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Fitness, Training, and the Growth Hormone→Insulin-Like Growth Factor I Axis in Prepubertal Girls*

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ABSTRACT

We recently demonstrated that a brief endurance type training program led to increases in thigh muscle mass and peak oxygen uptake ($\dot{V}O_2$) in prepubertal girls. In this study, we examined the effect of training on the GH→insulin-like growth factor I (GH→IGF-I) axis, a system known to be involved both in the process of growth and development and in the response to exercise. Healthy girls (mean age 9.17 ± 0.10 yr old) volunteered for the study and were randomized to control ($n = 20$) and training groups ($n = 19$) for 5 weeks. Peak $\dot{V}O_2$, thigh muscle volume, and blood samples [for IGF-I, IGF-binding proteins (IGFBP)-1 to -6, and GHBP] were measured. At baseline, IGF-I was significantly correlated with both peak $\dot{V}O_2$ ($r = 0.44$, $P < 0.02$) and muscle volume ($r = 0.58$, $P < 0.004$). IGFBP-1 was negatively correlated with muscle

volume ($r = -0.71$, $P < 0.0001$), as was IGFBP-2. IGFBP-4 and -5 were significantly correlated with muscle volume. We found a threshold value of body mass index percentile (by age) of about 71, above which systematic changes in GHBP, IGFBP-1, and peak $\dot{V}O_2$ per kilogram were noted, suggesting decreases in the following: 1) GH function, 2) insulin sensitivity, and 3) fitness. Following the training intervention, IGF-I increased in control ($19.4 \pm 9.6\%$, $P < 0.05$) but not trained subjects, and both IGFBP-3 and GHBP decreased in the training group ($-4.2 \pm 3.1\%$ and $-9.9 \pm 3.8\%$, respectively, $P < 0.05$). Fitness in prepubertal girls is associated with an activated GH→IGF-I axis, but, paradoxically, early in a training program, children first pass through what appears to be a neuroendocrine state more consistent with catabolism. (*J Clin Endocrinol Metab* 86: 2797–2802, 2001)

NORMAL GROWTH IN children is regulated in large measure through the actions of the GH→insulin-like growth factor I (GH→IGF-I) axis, a system of growth hormones and mediators that modulates growth in many tissues. A variety of environmental factors, the most thoroughly studied to date being nutrition (1), can influence elements of the GH→IGF-I axis and, ultimately, growth itself. Recent work from this and other laboratories in human and animal models has shown that exercise and levels of physical activity also influence the GH→IGF-I axis and growth (2, 3). The present study was designed to examine the role of fitness and the effect of brief exercise training on the GH→IGF-I axis in prepubertal girls.

This is an important yet relatively understudied group. Although it is recognized that optimal levels of exercise during childhood may attenuate obesity (4) and prevent osteoporosis and cardiovascular disease in adulthood (5), epidemiologic and physiologic evidence suggests that American girls are now becoming less physically active in early

puberty. The long-term consequences of reduced exercise and the underlying mechanisms responsible for beneficial effects of exercise in children are not well understood.

Controversy still surrounds the ability of exercise training to measurably influence functional fitness, muscle mass, or cardiorespiratory responses to exercise in children (6–9). Some investigators have reasoned that the generally high levels of physical fitness found naturally in prepubertal children would make it difficult to alter levels of activity sufficiently to produce a measurable response. Moreover, whether or not the GH→IGF-I axis, which naturally is changing so dynamically in children, could further be influenced by exercise is not known.

In the present cohort of prepubertal girls, the effect of the prospective exercise training program on peak oxygen uptake ($\dot{V}O_2$), body weight, height, and magnetic resonance imaging-determined muscle mass and body adiposity has already been published (10). In this previous study, we demonstrated that a relatively brief training intervention (5 weeks) led to small but significant increases in thigh muscle volume ($+4.3 \pm 0.9\%$, $P < 0.005$) and peak $\dot{V}O_2$ ($+9.5 \pm 6\%$, $P < 0.05$) that were not observed in untrained control subjects. Moreover, total energy expenditure, measured by the doubly labeled water technique, was significantly greater (17% , $P < 0.02$) in the training compared with control group subjects.

In previous studies of adults and children, levels of fitness are known to be correlated with circulating levels of IGF-I. Thus, we hypothesized that exercise training would stimulate the GH→IGF-I axis and be associated with increases in circulating levels of IGF-I.

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In the present study, we first examined the interrelationships among the mediators of the GH→IGF-I axis, fitness, body weight, and thigh muscle volume. We measured IGF-I, the major circulating IGF-binding proteins (IGFBP)-1 to -6, and GH-binding protein (GHBP). GHBP is the extracellular component of the GH receptor and is, in some circumstances, related to the relative quantity of tissue GH receptors (11). Because the study design included measurements of thigh muscle volume by magnetic resonance imaging and cardiorespiratory responses to exercise (*i.e.* peak $\dot{V}O_2$), we were uniquely able to examine the correlation between elements of the GH→IGF-I axis with these anatomic and functional correlates of fitness in a relatively homogeneous population of prepubertal girls. Following the initial baseline measurements, the girls were randomized to either control or exercise training groups, and we prospectively studied the effect of the 5-week endurance-type training intervention on the growth mediators.

Materials and Methods

Sample population and protocol

Thirty-nine girls volunteered to participate in the study. The subjects were all students in the Greater Hartford elementary school district (Hartford, CT) and enrolled in a 5-week summer school program in the town of West Hartford, with class hours from 0800–1100 h (5 days per week). The ethnic configuration of the group was 77% Caucasian, 10% African American, 10% Hispanic, and 3% Asian. No attempt was made to recruit subjects who participated in competitive extramural athletic programs. The study was designed to examine pre and early pubertal subjects with an age range of 8–10 yr (mean, 9.2 ± 0.1). Measurements of height and weight were made using standard techniques. Assessment of pubertal status was performed by examination of each subject. Thirty-four (87%) of the subjects were found to be at Tanner stage I, and 6 (13%) at Tanner stage II.

The participants were randomized to a control ($n = 20$, 4 at Tanner II) or training group ($n = 19$, 2 at Tanner II). All subjects participated in a daily 45-min science program in physiology. During the remaining time, the training group members participated in two sessions of endurance-type training (45 min each) consisting of running, jumping, aerobic dance, and age-appropriate competitive sports (*e.g.* basketball, soccer, *etc.*). These two exercise sessions were separated by an elective in-class traditional course (45 min), which was selected by the study participants from the summer school curriculum. The intervention was designed to mimic the type and intensity of exercise that elementary school girls normally perform. These activities were varied in duration and intensity throughout the week, and were designed primarily as games to encourage enthusiasm and participation of the subjects. Aerobic or endurance type activities accounted for about all of the time spent in training (about 50% team sports and 50% running games). Training was directed by a physical education instructor of the West Hartford Elementary School faculty.

During the same time, the control group subjects participated in three elective in-class courses from the summer school curriculum. No attempt was made to influence extracurricular levels of physical activity in either the control or training groups, but participants were asked not to change their activity patterns from those before the study. The study was approved by the Institutional Human Subject Review Board. Informed assent was obtained from the subjects and an informed consent from their parents or guardians.

Measurements of fitness

Fitness was assessed by traditional approaches using cardiorespiratory indices of exercise performance. The cardiorespiratory variables were derived from measurements of peak oxygen consumption ($\dot{V}O_2$ peak) before and after the training intervention. Each subject performed a ramp-type progressive exercise test on a cycle ergometer in which the subject exercised to the limit of her tolerance. Subjects were vigorously

encouraged during the high-intensity phases of the exercise protocol. Gas exchange was measured breath-by-breath (12) and the $\dot{V}O_2$ peak was determined as previously described for children and adolescents (13). Mean heart rate peak was 188 ± 3 beats per minute, and mean respiratory exchange ratio peak was 1.14 ± 0.01 suggesting that close to maximal values were likely achieved.

Height, weight, body mass index (BMI), and muscle volume

Standard, calibrated scales and stadiometers were used to determine height, weight, and BMI. Because BMI changes with age, we calculated BMI percentile for each child using the recently published standards from the Centers for Disease Control, National Center for Health Statistics (14). Serial sections of the thigh musculature were obtained using standard magnetic resonance techniques. Computerized planimetry was used to determine thigh muscle volume as previously described in our laboratory (10).

Fitness and body size data were normalized in a number of ways to facilitate correlation with growth mediators. For IGF-I and IGFBP-1 we used absolute muscle volume and peak $\dot{V}O_2$ because it is the amount of muscle tissue that is the major determinant of oxygen uptake during exercise. Peak $\dot{V}O_2$ normalized to body weight is an indirect estimate of muscle mass relative to body weight (15); consequently, peak $\dot{V}O_2$ per kilogram body weight is also an indicator of fitness when comparing subjects of different size. Peak $\dot{V}O_2$ normalized to body weight, GHBP, and IGFBP-I were plotted against BMI percentile. Because BMI itself changes with age, the BMI as a percentile allowed us to adequately normalize relative fatness among the subjects of the study.

Blood sampling protocols

Subjects were admitted to the General Clinical Research Center at the University of Connecticut Health Center. An early morning fasting blood sample was collected from a forearm vein. None of the subjects trained during the day preceding the blood sampling. All pre and postintervention specimens were analyzed in the same batch by technicians who were blinded to the group and order of the samples.

GHBP

GHBP was measured using the ligand-mediated immunofunctional assay (16). Interassay coefficient of variation (c.v.) was 9.7–12.9%, and intraassay c.v. was 6.3–8.9%. Assay sensitivity was 7.8 pmol/L.

IGF-I

IGF was extracted from IGFBPs using the acid-ethanol extraction method (17). Serum IGF-I concentrations were determined by a two-site immunoradiometric assay using the DSL-5600 Active kit (Diagnostics Systems Laboratories, Inc., Webster, TX). IGF-I interassay c.v. was 3.7–8.2% and intraassay c.v. was 1.5–3.4%. Assay sensitivity was 0.8 ng/mL.

IGFBPs 1–6

IGFBP-1 and -3 were measured by coated-tube immunoradiometric assays. IGFBP-2, and -4 to -6 were measured by RIA. IGFBP-1 to -3 and -6 were measured using commercially available kits (Diagnostics Systems Laboratories, Inc.). IGFBP-4 and -5 were measured in our coauthor's laboratory (S.M.) as recently described (18, 19). For IGFBP-1, interassay c.v. was 1.7–6.7% and intraassay c.v. was 2–4%. Assay sensitivity is 0.33 ng/mL. For IGFBP-2, interassay c.v. was 6.4% and intraassay c.v. was 6.5%. Assay sensitivity is 0.5 ng/mL. For IGFBP-3, interassay c.v. was 0.6–1.9% and intraassay c.v. was 1.8–3.9%. Assay sensitivity is 0.5 ng/mL. For IGFBP-4 interassay c.v. was less than 8.1% and intraassay c.v. was less than 5%. Assay sensitivity is less than 0.5 ng/mL. For IGFBP-5 and -6 interassay c.v. was less than 8% and intraassay c.v. was less than 4%. Assay sensitivity is less than 5 ng/mL.

Statistical analysis

Unpaired *t* tests were used to determine baseline differences in circulating components of the GH→IGF-I axis, between control and training group subjects before the training intervention. Correlation and

linear regression analyses were used to determine the correlation coefficients between elements of the GH→IGF-I axis and indices of fitness.

When the three outcome measures, GHBP, IGFBP-1, and peak $\dot{V}O_2$ per kilogram, were plotted against BMI percentile each of the three graphics strongly suggested a threshold effect. Based on this evidence we elected to fit each of the three relations using a continuous, piecewise linear regression model composed of two linear segments whose point of connection would locate a threshold for each model. This analysis was carried out using the SAS Nonlinear Regression Procedure (SAS Institute, Inc., Cary, NC) in which we specified a grid of initial parameter values and then used the Marquardt method to search for the models' parameters, which included the threshold value. In each case we calculated estimates for the two slope coefficients and the threshold value together with 95% confidence limits for each of these parameters.

Two-way repeated measures ANOVA was used to compare the effect of the intervention on circulating components of the GH→IGF-I axis with time serving as the within-group factor and training as the between-group factor. Statistical significance was taken at the P less than 0.05 level. Data are presented as mean $\pm$ SE.

Results

Height and weight

As previously reported (10), there were no significant differences in height, weight, and BMI between the groups before the intervention. Height increased to a small but significant degree in both groups during the course of the 5-week intervention (for the whole sample from 134.7 ± 1.3 cm to 135.6 ± 1.2 cm, $P < 0.001$), and there was no difference in the increase between control or trained subjects. Interestingly, weight increased significantly in the control subjects from 32.2 ± 2.2 kg to 32.9 ± 2.3 kg, $P < 0.04$, but no significant change was observed in the training group (pretraining 35.5 ± 2.3 kg, posttraining 35.7 ± 2.4 kg).

At baseline, mean BMI in the control subjects was 55 ± 7 percentile by age and did not significantly differ from training group subjects (60 ± 6 percentile). We did find a small but significant difference between the pre-post intervention change in BMI in the control ($+1.3 \pm 1.0\%$) compared with the training subjects ($-1.3 \pm 0.7\%$, $P < 0.05$).

Circulating components of the GH→IGF-I axis: cross-sectional data

The strongest correlations between either thigh muscle volume or peak $\dot{V}O_2$ and elements of the GH→IGF-I axis were found for IGF-I and IGFBP-1. IGF-I was significantly correlated with both peak $\dot{V}O_2$ and thigh muscle volume (Fig. 1). IGFBP-1 was negatively correlated with thigh muscle volume (Fig. 2).

Weaker but significant correlations were also found for other IGFBPs and GHBP. Like IGFBP-1, IGFBP-2 was inversely correlated with thigh muscle volume ($r = -0.42$, $P < 0.008$). IGFBP-3, which often parallels IGF-I, was weakly but not significantly correlated with muscle volume ($r = 0.34$, $P = 0.055$). IGFBP-4 and -5 were significantly correlated with thigh muscle volume ($r = 0.37$, $P < 0.04$; and $r = 0.43$, $P < 0.02$, respectively) but not with peak $\dot{V}O_2$. IGFBP-6 was weakly but significantly correlated with peak $\dot{V}O_2$ ($r = 0.37$, $P < 0.04$). GHBP was significantly correlated with body weight ($r = 0.58$, $P < 0.004$) and with muscle volume ($r = 0.45$, $P < 0.02$). GHBP was not correlated with peak $\dot{V}O_2$ but was inversely correlated with the normalized peak $\dot{V}O_2$ per kilogram ($r = -0.48$, $P < 0.007$).

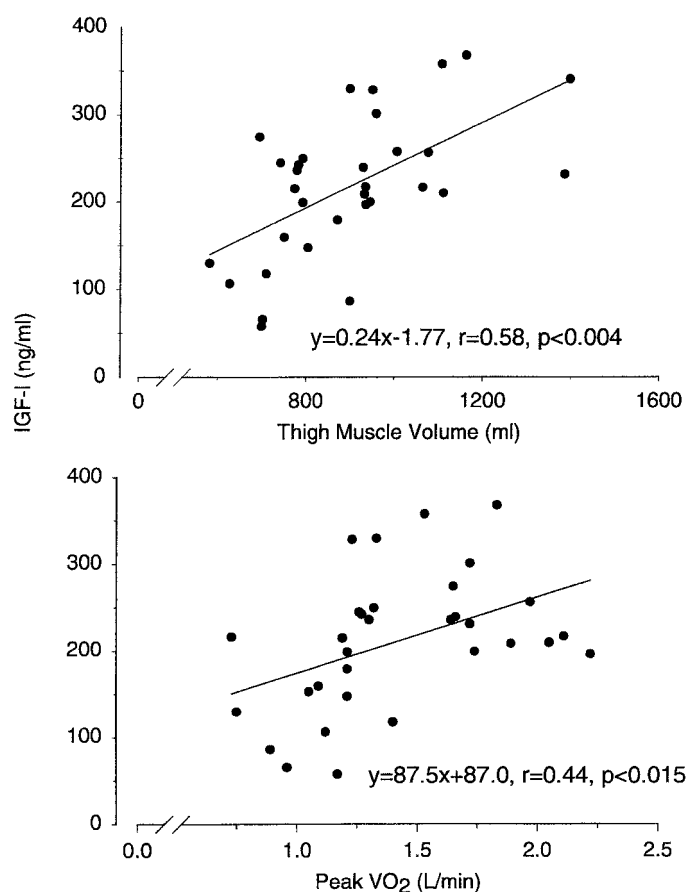


FIG. 1. The relationship between IGF-I and thigh muscle volume (top) and peak $\dot{V}O_2$ (bottom). IGF-I was correlated with both of these indices of cardiorespiratory fitness in a homogeneous population of prepubertal girls.

The relationship between body composition (estimated as BMI percentile) and GHBP, IGFBP-1, and peak $\dot{V}O_2$ per kilogram (Table 1, Fig. 3) was revealing. The model of fitting two straight lines (described above) suggested that there exists a threshold value of BMI percentile above which systematic changes in GHBP, IGFBP-1, and peak $\dot{V}O_2$ per kilogram seem to occur. There was a remarkable coincidence of the calculated thresholds: 72, 68, and 73 percentile for GHBP, IGFBP-1, peak $\dot{V}O_2$ per kilogram, respectively. Moreover, when the data above the threshold percentile were used, significant correlations were found between BMI percentile and GHBP ($r = 0.82$, $P < 0.0003$); IGFBP-1 ($r = -0.80$, $P < 0.003$), and peak $\dot{V}O_2$ per kilogram ($r = -0.76$, $P < 0.003$).

Effects of exercise training (Table 2 and Fig. 4)

No significant differences in elements of the GH→IGF-I axis were found between control and training group subjects before the training intervention. Repeated measures ANOVA revealed small but significant effects of the intervention. Significant increases in IGF-I were noted in the control group, but there was no significant change in IGF-I in the training subjects. IGFBP-3 declined significantly in the training subjects, but did not significantly change in controls. IGFBP-5 significantly increased in the control subjects, but no

significant change was observed in the training group. Exercise training also led to a significant reduction in GHBP, with no significant change observed in controls. No specific effect of exercise training was observed on IGFBP-1, IGFBP-2, and IGFBP-6. IGFBP-4 increased significantly in both groups.

Discussion

This study demonstrates that in healthy prepubertal girls, cardiorespiratory and anatomic indices of fitness are associated with an activated, more anabolic GH→IGF-I axis. In contrast, a brief endurance-type exercise training program seemed to have resulted in catabolic rather than anabolic responses of the GH→IGF-I system of mediators despite the fact that training led to increased muscle volume and improved cardiorespiratory responses to exercise. The data also showed a remarkable relationship in healthy girls among adiposity (judged by the BMI percentile), fitness, and indirect indicators of GH responsiveness (*i.e.* GHBP) and insulin sensitivity (*i.e.* IGFBP-1). It appears that above about the 68–73 percentile of BMI for age, fitness, GH levels, and insulin sensitivity all begin to decrease even in healthy children.

In the cross-sectional analysis, IGF-I was correlated with peak $\dot{V}O_2$ and, to an even greater extent, thigh muscle volume. These data in growing children are consistent with a

number of studies in adolescents and in adults (20, 21). Collectively, it seems that higher levels of physical activity are associated with increased GH pulsatility, and, eventually, with increased circulating IGF-I. It is compelling to speculate that stimulation of the GH→IGF-I axis by exercise contributes, along with genetic, nutritional, and other environmental factors, to an increase in muscle mass and, ultimately, to improved cardiorespiratory responses to exercise (such as peak $\dot{V}O_2$). Our data suggest that this mechanism operates in prepubertal girls even as spontaneous growth proceeds.

With the exception of IGFBP-3, the amount of IGFBPs in the circulation is low, and the role of these IGFBPs in the circulation has yet to be determined. Nonetheless, it is note-

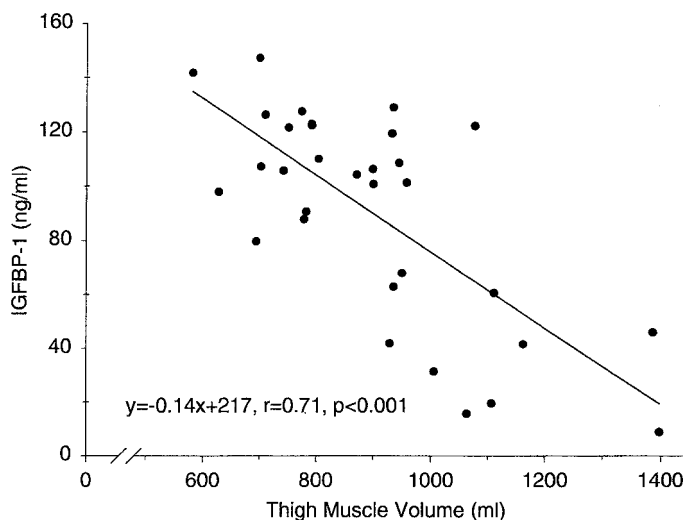


FIG. 2. IGFBP-1 as a function of thigh muscle volume in prepubertal girls. There was a significant inverse correlation between these two variables. Tissue studies suggest that IGFBP-1 may inhibit IGF-I bioactivity. Lower levels of IGFBP-1 along with higher levels of circulating IGF-I may represent a level of growth factors that optimize muscle growth.

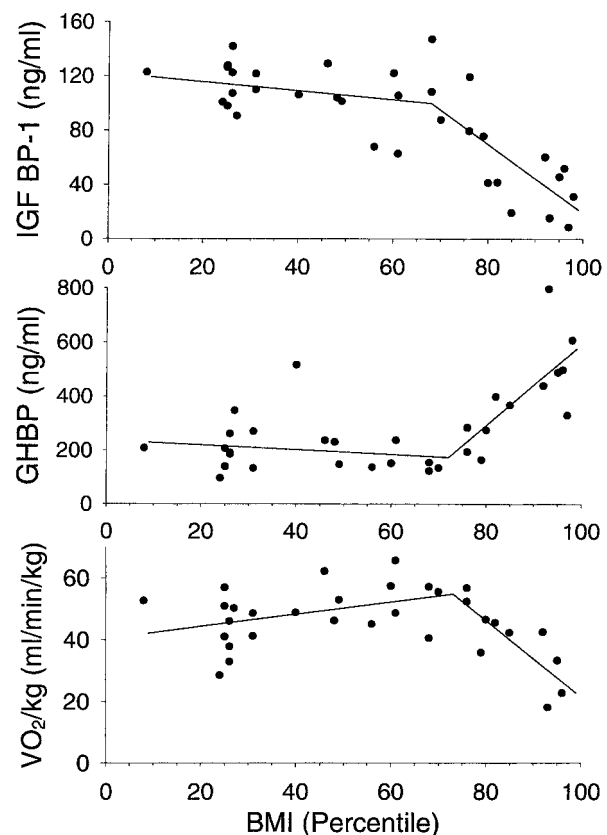


FIG. 3. Relationship between BMI (determined as percentile based on age) and IGFBP-1 (*top*), GHBP (*middle*), and peak $\dot{V}O_2$ /kg (*bottom*). Lines indicate the best fit regression for each of these variables for values above a threshold BMI percentile (see *Results* and Table 2). The data suggest that there exists a BMI percentile threshold above which insulin sensitivity, GH activity, and fitness all begin to decrease in otherwise healthy, prepubertal girls.

TABLE 1. Regression slopes and threshold for the relationship of BMI (percentile by age) to GHBP, IGFBP-1 and $\dot{V}O_2$ per kilogram as calculated using a continuous, piecewise linear regression model composed of two linear segments whose point of connection would locate a threshold for each model

Variables	BMI threshold (percentile)	Slope below	Slope above
GHBP	72.0 (61.3, 82.7)	-0.88 (-3.61, +1.85)	14.9 (7.1, 22.7)
IGFBP-1	68.0 (52.6, 83.4)	-0.33 (-0.91, +0.25)	-2.52 (-3.89, -1.15)
Peak $\dot{V}O_2$ /kg	73.1 (64.2, 82.0)	0.20 (-0.01, +0.41)	-1.24 (-1.97, -0.52)

The threshold, slope below, and slope above the threshold, and their respective 95% confidence intervals (lower, upper; in parentheses), are presented. For GHBP and IGFBP-1, the slope units are nanograms per mL/percentile; for peak $\dot{V}O_2$ /kg the slope unit is milliliters per min/kg · percentile.

TABLE 2. The effect of 5 weeks endurance-type exercise training on circulating components of the GH-IGF-I axis in prepubertal females

	Control (n = 20)		Trained (n = 19)	
	Pre	Post	Pre	Post
GHBP (pmol/L)	269.1 ± 26.2	274.8 ± 27.4	305.9 ± 48.9	276.6 ± 52.4 ^{a,b}
IGF-I (ng/mL)	209.8 ± 22.7	238.2 ± 23.5 ^{a,b}	231.4 ± 13.2	221.5 ± 11.5
IGFBP-1 (ng/mL)	92.7 ± 14.4	88.5 ± 14.1	86.6 ± 9.4	93.3 ± 7.8
IGFBP-2 (ng/mL)	492.8 ± 60.1	450.9 ± 74.7	502.5 ± 74.0	484.2 ± 57.8
IGFBP-3 (ng/mL)	4309 ± 185	4491 ± 184	4656 ± 232	4386 ± 165 ^{a,b}
IGFBP-4 (ng/mL)	414.7 ± 19.5	438.1 ± 23.1 ^a	417.1 ± 16.7	455.8 ± 17.7 ^a
IGFBP-5 (ng/mL)	229.5 ± 14.1	260.3 ± 14.0 ^{a,b}	244.4 ± 7.1	252.1 ± 6.6
IGFBP-6 (ng/mL)	144.8 ± 6.3	141.7 ± 6.7	147.4 ± 6.1	141.0 ± 6.8

Results are shown as mean ± SEM.

^a Statistically significant pre-post difference within group, $P < 0.05$.

^b Statistically significant pre-post difference between groups, $P < 0.05$.

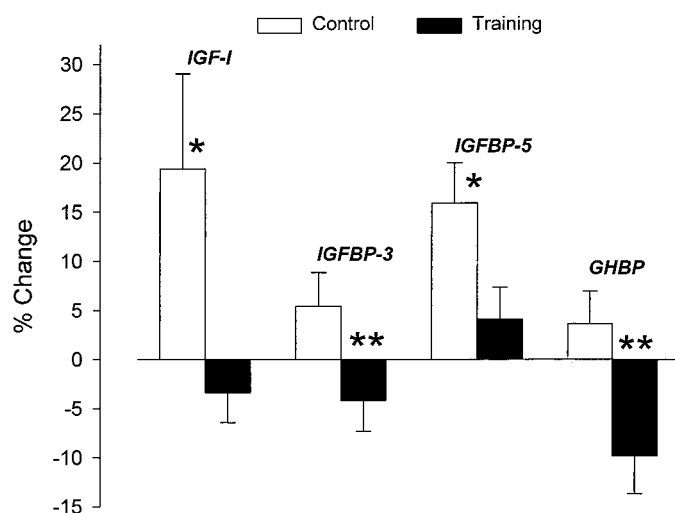


FIG. 4. Significant between-group effects of the 5 week intervention on IGF-I, IGFBP-3, IGFBP-5, and GHBP in prepubertal girls. Data are shown as percent change from baseline values. IGF-I and IGFBP-5 increased significantly ($*P < 0.05$) only in controls. IGFBP-3 and GHBP decreased significantly in training subjects ($**P < 0.05$). Training led to paradoxical responses in these mediators that were suggestive of a neuroendocrine catabolic state. Despite this, peak $\dot{V}O_2$ and thigh muscle volume increased in the training but not control subjects (data not shown).

worthy that our findings are consistent with current understanding of the biological activity of IGFBP-I based on tissue studies (22). IGFBP-1 and -2, known to inhibit IGF-I function, were inversely correlated with muscle mass whereas the IGF-I potentiating binding protein, IGFBP-5—recently discovered to have growth potentiating activity independent of IGF-I (23), was positively correlated with muscle mass. Accordingly, our data suggest the possibility that there may exist some combination of circulating levels of IGF-I and its binding proteins in which muscle growth and fitness are optimized in prepubertal girls.

The pattern of change of GHBP, IGFBP-1, and peak $\dot{V}O_2$ relative to BMI percentile was striking (Fig. 3). Increased GHBP and decreased IGFBP-1 in frankly obese children have recently been observed (24, 25). The decrease in IGFBP-1 may suggest the early manifestations of insulin insensitivity because circulating levels of IGFBP-1 vary inversely with levels of insulin. Furthermore, in obese subjects GH is known to be suppressed without reductions in IGF-I. This finding sug-

gests a tissue alteration in response to the low levels of GH probably through an increase in GH receptors. GHBP, the extracellular component of the GH receptor, may reflect GH receptor numbers. Finally, the inverse correlation between GHBP and peak $\dot{V}O_2$ per kilogram are consistent with BMI data. Subjects with low peak $\dot{V}O_2$ per kilogram tend to have relatively high fat stores. GH is suppressed in these subjects and GHBP is, consequently, elevated. Thus, GHBP was higher in the less lean girls, those whose $\dot{V}O_2$ per kilogram was low.

Fitness, independent of obesity, may also play a role in the regulation of GH and insulin sensitivity. Fitter subjects have increased GH pulsatility (21, 26, 27) and greater insulin sensitivity (28); indeed, exercise is a major treatment for type II diabetes mellitus, a syndrome characterized by profound insulin insensitivity. Our data show that there exists in healthy prepubertal girls some threshold level of adiposity that can be determined relatively easily from the BMI percentile. Above this threshold, an ominous combination of reduced fitness, low GH, and insulin insensitivity begin to manifest themselves. Such information might prove to be clinically useful in identifying children who would benefit from programs of physical activity.

Given the relatively strong correlation between IGF-I and both thigh muscle volume and cardiorespiratory fitness, the GH→IGF-I axis response to the prospective training intervention was paradoxical, namely, IGF-I seemed to be increasing in the control subjects but actually fell in the trained subjects (Fig. 4). Moreover, the apparent attenuation of IGF-I in these prepubertal children occurred despite the fact that both thigh muscle volume and peak $\dot{V}O_2$ increased with training.

The seemingly catabolic response to the 5 weeks of training [reductions in IGF-I, IGFBP-3 and GHBP, each of which is consistent with the GH-resistant states associated with trauma and sepsis (29, 30), and an attenuation of the increase in IGFBP-5] is qualitatively similar to what we have now observed in adolescent males and females using a similar protocol (3, 31). Reductions in IGF-I associated with exercise training have been reported previously in adults and adolescents, but usually in concert with clear evidence for negative energy balance such as weight loss (1, 32) which did not occur in the present study.

Thigh muscle mass and peak $\dot{V}O_2$ both increased in the training subjects despite hormonal evidence consistent with

a catabolic state. In contrast, the small but significant reduction in BMI in training subjects might, in the growing child, actually indicate systemic manifestations of catabolism. We now know that in children even a single (vigorous) exercise bout can lead to increases in the inflammatory cytokines interleukin-6 and tumor necrosis factor- α , both of which can inhibit IGF-I (33). We speculate that exercise associated elevation of circulating inflammatory cytokines leads to the reductions in IGF-I seen early in a training program. But the mechanisms that allow particular muscle groups to increase under these conditions, or when (and whether) there is a rebound in the GH→IGF-I axis at some point during a period of exercise training, remain largely unknown.

Our data begin to address potential biological mechanisms related to a number of critical issues concerning the optimal role of physical activity and exercise training in prepubertal children. For example, the American Academy of Pediatrics recently highlighted the potential risks of high-intensity training and sports specialization in young athletes but noted, "Although many concerns surround intense sports competition in children, little scientific information is available to support or refute these risks" (34). By examining the effect of exercise on catabolic and anabolic mediators, it may ultimately be possible to determine the boundary between healthy effects of exercise (characterized, perhaps, by activation of the GH→IGF-I axis) and harmful effects (characterized by excessive tissue cytokine and suppression of GH→IGF-I activity). A scientific basis for determining optimal levels of physical activity in children and adolescents does not yet exist.

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