

UC Irvine

UC Irvine Previously Published Works

Title

Physical fitness, endurance training, and the growth hormone-insulin- like growth factor I system in adolescent females

Permalink

<https://escholarship.org/uc/item/3vq2g19w>

Journal

The Journal of Clinical Endocrinology & Metabolism, 81(11)

ISSN

0021-972X

Author

Eliakim, A

Publication Date

1996-11-01

DOI

10.1210/jc.81.11.3986

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed

Physical Fitness, Endurance Training, and the Growth Hormone-Insulin-Like Growth Factor I System in Adolescent Females

ALON ELIAKIM†, JO ANNE BRASEL, SUBBURAMAN MOHAN,
THOMAS J. BARSTOW, NANCY BERMAN, AND DAN M. COOPER

Divisions of Respiratory and Critical Care and Pediatric Endocrinology, Department of Pediatrics, Harbor-University of California-Los Angeles Medical Center (A.E., J.A.B., T.J.B., N.B., D.M.C.), Torrance, California 90509; the Departments of Medicine, Biochemistry, and Physiology, Loma Linda University, Pettis Veterans Administration Medical Center (S.M.), Loma Linda, California 92357

ABSTRACT

We examined the relationship between physical fitness and circulating components of the GH-insulin-like growth factor I (IGF-I) system [*i.e.* GH, GH-binding protein (GHBP), IGF-I, and IGF-binding proteins 1–5 (IGFBP-1 through -5)] in adolescent females (age range, 15–17 yr). The study consisted of 1) a cross-sectional protocol ($n = 23$) in which GH-IGF-I components were correlated with fitness, as estimated by thigh muscle volume and maximal O_2 uptake; and 2) a prospective study in which fitness, GH-IGF-I system components, and osteocalcin were examined before and after a 5-week period of endurance-type training (control, $n = 6$; trained, $n = 10$). The cross-sectional analysis revealed significant ($P < 0.05$) positive correlations between fitness and 1) mean 12-h overnight GH levels, 2) GHBP, and 3) IGF-I. Muscle volume was negatively correlated with both IGFBP-2

and -4. The prospective training study was associated with 1) increases in circulating osteocalcin ($39 \pm 14\%$; $P < 0.007$), and 2) decreases in IGF-I ($-14 \pm 5\%$; $P < 0.05$) and IGFBP-5 ($-10 \pm 4\%$; $P < 0.04$). Unexpectedly, IGFBP-3 fell in both control ($-8 \pm 2\%$; $P < 0.01$) and trained subjects ($-5 \pm 3\%$; $P < 0.05$), and GHBP was reduced only among control subjects ($-10 \pm 7\%$; $P < 0.04$).

In summary, fitter adolescent girls tended to have increased mean serum GH, GHBP, and IGF-I. In contrast, brief endurance training led to increases in muscle mass and serum osteocalcin that were not accompanied by increases in GH or IGF-I. In fact, training may, in the short term, have led to a catabolic state hormonally expressed by reductions in IGF-I and IGFBP-5. (*J Clin Endocrinol Metab* 81:3986–3992, 1996)

IT IS BECOMING increasingly apparent that there exist substantial adaptations of the GH-insulin-like growth factor I (IGF-I) axis to physical activity and exercise. Acutely, GH increases dramatically and IGF-I modestly (in adult men) in response to brief exercise (1–3). Moreover, physically fit adults have generally higher levels of circulating IGF-I and increased amplitude of spontaneous GH pulses (4–6). Endurance-type training programs (lasting for a month or more) have been associated with increases in circulating IGF-I in older males (but not older females) and in mature rats (7, 8). In contrast, in training programs in which energy expenditure clearly exceeds energy intake, the level of circulating IGF-I falls even though training effects had occurred [*e.g.* female gymnasts (9)].

In this study, we focused on possible GH-IGF-I adaptations to exercise in adolescent females, a group known to be at high risk for physical inactivity (10) and in whom the long term consequences of a sedentary lifestyle can be profound. We hypothesized that 1) fitness would be correlated with GH output and circulating IGF-I, and might be related to circu-

lating GH-binding protein (GHBP) and IGF-binding proteins (IGFBPs) as well (we measured IGFBP-1 through -5); and 2) an endurance-type training intervention would lead to increases in GH secretion and circulating IGF-I.

The data reported here were obtained as part of a cross-sectional and prospective interventional study of 44 adolescent females who were randomly divided into a control or a trained group ($n = 22$ each) (11). We demonstrated a marked training effect after only 5 weeks, during which time maximum oxygen uptake ($\dot{V}O_{2\max}$) increased by 12.1%, and thigh muscle mass increased by 4.3%. Moreover, daily energy expenditure was 15.3% greater in the trained *vs.* the control subjects.

In the present study, we examined the relationship between circulating growth factors and both the functional adaptations to training (assessed by progressive cycle ergometer exercise testing) and structural adaptations. The latter were measured by 1) magnetic resonance imaging (MRI) of the thigh to detect muscle hypertrophy, and 2) serum osteocalcin levels to indicate new bone formation (12).

Subjects and Methods

Sample population

All 44 girls who participated in the study completed the full 5-week protocol as members of either the control or the trained group. We anticipated that not all subjects (or their parents or guardians) would agree to blood sampling, especially for the overnight GH studies. At the beginning of the study, 23 subjects agreed to blood sampling as outlined below, and the data from these subjects constituted the initial cross-

Received May 16, 1996. Revision received July 18, 1996. Accepted July 12, 1996.

Address all correspondence and requests for reprints to: Alon Eliakim, M.D., Division of Research, Connecticut Children's Medical Center, University of Connecticut, Dept. of Pediatrics, 282 Washington St., Hartford, CT 06102.

* This work was supported by NIH Grants HD-26939 and AR-31062 and General Clinical Research Grant RR-00425.

† Supported by the Joseph Drown Foundation.

sectional portion of the study. Subsequently, 16 subjects (6 from the control group and 10 from the trained group) agreed to repeat these measurements following the experimental protocol.

The participants were all students at Torrance High School (Torrance, CA) and enrolled in an anatomy and physiology class during the summer of 1995 (July–August) with class hours from 0800–1230 h. No attempt was made to recruit subjects who participated in competitive extramural athletic programs. The study was designed to examine late pubertal subjects with an age range of 15–17 yr. Measurements of height, weight, and body mass index [body mass index (wt/ht^2), an indirect estimate of lean body mass (13)] were made using standard techniques. Assessment of pubertal status was performed by examination in all subjects. Twenty-one of 23 subjects were found to be at Tanner level V, 1 subject was at Tanner stage IV–V, and 1 subject was at Tanner stage III–IV.

All subjects participated in the 2-h daily teaching program. During the remaining time, the trained group members underwent endurance-type training, consisting of running, aerobic dance, competitive sports (e.g. basketball), and occasional weight-lifting. Training was directed by a member of the Torrance High School faculty. The control group subjects participated in a computer workshop designed to improve their computer skills and used this time to analyze some of the data collected from the study. No attempt was made to influence extracurricular levels of physical activity in either the control or trained groups. The study was approved by the institutional human subject review board, and informed consent was obtained from the subjects and their parents or guardians.

Measurements of maximal oxygen uptake ($\dot{V}O_{2\max}$)

Each subject performed a ramp-type progressive exercise test on a cycle ergometer in which the subject exercised to the limit of her tolerance. Gas exchange was measured breath by breath (14), and the $\dot{V}O_{2\max}$ was determined as previously described in children and adolescents (15). Measurements were made before and immediately after the 5-week training protocol.

MRI of thigh musculature

Studies were performed before and immediately after the 5-week protocol in all subjects. We chose to examine the musculature of the right thigh because these muscles would be largely involved in the endurance-type training program described above. MRI has been used previously to assess the effects of training on muscle mass (11, 16, 17).

Blood sampling protocols

Subjects were admitted to the Clinical Research Center at Harbor-University of California-Los Angeles Medical Center, and an indwelling heparin lock catheter was inserted in a forearm vein at 1800 h. Baseline blood samples were collected for determination of circulating GHBP, IGF-I, IGFBP-1 through -5, osteocalcin, and estradiol levels. Serial blood sampling for GH was initiated at 2000 h and continued for 12 h. Samples were collected at approximately 20-min intervals. Subjects were restricted to limited physical activity (e.g. walking in the confines of the Clinical Research Center). The overnight protocol occurred the week before and during the week after the completion of the training intervention. No subjects trained during the day preceding the overnight blood sampling.

GH

GH serum concentrations were determined using the fluoroimmunoassay technique (18). The monoclonal antibody pair was obtained from Medix Biotex (San Carlos, CA). Europium-labeled streptavidin was obtained from Delfia (Wallac, Gaithersburg, MD). The interassay coefficient of variation (CV) ranged from 5.7–10.1%, and the intraassay CV ranged from 4.9–8.3%. The assay sensitivity was 0.1 ng/mL.

GHBP

GHBP was measured using the ligand-mediated immunofunctional assay (19). The interassay CV ranged from 9.7–12.9%, and the intraassay CV ranged from 6.3–8.9%. The assay sensitivity was 7.8 pmol/L.

IGF-I

IGFs were extracted from IGF-BPs using the acid-ethanol extraction method (20). A double antibody RIA was performed to measure serum IGF-I concentrations. Polyclonal recombinant IGF-I antiserum was obtained from the NIH (Baltimore, MD). Radiolabeled [^{125}I]IGF-I tracer was purchased from Amersham (Arlington Heights, IL). IGF-I was obtained from Bachem Chemicals (Torrance, CA). The IGF-I interassay CV ranged from 5.4–7.5%, and the intraassay CV ranged from 4.5–6.2%. The assay sensitivity was 0.1 ng/mL.

IGFBP-1 through -5

IGFBP-1 and -3 were measured by coated tube immunoradiometric assays. IGFBP-2, -4, and -5 were measured by RIA. IGFBP-1 through -3 were measured using commercially available kits (Diagnostic System Laboratories, Webster, TX). IGFBP-4 and -5 were measured in our co-author's laboratory (S.M.), as recently described (21, 22). For IGFBP-1, the interassay CV ranged from 1.7–6.7%, and the intraassay CV ranged from 2–4%. The assay sensitivity was 0.11 ng/mL. For IGFBP-2, the interassay CV was 6.4%, and the intraassay CV was 6.5%. The assay sensitivity was less than 0.6 ng/mL. For IGFBP-3, the interassay CV ranged from 0.6–1.9%, and the intraassay CV ranged from 1.8–3.9%. The assay sensitivity was 0.5 ng/mL. For IGFBP-4, the interassay CV was less than 8.1%, and the intraassay CV was less than 5%. The assay sensitivity was less than 0.5 ng/mL. For IGFBP-5, the interassay CV was less than 8%, and the intraassay CV was less than 4%. The assay sensitivity was less than 5 ng/mL.

Osteocalcin

Serum levels of osteocalcin were assayed by an immunoradiometric assay kit using two monoclonal antibodies developed against the 5–13 and 25–37 regions of osteocalcin (ELSA Osteo kit, CIS-US, Bedford, MA). Inter- and intraassay CVs were less than 8% and 5%, respectively. The sensitivity of this assay was 0.7 ng/mL.

Estradiol

Estradiol was measured by RIA using the Diagnostic System Laboratories ultrasensitive kit (DSL-4800). The interassay CV ranged from 9.7–12.2%, and the intraassay CV ranged from 6.5–6.9%. The assay sensitivity was 2.2 pg/mL.

Statistical analysis

GH peaks (number, width, and amplitude) were determined using the statistical algorithms developed previously (23). Standard techniques of regression and correlation were used for the cross-sectional studies relating GH-IGF-I axis components and the functional and structural fitness variables. Paired *t* tests were used to compare the effects of training on functional and structural fitness variables and on the hormonal data. Statistical significance was taken at the $P < 0.05$ level. Data are presented as the mean \pm SE.

Results

Cross-sectional study

Preintervention data. Mean preinterventional data for height, weight, body mass index, $\dot{V}O_{2\max}$ per kg BW, thigh muscle volume per kg BW, mean overnight GH level, number of GH peaks, GH peak width and amplitude, GHBP, IGF-I, IGFBP-1 through -5, estradiol, and osteocalcin are shown in Table 1. The fitness variables ($\dot{V}O_{2\max}$ and muscle mass) were normalized to body weight. This is a commonly used strategy to limit the confounding effect of body weight alone on exercise variables (24, 25).

Correlations between fitness and GH-IGF-I axis. There were significant correlations between the mean overnight GH level and $\dot{V}O_{2\max}$ per kg ($r = 0.36$; $P < 0.05$) and between

TABLE 1. Anthropometric, fitness, and hormonal characteristics of the participating subjects (cross-sectional study, n = 23)

	Mean ± SE
Ht (cm)	160.4 ± 1.0
Wt (kg)	58.1 ± 2.5
BMI (kg/m ²)	22.5 ± 0.8
$\dot{V}O_2$ max (mL/min · kg)	27.1 ± 0.8
Thigh muscle vol (cm ³ /kg)	16.9 ± 0.5
GH (ng/mL)	2.24 ± 0.3
GH peaks (no./12 h)	2.9 ± 0.3
GH peak width (min)	157 ± 9
GH peak height (ng/mL)	5.9 ± 0.6
GHBP (pmol/L)	394 ± 32
IGF-I (ng/mL)	441 ± 19
IGFBP-1 (ng/mL)	5.3 ± 1.4
IGFBP-2 (ng/mL)	178 ± 19
IGFBP-3 (ng/mL)	3684 ± 192
IGFBP-4 (ng/mL)	282 ± 17
IGFBP-5 (ng/mL)	256 ± 11
Estradiol (pg/mL)	84 ± 15
Osteocalcin (ng/mL)	34.5 ± 3.5

GHBP and $\dot{V}O_2$ max per kg ($r = 0.42$; $P < 0.03$). The correlation between IGF-I and $\dot{V}O_2$ max per kg did not achieve significance ($r = 0.34$; $P < 0.057$). The mean overnight GH level, GHBP, and IGF-I were all significantly correlated with muscle volume per kg BW (Fig. 1). The mean overnight GH concentration was significantly correlated with GH peak height ($r = 0.93$; $P < 0.00001$), but not with GH peak frequency or width. There were no correlations between GH peak frequency, peak width, and height and fitness indexes (*i.e.* $\dot{V}O_2$ max per kg and thigh muscle volume per kg). There were significant negative correlations between muscle volume and both IGFBP-2 and IGFBP-4 (Fig. 2). IGFBP-1, -3, and -5 did not correlate with either thigh muscle volume or $\dot{V}O_2$ max. There were no correlations between fitness indexes and serum osteocalcin levels. Finally, there was no correlation between any component of the GH-IGF-I axis and random serum estradiol measurements.

Prospective training intervention

As noted above, 6 of the 22 control and 10 of the 22 training subjects volunteered for both pre- and postintervention blood sampling. Anthropometric, GH, GHBP, and IGFBP data from the subjects who agreed to the blood sampling protocols are shown in Table 2. Note that there were no significant differences between these subsets of the control and trained groups with respect to size, fitness, or hormonal variables before the training intervention. There was a remarkable significant increase in $\dot{V}O_2$ max and thigh muscle volume in the trained, but not the control, subjects [similar to results obtained in the whole group, *i.e.* all 22 control and 22 training subjects (11)].

There was no change in mean GH level, the number of GH peaks, GH peak width, or GH amplitude in either group over the 5-week period of observation. There was a significant reduction in GHBP in the control group, but not in the trained subjects (Table 2). In contrast to our hypothesis, IGF-I (Fig. 3) and IGFBP-5 (Fig. 4) actually fell in the trained subjects, but there was no change in the controls. Finally, IGFBP-3 was significantly reduced after the interventional period in both

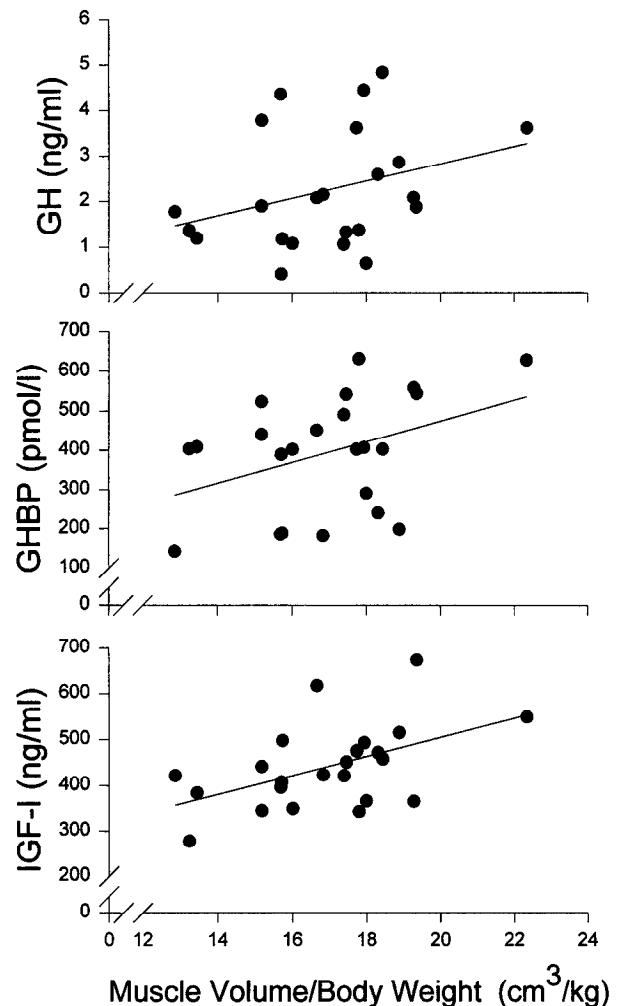


FIG. 1. Cross-sectional relationships between thigh muscle volume and mean overnight GH concentrations ($r = 0.35$; $P < 0.05$; top panel), GHBP ($r = 0.39$; $P < 0.04$; middle panel), and circulating IGF-I ($r = 0.5$; $P < 0.008$; bottom panel).

the control and trained groups (Table 2). There was no change in IGFBP-1, -2, and -4 over the 5-week training program.

There was a significant increase in osteocalcin level in the trained subjects (all 10 subjects demonstrated an increase; $P < 0.006$), but not among the control subjects, during the 5-week interventional period (Fig. 5). Note the high levels of osteocalcin in 1 of the control subjects. This individual was one of the younger volunteers and had the lowest Tanner pubertal score (III-IV) of the study population.

Discussion

The cross-sectional data suggest that fitness in adolescent females is associated with adaptations of the GH-IGF-I system, probably representing a hormonally expressed, anabolic state. These results support our first hypothesis, but in contrast to our second hypothesis, 5 weeks of endurance training did not lead to increases in GH or IGF-I. The relationship among GH-IGF-I system components, single brief exercise bouts, 5 weeks of endurance training, and the fit

FIG. 2. Cross-sectional correlations between thigh muscle volume and IGFBP-4 ($r = -0.45$; $P < 0.02$; left panel) and IGFBP-2 ($r = -0.44$; $P < 0.02$; right panel).

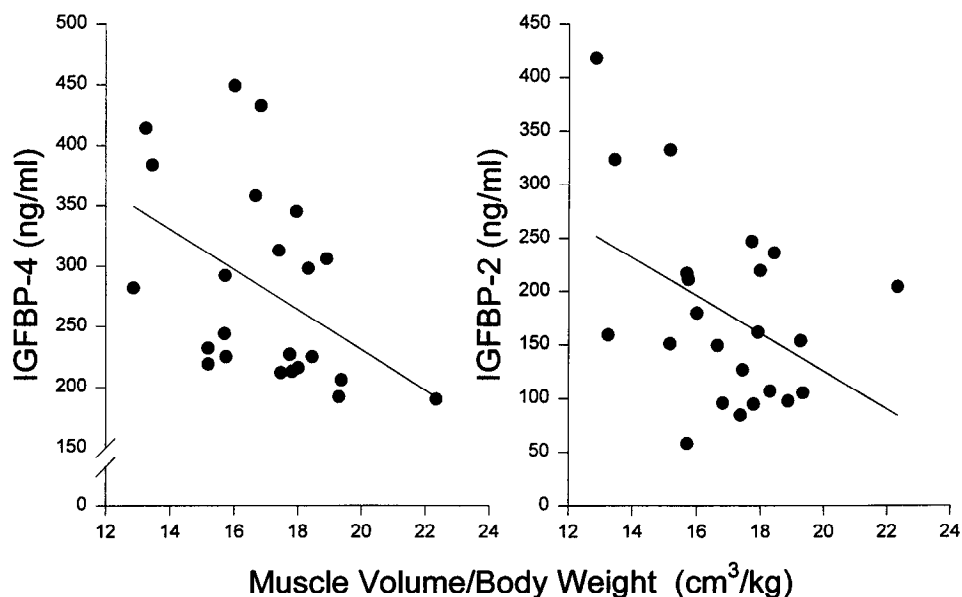


TABLE 2. Effects of 5 weeks endurance training intervention on anthropometric, fitness, and hormonal variables

	Control group (n = 6)		Trained group (n = 10)	
	Pre	Post	Pre	Post
Ht (cm)	157.5 ± 1.5	158.2 ± 1.6	161.4 ± 1.8	161.6 ± 1.9
Wt (kg)	52.9 ± 6.6	53.1 ± 6.8	61.6 ± 3.9	62 ± 4.0
BMI (kg/m ²)	21.2 ± 2.3	21.1 ± 2.4	23.5 ± 1.2	23.6 ± 1.2
VO ₂ max (L/min)	1.47 ± 0.2	1.38 ± 0.1	1.57 ± 0.1	1.68 ± 0.1 ^a
Muscle vol (mL)	431.1 ± 35	438.3 ± 30	487.6 ± 22	509.6 ± 22 ^a
Mean 12 h GH level (ng/mL)	2.33 ± 0.6	1.83 ± 0.5	1.69 ± 0.2	1.68 ± 0.3
GH peak frequency/12 h	3.7 ± 1.0	2.5 ± 0.2	2.8 ± 0.3	2.3 ± 0.3
GH peak width (min)	144 ± 26	151 ± 11	151 ± 17	164 ± 15
GH peak ht (ng/mL)	6.4 ± 1.5	5.7 ± 1.0	4.7 ± 0.6	4.5 ± 1.0
GHBP (pmol/L)	369 ± 47	317 ± 37 ^a	388 ± 36	345 ± 33
IGFBP-1 (ng/mL)	9.1 ± 4.5	6.1 ± 2.6	4.3 ± 1.4	4.1 ± 1.5
IGFBP-2 (ng/mL)	217 ± 47	258 ± 43	138 ± 23	135 ± 19
IGFBP-3 (ng/mL)	4217 ± 605	3837 ± 517 ^a	3617 ± 165	3254 ± 73 ^a
IGFBP-4 (ng/mL)	268 ± 38	319 ± 28	313 ± 27	328 ± 31
Estradiol (pg/mL)	87 ± 14	84 ± 12	92 ± 20	85 ± 15

Data for IGF-I, IGFBP-5, and osteocalcin are shown in Figs. 3, 4, and 5, respectively. Values are the mean ± SE.
^a Significant difference from precourse values ($P < 0.05$).

state (based on these and other data) is summarized in Table 3.

We did consider the interaction of GH and estradiol, as GH secretion is maximal during the late follicular phase of the menstrual cycle, when estradiol levels are highest (26). The relatively complex logistics of this study (e.g. a uniform training input, the need to schedule many pre- and postinterventional tests) precluded the possibility of studying each subject at precisely the same phase of the menstrual cycle. However, there was no correlation between estradiol levels and any component of the GH-IGF-I axis, nor did we find any differences in estradiol levels before and after the intervention period. Thus, variations in circulating estradiol probably had little influence on the results of the study.

We found that the mean overnight GH level was correlated with fitness. The increased mean GH most likely resulted from an increase in peak height, as only peak height (and not peak frequency or width) was significantly correlated with mean GH. This finding is consistent with studies by Weltman

et al. (6), who noted correlations between 24-h integrated GH concentrations and VO₂max in young healthy male adults, and with animal experiments by Borer *et al.* (27), who noted an increased GH pulse amplitude in physically active, rapidly growing hamsters compared with less rapidly growing, sedentary controls. The mechanism of this neuroendocrinological effect of chronic exercise is not yet understood.

The positive correlation between GHBP and fitness has not previously been reported. GHBP is the extracellular domain of the GH receptor (28) and is believed to reflect the tissue GH receptor capacity. Ligand-mediated receptor regulation appears to exist for GH and GHBP in a number of pathological situations (29–31), but does not appear to operate during normal prepubertal growth when both GH and GHBP increase (32). Our data suggest that the relatively fit state is another example of simultaneous increases in both GH and GHBP.

Although, as noted, exercise-associated increases in local muscle production of IGF-I can occur even in the absence of

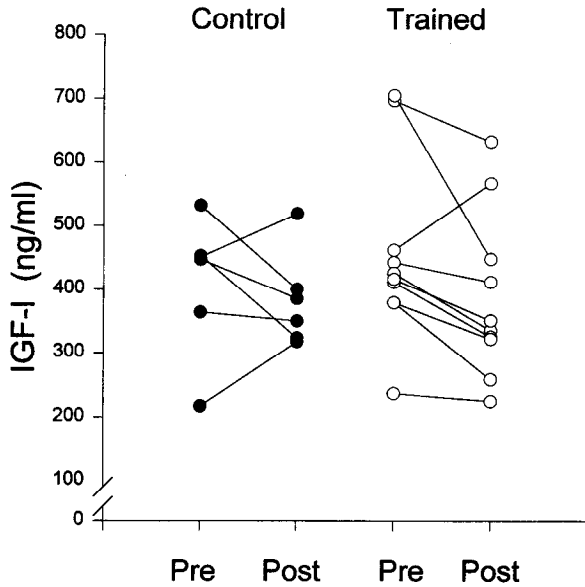


FIG. 3. Changes in IGF-I after the 5-week endurance exercise training intervention. There was a significant decrease in IGF-I (9 of 10 subjects; $-14 \pm 5\%$; $P < 0.05$) in the trained, but not the control, subjects.

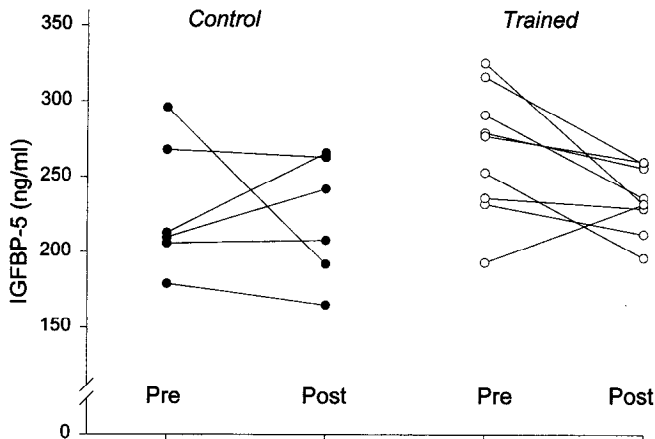


FIG. 4. The effect of endurance training on IGFBP-5. Five weeks of endurance-type exercise training resulted in a significant decrease in IGFBP-5 in trained girls (9 of 10 subjects; $-10 \pm 4\%$; $P < 0.05$), but not in the controls.

GH (33, 34), the present data suggest that the increased circulating IGF-I in fitter subjects resulted from the traditional pathway of GH-mediated increases in hepatic IGF-I production. Both GH secretory activity and GHBP were increased in fitter subjects; moreover, previous work in this laboratory has shown that exercise training in the rat is associated with increased hepatic IGF-I messenger ribonucleic acid (33). GH and IGF-I are known mitogens for skeletal muscle (35, 36), and this may be reflected in the specific significant correlation we found between muscle volume and circulating IGF-I. The extent to which these increases reflect hyperplasia *vs.* hypertrophy could not be determined.

Our data also suggest that the generally increased circulating IGF-I levels in fitter subjects might be related to IGFBPs. IGFBP-2 and -4 were inversely correlated with thigh muscle volume. The role of these binding proteins in the

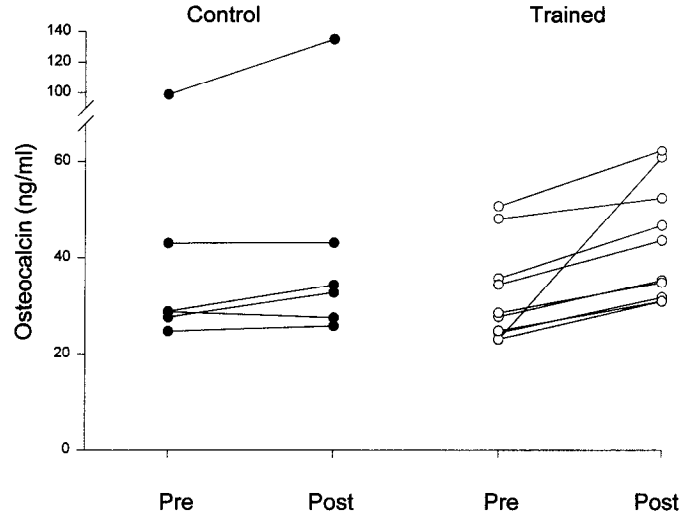


FIG. 5. The effect of training on circulating osteocalcin levels. There was a significant increase in serum osteocalcin levels in trained (all 10; $39 \pm 14\%$; $P < 0.05$), but not control, subjects.

TABLE 3. Qualitative relationship among circulating components of the GH-IGF-I system, a single brief bout of exercise, 5 weeks of endurance-type training, and the "fit" state in adolescent females

	Single brief bout of exercise ^a	5 weeks of endurance training	The "fit" state
GH ^b	↑ ↑	No change	↑
GHBP	?	No change	↑
IGF-I	↑	↓	↑
IGFBP-1	?	No change	No change
IGFBP-2	?	No change	↓
IGFBP-3	↑	?	No change
IGFBP-4	?	No change	↓
IGFBP-5	?	↓	No change

^a Data are summarized from Refs. 1-3. These studies were performed in young men, and the results have yet to be validated in adolescent females.

^b Refers to peak GH for brief exercise bout and mean GH for the remaining categories.

circulation is not known; however, it is intriguing that inverse correlations between IGF-I and IGFBP-2 have been noted in several pathological conditions (37, 38) and during states of protein restriction (39). In addition, cell culture experiments indicate that IGFBP-4 inhibits the anabolic functions of IGF-I (40). Thus, IGFBP-2 and -4 might attenuate the anabolic effects of IGF-I, and these proteins may be coregulated and sensitive to the dynamic energy expenditure conditions imposed by nutrition, level of physical activity, and other environmental factors.

We found a significant increase in serum osteocalcin levels among trained (all 10), but not among control subjects, after the training intervention. To our knowledge, these are the first data demonstrating an increase in serum osteocalcin after so brief a training program in late pubertal adolescent females. Circulating osteocalcin serves as an index of bone formation (41) and is used as a marker of skeletal growth in prepubertal boys and girls (42).

This is a potentially useful observation, as it is becoming increasingly apparent that it is precisely during the peripubertal stage that physical activity profoundly influences peak

bone mass in women (43), and reduced peak bone mass (reached in women during their mid to late 20s) is associated with increased incidence of osteoporosis later in life (44). In American girls, this appears to be a time of decreasing participation in physical activity (10). The success we had in implementing a training program by integrating it with course work might prove to be a useful approach for ultimately increasing the levels of physical activity in adolescent girls in general. It is important to note that osteocalcin is not an indicator of bone mass *per se*; thus, the lack of a correlation between osteocalcin and fitness in our data set does not mean that there is no relationship between fitness and bone mineral density.

Other results of the prospective interventional training study were unexpected. IGF-I and IGFBP-5 fell significantly in the trained, but not the control, subjects, and these were the only components of the GH-IGF-I axis that were specifically affected by the training intervention. The training associated reduction in IGF-I and IGFBP-5 [as noted, one of the binding proteins that seems to enhance some of the IGF-I mitogenic effects (22)] leads us to the surprising speculation that the 5-week training period may actually have led to a hormonal adaptation consistent with a catabolic state despite the increase in fitness, muscle mass, and osteoblastic activity brought about by the training.

IGF-I is classically reduced after calorie restriction in both human and animal experiments (45), and in studies of exercise training where energy expenditure exceeds energy intake, circulating IGF-I falls (46). Unlike those previous studies, however, we placed no restrictions on diet in our study, and in fact, there were no changes in body weight in either the control or the trained group (11). What emerges from our observations is the hypothesis that the sudden imposition of an endurance training program first leads to hormonal adaptations suggestive of a catabolic state, but at some point, presumably after 5 weeks, an anabolic rebound occurs (similar, perhaps, to the phenomenon of catch-up growth after a period of nutritional deprivation). Exactly how and when this switch takes place remain unknown.

Another unexpected, but nonetheless intriguing, finding was that some changes in the GH-IGF-I axis occurred over the period of observation in both the control and training groups. GHBP decreased in the control group (but not in the trained group), and IGFBP-3 was reduced in both the control and trained groups. Additionally, mean GH was lower in 5 of 6 subjects in the control group ($P < 0.01$, by nonparametric sign test; $P < 0.06$, by *t* test) at the end of the study, but GH was lower in only 5 of the 10 trained subjects. This constellation of findings, reductions in GH, GHBP, and IGFBP-3, suggest an overall reduction in GH secretory activity.

The mechanism for this is not readily apparent. Our program started at the end of the school academic year, just after final examinations, in the early summer. The role of factors such as stress or season on GH secretory patterns have been examined, but there are few studies in humans (47, 48), and no consistent relationships have emerged. Moreover, to our knowledge, there are no reports regarding seasonal effects, if any, on circulating GHBP, IGF-I, or IGFBP1 through -5 levels.

Acknowledgment

We thank Dr. Wai-Lee T. Wong, Department of Bioanalytical Technology, Genentech, for her generosity in performing the GHBP assays and Dr. J. Eller Lee of the Jerry L. Pettis Veterans Affairs Medical Center, Loma Linda, CA, for her help with the osteocalcin measurement.

References

1. Felsing NE, Brasel J, Cooper DM. 1992 Effect of low- and high-intensity exercise on circulating growth hormone in men. *J Clin Endocrinol Metab.* 75:157-162.
2. Cappon J, Brasel JA, Mohan S, Cooper DM. 1994 Effect of brief exercise on circulating insulin-like growth factor-I. *J Appl Physiol.* 76:1418-1422.
3. Schwarz AJ, Brasel JA, Hintz RL, Mohan S, 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.* In press.
4. Poehlman ET, Copeland KC. 1990 Influence of physical activity on insulin-like growth factor-I in healthy younger and older men. *J Clin Endocrinol Metab.* 71:1468-1473.
5. Kelley PJ, Eisman JA, Stuart MC, Pocock NA, Sambrook PN, Gwinn TH. 1990 Somatomedin-C, physical fitness, and bone density. *J Clin Endocrinol Metab.* 70:718-723.
6. Weltman A, Weltman JY, Hartman ML, et al. 1994 Relationship between age, percentage body fat, fitness, and 24-hour growth hormone release in healthy young adults: effects of gender. *J Clin Endocrinol Metab.* 78:543-548.
7. Poehlman ET, Rosen CJ, Copeland KC. 1994 The influence of endurance training on insulin-like growth factor-I in older individuals. *Metabolism.* 43:1401-1405.
8. Yeh JK, Aloia JF, Chen M, Ling N, Koo HC, Millard WJ. 1994 Effect of growth hormone administration and treadmill exercise on serum and skeletal IGF-I in rats. *Am J Physiol.* 266:E129-E135.
9. Jahreis G, Kauf E, Frohner G, Schmidt HE. 1991 Influence of intensive exercise on insulin-like growth factor I, thyroid and steroid hormones in female gymnasts. *Growth Regul.* 1:95-99.
10. Centers for Disease Control and Prevention. 1992 Vigorous physical activity among high school students—United States, 1990. *Morbidity Mortality Weekly Rep.* 41:33-35.
11. Eliakim A, Barstow TJ, Brasel JA, et al. The effect of exercise training on energy expenditure, muscle volume, and maximal oxygen uptake in adolescent females. *J Pediatr.* In press.
12. Robey PG, Bianco P, Termine JD. 1992 The cellular biology and molecular biochemistry of bone formation. In: Coe FL, Favus MJ. *Disorders of bone and mineral metabolism.* New York: Raven Press; 241-263.
13. Deurenberg P, Weststrate JA, Seidell JC. 1991 Body mass index as a measure of body fatness: age- and sex-specific prediction formulas. *Br J Nutr.* 65:105-114.
14. Beaver WL, Lamarra N, Wasserman K. 1981 Breath-by-breath measurement of true alveolar gas exchange. *J Appl Physiol.* 51:1662-1675.
15. Cooper DM, Weiler-Ravell D, Whipp BJ, Wasserman K. 1984 Aerobic parameters of exercise as a function of body size during growth in children. *J Appl Physiol.* 56:628-634.
16. Parkkola R, Kujala U, Rytokoski U. 1992 Response of the trunk muscles to training assessed by magnetic resonance imaging and muscle strength. *Eur J Appl Physiol.* 65:383-387.
17. Roman WJ, Fleckenstein J, Stray-Gundersen J, Alway SE, Peshock R, Gonyea WJ. 1993 Adaptations in the elbow flexors of elderly males after heavy-resistance training. *J Appl Physiol.* 74:750-754.
18. Strasburger C, Barnard G, Toldo L, et al. 1989 Somatotropin as measured by a two-site time resolved immunofluorometric assay. *Clin Chem.* 35:913-917.
19. Carlsson LM, Rowland AM, Clark RG, Gesundheit N, Wong WL. 1991 Ligand-mediated immunofunctional assay for quantitation of growth hormone-binding protein in human blood. *J Clin Endocrinol Metab.* 73:1216-1223.
20. Daughaday WH, Kapadia M, Mariz I. 1987 Serum somatomedin binding proteins: physiologic significance and interference in radioligand assay. *J Lab Clin Med.* 109:355-363.
21. Mohan S, Libanati C, Dony C, Lang K, Srinivasan N, Baylink DJ. 1995 Development, validation, and application of a radioimmunoassay for insulin-like growth factor binding protein-5 in human serum and other biological fluids. *J Clin Endocrinol Metab.* 80:2638-2645.
22. Mohan S, Nakao Y, Honda Y, et al. 1995 Studies on the mechanisms by which insulin-like growth factor (IGF) binding protein-4 (IGFBP-4) and IGFBP-5 modulate IGF actions in bone cells. *J Biol Chem.* 270:20424-20431.
23. Veldhuis JD, Iranmanesh A, Ho KK, Waters MJ, Johnson ML, Lizarralde G. 1991 Dual defects in pulsatile growth hormone secretion and clearance subserve the hypsomatotropism of obesity in man. *J Clin Endocrinol Metab.* 72:51-59.
24. Cooper DM. 1989 Development of the oxygen transport system in normal children. In: Bar-Or O, ed. *Advances in pediatric sport sciences.* Champaign: Human Kinetics Books; vol 3:67-100.

25. **Zanconato S, Reidy G, Cooper DM.** 1994 Calf muscle cross sectional area and maximal oxygen uptake in children and adults. *Am J Physiol.* 267:R720–R725.
26. **Ho KY, Evans WS, Blizzard RM.** 1987 Effects of sex and age on the 24H profile of growth hormone secretion in man: importance of endogenous estradiol concentration. *J Clin Endocrinol Metab.* 64:51–58.
27. **Borer KT, Nicoski DR, Owens V.** 1986 Alteration of pulsatile growth hormone secretion by growth-inducing exercise: involvement of endogenous opiates and somatostatin. *Endocrinology.* 118:844–850.
28. **Rosenfeld RG.** 1994 Circulating growth hormone binding proteins. *Horm Res.* 42:129–132.
29. **Leger J, Noel M, Czernichow P, Postel-Vinay MC.** 1995 Progressive normalization of growth hormone binding protein and IGF-I levels in treated growth hormone deficient children. *Pediatr Res.* 37:731–735.
30. **Kratzsch J, Blum WF, Ventz M, Selisko T, Birkenmeyer G, Keller E.** 1995 Growth hormone binding protein related immunoreactivity in the serum of patients with acromegaly is regulated inversely by growth hormone concentration. *Eur J Endocrinol.* 132:306–312.
31. **Jorgensen JO, Pedersen SB, Borglum J, et al.** 1995 Serum concentration of insulin-like growth factors, IGF binding proteins 1 and 3, and growth hormone binding proteins in obese women and the effect of growth administration: a double-blind, placebo controlled study. *Eur J Endocrinol.* 133:65–70.
32. **Baumann G, Shaw MA, Amburn K.** 1989 Regulation of plasma growth hormone binding proteins in health and disease. *Metabolism.* 38:683–689.
33. **Zanconato S, Moromisato DY, Moromisato MY, et al.** 1994 Effect of training and growth hormone suppression on insulin-like growth factor-I mRNA in young rats. *J Appl Physiol.* 76:2204–2209.
34. **DeVol DL, Rotwein P, Sadow JL, Novakofski J, Bechtel PJ.** 1990 Activation of insulin-like growth factor gene expression during work-induced skeletal muscle growth. *Am J Physiol.* 259:E89–E95.
35. **Carmeli E, Hochberg Z, Livne E, et al.** 1993 Effect of growth hormone on gastrocnemius muscle of aged rats after immobilization: biochemistry and morphology. *J Appl Physiol.* 1033:8697.
36. **Palmer RM, Flint DJ, MacRae JC, et al.** 1993 Effects of growth hormone and an antiserum to rat growth hormone on serum IGF-I and muscle protein synthesis and accretion in the rat. *J Endocrinol.* 139:395–401.
37. **Mohnike K, Kluba U, Blum WF, Aumann V, Vorwerk P, Mittler U.** 1995 Serum concentrations of insulin-like growth factors (IGF)-I and IGF-II and IGF binding proteins (IGFBP)-2 and IGFBP-3 in 49 children with ALL, NHL or solid tumors [German]. *Klin Padiatr.* 207:225–229.
38. **Tonshoff B, Blum WF, Wingen AM, Mehls O.** 1995 Serum insulin-like growth factors (IGFs) and IGF binding proteins 1, 2, and 3 in children with chronic renal failure: relationship to height and glomerular filtration rate. The European Study Group for Nutritional Treatment of Chronic Renal Failure in Childhood. *J Clin Endocrinol Metab.* 80:2684–2691.
39. **Smith WJ, Underwood LE, Clemmons DR.** 1995 Effects of caloric or protein restriction on insulin-like growth factor-I (IGF-I) and IGF-binding proteins in children and adults. *J Clin Endocrinol Metab.* 80:443–449.
40. **Mohan S, Bautista CM, Wergedal J, Baylink DJ.** 1989 Isolation of an inhibitory insulin-like growth factor (IGF) binding protein from bone cell-conditioned medium: a potential local regulator of IGF action. *Proc Natl Acad Sci USA.* 86:8338–8342.
41. **Hauska PV, Lian JB, Cole DEC.** 1989 Osteocalcin and matrix GLA protein: vitamin k dependent proteins in bone. *Physiol Rev.* 69:990–1047.
42. **Johansen JS, Giwercman A, Hartwell D, et al.** 1988 Serum bone GLA protein as a marker of bone growth in children and adolescents: correlation with age, height, serum insulin-like growth factor-I and serum testosterone. *J Clin Endocrinol Metab.* 67:273–278.
43. **Buchanan JR, Myers C, Lloyd T, Leuenberger P, Demers LM.** 1988 Determinants of peak trabecular bone density in women: the role of androgens, estrogen, and exercise. *J Bone Miner Res.* 3:673–680.
44. **Dalsky GP, Stocke KS, Ehsani AA, Slatopolsky E, Lee WC, Birge Jr SJ.** 1988 Weight-bearing exercise training, and lumbar bone mineral content in postmenopausal women. *Ann Intern Med.* 108:824–828.
45. **Thissen JP, Ketelslegers JM, Underwood LE.** 1994 Nutritional regulation of the insulin-like growth factors. *Endocr Rev.* 15:80–101.
46. **Suikkari AM, Sane T, Seppala M, Yki Jarvinen H, Karonen SL, Koivisto VA.** 1989 Prolonged exercise increases serum insulin-like growth factor-binding protein concentrations. *J Clin Endocrinol Metab.* 68:141–144.
47. **Malarkey WB, Hall JC, Pearl DK, Kiecolt-Glaser JK, Glaser R.** 1991 The influence of academic stress and season on 24 hour concentration of growth hormone and prolactin. *J Clin Endocrinol Metab.* 73:1089–1092.
48. **Weitzman ED, DeGraff AS, Sassin JF, et al.** 1975 Seasonal patterns of sleep stages and secretion of cortisol and growth hormone during 24 hour periods in northern Norway. *Acta Endocrinol (Copenh).* 78:65–76.