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Exercise Alone Reduces Insulin Resistance in Obese Children Independently of Changes in Body Composition

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Context: The number of obese children with insulin resistance and type 2 diabetes is increasing, but the best management strategy is not clear.

Objective: The objective of this study was to assess the effect of a structured 8-wk exercise training program on insulin resistance and changes in body composition in obese children.

Design: The study was 8 wk of structured supervised exercise intervention with outcome measures before and after the exercise period.

Subjects: Fourteen obese children (12.70 ± 2.32 yr; eight male, six female) with high fasting insulin levels were enrolled into the study.

Intervention: Intervention consisted of 8 wk of supervised circuit-based exercise training, composed of three fully supervised 1-h sessions per week.

Outcome Measures: Outcome measures were assessed pretraining program and posttraining program and included insulin sensitivity (euglycemic-hyperinsulinemic clamp studies), fasting insulin and glucose levels, body composition using dual energy x-ray absorptiometry scan, lipid profile, and liver function tests.

Results: Insulin sensitivity improved significantly after 8 wk of training (M_{lbm} 8.20 ± 3.44 to 10.03 ± 4.33 mg/kg·min, $P < 0.05$). Submaximal exercise heart rate responses were significantly lower following the training ($P < 0.05$), indicating an improvement in cardiorespiratory fitness. Dual energy x-ray absorptiometry scans revealed no differences in lean body mass or abdominal fat mass.

Conclusion: An 8-wk exercise training program increases insulin sensitivity in obese children, and this improvement occurred in the presence of increased cardiorespiratory fitness but is independent of measurable changes in body composition. (***J Clin Endocrinol Metab* 92: 4230–4235, 2007**)

COMPLICATIONS OF OVERWEIGHT and obesity are becoming major health care issues due to the increasing prevalence of childhood obesity and overweight. Possibly the largest health burden will result from type 2 diabetes mellitus (T2DM) and cardiovascular disease. Previously considered a disease of adults, T2DM is now increasing in children (1–3).

Insulin resistance precedes the development of T2DM; resultant high insulin levels and gradual development of impaired glucose tolerance are disease precursors (4). In adults, abdominal adiposity is associated with insulin resistance and T2DM (5–7), and the evidence for this in childhood is increasing (8–11). Similarly, insulin resistance, measured via euglycemic-hyperinsulinemic clamp studies, has been shown to improve with exercise programs over time in adult subjects (12–14). However data on the impact of exercise training on insulin resistance in overweight and obese children are limited. Most studies have used a cross-sectional analysis to examine insulin resistance in children of different fitness levels (15, 16) or with different levels of self-reported physical activity (15, 17). These studies have found that those who report greater levels of physical activity have lower insulin levels and, by inference, greater insulin sensitivity (17).

Some exercise intervention studies, in youth, using fasting insulin or oral glucose tolerance tests (OGTT) as measures of insulin resistance, have suggested a decrease in insulin resistance after exercise, but the effect was not quantifiable due to methodological limitations (18, 19). In children, there are no published longitudinal studies that have examined the effect of exercise training on insulin resistance or hyperinsulinism. Furthermore, no studies in children have examined changes in insulin resistance together with changes in body composition.

Euglycemic-hyperinsulinemic clamp techniques have been used in children to quantify insulin resistance in obesity; however, these have been cross-sectional studies.

In the present study, sedentary obese children with high fasting insulin levels were recruited to an 8-wk controlled exercise training program. Outcome measures included body composition, fitness, and insulin resistance.

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Abbreviations: BMI, Body mass index; DEXA, dual energy x-ray absorbtiometry; OGTT, oral glucose tolerance test; T2DM, type 2 diabetes.

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Subjects and Methods

Subjects

Sedentary obese children and adolescents aged between 9 and 16 yr were recruited from tertiary referral clinics. All children were above the 95th percentile for body mass index (BMI) for age (20), and all had elevated fasting insulin levels greater than 12.0 mU/liter (but normal fasting glucose) before commencement of the study. Exclusion criteria included secondary obesity, underlying genetic syndrome, and T2DM. The study was approved by the Princess Margaret Hospital Ethics Committee, and written informed consent was obtained from the parent and assent was obtained from the child or adolescent.

Exercise training intervention

The intervention comprised of 8 wk of group "circuit" exercise training involving three 1-h sessions per week, fully supervised by a trained Exercise Physiologist, for a total of 24 sessions. The sessions were circuit-based, involving mixed aerobic and resistance (modified for age) stations. A circuit consisted of aerobic cycle ergometer exercise, alternated with exercise performed on weight-stack machines (Pulsestar, Cheshire, UK). After a 10-min warm-up period of stretching and low-intensity cycle or treadmill exercise, each exercise session would begin with 1 min of cycle ergometry (initially maintained at 65% of maximum heart rate, progressed to 85% by wk 3) followed, at the sound of a buzzer, by movement to the first weight stack machine (12 repetitions per minute, initially maintained at ~55% of pretraining maximum voluntary contraction, progressed to ~65% by wk 3). After a minute of exercise on this machine, subjects returned to the cycle ergometer and the circuit continued until all 10 machine stations were completed. Subjects completed two sets of this circuit at each of the three weekly visits to the gymnasium for 8 wk. Inclusive of the final 10-min cool down period, the exercise sessions lasted approximately 60 min. To address the issue of relative exercise intensity, individual measurements of maximal strength were made for each of the resistance exercise stations and we determined age-predicted maximal exercise heart rate data. All subjects then exercised at individualized absolute workloads and resistances, but exercise was matched between subjects in relative terms.

Throughout the study period, the children were asked to maintain a healthy diet, but no standard dietary modifications were made to gauge the effect of added exercise alone to the child's lifestyle.

Assessment

Pretraining period and posttraining period medical assessment and insulin sensitivity was carried out by the same physician investigator (L.M.B.). Medical and family history, physical examination, anthropometric measurements, and Tanner staging were performed. Weight, height, waist and hip circumference, and blood pressure were measured and BMI was calculated as weight/height^2 and expressed as kilograms per square meter. Age- and sex-specific BMI z-scores were calculated from the 2000 Centers for Disease Control and Prevention Growth Reference, USA (21). All anthropometric parameters were obtained by taking the average of three sequential measurements.

Body composition was measured by whole-body dual energy x-ray absorptiometry (DEXA), using the Norland XR36 Quickscan DEXA scanner. Total lean mass, total fat mass, and percentage body fat was obtained for each subject, as well as lean and fat mass by body compartment. Five body compartments were used (head, trunk, abdomen, upper limbs, and lower limbs) as defined by bony landmarks. This analysis was performed blind by an independent investigator.

Before and after the 8-wk training period, a submaximal exercise test was performed in each subject consisting of three consecutive 4-min incremental epochs of exercise on a braked bicycle ergometer (Monark, Varberg, Sweden) with subjects continuously cycling at 50–60 revolutions per minute. Heart rate was continuously measured in beats per minute by telemetric method (Polar Electro, Kempele, Finland). Identical exercise intensities were used before and after exercise training in each subject and changes in fitness were assessed by comparing heart rate responses at these matched workloads.

Euglycemic-hyperinsulinemic clamp tests

Insulin sensitivity was measured by the euglycemic-hyperinsulinemic clamp technique. All clamp tests were performed not less than 48 h after completion of the last training session, to decrease the possibility of an acute impact of the final exercise bout. Each subject was admitted to the research center at 0800 h after an overnight fast and had two 18-gauge iv cannulae placed. One cannula was inserted into the dorsum of the hand for sampling blood glucose, and one into the contralateral cubital fossa for infusion of both a standard 60 mU/m^2·min of insulin, and variable rate infusion of 20% dextrose. At baseline, blood was obtained for fasting insulin and glucose samples, fasting lipid profile, and liver function tests. The insulin infusion was commenced at time 0, and the blood glucose level of the subject was taken from the sampling line at 5-min intervals and analyzed immediately using a YSI 2300 Stat Plus glucose and lactate analyzer. The 20% dextrose infusion was titrated accordingly to keep the blood glucose level of the subject at 5.0 mmol/liter. All calculations were performed on the results from time 120–180 min of the clamp, when steady state had been achieved. "$M_{(lbm)}$" was calculated as the measure of insulin sensitivity, defined as the milligrams of glucose infused per kilogram of lean body mass per minute to keep blood glucose at 5.0 mmol/liter during the steady-state period.

Measurements and biochemistry

Weight was measured to two decimal places on a digital balance scale in light clothing without shoes. Height was measured to the nearest millimeter on a wall-mounted stadiometer. Weight and hip circumference were measured using a standard nonelastic tape measure to the nearest 0.5 cm. Blood pressure was measured in the seated position with a Critikon Dinamap 8262-H4139 and an appropriate size cuff.

Plasma glucose was measured using the colorimetric method (VITROS GLU; Ortho-Clinical Diagnostics, Rochester, NY). Plasma insulin was determined by chemiluminescent immunometric assay (IMMULITE 2000; Diamond Diagnostics, Holliston, MA). Cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, and alanine aminotransferase were all were measured by colorimetric method (VITROS CHOL and VITROS 250; Ortho-Clinical Diagnostics).

Statistical analysis

All data are shown as mean ± SD or as percentages. Analysis was performed with the SPSS statistical package (SPSS, Chicago, IL) and Stata 8.0. The Wilcoxon signed ranks test was used to test the null hypothesis that there was no difference between the preexercise and postexercise data, due to the small number of subjects. Correlations were tested using Pearson's or Spearman's rank test as appropriate.

The study was powered to detect a 25% difference in insulin sensitivity (as measured by clamp test) using a paired study design, a type I error of 5%, and a power of 80% [based on the metabolic studies by Sunehag *et al.* (22)].

Initially, DEXA results were reported as grams of lean mass and grams of fat mass for each subject. However, for comparisons to be made between subjects, DEXA results were converted to percentages of the total body weight of each individual. This allows meaningful comparisons of body composition changes between individuals of different age, sex, and body shape.

Results

Fourteen subjects, eight males and six females, were enrolled (age 12.70 ± 2.32 yr). All subjects were obese (BMI 31.658 ± 4.436 kg/m^2 and BMI z-score 2.23 ± 0.30). There was no difference between males and females in age, BMI, or BMI z-score. Attendance for the 8-wk training period was over 87%. No subject missed more than four sessions.

Anthropometric measures

Over the 8 wk of intervention there was a significant increase in height (1.59 *vs.* 1.60 m, $P < 0.05$) but no change in weight (80.6 *vs.* 81.2 kg, $P = 0.47$). BMI z-score (2.23 *vs.* 2.20,

TABLE 1. Anthropometric data, blood pressure, and fitness results for the cohort before and after the 8-wk exercise training period

	Preexercise	Postexercise	*P* value
N	14	14	
Height (m)	1.59 ± 0.12	1.60 ± 0.11	0.003[a]
Weight (kg)	80.62 ± 19.20	81.20 ± 19.0	0.470
BMI (kg/m^2)	31.58 ± 4.36	31.19 ± 4.03	0.103
BMI z-score	2.23 ± 0.30	2.20 ± 0.30	0.032[a]
Waist (cm)	97.08 ± 13.70	94.82 ± 13.36	0.045[a]
Hips (cm)	106.34 ± 13.30	105.78 ± 14.27	0.700
BP systolic (mm Hg)	109.14 ± 29.23	104.50 ± 31.17	0.555
BP diastolic (mm Hg)	86.64 ± 25.79	83.14 ± 29.48	0.059
Fitness test (heart rate bpm)	164.54 ± 12.79	154.61 ± 8.97	0.011[a]

[a] $P \leq 0.05$.

$P < 0.05$) and waist circumference decreased ($P < 0.05$), but BMI, hip girth, and systolic and diastolic blood pressure were unchanged (see Table 1).

Body composition

Analysis of DEXA results by body compartment showed no significant differences between mean pretraining and posttraining body composition values (see Table 2) in either fat or lean body mass.

Aerobic fitness

Submaximal exercise heart rate responses were significantly lower after the training period ($P < 0.05$), indicating an improvement in cardiorespiratory fitness. Differences were evident at the highest workload (work load 3: heart rate 165.27 ± 12.65 to 154.61 ± 8.98 bpm, $P < 0.001$).

Insulin sensitivity

There was a wide range of pretraining $M_{(lbm)}$ values (3.68 to 13.40 mg/kg·min, mean 8.20 ± 3.44 mg/kg·min). There was no significant correlation between the pretraining $M_{(lbm)}$ and sex, age, or heart rate during the fitness test, or compartmental body composition. Posttraining $M_{(lbm)}$ values ranged between 4.09–17.42 mg/kg·min, with a mean of 10.02 ± 4.33 mg/kg·min. There were no significant correlations between posttraining $M_{(lbm)}$ and heart rate during the fitness test, or compartmental body composition data.

Insulin sensitivity improved after 8 wk of training (pretraining $M_{(lbm)}$ *vs.* posttraining $M_{(lbm)}$: 8.20 mg/kg·min *vs.* 10.02 mg/kg·min, $P < 0.05$ (Fig. 1). There was no relationship between the degree of improvement in $M_{(lbm)}$ and baseline insulin sensitivity.

There were no significant correlations of the change in $M_{(lbm)}$ with gender, age, improvement in fitness, the number of sessions attended, change in weight, or change in BMI or BMI z score. There was also no correlation between $M_{(lbm)}$ and degree of change in any parameter of body composition. Apart from insulin sensitivity, there were no other significant changes in fasting blood results (Table 3).

Discussion

Insulin resistance is one of the major complications of obesity. There are now reports of increasing T2DM in children, and this is considered a consequence of increasing obesity rates.

This study has found that an 8-wk exercise training program improves insulin resistance in obese children in the presence of improved exercise capacity, but in the absence of changes in body weight or body composition. The baseline insulin sensitivity [$M_{(lbm)}$] measurements taken in this study are similar to those measured in cross-sectional studies in children by other researchers (17, 23–25).

The strengths of this study include the involvement of a trained pediatric Exercise Physiologist and small numbers of subjects in each exercise session, resulting in high attendance rates (87%) and a high level of personal attention for each subject. The use of DEXA scans to define body compartments allowed the regional analysis of lean mass and fat mass. Although demanding and time-intensive, the use of euglycemic-hyperinsulinemic clamp tests as outcome measures has allowed us to detect changes in insulin sensitivity that would have been missed by using fasting insulin levels. Schmitz *et al.* (17) assessed the correlation between self-reported physical activity and insulin sensitivity in children using both a euglycemic-hyperinsulinemic clamp and fasting insulin in a cross-sectional study. They report mean values

TABLE 2. DEXA scan results for the cohort before and after the 8-wk exercise training period

	Pretraining period raw values (kg)	Pretraining period (% of total body mass)	Posttraining period (% of total body mass)	*P* value
N	14	14	14	
Total fat mass	39.66 ± 11.58	47.07 ± 5.23	46.50 ± 5.84	0.378
Trunk lean mass	17.28 ± 5.62	22.18 ± 3.26	22.72 ± 3.34	0.177
Trunk fat mass	17.13 ± 4.11	22.44 ± 1.93	22.50 ± 2.67	0.875
Abdominal lean mass	6.88 ± 2.27	9.93 ± 1.39	9.17 ± 1.54	0.414
Abdominal fat mass	7.55 ± 1.98	10.02 ± 0.90	9.73 ± 1.27	0.221
Arms lean mass	4.83 ± 1.77	6.37 ± 1.17	6.07 ± 1.37	0.272
Arms fat mass	6.50 ± 2.48	8.71 ± 2.23	8.97 ± 3.12	0.778
Legs lean mass	14.31 ± 4.19	18.47 ± 1.73	18.62 ± 2.10	0.875
Legs fat mass	12.50 ± 3.14	16.38 ± 2.41	16.13 ± 2.87	0.149

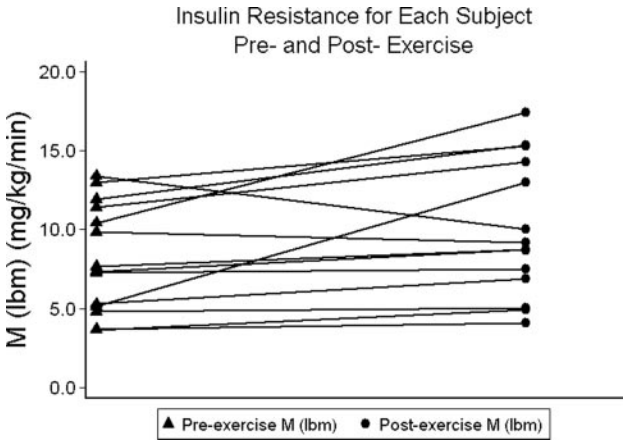

FIG. 1. Line graph of the changes in insulin resistance [$M_{(lbm)}$] for each subject before and after the 8-wk exercise training period.

between $M_{(lbm)}$ 11.80 ± 4.02 and 14.26 ± 4.33 mg/kg·min (for low and high levels of reported physical activity respectively). They also reported that "using fasting insulin as a measure of insulin sensitivity underestimates the magnitude of the potential for physical activity to improve insulin sensitivity" (17). Other research groups have reported values in a similar range for insulin sensitivity in obese children in cross-sectional studies (23–25). There are no other published results of clamp studies investigating insulin resistance in children involved in a longitudinal repeated measures study of the impact of exercise training.

Several limitations to the present study are germane. This study involved children of both sexes and included an age range across which puberty influences insulin resistance. Ideally, separate analysis of males and females using tighter age ranges would be used. To reduce this potential error, pubertal status was assessed by Tanner staging and was clinically unchanged for the short period of the study in all subjects.

The study would have been strengthened by using a control group of nonexercising children. However, it would be difficult and perhaps unethical to recruit obese children for invasive clamp studies without offering an intervention. Alternatively, a control arm could be achieved by extending the study to 16 wk and adding an 8-wk rest period before the 8-wk exercise period. This would necessitate three clamp tests (one at commencement of the study, one at 8 wk, and one at 16 wk) and be more invasive and potentially have a greater drop-out. We considered controlling the study using a cross-over design, but this too would have necessitated three clamp studies. Nevertheless, we think it unlikely that the improvement in insulin resistance we observed would have occurred spontaneously over an 8-wk period in subjects who remained sedentary. Although the improvement in insulin resistance we observed was independent of changes in segmental DEXA measures of fat and muscle, it is possible that changes in visceral or sc fat occurred that were not distinguished by our DEXA approach.

The medical literature is unclear as to whether obesity or a lack of fitness is the most important predictor of cardiovascular mortality and morbidity, and whether this varies between individuals. Data from adult men and women suggest that obese individuals who are fit have a lower risk of mortality compared with lean individuals who are unfit (26, 27). In addition, recent studies suggest that fitness is a stronger predictor of fasting insulin levels than fatness in overweight male middle-school children (28). The present study adds novel insight to this question, having established improvement in euglycemic-hyperinsulinemic clamp derived measures of insulin resistance, in the absence of change in DEXA measures of body composition, in response to a well-attended exercise training intervention that improved exercise capacity. Nonetheless, we concur with a recent discussion on the topic by Esposito and colleagues (29) who acknowledge that "from the standpoint of preventive medicine, the debate . . . seems largely academic", because regular physical activity is the treatment for both obesity and poor cardiovascular fitness.

Studies that investigate the relationship between body fat and insulin resistance after exercise have shown mixed results. Some show stable body composition after an exercise training program (30, 31), whereas others report decreases in fat mass and increases in lean body mass (32, 33). Treuth *et al.* (31) studied obese girls during a 5-month resistance exercise training program and found an increase in overall body fat, but visceral fat did not increase. Insulin as measured by OGTT improved nonsignificantly, but no more sophisticated measures of insulin resistance were used (31). These changes may also depend on the type of exercise undertaken (34) (*i.e.* resistance/weight training *vs.* aerobic/cardiovascular exercise) and the length of the exercise intervention period. The subjects in this study performed circuit training, involving both types of exercise in combination and, therefore, the effects of separate types of exercise cannot be distinguished. There are currently no published studies that compare the effects of endurance *vs.* resistance exercise on body composition and insulin resistance in children.

TABLE 3. Results of blood investigations and $M_{(lbm)}$ for the cohort before and after the 8-wk exercise training period

	Preexercise	Postexercise	*P* value
N	14	14	
M (lbm) (mg/kg·min)	8.20 ± 3.44	10.02±4.33	0.019[a]
Fasting PGL (mmol/liter)	4.63 ± 0.39	4.62 ± 0.23	0.893
Fasting insulin (mU/liter)	22.23 ± 16.27	19.40 ± 12.23	0.209
Total cholesterol (mmol/liter)	3.85 ± 1.30	4.07 ± 0.65	0.937
HDL (mmol/liter)	1.09 ± 0.44	1.13 ± 0.31	0.788
LDL (mmol/liter)	2.18 ± 0.82	2.27 ± 0.66	0.783
TG (mmol/liter)	1.24 ± 0.53	1.42 ± 0.49	0.583
ALT (mU/liter)	26.08 ± 12.22	26.00 ± 14.30	0.969

HDL, High-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides; ALT, alanine aminotransferase; PGL, plasma glucose level.
[a] $P \leq 0.05$.

It is interesting that waist circumference decreased significantly over the training period whereas abdominal fat and lean mass (as measured by DEXA) did not. This is important because waist circumference is known to be linked to long-term cardiovascular risk factors. This may imply redistribution of abdominal fat or a change in the ratio of visceral fat (inside the abdominal cavity surrounding the organs) from sc or abdominal wall fat (outside the abdominal cavity). Another hypothesis is that increased abdominal tone (without changes in abdominal lean or fat mass) may be reflected in decreased waist circumference before other changes are seen.

Mixed results have been shown in the few intervention studies that have attempted to determine whether exercise programs achieve improvements in insulin resistance through changes in body composition or through improvements in fitness. Gutin *et al*. (35, 36) used aerobic exercise training programs for obese girls and showed a trend toward decreases in fasting insulin (clamp studies were not used) in the absence of changes in body fat. However, in a later study, the same group found decreases in fasting insulin together with decreases in body fat after an exercise program (37). Both studies used DEXA as the measure of body composition. Treuth *et al.* (31) used only resistance exercise but found an improvement in OGTT parameters and static visceral fat levels in the face of increasing overall body fat. Conflicting findings from a number of studies may be due to differences in study design, study populations, and outcome measures. It is likely that different causal pathways to disease may become apparent as studies use more sophisticated outcome measures. Our data suggest that fitness is an important management approach to decrease insulin resistance. The reversal of obesity-related insulin resistance may have benefits in the prevention of impaired glucose tolerance and T2DM in children.

In summary, there are many issues to be resolved in this field, most involving the metabolic pathways involved in the relationships between fitness, fatness, and insulin resistance. However, this study has shown for the first time that insulin resistance can be improved with 8 wk of exercise training in obese children at risk of the development of T2DM.

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