Aerobic Exercise Increases Peripheral and Hepatic Insulin Sensitivity in Sedentary Adolescents

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Context: Data are limited on the effects of controlled aerobic exercise programs (without weight loss) on insulin sensitivity and glucose metabolism in children and adolescents.

Objective: To determine whether a controlled aerobic exercise program (without weight loss) improves peripheral and hepatic insulin sensitivity and affects glucose production (GPR), gluconeogenesis and glycogenolysis in sedentary lean and obese Hispanic adolescents.

Patients and Design: Twenty-nine post-pubertal adolescents (14 lean: 15.1 $\pm$ 0.3y; 20.6 $\pm$ 0.8kg/m^2; 18.9$\pm$1.5% body fat and 15 obese: 15.6 $\pm$ 0.4y; 33.2 $\pm$ 0.9kg/m^2; 38.4 $\pm$ 1.4% body fat) (mean $\pm$ SE), completed a 12 wk aerobic exercise program (4 $\times$ 30 min/week at $\geq$70% of VO_2 peak). Peripheral and hepatic insulin sensitivity and glucose kinetics were quantified using GCMS pre- and post-exercise.

Results: No weight loss occurred. Lean and obese participants complied well with the program ($\sim$90% of the exercise sessions attended, resulting in $\sim$15% increase in fitness in both groups). Peripheral and hepatic insulin sensitivity were higher in lean than obese adolescents but increased in both groups; peripheral insulin sensitivity by 35 $\pm$ 14% (lean) ($p < 0.05$) and 59 $\pm$ 19% (obese) ($p < 0.01$) and hepatic insulin sensitivity by 19 $\pm$ 7% (lean) ($p < 0.05$) and 23 $\pm$ 4% (obese) ($p < 0.01$). GPR, gluconeogenesis and glycogenolysis did not differ between the groups. GPR decreased slightly, 3 $\pm$ 1% (lean) ($p < 0.05$) and 4 $\pm$ 1% (obese) ($p < 0.01$). Gluconeogenesis remained unchanged, while glycogenolysis decreased slightly in the obese group ($p < 0.01$).

Conclusion: This well accepted aerobic exercise program, without weight loss, is a promising strategy to improve peripheral and hepatic insulin sensitivity in lean and obese sedentary adolescents. The small decrease in GPR is probably of limited clinical relevance. **(*J Clin Endocrinol Metab* 94: 4292–4299, 2009)**

Reduced physical activity and increased sedentary behavior are risk factors for the development of obesity and many chronic diseases (1). Thus, the dramatic decline in physical activity between childhood and adolescence is a serious concern. Troiano *et al.* (1) reported that only 8% of adolescents (12–19 y) obtained the recommended 60 min per day of exercise.

A number of studies in adults have demonstrated that regular moderate exercise improves insulin sensitivity and reduces the risk for cardiovascular disease, type 2 diabetes and some types of cancer (2–4). In addition, studies in adults have addressed effects of exercise on glucose kinetics (5, 6) but the results are inconclusive. While Bergman *et al.* (5) demonstrated increased at rest gluconeogenesis from lactate in response to exercise, Coggan *et al.* (6) reported unchanged at rest gluconeogenesis (from pyruvate) and glycogenolysis while gluconeogenesis (from pyruvate) and glycogenolysis during exercise decreased. With regard

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Abbreviations: BMI, Body mass index; CHO, carbohydrate; CRP, C-reactive protein; DXA, dual X-ray absorptiometry; EI, energy intake; FM, fat mass; GRP, glucose production rate; GNG, gluconeogenesis; HISI, hepatic insulin sensitivity index; LBM, lean body mass; NS, not significant; SLIVGTT, Stable Label Intravenous Glucose Tolerance Test.

to lipid metabolism, Phillips *et al.* (7) and Romijn *et al.* (8) demonstrated that intense and long term exercise increased lipid kinetics.

Improved insulin sensitivity has been shown in children and adolescents in response to various exercise programs (9–14). However, many exercise studies do not provide information about potential confounders such as attendance, intensity, physical activity outside the program and fitness at start of the program.

Further, to our knowledge no published studies have measured the effect of exercise on peripheral and hepatic insulin sensitivity separately, or reported the impact of training on glucose and lipid metabolism in children or adolescents.

The purpose of this study was to determine whether a controlled moderate aerobic exercise program (without weight loss or additional lifestyle education) improves peripheral and hepatic insulin sensitivity, and affects glucose production, gluconeogenesis, glycogenolysis and lipolysis in sedentary lean and obese Hispanic adolescents.

We focused on Hispanics because of their high risk of obesity and obesity related illnesses (15–17) and we included lean participants because a sedentary lifestyle *per se* is an additional risk factor (18).

Subjects and Methods

Subjects

After approval of the protocol by the Baylor College of Medicine Institutional Review Board for Human Subject Research, and the General Clinical Research Center Advisory Board, obese and lean adolescents were recruited by local advertisement. Adolescents were screened and enrolled in the study after written assent from the participant and consent from the legal guardian were obtained.

Twenty nine (29) post pubertal (Tanner IV – V) Hispanic adolescents (14 lean; 15 obese), were studied (Table 1). The lean participants had BMI $<85^{th}$ and the obese $>95^{th}$ percentile for age (19). BMI might, however, not be an optimal marker of leanness/obesity (20). Thus, to assure that our lean participants were indeed lean not only with regard to BMI criteria but also to fatness, they must have <27% body fat as measured by dual-energy x-ray absorptiometry (DXA) (Table 1). Participants had been lean or obese for ≥5 yr and reported stable body weight for at least 6 months. Only sedentary adolescents were included, *i.e.* they did not participate in any school or after school organized athletic activities and performed <45 min light to moderate physical activity/week.

All participants were Hispanic (parents and grandparents of Hispanic descent by self report). The participants were in good health as determined by a medical history, a physical examination and a standard blood chemistry analysis including blood lipids, liver- and kidney function tests, hemoglobin, hematocrit, hemoglobin A1c and fasting and 2 h post-prandial glucose response. Participants were taking no medications including birth control pills and had no first-degree relatives with diabetes. Adolescents with morbid obesity (body fat % >50, sleep apnea, Pickwick syndrome or cor pulmonale) were excluded.

Study design

Each participant was studied on two separate occasions: 1) The weekend before start of the exercise program (baseline), 2) Three days after the final exercise session of the 12 wk program (post). All procedures were identical on both study occasions.

To exclude effects of dietary intake on measurements obtained at baseline *vs.* post-exercise, before both studies, each participant received an identical 7 d low-carbohydrate (CHO)/high-fat diet at home (30% CHO, 55% fat, and 15% protein; 20% of the total CHO content as fructose) (21–23). Total energy intake corresponded to each individual's requirement according to the Institute of Medicine Dietary Reference Intakes (24). The food was delivered to the participants' homes by the metabolic research kitchen. Non-consumed food was returned and examined for constituents and the energy and macronutrient content of the consumed food was calculated by difference (21–23). To measure the effect of exercise alone, participants were told not to make lifestyle and dietary changes during the exercise program.

On both occasions, the participants were admitted to the General Clinical Research Center at Texas Children's Hospital in the evening before the metabolic study. After dinner and a snack, participants were fasted overnight (except for water) *i.e.* from 2000 h until completion of the isotope infusion study at 1300 h the next day.

Exercise program

For the duration of 12 wks, participants came to the physical therapy unit at Texas Children's Hospital twice a week for a 30

TABLE 1. Demographic characteristics (mean ± SE)

	Lean participants		Obese participants		
Subjects	Baseline	Post exercise	Baseline	Post exercise	Interaction (*P* value)[a]
Male/female	10/4	10/4	7/8	7/8	
Weight (kg)	57.2 ± 2.7	58.0 ± 2.9[b]	89.6 ± 3.2[e]	89.3 ± 3.1[e]	0.118
BMI (kg/m^2)	20.6 ± 0.8	20.7 ± 0.8	33.2 ± 0.9[e]	33.0 ± 0.8[e]	0.212
Body fat (%)	18.9 ± 1.5	18.6 ± 1.6	38.4 ± 1.5[e]	37.3 ± 1.5[c,e]	0.187
LBM (kg)	44.7 ± 2.3	46.0 ± 2.4[c]	53.3 ± 2.8[d]	54.4 ± 3.0[c,d]	0.764
FM (kg)	10.9 ± 1.0	10.9 ± 1.1	34.3 ± 1.5[e]	33.4 ± 1.4[b,e]	0.062

[a] GEE interaction between the effect of the exercise program and group.

[b,c] Different from baseline within each group: [b] $P < 0.05$; [c] $P < 0.01$.

[d,e] Different between lean and obese participants: [d] $P < 0.05$; [e] $P < 0.01$.

min aerobic exercise session on a treadmill, elliptical or bicycle (dependent on the participant's preference). Each exercise session was preceded and followed by 10 min of warm up/cool down and stretching. The exercise intensity level was designed to result in a heart rate corresponding to at least 70% of that obtained at $VO_{2\ peak}$ at baseline (see below), *i.e.* we aimed at heart rates >140 beats/min for the entire 30 min session. Experienced exercise physiologists were responsible for the training sessions together with the principal investigator. No more than two participants were supervised at the same time. Flexibility with appointment times and assistance with transportation when needed facilitated good attendance. Participants were instructed to perform a similar program (same duration and intensity) twice a week at home, *i.e.* a total of 4 exercise sessions per week. To assure that the desired heart rate (exercise intensity) was achieved and maintained for 30 min, each participant wore a heart rate monitor, Polar S-710 (Health Check Systems, Brooklyn, NY) during all home and hospital exercise sessions. Information from the monitors was downloaded and discussed with the participant on a weekly basis. Participants performed no exercise outside the program. Their weight was assessed twice a week in conjunction with the exercise sessions to assure weight stability. To avoid the acute effect of exercise on measurements obtained during the post exercise study, the last exercise session took place three days before the metabolic study.

Tracers

Deuterium oxide (99% ^2H); [$^2H_5$]glycerol (99% [^2H], 95% [$^2H_5$]); [1-^{13}C]glucose (99% [^{13}C]); and [6,6-$^2H_2$]glucose (99% [^2H], 98% [$^2H_2$]) were purchased from Cambridge Isotope Laboratories (Andover, MA). The isotopes were tested for sterility and pyrogenicity by the investigation pharmacy at Texas Children's Hospital (Houston, TX). The infusates were filtered through a Millex GP syringe filter (0.22 μm; Millipore Corporation, Bedford, MN) and stored at 4 C for no more than 24–48 h before administration.

Administration of tracers

On each study occasion, the participants received the following, stable isotopically labeled tracers as previously described (21, 22, 25).

1) During the overnight fast at 2100, 2300, 0100 and 0300 h, deuterium oxide (a total of 3 g/kg) was administered orally to measure total gluconeogenesis (26).

2) Between 0600 and 1300 h, a simultaneous, primed (60 x the minute infusion rate), constant rate i.v. infusion of [1-^{13}C]glucose (0.33 ± 0 μmol/kg $_{\text{non-bone lean body mass (LBM)}}$ $\cdot$ min) and [$^2H_5$]glycerol (0.14 ± 0 μmol/kg $_{LBM}$ $\cdot$ min) was administered to measure glucose production and the plasma turnover of glycerol, an indicator of lipolysis (21, 22, 25).

3) The Stable Label Intravenous Glucose Tolerance Test (SLIVGTT) was started at 0900 h after the 0 min blood sample (see below). A bolus injection of glucose, 0.35 ± 0 g/kg $_{LBM}$ containing 10% [6,6-$^2H_2$]glucose, was administered over 90–120 sec to measure insulin sensitivity (21, 22, 25).

Blood sampling

Blood samples were obtained just before start of the primed constant rate infusion of the [1-^{13}C]glucose and [$^2H_5$]glycerol (designated as t = −180) (13 mL) and subsequently at t = −30, −20, −10, and 0 min (8 mL/sample). The injection of the SLIVGTT bolus (after the 0 min sample) was followed by blood sampling (3.6 mL per sample) at +2, 3, 4, 5, 8, 10, 18, 20, 23, 28, 32, 40, 60, 120, 180, and 240 min (21, 22, 25).

Analyses

Glucose concentrations were measured using an YSI glucose analyzer (Yellow Springs, OH) and insulin concentrations by electrochemiluminescence using a Roche Elecsys 1010 analyzer (Roche Diagnostics Corporation, Indianapolis, IN). Plasma lipids were determined by standard laboratory techniques; Leptin and Adiponectin concentrations by non radioactive human ELISA kits (Linco Research, Inc., St Charles, MO), and high sensitive C-reactive protein (hs-CRP) by immunoturbidimetry. Non-bone lean body (LBM) and fat mass (FM) were measured by DXA (QDR 11.2; Hologic Bedford, MA) (21–23). Cardiovascular fitness was determined at baseline and post-exercise by peak oxygen uptake ($VO_{2\ peak}$) using a modified Bruce treadmill protocol (starting at a speed of 1.7 mph with subsequent increase of speed and incline every 3 min until the participant's maximal exercise capacity was reached). Oxygen consumption was measured with a Vmax-229 metabolic cart (Sensormedics, Anaheim, CA). $VO_{2\ peak}$ was determined using standard criteria, specifically a heart rate >195 beats/min or a respiratory quotient (RQ) >1.0 at peak exercise (23).

Calculations

Rates of glucose production and glycerol turnover were calculated under approximate steady-state conditions from the average isotopic enrichments obtained for [$^{13}C_1$]glucose and [$^2H_5$]glycerol, respectively, in the samples obtained at -30, -20, -10 and 0 min (21, 22, 25).

During the same period, the gluconeogenic contribution to glucose (GNG) was determined using ^2H_2O and the average ^2H enrichments of carbons 1, 3, 4, 5, and 6 of glucose as recently published (26).

Peripheral insulin sensitivity (the sensitivity of glucose disposition to insulin) was calculated by applying the minimal model to SLIVGTT data (21, 22, 25, 27).

Hepatic insulin sensitivity was calculated in the fasting state by the hepatic insulin sensitivity index (HISI): 1000/[GPR (μmol/kg $_{LBM}$ $\cdot$ min) x fasting plasma insulin (μU/mL)], where 1000 is a constant that results in numbers between 1 and 10, as described by Matsuda *et al.* (28).

Statistical methods

Data are presented as mean ± SE. Generalized Estimating Equations (GEE) (SPSS 17.0) were used to assess the effects of the exercise program, group (lean *vs.* obese participants) and the interaction between the effects of the exercise program and group. Post hoc procedures provided by GEE were used to compare groups at baseline and post-exercise and to assess exercise effect within each group. A $P < 0.05$ was considered statistically significant. The data on peripheral insulin sensitivity were log transformed to make the distribution bell shaped.

Results

Demographic and biochemical characteristics at baseline

Demographic characteristics of the participants are given in *Table 1*.

As expected, weight, BMI, body fat %, total fat mass and lean body mass were significantly higher in obese compared with lean participants.

Biochemical characteristics of the participants are given in *Table 2*.

While glucose concentrations were not different, insulin concentrations were higher in the obese participants ($P < 0.01$).

Dietary intake

In both lean and obese adolescents, total energy intake at baseline and post-exercise were not different, Lean: Baseline 2318 ± 94; Post 2314 ± 88 kcal/d; Obese: Baseline 2706 ± 166; Post 2677 ± 171 kcal/d. Similarly, macronutrient distribution of the intakes was identical on both study occasions in both groups (30 ± 1% CHO, 54 ± 1% fat, 16 ± 1% protein).

Compliance

Compliance with and response to the exercise program were equal in lean and obese adolescents. They attended 87 ± 2 (lean) and 89 ± 2% (obese) of the total 48 sessions NS, at an intensity of 85 ± 1 (lean) and 86 ± 1% (obese) of their heart rate at $VO_{2\ peak}$ (NS). $VO_{2\ peak}$ increased by ~16% in the lean (Baseline: 2.17 ± 0.14; Post: 2.47 ± 0.12 l/min; $P < 0.01$) and by ~12% in the obese participants (Baseline: 2.46 ± 0.16; Post: 2.75 ± 0.18 l/min; $P < 0.01$).

Effects of the exercise program

Body Composition

In lean participants, body weight increased (0.8 ± 0.3 kg, $P < 0.05$) due to an increase in lean body mass (1.3 ± 0.4 kg, $P < 0.01$) (Table 1). In obese participants, body weight did not change. However, lean body mass increased (1.1 ± 0.4 kg, $P < 0.01$) and fat mass decreased to the same extent (1.0 ± 0.5 kg, $P < 0.05$) (Table 1).

Insulin sensitivity

Peripheral insulin sensitivity. Compared with lean, obese adolescents had lower peripheral insulin sensitivity (Baseline: $P < 0.01$; Post: $P < 0.05$) (Fig. 1). In both lean and obese participants, peripheral insulin sensitivity increased in response to the exercise program, 35 ± 14% ($P < 0.05$) and 59 ± 19% ($P < 0.01$), respectively. Percentage change in lean vs. obese participants NS.

Hepatic insulin sensitivity. Compared with lean, obese participants had lower hepatic insulin sensitivity (Baseline and Post: $P < 0.01$) (Fig. 1). In both lean and obese adolescents, hepatic insulin sensitivity increased in response to the exercise program, 19 ± 7% ($P < 0.01$) and 23 ± 4% ($P < 0.01$), respectively. Percentage change in lean vs. obese participants NS.

Glucose production from gluconeogenesis and glycogenolysis

Glucose production rate (GPR) (μmol/kg $_{LBM}$ · min), did not differ between lean and obese participants (Fig. 1). Similarly, the contribution of gluconeogenesis (GNG) and glycogenolysis (GLY) to GPR were also not different (Baseline: Lean: GNG: 56 ± 2%; GLY 44 ± 2%; Obese: GNG 58 ± 2%; GLY 42 ± 2%).

TABLE 2. Biochemical characteristics (mean ± SE)

	Lean participants		Obese participants		
	Baseline	Post exercise	Baseline	Post exercise	Interaction (*P* value)[a]
Glucose (mmol/liter)	5.1 ± 0.1	5.0 ± 0.1	5.0 ± 0.1	5.0 ± 0.1	0.812
Insulin (μmol/liter)	7.3 ± 0.9	6.7 ± 0.9	20.1 ± 2.5[e]	17.2 ± 2.1[c,e]	0.005
Triglycerides (mg/dl)	68 ± 8	82 ± 9[b]	74 ± 10	73 ± 8	0.042
Free fatty acids (mmol/liter)	0.46 ± 0.03	0.50 ± 0.04	0.47 ± 0.03	0.51 ± 0.04	0.924
LDL cholesterol (mg/dl)	85 ± 8	82 ± 7	82 ± 6	79 ± 5	0.975
HDL cholesterol (mg/dl)	52 ± 4	52 ± 4	40 ± 3[e]	42 ± 2[d]	0.531
Total cholesterol (mg/dl)	152 ± 8	152 ± 6	141 ± 6	140 ± 4	0.827
Adiponectin (μg/ml)	7.2 ± 0.9	6.7 ± 0.9	5.9 ± 0.7	5.7 ± 0.7	0.538
Leptin (ng/ml)	5.5 ± 1.4	5.9 ± 1.6	37.3 ± 4.0[e]	34.4 ± 4.7[e]	0.089
hs-CRP (mg/liter)	0.2 ± 0.0	0.4 ± 0.1	1.1 ± 0.3[d]	1.1 ± 0.4	0.806

HDL, High-density lipoprotein; LDL, low-density lipoprotein.

[a] GEE interaction between the effect of the exercise program and group.

[b,c] Different from baseline within each group: [b] $P < 0.05$; [c] $P < 0.01$.

[d,e] Different between lean and obese participants: [d] $P < 0.05$; [e] $P < 0.01$.

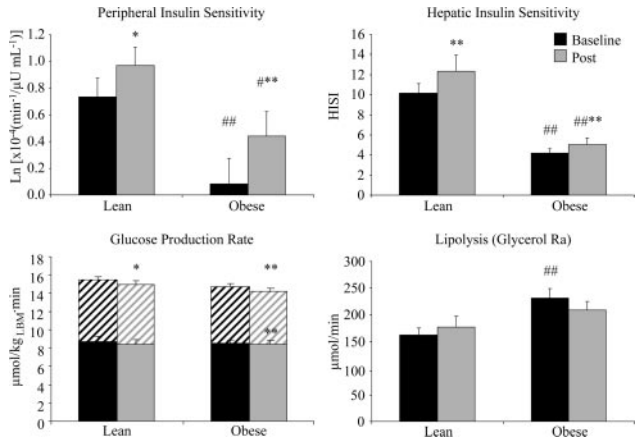

FIG. 1. Peripheral Insulin Sensitivity, calculated by the minimal model applied to SLIVGTT data (SI); Hepatic Insulin Sensitivity, measured by Hepatic Insulin Sensitivity Index (HISI); Glucose Production Rate (GPR) consisting of Gluconeogenesis (GNG) (solid part of the bar) and Glycogenolysis (GLY) (hatched part of the bar), and Lipolysis (Glycerol Ra) in the lean and obese participants at baseline and post-exercise (mean ± SE). Significant differences in GPR are depicted above the bars. Significant difference in GLY is depicted inside the bar. Different from baseline within each group: * $P < 0.05$, ** $P < 0.01$. Different between lean and obese participants: $^{\#}$ $P < 0.05$, $^{\#\#}$ $P < 0.01$.

In both lean and obese adolescents, the exercise program resulted in a small decrease in *GPR*, 3 ± 1% ($P < 0.05$) and 4 ± 1% ($P < 0.01$), respectively. In the obese participants, this decrease was accounted for by an 8 ± 3% decrease in glycogenolysis ($P < 0.01$). In the lean participants, the small decreases in GNG (3 ± 2%) and GLY (2 ± 3%), did not reach significance.

Lipolysis

At baseline, total glycerol Rate of appearance (Ra) (μmol/min), was higher in obese compared with lean adolescents ($P < 0.01$) (Fig. 1). Glycerol Ra, expressed in μmol/per kg $_{FM}$ · min, was lower in obese participants (Baseline: Lean: 17.9 ± 3.0; Obese: 6.9 ± 0.6 μmol/kg $_{FM}$ · min, $P < 0.01$).

Except for higher HDL cholesterol in the lean participants ($P < 0.01$), baseline blood lipids did not differ between the two groups (Table 2).

The exercise program did not significantly affect glycerol Ra in either lean or obese adolescents (Fig. 1). Except for a slight increase in triglyceride concentration (within normal range) ($P < 0.05$) in lean participants, blood lipids were also not affected by the program (Table 2).

Plasma adiponectin, leptin, and hs-CRP

Adiponectin concentration did not differ between lean and obese adolescents, whereas leptin and hs-CRP were higher in obese participants (Leptin: baseline and post $P < 0.01$; hs-CRP: baseline $P < 0.01$, post NS) (Table 2). The exercise program did not significantly change adiponectin, leptin or hs-CRP concentrations in either group.

Interactions between exercise and group (lean and obese)

There was a significant interaction between the effect of the exercise program and group with respect to insulin and triglyceride concentration ($P = 0.005$ and $P = 0.042$, respectively). All other measured variables had no significant interactions indicating that the response to the exercise program was not different in lean and obese adolescents.

Discussion

The present study demonstrates that a moderate aerobic exercise program resulted in substantial increases in peripheral and hepatic insulin sensitivity in both lean and obese sedentary Hispanic adolescents. The percentage change was not different in lean and obese participants despite significantly lower baseline insulin sensitivity in the obese. Insulin resistance is a major component of obesity and its co-morbidities such as metabolic syndrome and type 2 diabetes. It is, therefore, of great importance, that this program that was of moderate intensity and well accepted by both lean and obese participants (~90% attended sessions at a heart rate corresponding to 85% of that obtained at VO_2 peak) improved fitness as well as insulin sensitivity.

Exercise induced improvements of whole body insulin sensitivity have previously been demonstrated in children and adolescents (9, 10, 14). However, the methods used, unlabeled oral glucose tolerance test (9), unlabeled euglycemic hyperinsulinemic clamp (10) and the unlabeled frequently sampled intravenous glucose tolerance test (14), do not distinguish peripheral insulin sensitivity (the sensitivity of glucose uptake by peripheral tissue to insulin) and hepatic insulin sensitivity (the sensitivity of hepatic glucose production to insulin). These processes represent different mechanisms for maintenance of normoglycemia. Thus, individual measurements of the two processes would provide new and potentially important information on the physiological effects of exercise on insulin sensitivity. We used the Stable Label Intravenous Glucose Tolerance Test to measure peripheral insulin sensitivity (27), while the Hepatic Insulin Sensitivity Index allowed us to determine hepatic insulin sensitivity in the fasting state (28). This approach enabled us to demonstrate that our aerobic exercise program has significant positive effects both at the site of the liver and peripheral tissue (primarily muscle) in sedentary adolescents. We reported in a previous manuscript (including in part the same participants) (29), that our aerobic exercise program decreased intrahepatic fat content in obese adolescents (primarily those with high hepatic fat content) but did not affect

intramyocellular fat in either lean or obese participants. These findings indicate that increased peripheral and hepatic insulin sensitivity are not simply the result of changes in intramyocellular and hepatocellular fat accumulation. Hawley and Lessard (30) recently reviewed various possible mechanisms for exercise induced increase in muscular glucose uptake (peripheral insulin sensitivity) *e.g.* increased expression of signaling proteins involved in the regulation of glucose uptake and metabolism in skeletal muscle, changes in expression and/or activity of proteins involved in insulin signaling in the muscle cell and increased lipid turnover and/or oxidation (30). The mechanisms behind exercise effects on hepatic insulin sensitivity are not well understood in humans. However, Heled *et al.* (31) reported that exercise ameliorated the insulin signaling response and inhibited PEPCK activity in the hepatocyte of diabetes prone fat sand rats. Since it is unethical to perform muscle and liver biopsies in healthy adolescents, we could not explore these avenues in our population. Glucose production, gluconeogenesis and glycogenolysis did not differ between lean and obese participants despite the obese had almost three times higher insulin concentrations, demonstrating their hepatic insulin resistance. In both groups, a small decrease in glucose production was observed in response to the exercise program. This decrease had most likely no clinical relevance in our normoglycemic obese participants with normal glucose tolerance and glucose production rates within the normal range. Thus, a large decrease in glucose production would be unexpected and physiologically unnecessary. The greater increase in hepatic insulin sensitivity than needed for maintenance of normal glucose production might reflect a reserve capacity. If the same effects of an aerobic exercise program would occur in glucose intolerant or diabetic subjects with increased glucose production and resultant increased glucose concentrations, the exercise induced effects on hepatic insulin sensitivity might result in greater effects on glucose production rates with subsequent reduction of glucose concentrations (32). Further research in these populations is needed to address this issue.

We did not observe any effects of exercise on gluconeogenesis. Our method measures total gluconeogenesis, *i.e.* the contribution from all potential gluconeogenic substrates (glycerol, amino acids and lactate). To our knowledge there are no other reports on the effect of exercise on *total* gluconeogenesis. Bergman *et al.* (5) showed that in the fed at rest state, gluconeogenesis from lactate, which represents about 10% of glucose production, increased in response to an 8/9 wk aerobic exercise program in lean, sedentary adult males. In contrast, Coggan *et al.* (6) did not find any effect of a 12 wk aerobic exercise program on fasting at rest gluconeogenesis (from pyruvate) or glycogenolysis.

In our study, the exercise program did not affect fasting lipolysis. Increased lipolysis has been reported after intensive exercise in untrained adult males (7), and in adult male athletes (8). These findings suggest that more intensive aerobic exercise might be needed to affect lipolysis. In agreement with the observations by Wolfe *et al.* (33), fasting lipolysis was lower per kg fat mass in our obese participants compared with their lean counterparts, which might indicate down regulation of lipolysis at the level of the fat cell in obese adolescents (33).

Changes in adiponectin, leptin and hs-CRP concentration did not reach significance as a result of the 12 wk exercise program. Data from other studies on the effects of exercise on these parameters in children, adolescents and adults are inconclusive (9, 34–39). Higher adiponectin concentrations in lean compared with obese subjects have been observed by us and others (21, 40). Further, higher adiponectin concentrations have been reported in post-pubertal girls compared with post-pubertal boys (41). Thus, we believe the larger number of males compared with females in our lean group (4 f/10 m) might explain the lack of baseline difference in adiponectin concentrations in our study. The four lean girls had, in fact, significantly higher adiponectin concentrations than the lean boys as well as the obese girls.

In conclusion, our results demonstrate that a moderate aerobic exercise program that both lean and obese sedentary adolescents could easily comply with resulted in substantial improvements in both peripheral and hepatic insulin sensitivity. Thus, this program could be a useful tool to prevent obesity related illness in Hispanic adolescents. A strength of our study is that a number of potentially confounding factors were controlled; no weight loss; no exercise activity outside the program; a 7-day controlled diet preceding pre- and post-exercise measurements; all participants post-pubertal; strict requirements for attendance and exercise intensity; and all participants sedentary before enrolment.

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