The Endocrine Response to Exercise and Training in Young Athletes

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The manuscript “Plasma Somatomedin-C in 8- to 10-Year-Old Swimmers” by Denison and Ben-Ezra published in the first issue of Pediatric Exercise Science in 1989 was among the first to address the relationship between growth, the growth hormone (GH)/insulin like growth factor-1 (IGF-1) axis, and exercise. Since their pioneering article, this topic has become of great interest to pediatricians and pediatric exercise researchers, and today our understanding of the effects of exercise training on the growth axis during childhood and puberty, on differences between systemic and local (i.e., muscle) responses to exercise, and our ability to use these responses to assist the adolescent competitive athlete in the evaluation of the training load have markedly improved. The aim of the present review is to summarize our current knowledge on this topic.

Introduction

In recent years, exercise-associated hormonal changes have been studied extensively, focusing mainly on changes in circulating components of the growth hormone (GH)/insulin-like growth factor-1 (IGF-1) axis (11). The effect of exercise training on anabolic hormones and catabolic/inflammatory mediators is particularly important during childhood and puberty, a period of spontaneous increases in anabolic hormones leading to the marked pubertal growth spurt. Therefore, any training-associated hormonal and/or inflammatory effect during this critical period may have profound consequences on growth and development, especially if maintained for long periods. Our understanding of the effects of exercise training on the growth axis during childhood and puberty, on differences between systemic and local (i.e., muscle) responses to exercise, and our ability to use these responses to assist the adolescent competitive athlete in the evaluation of the training load have markedly improved since the Denison and Ben-Ezra’s study (6) in the first issue of Pediatric Exercise Science in 1989. This review will summarize the advances in this field thus far.
Where Were We 25 Years Ago?

Studies in the late ‘80s and early ‘90s were among the first to investigate the relationship between exercise and circulating insulin-like growth factor-I (IGF-I). Poehlman and Copeland (31) studied the influence of physical activity on IGF-I in younger and older adult males. They demonstrated, using multiple regression analysis controlling for age, that leisure time physical activity and VO2max were the only factors positively related to IGF-I, suggesting, for the first time, possible relationships between fitness and IGF-I. Consistently, other investigators have demonstrated increases in IGF-I levels following resistance exercise in young adults (19), and that higher levels of IGF-I correlated with hours of muscle-building activities in college females, and were associated with increased bone mineral density (5).

Interestingly, few adult studies suggested possible mechanisms mediating the effects of exercise on the GH/IGF-I axis. Kraemer et al. were the first to demonstrate that exercise-induced changes in IGF-I are GH-independent (20). In addition, Suikkari and colleagues (36) demonstrated exercise-induced changes in IGF binding proteins suggesting that exercise can affect IGF-I activity not only by changes in IGF per se, but also by alterations in its binding proteins.

Several studies at that time investigated the effect of negative energy balance induced by both inadequate caloric intake and excessive exercise on circulating insulin-like growth factor-I (IGF-I) levels. Smith et al. (34) demonstrated that caloric deficit induced by diet or exercise was associated with reduced plasma IGF-I in adult male athletes. The authors concluded that negative energy balance, whether caused by increasing energy expenditure with an exercise training program or by reducing energy intake without increasing exercise, causes a reduction in circulating IGF-I within several days.

The study of Denison and Ben-Ezra (6) published in the first issue of Pediatric Exercise Science in Feb 1989 was the first to examine this phenomenon in children. The authors demonstrated that 8- to 10-year-old male and female swimmers (n = 18) who trained regularly, in combination with adequate energy and protein intake, had IGF-I levels within the normal range for this age. In addition, since the swimmers were significantly older than the inactive control participants, the authors also performed an age and sex-matched comparison showing that IGF-I levels were not significantly different from controls. Denison and Ben-Ezra concluded that exercise in conjunction with adequate nutrition does not promote decreased IGF-I levels. They stated that further research on the relationship between exercise training and IGF-I needs to take into account the effect of maturational status, assessment of energy expenditure and in particular the effect of inadequate caloric intake and energy imbalance. In the same year, Crist and Hill (3) found that differences in body composition between exercising women with or without exercise-induced secondary hypothalamic amenorrhea were related to reduced IGF-I levels. Later, Jahreis et al. showed a parallel decrease in IGF-I and triiodothyronine (T3), and an increase in cortisol levels following three days of intensive training in adolescent female gymnasts, introducing the possibility that exercise-induced hormonal modifications are related to development, growth and maturational delay (17). Finally, the concept that diet composition plays an important role in the GH-IGF response to exercise was also established. It was
found that caloric restriction (92 KJ/FFM/day using high and normal carbohydrate diet), regardless of dietary composition, increased anaerobic exercise-associated GH response (Wingate anaerobic Test), but the increase was significantly lower in the high carbohydrate group (22).

**How Far Have We Advanced Since Then?**

Since the late 80’s both cross-sectional and longitudinal studies have improved our understanding of the relationships between exercise, fitness and anabolic hormones.

**Cross-sectional Studies**

Previous studies described (7,14) that both functional (VO2max) and structural (thigh muscle volume determined by magnetic resonance images) indices of fitness correlated with mean overnight GH levels, GH binding protein (GHBP) and serum IGF-I levels in pre and late pubertal girls. This suggested that fitness in healthy, prepubertal and adolescent females is associated with anabolic adaptations of the GH/IGF-I system. The significant correlation between fitness and mean overnight GH levels resulted probably from an increase in peak GH amplitude since only peak amplitude (and not peak frequency) correlated with mean GH. The positive correlation between GH, GHBP (an index for GH receptor) and fitness is unique because it suggests anabolic adaptations of both the ligand and the receptor. Collectively, it seems that increasing levels of physical activity stimulate GH secretion, and as a consequence, 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 (like peak VO2). The data suggests that this mechanism is active both in prepubertal and in adolescent girls and boys (8) even while spontaneous growth and natural increase in muscle mass proceeds.

Other studies in adolescent rhythmic gymnasts demonstrated no difference in circulating IGF-I levels compared with sedentary controls despite reduced adiposity and leptin levels (2). Since IGF-I is affected by energy balance, reduced body weight and fat mass is often associated with decreased IGF-I levels. Therefore, the authors suggested that exercise preserved IGF-I levels in the rhythmic gymnasts. Consistent with these observations, a follow-up of 4 years during puberty demonstrated that while rhythmic gymnastics training was associated with delayed sexual maturation, there was no effect on linear growth (1).

Virtually all of the major IGF binding proteins [(IGFBP) 1 through 6], each of which is known to influence IGF-I bioactivity, were also related to indexes of fitness suggesting that the BPs may play a role in the interaction between fitness and exercise (7,13,14). The cross-sectional relationships between fitness and IGFBPs were consistent with current understanding of the biological activity of IGF-I binding proteins based on tissue studies. IGFBP-1–2, and -4, known to inhibit IGF-I function, were found to be inversely correlated with muscle mass and/or VO2max (7,14). In contrast, the IGF-I potentiating binding protein, IGFBP-5, was positively correlated with muscle mass (13). Accordingly, these data reinforce the possibility that the generally increased IGF-I bioactivity in fitter subjects might not be related only to changes in circulating IGF-I, but also to changes in IGFBPs.
Longitudinal Studies

Very few longitudinal studies examined the effect of exercise training on the GH/IGF-I axis in children. Reduced IGF-I associated with training has been observed in high school male wrestlers and in highly trained young female gymnasts (17,32). In these studies the training program was accompanied by a loss of body mass providing clear evidence for a negative energy balance and catabolic state. We previously examined the effect of a 5 week randomized, prospective endurance-type training intervention on the GH/IGF-I axis in pre and late pubertal males and females. Based on the cross-sectional data, we hypothesized that training would lead to increases in circulating GH and IGF-I levels. Training was associated with a 15% higher total energy expenditure (by the doubly labeled water technique), and resulted in significant increases in VO2max and thigh muscle volume (7,8,14,33). In contrast to our hypotheses, based on the cross-sectional findings of higher IGF-I among fitter subjects, training was associated with a significant decrease in IGF-I and some of the anabolic IGFBPs in the pre and late pubertal males and females with no change among controls. These effects are commonly observed in energy deficient states like food deprivation or disease associated malnutrition (34,38), but the catabolic adjustments occurred in the those studies despite training-induced increased thigh muscle volume and no weight loss. Thus, reduction in IGF-I is sensitive to negative energy balance, but even when energy balance is maintained and weight is stable, exercise training by itself, may lead to small, yet significant, reductions in IGF-I (27).

Scheett et al. suggested the intriguing hypothesis that proinflammatory cytokines were involved in the training-induced decreases of IGF-I (33). They demonstrated that in a similar five weeks endurance training in prepubertal boys, increases in VO2max correlated with increases in tumor necrosis factor-α (TNF-α). This suggested that children who trained the hardest, and had the biggest increase in fitness, had also the largest increase in proinflammatory cytokines. Changes in the anabolic IGFBP-3 correlated inversely with changes in TNF-α and Interleukin-6 (IL-6), suggesting that the increase in the inflammatory response mediates the training-associated decrease of components of the GH/IGF-I axis.

These observations suggest the hypothesis that a sudden imposition of a training program which is associated with substantial increase in energy expenditure leads initially to an increase in proinflammatory cytokines, and as a consequence, to decreases in IGF-I levels. Further, if the training adaptation is successful, the proinflammatory cytokines fall, and with that decrease, the suppression of IGF-I diminishes, an anabolic rebound of the growth axis may follow, and IGF-I level exceed pretraining levels (Figure 1). Exactly how and when this switch takes place, and whether the initial catabolic-type stage is necessary for the ultimate anabolic adaptation remains unknown.

Consistent with this theory, fitter pre and early-pubertal males had lower levels of interleukin 1 receptor antagonist (IL1ra; 33). IL1ra is stimulated by inflammatory cytokines and blocks their biological activity at the receptor level. Therefore, training-associated reduced inflammatory response leads to lower level cytokines and lower steady-state level of IL1ra. Finally, and consistent with the two-phase hypothesis, longer periods of training [5 months (18), one year (39), and 18 months (4)] were indeed associated with stable or increased GH and IGF-I levels.
The training-induced increase in muscle mass despite circulating decrease in IGF-I level suggested that the local tissue effect of exercise on growth factors differ from systemic effects. Very few studies examined the effect of brief exercise or training on skeletal muscle IGF-I levels. An acute bout of eccentric exercise led to an increase in IGF-I immuno-reactivity in rat Type II muscle four days postexercise (40). Consistently, we found (9) that 5 days of treadmill training in young female rats resulted in a significant increase in muscle size and muscle IGF-I, without changes in IGF-I mRNA or circulating IGF-I. These results suggest that the early mechanisms of the training adaptation involve translational or posttranslational increases in muscle IGF-I, and that local muscle IGF-I regulation may be dissociated from central control mechanisms. Moreover, it was suggested that increases in local IGF-I was not due to increase in local synthesis, but rather to an increase in IGF-I uptake from the circulation by IGFBPs that are strongly attached to the cell surface (30).

Longer periods of exercise training lead also to stimulation of IGF-I gene expression. Zanconato et al., found an increase in hepatic IGF-I gene expression following 4 weeks of endurance training in young rats (41). In addition, the authors
showed that the 4 weeks of endurance training led to increases in exercising muscle IGF-I gene expression and protein. Interestingly, inhibition of GH (by GH releasing hormone antibody) actually enhanced the local IGF-I response to increased muscular effort. It is clear from these observations that inhibition of GH alone cannot block the autocrine and paracrine effects of IGF-I, emphasizing the GH-independence of the local IGF-I anabolic adaptations to physical activity.

What is the advantage of simultaneous central catabolism and local anabolism early in the adaptation to increased physical activity? This adaptive mechanism might reduce global anabolic function thereby conserve energy sources, but still allow for local tissue growth in response to environmental stresses like exercise training (Figure 1). Consistent with this speculation is the phenomenon of attenuated somatic growth and reduced circulating IGF-I despite muscle adaptation to intense exercise training in nutritionally self-deprived young female gymnasts (37). Dissociation between target tissue and circulating IGF-I responses was found also in other conditions (26). Rats exposed to hypoxia had reduced circulating IGF-I and growth rate, but their heart and lung size, along with local IGF-I gene expression, was increased. This indicates that local anabolic adjustment to hypoxia had occurred, but the central response was catabolic and overall growth was reduced.

**Implication to Young Competitive Athletes**

Measurements of IGF-I levels can also assist athletes in the preparation for competition. The effect of four weeks of training on fitness, self-assessment physical conditioning scores and IGF-I level was assessed in elite handball players during the preparation for the junior world championships (10). Training consisted of 2 weeks of intense training followed by 2 weeks of relative tapering. Circulating IGF-I and physical conditioning scores decreased initially, and returned to baseline levels at the end of training. Changes in IGF-I correlated with physical conditioning scores suggesting that the athlete’s self-assessment can serve as a reliable tool when laboratory assistance is unavailable. Similarly, IGF-I levels during the training season in elite adolescent wrestlers also decreased during heavy training periods, and returned to baseline during tapering down before the competition season (28). Changes in the pro- and anti-inflammatory mediators IL-6 and IL1ra correlated negatively with changes in IGF-I, being high when IGF-I level was low, and normalized when IGF-I levels normalized, emphasizing their potential contributing role for the training-associated change in IGF-I (Figure 1). Likewise, levels of IGF-I and IGF-I/BP-3 ratio, as an index of IGF-I bioactivity, increased significantly throughout the competitive season in late pubertal triathletes (21).

Tapering down training intensity before competition is a well-known methodology in the elite competitive world to improve performance (35). Since this strategy is associated with a parallel increase in IGF-I levels, repeated IGF-I measures may assist the coaching team in their training preparations. Interestingly, athletes that do not plan for a specific target, and train in similar relative intensity throughout the season (e.g., soccer), changes in IGF-I level and its major binding protein IGFBP-3, were not found (25). In optimal conditions, during training intensity tapering, IGF-I level will increase above baseline levels and will be associated with improved performance. In a real life setting, this does not always occur. IGF-I can be reduced by weight loss. Thus, it is possible that a deliberate decrease in body weight in weight category sports (e.g., judokas, wrestlers) before major championships may
prevent an increase in IGF-I, and will be associated “only” with a significant return to baseline values (28;32).

In addition, despite the decrease in circulating IGF-I (7,8,14,33) during periods of intense training, fitness may still improve. This suggests that while changes in circulating IGF-I are good markers of the athlete’s general condition and energy balance, they are not good predictors of performance. It is probably the local autocrine or paracrine muscle hormonal secretion that better indicates performance (15,41). Tapering of training intensity, however, is associated with both increased IGF-I level and improved athletic performance (16,35).

What should be the appropriate decrease of IGF-I levels during heavy training periods, or what should be its optimal increase during periods of tapering down is still unknown. It is believed that an inability to increase circulating IGF-I levels before the target competition should be a sign of alert that the athlete’s general condition is not optimal. Collection of baseline and training-related hormonal changes—a comparison with previous season’s hormonal responses, past success experience, and an appropriate adaptation to growth induced changes—may prove to be of significant relevance.

Previous studies have focused mainly on the effect of endurance type exercise on GH/IGF-I secretion. Recently, efforts have been made to characterize the GH response to anaerobic-type exercise. Studies in elite junior handball players (17–25 years) found a significant increase in GH and IL-6 levels following different types of interval training [constant distance: 4 × 250 m (23) increasing: 100–200–300–400 m and decreasing distances: 400–300–200–100 m (24)]. Differences in the magnitude of response (i.e., greater GH response in the decreasing regimen) suggested that measurements of these mediators may be used to assess training intensity following different anaerobic training protocols.

Finally, we examined the effect of 7 weeks of training during the initial phases of the training season on hormonal and inflammatory response to a single volleyball practice in elite male and female adolescent players. Training resulted in significantly greater GH response and reduced IL-6 and cortisol response to the same relative intensity volleyball practice (12,29). These studies suggested uniquely that along with improvement of anaerobic and aerobic performance, training leads to a greater anabolic and to reduced catabolic/inflammatory response to exercise.

What Does the Future Hold In This Area?

As noted, one of the unique features of exercise is that it leads to a simultaneous increase of antagonistic mediators. On the one hand, exercise stimulates anabolic components of the GH/IGF-I axis, and on the other hand, exercise elevates catabolic hormones and proinflammatory cytokines. The very fine balance between the anabolic and inflammatory/catabolic response to exercise will determine the effectiveness of training and the health consequences of exercise (Figure 2). A greater anabolic response will probably lead ultimately to increased muscle mass and improved fitness. A greater catabolic response, in particularly if persists for long duration, may lead to overtraining. This suggests that changes in the anabolic-catabolic/inflammatory hormonal balance may be used by adolescent athletes to gauge training intensity in individual and team sports. Future studies in the area will focus on investigating these mediators’ response to different types of
sports, training sessions, and training protocols to find a possible objective tool to monitor the training load and to better plan training cycles throughout a competitive season.

Finally, many research efforts are made in recent years to find genetic polymorphism or genetic scores that would serve as an additional tool to predict success in sports. It should be noted that while a favorable genetic predisposition is important, many other environmental and psychological factors like training facilities, personal equipment, nutrition, familial support, motivation, and socioeconomic factors, are crucial for the development of a top-level athlete. However, future studies will focus on potential genetic polymorphisms related to the GH/IGF-I axis as possible predictors of athletic success.

References


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