Effects of Aerobic Versus Resistance Exercise Without Caloric Restriction on Abdominal Fat, Intrahepatic Lipid, and Insulin Sensitivity in Obese Adolescent Boys

A Randomized, Controlled Trial

SoJung Lee,[1] Fida Bacha,[2,3] Tamara Hannon,[1,4] Jennifer L. Kuk,[5] Chris Boesch,[6] and Silva Arslanian[1,2]

The optimal exercise modality for reductions of abdominal obesity and risk factors for type 2 diabetes in youth is unknown. We examined the effects of aerobic exercise (AE) versus resistance exercise (RE) without caloric restriction on abdominal adiposity, ectopic fat, and insulin sensitivity and secretion in youth. Forty-five obese adolescent boys were randomly assigned to one of three 3-month interventions: AE, RE, or a nonexercising control. Abdominal fat was assessed by magnetic resonance imaging, and intrahepatic lipid and intramyocellular lipid were assessed by proton magnetic resonance spectroscopy. Insulin sensitivity and secretion were evaluated by a 3-h hyperinsulinemic-euglycemic clamp and a 2-h hyperglycemic clamp. Both AE and RE prevented the significant weight gain that was observed in controls. Compared with controls, significant reductions in total and visceral fat and intrahepatic lipid were observed in both exercise groups. Compared with controls, a significant improvement in insulin sensitivity (27%) was observed in the RE group. Collapsed across groups, changes in visceral fat were associated with changes in intrahepatic lipid ($r = 0.72$) and insulin sensitivity ($r = -0.47$). Both AE and RE alone are effective for reducing abdominal fat and intrahepatic lipid in obese adolescent boys. RE but not AE is also associated with significant improvements in insulin sensitivity. ***Diabetes*** **61:2787–2795, 2012**

According to the recent National Health and Nutrition Examination Survey (2009–2010), a third (33.6%) of U.S. children and adolescents (12–19 years old) are overweight or obese (1). It is suggested that abdominal obesity, in particular visceral fat, is an important culprit for many obesity-related comorbidities in youth (2). In light of the secular increases in waist circumference (WC) among children and adolescents (3,4) and the finding that abdominal obesity is a stronger risk factor for insulin resistance and cardiometabolic diseases than BMI (5,6), effective intervention strategies are needed for targeting abdominal fat reduction in youth.

In adults, randomized, controlled studies have reported that regular exercise (performed for 30–60 min/day ≥3 days/week) is associated with significant reductions in abdominal fat and improvements in glycemia and insulin resistance in nondieting men and women (7–11). In obese adolescents, the utility of exercise alone (no caloric restriction) as a strategy for reducing obesity-related health risk is not clear. Although previous studies have examined the effect of aerobic exercise (12,13) or resistance training (14,15) on insulin sensitivity in obese children and adolescents, interpretation is limited because these studies did not include nonexercising controls (12,13,15) and did not measure ectopic fat (e.g., visceral obesity, liver fat, intramyocellular lipid (IMCL) mobilizations with exercise treatments (12,14). Further, although it is generally accepted that regular physical activity provides substantial health benefits in obese adolescents, it is unclear which exercise modality is most beneficial for reducing comorbidities associated with obesity in adolescents. A recent meta-analysis (16) reported that aerobic exercise performed for 60 min 3 times/week improves LDL cholesterol and triglyceride concentrations in obese children, whereas combined exercise increases HDL concentration. Further, Suh et al. (17) demonstrated that in overweight Asian adolescents improvements in insulin sensitivity index (oral glucose tolerance test) were similar between aerobic and resistance training, and the improvements in the exercise training groups did not differ from those with diet alone. By contrast, adult studies have reported greater improvements in insulin sensitivity after aerobic versus resistance training (11,18).

We therefore conducted a randomized, controlled study to examine the effects of aerobic versus resistance exercise, without caloric restriction, on abdominal obesity, ectopic fat in the liver and skeletal muscle, and insulin action and secretion in obese adolescent boys. We hypothesized that in youth both aerobic and resistance exercise training would be associated with reductions in abdominal fat and improvements in insulin sensitivity and also the improvements in obesity-related risk factors would be greater in response to aerobic exercise than resistance exercise.

RESEARCH DESIGN AND METHODS

We conducted a 3-month randomized, controlled trial with a parallel group design. This study was conducted from November 2007 through October 2011 at Children's Hospital of Pittsburgh (CHP) of University of Pittsburgh Medical

From the [1]Division of Weight Management & Wellness, Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; the [2]Division of Pediatric Endocrinology, Metabolism and Diabetes Mellitus, Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; the [3]Children's Nutrition Research Center, Baylor College of Medicine, Houston, Texas; the [4]Department of Pediatrics, Section of Pediatric Endocrinology & Diabetology, Riley Hospital for Children, Indiana University School of Medicine, Indianapolis, Indiana; the [5]School of Kinesiology and Health Science, York University, Toronto, Ontario, Canada; and the [6]Department of Clinical Research/AMSM, University of Bern, Bern, Switzerland.
Corresponding author: SoJung Lee, SoJung.Lee@chp.edu.
Received 21 February 2012 and accepted 4 May 2012.
DOI: 10.2337/db12-0214. Clinical trial reg. no. NCT00739180, clinicaltrials.gov.

Center. Obese (BMI ≥95th percentile) (19) adolescent boys were recruited by means of flyers posted in the city public transportation and posters placed on campus and from the Weight Management and Wellness Center at CHP. The investigation was approved by the University of Pittsburgh institutional review board. Parental informed consent and child assent were obtained for all participants before participation. Inclusion criteria included that the subjects be 12–18 years of age, pubertal (Tanner stages III–V), nonsmokers, nondiabetic, and physically inactive (no participation in structured physical activity for previous 3 months except school physical education classes). Exclusion criteria included participation in structured exercise, significant weight change (BMI >2–3 kg/m^2), endocrine disorders, syndromic obesity (e.g., Prader-Willi syndrome), psychiatric disorders, and chronic use of medications known to influence glucose metabolism and body composition. Participants self-identified as black or white. Pubertal development was assessed according to Tanner criteria (genital development and pubic hair) by a certified nurse practitioner. All participants underwent a complete physical examination and routine hematological and biochemical tests at the Pediatric Clinical and Translational Research Center at CHP.

Randomization was performed after completing two baseline overnight admissions at CHP for assessments of insulin sensitivity and secretion and of body composition. Staff members who were not involved in the study randomly selected pieces of paper from a container with group assignments. Subjects were randomly assigned, with a completely randomized design and cell sizes of 16, to one of three groups: aerobic exercise, resistance exercise, or a nonexercise control group. Participants were compensated for two inpatient admissions for baseline evaluations ($150 total) and for another two inpatient admissions for postintervention evaluations ($200 total). For exercise training groups, we compensated $5 per session for travel (e.g., either bus ticket for a subject or parking for parents) to attend each exercise session and the compensation was made after finishing both post intervention clamp tests.

Dietary regimen. At baseline, subjects participated in a 1-h individual nutrition session, wherein the study nutritionist taught proper food selection and preparation. During this session, daily energy requirements for all subjects were determined by estimating resting energy expenditure and multiplying the obtained value by a factor of 1.2 (20). All subjects were asked to follow a weight maintenance diet (55–60% carbohydrate, 15–20% protein, and 20–25% fat) during the intervention period to allow the assumption that any changes in abdominal fat and insulin sensitivity were consequent to the effects of regular exercise alone without caloric restriction. Adherence to this regimen was determined by examination of body weight before each exercise session. If weight deviated significantly (>4% of initial weight on two consecutive weeks), nutrition counseling was provided to identify the deviation.

Exercise regimen. The exercise groups exercised at either the downtown Pittsburgh YMCA exercise facility or the exercise laboratory at CHP for 3 months. All exercise sessions were by appointment and were directly supervised by physical education graduate students. The aerobic exercise program required participants to exercise three times per week for 60 min/session (including 5 min warm-up and 5 min cool down) with treadmills, ellipticals, or stationary bikes. Aerobic exercise programs progressively increased in duration and intensity, beginning at 40 min at ~50% of $V\mathrm{O}_{2\mathrm{peak}}$, increased up to 60 min at 60–75% of $V\mathrm{O}_{2\mathrm{peak}}$ by week two. Participants wore a heart rate monitor (Polar Oy, Kempele, Finland) during the exercise sessions to ensure achievement of the target heart rate. Energy expenditure was estimated with the heart rate–$V\mathrm{O}_2$ relationship observed during the $V\mathrm{O}_{2\mathrm{peak}}$ test. The heart rates were translated into estimated energy expenditure according to the assumption that 1 L oxygen equals 5 kcal of energy expenditure (21). The heart rate range associated with 60–75% of $V\mathrm{O}_{2\mathrm{peak}}$ was determined from the baseline maximal oxygen uptake test for each subject. The relationship between the heart rate and $V\mathrm{O}_2$ was reevaluated during the subsequent maximal treadmill tests at weeks 4 and 8 to reassess the heart rate–energy expenditure relationship.

The resistance program included a series of 10 whole-body exercises three times per week for 60 min/session. Each training session included leg press, leg extension, leg flexion, chest press, latissimus pull down, seated row, biceps curl, and triceps extension with stack weight equipment. In addition, a single set each of push-ups and sit-ups were performed. For the first 4 weeks, participants performed one or two sets of 8–12 repetitions at 60% of baseline repetition maximum (RM) with proper lifting techniques. During weeks 4–12, subjects performed two sets of 8–12 repetitions to fatigue. Subjects took 1–2 min of rest between sets or machines.

Control subjects were asked to maintain their current leisure time activity (no participation in structured physical activities). To reduce dropouts and maintain adherence, participants were given the opportunity to participate in exercise sessions after the completion of postintervention evaluations.

Anthropometrics. Body weight was measured to the nearest 0.1 kg, and height was measured to the nearest 0.1 cm. WC was measured at the level of the last rib by standard procedures (22), and the average of two measures was used in the analyses.

Oral glucose tolerance test. Participants reported to the Pediatric Clinical and Translational Research Center after an overnight fast (minimum 8 h) for a 2-h oral glucose tolerance test (1.75 g/kg, maximum 75 g). Blood samples were obtained at −15, 0, 15, 30, 60, 90, and 120 min for determination of glucose and insulin levels.

Measurement of β-cell function and insulin sensitivity by the clamp technique. Participants underwent hyperglycemic and hyperinsulinemic-euglycemic clamps on two separate days chosen at random, separated by 1–3 weeks before the intervention and separated by 1 week after the intervention. A 2-h hyperglycemic clamp (12.5 mmol/L) was performed from 9:00–11:00 A.M. to evaluate first- and second-phase insulin secretion as described previously (23). On a separate visit, a 3-h 80 μm^2/min hyperinsulinemic-euglycemic clamp was performed to measure insulin sensitivity as reported elsewhere (24). Plasma glucose was clamped at 5.6 mmol/L, with a variable-rate infusion of 20% dextrose based on arterialized plasma glucose determinations every 5 min. Insulin sensitivity was calculated by dividing insulin-stimulated glucose disposal rate by the steady-state plasma insulin concentration during the last 30 min of the clamp. In the exercise groups, postexercise clamp measurements were obtained 12 and 13 weeks after exercise. Each clamp measurement was obtained 48–72 h after exercise to control for the well-established effects of acute exercise on glucose uptake (25). To avoid the potential detraining effect on insulin sensitivity, participants in the exercise groups exercised three times during the week between the two clamp measurements (between 12 and 13 weeks), which amounted to a total of 39 exercise sessions in both exercise programs. One control subject did not complete the post intervention clamp tests.

Biochemical measurements. Plasma glucose was measured by the glucose oxidase method with a glucose analyzer (YSI, Inc., Yellow Springs, OH), and the insulin concentration was determined by radioimmunoassay (23).

Total and abdominal fat and skeletal muscle mass. Fat free mass was assessed by dual energy X-ray absorptiometry using Lunar iDXA (GE Healthcare, Madison, WI). Whole-body magnetic resonance imaging (MRI) data were obtained with a 3.0-T MRI scanner (Magnetom TIM Trio; Siemens, Erlangen, Germany) to quantify total adipose tissue (AT), skeletal muscle, and visceral and abdominal subcutaneous fat as shown previously (22,26).

IMCL and intrahepatic lipid by proton magnetic resonance spectroscopy. Because of technical difficulties, IMCL and intrahepatic lipid were only measured in a subset of participants (10 control, 10 aerobic, and 9 resistance). IMCL was measured in the tibialis anterior muscle of the right leg with a 3.0-T MRI system (TIM Trio) with a CP extremity coil (Siemens). Repositioning of the subject and placement of the coil and voxels were carefully monitored on the localizer images to ensure that the repeat scan was performed in the same location. Spectra were acquired with a PRESS sequence with a repetition time (TR) of 2.0 s, number of averaged spectra 128, and an echo time (TE) of 30 ms. A voxel ($12 \times 11 \times 18$ mm^3) was placed in the tibialis anterior muscle, carefully avoiding vascular structures and AT deposits within the voxels. The proton magnetic resonance spectra were acquired with water suppression for the determination of IMCL, and one single shot was acquired without water suppression for the quantitation. Absolute concentrations of IMCLs were obtained from the area under the curve of the methylene signals of lipids at 1.28 ppm, with tissue water content as an internal reference according to the literature (27).

For liver triglyceride contents, proton magnetic resonance spectra were acquired in the same proton magnetic resonance spectroscopic system with a body matrix coil and a spine matrix (Siemens). A voxel ($30 \times 30 \times 20$ mm^3) was placed within the posterior part of segment 7 of the liver, avoiding blood vessels and intrahepatic bile ducts with the following parameters: TR = 4,000 ms and TE = 30 ms. Eight acquisitions were recorded in a measuring time of 32 s without water suppression, and the average of eight spectra was used for liver triglyceride calculation. To avoid motion artifact, subjects were asked to breathe within the TR interval and to be in expiration during each data acquisition. Both IMCL and liver spectra were fitted with the AMARES algorithm in the Java-based magnetic resonance user interface (jMRUI) software package (28).

Cardiorespiratory fitness and muscular strength. Cardiorespiratory fitness was determined with a graded treadmill test with the use of standard open-circuit spirometry techniques (AEI Technologies, Pittsburgh, PA) until volitional fatigue. For the initial 2 min, the grade was set at 0%, after which time it was increased to 2% for the 3rd min and increased by 1% increments every minute thereafter. $V\mathrm{O}_{2\mathrm{peak}}$ was attained when at least two of the following three criteria were achieved: *1*) a change in $V\mathrm{O}_2$ of <2.1 mL/kg/min with increasing exercise intensity at nearly maximum higher treadmill stages, *2*) a respiratory exchange ratio in excess of 1.05, and *3*) heart rate >90% of the age-predicted maximum (220-age).

Muscular strength was assessed with an RM test for the supine chest press and seated leg press with weight stack equipment (Life Fitness, Schiller Park, IL). Muscular strength index was calculated as the sum of the RM scores for the chest and leg press expressed per kg of body weight (29).

Statistical analysis. The primary outcome of the study was visceral fat at 3 months after intervention. We selected a sample size 14 to provide a statistical power of 95% to detect a difference of 0.56 kg in visceral fat (30) between any two groups at 3 months with a repeated measures ANCOVA at an α of 0.05. We increased the sample size to 16 to allow for withdrawals.

A one-way ANOVA was performed to examine group differences at baseline. We examined the effect of the intervention with an intent-to-treat analysis for only randomized subjects with baseline data. Missing follow-up data values were estimated by multiple imputations procedure (Proc mi) with 100 imputations (31). Repeated measures ANOVA was used to determine treatment differences with the imputed data. Two participants had missing baseline images for skeletal muscle and visceral and abdominal subcutaneous fat and were excluded from the intent-to-treat analyses.

We also examined the effect of the exercise intervention with as-treated analyses in participants who had complete baseline and follow-up data. Least squared means difference post hoc tests were used to determine differences between the control and intervention groups. The relationships between changes in total and abdominal fat and insulin sensitivity were evaluated by Pearson correlation coefficients.

P values of less than 0.05 were accepted to indicate statistical significance. All analyses were performed with commercially available software (SAS, version 9.2; SAS Institute Inc, Cary, NC). Unless otherwise indicated, data are expressed as mean (SE).

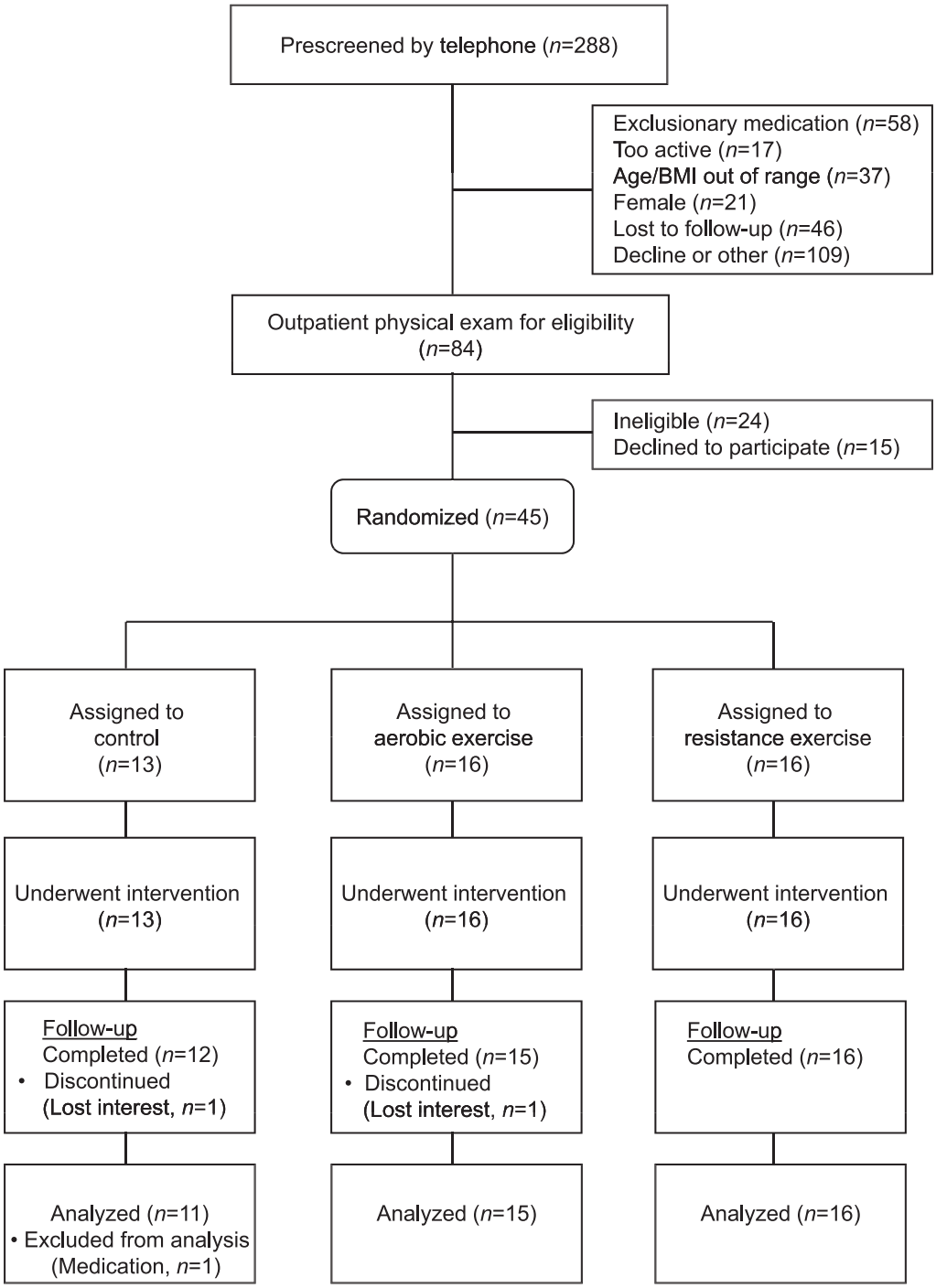

FIG. 1. Participant flow diagram. All subjects assigned to each group (including subjects who discontinued the study) were included in intent-to-treat analyses.

RESULTS

Adherence. Of the 45 boys randomized, 43 completed their assigned treatment (Fig. 1). Two subjects (one each in aerobic and control groups) did not complete the study because of lack of interest. We excluded one control subject from data analyses who was found to be taking metformin during the intervention period. Average (mean ± SD) attendance at the exercise sessions was >99% in both the aerobic (99.7 ± 0.8%) and resistance (99.0 ± 2.1%) groups, and average exercise durations were similar between the aerobic (57.7 ± 1.2 min/session) and resistance (59.4 ± 3.6 min/session) exercise groups. In the aerobic exercise group, the mean heart rate was 153.8 ± 7.2 bpm (range, 144–175 bpm) and energy expenditure was 713.9 ± 166.4 kcal/session (range, 303–943 kcal/session).

Baseline characteristics. There were no significant differences between groups for baseline variables (Table 1).

Changes in fitness. Compared with controls, cardiorespiratory fitness increased significantly ($P < 0.05$) by similar magnitudes in the aerobic and resistance exercise groups (Table 2). Compared with controls, muscular strength increased significantly ($P < 0.05$) in the resistance exercise group but not in the aerobic exercise group.

Changes in body weight and WC. After 3 months, both aerobic and resistance exercise (aerobic, −0.04 ± 0.8 kg; resistance, −0.6 ± 0.8 kg) prevented the significant weight gain that was observed in controls (2.6 ± 0.1 kg) (Table 2). A significant ($P < 0.05$) reduction in WC was observed in both exercise groups compared with controls. There was a small but significant decrease in BMI in the resistance exercise group but not the aerobic group.

Changes in total fat and skeletal muscle mass. Compared with controls, a significant ($P < 0.05$) reduction in total adiposity (%) was observed within the exercise groups (Table 2). A significant increase in total skeletal muscle mass (1.4 ± 0.3 kg; $P = 0.01$) was observed in the resistance exercise group alone compared with controls.

Changes in abdominal fat, intrahepatic lipid, and IMCL. Compared with controls, significant ($P < 0.05$) reductions in abdominal subcutaneous and visceral fat (kg) were observed within the aerobic and resistance exercise groups (Table 2 and Fig. 2*A*). Compared with controls, intrahepatic lipid (%) was reduced ($P < 0.05$) in the aerobic (−1.9 ± 1.0%) and resistance (−2.0 ± 1.0%) exercise groups by similar magnitudes (Fig. 2*B*). No significant within or between group changes in IMCL were observed in any group.

TABLE 1
Subject characteristics at baseline

Characteristics	Control (n = 13)	Aerobic exercise (n = 16)	Resistance exercise (n = 16)	P value
Black/white/mixed (n)	6/6/1	9/7/0	7/9/0	0.69
Puberty, III/IV/V (n)	2/3/8	1/4/11	6/1/9	0.65
Anthropometric				
Age (years)	14.8 ± 1.4	15.2 ± 1.9	14.6 ± 1.5	0.596
Body weight (kg)	100.0 ± 14.4	106.5 ± 19.3	97.7 ± 10.8	0.251
BMI (kg/m^2)	33.9 ± 4.2	36.6 ± 5.9	34.5 ± 2.4	0.224
WC (cm)	99.3 ± 10.3	105.2 ± 11.2	101.1 ± 8.0	0.270
DXA				
FFM (kg)	58.9 ± 8.1	62.7 ± 9.6	56.1 ± 6.8	0.091
MRI				
Total adiposity (%)*	42.7 ± 8.3	43.2 ± 4.9	43.8 ± 6.1	0.895
Total AT (kg)*	43.2 ± 12.4	46.5 ± 12.1	43.4 ± 9.0	0.679
Skeletal muscle (kg)*	27.4 ± 4.8	30.7 ± 5.3	27.2 ± 4.0	0.094
Visceral AT (kg) *	1.2 ± 0.4	1.5 ± 0.5	1.4 ± 0.6	0.413
Abdominal subcutaneous AT (kg)*	6.7 ± 2.5	7.8 ± 2.5	6.8 ± 1.8	0.306
Intrahepatic lipid (%)†	2.2 ± 2.2	4.7 ± 4.0	2.9 ± 2.4	0.190
IMCL (mmol/kg wet weight)†	2.5 ± 1.8	3.4 ± 1.5	2.2 ± 1.0	0.194
Metabolic				
Fasting glucose (mg/dL)	96.9 ± 5.0	95.9 ± 4.2	94.8 ± 4.3	0.461
Fasting insulin (μU/mL)	32.9 ± 13.6	38.3 ± 21.2	27.6 ± 7.3	0.152
First-phase insulin (μU/mL)	244.3 ± 136.0	292.7 ± 164.8	213.9 ± 119.0	0.295
Second-phase insulin (μU/mL)	270.1 ± 158.1	344.0 ± 219.3	241.4 ± 93.4	0.210
Insulin sensitivity‡ (mL/kg/min per μU/mL)	2.7 ± 1.2	2.2 ± 1.0	2.9 ± 1.0	0.159
Insulin sensitivity‡ (mL/FFM · kg/min per μU/mL)	4.5 ± 1.6	3.7 ± 1.7	4.9 ± 1.5	0.099
Disposition index	545.3 ± 206.7	538.9 ± 341.8	545.5 ± 201.7	0.997
Fitness				
$V_{O_{2peak}}$ (L/min)	3.0 ± 0.6	3.1 ± 0.8	3.0 ± 0.5	0.849
$V_{O_{2peak}}$ (mL/kg/min)	30.0 ± 4.3	29.0 ± 4.8	30.4 ± 5.0	0.706
Chest press RM (kg)	49.3 ± 13.1	59.4 ± 15.9	49.6 ± 13.8	0.099
Leg press RM (kg)	61.2 ± 13.5	68.5 ± 14.5	63.6 ± 12.5	0.340
Muscular strength index	1.1 ± 0.2	1.2 ± 0.2	1.2 ± 0.3	0.547

Data are means ± SD except as marked. DXA, dual energy X-ray absorptiometry. FFM, fat-free mass. *Total adiposity, skeletal muscle, visceral AT, and abdominal subcutaneous AT (all in kilograms) were quantified in 14 subjects in the resistance exercise group as a result of missing data during data transfer. †10 control, 10 aerobic, and 9 resistance. ‡Resistance n = 15 as a result of intravenous issue during the clamp.

TABLE 2
Absolute changes in total and regional body composition and fitness after 3 months

	Control (n = 11, ITT = 13)	Aerobic exercise (n = 15, ITT = 16)		Resistance exercise (n = 16, ITT = 16)	
	Value	Value	P value	Value	P value
ITT analysis (n = 45)					
Body weight (kg)	2.6 ± 1.0	−0.04 ± 0.8	0.039	−0.6 ± 0.8	0.009
BMI (kg/m^2)	0.3 ± 0.3	−0.3 ± 0.3	0.191	−0.6 ± 0.3	0.047
WC (cm)	1.1 ± 1.0	−2.0 ± 0.9	0.027	−3.2 ± 0.9	0.001
Fat free mass (kg, DXA)	1.38 ± 0.39	1.23 ± 0.34	0.774	2.11 ± 0.33	0.152
Total adiposity (%)	0.02 ± 0.6	−2.6 ± 0.6	0.002	−2.5 ± 0.6	0.004
Total AT (kg)	1.2 ± 0.9	−3.0 ± 0.8	0.001	−2.5 ± 0.8	0.002
Skeletal muscle (kg)	0.5 ± 0.3	1.0 ± 0.3	0.155	1.4 ± 0.3	0.01
Visceral AT (kg)	0.2 ± 0.1	−0.1 ± 0.04	<0.0001	−0.2 ± 0.04	<0.0001
Abdominal subcutaneous AT (kg)	0.2 ± 0.2	−0.5 ± 0.1	0.004	−0.4 ± 0.1	0.005
Liver fat (%)	0.9 ± 0.7	−1.9 ± 1.0	0.049	−2.0 ± 1.0	0.047
IMCL (mmol/kg ww)	0.7 ± 0.5	1.0 ± 0.6	0.087	−0.05 ± 0.5	0.909
$V_{O_{2peak}}$ (L/min)	0.1 ± 0.1	0.9 ± 0.1	<0.0001	0.7 ± 0.1	<0.0001
$V_{O_{2peak}}$ (mL/kg/min)	−0.04 ± 1.1	9.1 ± 0.9	<0.0001	7.7 ± 0.9	<0.0001
Chest press RM (kg)	0.13 ± 1.3	2.1 ± 1.1	0.28	13.6 ± 1.1	<0.0001
Leg press RM (kg)	4.6 ± 5.9	6.6 ± 5.0	0.79	29.8 ± 4.8	0.001
Muscular strength index	0.02 ± 0.1	0.2 ± 0.2	0.36	1.0 ± 0.2	<0.0001
Per protocol analysis (n = 42)					
Body weight (kg)	2.7 ± 0.9	0.04 ± 0.8	0.039	−0.6 ± 0.8	0.011
BMI (kg/m^2)	0.3 ± 0.3	−0.3 ± 0.3	0.179	−0.5 ± 0.3	0.047
WC (cm)	1.2 ± 1.0	−1.9 ± 0.9	0.028	−3.2 ± 0.8	0.002
Fat free mass (kg, DXA)	1.42 ± 0.38	1.25 ± 0.33	0.748	2.13 ± 0.32	0.160
Total adiposity (%)	0.02 ± 0.6	−2.7 ± 0.6	0.004	−2.5 ± 0.6	0.004
Total AT (kg)	1.2 ± 0.9	−3.1 ± 0.8	0.001	−2.6 ± 0.8	0.003
Skeletal muscle (kg)	0.5 ± 0.3	1.0 ± 0.3	0.170	1.5 ± 0.2	0.008
Visceral AT (kg)	0.2 ± 0.1	−0.1 ± 0.04	<0.0001	−0.2 ± 0.04	<0.0001
Abdominal subcutaneous AT (kg)	0.2 ± 0.2	−0.5 ± 0.1	0.005	−0.4 ± 0.1	0.006
Liver fat (%)	0.9 ± 0.7	−1.1 ± 0.7	0.061	−1.2 ± 0.6	0.042
IMCL (mmol/kg ww)	0.7 ± 0.5	1.1 ± 0.5	0.639	−0.03 ± 0.4	0.231
$V_{O_{2peak}}$ (L/min)	0.1 ± 0.1	0.9 ± 0.1	<0.0001	0.7 ± 0.1	<0.0001
$V_{O_{2peak}}$ (mL/kg/min)	−0.1 ± 1.0	9.0 ± 0.9	<0.0001	7.6 ± 0.9	<0.0001
Chest press RM (kg)	0.3 ± 1.3	2.1 ± 1.1	0.29	13.7 ± 1.1	<0.0001
Leg press RM (kg)	4.7 ± 5.8	6.6 ± 5.0	0.81	29.8 ± 4.8	0.002
Muscular strength index	0.03 ± 0.10	0.2 ± 0.2	0.37	1.0 ± 0.1	<0.0001

Data are means ± SE. Values for the control group are imputed means ± SE. Change values for the intervention groups are the difference as compared with control with SE. P values are as compared with the control group. DXA, dual energy X-ray absorptiometry; FFM, fat-free mass; ITT, intent-to-treat.

Collapsed across all groups, changes in abdominal fat (r = 0.73) and visceral fat (r = 0.67) were associated ($P <$ 0.001) with the corresponding change in WC. Further, collapsed across all groups (n = 26), the change in visceral fat was significantly related to the corresponding change in intrahepatic lipid (r = 0.72; $P <$ 0.001).

Changes in insulin action and secretion. Compared with controls, insulin sensitivity improved significantly in the resistance exercise group (0.8 ± 0.2 mL/kg/min per μU/mL; P = 0.009), and this remained significant when data were expressed per unit of fat-free mass (Table 3 and Fig. 2*C*). No significant changes in insulin secretion during the hyperglycemic clamp, disposition index (first-phase insulin × insulin sensitivity), and oral glucose tolerance (data not shown) were observed in any groups (Table 3). Collapsed across groups, the change in insulin sensitivity was significantly related to the corresponding changes in visceral AT in kilograms (r = −0.47; P = 0.003).

DISCUSSION

We examined the effects of aerobic versus resistance exercise alone without caloric restriction on abdominal obesity, ectopic fat, and insulin sensitivity and secretion in previously sedentary obese adolescent boys. This is the first randomized trial in the adolescent age group designed specifically to investigate the role of regular exercise alone on obesity-related risk factors with criterion measures including whole-body MRI, proton magnetic resonance spectroscopy, and the 2-h hyperglycemic and 3-h hyperinsulinemic-euglycemic clamp techniques. The primary finding is that both aerobic and resistance exercise performed for 180 min per week without caloric restriction resulted in significant reductions in total fat, visceral adiposity, WC, and intrahepatic lipid and in improvement in cardiorespiratory fitness in obese adolescent boys. Furthermore, resistance exercise was effective in improving insulin sensitivity, skeletal muscle mass, and muscular strength. Our findings have important health implications and provide therapeutic strategies to health care professionals for the treatment of childhood obesity and the reduction in insulin resistance in moderately obese boys.

Our finding that regular exercise, independent of modality, is associated with significant reductions in intrahepatic lipid in previously sedentary obese adolescent

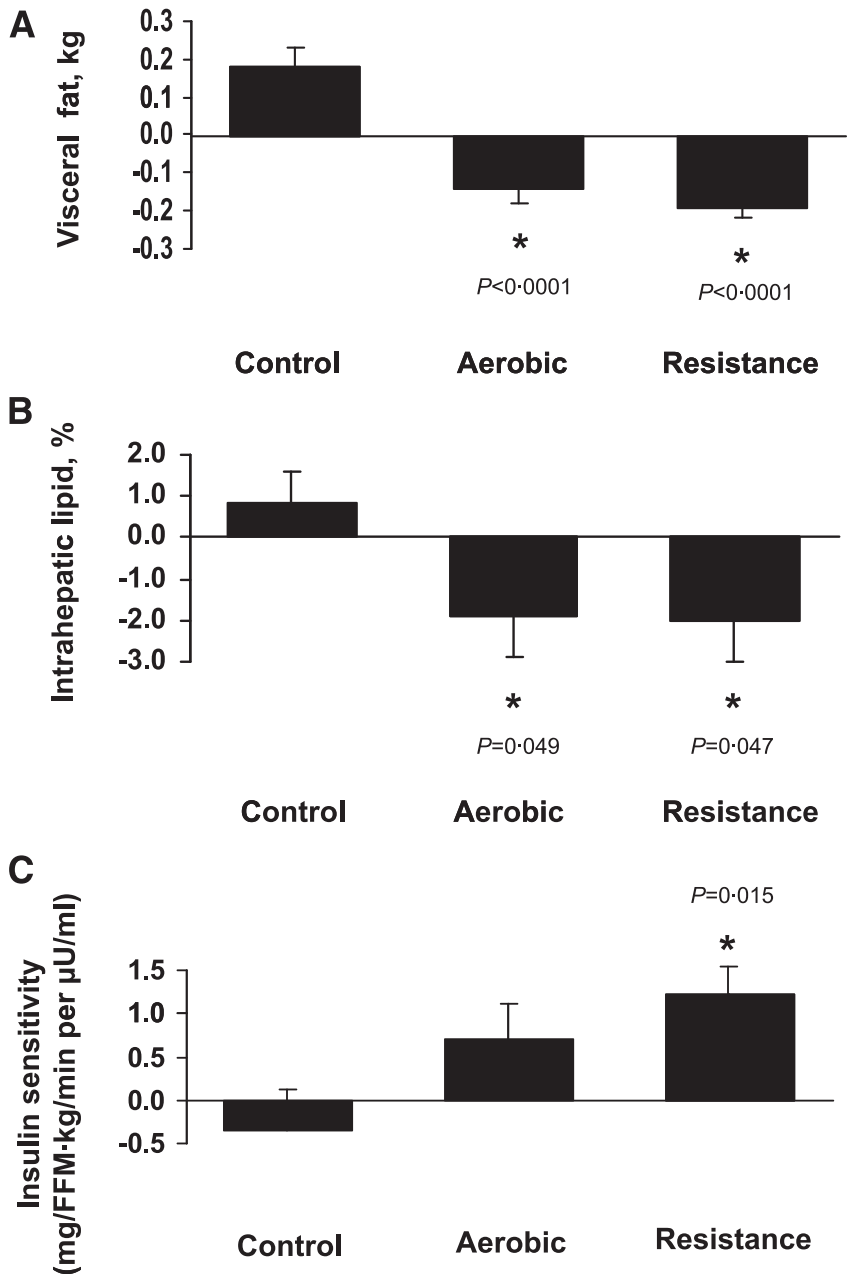

FIG. 2. Absolute changes in visceral fat (*A*), intrahepatic lipid (*B*), and insulin sensitivity (*C*) for each intervention group. **P* values are as compared with the control group (intent-to-treat analyses). FFM, fat-free mass.

boys is noteworthy, given that nonalcoholic fatty liver disease is a common feature of childhood obesity (32) and that increased liver fat is strongly associated with insulin resistance and hypertriglyceridemia in adolescents (33). Although the pathogenesis of nonalcoholic fatty liver in obese adolescents remains unclear, our observation that visceral fat is associated with intrahepatic lipid (r = 0.55) at baseline and that changes in visceral fat are related to corresponding changes in intrahepatic lipid (r = 0.72) suggests a possible link between the two fat depots.

In this study, we did not observe significant changes in IMCL content in response to either aerobic or resistance exercise training, despite improved in vivo insulin sensitivity. This is consistent with previous studies reporting no changes in IMCL after aerobic training in previously sedentary obese adults (34,35) and adolescents (36) despite improvements in insulin resistance. The implication of a lack of association between changes in IMCL and insulin sensitivity with exercise training is unclear, as cross-sectional studies have demonstrated significant relationships between IMCL and insulin resistance in individuals with obesity (37), type 2 diabetes (T2D) (38), and a family history of T2D (39). Some suggest that IMCL content per se is metabolically inert and is not likely to be a determinant of insulin resistance in skeletal muscle (35). Others have demonstrated that skeletal muscle quality, such as oxidation capacity of muscle and muscle fiber type distribution, plays a role in the association between excess IMCL and insulin resistance in obesity (40,41).

It has been shown that weight loss induced by either exercise or diet improves insulin sensitivity (9,42). Our data extend these observations and suggest that regular

TABLE 3
Absolute changes in insulin secretion and insulin sensitivity after 3 months

	Control (n = 11, ITT = 13)	Aerobic exercise (n = 15/ITT = 16)		Resistance exercise (n = 16/ITT = 16)	
	Value	Value	P value	Value	P value
ITT analysis (n = 45)					
Fasting glucose (mg/dL)	−0.3 ± 0.6	−0.4 ± 0.5	0.461	0.1 ± 0.5	0.856
Fasting insulin (μU/mL)	6.1 ± 19.1	−18.0 ± 16.1	0.263	−10.4 ± 15.8	0.509
First-phase insulin (μU/mL)	−14.5 ± 26.9	3.9 ± 22.4	0.601	−38.2 ± 21.5	0.489
Second-phase insulin (μU/mL)	−54.6 ± 27.7	−36.2 ± 23.2	0.618	−48.6 ± 22.1	0.866
Insulin sensitivity (mL/kg/min per μU/mL)	−0.1 ± 0.3	0.4 ± 0.2	0.125	0.8 ± 0.2	0.009
Insulin sensitivity (mL/FFM · kg/min per μU/mL)	−0.3 ± 0.5	0.7 ± 0.4	0.095	1.2 ± 0.4	0.015
Disposition index	−24.5 ± 94.8	105.7 ± 78.0	0.292	37.4 ± 77.1	0.611
Per protocol analysis (n = 42)					
Fasting glucose (mg/dL)	−0.1 ± 0.6	−0.3 ± 0.5	0.874	0.2 ± 0.5	0.659
Fasting insulin (μU/mL)	7.1 ± 19.1	−18.2 ± 15.9	0.315	−10.6 ± 15.9	0.481
First-phase insulin (μU/mL)	−14.3 ± 26.7	2.8 ± 22.3	0.628	−38.3 ± 21.5	0.486
Second-phase insulin (μU/mL)	−53.0 ± 27.6	−35.7 ± 23.3	0.643	−47.3 ± 22.0	0.872
Insulin sensitivity (mL/kg/min per μU/mL)	−0.1 ± 0.3	0.4 ± 0.2	0.150	0.8 ± 0.2	0.015
Insulin sensitivity (mL/FFM · kg/min per μU/mL)	−0.2 ± 0.4	0.7 ± 0.4	0.174	1.0 ± 0.4	0.037
Disposition index	−18.9 ± 94.9	104.8 ± 77.5	0.319	37.3 ± 77.5	0.649

Data are means ± SE. Values for the control group are imputed means ± SE. Change values for the intervention groups are the difference as compared with control with SE. P values are as compared with the control group. FFM, fat free mass; ITT, intent-to-treat.

exercise without caloric restriction is associated with 19% and 28% improvements in insulin sensitivity in the aerobic and resistance exercise groups, respectively. It has been reported that improvements in insulin sensitivity are associated with improvements in aerobic fitness (34) and skeletal muscle mass (43) in adult men. Thus the significant improvements in insulin sensitivity in the resistance group observed in the current study are likely explained in part by significant increases in skeletal muscle mass with training. In the aerobic group, there were similar significant improvements in aerobic fitness but smaller and nonsignificant improvements in skeletal muscle mass and insulin sensitivity. Further, it is important to consider that insulin sensitivity was measured 48–72 h after the last exercise session, and this may have contributed to our inability to observe a significant improvement in insulin sensitivity. Nevertheless, the improvements in insulin sensitivity within the exercise training groups are explained by reductions in total fat ($r = -0.43$; $P < 0.05$) and visceral adiposity ($r = -0.42$; $P < 0.05$), highlighting the importance of adiposity reduction to improve insulin sensitivity in adolescents.

We did not observe improvements in insulin secretion in the exercise training groups. Because our study participants were nondiabetic, it is reasonable to believe that they had appropriate β-cell function to compensate for insulin resistance and maintain euglycemia, and thus regular exercise alone would have little effect on insulin secretion in this nondiabetic adolescent population. It is currently unclear whether regular exercise alone is effective in improving insulin secretion in adolescents with impaired β-cell function and prediabetes or T2D.

In the current study, obese adolescent boys complied well with the prescribed exercise regimens, resulting in high attendance rates in both aerobic (99.7 ± 0.8%) and resistance (99.0 ± 2.1%) groups. This observation suggests that our exercise regimen (three times/week or 180 min/week) is feasible and effective for obese adolescent boys. Anecdotally, however, there were differences in how much the boys enjoyed the exercise intervention. In the aerobic group, the participants found the exercise to be boring, whereas those in the resistance group were much more enthusiastic and seemingly enjoyed the exercise intervention. Given the superior improvements with resistance exercise and the enjoyment factor, we propose therefore that resistance exercise may be a better mode of exercise for moderately obese boys of this age group.

The limitations of this study warrant mention. Although this is the first study in adolescents to use state-of-the-art methodologies to examine the effects of different exercise modalities without caloric restriction on adiposity reduction and insulin resistance, our observations are based on healthy pubertal moderately obese adolescent boys, who were black or white. Whether our findings would remain true in girls, other ethnic groups, or youth at different pubertal developmental stages is unknown. This was a tightly controlled efficacy study, and all exercise was completed under supervision, and thus our findings cannot be generalized to the general population of obese adolescent boys. Supervision, access, cost, and the support received during the study may have helped to improve compliance; however, the high level of compliance allowed us to assess more effectively the effects of exercise training on our outcomes of interest. During the study, leisure time physical activity was not measured with pedometers or accelerometers, and although subjects were asked to log their energy intake, this was not completed by a significant portion of subjects and was generally done very poorly.

In our study, subject recruitment was an ongoing process during the entire study period. Seasonal variations and age have been shown to affect physical activity patterns in youth (44). In addition, although our findings from a short-term exercise intervention are encouraging, evidence regarding the benefits of long-term exercise on obesity-related health outcomes in youth is unclear. In adults, the findings from short-term (<4 months) exercise intervention

studies generally report higher energy expenditure and thus much greater reductions in body weight and total fat than long-term (> 6months) exercise intervention studies (45). It is unclear whether the health benefits and compliance observed in our study can be maintained long-term in obese adolescents. Finally, biomarkers such as retinol binding protein 4 and inflammatory factors have not been analyzed, which is also a limitation of the study. Examining biomarkers is important, as they are useful in illuminating the potential cross talk between organs in our efforts to identify risk factors for diabetes and cardiovascular disease (46,47).

In summary, both aerobic and resistance exercise without caloric restriction are effective for reducing abdominal fat and intrahepatic lipid in moderately obese adolescent boys. Resistance exercise but not aerobic exercise is also associated with significant improvements in insulin sensitivity.

ACKNOWLEDGMENTS

This research was funded by American Diabetes Association Junior Faculty Award 7-08-JF-27 to S.L.; by Department of Defense Grant FA7014-02-2-001 to S.L. and S.A.; by National Institutes of Health Grants K24-HD-01357 to S.A. and UL1-RR-024153 and UL1-TR-000005 to S.L.; and by the Cochrane-Weber Foundation at Children's Hospital of Pittsburgh to S.L.

No potential conflicts of interest relevant to this article were reported.

The funders played no role in the design and conduct of the study, collection of data, management of the study, analysis of data, interpretation of the data, or preparation of the manuscript.

S.L. designed the study, obtained funding, researched data, and wrote the manuscript. F.B. and T.H. researched data and reviewed the manuscript. J.K. performed statistical analyses and provided critical revision of the manuscript. C.B. together with S.L. established the magnetic resonance spectroscopy protocol at the University of Pittsburgh and assisted in magnetic resonance spectroscopic data analyses and interpretations. S.A. obtained funding, researched data, and provided critical revision of the manuscript. S.L. is the guarantor of this work and, as such, had full access to all the data in this study and takes full responsibility for the integrity of the data and the accuracy of the data analysis.

The authors thank the study participants and their parents, as well as Nancy Guerra (nurse practitioner, Children's Hospital of Pittsburgh), Allison Prince (project coordinator, Case Western Reserve University), Yoonmyung Kim (research assistant, Yonsei University), Resa Stauffer (laboratory research technician, Children's Hospital of Pittsburgh), the Pediatric Clinical and Translational Research Center nursing staff, and the YMCA of Greater Pittsburgh.

REFERENCES

1. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999-2010. JAMA 2012;307:483–490
2. Bacha F, Saad R, Gungor N, Janosky J, Arslanian SA. Obesity, regional fat distribution, and syndrome X in obese black versus white adolescents: race differential in diabetogenic and atherogenic risk factors. J Clin Endocrinol Metab 2003;88:2534–2540
3. Li C, Ford ES, Mokdad AH, Cook S. Recent trends in waist circumference and waist-height ratio among US children and adolescents. Pediatrics 2006;118:e1390–e1398
4. McCarthy HD, Jarrett KV, Emmett PM, Rogers I. Trends in waist circumferences in young British children: a comparative study. Int J Obes (Lond) 2005;29:157–162
5. Lee S, Bacha F, Arslanian SA. Waist circumference, blood pressure, and lipid components of the metabolic syndrome. J Pediatr 2006;149:809–816
6. Lee S, Bacha F, Gungor N, Arslanian SA. Waist circumference is an independent predictor of insulin resistance in black and white youths. J Pediatr 2006;148:188–194
7. Irwin ML, Yasui Y, Ulrich CM, et al. Effect of exercise on total and intraabdominal body fat in postmenopausal women: a randomized controlled trial. JAMA 2003;289:323–330
8. Sigal RJ, Kenny GP, Boulé NG, et al. Effects of aerobic training, resistance training, or both on glycemic control in type 2 diabetes: a randomized trial. Ann Intern Med 2007;147:357–369
9. Ross R, Dagnone D, Jones PJ, et al. Reduction in obesity and related comorbid conditions after diet-induced weight loss or exercise-induced weight loss in men. A randomized, controlled trial. Ann Intern Med 2000;133:92–103
10. Ross R, Janssen I, Dawson J, et al. Exercise-induced reduction in obesity and insulin resistance in women: a randomized controlled trial. Obes Res 2004;12:789–798
11. Poehlman ET, Dvorak RV, DeNino WF, Brochu M, Ades PA. Effects of resistance training and endurance training on insulin sensitivity in nonobese, young women: a controlled randomized trial. J Clin Endocrinol Metab 2000; 85:2463–2468
12. Nassis GP, Papantakou K, Skenderi K, et al. Aerobic exercise training improves insulin sensitivity without changes in body weight, body fat, adiponectin, and inflammatory markers in overweight and obese girls. Metabolism 2005;54:1472–1479
13. van der Heijden GJ, Toffolo G, Manesso E, Sauer PJ, Sunehag AL. Aerobic exercise increases peripheral and hepatic insulin sensitivity in sedentary adolescents. J Clin Endocrinol Metab 2009;94:4292–4299
14. Shaibi GQ, Cruz ML, Ball GD, et al. Effects of resistance training on insulin sensitivity in overweight Latino adolescent males. Med Sci Sports Exerc 2006;38:1208–1215
15. Van Der Heijden GJ, Wang ZJ, Chu Z, et al. Strength exercise improves muscle mass and hepatic insulin sensitivity in obese youth. Med Sci Sports Exerc 2010;42:1973–1980
16. Escalante Y, Saavedra JM, García-Hermoso A, Domínguez AM. Improvement of the lipid profile with exercise in obese children: a systematic review. Prev Med 2012;54:293–301
17. Suh S, Jeong IK, Kim MY, et al. Effects of resistance training and aerobic exercise on insulin sensitivity in overweight korean adolescents: a controlled randomized trial. Diabetes Metab J 2011;35:418–426
18. Davidson LE, Hudson R, Kilpatrick K, et al. Effects of exercise modality on insulin resistance and functional limitation in older adults: a randomized controlled trial. Arch Intern Med 2009;169:122–131
19. Kuczmarski RJ, Ogden CL, Guo SS, et al. 2000 CDC Growth Charts for the United States: methods and development. Vital Health Stat 11 2002;(246): 1–190
20. Harris JA, Benedict FF. *A Biometric Study of Basal Metabolism in Man*. Washington, DC, Carnegie Institution of Washington, 1919
21. McArdle WD, Katch FI, Katch VL. Essentials of Exercise Physiology. 3rd ed. Baltimore, Lippincott Williams & Wilkins, 2006
22. Ross R, Rissanen J, Pedwell H, Clifford J, Shragge P. Influence of diet and exercise on skeletal muscle and visceral adipose tissue in men. J Appl Physiol 1996;81:2445–2455
23. Arslanian SA, Saad R, Lewy V, Danadian K, Janosky J. Hyperinsulinemia in African-American children: decreased insulin clearance and increased insulin secretion and its relationship to insulin sensitivity. Diabetes 2002;51: 3014–3019
24. Arslanian SA, Lewy VD, Danadian K. Glucose intolerance in obese adolescents with polycystic ovary syndrome: roles of insulin resistance and beta-cell dysfunction and risk of cardiovascular disease. J Clin Endocrinol Metab 2001;86:66–71
25. Perseghin G, Price TB, Petersen KF, et al. Increased glucose transport-phosphorylation and muscle glycogen synthesis after exercise training in insulin-resistant subjects. N Engl J Med 1996;335:1357–1362
26. Lee S, Kim Y, Kuk JL, Boada FE, Arslanian S. Whole-body MRI and ethnic differences in adipose tissue and skeletal muscle distribution in overweight black and white adolescent boys. J Obes 2011;2011:159373
27. Boesch C, Machann J, Vermathen P, Schick F. Role of proton MR for the study of muscle lipid metabolism. NMR Biomed 2006;19:968–988
28. Naressi A, Couturier C, Devos JM, et al. Java-based graphical user interface for the MRUI quantitation package. MAGMA 2001;12:141–152
29. Jurca R, Lamonte MJ, Church TS, et al. Associations of muscle strength and fitness with metabolic syndrome in men. Med Sci Sports Exerc 2004; 36:1301–1307

30. Lee S, Kuk JL, Davidson LE, et al. Exercise without weight loss is an effective strategy for obesity reduction in obese individuals with and without Type 2 diabetes. J Appl Physiol 2005;99:1220–1225
31. Ratitch B, O'Kelly M. Implementation of Pattern-Mixture Models Using Standard SAS/STAT Procedures. PharmaSUG 2011: Paper-SP04. Available from http://www.pharmasug.org/proceedings/2011/SP/PharmaSUG-2011-SP04.pdf
32. Schwimmer JB, Deutsch R, Kahen T, Lavine JE, Stanley C, Behling C. Prevalence of fatty liver in children and adolescents. Pediatrics 2006;118:1388–1393
33. Burgert TS, Taksali SE, Dziura J, et al. Alanine aminotransferase levels and fatty liver in childhood obesity: associations with insulin resistance, adiponectin, and visceral fat. J Clin Endocrinol Metab 2006;91:4287–4294
34. Gan SK, Kriketos AD, Ellis BA, Thompson CH, Kraegen EW, Chisholm DJ. Changes in aerobic capacity and visceral fat but not myocyte lipid levels predict increased insulin action after exercise in overweight and obese men. Diabetes Care 2003;26:1706–1713
35. Larson-Meyer DE, Heilbronn LK, Redman LM, et al. Effect of calorie restriction with or without exercise on insulin sensitivity, beta-cell function, fat cell size, and ectopic lipid in overweight subjects. Diabetes Care 2006;29:1337–1344
36. van der Heijden GJ, Wang ZJ, Chu ZD, et al. A 12-week aerobic exercise program reduces hepatic fat accumulation and insulin resistance in obese, Hispanic adolescents. Obesity (Silver Spring) 2010;18:384–390
37. Thamer C, Machann J, Bachmann O, et al. Intramyocellular lipids: anthropometric determinants and relationships with maximal aerobic capacity and insulin sensitivity. J Clin Endocrinol Metab 2003;88:1785–1791
38. Misra A, Sinha S, Kumar M, Jagannathan NR, Pandey RM. Proton magnetic resonance spectroscopy study of soleus muscle in non-obese healthy and Type 2 diabetic Asian Northern Indian males: high intramyocellular lipid content correlates with excess body fat and abdominal obesity. Diabet Med 2003;20:361–367
39. Perseghin G, Scifo P, De Cobelli F, et al. Intramyocellular triglyceride content is a determinant of in vivo insulin resistance in humans: a ^{1}H-^{13}C nuclear magnetic resonance spectroscopy assessment in offspring of type 2 diabetic parents. Diabetes 1999;48:1600–1606
40. Goodpaster BH, He J, Watkins S, Kelley DE. Skeletal muscle lipid content and insulin resistance: evidence for a paradox in endurance-trained athletes. J Clin Endocrinol Metab 2001;86:5755–5761
41. Malenfant P, Joanisse DR, Thériault R, Goodpaster BH, Kelley DE, Simoneau JA. Fat content in individual muscle fibers of lean and obese subjects. Int J Obes Relat Metab Disord 2001;25:1316–1321
42. Goodpaster BH, Kelley DE, Wing RR, Meier A, Thaete FL. Effects of weight loss on regional fat distribution and insulin sensitivity in obesity. Diabetes 1999;48:839–847
43. Miller WJ, Sherman WM, Ivy JL. Effect of strength training on glucose tolerance and post-glucose insulin response. Med Sci Sports Exerc 1984; 16:539–543
44. Carson V, Spence JC. Seasonal variation in physical activity among children and adolescents: a review. Pediatr Exerc Sci 2010;22:81–92
45. Ross R, Janssen I. Physical activity, total and regional obesity: dose-response considerations. Med Sci Sports Exerc 2001;33(6 Suppl.):S521–S529
46. Eckel RH, Kahn R, Robertson RM, Rizza RA. Preventing cardiovascular disease and diabetes: a call to action from the American Diabetes Association and the American Heart Association. Diabetes Care 2006;29: 1697–1699
47. Balagopal PB, de Ferranti SD, Cook S, et al.; American Heart Association Committee on Atherosclerosis Hypertension and Obesity in Youth of the Council on Cardiovascular Disease in the Young; Council on Nutrition, Physical Activity and Metabolism; Council on Epidemiology and Prevention. Nontraditional risk factors and biomarkers for cardiovascular disease: mechanistic, research, and clinical considerations for youth: a scientific statement from the American Heart Association. Circulation 2011;123:2749–2769