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Authors
Nemet, Dan
Pontello, Andria M
Rose-Gottron, Christie
et al.

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Cytokines and Growth Factors during and after a Wrestling Season in Adolescent Boys

DAN NEMET, ANDRIA M. PONTELLO, CHRISTIE ROSE-GOTTRON, and DAN M. COOPER

Center for the Study of Health Effects of Exercise in Children, University of California, Irvine, Children's Hospital, College of Medicine, Orange, CA

ABSTRACT

NEMET, D., A. M. PONTELLO, C. ROSE-GOTTRON, and D. M. COOPER. Cytokines and Growth Factors during and after a Wrestling Season in Adolescent Boys. *Med. Sci. Sports Exerc.*, Vol. 36, No. 5, pp. 794–800, 2004. **Purpose:** Brief periods of aerobic exercise training lead to reductions, rather then the expected increases in circulating IGF-I. We hypothesized that intense exercise training in adolescents initially leads to simultaneous increases in proinflammatory cytokines and decreases in activity of the GH/IGF-I axis; and that as exercise training proceeds, levels of proinflammatory cytokines become reduced, and a rebound in IGF-I ensues leading to the higher IGF-I levels. **Method:** To test this, we evaluated the GH/IGF-I axis and levels of inflammatory cytokines (IL-6, TNF-α, IL-1β, IL-1ra), body composition, and fitness in 13 healthy adolescent boys (mean age 15.9 $\pm$ 0.3 yr) over the course of a high-school wrestling season. Subjects were tested preseason, midseason (6 wk), peak season (12–14 wk), and 4 wk postseason. **Results**: No significant weight loss was noted throughout the season. During the wrestling season (mid and peak) both total ($P < 0.046$) and free ($P < 0.002$) IGF-I levels decreased, whereas proinflammatory cytokines (IL-1ra, $P < 0.005$; IGFBP-1, $P < 0.013$; and IGFBP-2, $P < 0.025$) increased. GHBP ($P < 0.018$) levels also decreased during the season. In the postseason, there were significant increases in GHBP, and free and total IGF-I, whereas proinflammatory cytokines decreased. **Conclusions:** An initial catabolic-type hormonal response occurs with intense exercise training in adolescents. This is followed by a rebound in circulating growth factors when the period of heavy training ceases. **Key Words:** EXERCISE, INFLAMMATION, GROWTH, ADOLESCENCE

In 1997, Roemmich and Sinning (31) showed that circulating levels of IGF-I fell in high-school wrestlers during the course of a standard 3- to 4-month season. Because their subjects purposefully under-ate in order to lose weight, the authors suggested that the reduction in IGF-I was primarily nutritional and probably resulted from a diet-induced GH-resistant state. Indeed, when the period of intense training was over, the subjects gained weight and IGF-I returned to baseline. In a series of exercise training studies in pre- and postpubertal children in our laboratory, we also demonstrated the development of GH resistance (9,10). However, unlike the Roemmich study, the subjects in our investigations continued to gain weight and height. Our subjects also increased muscle mass and fitness as a result of the training despite the reduction in IGF-I.

These and other recent studies have raised key questions regarding the relationship between training and the GH/IGF-I axis in children and adolescents. First, are there mechanisms related to the exercise itself and not changes in body weight that could account for the reduction in IGF-I with intense training? Second, how might one explain the reduced IGF-I when cross-sectional studies show that IGF-I levels are actually higher in fitter adults and children (11,29)?

We have proposed that these seemingly disparate phenomena could be explained by an initial training associated suppression of the GH/IGF-I axis that was mediated by inflammatory cytokines. In support of this idea, we recently demonstrated that a *single bout* of intense exercise, even in healthy adolescents, can lead to stimulation of interleukin- 6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α)] all of which can directly suppress the GH/IGF-I axis (26).

In the present study, we hypothesized: 1) that intense exercise training in adolescents would initially lead to simultaneous increases in proinflammatory cytokines and decreases in activity of the GH/IGF-I axis; and 2) that as exercise training proceeds, levels of proinflammatory cytokines would become reduced while an increase in IGF-I (rebound) ensues. Moreover, in recent years it has become apparent that measurements of total circulating IGF-I alone may not reveal potentially biologically significant alterations in the free and bound components of the circulating IGF-I pool (18), and in the circulating levels of IGF binding proteins (BP). Thus, we hypothesized that part of the compensatory response to intense training would be explained by a changes in concentration of circulating free and bound IGF-I and IGFBPs.

Address for correspondence: Dan M. Cooper, M.D., Professor of Pediatrics–UCI College of Medicine, Clinical Research Center, Bldg. 25, ZOT 4094-03, 101 The City Drive, Orange, CA 92868; E-mail: dcooper@uci.edu.
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TABLE 1. Subject characteristics ($N = 13$).

	Preseason	Midseason	Peak season	Postseason
Age (yr)*	15.9 ± 0.3	16.13 ± 0.3	16.29 ± 0.3	16.45 ± 0.3
Height (cm)*	174.0 ± 2.2	174.6 ± 2.0	174.7 ± 2.3	175.4 ± 1.9
Weight (kg)	73.8 ± 3.8	71.93 ± 4.0	72.88 ± 4.7	74.86 ± 4.8
BMI ($kg \cdot m^{-2}$)	24.26 ± 0.85	23.42 ± 0.90	23.67 ± 1.01	24.46 ± 1.12
BMI percentile	77.18 ± 4.62	69.57 ± 5.87	72.03 ± 5.23	74.55 ± 4.87
Fat (%)*	19.19 ± 2.42	17.52 ± 2.30	17.26 ± 2.72	19.83 ± 2.96
Peak VO_2* ($mL \cdot kg^{-1} \cdot min^{-1}$)	42.01 ± 1.60	44.37 ± 2.24	46.95 ± 2.46	43.05 ± 1.36
Hematocrit (%)	51.8 ± 1.6	51.5 ± 1.0	51.0 ± 1.6	50.6 ± 1.3

Data are presented as mean ± SEM.
* Significant change with time.

METHODS

Sample Population

The study was approved by the Institutional Review Board, University of California, Irvine (UCI), and written informed consent was obtained. Fifteen healthy adolescent boys enrolled for the study at the beginning of the season, but two were excluded due to typical relatively minor wrestling associated injuries that did, however, prevent them from completing the season. The data from these two subjects were not included in the wrestling season data.

Wrestling practice sessions occurred on average 5–6 $d \cdot wk^{-1}$, and typically each practice lasted 2–3 h. The exercise consisted of a mix of aerobic, endurance-type training, wrestling skill enhancement, and strength training exercises. Each wrestler would participate in roughly 8–10 meets in the course of a season. In this particular high school, the team coaches discouraged subjects from excessive weight loss through a variety of low calorie diets, as is, unfortunately, the practice in many high schools. The motivation for this practice is the unproven idea that wrestlers gain an advantage by competing at as low a body mass as possible.

Thirteen subjects completed the study (Table 1). Subjects were tested four times. The first test was 1–2 wk *prior* to the beginning of the wrestling season. Subjects were tested again: at *midseason* (6 wk into training), before entering the competition phase of the season; at *peak season*, tournament competition (12–14 wk into training); and *postseason*, approximately 4 wk after the last training session. At all visits the subjects were tested at least 16 h after their last exercise bout.

Height, Weight, and Body Mass Index (BMI) Measurements

Standard, calibrated scales and stadiometers were used to determine height, weight, and BMI (weight/height^2). Because BMI changes with age, we calculated the BMI percentile for each child using the recently published standards from the Centers for Disease Control, National Center for Health Statistics (21).

Body composition. Body composition was assessed using a pediatric specific two-site (triceps and calf) skinfold equation (23). All skinfold measurements were preformed by the same technician using a Lange skin-fold caliper (Beta Technology, Inc, Santa Cruz, CA).

Dietary assessment. To assess each subject's dietary intake and diet composition, participants completed a 3-d food record before each visit (35). The records were analyzed using the Nutritionist Pro computerized database (First DataBank Inc., San Bruno, CA).

Measurement of cardiorespiratory fitness. On every visit the subjects performed a ramp-type progressive exercise test on an electronically braked, servo-controlled, cycle ergometer (Ergoline 800S SensorMedics Corp., Yorba Linda, CA). After an initial warm-up (0-W pedaling), the work rate increased progressively (ramp function) until the limit of the subject's tolerance was reached. The ramp slope was chosen so that the subject would complete the exercise 8–12 min. Subjects were instructed to maintain a constant pedaling frequency at 60 rpm. Subjects were vigorously encouraged during the high-intensity phases of the exercise protocol. Gas exchange was measured breath-by-breath (2), and the $\dot{V}O_{2peak}$ was determined as previously described for children and adolescents (6).

Serum Measurements

Hematocrit. Hematocrit levels were determined using a standard microcapillary technique (17).

IGF-I (free and total). IGF -I was extracted from IGFBP using the acid-ethanol extraction method (7). Serum IGF-I concentrations were determined by ELISA using the DSL-10–5600 Active kit (Diagnostic System Laboratories, Inc., Webster, TX). IGF-I interassay CV was 6.4–8.8%, and intra-assay CV was 6.5–7.1%. Assay sensitivity was 0.03 $ng \cdot mL^{-1}$. Free IGF-I was determined by ELISA with the use of the DSL-10–9400 Active kit (Diagnostic System Laboratories). Intra-assay CV was 3.74–4.8%, interassay CV was 6.2–11.1%, and the sensitivity was 0.015 $ng \cdot mL^{-1}$. This commercially available assay measures the sum of free plus readily dissociable IGF-I. Free IGF-I levels by ELISA are known to be slightly elevated compared with those detected by ultrafiltration method (14) or the recently described IGF-I kinase receptor activation assay (5), both not commercially available.

IGFBP. IGFBP-1 was measured by ELISA with the use of the DSL-10–7800 Active kit (Diagnostic System Laboratories). For IGFBP-1, interassay CV was 6.2–7.6% and intra-assay CV was 1.7–4.6%. Assay sensitivity is 0.25 $ng \cdot mL^{-1}$ (results for IGFBP-1 were not obtainable for one subject). IGFBP-2 serum concentrations were determined by RIA with the use of the DSL-7100 kit (Diagnostic System Laboratories). Intra-assay CV was 4.7–8.5%, interassay CV was 7.2–7.4%, and the sensitivity was 0.5 $ng \cdot mL^{-1}$. IGFBP-3 serum concentrations were determined

by ELISA with the use of the DSL, 10-6600 Active kit (Diagnostic System Laboratories). Intra-assay CV was 7.3–9.6%, interassay CV was 8.2–11.4%, and the sensitivity was 0.04 ng·mL^{-1}.

Growth hormone binding protein (GHBP). GHBP serum concentrations were determined by ELISA with the use of the DSL-10-48100 Active kit (Diagnostic System Laboratories). Intra-assay CV was 3.17–5.56%, interassay CV was 5.11–8.36%, and the sensitivity was 1.69 ng·mL^{-1}.

TNF-α. TNF-α serum levels were determined by ELISA with the use of the R&D system Quantikine High Sensitivity kit (R&D system; Minneapolis, MN). Intra-assay CV was 8.7–14.8%, interassay CV was 16.1–22.6%, and the sensitivity was 0.18 pg·mL^{-1}.

IL-6. IL-6 serum levels were determined by ELISA with the use of the R&D system Quantikine High Sensitivity kit (R&D system). Intra-assay CV was 3.8–11.1%, interassay CV was 7.1–29.5%, and the sensitivity was 0.0094 pg·mL^{-1}.

IL-1β. IL-1β serum levels were determined by ELISA with the use of the R&D system Quantikine High Sensitivity kit (R&D system). Intra-assay CV was 1.6–4.0%, interassay CV was5.3–9.0%, and the sensitivity was 0.059 pg·mL^{-1}.

IL-1ra. IL-1ra serum levels were determined by ELISA with the use of the R&D system Quantikine High Sensitivity kit (R&D system). Intra-assay CV was 3.1–6.2%, interassay CV was 4.4–6.7%, and the sensitivity was 22 pg·mL^{-1}.

Statistical Analysis

Data were analyzed using repeated-measures ANOVA over time. Statistical significance was set at $P < 0.05$. Differences between baseline, mid, peak, and postexercise means were tested using single degree-of-freedom contrasts across the group means. For example, coefficients for the contrast between mid and peak season means were [0 (pre), 1 (mid), −1 (peak), 0 (post)]. Graphics were used to evaluate the distribution of values at each time point. Correlation and linear regression analyses were computed between growth factors and cytokines at baseline. Data are presented as mean ± SEM.

RESULTS

Height, Weight, and Body Mass Index (BMI) Measurements

Subject characteristics are presented in Table 1. Height increased significantly throughout the season ($P < 0.022$). No significant changes in weight or BMI percentiles for age occurred during the training season.

Body composition. There was a significant decrease in body fat reaching a nadir at peak season (Table 1, $P < 0.002$).

Dietary assessment. No significant differences were found in dietary intake or diet composition throughout the season (Fig. 1).

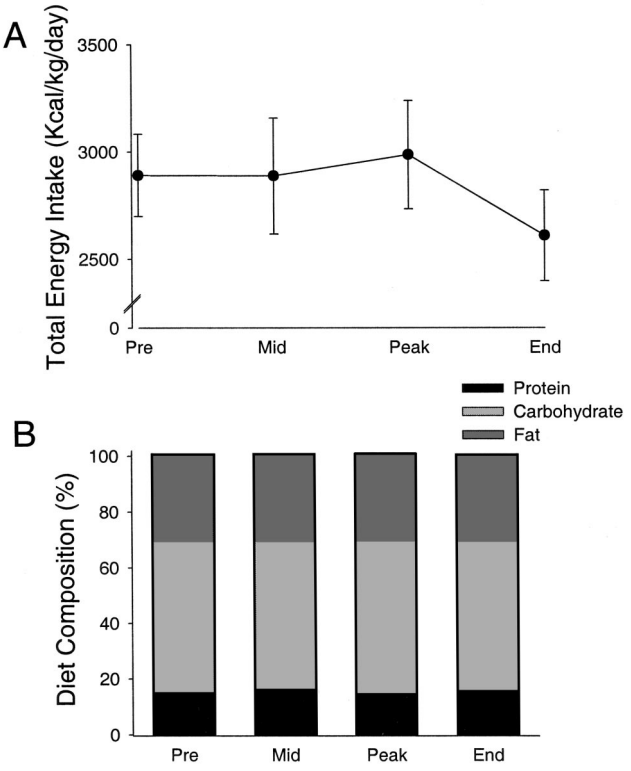

FIGURE 1—Total energy intake and diet composition during a wrestling season. No significant changes in both total energy intake (A) or diet composition (B) were noted throughout the wrestling season.

Cardiorespiratory Fitness

The effect of a wrestling season on cardiorespiratory fitness is shown in Table 1. There was a significant increase in fitness (compared with pretraining levels), with the highest fitness level achieved at peak season (competition period, $P < 0.042$).

Circulating Growth Factors and Cytokines

Baseline correlations. At baseline (visit 1, Fig. 2) IGF-I was negatively correlated to the levels of IL-6 ($r = -0.543$, $P < 0.036$), TNF-α ($r = -0.529$, $P < 0.043$) and IL-1ra ($r = -0.656$, $P < 0.008$). IL-6 was correlated with IL-1ra ($r = 0.831$, $P < 0.0005$).

Effects of Training Season

Hematocrit. No significant change in hematocrit level was noted throughout the training season (Table 1).

Insulin-like growth factor-I. The effect of exercise on serum total and free IGF-I is shown in Figure 3. There was a significant change in circulating IGF-I level over time ($P < 0.013$). IGF-I level decreased at midseason followed by an increase at peak season and a further increase at the end of season. Free IGF-I decreased at midseason, followed by a significant increase to above baseline levels at peak season and postseason ($P < 0.002$).

IL-1ra. There was a significant increase in IL-1ra peaking at midseason (Fig. 4) followed by a decrease to lower

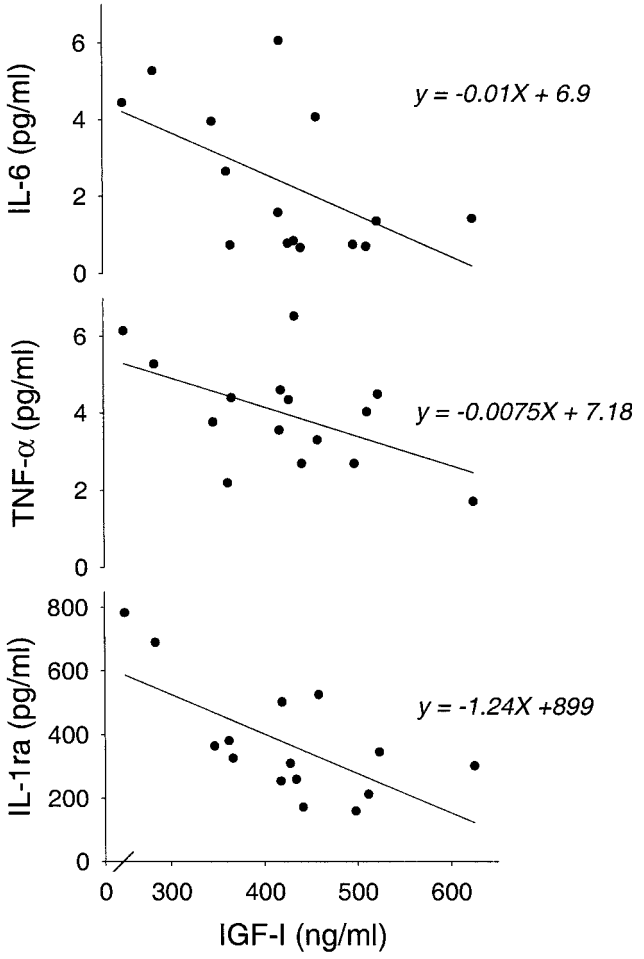

FIGURE 2—Correlation between baseline IGF-I levels and levels of IL-6, TNF-α, and IL-1ra. IGF-I was inversely related to the levels of IL-6 ($r = -0.543$, $P < 0.036$), TNF-α ($r = -0.529$, $P < 0.043$), and IL-1ra ($r = -0.656$, $P < 0.008$).

then baseline levels postseason. There was a significant change in IL-1ra over time ($P < 0.005$).

IL-6. There was an increase in IL-6 levels peaking at midseason, followed by a decrease to lower then baseline levels postseason with a pattern of change similar to that observed for IL-1ra; however, this change was not found to be significant over time (Fig. 4).

IGFBP-1. There was a significant increase in IGFBP-1 peaking at midseason (Fig. 5), followed by a decrease to below baseline levels. There was a significant change in IGFBP-1 over time ($P < 0.013$).

IGFBP-2. There was a significant increase in IGFBP-2 peaking at midseason (Fig. 5) with a pattern of change similar to that observed for IGFBP-1. There was a significant change in IGFBP-2 over time ($P < 0.025$).

GHBP. There was a decrease in the levels of GHBP after initiation of training. Postseason, GHBP levels rebounded to reach an above baseline levels. There was a significant change in GHBP over time ($P < 0.018$, Fig. 4).

IGFBP-3, TNF-α, and IL-1β. No significant effects of exercise were observed in the circulating levels of IGFBP-3, TNF-α, and IL-1β during the wrestling season.

DISCUSSION

This study demonstrates that the response to a period of exercise training in adolescence is characterized by a remarkable inverse relationship between proinflammatory, predominantly catabolic mediators, and the anabolic hormone IGF-I. The first response that we measured was during the sixth week of intensive training and was characterized by a reduction in both free and bound IGF-I with a simultaneous increase in mediators known to indicate inflammatory states (IGFBP-1, IGFBP-2, and IL-1ra). As the season progressed, these mediators returned to pretraining levels. Finally, during the recovery, there was evidence for a rebound effect: anabolic mediators like free IGF-I exceeded pretraining levels, and largely catabolic mediators decreased to levels below pretraining.

Roemmich and Sinning (31) in their study of high-school wrestlers also noted a reduced IGF-I with intense training but attributed the finding to energy imbalance. It is a common practice among many high school wrestlers to undereat and lose weight in order to gain the putative advantage of wrestling at the upper end of a lower weight class. The subjects in the Roemmich study lost a significant amount of weight. In our study, the change in weight was not significant, and in three subjects, a decreasing IGF-I was observed in the face of a weight *gain*. The coaches in the particular high school that we studied had made a conscious decision not to pursue a weight-loss agenda for their wrestlers.

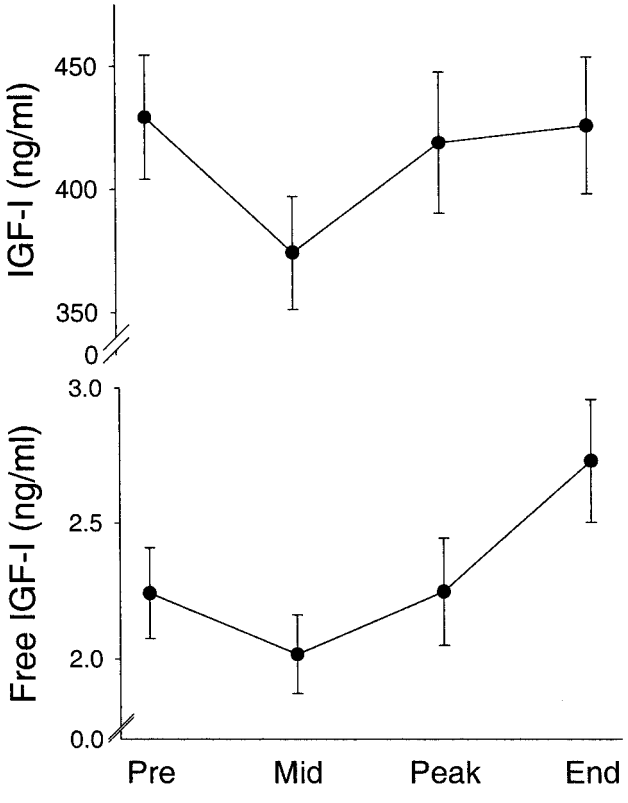

FIGURE 3—The effect of a wrestling season on total and free IGF-I circulating levels. There was a significant effect of time on both total IGF-I ($P < 0.046$) and free IGF-I levels ($P < 0.02$). After an initial decrease, total IGF-I levels returned to baseline at end season, whereas free IGF-I rebounded reaching an above baseline levels.

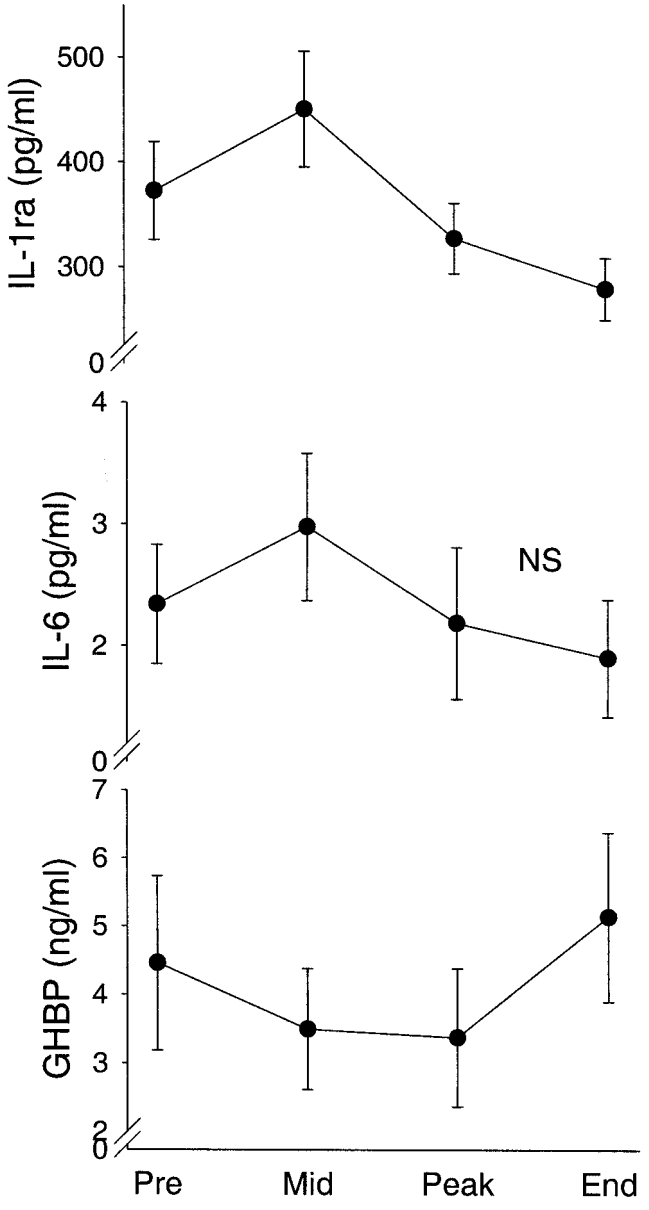

FIGURE 4—The effect of a wrestling season on IL-6, IL-1ra, and GHBP circulating levels. There was a significant effect of time on IL-1ra ($P < 0.005$), whereas IL-6 followed the same pattern, but this was *not* found to significant. A significant yet inverse effect of training was observed for GHBP ($P < 0.018$).

Thus, our data support the idea that factors related specifically to exercise, namely, the increase in proinflammatory cytokines, contributed to the reduction in IGF-I early in the training season. It is well established that mediators like IL-6 directly inhibit IGF-I production (22), and with single bouts of exercise of sufficient intensity and duration, such as would be encountered daily during the wrestling season, circulating IGF-I is reduced and IL-6 increased immediately after exercise (26). Increases in IL-6 are also associated with GH resistance. Indirect support that the wrestlers had developed a GH resistant state was our observation that GHBP fell during the season and rebounded during the postseason recovery. Circulating GHBP is the extracellular component of the GH receptor and is felt, by some, to reflect GH receptor activity in tissues (1).

We were able to detect these relationships in anabolic and catabolic factors with measurements that were made with the subjects under resting conditions and at least 16 h after any individual exercise bout. This suggests that a chronic adaptation of these hormones had occurred in response to the overall training. For example, elevations in IL-6 and IL-1ra are the most consistent inflammatory response associated with acute bouts of exercise, and in our previous study of high school wrestlers, these mediators increased substantially immediately after exercise. The half-life of IL-6 in the circulation is only 1–2 h, whereas our measurements were made at least several half-lives beyond this.

IL-6 stimulates the production of IL-1ra, which binds to and blocks the IL-1 receptor, thus exerting strong anti-inflammatory effects (36). With exercise, peak IL-1ra is found 1–2 h *after* peak IL-6 (25,27). From this, it is assumed that the level of IL-1ra reflects the production of IL-6 (32) and serves *as a marker* of the degree of the inflammatory process. In the present study, the sustained elevation of IL-1ra likely represents the lingering effect of an overall inflammatory stimulus.

Although little is known about the biological effects of proinflammatory cytokines in healthy subjects, one relevant and surprising observation was that in the preseason, we found relatively strong inverse correlations between circulating TNF-α, IL-6, and IL-1ra with IGF-I (Fig. 2). An inverse relationship between these catabolic and anabolic mediators has been noted in children with specific pathological states such as cystic fibrosis (37), juvenile idiopathic arthritis (8), and chronic HIV infection (19). In these disease

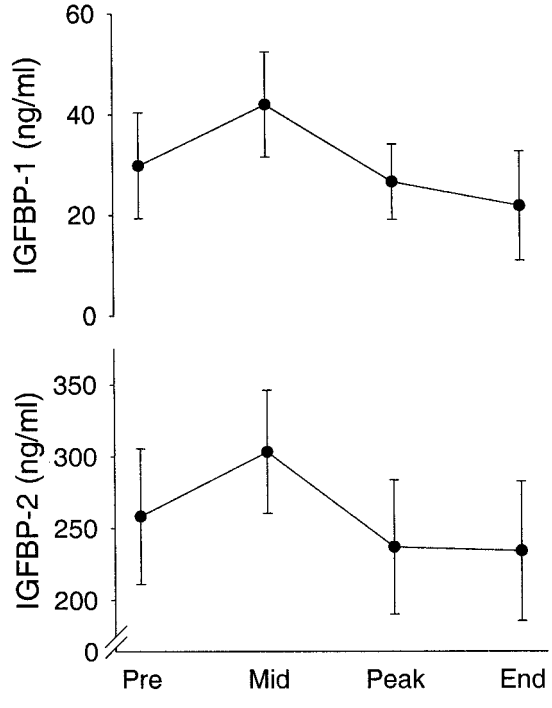

FIGURE 5—The effect of a wrestling season on insulin like binding proteins 1 and 2. Both IGFBP-1 and IGFBP-2 ($P < 0.013$ and $P < 0.025$, respectively) showed a similar pattern of initial increase at midseason followed by a decrease to below baseline levels at the end of season.

states, proinflammatory cytokine levels are high, IGF-I low, and growth is impaired.

Although most literature suggests that proinflammatory cytokines promote catabolism (38), there is a growing body of evidence to suggest that under specific conditions and, possibly, at lower levels (like those observed in the present study), proinflammatory cytokines like IL-6 may actually promote growth of muscle and blood vessels and serve as a beneficial response to exercise (24,28). In fact, in the present study, as we previously demonstrated in shorter periods of exercise training (9,10), a significant increase in fitness level was achieved during this seemingly catabolic hormonal environment. The biological effects of the interaction of proinflammatory cytokines with anabolic mediators like IGF-I in the *healthy* child has yet to be determined.

The mechanism for the increase in indicators of a catabolic, inflammatory response (IGFBP-1 and 2, and IL-1ra) is not entirely clear. Controversy exists as to whether exercise associated increases in proinflammatory cytokines result from adrenergic stimulation of peripheral blood mononuclear cells [which are known to secrete these agents (12)] or from production by muscle tissue (20). Another major tissue that is known to produce cytokines is the fat tissue (13). But in the present study, the increase in cytokines occurred despite a decrease in body fat (Table 1), quite the opposite of what has been observed in studies involving weight loss in healthy children and adults (15,39). Our data, therefore, do support the idea that the increase in cytokines is likely to be exercise related, but the precise mechanism of this increase awaits further investigation.

IGFBP-1 is found predominately in tissues, not in circulating blood, and acts primarily to inhibit anabolic effects of IGF-I (30). Circulating IGFBP-1 is elevated in pathologic, catabolic states like sepsis and burns, consistent with evidence that IGFBP-1 may actually be stimulated by IL-1β, IL-6, and TNF-α (33). IGFBP-1 is known to be inversely related to circulating insulin (not measured in the current study); however, there are data indicating that the specific exercise associated increase in IGFBP-1 occurs even when insulin concentrations are unchanged (16). Finally, less is known about IGFBP-2, but like IGFBP-1, its physiologic role is primarily to inhibit anabolic functions of IGF-I and, similar to IGFBP-1, IGFBP-2 is known to be elevated in pathologic, catabolic states (4).

The training associated increases in catabolic mediators and decreases in anabolic agents were paralleled by an apparent rebound for each of these types of markers in the postseason, recovery period. Roemmich and Sinning noted in their wrestling study that during the postseason recovery phase there was a return to preseason IGF-I levels, and our data on total IGF-I showed a similar response. However, when we further examined free IGF-I (a measurement that was not readily available at the time of Roemmich's investigation), we found that the postseason values had, in fact, significantly exceeded those found before training (Fig. 3).

The bulk of circulating IGF-I is bound in a ternary complex (IGF-I, IGFBP-3, and an acid-labile subunit (30) that is too large to cross the capillary membranes. A small percentage of IGF-I circulates in an unbound form, which, because it can more readily permeate capillaries, is likely to be more accessible to mediate growth effects on target tissues. Thus, an increasing number of investigators have chosen to examine the effect of physiological perturbations like exercise on the bound and free IGF-I pools. More recently, investigators have identified a number of situations, like in the present study, in which free IGF-I levels exceeded the changes in bound IGF-I and were associated with increased growth (3).

One possible mechanism for this discrepancy could be increased IGFBP-3 proteolysis, and, indeed, IGFBP-3 proteolysis is acutely increased in wrestlers after a single practice (26). The growth and development implications of the increase in free IGF-I in the recovery period after intense exercise training in adolescence remains uninvestigated. Finally, whether or not the increase in free IGF-I precedes the generally higher levels of total IGF-I found in trained individuals, is not known.

In summary, we demonstrated significant, exercise-training associated changes in both anabolic and catabolic mediators throughout a wrestling season. These data suggest that the initiation of training induces a systemic, catabolic environment (high IL-1ra, IGFBP-1 and -2; and low IGF-I and GHBP). However, as training proceeds, an anabolic rebound ensues with increases in anabolic mediators and a decrease in proinflammatory markers. This might explain the previously observed IGF-I "paradox" (26,34) in which the initial response to exercise training is accompanied by reductions in IGF-I despite the fact that in cross-sectional studies, fitter subjects have higher IGF-I (11,29). How these exercise-training alterations in catabolic and anabolic mediators influence subsequent growth and development in healthy adolescents is not yet known.

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