

# Combined Hyperlipidemia Is Associated With Increased Exercise-Induced Muscle Protein Release Which Is Improved by Triglyceride-Lowering Intervention

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Although myopathy is considered an adverse effect of treatment with 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors and fibrates in combined hyperlipidemia, the present study was performed to investigate whether combined hyperlipidemia itself is associated with skeletal muscle pathology and whether lipid-lowering intervention has beneficial effects. To investigate whether combined hyperlipidemia is associated with skeletal muscle pathology, 10 male patients and 15 normolipidemic controls underwent a 45-minute standardized bicycle ergometer test at a load of 2 W/kg lean body mass (parallel study). One- and 8-hour postexercise increments in the plasma level of the muscle proteins creatine kinase (CK), myoglobin (Mb), and fatty acid-binding protein (FABP) were assessed as parameters for (subclinical) skeletal muscle pathology. The 8-hour postexercise increments in CK and Mb and 1-hour postexercise increment in Mb were significantly higher in patients than in controls, thus indicating increased exercise-induced muscle membrane permeability in combined hyperlipidemia. To investigate the effects of lipid-lowering intervention on skeletal muscle in combined hyperlipidemia, 21 subjects with combined hyperlipidemia were randomized double-blindly to receive 6 weeks of treatment with fluvastatin 40 mg/d, gemfibrozil 600 mg twice daily, or combination therapy. All subjects underwent an ergometer test before and after treatment. Gemfibrozil treatment alone reduced the CK increments 8 hours postexercise by 47% and the FABP increments 1 and 8 hours postexercise by 83% and 101%, respectively (all  $P < .05$ ). Combined treatment reduced Mb increments 1 hour postexercise by 54% and FABP increments 8 hours postexercise by 44% (all  $P < .05$ ). A highly significant correlation existed between therapy-induced changes in plasma triglycerides and changes in postexercise increments of FABP and Mb. In conclusion, combined hyperlipidemia is associated with an increased exercise-induced release of muscle proteins, which is ameliorated by triglyceride-lowering intervention. As FABP is an indicator for ischemia-induced skeletal muscle pathology, a possible explanation is the impaired muscle blood flow during hypertriglyceridemia, which may be reversed by triglyceride-lowering intervention. The mechanism and clinical relevance of these findings remain to be investigated.

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**W**HILE THE RELATIONSHIP between elevated cholesterol levels and cardiovascular disease is beyond dispute,<sup>1</sup> controversy exists about the role of elevated triglyceride-rich lipoproteins in atherosclerosis. Recent studies have indicated a role of hypertriglyceridemia as a risk factor or risk indicator of cardiovascular disease.<sup>2-4</sup> As a consequence, triglyceride-carrying lipoproteins should be taken into account when considering lipid-lowering therapy in combined hyperlipidemia. The treatment modalities in combined hyperlipidemia are nicotinic acid, inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase,<sup>5</sup> and fibric acid derivatives, which decrease serum triglyceride levels by decreasing the synthesis of very-low-density lipoprotein cholesterol and increasing lipoprotein lipase activity.<sup>6</sup> Combination therapy with HMG-CoA reductase inhibitors plus fibrates is effective in the treatment of combined hyperlipidemia, which has been supported by several studies.<sup>7-9</sup> However, concern has arisen about myopathy and rhabdomyolysis during therapy with HMG-CoA reductase inhibitors combined with gemfibrozil.<sup>10-15</sup> Moreover, gemfibrozil itself has also been associated with

myopathy.<sup>16</sup> Although a relationship with these medications seems apparent, elevated plasma muscle protein levels both at rest and after exercise have been observed in untreated familial hypercholesterolemia, as well,<sup>17,18</sup> leading to the conclusion that elevations of creatine kinase (CK) during therapy with HMG-CoA reductase inhibitors may not be caused by these agents alone. It has not been investigated whether combined hyperlipidemia is also associated with increased serum levels of muscle proteins. This may be of importance, because elevated CK levels, which may be observed during therapy for combined hyperlipidemia, are usually attributed to this therapy and not to the disease. Moreover, it can be hypothesized that if combined hyperlipidemia is indeed associated with pathological serum muscle protein levels, lipid-lowering intervention may have beneficial effects.

One of the explanations offered for the elevated muscle protein levels in familial hypercholesterolemia is impaired peripheral muscle blood flow, leading to diminished muscle blood flow. Indeed, it has been demonstrated that apart from coronary blood flow,<sup>19-21</sup> peripheral blood flow is also impaired in hypercholesterolemia, which can be reversed by lipid-lowering therapy.<sup>22-24</sup> In hypertriglyceridemia, peripheral vascular function is impaired as well, which also can be restored by lipid-lowering intervention.<sup>25-27</sup>

The exercise-induced release of the muscle proteins CK, myoglobin (Mb), and heart-type fatty acid-binding protein (FABP)<sup>28-32</sup> is a well-established parameter for (sub)clinical muscular pathology. To assess whether combined hyperlipidemia is associated with skeletal muscle pathology, the exercise-induced release of muscle proteins was compared in subjects with combined hyperlipidemia versus normolipidemic controls. To investigate whether therapy for combined hyperlipidemia has beneficial effects on skeletal muscle, a double-blind,

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Submitted December 9, 1998; accepted June 14, 1999.

Supported in part by a Pioneer Grant from the Dutch Foundation for Scientific Research (T.W.A.D.B.).

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0026-0495/99/4812-0012\$10.00/0

randomized, placebo-controlled intervention study was performed. In this study, the release of muscle proteins CK, Mb, and FABP after standardized exercise was assessed before and after 6 weeks of treatment with fluvastatin and gemfibrozil, both as monotherapy and combined.

## SUBJECTS AND METHODS

### *Intervention Study*

Informed consent was obtained from all patients. The study protocol was approved by the Medical Ethics Committee of the University Hospital Utrecht. In the intervention study, 21 patients with primary combined hyperlipidemia (10 men and 11 women aged  $54 \pm 2$  years, mean  $\pm$  SE; body mass index [BMI],  $26.6 \pm 0.5$  kg/m<sup>2</sup>) were selected among recently diagnosed hyperlipidemic patients from the Lipid Clinic of the University Hospital Utrecht. Patients with diabetes mellitus, renal, hepatic, muscle, or cardiac disease, or therapy with other medications known to be accompanied by myopathy or elevated muscle protein levels were excluded. Secondary causes for combined hyperlipidemia were also excluded. Habitual physical exercise was scored as described previously<sup>18</sup> using the following scale: 0, no exercise; 1, once per month but less than once per week; 2, at least once per week but of mild or moderate intensity (eg, sports for recreational purposes only); and 3, at least once per week but of high intensity (eg, sports competition or occupation involving heavy and frequent physical activity). The patients entered a dietary baseline period of 8 weeks. A standard lipid-lowering diet was prescribed by a dietician, containing 50% of calories from carbohydrate, 20% from protein, and 30% from fat, with a polyunsaturated to saturated lipid ratio of 1. Daily intake of cholesterol was less than 300 mg. At the end of the 8-week baseline period, patients with low-density lipoprotein (LDL) cholesterol of at least 4.14 mmol/L and fasting triglycerides of at least 2.3 mmol/L were randomized in a double-blind manner to be treated for 6 weeks with either fluvastatin 40 mg/d taken at bedtime and gemfibrozil placebo (fluvastatin group,  $n = 7$ ), gemfibrozil 600 mg twice daily and fluvastatin placebo (gemfibrozil group,  $n = 7$ ), or a combination of fluvastatin 40 mg/d and gemfibrozil 600 mg twice daily (combined treatment group,  $n = 7$ ). The placebo tablets contained lactose and resembled the fluvastatin or gemfibrozil tablets. In the last week of the dietary baseline period and after 6 weeks of active treatment, an exercise provocation test was performed.

### *Comparison of Subjects With Combined Hyperlipidemia Versus Normolipidemic Controls*

To investigate whether combined hyperlipidemia is associated with a pathological exercise-induced release of muscle proteins, the results from a subgroup of 10 male patients with primary combined hyperlipidemia from the intervention study (age,  $43 \pm 2$  years; BMI,  $26.1 \pm 0.6$  kg/m<sup>2</sup>) were compared with those of an age-, BMI-, and habitual exercise-matched normolipidemic control group consisting of 15 healthy males (age,  $48 \pm 2$ ; BMI,  $25.8 \pm 0.8$ ) recruited from laboratory personnel and used previously to assess whether primary hypercholesterolemia is associated with increased exercise-induced release of muscle proteins.<sup>22</sup> Controls were screened for conditions known to influence muscle protein release. Since they were normolipidemic, subjects in the control group were not prescribed a diet.

### *Ergometer Test*

The bicycle ergometer test was used previously to detect subjects with muscular disease and to study exercise-induced skeletal muscle protein release in hypercholesterolemia, and is described in detail elsewhere.<sup>22</sup> In short, a 45-minute bicycle ergometer test was performed with a load of 2 W/kg lean body mass. The actual workload was registered every 5 minutes. In the intervention study, the workload

during the second exercise test (in the last week of the active treatment period) was kept identical to the workload during the first test at any time point for each individual. Female participants performed the second exercise test in the same phase of the menstrual cycle as the first test. The patients were told to avoid strenuous exercise for 48 hours before both tests. Blood samples for CK, Mb, and FABP analysis were taken before the exercise test and 1 and 8 hours after the test. It was demonstrated that peak CK levels occur 8 hours after this test.<sup>18,28</sup>

Peak Mb levels are observed 1 hour after exercise and the same is expected for FABP, as FABP and Mb plasma levels are usually strongly correlated.<sup>30-32</sup> Exercise-induced muscle damage is reflected by an increment in muscle protein levels after exercise. In the normolipidemic control group, only CK and Mb levels were assessed, and therefore, no comparison with the hyperlipidemic patients for exercise-induced FABP levels could be performed.

### *Laboratory Methods*

Total cholesterol, triglycerides, and CK were determined by enzymatic-colorimetric methods (CHOD-PAP and GPO-PAP; Boehringer, Mannheim, Germany). High-density lipoprotein (HDL) cholesterol was determined in the supernatant after precipitation of apolipoprotein B-containing lipoproteins. LDL cholesterol was calculated using the Friedewald formula, since fasting triglycerides were less than 5.6 mmol/L in all subjects on all occasions.<sup>33</sup> Mb was determined using the Behring Latex Myoglobin Kit (Behring Diagnostics, Frankfurt, Germany). Heart-type FABP was determined in plasma using an enzyme-linked immunosorbent assay of the antigen-capture type (sandwich ELISA). This method has been described in detail elsewhere.<sup>30</sup> Samples from each subject were measured in duplicate in the same assay, using the average of both values.

### *Safety Parameters*

The laboratory safety parameters were plasma creatinine, sodium, potassium, bilirubin, alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyl transferase, a hematological profile, and a urinary analysis. A physical examination and measurement of the blood pressure and pulse were performed at each visit during the intervention study. A 12-lead electrocardiogram was performed at the beginning of the baseline period.

### *Statistical Methods*

All values are presented as the mean  $\pm$  SE. In the intervention study, lipid parameters and preexercise CK, Mb, and FABP levels before and after treatment within each group were analyzed with a two-sided, paired Student's *T* test. The exercise-induced elevations of CK, Mb, and FABP were analyzed within each group using a paired Wilcoxon test. Data from patients and normolipidemic controls were compared using an unpaired *T* test for age, BMI, lipids, and baseline CK and Mb. Exercise-induced levels of muscle proteins between the two groups were compared with an unpaired Wilcoxon test. Correlations between lipid levels and exercise-induced muscle protein increments were calculated with linear regression. A *P* value less than .05 was considered statistically significant.

## RESULTS

### *Comparison of Subjects With Combined Hyperlipidemia and Normolipidemic Controls*

**Patients.** In the parallel study, both groups were identical with regard to age, BMI, and habitual exercise (Table 1).

**Ergometer test.** The exercise-induced CK increase after 1 hour was the same, but at 8 hours after exercise, it was significantly higher in patients with combined hyperlipidemia

**Table 1. Comparison of Subjects With Combined Hyperlipidemia and Normolipidemic Controls**

Characteristic	Patients	Controls
No. of subjects	10	15
Age (yr)	43.3 ± 2.2	48 ± 1.7
BMI (kg/m <sup>2</sup> )	26.1 ± 0.6	25.8 ± 0.8
Exercise score	1.7 ± 0.2	1.4 ± 0.6
LDL cholesterol (mmol/L)	5.7 ± 0.5	3.7 ± 0.3
HDL cholesterol (mmol/L)	0.9 ± 0.05	1.1 ± 0.1
Triglycerides (mmol/L)	4.2 ± 0.5	1.2 ± 0.1

NOTE. Values are the mean ± SD.

than in normocholesterolemic controls ( $39.1 \pm 6.9$  v  $9.7 \pm 3.3$  U/L,  $P = .0002$ ; Fig 1). The increase in Mb differed significantly between patients and controls both 1 hour after exercise ( $17.7 \pm 4.2$  ng/L for patients v  $4.1 \pm 2.8$  ng/L for controls,  $P = .006$ ) and 8 hours after exercise ( $9.2 \pm 2.4$  v  $-5.9 \pm 2.2$  ng/L,  $P = .0003$ ).

#### Intervention Study

**Patients.** Characteristics of the three treatment groups are listed in Table 2. No clinical adverse effects occurred during the study period or thereafter. One patient from the gemfibrozil group left the study because he found the procedures too burdensome. This patient was not included in any analysis.

**Lipid parameters.** Plasma lipid concentrations are presented in Table 3. The combined treatment group showed the highest reductions in LDL cholesterol and triglycerides, which were significantly decreased by 29% and 49%, respectively.

**Ergometer test.** Each subject had an identical workload at any time point during both exercise tests. Preexercise plasma CK, Mb, and FABP and exercise-induced increments are shown in Table 4. Preexercise plasma muscle protein levels did not differ between the baseline exercise test and the second exercise test in all three treatment groups. The plasma ratio Mb/FABP was more than 10 in all groups before and after both exercise tests (data not shown), which is in line with skeletal muscle as a source of these proteins.<sup>30-32</sup> After gemfibrozil treatment, postexercise increments of CK (8 hours postexercise) and FABP (1 and 8 hours postexercise) were significantly lower versus before therapy. In addition, after combination therapy, the 1-hour postexercise increment of Mb and the 8-hour postexercise increment of FABP were significantly lower versus before treatment.

**Table 2. Patient Characteristics in the Intervention Study (mean ± SD)**

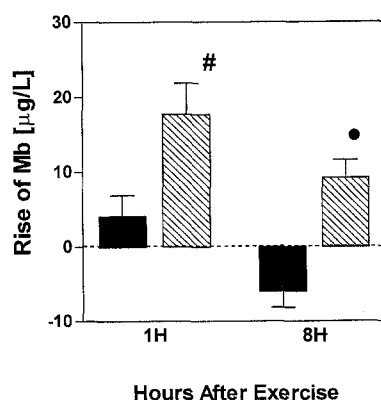
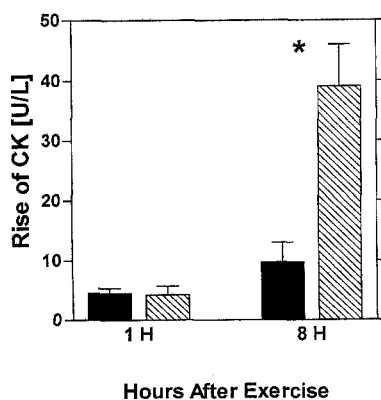
Characteristic	Fluvastatin	Gemfibrozil	Combination
Sex ratio (male/female)	3/4	3/3	3/4
Age (yr)	56 ± 8	50 ± 4	56 ± 2
Weight (kg)	77.6 ± 2.9	78.4 ± 4.9	80.3 ± 2.6
BMI (kg/m <sup>2</sup> )	27.3 ± 0.7	25.4 ± 0.4	26.9 ± 0.5

**Correlation between lipid parameters and muscle proteins.** No correlation was found between absolute plasma lipid levels (before or after treatment) and exercise-induced increments of muscle proteins. However, in the intervention study, significant correlations existed between therapy-induced changes in plasma triglyceride levels and changes in Mb increments (1 hour after exercise,  $r = .54$ ,  $P = .016$ ; 8 hours after exercise,  $r = .68$ ,  $P = .001$ ) and FABP increments 1 hour after exercise ( $r = .62$ ,  $P = .016$ ; Fig 1). A striking finding was that in 19 of 20 subjects who completed the intervention study, the direction (increase or decrease) of the therapy-induced change in triglycerides paralleled the direction of change in the 1-hour postexercise FABP increment (Fig 2). No correlations were observed between therapy-induced changes in total cholesterol, LDL cholesterol, or HDL cholesterol and changes in exercise-induced increments in muscle proteins.

#### DISCUSSION

The present study was performed to assess whether combined hyperlipidemia is associated with increased exercise-induced release of muscle proteins and whether lipid-lowering intervention has beneficial effects.

We found an indication for increased exercise-induced release of muscle proteins in subjects with combined hyperlipidemia compared with normolipidemic controls. Although the comparison of results between patients and controls should be performed carefully since it cannot be excluded that unknown selection factors may have played a role, special care was taken to exclude the influence of conditions that are known to affect exercise-induced muscle protein release. In the intervention study in both the gemfibrozil treatment group and the combination therapy group, the exercise-induced increments of muscle proteins were smaller as compared with pretreatment values. Although, theoretically, the decreased increments may result from decreased release or increased clearance of muscle



**Fig 1. Exercise-induced increments in plasma CK and Mb after standardized exercise in 10 male subjects with combined hyperlipidemia (hatched) and 15 normolipidemic male controls (solid).** Increases in CK 8 hours after exercise and Mb 1 and 8 hours after exercise differed significantly between patients and controls. \* $P = .0002$ , # $P = .006$ , • $P = .0003$ .

**Table 3. Lipid Profile (mmol/L) in 20 Subjects With Combined Hyperlipidemia Before and After 6 Weeks of Treatment With Fluvastatin 40 mg/d, Gemfibrozil 600 mg Twice Daily, or a Combination of Both (Intervention Study)**

Parameter	Fluvastatin (n = 7)	$\Delta\%$	Gemfibrozil (n = 6)	$\Delta\%$	Combination (n = 7)	$\Delta\%$
Baseline						
Cholesterol	8.4 $\pm$ 0.4		9.0 $\pm$ 0.8		8.3 $\pm$ 0.4	
LDLC	5.4 $\pm$ 0.4		6.3 $\pm$ 0.7		5.5 $\pm$ 0.4	
HDLC	1.1 $\pm$ 0.1		1.1 $\pm$ 0.1		1.2 $\pm$ 0.1	
TG	4.3 $\pm$ 0.7		3.9 $\pm$ 0.4		3.5 $\pm$ 0.7	
After treatment						
Cholesterol	6.5 $\pm$ 0.4*	-23	7.8 $\pm$ 0.5	-13	6.0 $\pm$ 0.5§	-28
LDLC	3.4 $\pm$ 0.3†	-37	5.4 $\pm$ 0.5	-14	3.9 $\pm$ 0.9	-29
HDLC	1.1 $\pm$ 0.1	0	1.3 $\pm$ 0.5	+18	1.3 $\pm$ 0.1	+8
TG	4.4 $\pm$ 1.1	+2	2.4 $\pm$ 0.3‡	-38	1.8 $\pm$ 0.3¶	-49

Abbreviations: LDLC, LDL cholesterol; HDLC, HDL cholesterol; TG, triglycerides.

\* $P = .009$ , † $P = .003$ , ‡ $P = .006$ , § $P = .034$ , || $P = .012$ , ¶ $P = .036$ :  $\nu$  corresponding baseline value.

proteins, the latter seems unlikely since it is known from the literature that neither lipid-lowering drugs as applied in this study nor hyperlipidemia itself affect kidney function in otherwise healthy patients. In addition, creatinine levels in the patient groups remained unchanged throughout the study. In one study,<sup>17</sup> hypercholesterolemia was associated with increased serum CK-MM and not CK-MBs, which makes an effect of hyperlipidemia on CK clearance unlikely. The decrease in the postexercise FABP increment during gemfibrozil was remarkable, since this agent is known to induce peroxisomes and hence to increase intracellular FABP levels.<sup>34</sup> If gemfibrozil therapy influenced plasma FABP levels directly, elevated rather than reduced FABP increments would be expected. Analysis of the therapy-induced changes in plasma lipid levels and postexercise muscle protein increments showed a highly significant correlation between improved plasma triglycerides and postexercise Mb and FABP increments. The correlation between these parameters was even stronger when the direction of the change (positive or negative) was considered: in all but one subject, the direction of the change in triglycerides paralleled the direction of change in the 1-hour postexercise FABP increment. In contrast, no correlation was found between changes in total or LDL cholesterol and changes in muscle proteins. This is in line with the observation that in the groups with the greatest reduction in triglycerides, ie, the gemfibrozil and combined treatment groups, favorable effects on postexercise increments of muscle proteins were found.

These results suggest that combined hyperlipidemia is associated with increased exercise-induced release of muscle proteins and that reducing triglyceride levels has a beneficial effect. As an explanation, it may be suggested that changes in triglyceride-carrying lipoproteins affect muscle membrane stability directly, explaining the reduced leakage of muscle proteins after exercise. This seems unlikely, because cholesterol and phospholipid composition determine cellular membrane stability, rather than plasma triglyceride and fatty acid concentrations. Moreover, the literature suggests a decrease in membrane stability associated with decreased lipid levels.<sup>35</sup> A direct beneficial effect of the pharmaceutical compounds on muscle is even more unlikely, as

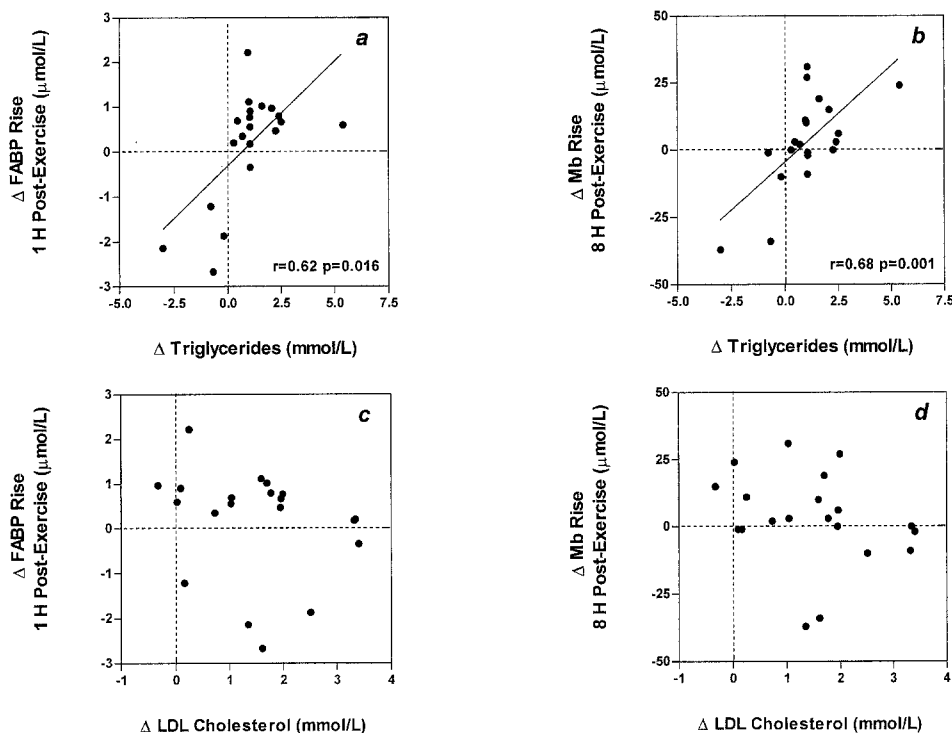
both HMG-CoA reductase inhibitors and fibrates have been associated with myopathy.<sup>10-15</sup> As another explanation, it may be hypothesized that triglyceride-lowering intervention may affect the metabolism of carbohydrates or fatty acids in skeletal muscle, thereby influencing the exercise endurance. However, no such effects were found in a study with gemfibrozil in humans<sup>36</sup> or a study with peroxisomal proliferators in rats.<sup>37</sup> A more suitable explanation for the observed reduction in the exercise-induced increment of muscle proteins is an improvement in muscle blood flow and, consequently, blood supply to skeletal muscle during triglyceride-lowering therapy. Improved peripheral vascular function has been demonstrated in hypertriglyceridemic subjects treated with fibrates.<sup>25</sup> Although we did not measure muscle blood flow directly, it has been demonstrated that plasma FABP is a sensitive parameter for ischemia-induced muscular damage.<sup>30-32</sup> Therefore, we believe improved muscle blood flow is a possible explanation for the beneficial effects on FABP and Mb release observed during triglyceride reduction. However, the exact mechanism of the relation between triglyceride and exercise-induced muscle protein lev-

**Table 4. Influence of Standardized Exercise on Plasma Levels of CK, Mb, and FABP in 20 Subjects With Combined Hyperlipidemia Before and After 6 Weeks of Treatment With Fluvastatin 40 mg/d, Gemfibrozil 600 mg Twice Daily, or a Combination of Both (Intervention Study)**

Parameter	Fluvastatin (n = 7)	Gemfibrozil (n = 6)	Combination (n = 7)
CK (U/L)			
First exercise test			
Preexercise	71.9 $\pm$ 7.6	74.5 $\pm$ 7.1	52.9 $\pm$ 4.3
$\Delta t = 1$ h	4.0 $\pm$ 2.2	2.7 $\pm$ 1.0	2.9 $\pm$ 1.5
$\Delta t = 8$ h	41.0 $\pm$ 12.0	43.3 $\pm$ 13.8	31.9 $\pm$ 8.2
Second exercise test			
Preexercise	71.6 $\pm$ 7.3	73.3 $\pm$ 11.0	45.1 $\pm$ 14.6
$\Delta t = 1$ h	5.1 $\pm$ 1.9	3.5 $\pm$ 3.0	8.0 $\pm$ 2.5
$\Delta t = 8$ h	46.3 $\pm$ 19.6	23.0 $\pm$ 6.9*	52.9 $\pm$ 24.8
Mb ( $\mu$ g/L)			
First exercise test			
Preexercise	30.1 $\pm$ 4.1	30.5 $\pm$ 3.3	23.2 $\pm$ 3.0
$\Delta t = 1$ h	17.0 $\pm$ 5.9	15.5 $\pm$ 4.7	12.3 $\pm$ 9.2
$\Delta t = 8$ h	5.1 $\pm$ 6.9	9.5 $\pm$ 4.7	7.29 $\pm$ 10.0
Second exercise test			
Preexercise	31.7 $\pm$ 2.9	30.5 $\pm$ 2.4	30.4 $\pm$ 7.3
$\Delta t = 1$ h	20.69 $\pm$ 8.6	11.7 $\pm$ 4.1	5.7 $\pm$ 3.1†
$\Delta t = 8$ h	13.3 $\pm$ 6.3	3.8 $\pm$ 3.9	-8.9 $\pm$ 15.9
FABP ( $\mu$ g/L)			
First exercise test			
Preexercise	2.46 $\pm$ 0.57	2.44 $\pm$ 0.65	2.16 $\pm$ 0.71
$\Delta t = 1$ h	0.78 $\pm$ 0.61	1.20 $\pm$ 0.93	0.81 $\pm$ 0.81
$\Delta t = 8$ h	0.73 $\pm$ 0.82	0.92 $\pm$ 0.86	0.27 $\pm$ 0.68
Second exercise test			
Preexercise	2.73 $\pm$ 1.02	2.96 $\pm$ 0.52	2.29 $\pm$ 0.90
$\Delta t = 1$ h	1.55 $\pm$ 1.16	0.21 $\pm$ 0.55*	1.02 $\pm$ 1.43
$\Delta t = 8$ h	0.53 $\pm$ 0.52	-0.01 $\pm$ 0.65†	0.15 $\pm$ 1.32‡

NOTE. First exercise test, before any treatment; second exercise test, after 6 weeks of treatment. For  $\Delta t = 1$  h, data on plasma CK levels are calculated as follows: 1 h postexercise minus preexercise CK level.

\* $P = .028$ , † $P = .043$ , ‡ $P = .046$ :  $\nu$  first exercise test.



**Fig 2.** Correlations between changes ( $\Delta$ ) in plasma triglycerides or LDL cholesterol and changes in exercise-induced increments of plasma muscle proteins (FABP 1 hour postexercise and Mb 8 hours postexercise) in 20 subjects with combined hyperlipidemia. The data reflect changes *v* baseline (before therapy) after 6 weeks of treatment with fluvastatin 40 mg/d, gemfibrozil 600 mg twice daily, or a combination of both.  $\Delta$ , baseline value minus value after therapy.

els remains to be elucidated. In addition, the question remains as to why changes in LDL cholesterol levels with fluvastatin appeared not to contribute to the improved postexercise muscle protein release. In this study, we found evidence for skeletal muscle pathology in untreated hypertriglyceridemia. As a consequence, the elevated muscle protein levels observed directly after starting therapy for combined hyperlipidemia may result from the disease rather than the therapy. However, we still advise monitoring patients on combination therapy for adverse effects. It appears from the literature that myopathy during therapy with HMG-CoA reductase inhibitors is associated with elevated systemic levels of these agents, which can occur in the case of hepatic or, multiple-organ failure or during concomitant therapy with agents that interfere with the hepatic clearance of HMG-CoA reductase inhibitors (eg, cyclosporin).<sup>38</sup> The mechanism of muscle toxicity by statins may be a direct toxic effect<sup>39</sup>

or perhaps represents a yet unknown interaction with a genetic muscle susceptibility. Gemfibrozil may induce myopathy, especially when renal function is impaired.

In conclusion, in this study, evidence has been found that combined hyperlipidemia is associated with increased release of muscle proteins after exercise and that decreasing triglyceride-carrying lipoproteins ameliorates the exercise endurance of skeletal muscle. The clinical significance of these observations remains to be proven. The decision on which therapy to use in the prevention of coronary heart disease should be based primarily on efficacy with regard to clinical relevant endpoints.

#### ACKNOWLEDGMENT

The authors gratefully acknowledge M. Pelsers for expert technical assistance.

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