

Reduced exercise-associated response of the GH-IGF-I axis and catecholamines in obese children and adolescents

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Eliakim, Alon, Dan Nemet, Frank Zaldivar, Robert G. McMurray, Floyd L. Culler, Pietro Galassetti, and Dan M. Cooper. Reduced exercise-associated response of the GH-IGF-I axis and catecholamines in obese children and adolescents. *J Appl Physiol* 100: 1630–1637, 2006. First published December 22, 2005; doi:10.1152/jappphysiol.01072.2005.—Obesity blunts catecholamine and growth hormone (GH) responses to exercise in adults, but the effect of obesity on these exercise-associated hormonal responses in children is unclear. Therefore, the aim of the present study was to assess the effect of childhood obesity on the counterregulatory hormonal response to acute exercise. Twenty-five obese children (Ob; body mass index > 95%), and 25 age, gender, and maturity-matched normal-weight controls (NW) participated in the study. Exercise consisted of ten 2-min bouts of constant-cycle ergometry above the anaerobic threshold, with 1-min rest intervals between each bout. Pre-, post-, and 120-min postexercise blood samples were collected for circulating components of the GH-IGF-I axis and catecholamines. There were no differences in peak exercise heart rate, serum lactate, and peak O₂ uptake normalized to lean body mass between the groups. Obesity attenuated the GH response to exercise (8.9 ± 1.1 vs. 3.4 ± 0.7 ng/ml in NW and Ob participants, respectively; $P < 0.02$). No significant differences in the response to exercise were found for other components of the GH-IGF-I axis. Obesity attenuated the catecholamine response to exercise (epinephrine: 52.5 ± 12.7 vs. 18.7 ± 3.7 pg/ml, $P < 0.02$; norepinephrine: 479.5 ± 109.9 vs. 218.0 ± 26.0 pg/ml, $P < 0.04$; dopamine: 17.2 ± 2.9 vs. 3.5 ± 1.9 pg/ml, $P < 0.006$ in NW and Ob, respectively). Insulin levels were significantly higher in the obese children and dropped significantly after exercise in both groups. Despite the elevated insulin levels and the blunted counterregulatory response, none of the participants developed hypoglycemia. Childhood obesity was associated with attenuated GH and catecholamine response to acute exercise. These abnormalities were compensated for, so that exercise was not associated with hypoglycemia, despite increased insulin levels in obese children.

overweight; growth hormone-insulin-like growth factor-I axis; physical activity

THE EMERGING EPIDEMIC OF PEDIATRIC obesity has complex, poorly understood causes (40) and represents a substantial challenge for the long-term health and well-being of children. Many of the detrimental health effects of obesity can be traced to a low-level, chronic inflammatory state, the result of adipocyte cytokine production in the body's fat stores (8). Many of these adipose-derived mediators have been related to alterations in catecholamines, glucocorticoids, insulin, and growth hormone

(GH) (28). Consequently, an increased understanding of the mechanisms that control body composition will be essential to optimally “re-balance” energy intake and expenditure in today's children and adolescents.

Of particular importance are the ways in which obesity alters the hormonal response to physical activity, a major factor in the distribution of fat and lean tissue in adults and children (27). GH and other elements of the GH→IGF-I axis, key regulators of fat and lean tissue, are remarkably sensitive to brief bouts of physical activity and to fitness in general (12). Previous adult studies (19, 45) suggested that the GH response to brief exercise may be attenuated by obesity, but little is known about the effect of obesity on the response of other elements of the GH→IGF-I axis to exercise in general and in particular in adolescents and children in whom the GH→IGF-I activity changes rapidly. It has been suggested that the exercise-associated GH attenuation in adults results from impaired catecholamine response (45). However, whether obesity in otherwise healthy children and adolescents depresses the GH→IGF-I axis by a general central mechanism, or, alternatively, the defect is neuroadrenergic and mediated by a blunted catecholamine responses, is not known.

We hypothesized that, in response to exercise, obese children would have both reduced GH→IGF-I axis and impaired neuroadrenergic function. To test this, we compared the effect of acute exercise in healthy obese and normal-weight children and adolescents on 1) circulating mediators of the GH→IGF-I axis, namely, GH, GH binding protein (GHBP) (the extracellular domain of the GH receptor), total and free IGF-I, and IGF binding proteins (IGFBP)-1 to -4; and 2) circulating mediators of the neuroadrenergic response to exercise, namely, epinephrine (Epi), norepinephrine (NE), and dopamine. In addition, we measured physiological responses to exercise [e.g., peak heart rate, respiratory exchange ratio (RER), and lactate levels] to ensure that the exercise input was comparable in the two groups. This is important because differences in the relative intensity of the exercise input can confound the critical hormonal outcome variables. Finally, because both GH→IGF-I axis hormones and catecholamines play a role in glucose homeostasis during exercise (45), and because obesity is associated with hyperinsulinism, we also measured circulating levels of both glucose and insulin.

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MATERIALS AND METHODS

Subjects

Fifty participants (age range 8–17 yr; 26 girls, 24 boys) were recruited by the University of California Irvine Pediatric Exercise Research Center to participate in this study (Table 1). Twenty-five participants were obese [body mass index (BMI) > 95%], and 25 subjects had BMI percentiles within the normal range (3.5 to 77.8). Individuals participating in competitive sports and individuals with history of any chronic medical conditions or chronic use of any medications were excluded from participation. The Institutional Review Board at the University of California Irvine approved the study. Written, informed assent was obtained from all participants, and their parents gave written consent upon enrollment.

Anthropometric Measurements

Standard, calibrated scales and stadiometers were used to determine height, body mass, and BMI. Since BMI changes with age during normal growth in children, we calculated BMI percentile for each child using the recently published standards from the Centers for Disease Control, National Center for Health Statistics (22). Maturity of the study participants was assessed by a validated self-administered questionnaire that has been widely used as a noninvasive indicator of pubertal status (33, 36).

Body Composition Assessment by Dual-energy X-ray Absorptiometry

Since BMI does not measure lean body mass and does not invariably correlate with fat mass (17), body composition was also measured by dual-energy X-ray absorptiometry (DEXA) using the Hologic QDR 4500 densitometer (Hologic, Bedford, MA). Subjects were scanned in light clothing, while lying flat on their backs. DEXA scans were performed and analyzed using pediatric software. On the days of each test, the DEXA instrument was calibrated using the procedures provided by the manufacturer.

Measurement of Fitness

Each subject performed a cycle ergometer ramp-type progressive exercise test to the limit of his or her tolerance. Subjects were vigorously encouraged during the high-intensity phases of the exercise protocol. Gas exchange was measured breath by breath, and the anaerobic (ventilatory/lactate) threshold, RER, and peak O₂ uptake ($\dot{V}O_{2\text{peak}}$) were calculated using a Sensor Medics metabolic system (7).

Table 1. Anthropometric characteristics of study participants

	Normal Weight	Obese
<i>n</i>	25	25
Age, yr	12.8 ± 0.5	12.3 ± 0.5
Male/female	12/13	12/13
Maturity (Tanner stage)	3.2 ± 0.2	2.9 ± 0.2
Ethnicity (H/As/C/AA)	3/8/12/2	8/5/9/3
Height, cm	153.8 ± 3.4	155.2 ± 2.6
Body weight, kg	44.5 ± 2.8	76.2 ± 5.0*
BMI, kg/m ²	18.2 ± 0.5	30.8 ± 1.3*
BMI percentile	42.1 ± 4.5	98.1 ± 0.3*
Body fat, %	19.9 ± 1.6	37.8 ± 1.9*
Lean body mass, kg	34.9 ± 3.1	42.9 ± 2.2*
$\dot{V}O_{2\text{peak}}$, ml·kg ⁻¹ ·min ⁻¹	32.7 ± 1.5	22.9 ± 1.5*
$\dot{V}O_{2\text{peak}}$, ml·kg LBM ⁻¹ ·min ⁻¹	41.7 ± 1.5	40.2 ± 2.2
LAT, ml·kg ⁻¹ ·min ⁻¹	19.5 ± 0.8	12.9 ± 0.7*
LAT, % $\dot{V}O_{2\text{peak}}$	59.4 ± 1.5	60.4 ± 1.7

Values are means ± SE; *n*, no. of subjects. H, Hispanic; As, Asian; C, Caucasian; AA, African American; BMI, body mass index; $\dot{V}O_{2\text{peak}}$, peak O₂ uptake; LBM, lean body mass; LAT, lactate threshold. **P* ≤ 0.001, normal-weight vs. obese children.

Exercise Protocol

Exercise consisted of ten 2-min bouts of constant work rate cycle ergometry, with a 1-min rest interval between each of the 10 bouts of exercise. The work rate was individualized for each child and was calculated to be equivalent to the work rate corresponding to 50% between the ventilatory/lactate threshold (as determined noninvasively from the ramp-type test) and the peak $\dot{V}O_{2\text{peak}}$. We have used this protocol in the past to ensure that the exercise input was standardized to physiological indicators of each subject's exercise capacity (42). The total duration of the exercise session is 30 min (20-min cycling interspersed by 10-min resting).

Blood Sampling and Analysis

Morning (following an overnight fast) pre-, immediately post-, and 120-min postexercise (recovery) blood samples were drawn from an indwelling venous catheter that was inserted 30 min before the first blood draw. Blood samples were immediately spun at 3,000 rpm, at 4°C for 20 min. The serum was separated and stored at -80°C. All pre- and postexercise specimens from each individual were analyzed in the same batch by an experienced technician, who was blinded to the individual's group (normal weight vs. obese) and to the order of samples.

GH. GH serum concentrations were determined by ELISA with the use of the DSL-10-1900 Active kit (Diagnostic System Laboratories, Webster, TX). Intra-assay coefficient of variation (CV) was 3.3–4.5%, interassay CV was 5.5–12.9%, and the sensitivity was 0.03 ng/ml.

GHBP. GHBP serum levels were measured using ELISA with the use of the DSL-10-4800 Active kit (Diagnostic Systems Laboratories). Intra-assay CV was 3.2–5.6%, interassay CV was 5.0–8.0%, and assay sensitivity was 1.69 pmol/l.

IGF-I: total and free. IGF-I was extracted from IGF-BPs by using the acid-ethanol extraction method (9). Serum IGF-I concentrations were determined by a two-site immunoradiometric assay by using the DSL-5600 Active kit (Diagnostic System Laboratories). IGF-I intra-assay CV was 1.5–3.4%, and the interassay CV was 3.7–8.2%. Assay sensitivity was 0.8 ng/ml. Free IGF-I was determined by ELISA with the use of the DSL-10-9400 Active kit (Diagnostic System Laboratories). Intra-assay CV was 3.74–4.8%, interassay CV was 6.2–11.1%, and the sensitivity was 0.015 ng/ml.

IGFBPs. IGFBP-1 was measured by a coated-tube immunoradiometric assay with the use of the DSL-10-7800 Active kit (Diagnostic System Laboratories). Intra-assay CV was 2–4%, and interassay CV was 1.7–6.7%. Assay sensitivity is 0.33 ng/ml. IGFBP-2 serum concentrations were determined by RIA with the use of the DSL-7100 kit (Diagnostic System Laboratories). Intra-assay CV was 4.7–8.5%, interassay CV was 7.2–7.4%, and the sensitivity was 0.5 ng/ml. IGFBP-3 serum concentrations were determined by ELISA with the use of the DSL 10-6600 Active kit (Diagnostic System Laboratories). Intra-assay CV was 7.3–9.6%, interassay CV was 8.2–11.4%, and the sensitivity was 0.04 ng/ml. IGFBP-4 serum concentrations were determined by ELISA with the use of the DSL 10-7300 Active kit (Diagnostic System Laboratories). Intra-assay CV was 2.8–6.4%, interassay CV was 2.3–6.7%, and the sensitivity was 1 ng/ml.

Lactate. Serum lactate was measured spectrophotometrically (YSI 1500, Yellow Springs, OH). Intra-assay CV was 2.8%, interassay CV was 3.5%, and the sensitivity was 0.2 mg/dl.

Glucose. Serum glucose levels were determined by YSI 2300 STAT Plus analyzer. The assay precision is ±2.0% or 2.5 mg/l (the higher value of the two).

Insulin. Serum insulin levels were determined by ELISA with the use of the DSL-10-1600 Active kit (Diagnostic System Laboratories). Intra-assay CV was 1.3–2.6%, interassay CV was 5.2–6.2%, and the sensitivity was 0.26 μIU/ml.

Cortisol. Serum cortisol levels were determined by a commercial RIA (Diagnostic Products, Los Angeles, CA). The intra- and interassay CV for this assay were 3.2 and 6.8%, respectively.

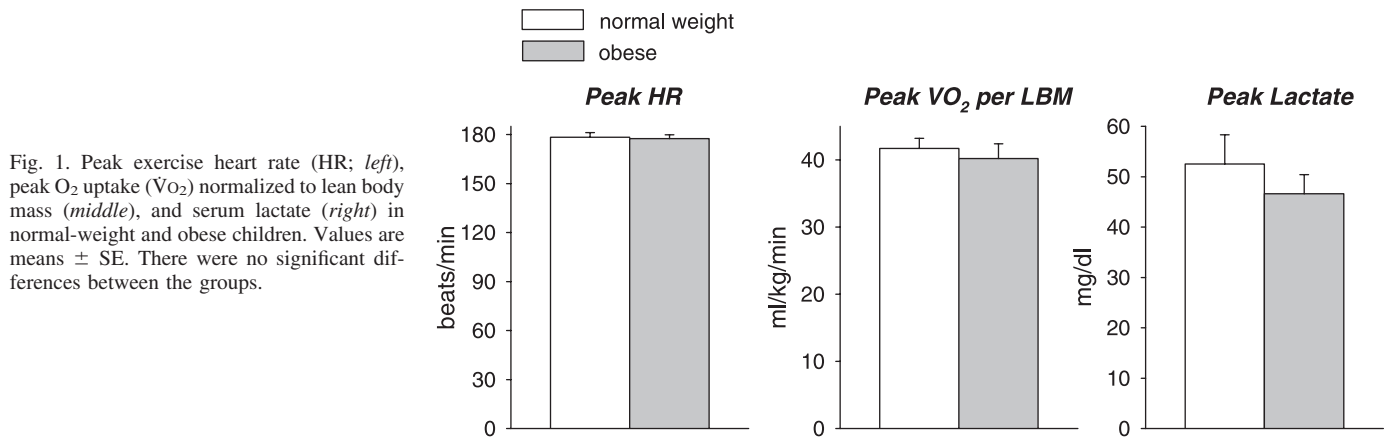


Fig. 1. Peak exercise heart rate (HR; left), peak O₂ uptake (V_{O₂) normalized to lean body mass (middle), and serum lactate (right) in normal-weight and obese children. Values are means \pm SE. There were no significant differences between the groups.}

Epi, NE, and dopamine. These catecholamines were measured by a radio-enzymatic technique based on the conversion of the catecholamine to radiolabeled metanephrine and normetanephrine. This catecholamine assay uses an extraction technique that eliminates substances that may inhibit the radio-enzymatic assay and concentrates the catecholamine to provide a more sensitive assay. Plasma samples of 1 ml were extracted and then concentrated into a 0.1-ml volume before conversion into the radiolabeled metabolites. The assay has an extraction efficiency of 78%. The sensitivity of the assay is 10 and 6 pg/ml for NE and Epi, respectively. The intra-assay CV are 4 and 13%, respectively, for samples containing low levels of catecholamine; variation is less for samples with high levels of catecholamine. The interassay CV are 10 and 16%, respectively, for NE and Epi, so the assay is consistent over time. This technique is \sim 10 times more sensitive than the more commonly used assays and thus can reveal changes in venous catecholamine levels that often go undetected (20).

Statistical Analysis

Unpaired *t*-tests were used for baseline comparison between obese and normal-weight children. Exploratory mixed-model ANOVA was used to assess the effect of exercise on the circulating components of the GH-IGF-I axis, catecholamines, cortisol, lactate, glucose, and insulin, with time (pre-, post-, and recovery) serving as the within-group factor and BMI (normal range vs. obese) as the between-group factor. In addition, simple correlations were computed between changes in the GH-IGF-I axis and body fat, lean body mass, peak aerobic power, and changes in catecholamine levels. Data are presented as means \pm SE. Significance was taken at $P < 0.05$.

RESULTS

Anthropometric and Fitness Data

Characteristics of the study participants are summarized in Table 1. Body weight, BMI, BMI percentile, body fat, and lean

body mass were significantly higher in the obese children. Fitness as expressed by peak V_{O₂ normalized to body weight was significantly lower in the obese children. There were no differences between normal-weight and obese children in peak exercise heart rate, peak exercise serum lactate levels, and peak V_{O₂ normalized to lean body mass (Fig. 1). There was no difference in the RER between normal-weight and obese children (1.07 ± 0.01 vs. 1.09 ± 0.02 in normal-weight and obese participants, respectively).}}

GH, GHBP, IGF-I, and IGFBP-3 and -4

See Table 2 and Fig. 2.

Baseline. GHBP was significantly greater in obese compared with normal-weight participants. No significant differences were noted at baseline for GH, total and free IGF-I, and IGFBP-3 and -4.

Exercise. GHBP was unchanged by exercise in both groups. GH increased significantly in both groups. However, the magnitude of the GH increase was significantly smaller in the obese children. Total IGF-I (but not free) increased significantly following exercise only in obese subjects. No significant exercise-induced change in IGFBP-3 and -4 was found between the groups.

Exercise-associated changes in GH levels were inversely correlated with BMI percentile and body fat. No significant correlations were found between the GH response to exercise and insulin or IGF-I levels (Table 3).

Catecholamines

See Fig. 3.

Baseline. There were no significant baseline differences between the groups in Epi, NE, or dopamine levels.

Table 2. Effects of exercise on several circulating components of the GH-IGF-I axis and cortisol

	Normal Weight (n = 25)			Obese (n = 25)		
	Pre	Peak exercise	120 min Post	Pre	Peak Exercise	120 min Post
Free IGF-1, ng/ml	2.0 \pm 0.2	2.2 \pm 0.3	1.8 \pm 0.2	1.4 \pm 0.2	1.6 \pm 0.2	1.5 \pm 0.2
IGFBP-2, ng/ml	190.2 \pm 40.3*	211.8 \pm 42.8*	206.4 \pm 42.7*	89.0 \pm 20.1	92.1 \pm 21.1	86.6 \pm 17.5
IGFBP-3, ng/ml	3,351.5 \pm 199.3	3,597.2 \pm 209.7	3,404.5 \pm 234.6	3,561.5 \pm 282.7	3,748.5 \pm 263.0	3,533.5 \pm 272.9
IGFBP-4, ng/ml	30.1 \pm 2.7	30.6 \pm 2.5	28.2 \pm 2.0	35.3 \pm 2.2	35.1 \pm 3.0	33.8 \pm 1.9
Cortisol, μ U/ml	9.8 \pm 1.0	10.6 \pm 1.0	7.2 \pm 0.7	9.1 \pm 1.1	8.2 \pm 0.8	5.5 \pm 0.6

Values are means \pm SE; n, no. of subjects. IGFBP, IGF-binding protein. There were no significant effects of exercise on any of the measurements in both groups. * $P < 0.05$ for differences between normal-weight and obese children.

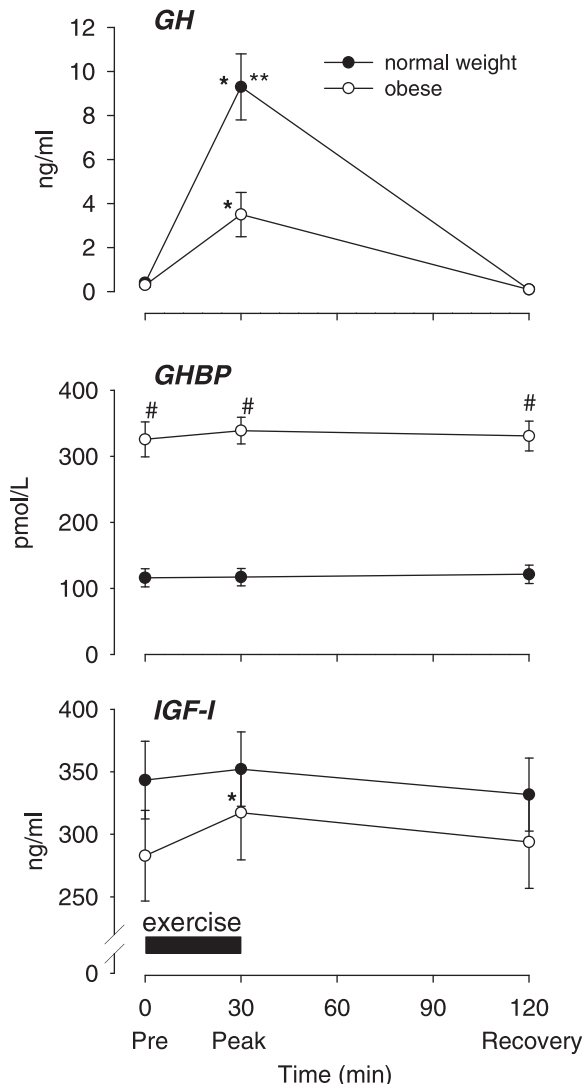


Fig. 2. Exercise-associated changes in circulating components of the growth hormone (GH)-IGF-I axis. GH (top), but not GH binding protein (GHBP; middle), and IGF-I (bottom) response were significantly reduced in obese children. *Within-group changes from preexercise values ($P < 0.05$). **Between-group differences for change from preexercise values ($P < 0.05$). #Different levels between normal-weight and obese children ($P < 0.05$).

Exercise. Epi and NE increased significantly in both obese and normal-weight subjects. However, the magnitude of the increase was significantly smaller in the obese subjects. While dopamine increased in the normal-weight children, no

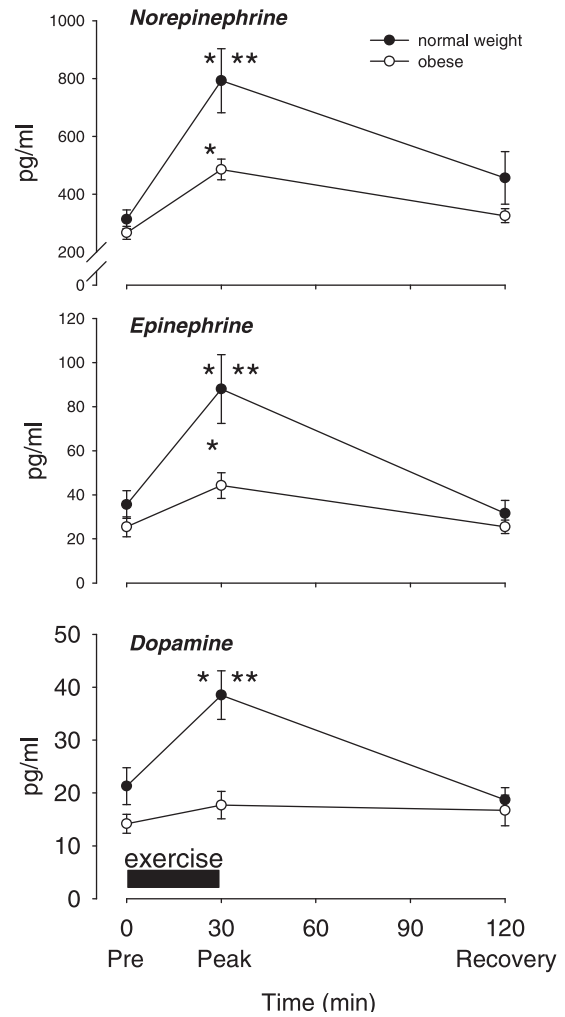


Fig. 3. The effect of exercise on the catecholamine response in obese children. Peak levels of epinephrine, norepinephrine, and dopamine at the end of exercise were significantly reduced in obese compared with normal-weight children and returned to baseline levels 120 min postexercise. *Within-group changes from preexercise values ($P < 0.05$). **Between-group differences for changes from preexercise values ($P < 0.05$).

significant increase in dopamine was found in obese subjects.

There was a significant correlation between fitness and the exercise-associated changes in catecholamines (Table 3). There was an inverse correlation between BMI percentiles and percent body fat and the exercise-associated changes in cat-

Table 3. The relationship between anthropometric characteristics, fitness measures, and baseline insulin and IGF-I levels and exercise-associated changes in circulating GH and catecholamines

	GH Changes		Dopamine Changes		Epinephrine Changes		Norepinephrine Changes	
	r	P	r	P	r	P	r	P
BMI percentile	-0.36	0.01	-0.28	0.048	-0.31	0.03	-0.29	0.043
%Body fat	-0.43	0.002	-0.46	0.0006	-0.49	0.0004	-0.43	0.002
Peak $\dot{V}O_2/kg$	0.28	0.048	0.31	0.03	0.42	0.003	0.47	0.0005
Peak $\dot{V}O_2/kg$ LBM	-0.09	NS	0.18	NS	0.5	0.0003	0.57	<0.0001
Insulin	-0.13	NS	-0.18	NS	-0.16	NS	-0.06	NS
IGF-I	0.03	NS	0.19	NS	0.07	NS	0.15	NS

GH, growth hormone; NS, not significant.

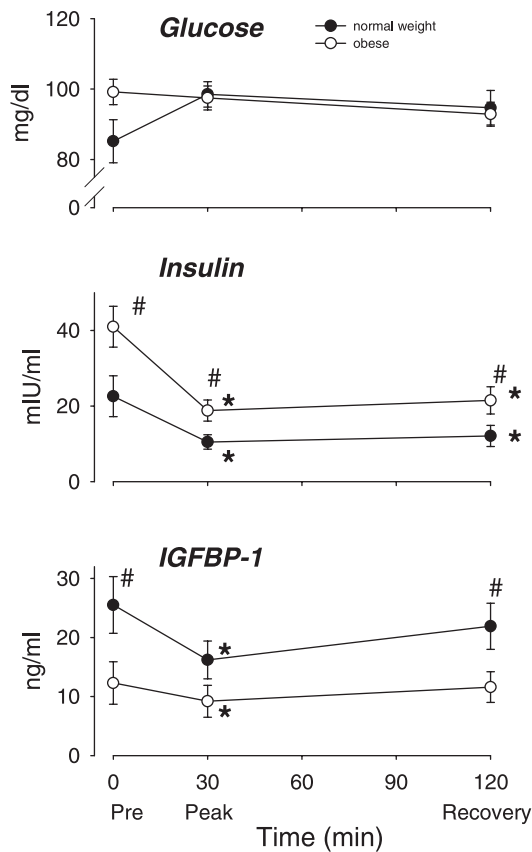


Fig. 4. Exercise-associated changes in serum glucose, insulin, and IGF-binding protein-1 (IGFBP-1) levels in normal and obese children and adolescents. Despite higher insulin levels in obese children at all time points, none of the participants developed hypoglycemia. *Within-group changes from pre-exercise values ($P < 0.05$). #Different levels between normal weight and obese children ($P < 0.05$).

echolamines (Table 3). There was a significant correlation between exercise-associated changes in Epi and GH among the participants ($r = 0.35$, $P < 0.01$).

Glucoregulation (Glucose, Insulin, Cortisol, IGFBP-1 and -2)

See Table 2 and Fig. 4.

Baseline. Insulin was significantly higher in obese compared with normal-weight subjects. IGFBP-1 and -2 were significantly lower in the obese subjects. Glucose and cortisol did not differ between the two groups.

Exercise. Insulin was reduced by exercise in both groups and remained lower through the recovery period. Although the pattern of the exercise effect was similar, insulin levels were significantly higher in the obese subjects. IGFBP-1 was significantly reduced by exercise in both groups, and there was no difference in the magnitude of the reduction between the groups. Glucose, cortisol, and IGFBP-2 were not affected by exercise in either group.

DISCUSSION

To our knowledge, there have been few studies of GH response to exercise in children (15, 39, 48) and none in which both key GH→IGF-I regulatory elements as well as neuroad-

renergic factors were measured simultaneously. We found that both GH→IGF-I axis hormones and neuroadrenergic hormones were influenced by obesity, either at baseline and/or in response to exercise. The major finding of this study was that, in obese children and adolescents, the GH and catecholamine responses to exercise were substantially attenuated (Figs. 2 and 3).

This study highlighted a number of possible mechanisms for the observed blunted GH response to exercise in obese children. First, the lower GH response in the obese children, whose fitness levels are generally lower than normal-weight children (10), cannot be attributed to a smaller magnitude of the exercise stress. This is relevant because, when work is performed above the subject's lactate anaerobic threshold (heavy exercise, as was done in the present study), relatively small changes in the exercise input can lead to large differences in the response of hormones like GH and catecholamines (14). The similar peak heart rate, RER, serum lactate levels, and peak $\dot{V}O_2$ normalized to lean body mass of the participants (Fig. 1) indicate that we were able to achieve virtually identical metabolic and cardiovascular responses in the maximal exercise test in the two groups. As a consequence, the relative intensity of the interval exercise session was also similar in the two groups.

Increased insulin levels and increased IGF-I levels have also been suggested as possible causes for the reduced GH response to exercise in obese individuals (19). The mechanism of these effects is not fully understood but could be related to down-regulation of GH cellular receptors by insulin and IGF-I (23). Consistent with this, baseline insulin levels were significantly higher in the obese children in the present study. Moreover, insulin in obese subjects remained higher, even though insulin significantly decreased with exercise in both groups (Fig. 4), typically encountered with brief bouts of heavy exercise (31). However, there was no correlation between baseline insulin levels and the exercise-associated GH response. Along these lines, there is an inverse relationship between circulating levels of cortisol and GH (30), but cortisol was not different between the two groups at baseline and was not affected by exercise.

With regard to IGF-I, there was no significant difference in preexercise free or total IGF-I between normal-weight and obese subjects. IGF-I levels increased acutely with exercise in the obese subjects [by ~15%, an observation made in healthy subjects previously (4, 38)], although the increase in IGF-I in the normal-weight children was not significant. Similar to insulin, no correlations were found between IGF-I levels (total and free) and the change in the GH response to exercise. Collectively, the data suggest the possibility that the exercise-associated increase in circulating IGF-I levels could play a partial role in the blunted GH response observed in the obese children and adolescents.

In addition, our data do support the idea that the attenuated GH response to exercise is related to an obesity-associated generalized impairment of the adrenergic response to exercise, as was suggested by Vettor et al. (45). Although Epi and NE increased significantly in both the obese and control subjects, the magnitude of the increase was significantly lower in the obese children. While circulating dopamine increased in normal-weight children, no significant increase in dopamine was observed in obesity (Fig. 3). In addition, exercise-associated changes in GH levels were significantly correlated with changes in Epi.

Catecholamines are increased with heavy exercise, in part because of central nervous system mechanisms. Activation of the hypothalamic-pituitary axis and sympathetic-adrenal-medullary activation lead to Epi release from the adrenal medulla and NE and, to a lesser degree, dopamine release, from nerve endings into the circulation (32, 43). Thus exercise shares with other stresses (e.g., psychosocial) some common pathways, leading to increased catecholamine output (49). In addition, the catecholamine response to heavy exercise is further stimulated by systemic changes in acid-base balance and reduced oxygen availability to the working tissues (37).

Remarkably, the increase in circulating dopamine in response to exercise found in healthy children was absent in obese children and adolescents (Fig. 3). Previous studies have demonstrated an increase in circulating dopamine in response to cycle ergometer (29) and resistance exercise (21) in adults, as well as in healthy children (47). Whether the lack of a peripheral dopamine response in obesity is related to a systemic "dopamine deficit" (25, 46) or, alternatively, simply to less stimulation of the sympathetic system in response to exercise has yet to be determined.

There are growing data that blunting central neuroadrenergic pathways can simultaneously attenuate the GH and catecholamine arms of the global stress response. For example, Giordano et al. (16) showed that alprazolam (a benzodiazepine that activates GABA receptors in the brain) inhibited both the GH and catecholamine response to insulin-induced hypoglycemia, and previous studies have shown that benzodiazepines inhibit the catecholamine response to exercise as well (41). Reduced central dopaminergic tone could explain our findings of blunted catecholamines and GH in response to exercise in obese subjects. There are indirect data suggesting that dopamine-2 receptor gene may be abnormal in obese subjects (34), and this could lead to reduced central dopaminergic tone.

Intriguingly, we recently demonstrated a virtually identical pattern of blunted catecholamine responses to exercise in normal-weight children with attention deficit hyperactivity disorder (ADHD) (note: we did not measure GH) (47). Surprisingly, despite the common belief that children with ADHD are physically hyperactive during early childhood, and therefore leaner, Holtkamp et al. (18) demonstrated that the prevalence of obesity in children with ADHD is, in fact, higher compared with the normal population. Similarly, Agranat-Meged and coworkers (1) recently discovered a comorbidity between childhood obesity and ADHD among a subset of children hospitalized for treatment of refractory morbid obesity. They suggested that "...obese children should be screened for ADHD." Recently, it was shown that the presence of dopamine-4 receptor gene, a variant associated with decreased affinity to dopamine, was higher in obese women who had ADHD, suggesting a genetic linkage between the two common medical conditions (24). The mechanisms responsible for the potential link between childhood obesity and altered neuroadrenergic responses remain unknown.

There were no differences in the response to exercise of the other components of the GH-IGF-I axis that we chose to measure (i.e., GHBP, IGF-I, free IGF-I, and IGFBPs). Several investigators [e.g., Kanaley and coworkers (19)] speculated that the beneficial effects of exercise in obese subjects might be limited due to the suppressed GH response to exercise. However, it is now well established that many of the health effects

of exercise training are mediated by IGF-I and are GH independent (11, 50). Despite the reduced GH response to exercise in obese subjects, levels of total IGF-I did not differ between the two groups (perhaps because of significantly greater GHBP), and IGF-I increased significantly with exercise only in the obese subjects. Thus the attenuated GH response to exercise in obesity appears to be compensated by other hormonal mechanisms. These results also suggest that a limited effect of exercise interventions might be found in a subgroup of obese children with low baseline IGF-I levels and low IGF-I response to exercise [such as seen, for example, in obese children with Prader-Willi syndrome (44)]. This group may possibly benefit from an intensive therapy of both exercise and exogenous GH.

We also found marked effects of obesity on circulating IGFBP-1 and -2. These binding proteins are elevated in catabolic states, tend to antagonize IGF-I physiological function, and contribute to the bioavailability of IGF-I in tissues (35). Circulating levels of both IGFBP-1 and -2 are inversely related to insulin levels, and, consequently, have been found to be low in obese adults and children (2, 3, 12), consistent with our data. Insulin levels decreased following exercise; thus we expected that both IGFBP-1 and -2 would increase. In fact, IGFBP-2 was not significantly affected by exercise, whereas IGFBP-1 significantly decreased (concomitantly with insulin) in both groups. Why the exercise responses for both insulin and IGFBP-1 were parallel and not inverse in the present study is not clear.

As noted, pre- and postexercise insulin levels were significantly elevated in the obese children. The combination of hyperinsulinemia with suppressed GH and catecholamine responses, both counterregulatory hormones, could potentially set the stage for increased risk of hypoglycemia during and after exercise. In fact, none of the participants in our study developed hypoglycemia. Apparently, the counterregulatory hormonal response to hypoglycemia is sufficiently robust and redundant in obese children such that hypoglycemia does not occur in response to exercise, despite the increased glucose demand and the attenuated GH and catecholamine responses.

In conclusion, in response to a metabolically matched exercise input, the GH response to exercise was reduced in obese children and adolescents. This likely resulted in part from changes in IGF-I levels and from baseline hyperinsulinemia found in the obese subjects. In addition, the reduced Epi and NE and the absent dopamine response to exercise in obese subjects suggested the possibility of a centrally mediated attenuation of hypothalamic-pituitary-adrenal axis and/or sympathetic adrenal-medullary function. It is possible that the blunted GH and catecholamine response to exercise leads to reduced carbohydrate and fat utilization during exercise (5, 6) and, as a result, to a greater protein utilization (26). Consistent with this, previous studies have demonstrated that elevated BMI was associated with a reduced training effect in children and adolescents, following a prolonged resistance training intervention (13).

The reduced GH and catecholamine responses to exercise were compensated for such that hypoglycemia did not occur with exercise, despite increased insulin levels in the obese children and adolescents. Thus these results support the use of exercise, even vigorous exercise, as part of the treatment regimen for obese children. Further studies are needed to clarify the mechanistic role of IGF-I, hyperinsulinemia, and the

reduced catecholamine response (in particularly dopamine) for the diminished exercise-associated GH response and the extent to which these hormonal abnormalities persist after weight loss and/or exercise training programs in obese children and adolescents.

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REFERENCES

- Agranat-Meged AN, Deitcher C, Goldzweig G, Leibenson L, Stein M, and Galili-Weisstub E. Childhood obesity and attention deficit/hyperactivity disorder: a newly described comorbidity in obese hospitalized children. *Int J Eat Disord* 37: 357–359, 2005.
- Argente J, Caballo N, Barrios V, Pozo J, Muanoz MT, Chowen JA, and Hernandez M. Multiple endocrine abnormalities of the growth hormone and insulin-like growth factor axis in prepubertal children with exogenous obesity: effect of short- and long-term weight reduction. *J Clin Endocrinol Metab* 82: 2076–2083, 1997.
- Attia N, Tamborlane WV, Heptulla R, Maggs D, Grozman A, Sherwin RS, and Caprio S. The metabolic syndrome and insulin-like growth factor I regulation in adolescent obesity. *J Clin Endocrinol Metab* 83: 1467–1471, 1998.
- Bang P, Brandt J, Degerblad M, Enberg G, Kaijser L, Thoren M, and Hall K. Exercise-induced changes in insulin-like growth factors and their low molecular weight binding protein in healthy subjects and patients with growth hormone deficiency. *Eur J Clin Invest* 20: 285–292, 1990.
- Blaak EE and Saris WHM. Substrate oxidation, obesity and exercise training. *Best Pract Res Clin Endocrinol Metab* 16: 667–678, 2002.
- Brandou F, Dumortier M, Garandeau P, Mercier J, and Brun JF. Effects of a two-month rehabilitation program on substrate utilization during exercise in obese adolescents. *Diabetes Metab* 29: 20–27, 2003.
- Cooper DM, Weiler-Ravell D, Whipp BJ, and Wasserman K. Aerobic parameters of exercise as a function of body size during growth in children. *J Appl Physiol* 56: 628–634, 1984.
- Dandona P, Aljada A, and Bandyopadhyay A. Inflammation: the link between insulin resistance, obesity and diabetes. *Trends Immunol* 25: 4–7, 2004.
- Daughaday WH, Kapadia M, and Mariz I. Serum somatomedin binding proteins: physiologic significance and interference in radioligand assay. *J Lab Clin Med* 109: 355–363, 1987.
- Deforche B, Lefevre J, De Bourdeaudhuij I, Hills AP, Duquet W, and Bouckaert J. Physical fitness and physical activity in obese and nonobese Flemish youth. *Obes Res* 11: 434–441, 2003.
- DeVol DL, Rotwein P, Sadow JL, Novakofski J, and Bechtel PJ. Activation of insulin-like growth factor gene expression during work-induced skeletal muscle growth. *Am J Physiol Endocrinol Metab* 259: E89–E95, 1990.
- Eliakim A, Scheett TP, Newcomb R, Mohan S, and Cooper DM. Fitness, training, and the growth hormone–insulin-like growth factor I axis in prepubertal girls. *J Clin Endocrinol Metab* 86: 2797–2802, 2001.
- Falk B, Sadres E, Constantini N, Zigel L, Lidor R, and Eliakim A. The association between adiposity and the response to resistance training among pre- and early-pubertal boys. *J Pediatr Endocrinol Metab* 15: 597–606, 2002.
- Felsing NE, Brasel J, and Cooper DM. Effect of low- and high-intensity exercise on circulating growth hormone in men. *J Clin Endocrinol Metab* 75: 157–162, 1992.
- Garlaschi C, Di Natale B, Del Guercio MJ, Caccamo A, Gargantini L, and Chiumello G. Effect of physical exercise on secretion of growth hormone, glucagon, and cortisol in obese and diabetic children. *Diabetes* 24: 758–761, 1975.
- Giordano R, Grotto S, Brossa P, Pellegrino M, Destefanis S, Lanfranco F, Gianotti L, Ghigo E, and Arvat E. Alprazolam (a benzodiazepine activating GABA receptor) reduces the neuroendocrine responses to insulin-induced hypoglycaemia in humans. *Clin Endocrinol (Oxf)* 59: 314–320, 2003.
- He M, Tan KC, Li ET, and Kung AW. Body fat determination by dual energy X-ray absorptiometry and its relation to body mass index and waist circumference in Hong Kong Chinese. *Int J Obes Relat Metab Disord* 25: 748–752, 2001.
- Holtkamp K, Konrad K, Muller B, Heussen N, Herpertz S, Herpertz-Dahlmann B, and Hebebrand J. Overweight and obesity in children with attention-deficit/hyperactivity disorder. *Int J Obes Relat Metab Disord* 28: 685–689, 2004.
- Kanaley JA, Weatherup-Dentes MM, Jaynes EB, and Hartman ML. Obesity attenuates the growth hormone response to exercise. *J Clin Endocrinol Metab* 84: 3156–3161, 1999.
- Kennedy B and Ziegler MG. A more sensitive and specific radioenzymatic assay for catecholamines. *Life Sci* 47: 2143–2153, 1990.
- Kraemer WJ, Fleck SJ, Maresh CM, Ratamess NA, Gordon SE, Goetz KL, Harman EA, Frykman PN, Volek JS, Mazzetti SA, Fry AC, Marchitelli LJ, and Patton JF. Acute hormonal responses to a single bout of heavy resistance exercise in trained power lifters and untrained men. *Can J Appl Physiol* 24: 524–537, 1999.
- Kuczmariski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, Wei R, Curtin LR, Roche AF, and Johnson CL. 2000 CDC Growth Charts for the United States: methods and development. *Vital Health Stat* 11: 1–190, 2002.
- Leung KC, Waters MJ, Markus I, Baumbach WR, and Ho KK. Insulin and insulin-like growth factor-I acutely inhibit surface translocation of growth hormone receptors in osteoblasts: a novel mechanism of growth hormone receptor regulation. *Proc Natl Acad Sci USA* 94: 11381–11386, 1997.
- Leviton RD, Masellis M, Lam RW, Muglia P, Basile VS, Jain U, Kaplan AS, Tharmalingam S, Kennedy SH, and Kennedy JL. Childhood inattention and dysphoria and adult obesity associated with the dopamine D4 receptor gene in overeating women with seasonal affective disorder. *Neuropsychopharmacology* 29: 179–186, 2004.
- Levy F. The dopamine theory of attention deficit hyperactivity disorder (ADHD). *Aust NZ J Psychiatry* 25: 277–283, 1991.
- Lopes IM, Forga L, and Martinez JA. Effects of leptin resistance on acute fuel metabolism after a high carbohydrate load in lean and overweight young men. *J Am Coll Nutr* 20: 643–648, 2001.
- Maccario M, Grotto S, Procopio M, Oleandri SE, Rossetto R, Gauna C, Arvat E, and Ghigo E. The GH/IGF-I axis in obesity: influence of neuro-endocrine and metabolic factors. *Int J Obes Relat Metab Disord* 2: S96–S99, 2000.
- McMurray RG and Hackney AC. Interactions of metabolic hormones, adipose tissue and exercise. *Rev Environ Health* 35: 393–412, 2005.
- Nagao F, Suzui M, Takeda K, Yagita H, and Okumura K. Mobilization of NK cells by exercise: downmodulation of adhesion molecules on NK cells by catecholamines. *Am J Physiol Regul Integr Comp Physiol* 279: R1251–R1256, 2000.
- Nass R and Thorner MO. Impact of the GH-cortisol ratio on the age-dependent changes in body composition. *Growth Horm IGF Res* 12: 147–161, 2002.
- Nemet D, Oh Y, Kim HS, Hill MA, and Cooper DM. The effect of intense exercise on inflammatory cytokines and growth mediators in adolescent boys. *Pediatrics* 110: 681–689, 2002.
- Pedersen BK and Hoffman-Goetz L. Exercise and the immune system: regulation, integration, and adaptation. *Physiol Rev* 80: 1055–1081, 2000.
- Petersen AC, Crockett L, Richards M, and Boxer A. Self-report measure of pubertal status-reliability, validity, and initial norms. *J Youth Adolesc* 17: 117–133, 1988.
- Pijl H. Reduced dopaminergic tone in hypothalamic neural circuits: expression of a “thrifty” genotype underlying the metabolic syndrome? *Eur J Pharmacol* 480: 125–131, 2003.
- Rajaram S, Baylink DJ, and Mohan S. Insulin-like growth factor binding proteins in serum and other biological fluids: regulation and functions. *Endocr Rev* 18: 801–831, 1997.
- Robertson EB, Skinner ML, Love MM, Elder GH, Conger RD, Dubas JS and Petersen AC. The Pubertal Development Scale: a rural and suburban comparison. *J Early Adolesc* 12: 174–186, 1992.
- Schneider DA, McGuiggin ME, and Kamimori GH. A comparison of the blood lactate and plasma catecholamine thresholds in untrained male subjects. *Int J Sports Med* 13: 562–566, 1992.
- Schwarz AJ, Brasel JA, Hintz RL, Mohan S, and Cooper DM. Acute effect of brief low- and high-intensity exercise on circulating IGF-I, II, and IGF binding protein-3 and its proteolysis in young healthy men. *J Clin Endocrinol Metab* 81: 3492–3497, 1996.

39. **Singh SK, Agrawal JK, Rai M, and Gupta SS.** Growth hormone response to clonidine in obese children. *Indian Pediatr* 28: 737–740, 1991.
40. **Speiser PW, Rudolf MCJ, Anhalt H, Camacho-Hubner C, Chiarelli F, Eliakim A, Freemark M, Gruters A, HersHKovitz E, Iughetti L, Krude H, Latzer Y, Lustig RH, Pescovitz OH, Pinhas-Hamiel O, Rogol AD, Shalitin S, Sultan C, Stein D, Vardi P, Werther GA, Zadik Z, Zuckerman-Levin N, Hochberg Z; Obesity Consensus Working Group.** Childhood obesity. *J Clin Endocrinol Metab* 90: 1871–1887, 2005.
41. **Stratton JR and Halter JB.** Effect of a benzodiazepine (alprazolam) on plasma epinephrine and norepinephrine levels during exercise stress. *Am J Cardiol* 56: 136–139, 1985.
42. **Tirakitsoontorn P, Nussbaum E, Moser C, Hill M, and Cooper DM.** Fitness, acute exercise, and anabolic and catabolic mediators in cystic fibrosis. *Am J Respir Crit Care Med* 164: 1432–1437, 2001.
43. **Van Loon GR.** Plasma dopamine: regulation and significance. *Fed Proc* 42: 3012–3018, 1983.
44. **Van Mil EGAH, Westerterp KR, Gerver WJ, Van Marken Lichtenbelt WD, Kester ADM, and Saris WHM.** Body composition in Prader-Willi syndrome compared with nonsyndromal obesity: relationship to physical activity and growth hormone function. *J Pediatr* 139: 708–714, 2001.
45. **Vettor R, Macor C, Rossi E, Piemonte G, and Federspil G.** Impaired counterregulatory hormonal and metabolic response to exhaustive exercise in obese subjects. *Acta Diabetol* 34: 61–66, 1997.
46. **Volkow ND, Wang GJ, Fowler JS, Logan J, Franceschi D, Maynard L, Ding YS, Gatley SJ, Gifford A, Zhu W, and Swanson JM.** Relationship between blockade of dopamine transporters by oral methylphenidate and the increases in extracellular dopamine: therapeutic implications. *Synapse* 43: 181–187, 2002.
47. **Wigal SB, Nemet D, Swanson JM, Regino R, Trampush J, Ziegler MG, and Cooper DM.** Catecholamine response to exercise in children with attention deficit hyperactivity disorder. *Pediatr Res* 53: 756–761, 2003.
48. **Wilkinson PW and Parkin JM.** Letter: Growth-hormone response to exercise in obese children. *Lancet* 2: 55, 1974.
49. **Wright RJ, Rodriguez M, and Cohen S.** Review of psychosocial stress and asthma: an integrated biopsychosocial approach. *Thorax* 53: 1066–1074, 1998.
50. **Zanconato S, Moromisato DY, Moromisato MY, Woods J, Brasel JA, LeRoith D, Roberts CT Jr, and Cooper DM.** Effect of training and growth hormone suppression on insulin-like growth factor-I mRNA in young rats. *J Appl Physiol* 76: 2204–2209, 1994.

