

Effect of Exercise Training on Glucose Tolerance, In Vivo Insulin Sensitivity, Lipid and Lipoprotein Concentrations in Middle-Aged Men With Mild Hypertriglyceridemia

R.M. Lampman, J.T. Santinga, P.J. Savage, D.R. Bassett, C.R. Hydrick, J.D. Flora, Jr., and W.D. Block

The effects of 9 weeks of aerobic exercise training with maintenance of stable body weight upon insulin sensitivity and upon glucose, lipid, and lipoprotein concentrations were studied in 10 middle-aged men with mild hypertriglyceridemia. Following training, mean maximum oxygen consumption improved from 33.5 ± 1.9 to 39.3 ± 1.9 mL/kg/min ($\bar{x} \pm$ SEM), ($P < 0.01$). Glucose concentrations, both fasting and during oral glucose tolerance testing, remained stable but both fasting insulin concentrations and insulin responses to oral glucose decreased ($P < 0.1$ and < 0.01 , respectively). In vivo insulin sensitivity improved $25 \pm 6.1\%$ ($P < 0.01$) following training. Exercise training resulted in decreases in fasting serum triglyceride concentrations from 203 ± 12.6 to 126 ± 9.0 mg/dL ($P < 0.01$), primarily as a result of the reduction in VLDL-triglycerides ($P < 0.01$). The magnitude in percentage decrease of VLDL-triglycerides was found to be significantly correlated ($r = 0.71$, $P < 0.05$) with the magnitude in percent increase in max $\dot{V}O_2$. Serum cholesterol levels declined from 211 ± 8.9 to 193 ± 11.9 mg/dL ($P < 0.01$), and the ratio of HDL-cholesterol to total cholesterol was improved. This study demonstrates that exercise training at a level of intensity feasible for many middle-aged men has beneficial effects on several factors that have been associated with an increased risk of cardiovascular disease.

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PREVIOUS WORK from our laboratory has shown that physical training of middle-aged men with hyperlipidemia significantly lowers plasma triglyceride concentrations,¹⁻³ and reduces fasting insulin levels,² a simple measurement that has been shown to correlate with in vivo insulin sensitivity.⁴ Elevated concentrations of plasma triglycerides have been associated with abnormalities in glucose tolerance, increased plasma insulin concentrations, and in vivo resistance to insulin action.⁵⁻⁷ In addition, since increased triglyceride levels frequently are associated with increased low density lipoprotein (LDL) levels and reduced high density lipoprotein (HDL) cholesterol concentrations, hypertriglyceridemic patients are often at increased risk for the development of coronary heart disease.⁸⁻¹⁰ Since physical conditioning has major effects upon the metabolism of glucose and other metabolic fuels,¹¹ this study was conducted to assess the effects of moderate dynamic exercise training while weight was held steady upon glucose tolerance, insulin response to oral glucose, and in vivo insulin resistance, as well as upon levels of cholesterol, triglyceride, and lipoprotein fractions.

MATERIALS AND METHODS

Subjects

Ten sedentary, male subjects, aged 34 to 58 years ($\bar{x} \pm$ SD; 44.5 ± 2.61 years), with $\bar{x} \pm$ SD height of 179.3 ± 2.6 cm were selected from University of Michigan staff members known to have mild endogenous hypertriglyceridemia, defined as having fasting plasma triglyceride levels in excess of 150 mg/dL, and plasma cholesterol levels less than 260 mg/dL. All subjects gave written informed consent prior to participation in the study. None had acute or chronic infectious disease, or evidence of cardiovascular, respiratory, hepatic, or renal disease. All denied taking any medication known to alter glucose or lipid metabolism in the weeks preceding or during the time of the study.

Experimental Protocol

General

Upon entry into the study, a baseline fasting blood sample was obtained for measurement of glucose, insulin, lipid, and lipoprotein concentrations. A treadmill stress test, an oral glucose tolerance test, and an insulin sensitivity test were performed. Subjects then were started on a 9-week exercise program.³ The intensity of exercise prescribed was based upon the initial treadmill exercise test. Subjects returned to the hospital at three-week intervals throughout the study for weighing, dietary consultation, and measurement of fasting glucose, insulin, lipid, and lipoprotein concentrations. After completion of the 9-week program, the initial series of studies was repeated.

Biochemical Measurements

Blood for biochemical determinations was drawn into test tubes containing EDTA, the plasma immediately separated, and aliquots obtained for determinations of glucose,^{12,13} insulin,^{14,15} and lipid¹⁶⁻¹⁸ concentrations. Chylomicrons were removed¹⁶ from samples prior to lipoprotein determinations and the very low density lipoprotein (VLDL) then were separated by ultracentrifugation. In the infranate, the HDL and LDL were separated by precipitation of the latter by the heparin-manganese chloride method.¹⁷ Plasma chylomicrons, VLDL, total HDL + LDL, and HDL fractions subsequently were

From the Divisions of Cardiology, Endocrinology and Metabolism, and Hypertension, Department of Internal Medicine; the Clinical Research Center; and the Departments of Biostatistics and Community Health Programs, University of Michigan, Ann Arbor.

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Address reprint requests to Richard M. Lampman, PhD, Division of Cardiology, Department of Internal Medicine, University of Michigan Medical Center, 1405 East Ann Street, Ann Arbor, MI 48109.

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analyzed for cholesterol and triglyceride concentrations.¹⁸ LDL fraction values were obtained by subtraction of HDL levels from those of the total fraction of HDL + LDL.

Dietary Measures

Initially, a history of each subject's usual food intake was obtained by a dietitian using the dietary interview method. The dietitian then instructed each subject to continue his typical eating patterns and to maintain weight by slightly increasing (150–170 Kcal/d) his total caloric intake to compensate for the additional caloric expenditure due to exercise training. Success was monitored by having the subjects keep three-day food diaries that were reviewed at three-week intervals throughout the study. Data from these records were subsequently analyzed to assess the subject's caloric consumption, food composition, and compliance to dietary protocol.¹⁹

Progressive Treadmill Exercise Test and Exercise Training Prescription

The cardiovascular response during acute exercise of all subjects was measured on a treadmill as previously described.¹ Each subject was encouraged to walk to a termination point of subjective exhaustion. During the test, a bipolar C_M electrocardiogram was monitored, blood pressures were obtained by auscultation, and maximal oxygen uptake ($\text{Max } \dot{V}O_2$) was measured by indirect spirometry.²⁰ The data from the initial test were used to prescribe the desired work intensity (effort needed to attain 85% of maximal heart rate for each subject by jogging). Three 30–40-minute exercise sessions were scheduled each week over the 9-week period as previously described.³ With this training protocol, the subjects averaged between 9 to 12 miles of jogging per week.

Oral Glucose Tolerance Test (OGTT)

Subjects underwent a 3-hour oral glucose tolerance test (glucose = 1.75 gm/kg ideal body weight) after an overnight fast. In preparation for the test, all were instructed by the dietitian to follow an isocaloric diet with 50% of calories from carbohydrates for three days. Subjects were classified as having normal glucose tolerance on the basis of criteria from the National Diabetes Data Group.²¹

Insulin Sensitivity Test

Forty-eight hours following the OGTT and while still continuing on the isocaloric 50% carbohydrate diet, each subject underwent a test of in vivo insulin sensitivity according to the procedure described by Shen et al.²² This involves a continuous intravenous infusion of epinephrine (6 $\mu\text{g}/\text{min}$), propranolol (0.08 mg/min), glucose (6 mg/kg/min), and insulin (80 mU/min) for a period of 150 minutes, using a constant infusion pump. The plasma concentrations of insulin and glucose were measured every 10 minutes from 90 to 150 minutes on samples obtained from an indwelling needle placed in the opposite forearm. Since this technique produces similar insulin concentrations in all subjects, the average level of glucose maintained can be taken as an index of insulin sensitivity.²² Before, during, and for 15 minutes after this test, blood pressures were measured frequently and heart rate responses of the patients were monitored constantly.

Intervention and Final Assessment

After initial assessment, subjects initiated their exercise program and returned to the hospital at three-week intervals for interim and final assessments. At the three- and six-week visits, a blood sample was drawn (after a 12-hour fast and 48 hours after the last period of exercise) for determinations of glucose, insulin, and lipid concentrations. Body weight was measured to assure that stable weights were

being maintained and, if necessary, the dietitian made minor modifications in the diet plan. At the end of the 9-week intervention period, the initial series of tests was repeated.

Statistical Methods

Statistical analyses were performed using standard techniques.²³ Students' paired *t*-tests were employed on data obtained from the treadmill exercise and insulin sensitivity tests, while glucose and insulin values obtained during the oral glucose tolerance tests and fasting glucose, insulin, lipid, and lipoprotein concentrations were analyzed using a one-way repeated measures analysis of variance (ANOVA).^{24,25}

RESULTS

Measurement of Physical Fitness Level

Results (mean \pm SEM) of treadmill exercise testing to maximum tolerance are shown in Table 1. After the 9-week physical training program, the subjects increased both their aerobic capacities (33.5 ± 1.9 to 39.3 ± 1.9 mL/kg/min, $P < 0.01$) and total time walking on the treadmill prior to subjective exhaustion (22 ± 1.6 to 27 ± 1.7 minutes, $P < 0.01$), indicating an improved level of physical fitness. No change was found between baseline and final maximum exercise heart rate, systolic blood pressure, and rate pressure product values, indicating that equal cardiovascular stress was obtained during both stress tests.

Effects of Physical Training on Body Weight and Dietary Compliance

Stable body weights were maintained during the exercise training program (82.3 ± 4.3 kg initial, 81.2 ± 4.1 final, NS). Mean \pm SD body mass index [BMI = weight (kg)/height(M)²]²⁶ at baseline was 25.5 ± 1.0 . Ideal BMI was considered to be $22.5 \text{ kg}/\text{M}^2$. Relative body weight was calculated by dividing the subject's BMI by $22.5 \text{ kg}/\text{M}^2$. BMI values greater than 20% above ideal are considered obese²⁷; as a group, our subjects were not obese by this criterion. Subjects initially reported diets containing ($\bar{x} \pm \text{SD}$) 2487.6 ± 173.7 Kcal and having compositional mean values of 17.5% protein, 40.5% fat, 41% carbohydrate, and 1.0%

Table 1. Maximum Heart Rate, Systolic Blood Pressure, and Aerobic Capacity During Treadmill Exercise Stress Testing (Mean \pm SEM)

Measure	Baseline	Final (9 Weeks)
Maximum heart rate (beats/min)	187.0 \pm 2.4	185.0 \pm 2.6
Maximum systolic blood pressure (mmHg)	195.0 \pm 8.3	192.0 \pm 6.5
Maximum rate pressure product (heart rate \times systolic blood pressure \div 100)	365.0 \pm 17.9	357.0 \pm 14.7
Aerobic capacity (mL/kg/min)	33.5 \pm 1.9	39.3 \pm 1.9*
Total treadmill exercise stress time (minutes)	22.0 \pm 1.6	27.4 \pm 1.7*

*Significantly ($P < 0.01$) different from baseline value by paired *t*-test.

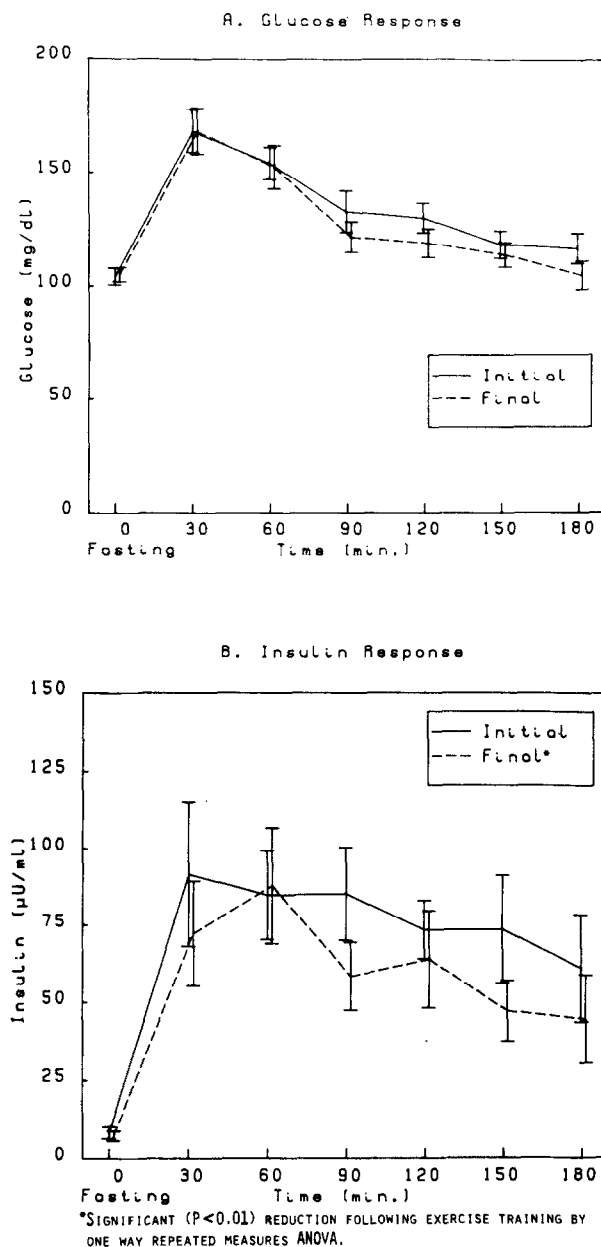


Fig 1. Glucose and insulin concentrations during initial and final oral glucose tolerance test (Mean \pm SEM).

ethanol. By dietary history, exercise energy expenditure was accompanied by a mean increase of 166 Kcal/d. No significant differences in dietary composition were observed throughout the study (data not presented).

Three-Hour Oral Glucose Tolerance Test

Plasma glucose and insulin responses for the oral glucose tolerance tests, both before and after physical training, are shown in Figure 1. Little change was observed in glucose concentrations between initial and final tests (NS). In contrast, a significant ($P < 0.01$) reduction was found in plasma insulin concentrations during the final oral glucose tolerance test.

Effects of Exercise Training on Metabolic Variables

Glucose and Insulin

Fasting plasma glucose and insulin concentrations, determined initially and at 3, 6, and 9 weeks, are shown in Table 2. No significant alteration was found in fasting glucose concentrations during exercise training. During the period of exercise training, however, fasting insulin concentrations declined somewhat ($P = 0.09$). A modest correlation of 0.44 (Spearman's rho), $P = 0.15$, was found between initial fasting plasma insulin and triglyceride concentrations. A weak association was found between fasting triglyceride levels and insulin levels ($r = 0.14$, NS) following an oral glucose challenge.

Lipids and Lipoproteins

Fasting plasma cholesterol, HDL-cholesterol and LDL-cholesterol, triglyceride, and VLDL-triglyceride concentrations and the ratio of HDL-cholesterol to total cholesterol, expressed as a % of total cholesterol, are shown in Table 3. Both total cholesterol and triglyceride concentrations decreased ($P < 0.01$) during the training program. A decrease in VLDL-cholesterol concentrations accounted for the majority of change seen in total cholesterol concentrations ($P < 0.01$). VLDL-triglyceride concentrations declined ($P < 0.01$), and these changes correlated with changes in total triglyceride levels ($r = 0.78$; $P < 0.01$). The major reduction in both total triglycerides and VLDL-triglycerides was observed at the end of the six weeks, and these decreased levels persisted to the final study period (Table 3). The magnitude in percent decrease of VLDL-triglycerides was found to be significantly correlated ($r = 0.71$, $P < 0.05$) with the magnitude in percent increase in maximum oxygen consumption (max $\dot{V}O_2$). While HDL-cholesterol concentrations were initially low at 37.6 ± 3.5 , the exercise intervention resulted in only a slight increase of 2.5 mg/dL

Table 2. Fasting Plasma Glucose and Insulin Concentrations (Mean \pm SEM)

Measure	Time Period			
	Initial	3 Weeks	6 Weeks	Final (9 Weeks)
Glucose (mg/dL)	106.7 \pm 2.7	107.1 \pm 2.6	103.2 \pm 1.9	102.6 \pm 3.4
Insulin (μ U/mL)*	13.2 \pm 1.3	9.9 \pm 1.1	10.3 \pm 1.7	10.2 \pm 1.2

*Reduction with respect to time by one-way repeated measures ANOVA ($P < 0.1$).

Table 3. Lipid and Lipoprotein Concentrations (Mean \pm SEM)

Lipid and Lipoprotein	Time Period			
	Initial	3 Weeks	6 Weeks	Final (9 Weeks)
Cholesterol* (mg/dL)	210.9 \pm 8.9	180.7 \pm 9.4	189.7 \pm 8.3	193.2 \pm 11.9
HDL-Cholesterol (mg/dL)	37.6 \pm 3.5	35.5 \pm 2.9	37.0 \pm 2.8	40.1 \pm 4.1
LDL-Cholesterol (mg/dL)	125.5 \pm 9.0	114.3 \pm 9.1	125.5 \pm 7.6	125.9 \pm 11.0
HDL-Cholesterol/total cholesterol \times 100 (%)	17.9 \pm 1.5	20.2 \pm 1.8	19.6 \pm 1.5	21.1 \pm 2.2
Triglycerides† (mg/dL)	202.8 \pm 12.6	133.8 \pm 13.6	128.1§ \pm 9.7	125.7‡ \pm 10.4
VLDL-Triglycerides† (mg/dL)	159.9 \pm 10.6	99.5 \pm 13.2	73.4§ \pm 9.9	87.9§ \pm 9.0

*Significant ($P < 0.05$) reduction during time of study by one-way repeated measures ANOVA.

†Significant ($P < 0.01$) reduction during time of study by one-way repeated measures ANOVA.

‡Significantly different from initial value ($P < 0.05$).

§Significantly different from initial value ($P < 0.01$).

(NS). The change in HDL-cholesterol/total cholesterol ratio, however, reached levels of borderline significance ($P = 0.06$).

Correlation analysis showed only a minimal inverse association between initial total triglyceride and HDL-cholesterol concentrations (Spearman's rho = -0.25 ; NS).

Plasma Glucose and Insulin Values During the Insulin Sensitivity Test

In vivo insulin resistance, as measured by mean glucose concentrations during the 90–150-minute period of the insulin sensitivity test, is shown in Figure 2. Following physical training, steady state plasma glucose levels decreased from 140 ± 11.7 to 104 ± 11.3 mg/dL ($P < 0.01$), indicating improved insulin

mediated glucose uptake. The steady state plasma insulin values did not change significantly (91.4 ± 16.5 μ U/mL and 88.1 ± 12.2 μ U/mL at baseline and final studies, respectively), indicating that the change in glucose levels was related to a change in tissue sensitivity to insulin.

No significant association was found in this study between insulin sensitivity and physical fitness levels as estimated by measurements of max $\dot{V}O_2$. At baseline measurements, the correlation between insulin sensitivity and max $\dot{V}O_2$ was 0.57 ($0.05 < P < 0.1$). Following exercise training, this correlation was 0.36, NS. When baseline and final values were considered together, neither the absolute nor the percentage change in max $\dot{V}O_2$ was correlated with the absolute or percentage change in insulin sensitivity ($r = 0.22$ and 0.06, NS, respectively). No significant association was found between absolute or percent change in max $\dot{V}O_2$ and other metabolic variables with the exception (see above) of VLDL-triglycerides and max $\dot{V}O_2$.

DISCUSSION

Results from this study are consistent with previous reports¹⁻³ from our laboratory showing that an exercise training program prescribed for relatively sedentary, mildly hyperlipidemic middle-aged men is a potent intervention for lowering plasma triglyceride concentrations. This training program involved an exercise effort of 85% maximum heart rate, with an average of between 9 to 12 miles of walking-jogging per week by the end of the 9-week study, and resulted in an increase in aerobic capacity of 17% at conclusion of the exercise program.

In some reports, a link has been suggested between increased peripheral tissue insulin resistance and endogenous hypertriglyceridemia.⁵⁻⁷ To investigate

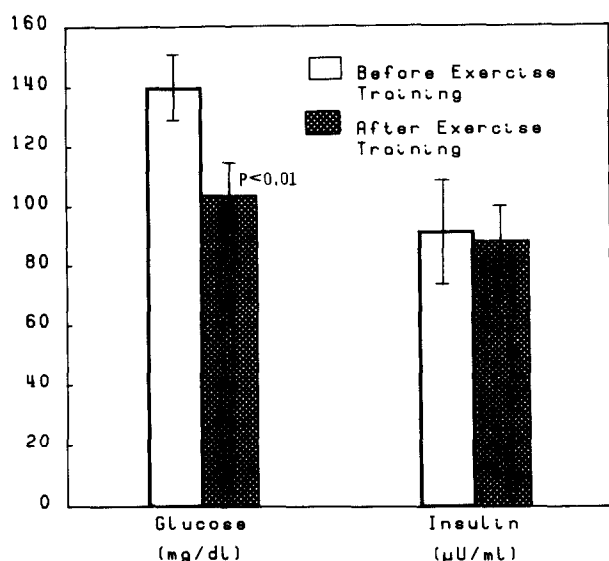


Fig 2. Initial and final plasma glucose and insulin levels during the in vivo insulin sensitivity tests (Mean \pm SEM).

this further, oral glucose tolerance tests and insulin sensitivity tests were administered at baseline and after the exercise program in order to provide an assessment of changes in in vivo resistance to both endogenous and exogenous insulin, respectively.

Insulin levels during the final oral glucose tolerance test were significantly decreased, and fasting plasma insulin measurements made over the 9-week training period tended to decline even though no significant changes were observed in oral glucose tolerance or in fasting glucose levels following exercise training. These interesting findings suggest enhanced sensitivity to endogenous insulin following exercise training. Similar results have been reported for patients of normal weight with Type II diabetes undergoing an exercise program.²⁸ However, these findings are not universal, since subjects having fasting hyperglycemia²⁹ or extreme obesity³⁰ do not show similar reduced insulin levels following oral glucose challenge. These conflicting findings suggest that exercise training may have differing effects on circulating insulin and insulin response to oral glucose tolerance, dependent on the degree of glucose impairment and/or obesity.

An important result of this study was that exercise training, without weight loss, resulted in a significant improvement in in vivo insulin sensitivity of these hypertriglyceridemic subjects as assessed by the insulin sensitivity test of Shen et al.²² Few studies exist that have directly measured in man the effect of exercise training on insulin resistance, and none until the current study have addressed this problem in hypertriglyceridemic patients. Results from one study showed improved insulin sensitivity in young, nondiabetic, athletic subjects participating in a very strenuous physical training program.³¹ Wallberg-Henriksson et al³² reported similar findings in young, nonobese Type I diabetics undergoing a more moderate training program. These reports, together with findings from the current study, suggested that exercise training is of benefit in altering insulin resistance, and may especially be helpful if hypertriglyceridemia is present.

Both Rosenthal et al³³ and Bogardus et al³⁴ recently have reported significant associations between measurements of insulin sensitivity using the euglycemic clamp technique³⁵ and estimates of fitness level as measured by max $\dot{V}O_2$ in cross-sectional studies. Since Greenfield et al³⁶ reported a high correlation between insulin sensitivity measurements during the steady state plasma glucose test and the euglycemic clamp technique ($r = 0.93$, $P < 0.001$), we looked for a relationship between measures of insulin sensitivity and max $\dot{V}O_2$ in our subjects. Although the correlation between these variables at baseline were similar to that reported in the above studies, the correlation declined

following exercise training and we found no evidence of an association between changes in insulin sensitivity and in max $\dot{V}O_2$ that occurred during our study.

Our data are consistent with those of Reaven et al,³⁷ showing that mild endogenous hypertriglyceridemia and some degree of insulin resistance can occur even in subjects who are not obese. Weight and diet were successfully maintained in the current study, so as to not have these factors as confounding variables. As found in this study and in previous reports from our laboratory,¹⁻³ exercise training alone is a potent factor in attenuating hypertriglyceridemia; the present report shows that the major reductions occur in the VLDL-triglyceride levels.

It is conceivable that the moderate degree of insulin resistance displayed by these hyperlipidemic individuals resulted in increased hepatic production of VLDL-triglyceride.⁵⁻⁷ Our results show that no simple relationship existed between insulin responses to oral glucose and basal triglyceride levels, or between insulin responses to oral glucose and basal triglyceride levels, or between insulin resistance and plasma triglyceride levels. This negative finding is probably due to the somewhat narrow distribution of plasma triglyceride levels seen in our patient population, and suggests that our selection criteria of patients exhibiting only slight impairments in glucose tolerance represented just a small segment in the continuous spectrum of endogenous hypertriglyceridemia. The mild hypertriglyceridemia seen in our patients may have been sustained and possibly even caused by tissue insulin resistance. Our finding of reduced fasting total triglyceride and VLDL-triglyceride levels in combination with improved insulin sensitivity and reduced insulin levels following exercise training supports this contention. Exercise training, having significantly reduced insulin resistance and decreased insulin levels, should lead to a decreased hepatic VLDL-triglyceride production, and decreased plasma VLDL-triglyceride concentrations.

Hypertriglyceridemia may also be associated with diminished clearance,^{38,39} or, in some subjects, a combination of both increased synthesis and reduced clearance of VLDL-triglycerides.⁴⁰ Our findings of reduced insulin response to oral glucose without deterioration of glucose tolerance following training suggest enhanced insulin action. This factor may have improved the ability of insulin to regulate the delipidation of VLDL-triglyceride; abnormalities in this process may be associated with hypertriglyceridemia.⁴¹ Consistent with this reasoning is the report of Nikkilä et al⁴² showing increased lipoprotein lipase activity in adipose tissue and skeletal muscle of athletes, a finding that they consider could account for the increased turnover rates of triglyceride-rich lipoproteins. Our

findings in this study are consistent with this view, since the major lipoprotein fraction influenced by exercise training was the very low density lipoproteins.

Results from the current study indicate that hypertriglyceridemic subjects have decreased concentrations of high density lipoprotein cholesterol, and confirm earlier work indicating an inverse association between high density lipoprotein cholesterol and total triglyceride concentrations.⁸ Although cholesterol concentrations significantly decreased with training, high density lipoprotein cholesterol levels only slightly increased. Since a threshold of approximately 8–10 miles of running per week for an extended training period appears necessary to beneficially alter low and high density lipoprotein concentrations,^{43,44} a physical training program longer than 9 weeks may prove even more beneficial for middle-aged men with hyperlipidemia.

This study demonstrates that moderate intensity exercise training that succeeded in significantly increasing aerobic capacity results in enhanced insulin-mediated glucose disposal, a marked decrease

in serum triglyceride and cholesterol concentrations, lower insulin response to oral glucose without change in glucose tolerance, and diminished fasting insulin levels in middle-aged subjects with mild endogenous hypertriglyceridemia. This exercise training regime with maintenance of stable weight was also effective in reducing very low density lipoprotein cholesterol and triglyceride concentrations, and favorably altered the ratio of high density lipoprotein cholesterol to total cholesterol. Although control studies would be necessary to fully quantify the changes attributed to exercise training alone, the numerous changes observed in this study strongly suggest that exercise training is an effective means for the clinical management of patients with endogenous hypertriglyceridemia, and may be a valuable adjunctive therapy to dietary management, especially where a reduction in weight is desirable.

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