Exercise Training, Without Weight Loss, Increases Insulin Sensitivity and Postheparin Plasma Lipase Activity in Previously Sedentary Adults

GLEN E. DUNCAN, PHD, RCEPSM[1]
MICHAEL G. PERRI, PHD[2]
DOUGLAS W. THERIAQUE, MS[3]
ALAN D. HUTSON, PHD[4]
ROBERT H. ECKEL, MD[5]
PETER W. STACPOOLE, PHD, MD[1,6]

OBJECTIVE — To determine the effects of exercise, without weight loss, on insulin sensitivity (S_I), postheparin plasma lipase activity (PHPL), intravenous fat clearance rate (K_2), and fasting lipids in sedentary adults.

RESEARCH DESIGN AND METHODS — At baseline and after 6 months of walk training (intensity 45–55 or 65–75% heart rate reserve, frequency 3–4 or 5–7 days/week, duration 30 min/session), anthropometric indexes, S_I, PHPL, K_2, and fasting lipids were measured in 18 sedentary adults (12 women, 6 men; 51.9 ± 5.8 years of age, BMI 28.9 ± 4.6 kg/m^2).

RESULTS — Exercise increased S_I (2.54 ± 2.74 vs. 4.41 ± 3.30 $\mu U \cdot ml^{-1} \cdot min^{-1}$, $P < 0.005$) and both lipoprotein lipase (LPL) (1,890 ± 1,380 vs. 4,926 ± 1,858 nEq free fatty acid [FFA] $\cdot ml^{-1} \cdot h^{-1}$) and hepatic lipase (HL) activities (3,326 ± 1,605 vs. 4,636 ± 1,636 nEq FFA $\cdot ml^{-1} \cdot h^{-1}$) (both $P < 0.001$), without altering BMI, waist circumference, K_2, or fasting lipids. Correlations between changes in LPL and the total:HDL cholesterol ratio ($r = -0.54$) and changes in the LPL:HL ratio and waist circumference ($r = -0.50$) were significant ($P < 0.05$).

CONCLUSIONS — Exercise, without weight loss, increases S_I and PHPL activity in previously sedentary adults, without changing K_2 or fasting lipid levels. Furthermore, increased LPL is associated with a decreased total:HDL ratio, and an increased LPL:HL ratio is associated with a decreased waist circumference. Therefore, even modest amounts of exercise in the absence of weight loss positively affect markers of glucose and fat metabolism in previously sedentary, middle-aged adults.

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Insulin resistance (IR) is defined as an inappropriately high level of insulin required to maintain metabolic homeostasis (1) and is characterized by diminished peripheral insulin sensitivity (S_I). Obesity and central body fat distribution are strong predictors of IR (2). Previous research demonstrates that weight loss through caloric restriction is associated with improvement in visceral adiposity, S_I, and lipid risk factors for coronary artery disease (3).

Physical inactivity also results in markedly decreased S_I (4). Several training studies (5–7) have demonstrated that regular aerobic exercise leads to enhanced S_I in previously sedentary adults. Improvements in S_I with training have been accompanied by significant reductions in body weight and body composition in some (5), but not all (6,7), of these studies.

In addition to the profound effects of enhanced insulin action on glucose homeostasis, S_I is an important independent determinant of the variation in free fatty acid (FFA) and triglyceride (TG) concentrations in adults (8). Exercise training is known to decrease TG concentrations (9,10) and has been shown to increase the intravenous fat clearance (K_2) of a TG emulsion (11,12). Enhanced K_2 (92% greater clearance rate) has also been reported for endurance athletes, compared with sedentary men, in a cross-sectional study (13).

One potential mechanism by which exercise enhances lipid metabolism is alteration of plasma lipase activity (i.e., lipoprotein lipase [LPL] and hepatic lipase [HL]). The activity of LPL is a key determinant in the rate of catabolism of TG-rich lipoproteins (14), and impaired function of LPL has been found in individuals with IR (15,16). Increased LPL is a common finding in several (10,11, 12,17), but not all (18), training studies. Furthermore, although LPL was only 2% higher, while K_2 was 92% higher, in endurance-trained athletes compared with sedentary subjects, there was a direct correlation between these parameters (13). Together, these studies suggest that insulin may be an important regulator of LPL and that increased K_2 may be at least partly explained by an increase in LPL activity. Some studies (18,19) have also reported significant training-induced decrements in HL. Whereas loss of intra-abdominal fat is associated with a reduc-

From the [1]Department of Medicine (Division of Endocrinology and Metabolism), University of Florida, Gainesville, Florida; the [2]Department of Clinical and Health Psychology, University of Florida, Gainesville, Florida; the [3]General Clinical Research Center, University of Florida, Gainesville, Florida; the [4]Department of Biostatistics, University of Florida, Gainesville, Florida; the [5]Department of Medicine (Division of Endocrinology, Metabolism and Diabetes), University of Colorado Health Sciences Center, Denver, Colorado; and the [6]Department of Biochemistry and Molecular Biology, University of Florida, Gainesville, Florida.

Address correspondence and reprint requests to Glen E. Duncan, PhD, $RCEP_{SM}$, Box 100226 JHMHSC, University of Florida, Gainesville, FL 32610-0226. E-mail: gduncan@ufl.edu.

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Abbreviations: GCRC, General Clinical Research Center; HL, hepatic lipase; IR, insulin resistance; K_2, intravenous fat clearance rate; LPL, lipoprotein lipase; PHPL, postheparin plasma lipase activity; S_I, insulin sensitivity; TG, triglyceride.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

See accompanying editorial, p. 944.

tion in HL and subsequent beneficial effects on lipid levels (3), there is no consistent pattern in documenting positive effects of exercise per se, in the absence of weight loss, on plasma lipase activity, K_2, and lipid levels.

To our knowledge, there are no investigations that have directly linked improvements in S_I to enhanced postheparin plasma lipase activity (PHPL), and subsequent improvements in lipid metabolism, while body weight is maintained in sedentary adults engaged in an exercise training program. Therefore, we tested the hypothesis that aerobic exercise training, without concomitant weight loss, significantly increases S_I in previously sedentary adults. We also postulated that the training-induced increase in S_I would enhance PHPL, and subsequently, K_2 and other markers of lipid metabolism.

RESEARCH DESIGN AND METHODS

Subjects

Sedentary adults (12 women, 6 men; 51.9 ± 5.8 years of age) were recruited (primarily through newspaper advertisement) for this 6-month training study. We excluded individuals who had known disease (e.g., heart disease and diabetes) or who engaged in structured physical activity on more than two occasions per week, each session lasting 30 min or more, over the previous 12 months. Participants who passed this initial screening were invited to attend an information session during which they completed demographic, health history, and two physical activity questionnaires to further establish that they were sedentary. Individuals interested in continuing their participation were scheduled for a series of medical evaluations that included standard tests of cardiac, endocrine, hematological, and metabolic function.

This study was conducted on the General Clinical Research Center (GCRC), Shands Hospital, at the University of Florida. Before testing, all participants provided written informed consent. For all testing requiring blood sampling, participants reported to the GCRC in the morning after an overnight fast. For all baseline assessments, participants were instructed to keep physical activity to a minimum on the day preceding the test. For all 6-month assessments, participants were studied 24–48 h after their last training session to minimize any acute exercise effects.

Measures

Anthropometric. BMI was calculated as an index of total body mass. Height was measured using a wall-mounted stadiometer and weight was measured using a balance-beam scale; both measurements were recorded with the patient's shoes removed. Waist circumference was measured at the narrowest part of the torso between the xiphoid process and the umbilicus with a spring-retractable tape measure and was used as an index of abdominal fat content.

Insulin sensitivity. An estimate of S_I was obtained from minimal model analysis of the frequently sampled intravenous glucose tolerance test (FSIVGTT) (20). An antecubital vein in each arm was cannulated for blood sampling and for glucose infusion, respectively. Baseline blood samples were obtained after a 10-min rest (after placement of the cannulas) for fasting insulin and glucose concentrations. A dextrose-saline solution (0.5 g dextrose/kg body wt) was infused over 3 min, and 14 blood samples were obtained over the subsequent 3 h at the following time points: 3, 6, 9, 12, 15, 20, 25, 30, 40, 50, 65, 80, 120, and 180 min. Whole blood was measured for glucose in duplicate on an automated analyzer (YSI, Yellow Springs, OH), and the average value was used for subsequent data analysis. Serum samples were measured for insulin using a standard double-antibody, competitive radioimmunoassay technique.

Plasma lipase activity. Lipolytic activity was measured in plasma 15 min after an intravenous injection of heparin (100 IU heparin sodium/kg body wt) (21). Briefly, PHPL assays were performed by addition of 0.05 ml plasma to 0.15 ml substrate. Two substrates were used for measurement of total lipolytic and HL activities in the same assay. For total lipolytic activity, the substrate was prepared with 10 mg triolein (Sigma, St. Louis, MO), 8 μCi [1-^{14}C]triolein (Amersham, Arlington Heights, IL), and 0.48 mg egg phosphatidylcholine (Calbiochem-Behring, La Jolla, CA). After drying under nitrogen, the contents were emulsified in a 4-ml mixture of 10% fatty acid–poor BSA (Miles, West Haven, CT), pooled normal human serum, 2 mol/l Tris Buffer (pH 8.2), and distilled H_20 (0.8:1.3:1.0:0.9) by 90 s of sonication (10 s on and 10 s off per cycle for nine cycles) with a sonicator (model XL-2020; Misonix, Farmingdale, NY) at 4°C. For HL, the substrate was altered by the addition of NaCl to a final concentration of 3.89 mol/l, and the final pH was adjusted to 8.6 with 2 mol/l Tris-HCl. Serum was omitted, and the substrate volume was maintained with distilled H_2O.

Aliquots of substrate (0.05 ml) were incubated for 90 min in a shaking water bath at 37°C. Postheparin plasma was diluted 1:25 in NaBarbital buffer (total lipase activity) or 1.37 mol/l NaCl in NaBarbital buffer (HL). Diluted plasma (0.15 ml) was added to the substrate, which was returned to a shaking water bath (37°C) for 90 min. The reaction was stopped with the fatty acid extraction method of Belfrage and Vaughn (22). The reaction vessels were shaken for 5 min on a shaker and centrifuged at 600*g* for 20 min. A 0.5-ml aliquot of the upper phase was removed and counted on a scintillation counter (model LS 6000 IC; Beckman-Coulter, Fullerton, CA).

For both total and HL activities, upper-phase fatty acid recoveries were determined with a standard solution of [1-^{14}C]oleic acid in the presence of substrate. The results were expressed in nanoequivalents of fatty acid released per hour per milliliter of postheparin plasma. LPL was the difference between total lipolytic and HL activity.

Intravenous fat tolerance and lipids. After collection of an initial blood sample to measure fasting TG, 10% Intralipid (Baxter-Travenol, Deerfield, IL), 1 ml/kg body wt, was infused intravenously over 1 min. Blood samples were collected every 5 min for 40 min for measurement of serum TG concentrations. The disappearance rate constant (K_2) was calculated as described previously (11–13).

Fasting serum was also collected on two of the test days for measurement of lipids (TG, total cholesterol, HDL cholesterol, and calculated LDL cholesterol [Friedewald equation]), and the average of values was used for data analysis. Both the lipid profile and measurement of serial TG levels (for K_2) were analyzed using standard enzymatic techniques.

Aerobic capacity. Graded treadmill exercise (Bruce protocol) was performed to volitional fatigue to measure $V_{O_{2max}}$ and maximal heart rate. Participants were required to meet two of three standard criteria for having achieved $V_{O_{2max}}$: heart

rate ≥ age-predicted maximum heart rate, respiratory exchange ratio ≥ 1.10, rating of perceived exertion ≥ 19. Pulmonary gas exchange variables were measured continuously using a metabolic cart (TrueMax 2400; ParvoMedics, Sandy, UT). Pulmonary ventilation (V_E – l · min^{-1}) was measured by a pneumotach that was calibrated daily, and fractions of O_2 and CO_2 were measured via analyzers that were calibrated with gases of known concentration before each test. Heart rate was measured by continuous 12-lead electrocardiography. Resting heart rate was the average of three seated measurements, performed and averaged over 2 different days.

Intervention

Participants were instructed not to change their diet or to attempt to alter their body weight during the course of the study. Each participant was instructed regarding recording the types and amounts of foods and beverages consumed, which were recorded on 2 different days during the week and weekend. Total caloric intake (kcal/day) and the percentage of total kcal from fat, carbohydrate, and protein were estimated from these 4-day food records before and after training. The data were analyzed using the Nutrition Data System, version 4.01 (Food and Nutrient Database 29; Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN). Any participant who experienced changes in weight during the study was counseled by a member of the investigative team to determine the cause of the weight loss (or gain) and to encourage maintenance of habitual dietary intake.

Each participant was assigned an individualized exercise prescription. The training program consisted of walking, prescribed at an intensity of either 45–55% (moderate intensity [M]) or 65–75% (high intensity [H]) of individual heart rate reserve (maximal heart rate – resting heart rate), and a frequency of either 3–4 (low frequency, L) or 5–7 (high frequency, H) days per week. Manipulation of intensity and frequency led to subject randomization to one of three possible groups (high intensity–high frequency [HH], high intensity–low frequency [HL], or moderate intensity–high frequency [MH]). There were no within-group or between-group differences with respect to S_I (primary outcome measure). Therefore, the data reflect all subjects combined, regardless of their group assignment.

Participants were required to walk within the individualized target heart rate zone for 30 min per day (either in a continuous bout or in up to three bouts, each at least 10 min in duration) for the prescribed number of days per week. Training could occur at home, at a work site, or both (i.e., lifestyle model of exercise training). Although participants were given flexibility in scheduling their exercise routines, the importance of achieving 30 min of exercise in the target heart rate zone on each training day was strongly emphasized. Participants wore a heart rate monitor (Polar Beat; Polar Electro, Port Washington, NY) during each training session to gauge exercise intensity and were instructed to record the most frequently observed heart rate during the exercise session in an exercise log (see below).

Participants were instructed in the use of daily training logs for self-monitoring of exercise, including duration (i.e., number of minutes) and intensity (i.e., average heart rate) of all bouts of walking of at least 10 min in duration. Because each bout of walking was recorded separately, the frequency of walking was also recorded. Adherence and compliance with the exercise prescription was fostered through continuous communication with a member of the investigative team (via telephone and e-mail) and by review of participant-completed training logs.

Statistical analysis

Two-tailed Student's *t* tests were used to evaluate whether the change (6 months − baseline) in a given parameter was significantly different from zero. A corrected $\alpha = 0.05/9 = 0.006$ was used to determine statistical significance in the primary and secondary outcome measures (S_I, LPL, HL, K_2, TG, total cholesterol, HDL cholesterol, LDL cholesterol, and total:HDL ratio). Two-tailed Student's *t* tests were also used to evaluate significant changes ($\alpha = 0.05/7 = 0.007$) in anthropometric (BMI and waist circumference), fitness ($V_{O_{2max}}$), and dietary intake measures (total kcal and percentage of total kcal from fat, carbohydrate, and protein). Pearson's product-moment correlation coefficient was used to examine significant relationships ($\alpha = 0.05$) among the outcome measures. Data are presented as mean ± SD. SAS statistical software (version 8; SAS Institute, Cary, NC) was used to perform the analyses.

RESULTS — There were no changes ($P > 0.07$) in BMI (28.9 ± 4.6 vs. 29.1 ± 4.6 kg/m^2), waist circumference (91.5 ± 12.5 vs. 90.8 ± 13.4 cm), $V_{O_{2max}}$ (25.2 ± 6.0 vs. 26.5 ± 7.2 ml · min^{-1} · kg^{-1}), or any of the dietary intake measures over the 6-month training period. The pre- and post-training values for the dietary measures were 1,889 ± 555 vs. 1,749 ± 629 kcal/day, 31.4 ± 8.7 vs. 34.6 ± 7.3% fat, 52.6 ± 10.1 vs. 49.9 ± 10.8% carbohydrate, and 14.8 ± 3.1 vs. 15.4 ± 2.7% protein.

Values for baseline, 6 months post–exercise training, and the change in each primary and secondary outcome measure are listed in Table 1. Exercise training significantly increased S_I ($P < 0.005$). Likewise, the activities of LPL and HL measured in postheparin plasma increased (both $P < 0.001$) with training. Although both LPL and HL increased significantly, LPL comprised a greater and HL comprised a lesser percentage of the total lipolytic activity after training (Fig. 1). We therefore examined the LPL:HL ratio before and after training and found that LPL:HL increased significantly after training (0.75 ± 0.60 vs. 1.15 ± 0.53, $P = 0.02$). Despite significant findings for S_I and PHPL, there was no change in either K_2 or fasting lipid levels with training.

As expected, changes in S_I and BMI were negatively correlated ($r = -0.48$, $P = 0.046$). Similarly, changes in LPL were negatively correlated with changes in both BMI ($r = -0.55$, $P = 0.02$) and waist circumference ($r = -0.51$, $P = 0.03$). Furthermore, changes in LPL and total:HDL ratio were negatively correlated ($r = -0.54$, $P = 0.02$). The change in waist circumference was also positively correlated with the change in both fasting TG ($r = 0.49$, $P = 0.04$) and total:HDL ratio ($r = 0.53$, $P = 0.02$) and negatively correlated with LPL:HL ratio ($r = -0.50$, $P = 0.04$). Similarly, changes in BMI and total:HDL ratio were both negatively correlated with changes in LPL:HL ratio ($r = -0.71$, $P = 0.001$ and $r = -0.51$, $P = 0.03$, respectively).

CONCLUSIONS — The major new finding from this study is that 6 months of aerobic exercise training in previously

Table 1—*Metabolic parameters before and after training in previously sedentary adults* (n = 18)

Variable	Baseline value	6-Month value	Change
S_I ($\mu U \cdot ml^{-1} \cdot min^{-1}$)	2.54 ± 2.74	4.41 ± 3.30	1.87 ± 2.45*
LPL nEq FFA $\cdot ml^{-1} \cdot h^{-1}$	1,890 ± 1,380	4,926 ± 1,858	3,035 ± 2,192*
HL nEq FFA $\cdot ml^{-1} \cdot h^{-1}$	3,326 ± 1,605	4,636 ± 1,636	1,310 ± 1,140*
K_2 (%/min)	3.37 ± 0.90	3.25 ± 0.90	−0.05 ± 0.84
TG (mg/dl)	123.3 ± 67.2	118.2 ± 64.7	−5.1 ± 22.9
Total cholesterol (mg/dl)	196.3 ± 41.2	186.5 ± 34.4	−9.8 ± 23.3
LDL cholesterol (mg/dl)	117.7 ± 31.9	110.2 ± 28.2	−7.4 ± 19.2
HDL cholesterol (mg/dl)	54.4 ± 8.8	52.6 ± 8.7	−1.8 ± 6.6
Total-to-HDL ratio	3.73 ± 1.00	3.72 ± 1.10	−0.02 ± 0.29

Data are means ± SD. *$P < 0.006$ for change from baseline to 6 months.

sedentary adults, in the absence of weight loss, increases both S_I and PHPL activity without concomitant changes in K_2 or fasting lipid levels. Therefore, our results are consistent with the concept (6,7) that regular aerobic exercise improves S_I, independent of changes in BMI.

Similar to the findings for S_I, we also found that the activities of both LPL and HL increased significantly with training in the absence of weight loss. Increased LPL is a common finding in several (10,11, 12,17), but not all (18), exercise training studies. In contrast to our results, others (18,19) have reported significant reductions in HL with training. Although HL activity did not decrease, the proportion of LPL and HL comprising the total lipolytic activity was altered with training (Fig. 1). Consistent with these changes, we found that the LPL:HL increased significantly after training. Therefore, although HL activity did not decrease, LPL comprised a greater and HL comprised a lesser percentage of the total lipase activity after training. This, in turn, may favor a less atherogenic lipoprotein profile (18).

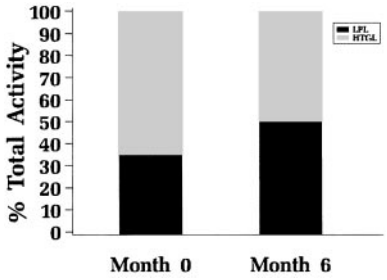

Figure 1—*Relative percentages of LPL (dark bars) and HL (light bars) comprising the total PHPL activity before and after 6 months of exercise training in 18 sedentary adults. The LPL:HL ratio increased significantly after training (0.75 ± 0.60 vs. 1.15 ± 0.53,* P = *0.02).*

Despite significant increases in S_I and PHPL activity, neither dynamic (K_2) nor static (fasting lipids) measures of lipid metabolism were affected by training. This suggests that exercise-induced increases in S_I and PHPL do not necessarily translate into measurable alterations in lipid metabolism. In contrast to our results, previous training studies have reported decreased fasting TG concentrations (9,10), increased HDL cholesterol levels (11,12,18), and increased K_2 (11,12) with exercise. All but one (18) of these studies was designed to maintain body weight throughout the training program. Therefore, the fact that our participants did not undergo changes in total body mass (BMI) or abdominal fat content (waist circumference) can be ruled out as the reason why changes in lipid metabolism did not occur with training. There are, however, several possible explanations for this discrepancy.

First, $V_{O_{2max}}$ did not increase, which is likely due to the large variation in the response to training measured in our participants. This is in contrast to other studies that demonstrated favorable changes in lipid levels coupled with improvements in fitness (9–13,18). Therefore, it is possible that more vigorous exercise training, which results in greater energy expenditure, is required to significantly impact circulating lipids. Second, previous studies (9–13) showing favorable changes in lipid metabolism in the absence of weight loss were conducted in relatively lean men only. Therefore, it is possible that overweight and/or obese subjects require weight loss, in addition to improvements in fitness, to favorably improve lipid levels. This is supported by Despres et al. (18), who reported favorable improvements in fitness and in carbohydrate (decreased insulinogenic index) and lipid metabolism (decreased total and LDL cholesterol, increased HDL cholesterol, decreased HL activity) in obese premenopausal women trained for 14 months. However, this regimen also resulted in significant reductions in fat mass (~4.6 kg) and abdominal adipose tissue content. Reductions in fat mass and abdominal fat, but not $V_{O_{2max}}$, correlated with favorable changes in the metabolic responses, suggesting that changes in adiposity are more important correlates of training-induced changes in carbohydrate and lipid metabolism than changes in fitness (18). Our study cohort comprised primarily postmenopausal, overweight women, and the exercise program failed to change both fitness and anthropometric indexes. Finally, changes in lipid metabolism with training may be dependent on sex, but our study was not powered to examine differences in the exercise response between women and men.

When correlational analyses were performed, the major finding was that changes in LPL activity and total:HDL ratio were inversely related. Because LPL increased more than HL with training, we also examined correlations among changes in LPL:HL ratio and the various outcome measures. By doing so, we found that BMI, waist circumference, and total:HDL ratio were all correlated inversely with LPL:HL ratio. Together, these results are consistent with the notion that increased LPL and decreased HL are related to a more favorable lipoprotein profile. For example, high postheparin HL activ-

ity has been associated with low HDL cholesterol levels (23), and significant training-induced decrements in HL are related to decreased TG levels and increased HDL cholesterol (18,19). Furthermore, increased LPL and decreased HL are believed to contribute to the increase in HDL cholesterol with exercise (24). Finally, the finding that the change in waist circumference is inversely related to the change in LPL:HL ratio demonstrates that greater abdominal fat is associated with reduced LPL and increased HL activity (i.e., a decreased LPL:HL ratio). This is consistent with a previous report in which HL activity was positively correlated with visceral abdominal fat in obese women (25), and a previous report in which changes in intra-abdominal fat and changes in HL activity were linearly related in men undergoing diet-induced weight loss (3).

We were, however, surprised at the lack of association between changes in S_I and LPL, and LPL and K_2. With respect to S_I and LPL, impaired function of LPL has been found in individuals with IR (15,16). However, the study by Reynisdottir et al. (15) examined adipose tissue–specific LPL and HL activities only. Because LPL activity measured in postheparin plasma reflects all heparin-releasable pools, the lack of association between S_I and LPL in our study may be a function of differences in insulin's regulation of LPL in adipose tissue compared with muscle. Interestingly, another study (26) demonstrated that HL activity correlated negatively with S_I and positively with fasting insulin, but not with LPL activity, in a group of men with type 2 diabetes. Similarly, Purnell et al. (3) found that an improvement in S_I correlated with a decrease in HL activity in men undergoing diet-induced weight loss. Consistent with these findings, we found that increased S_I tended to correlate with a decrease in HL activity, although this did not reach statistical significance ($r = -0.42$, $P = 0.08$).

With respect to relationships between LPL and TG or K_2, exercise significantly increases both K_2 and postheparin LPL activity in men (11,12). However, TG and K_2 were not altered in our study, despite significant improvements in LPL activity. The lack of association between these parameters may be because neither $V_{O_{2max}}$ nor anthropometric indexes changed with training. Furthermore, increased K_2 can only be partly explained by an increase in LPL activity (13). Therefore, it is likely that factors other than LPL activity influence K_2, including sex, fitness, and level of adiposity.

In conclusion, our results demonstrate that 6 months of exercise training, in the absence of weight loss, increases S_I and PHPL activity in previously sedentary adults, without concomitant changes in K_2 or fasting lipid levels. Although a potential limitation of the present study is that the exercise sessions were not monitored, the large increase in S_I (~1.74-fold) measured in our subjects demonstrates that the lifestyle training model results in important health benefits in previously sedentary adults. Furthermore, increased LPL activity is associated with a decreased total:HDL ratio, and an increased LPL:HL ratio is associated with a decreased waist circumference. Therefore, even modest amounts of exercise in the absence of weight or abdominal fat loss improves markers of glucose and fat metabolism in previously sedentary, middle-aged adults, a group particularly at risk for type 2 diabetes.

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