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Effects of Exercise and Lifestyle Modification on Fitness, Insulin Resistance, Skeletal Muscle Oxidative Phosphorylation, and Intramyocellular Lipid Content in Obese Children and Adolescents

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Abstract

Background—Obesity is associated with poor fitness and adverse metabolic consequences in children.

Objective—To investigate how exercise and lifestyle modification may improve fitness and insulin sensitivity in this population.

Design and Subjects—RCT, 21 obese (BMI ≥ 95%ile) subjects, ages 10 to 17 years.

Methods—Subjects were given standardized healthful lifestyle advice for 8 weeks. In addition, they were randomized to an in-home supervised exercise intervention (n = 10) or control group (n=11).

Measurements—Fasting laboratory studies (insulin, glucose, lipid profile) and assessments of fitness, body composition, skeletal muscle oxidative phosphorylation and intramyocellular lipid content (IMCL), were performed at baseline and study completion.

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CONFLICT OF INTEREST STATEMENT
The authors have no conflicts of interest to disclose.

Results—Subjects were 13.0 ± 1.9 (SD) years old, 72% female, and 44% non-white. Exercise improved fitness (p = 0.03) and power (p = 0.01), and increased IMCL (p = 0.02). HOMA-IR decreased among all subjects in response to lifestyle modification advice (p = 0.01), regardless of exercise training assignment. In univariate analysis over all subjects, change in cardiovascular fitness was associated with change in HOMA-IR. In exploratory analyses, increased IMCL was associated with greater resting energy expenditure (r = 0.78, p = 0.005) and a decrease in fasting RQ (r = −0.70, p = 0.02) (n=11).

Conclusions—Change in fitness was found to be related to change in insulin resistance in response to lifestyle modification and exercise in obese children. IMCL increased with exercise in these obese children, which may reflect greater muscle lipid oxidative capacity.

Keywords

fitness; insulin resistance; pediatric obesity; mitochondrial function; IMCL

BACKGROUND

The global burden of type 2 diabetes is increasing[1] and its antecedents (obesity, insulin resistance, and beta-cell dysfunction) are becoming more prevalent in children and adolescents.[2] As a result, the need for rational and effective prevention strategies is acute.[3]

Epidemiologic studies support the role of cardiovascular fitness in preventing some of the adverse metabolic consequences of obesity[4, 5], and suggest that lifestyle modification programs that include exercise can promote health.[6, 7] Despite substantial evidence of its salutary effects, how exercise achieves these results remains incompletely understood.

Among adult patients with type 2 diabetes,[8] reduced mitochondrial size, number, and function are observed. One useful effect of exercise may be to increase mitochondrial number and size, which may account for improved function as well as insulin sensitivity with an intervention. However, mitochondrial function may not be the primary mediator of this effect; decreased fatty acid mobilization may also play a role.[9] Increased lipid availability in skeletal muscle, manifest in endurance athletes as higher concentrations of IMCL, may in turn increase availability of lipid for oxidation during exercise.[10]

The aim of the current study was to investigate the metabolic effects of a randomized trial of healthful lifestyle advice with or without an 8-week in-home intensive exercise intervention in obese children and adolescents. Specifically, we sought to investigate: 1) The effects of lifestyle intervention with or without exercise training on fasting insulin resistance, as reflected in HOMA-IR. We hypothesized that insulin resistance would improve to a greater extent (reflected in a fall in HOMA-IR) when exercise training was added to lifestyle modification. 2) Candidate mediators of change in an index of mitochondrial function (change in HOMA-IR, change in fitness) in response to lifestyle modification with or without exercise training. We hypothesized that both improvement in HOMA-IR and better fitness would result in improved mitochondrial function. 3) Other metabolic effects (IMCL, REE) of exercise training in exploratory analyses. Specifically, we hypothesized that IMCL

would rise in proportion to greater endurance capacity with exercise training, and REE would be greater as compared to lifestyle modification alone.

METHODS

Subjects

Subjects were recruited by local advertisements, pediatricians in the community, and the obesity programs at MGH and Children's Hospital Boston from October 2009 through June 2011. Participants were ages 10 to 17 years, inclusive, with BMIs greater than or equal to the 95th percentile for age and sex.[11] Inclusion criteria were: insulin resistance (fasting insulin > 12 uIU/mL, chosen to permit inclusion of subjects with mild insulin resistance throughout pubertal development), and relatively reduced mitochondrial function, as characterized by ATP recovery by ^{31}P spectroscopy greater than the median value defined in a prior control cohort.[12] Exclusion criteria were: inability to have an MRI, high level of physical activity (greater than the training regimen), and any underlying medical condition or medication potentially affecting growth, pubertal development, or glucose homeostasis. Three subjects were eligible and randomized but did not complete the initial baseline evaluation visits. Therefore, results are reported for the 18 subjects who completed the baseline assessment.

The study was approved by the Partners Institutional Review Board. Written informed parental consent and participant assent were obtained from all participants. The investigation was conducted according to the principles of the Declaration of Helsinki and registered with ClinicalTrials.gov, NCT00962806.

Evaluation

At baseline, subjects underwent a comprehensive evaluation including medical and family histories, physical examination, and Tanner staging by a pediatric endocrinologist (A.F., S.M.). Vital signs, including blood pressure by oscillometry, were performed at the initial and final study visits. Blood pressure Z-scores were calculated for age, sex, and height according to published standards.[13]

Physical fitness and habitual physical activity

Standardized incremental exercise testing using a stationary cycle ergometer (University of Massachusetts, Boston: Ergoline 800, SensorMedics; Yorba Linda CA or MGH: Ergoselect 200, Ergoline; Bitz, Germany) was performed to determine the cardiorespiratory fitness of each participant at baseline and following the 8-week study. Heart rate was monitored continuously using a Polar heart rate monitor (Kempele, Finland) with subjects wearing a telemetry-style chest belt. Expired gas exchange was measured by open-circuit spirometry (University of Massachusetts, Boston: CosMed K4 system; Rome Italy or MGH: Vmax Encore 29, SensorMedics; Yorba Linda CA). Exercise testing was considered complete after either of the following criteria was met: 1) subjects reached a consistent respiratory exchange ratio (RER) of greater than or equal to 1.0 or 2) subjective fatigue prevented subjects from maintaining the prescribed pedaling cadence. A conservative RER threshold of 1.0 has been used successfully for determination of fitness in pediatric studies. [14] For the

initial fitness test, seventy-two percent of subjects achieved an RER of at least 1.0 (the balance stopped testing on the basis of subjective fatigue); 83% of the subjects achieved the RER threshold during the final fitness test.

Self-reported levels of physical activity were assessed with pediatric-specific modifications made to the Modifiable Activity Questionnaire.[15]

Dietary intake

Three-day food records were collected at baseline and at the conclusion of the 8-week study. These were reviewed by nutrition staff with analysis by Nutrition Data Systems, Minneapolis, MN.

Resting energy expenditure (REE) and respiratory quotient (RQ)

Fasting REE and RQ were measured using indirect calorimetry (Vmax Encore 29, SensorMedics; Yorba Linda CA).

Anthropometric measurements and body composition

Anthropometric measurements were performed by nutrition staff at baseline and end of study. BMI Z-scores for age and sex were determined using the CDC 2000 growth charts.[11] Dual-energy x-ray absorptiometry (Discovery A Bone Densitometer, Hologic; Bedford MA) was used to determine the whole body and regional lean mass and fat mass.

^{31}P magnetic resonance spectroscopy (MRS)

^{31}P MRS was used to estimate time to phosphocreatine (PCr) recovery after an exercise protocol at baseline and final visits. This procedure was performed as described previously[12] in the late afternoon and subjects were instructed to refrain from caffeine and vigorous physical exercise on the day of the measurement. Measurement of PCr recovery provides a non-invasive assessment of skeletal muscle oxidative phosphorylation; prolonged time to PCr recovery implies relatively decreased mitochondrial oxidative capacity.[16,17] This technique has been utilized in healthy controls for assessment of mitochondrial ATP production and mitochondrial function *in vivo* with good intra-subject reliability of 7.5% (*personal communication*).

^{1}H spectroscopy

^{1}H-MRS was performed using a 3.0 Tesla (Siemens Trio; Siemens Medical Systems, Erlangen, Germany) MRI system. IMCL in the leg (tibialis anterior) was assessed as previously described.[18] IMCL data were obtained in the subset of subjects who were able to attend additional scanning sessions.

Insulin sensitivity

Fasting laboratory testing was performed during mid-morning for all subjects. Glucose and insulin values were obtained at baseline under fasting conditions and every 30 minutes for 120 minutes after a 1.75 g/kg (up to a maximum of 75 g) oral glucose load. Homeostasis model assessment for insulin resistance (HOMA-IR) was calculated for each participant.[19]

Laboratory studies

Serum insulin was measured using Access Chemluminescent Immunoassay (Beckman Coulter, Fullerton CA) with a dynamic range of 0.03 – 300 uIU/mL; non-parametric estimate of 95% confidence interval was 1.9 – 23. Total imprecision is less than 10%. Serum glucose, lipids, and chemistries were measured using standard methodologies in the medical laboratories of MGH.

Intervention

All participants received standardized weekly lifestyle modification messages designed to encourage healthful habits. Subjects were randomized in a 1:1 ratio to intensive exercise training or control groups stratified for sex and pubertal stage. Children randomized to the exercise training group received three training sessions per week for 8 weeks. All sessions were monitored in-person by a study staff member in the subjects' homes. Subjects performed 20 minutes of aerobic training on a stationary bicycle with exer-gaming capacity (GB300S/L, GameBike Fitness, Dallas TX) at 60% – 80% of heart rate reserve as determined by initial exercise testing for up to 35 minutes per session.[20] Heart rate was monitored continuously using a Polar heart rate monitor (Kempele, Finland) with subjects wearing a telemetry-style chest belt. To determine adherence to the prescribed exercise regimen, heart rate was recorded at the end of each minute during each exercise training session. In addition, subjects chose combinations of stretching and resistance training exercises from those available on the Wii Fit (Nintendo Company Limited, Kyoto Japan) for up to 25 minutes per session.

Statistical analysis

Descriptive statistics were calculated for all subjects and by randomization group. Fitness (peak VO_2 during cycle ergometer testing) was allometrically adjusted for lean body mass; an exponent of 0.75 has been proposed previously and was consistent with our data.[21] T-tests or Chi-squared analyses, as appropriate, were used to check for differences in baseline characteristics between the randomization groups. Multivariate repeated measures analysis was used to identify the effects of randomization group (exercise or control), time (pre- or post-study), and the interaction between group and time on the outcome variables of interest. Parametric (Pearson's) or non-parametric (Spearman's) correlation analyses, as appropriate, were performed to investigate the relationships between changes in continuous outcome variables of interest. Univariate analyses for potentially relevant covariates on outcomes of interest were performed. Statistical analyses were performed using JMP software (Version 9, SAS Institute, Inc., Cary, NC). Two-tailed p-values less than 0.05 were considered statistically significant.

Sample Size Calculations

Prior studies in overweight children and adolescents indicate a standard deviation of HOMA-IR ranging from 1.8 to 2.5.[7, 12,14] Studies suggest that maximal treatment effect of lifestyle intervention is a change in HOMA-IR of 2.4.[22] Thus, for HOMA-IR, a parallel design study with 20 subjects (10 subjects/group) has an 80% probability of detecting a treatment effect HOMA-IR of 2.4, assuming an SD of 1.8, with two-sided p value of 0.05.[23]

For τPCr, a marker of mitochondrial function and other endpoints, including fitness, the study provides 80% power to detect a difference of 1.35 SD between treatment groups, based on enrollment of 20 subjects (10 patients/group). HOMA-IR was pre-specified as the primary indicator of fasting insulin resistance that was used for study entry, and has been shown to be associated with τPCr tau, the index of mitochondrial function, in previous studies of obese children.[12]

RESULTS

Subject characteristics

Baseline demographic, anthropometric, clinical, laboratory, fitness, and ^{31}P and ^{1}H MRS characteristics are shown in Table 1. Subjects were an average of 13.0 (± 1.9, SD) years old, 72% female, and racially and ethnically diverse. As noted previously, three subjects were eligible and randomized but did not complete the initial baseline evaluation visits. Subjects had poor initial cardiovascular fitness, as indicated by low peak VO_2 on cycle ergometer testing and were insulin resistant, with a mean HOMA-IR of 5.95 (± 3.47). Despite this, none had diabetes mellitus or impaired fasting glucose, and only 3 (17%) had impaired glucose tolerance by oral glucose tolerance test. Baseline skeletal muscle oxidative phosphorylation capacity, as assessed by ^{31}P MRS, and intramyocellular lipid content (IMCL) were similar in both randomization groups. No statistically significant differences were identified in clinical characteristics between these groups.

Effects of study interventions

Table 2 shows the effects of the lifestyle modification messages (in all subjects) and supervised physical activity (in the exercise training group) on the outcome variables of interest.

Cardiovascular fitness, maximal power, and strength—There was an effect of intervention group (time × group effect), such that peak VO_2, adjusted for lean body mass (5 [95% CI, −11 – 20] versus −18 [−33 – −3] ml/kg$^{3/4}$ lean body mass/minute, p=0.03), as well as maximal power generated during exercise testing (32 [−3 – 67] versus −20 [−−30 – −10] Watts, p=0.01) improved in the exercise group relative to control.

Adherence to in-home exercise regimen—Subjects in the exercise group underwent an average of 21 (95% CI, 18 – 23) out of a possible 24 supervised training sessions each. They remained in or above the prescribed target heart range for an average of 81% of the minutes (95% CI, 65% – 97%) of supervised training. A higher proportion of time spent in or above the prescribed target heart range was associated with greater fitness gains, as measured by change in peak VO_2 adjusted for lean body mass (Spearman's Rho, 0.66, p=0.04).

Metabolic Effects—There was an overall benefit of study participation among all subjects (lifestyle modification messages with or without additional supervised exercise training) on fasting insulin (p = 0.01) and HOMA-IR (p = 0.01). On average, HOMA-IR decreased 2.43 in the exercise group and 1.21 in the control group, but the effect of group assignment did

not reach statistical significance. In all subjects, change in cardiovascular fitness was significantly and positively associated with change in insulin sensitivity, as reflected by a drop in HOMA-IR ($r = -0.64$, $p = 0.004$), as shown in Figure 1. There were no statistically significant effects of group assignment or overall study participation on glycemia, blood pressure, or lipid profile.

Body weight and composition—Height ($p = 0.002$) and body weight ($p = 0.03$) increased over the course of the study for all participants, regardless of group assignment. In the exercise group, better adherence to the training regimen (more time spent in the target heart rate range) was correlated with favorable change in weight (less weight gain or more weight loss, $r = -0.65$, $p = 0.04$).

Energy intake and expenditure—There was a trend toward preserved resting energy expenditure, adjusted for body weight, in the exercise group ($p = 0.07$ for the effect of group). Among all subjects, change in absolute resting energy expenditure was not related to change in fitness, but was positively associated with gain in lean mass ($r = 0.60$, $p = 0.01$), and negatively associated with change in fat mass ($r = -0.57$, $p = 0.02$), and percentage of body fat ($r = -0.72$, $p = 0.002$). There was a trend ($p = 0.05$) towards decreased self-reported daily caloric intake over both groups.

Skeletal muscle oxidative phosphorylation—An index of skeletal muscle oxidative phosphorylation, τPCr, tended to improve for all study participants ($p = 0.05$); there was no discernible effect of treatment group assignment ($p = 0.50$).

IMCL—A subset (11 of 18, six exercise and five control subjects) had IMCL measurements performed and exploratory analyses are presented. Subjects in the exercise group had an average increase in IMCL of 15% over the course of the study, and in the control group, a decrease of 22% was observed; the effect of randomization group was statistically significant with $p = 0.02$. In exercising subjects, more time spent in or above the prescribed heart rate training range was associated with a greater rise in IMCL (Spearman's Rho 0.89, $p = 0.02$, $n = 6$). In all subjects, an increase in IMCL was related to a rise in cardiovascular fitness, expressed as peak VO_2 (ml/min) ($r = 0.60$, $p = 0.0498$) and resting energy expenditure (kcal/day) ($r = 0.78$, $p = 0.005$), and a decrease in fasting RQ ($r = -0.70$, $p = 0.02$, see Figure 2).

Univariate analyses of change in insulin resistance (HOMA-IR)—In all subjects, change in HOMA-IR was related to change in cardiovascular fitness ($r = -0.64$, $p = 0.004$). We did not identify a relationship between change in HOMA-IR and change in skeletal muscle oxidative phosphorylation ($r = -0.22$, $p = 0.38$).

DISCUSSION

This randomized controlled trial in obese children and adolescents demonstrated that an 8-week, in-home lifestyle modification program with intensive exercise training using modern exer-gaming equipment was successful in ensuring compliance and improving cardiovascular fitness, peak power and resting energy expenditure. All subjects received

lifestyle modification counseling, and all participants improved HOMA-IR regardless of whether they also received in-home exercise. Fitness-related changes in insulin resistance appeared to be independent of changes in weight, and not related to mitochondrial function. We noted a training-related rise in IMCL in proportion to exercise capacity that was associated with increased resting energy expenditure and lower respiratory quotient, suggestive of greater lipid oxidation.

Our results suggest that lifestyle modification recommendations in high-risk obese children and adolescents can improve insulin resistance as estimated by HOMA-IR. Prior studies demonstrate that judiciously timed reinforcement of these lifestyle changes can alter the typical trajectory of pediatric diet-induced obesity for some patients.[24] We demonstrated a clinically relevant improvement of 27% in HOMA-IR in response to lifestyle modification alone after 8 weeks. In the combined lifestyle modification and exercise group, the improvement in HOMA-IR was 34%, suggesting that exercise could add to this effect. This physiologic study, focused on elucidating the mechanism underlying exercise-related improvements in insulin sensitivity, complements a growing body of evidence that, with sufficient training intensity and monitoring, physical activity alone can be an effective intervention in children and adolescents at increased risk of diabetes.[25] Larger studies will be necessary to definitively determine the effects of exercise added to lifestyle modification advice, given the improvement shown with lifestyle modification alone in our population of obese, insulin-resistant children.

The current study underscores the complexity of the relationship between exercise and glucose homeostasis. Improved fitness contributed significantly and independently to reductions in HOMA-IR regardless of change in weight or body composition. This is consistent with longitudinal data in adults suggesting that fitness and adiposity can mediate cardiovascular risk independently.[26] BMI Z-score did not change significantly and body weight actually increased, consistent with prior pediatric interventional studies in which insulin sensitivity by clamp[27] or HOMA-IR/OGTT[28] improved after aerobic exercise without reduction in body weight. In contrast to the current study, these prior studies lacked a control group that did not perform supervised exercise.

We also sought to identify the determinants of altered mitochondrial function in children and adolescents with obesity and insulin resistance. Our findings support the assertion that despite their frequent association, insulin signaling, measured by HOMA IR and mitochondrial metabolism, measured as change in τPCr, can also behave independently. However, HOMA-IR is a measure of hepatic insulin resistance, and results may have differed if we had used an index of skeletal muscle insulin sensitivity. There is previous evidence of this dissociation, as, for example, diet-induced weight loss in adults produced an improvement in insulin sensitivity but did not alter mitochondrial function, and led to a decrease in mitochondrial size.[29]

To add to our understanding of the metabolic changes that accompany lifestyle modification with or without exercise training, we studied intramyocellular lipid content as a potential mediator of the metabolic effects. High IMCL is associated with low insulin sensitivity in individuals with diet-induced obesity but high insulin sensitivity in endurance athletes, a

phenomenon called the athlete's paradox.[10] In obese children and adolescents who are sedentary, overnutrition may lead to lipid accumulation in skeletal muscle[30], which may be worse in those who also have type 2 diabetes mellitus.[31] We demonstrated that IMCL increased in response to an 8-week intensive exercise intervention even in these already obese children. The rise in IMCL was in proportion to adherence to the training regimen and to the fitness gains achieved, as well as to a rise in resting energy expenditure. Increase in IMCL was also related to a decrease in fasting RQ, which is suggestive of a metabolic shift towards greater reliance on lipid oxidation. Previously, *in vitro* measurements of intramyocellular lipid oxidation were reflected in fasting RQ in both lean subjects and obese subjects with type 2 diabetes.[29] A seminal investigation in overweight adults similarly demonstrated that increased IMCL can be an early response to training.[32]

Despite the small sample size, we were able to demonstrate a statistically significant impact of supervised training on peak VO_2, peak workload, and an overall benefit of lifestyle modification on HOMA-IR. Our exploratory analyses suggest an impact of exercise training on IMCL. We were also able to investigate critical relationships between peak VO_2, HOMA-IR and mitochondrial function during lifestyle modification that, to our knowledge, have not been previously studied in children. We speculate that there are several reasons that some of the participants either failed to gain fitness and/or lost fitness. The season and level of baseline activity may be factors, as been previously described.[33] Small sample size limits our ability to draw definitive conclusions, but these findings suggest factors to consider in future studies.

An additional limitation to the current study was the use of HOMA IR as a proxy for insulin resistance. HOMA-IR was used as a pre-specified surrogate for insulin resistance because of its demonstrated association with τPCr, and because it has been shown to correlate with the gold-standard hyperinsulinemic euglycemic clamp.[34] Finally, ^{31}P MRS estimates skeletal muscle oxidative phosphorylation, and thus does not capture other potentially important effects of exercise on the mitochondria.

In summary, obese children and adolescents receiving lifestyle modification advice randomized to an in-home intensive, supervised exercise training regimen had better preserved fitness, maximal power, and energy expenditure. Change in fitness was also a major determinant of change in insulin sensitivity, and this effect was independent of weight loss. In addition, we showed that improvement in insulin resistance was not associated with a change in skeletal muscle oxidative phosphorylation, suggesting that insulin signaling and mitochondrial metabolism may sometimes be dissociable processes in this population. Finally, in this prospective, controlled pediatric study, we demonstrated that exercise training may increase IMCL in relationship to improved fitness. These insights yield a better understanding of the adaptive mechanisms that underlie improved metabolism in response to lifestyle modification and exercise training in obese children and adolescents.

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AF conceived study design, carried out experiments, analyzed and interpreted data, and participated in manuscript preparation. SG participated in study design, interpretation of data, and participated in manuscript preparation. SM carried out experiments, analyzed and interpreted data, wrote the manuscript. MM, SH, LF, MH, and BT carried out experiments. DS, MT, and KM provided technical expertise and participated in study design. All authors were involved in reviewing the paper and had final approval of the submitted version.

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What is already known about this subject

- Obesity-related insulin resistance is highly prevalent in children and adolescents, and contributes to an increased lifetime risk of type 2 diabetes mellitus and cardiovascular disease.

  Intensive exercise training may improve insulin sensitivity.

What this study adds

- Three monitored exercise training sessions per week for 8 weeks can improve fitness-related insulin sensitivity in obese, insulin resistant children.
- Insulin sensitivity and skeletal muscle oxidative phosphorylation may be dissociable in this population.
- Improvements in fitness may be accompanied by a rise in intramyocellular lipid content and an associated increase in resting energy expenditure.

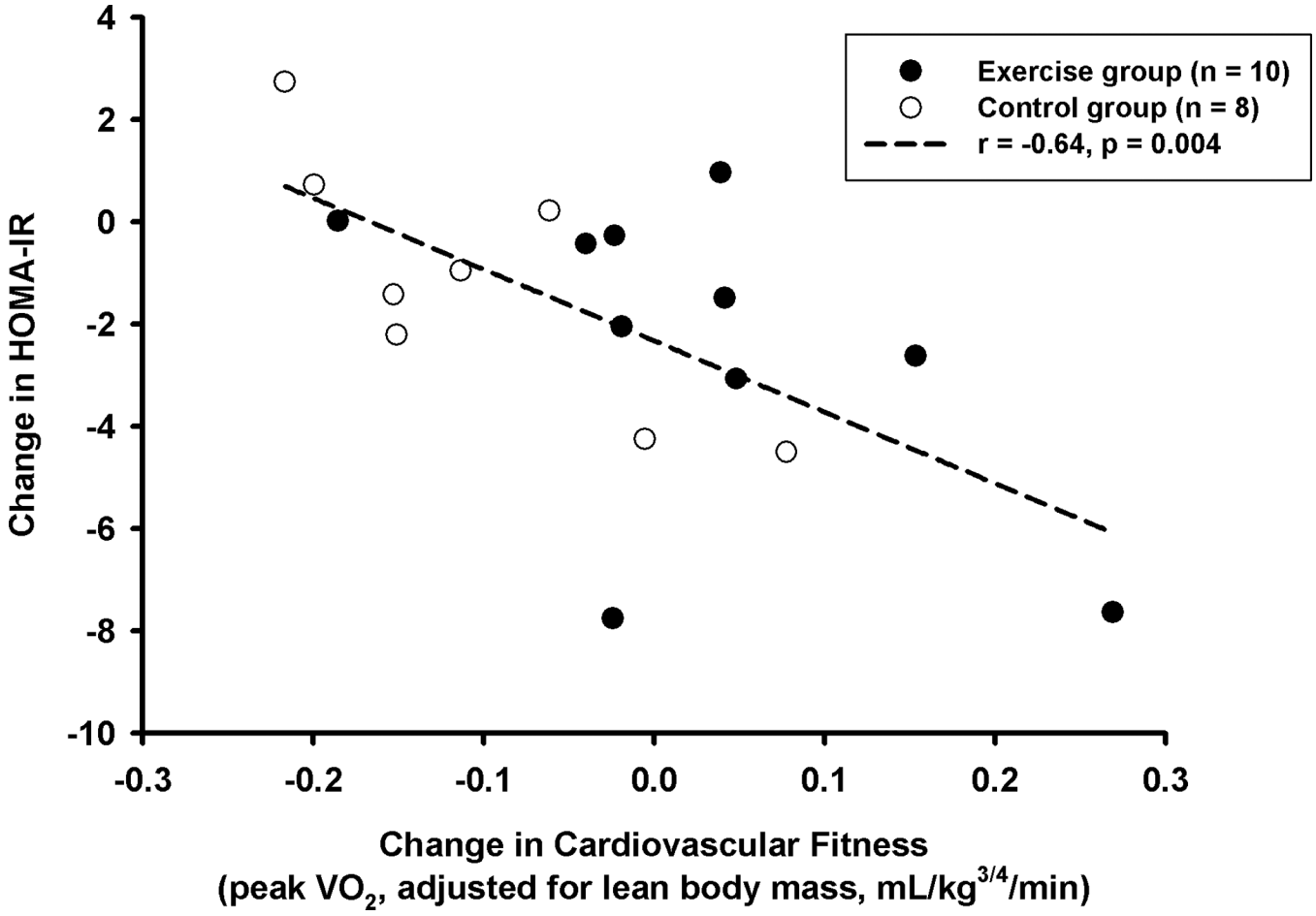
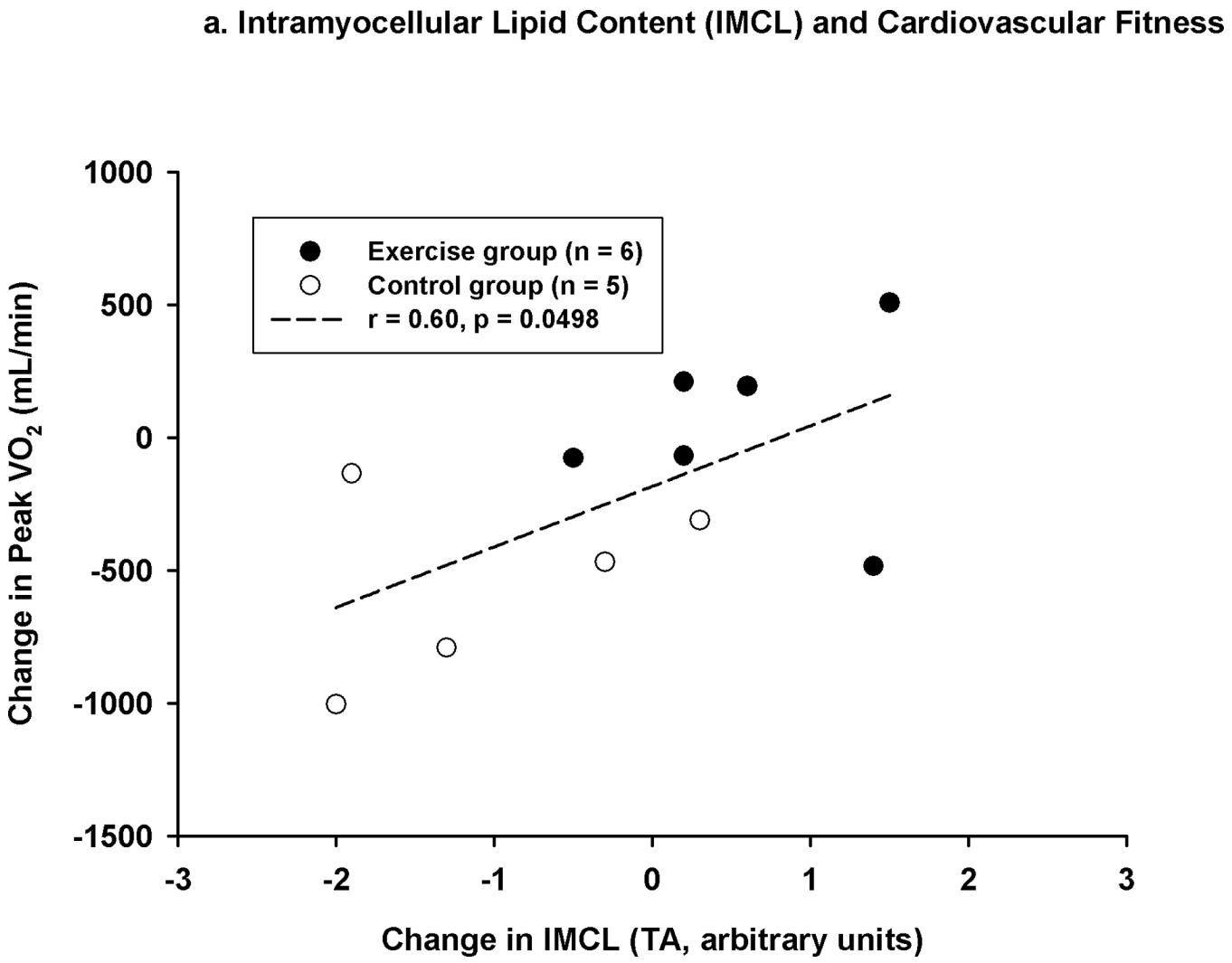
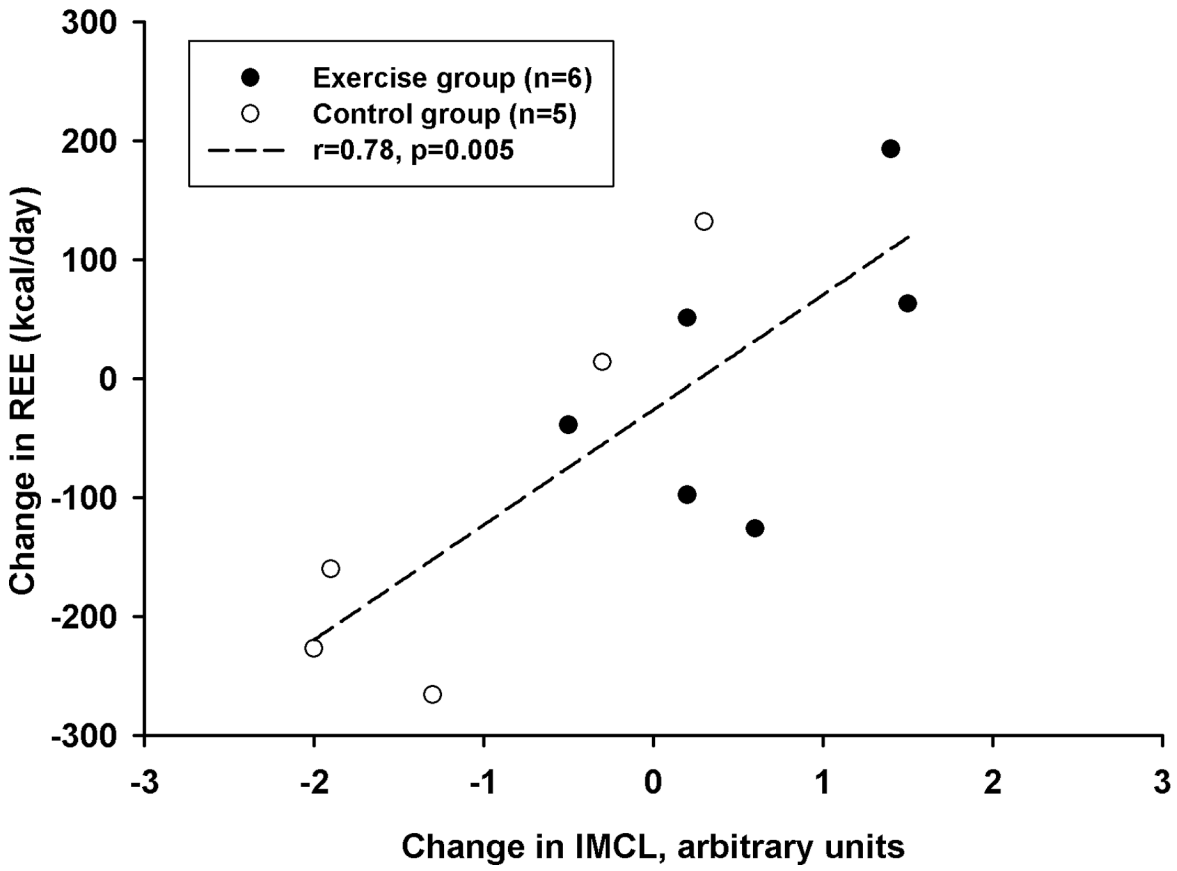


Figure 1.
Change in cardiovascular fitness and change in insulin resistance (HOMA-IR).



b. Intramyocellular Lipid Content (IMCL) and Resting Energy Expenditure (REE)



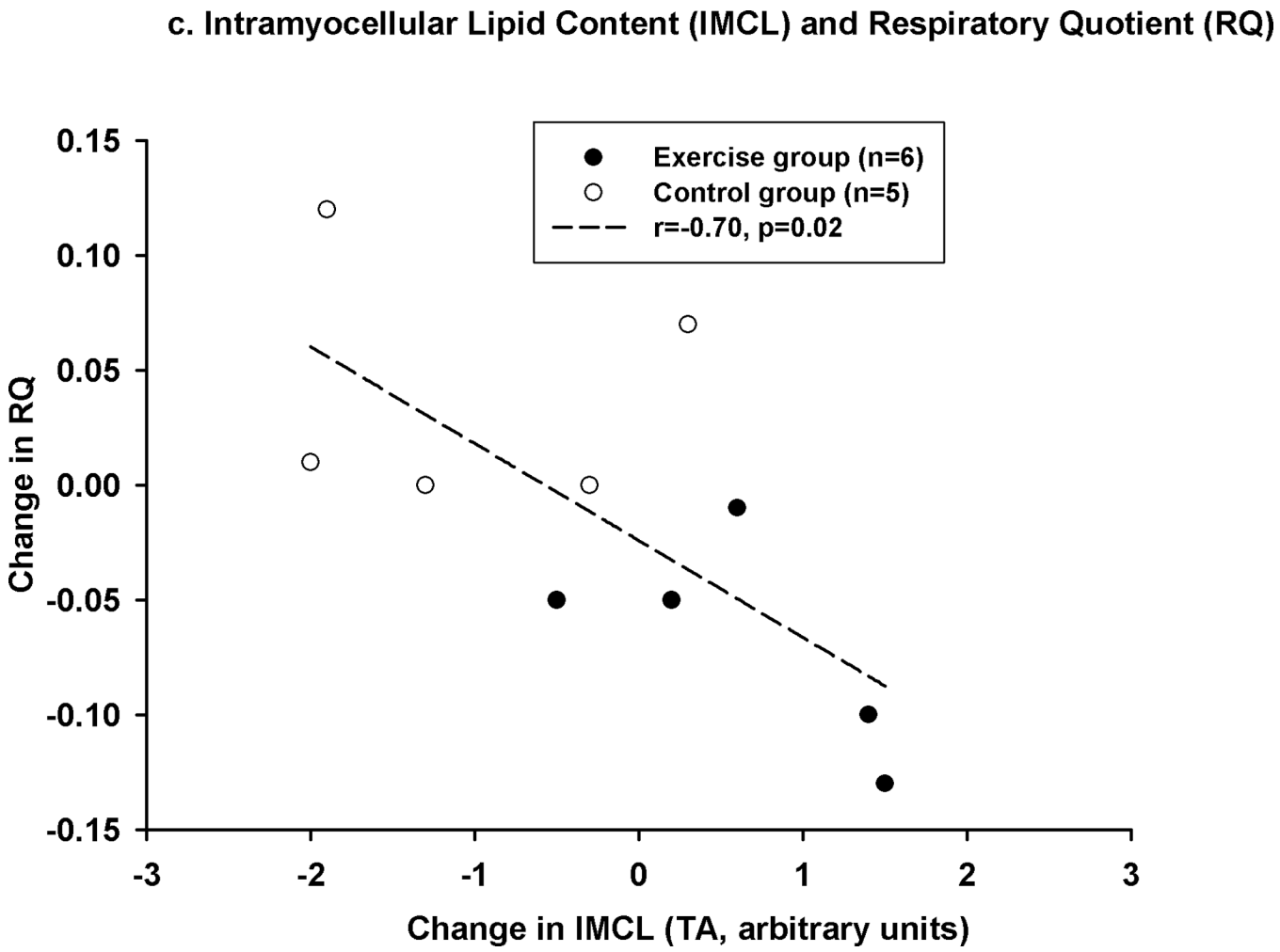


Figure 2.

Change in intramyocellular lipid (IMCL) content and changes in cardiovascular fitness **(a)**, resting energy expenditure **(b)**, and fasting respiratory quotient **(c)**.

Table 1

Baseline characteristics (all randomized subjects with complete screening data.)

	All (n = 18)	**Exercise group (n = 10)**	**Control group (n = 8)**
Age, years	13.0 ± 1.9	13.8 ± 2.2	12.1 ± 1.2
Girls/boys, *n/n*	13/5	8/2	5/3
Tanner Stage			
II, *n* (%)	2 (11%)	1 (10%)	1 (13%)
III, *n* (%)	5 (28%)	2 (20%)	3 (38%)
IV, *n* (%)	8 (44%)	4 (40%)	4 (50%)
V, *n* (%)	3 (17%)	3 (30%)	
Race			
African-American, *n* (%)	2 (11%)	2 (20%)	0 (0%)
White, *n* (%)	10 (56%)	6 (60%)	4 (50%)
Other, more than one race, *n* (%)	6 (33%)	2 (20%)	4 (50%)
Ethnicity			
Hispanic, *n* (%)	6 (33%)	2 (20%)	4 (50%)
Non-Hispanic, *n* (%)	12 (67%)	8 (80%)	4 (50%)
Family history of T2DM (17)*			
Yes	5 (29%)	3 (33%)	2 (25%)
No	12 (71%)	6 (67%)	6 (75%)
Anthropometric parameters and body composition			
BMI, kg/m^2	37.0 ± 7.1	39.1 ± 6.5	34.3 ± 7.4
BMI, Z-score	2.45 ± 0.32	2.53 ± 0.25	2.35 ± 0.38
Fat mass, %	44 ± 4	44 ± 4	42 ± 4
Blood pressure			
Systolic, mm Hg	110 ± 9	110 ± 6	110 ± 12
Systolic, Z-score	0.08 ± 0.64	0.12 ± 0.50	0.02 ± 0.82
Diastolic, mm Hg	68 ± 8	68 ± 7	68 ± 9
Diastolic, Z-score	0.29 ± 0.63	0.28 ± 0.61	0.31 ± 0.69
Energy intake and expenditure†			
Caloric intake, kcal/total body lean mass (kg)/day	37 ± 12	41 ± 12	32 ± 11
Resting energy expenditure, kcal/total body lean mass (kg)/day	33 ± 7	32 ± 7	34 ± 8
RQ	0.86 ± 0.07	0.85 ± 0.06	0.86 ± 0.07
Exercise and strength testing			
Peak VO2, ml/total body lean mass (kg)$^{3/4}$/min	83 ± 21	76 ± 16	92 ± 23
Peak workload, Watts	113 ± 45	106 ± 42	123 ± 50
Peak heart rate, % predicted for age	80 ± 10	81 ± 7	79 ± 13
Peak RER	1.01 ± 0.04	1.01 ± 0.05	1.00 ± 0.01
Maximum voluntary contraction, kg	38.9 ± 13.0	37.8 ± 12.4	40.4 ± 14.7

	All (n = 18)	**Exercise group (n = 10)**	**Control group (n = 8)**
Metabolic profile			
Fasting insulin, pmol/L	214 ± 129	252 ± 153	168 ± 74
Fasting glucose, mmol/L	4.37 ± 0.28	4.45 ± 0.27	4.27 ± 0.28
2-hour glucose, mmol/L	6.63 ± 1.22	6.76 ± 1.01	6.47 ± 1.49
HOMA-IR	5.95 ± 3.47	7.09 ± 4.08	4.54 ± 1.92
Cholesterol, mg/dL	3.68 ± 0.81	3.67 ± 1.04	3.71 ± 0.43
LDL, mg/dL	2.07 ± 0.73	2.03 ± 0.94	2.11 ± 0.41
HDL, mg/dL	1.02 ± 0.16	0.98 ± 0.15	1.08 ± 0.15
Triglyceride, mg/dL	1.30 ± 0.58	1.43 ± 0.65	1.15 ± 0.47
Mitochondrial function (^{31}P MRS)			
τPCr, seconds	45.3 ± 10.3	43.9 ± 12.1	47.1 ± 7.8
^{1}H MRS**			
TA IMCL/W, arbitrary units	5.1 ± 1.5	4.7 ± 1.4	5.7 ± 1.7

Data are reported as mean ± SD. Note that if *n* is different from the total number in the group, this is included in parentheses. No statistically significant differences in any of these parameters were noted between randomization groups. To convert insulin to μIU/mL, divide by 6.945. To convert glucose to mg/dL, divide by 0.0555. To convert cholesterol, LDL, and HDL to mg/dL, divide by 0.0259. To convert triglycerides to mmol/L, divide by 0.0113.

*One subject was adopted; family history was unknown.

†Complete dietary records are available for 10 subjects; complete indirect calorimetry data are available for 16 subjects.

**Complete ^{1}H MRS data are available for 11 subjects (6 exercise, 5 control).

Table 2

Repeated measures analysis of variance, indicating the effect of time, and the interaction group and time over the study period.

	Exercise Group (n = 10) change, 95% CI	**Control Group (n = 8) change, 95% CI**	**P value, over time (effect of lifestyle advice over all subjects)**	**P value, time-by-group (effect of addition of supervised exercise)**
Exercise testing				
Peak VO_2, /total body lean mass (kg)$^{3/4}$/min	5 (−11 – 20)	−18 (−33 – −3)	0.17	**0.03**
Peak workload, Watts	32 (−3 – 67)	−20 (−30 – −10)	0.51	**0.01**
Metabolic profile				
Fasting insulin, pmol/L	−86 (−159 – −13)	−41 (−119 – 36)	**0.01**	0.35
Fasting glucose mmol/L	−0.07 (−0.22 – 0.08)	−0.03 (−0.16 – 0.11)	0.28	0.63
2-hour glucose mmol/L	0.40 (−0.64 – 1.44)	−0.16 (−1.29 – 0.98)	0.72	0.42
HOMA-IR	−2.43 (−4.61 – −0.26)	−1.21 (−3.27 – 0.85)	**0.01**	0.37
Anthropometric parameters and body composition				
BMI, kg/m^2	0.36 (−0.24 – 0.96)	−0.19 (−0.7 – 0.31)	0.65	0.14
BMI, Z-score	0.005 (−0.02 – 0.03)	−0.03 (−0.07 – 0.01)	0.25	0.11
Weight, kg	2.1 (0.3 – 3.9)	0.6 (−1.1 – 2.2)	**0.03**	0.19
Height, cm	0.8 (0 – 1.7)	1.1 (0.3 – 1.9)	**0.002**	0.62
Total body lean mass, kg	2.0 (−0.2 – 4.2)	0.6 (−0.8 – 2.1)	**0.05**	0.28
Fat mass, %	−1 (−3 – 0)	−1 (−2 – 1)	0.10	0.53
Energy intake and expenditure *				
Caloric intake, kcal/total body lean mass (kg)/day	−7 (−22 – 7)	−6 (−14 – 1)	0.05	0.84
REE, kcal/total body lean mass (kg)/day	0.14 (−1.9 – 2.2)	−2.9 (−6.0 – 0.3)	0.10	0.07
RQ	−0.03 (−0.08 – 0.02)	−0.00 (−0.09 – 0.08)	0.41	0.49
Mitochondrial function ^{31}P MRS				
τPCr, seconds	−5 (−18 – 8)	−10 (−19 – −1)	**0.05**	0.50
Intramyocellular lipid content (IMCL, ^{1}H MRS)†				
TA IMCL/W, arbitrary units	0.57 (−0.24 – 1.4)	−1.0 (−2.3 – 0.21)	0.40	**0.02**

Multivariate repeated measures analysis was used to identify the effects of randomization group (exercise or control), time (pre- or post-study), and the interaction between group and time on the outcome variables of interest. To convert insulin to μIU/mL, divide by 6.945. To convert glucose to mg/dL, divide by 0.0555.

*Complete dietary records are available for 7 subjects; complete indirect calorimetry data are available for 16 subjects.

†Complete ^{1}H MRS data are available for 11 subjects (6 exercise, 5 control).