Reduced Exercise-Associated Response of The GH-IGF-I Axis and Catecholamines in Obese Children and Adolescents

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**Running Head**: Obesity and the counter-regulatory response to exercise

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Abstract

Obesity blunts catecholamine and growth hormone 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 counter-regulatory hormonal response to acute exercise. Twenty-five obese children (Ob, BMI> 95%), and 25 age, gender and maturity matched normal weight controls (NW) participated in the study. Exercise consisted of ten two-min bouts of constant cycle-ergometry above the anaerobic threshold, with one-min rest intervals between each bout. Pre, post and 120-min post exercise 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 VO2 normalized to lean body mass between the groups. Obesity attenuated the GH response to exercise (8.9±1.1 versus 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 versus 18.7±3.7 pg/ml, p<0.02; norepinephrine: 479.5±109.9 versus 218.0±26.0 pg/ml, p<0.04; dopamine: 17.2±2.9 versus 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 counter-regulatory 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.

Key words: Overweight, Children, GH-IGF-I axis, Catecholamines, Physical activity.
Introduction

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 (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). Growth hormone 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 extra-cellular domain of the GH receptor, total and free IGF-I, and IGF binding proteins 1-4 and 2) circulating mediators of the neuroadrenergic response to exercise, namely, epinephrine, norepinephrine, and dopamine. In addition, we measured physiologic responses to exercise (e.g. peak heart rate, respiratory exchange ratio 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, since both GH→IGF-I axis hormones and catecholamines play a role in glucose homeostasis during exercise (45), and since obesity is associated with hyperinsulinism, we also measured circulating levels of both glucose and insulin.
Materials and Methods

Subjects

Fifty participants (age range 8-17; 26 females, 24 males) were recruited by the UCI 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 non-invasive indicator of pubertal status (33; 36).

Body composition assessment by DEXA.

Since BMI does not measure lean body mass and does not invariably correlate with fat mass (17), body composition was also measured by DEXA using the hologic QDR 4500 densitometer (Hologic, Inc. Bedford, MA, U.S.A.). 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/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, respiratory exchange ratio (RER) and peak VO₂ were calculated using a Sensor Medics metabolic system (7).

Exercise protocol

Exercise consisted of 10 two-minutes bouts of constant work rate cycle ergometry, with one minute 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 non-invasively from the ramp-type test) and the peak VO₂. We have used this protocol in the past in order 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 minutes (20 minutes cycling interspersed by 10 minutes resting).

Blood Sampling and analysis

Morning (following an overnight fast) pre, immediately post and 120 min post exercise (recovery) blood samples were drawn from an indwelling venous catheter that was inserted 30 minutes prior to the first blood draw. Blood samples were immediately spun at 3000 rpm, at 4°C for 20 minutes. The serum was separated and stored at –80°C. All pre and post exercise specimens from each individual were analyzed in the same batch by an experienced technician who was blinded to the individual’s group (normal weight versus obese), and to the order of samples.

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

**Growth Hormone Binding Protein.** GHBP serum levels were measured using ELISA with the use of the DSL-10-4800 Active kit (Diagnostic Systems Laboratories, Webster, TX). Intra-assay CV was 3.2-5.6%, inter-assay CV was 5.0-8.0%. Assay sensitivity was 1.69 pmol/L.

**Insulin-like Growth Factor-I: total and free.** IGF-I was extracted from IGF-binding proteins (IGFBPs) 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, Webster, TX). IGF-I intra-assay CV was 1.5-3.4% and the inter-assay 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%, inter-assay CV was 6.2-11.1%, and the sensitivity was 0.015 ng/ml.

**IGF Binding Proteins.** 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 inter-assay 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%, inter-assay 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%, inter-assay 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%, inter-assay 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%, inter-assay 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 2.5mg/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%, inter-assay 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 Corporation, Los Angeles, CA). The intra and inter assay CV for this assay were 3.2% and 6.8% respectively.

**Epinephrine, Norepinephrine,, and Dopamine.** These catecholamines were measured by a radioenzymatic technique based on the conversion of the catecholamine to radio-labeled metanephrine and normetanephrine. This catecholamine assay uses an extraction technique that eliminates substances that may inhibit the radioenzymatic assay, and concentrates the catecholamine to provide a more sensitive assay. Plasma samples of one ml were extracted and then concentrated into a 0.1ml volume before conversion into the radio-labeled metabolites. The assay has an extraction efficiency of 78%. The sensitivity of the assay is 10 and 6 pg/mL for NE and EPI. The intra-assay CV are 4 and 13% for samples containing low levels of catecholamine; variation is less for samples with high levels of catecholamine. The inter-assay CV are 10% and 16%, respectively, for NE and EPI, so the assay is consistent over time. This technique is approximately 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 mean ± SEM. 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 VO₂ 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 VO₂ normalized to lean body mass (figure 1). There was no difference in the respiratory exchange ratio between normal weight and obese children (1.07±0.01 versus 1.09±0.02 in normal weight and obese participants, respectively).

GH, GHBP, IGF-1, and IGFBP-3 and 4 (Table 2, Figure 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 (Figure 3)**

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

Exercise. Epinephrine and norepinephrine 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 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 catecholamines (Table 3). There was a significant correlation between exercise-associated changes in epinephrine and GH among the participants (r= 0.35, p<0.01).

**Glucoregulation (glucose, insulin, cortisol, IGFBP-1 and 2; Table 2 and Figure 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 neuroadrenergic factors were measured simultaneously. We found that both GH→IGF 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 (Figure 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 subjects LAT (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, respiratory exchange ratio, serum lactate levels and peak VO₂ normalized to lean body mass of the participants (Figure 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 (figure 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 regards to IGF-I, there was no significant difference in pre-exercise free or total IGF-I between normal-weight and obese subjects. IGF-I levels increased acutely with exercise in the obese subjects [by about 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 suggests 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 epinephrine and norepinephrine 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 (Figure 3). In addition, exercise associated changes in GH levels were significantly correlated with changes in epinephrine.

Catecholamines are increased with heavy exercise, in part because of CNS mechanisms. Activation of the hypothalamic-pituitary axis and sympathetic-adrenal-medullary activation lead to epinephrine release from the adrenal medulla and
norepinephrine 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 (Figure 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 (D2) 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) (n.b., 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 to the normal population. Similarly, Agranat-Meged and coworkers (1) recently discovered a co-morbidity 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 IGFBP’s). 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 while IGFBP-1 significantly decreased (concomitantly with insulin) in both groups. Why the exercise response for both insulin and IGFBP-1 were parallel and not inverse in the present study is not clear.

As noted, pre- and post exercise 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.

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 epinephrine and norepinephrine 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 lead 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.
Grants:

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References


**Figure legends**

Figure 1: Peak exercise heart rate (left panel), peak VO$_2$ normalized to lean body mass (middle panel) and serum lactate (right panel) in normal weight and obese children. Data presented as mean ± SEM. There were no significant differences between the groups.

Figure 2. Exercise-associated changes in circulating components of the GH-IGF-I axis. GH (upper panel), but not GHBP (middle panel), and IGF-I (lower panel) response was significantly reduced in obese children. * Within-group changes from pre-exercise values (p<0.05). ** Between group differences for change from pre-exercise values (p<0.05). # Different levels between normal weight and obese children (p<0.05).

Figure 3: The effect of exercise on the catecholamine response in obese children. Peak levels of epinephrine, nor-epinephrine and dopamine at the end of exercise were significantly reduced in obese compared to normal weight children, and returned to baseline levels 120 minutes post-exercise. * Within-group changes from pre-exercise values (p<0.05). **Between group differences for changes from pre-exercise values (p<0.05).

Figure 4: Exercise-associated changes in serum glucose, insulin, and 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).
Table 1: Anthropometric characteristics of study participants.

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<th>Normal weight (n = 25)</th>
<th>Obese (n = 25)</th>
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<tr>
<td>Age (yr)</td>
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<td>12.3 ± 0.5</td>
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<td>12/13</td>
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<td>Maturity (Tanner stage)</td>
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<td>Ethnicity (H/As/C/AA)</td>
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<td>Height (cm)</td>
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<td>Body weight (kg)</td>
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<td>Body Fat (%)</td>
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<td>LAT (%VO\textsubscript{2}peak)</td>
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Data presented as means ± SEM. * = p≤0.001 Normal weight vs. Obese children

H-Hispanic, As-Asian, C- Caucasian, AA-African American.
Table 2: The effects of exercise on several circulating components of the GH-IGF-I axis and cortisol. There were no significant effects of exercise on any of the measurements in both groups.

<table>
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<td>Pre</td>
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<td>Free IGF-I (ng/ml)</td>
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<td>IGFBP-2 (ng/ml)</td>
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<td>211.8±42.8*</td>
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<td>3351.5±199.3</td>
<td>3597.2±209.7</td>
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<td>IGFBP-4 (ng/ml)</td>
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<td>Cortisol (μU/ml)</td>
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Data presented as mean ± SEM. * p<0.05 for differences between normal weight and obese children.
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.

<table>
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<td>r= -0.28, p=0.048</td>
<td>r= -0.31, p=0.03</td>
<td>r= -0.29, p=0.043</td>
</tr>
<tr>
<td>Percent body fat</td>
<td>r= -0.43, p=0.002</td>
<td>r= -0.46, p=0.0006</td>
<td>r= -0.49, p=0.0004</td>
<td>r= -0.43, p=0.002</td>
</tr>
<tr>
<td>Peak VO(_2)/kg</td>
<td>r= 0.28, p=0.048</td>
<td>r= 0.31, p=0.03</td>
<td>r= 0.42, p=0.003</td>
<td>r= 0.47, p=0.0005</td>
</tr>
<tr>
<td>Peak VO(_2)/kg/LBM</td>
<td>r= -0.09, NS</td>
<td>r= 0.18, NS</td>
<td>r= 0.5, p=0.0003</td>
<td>r= 0.57, p&lt;0.0001</td>
</tr>
<tr>
<td>Insulin</td>
<td>r= -0.13, NS</td>
<td>r= -0.18, NS</td>
<td>r= -0.16, NS</td>
<td>r= -0.06, NS</td>
</tr>
<tr>
<td>IGF-I</td>
<td>r= 0.03, NS</td>
<td>r= 0.19, NS</td>
<td>r= 0.07, NS</td>
<td>r= 0.15, NS</td>
</tr>
</tbody>
</table>
Figure 1: Peak exercise heart rate (left panel), peak VO\(_2\) normalized to lean body mass (middle panel) and serum lactate (right panel) in normal weight and obese children. Data presented as mean ± SEM. There were no significant differences between the groups.
Figure 2. Exercise-associated changes in circulating components of the GH-IGF-I axis. GH (upper panel), but not GHBP (middle panel), and IGF-I (lower panel) response was significantly reduced in obese children. * Within-group changes from pre-exercise values (p<0.05). ** Between group differences for change from pre-exercise values (p<0.05). # Different levels between normal weight and obese children (p<0.05).
Figure 3: The effect of exercise on the catecholamine response in obese children. Peak levels of epinephrine, nor-epinephrine and dopamine at the end of exercise were significantly reduced in obese compared to normal weight children, and returned to baseline levels 120 minutes post-exercise. * Within-group changes from pre-exercise values (p<0.05). **Between group differences for changes from pre-exercise values (p<0.05).
Figure 4: Exercise-associated changes in serum glucose, insulin, and 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).