in the second stage of chylomicron remnant removal. Three months of bezafibrate therapy "normalized" this defect in postprandial lipoprotein metabolism, reduced plasma lipoprotein levels, and significantly increased fasting HDL-C levels. This increase continued with time, and after 6 months of therapy HDL-C levels were significantly higher than they had been after 3 months. Bezafibrate therapy also reduces nonchylomicron areas in responders. This may be important, since it is thought that chylomicron remnants may be atherogenic particles. However, it is possible that this decrease is mainly due to enhanced lipolysis of the smaller chylomicrons (Sf < 1,000) found in this fraction.

In eight patients with isolated low HDL-C levels, postprandial lipoprotein metabolism was normal. These patients' postprandial lipoprotein and fasting HDL-C levels were not affected by bezafibrate therapy: there was neither a reduction in postprandial lipoprotein levels nor an increase in HDL-C levels. Also, the magnitude of postprandial lipemia in these patients did not correlate at all with fasting HDL-C levels, as found in the responders. Bezafibrate did cause a significant reduction of LDL-C levels in these patients. HDL production is considered to occur in two main metabolic steps. Initially, HDL particles are formed in the liver and intestine as discoidal lipoproteins composed of phospholipids, apolipoproteins, and small amounts of free cholesterol,[40,41] which enter the bloodstream. In the second step, the particles are transformed into mature spherical particles by interacting with lipid and protein constituents released from lipolyzed TG-rich lipoproteins (surface remnants) as very-low-density lipoproteins and chylomicrons.[42] The main determinants of the first step are genetic control of HDL apoprotein synthesis and amount of saturated fat and cholesterol in the diet. Positive correlations were found between plasma HDL-C levels and dietary animal fat, as well as with dietary

Table 4. Differences in Clinical Characteristics Between Responders (n = 15) and Nonresponders (n = 8)

Group	Age (yr)	BMI (kg/m²)	TC (mg/dL)	TG (mg/dL)	LDL-C (mg/dL)	HDL-C (mg/dL)	Smoker	IHD	Hyper-tension	BB	ACE-I	CA	Diet
Responders													
Mean ± SD	54 ± 16	23.9 ± 1.9	185 ± 1.7	147 ± 14	126 ± 10	34 ± 2.6	2	5	6	4	3	3	Good low-fat
Range		20.5-26.4	167-200	127-166	105-144	29-37							
Nonresponders													
Mean ± SD	53 ± 6	24.5 ± 1	194 ± 4	98 ± 6.4	138 ± 5	38.8 ± 8	1	3	3	2	1	2	Strict low-fat
Range		23.4-26.1	191-200	92-105	120-145	27-39							
P	NS	NS	<.056	<.0001	<.002	<.0001	NS	NS	NS	NS	NS	NS	

NOTE. Abbreviations are as in Table 1.

Table 5. Effect of 3 and 6 Months of Bezafibrate 400 mg/d on Fasting Lipids and Lipoproteins in the Entire Patient Group (N = 23) and in Responders (n = 15) and Nonresponders (n = 8)

Parameter	Entire Group			Responders			Nonresponders		
	Before Therapy	3 Months	6 Months	Before Therapy	3 Months	6 Months	Before Therapy	3 Months	6 Months
BMI (kg/m²)	24.2 ± 1.6	24.2 ± 1.7	24 ± 1.9	24 ± 1.8	24 ± 1.9	24 ± 1	24 ± 1	24 ± 1	24 ± 1
TC (mg/dL)	189 ± 14	187 ± 8	189 ± 10	186 ± 16	186 ± 9	191 ± 11†	194 ± 4	187 ± 6*	184 ± 6*
TG (mg/dL)	130 ± 26	107 ± 10*	102 ± 19‡	147 ± 13	107 ± 9*	99 ± 8†	99 ± 6	101 ± 9	102 ± 6
LDL-C (mg/dL)	131 ± 10	127 ± 18	128 ± 9	127 ± 10	127 ± 9	130 ± 0	138 ± 4.8	128 ± 5.6*	125 ± 5.9*
HDL-C (mg/dL)	35 ± 3	38 ± 1.4*	40 ± 2.2†	34 ± 2.6	38 ± 1.6*	40 ± 2.0†	38 ± 0.8	38 ± 1.0	38 ± 1.5

*$P < .0001$ *v* before therapy.
†$P < .001$ *v* 3 months of therapy.
‡$P < .01$ *v* 3 months of therapy.

cholesterol.[43-47] The main determinant of the second step is the efficacy of TG-rich lipoprotein lipolysis. A careful evaluation of nonresponder dietary charts showed that these eight patients were on a strict low-fat, low-cholesterol diet, AHA phase III, as compared with the rest of the patients who were on AHA phase I and II.

It seems that the low levels of HDL-C in the nonresponder group were secondary mainly to the strict low-fat, low-cholesterol diet. Of course, this parameter is not expected to respond to pharmaceutical therapy. In the responder group, on the other hand, low HDL-C levels were most probably secondary to inefficient TG-rich lipoprotein lipolysis, resulting in a low "supply" of surface remnants from these particles for HDL particles. Therefore, in this group, we would expect bezafibrate to be effective because, as shown previously, fibric acid derivatives enhance the rate of lipolysis by stimulating lipoprotein lipase.[16,17] Indeed, in the present study, bezafibrate therapy proved effective in normalizing the defect in TG-rich lipoprotein catabolism in the responder group. It significantly reduced postprandial lipoprotein levels and increased HDL-C levels.

Two lines of thought have developed to explain the negative association between HDL level and atherosclerosis. According to the first, HDL is actively involved in retarding the development of atheromatous lesions in its role in reverse cholesterol transport from the artery wall to the liver.[7] According to the second assumption, HDL levels reflect only the efficacy of TG-rich lipoprotein catabolism, and HDL particles are not directly involved in any antiatherogenic activity. Thus, any intervention that increases lipoprotein lipase activity and TG-rich lipoprotein catabolism (such as physical activity, weight loss, or bezafibrate therapy) will reduce postprandial lipoprotein levels and increase fasting HDL-C levels. The reduction in vessel-wall exposure to these lipid particles with possible atherogenic properties[9-14] is responsible for a beneficial effect of such intervention on atherosclerosis prevention.

It is certainly possible that both views are correct. That is, a low HDL level might directly promote development of coronary lesions while signifying an excess of atherogenic lipoproteins of another type.

Our study shows that most patients with isolated low HDL-C levels also have an accumulation of postprandial lipoproteins in the circulation and that bezafibrate has a dual effect: it reduces postprandial lipoprotein levels and increases fasting HDL-C levels. In the rest of the patients with isolated low HDL-C, those with a normal postprandial lipoprotein metabolism, bezafibrate significantly reduces fasting LDL-C levels. A recent study has also demonstrated an increase in HDL-C levels in patients with isolated low HDL-C by gemfibrozil treatment.[5] The Helsinki study[6] showed the separate effect that increasing HDL-C levels

Table 6. Correlations Between Chylomicron RP, Nonchylomicron RP, and Plasma TG Areas and Fasting Lipids and Lipoproteins

Variable	Fraction Areas	All Patients (N = 23)	Responders (n = 15)	Nonresponders (n = 8)
TC	Chylomicron	NS	NS	NS
	Nonchylomicron	NS	NS	NS
	TG	NS	NS	NS
TG	Chylomicron	+.7152*	+.7876*	NS
	Nonchylomicron	NS	NS	NS
	TG	NS	NS	NS
LDL-C	Chylomicron	NS	NS	NS
	Nonchylomicron	NS	NS	NS
	TG	NS	NS	NS
HDL-C	Chylomicron	−.8885*	−.8277*	NS
	Nonchylomicron	NS	NS	NS
	TG	−.6493*	−.7845*	NS

*$P < .001$.

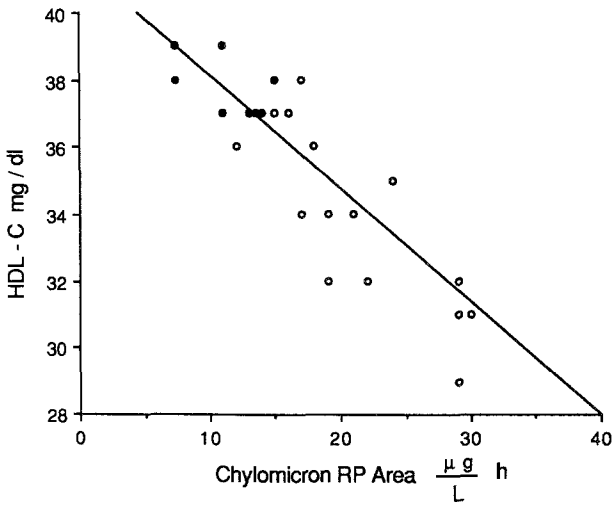

Fig 4. Significant correlation between HDL-C levels and chylomicron RP areas in patients with isolated low HDL-C. Chylomicron RP area is plotted against HDL-C levels in 15 responders (○) and 8 nonresponders (●).

has on reducing the incidence of CAD. Our study is the first to examine the effect of fibric acid derivatives on HDL-C levels and on postprandial lipoprotein levels in patients with isolated low HDL-C. The results suggest a possible mechanism for the beneficial effect of drugs from this group in reducing CAD incidence in such patients, and support the use of these drugs in patients with isolated low HDL-C levels, especially those at high risk.

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