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Acute and Chronic Effects of Physical Exercise on Growth Hormone (GH)/ IGF-I Axis in Children and Adolescents: A Narrative Review

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Abstract

The aim of this review was to describe the kinetics of GH/IGF-I axis in relation to acute and chronic stimuli from physical exercise in children and adolescents. The GH/IGF-I system comprises a series of growth mediators, receptors, and binding proteins that regulate somatic and tissue growth in several species. It has been shown that exercise programs affect this anabolic function through changes in the levels of the components of the GH/IGF-I axis. Some studies have demonstrated a reduction in the circulating levels of GH/IGF-I axis components in adolescents and children in response to training sessions, possibly due to an increase in cytokine levels triggered by intense exercise. High training intensity leads to an important metabolic modulation characterized by a rise in inflammatory markers (cytokines) and, consequently, suppression of GH/IGF-I axis. Changes in the anabolic/catabolic balance and inflammatory mediators, followed by different types of training sessions and programs at different moments in a training season can help coaches and athletes to plan training so as to achieve better performances and health indexes. In children and adolescents, the combination of fast growth and development, high levels of physical activity, and spontaneous increase in anabolic hormones related to puberty (GH, IGF-I, and sex steroids) suggest that integrated mechanisms exist between exercise and several of anabolic/catabolic responses, which must be further investigated.

Key Points

1. The kinetics of circulating levels of growth mediators suggest no direct correlation between changes in GH/IGF-I axis induced by a short training period and those caused by a longer training period;

2. IGF-I is sensitive to the acute and chronic effects of training, exhibiting biphasic behaviour throughout the season. IGFBP-3 is only sensitive to the chronic effects of training;

3. Serum IGF-I and IGFPB-3 have proven to be sensitive markers of training status and, thus, could be used as guides for coaches and athletes in the challenging task of modulating training intensity in young athletes.

Introduction

Regular exercise during childhood and adolescence can influence the growth and development of muscle and bone mass. Thus, physical exercise is closely related to the anabolic function triggered by the growth hormone (GH)/IGF (insulin-like growth factor-I) axis, a system of growth mediators, receptors, and binding proteins that regulate somatic and tissue growth in several species. Basal IGF-I levels are positively correlated to muscle mass and physical aptitude in children, adolescents, and adults [1,2]. The GH/IGF-I axis behaves similarly in both genders and is the main mediator of linear growth acceleration; is involved in determining bone thickness, length, and density; and influences skeletal architecture by increasing body ratios during childhood and adolescence [3]. The adverse effects of physical exercise during childhood and adolescence, such as stress and reduction in growth velocity, seem to be independent of the type of sport practiced but occur as a result of the training intensity to which children and adolescents are exposed [4]. High intensity training results in an important metabolic modulation characterized by the elevation of inflammatory markers (cytokines) and, consequently, suppression of the GH/IGF-I axis [4]. IL-6, IL-1β, IL-1ra, and TNF-α are the main cytokines involved in directly inhibition of the anabolic action of the GH/IGF-I axis [5,6]. The duration of the reduction in GH and IGF-I levels observed following intense training is an important point to be addressed. Few studies have analysed the duration in the reduction of IGF-I levels or GH/IGF-I axis after a series of intense exercises in children or adolescents, and fewer still have analysed the kinetics of anabolic and catabolic mediators throughout a training season [7-10]. IGF-I response to chronic training has yet to be elucidated [11]. It has been suggested that the kinetics of serum IGF-I indicates that there is no direct correlation between IGF-I changes induced by a short training period and those resulting from longer training periods [12]. Currently, it has been questioned whether IGF-I and IGFBPs (IGF binding proteins) levels observed in acute responses to exercise differ from those in response to chronic training or long-term changes to the level of physical activity, as well as variation between the different types of sport (individual or in group) and the different types of planning [13, 14]. Thus, the aim of the present review was to describe the kinetics of the GH/IGF-I axis in children and adolescent in response to acute and chronic stimuli from physical exercise.

Physical exercise and acute suppression of the GH/IGF-I axis

The GH/IGF-I axis is a system of growth mediators, receptors, and binding proteins that regulate somatic and tissue growth in several species. Exercise programs influence this anabolic function by interfering with the action of the GH/IGF-I axis. A reduction in the circulation of GH/IGF-I axis components has been reported in children and adolescents in response to training sessions [5, 6, 15-17]. This is probably due to increased levels of cytokine, as a result of intense exercise [18, 19]. Cytokines are known to directly inhibit the anabolic action of the GH/IGF-I axis, especially IL-6, IL-1β, IL-1ra, and TNF-α [5, 6]. Significant reduction in total serum IGF-I ($\mathbf{\Delta}_{\text{IGF-I}}$: - 11.2 ± 2.3%, P<0.002), bound IGF-I ($\mathbf{\Delta}_{\text{IGF-I}}$ bound: - 11.2 ± 2.4%, P<0.002), and insulin (ΔInsulin: - 42 ± 10%, P<0.037) have been reported in male adolescents, aged between 14 and 18.5 years, following a typical training session of wrestling [5]. Increases in IL-6 ($\mathbf{\Delta}_{\text{IL-6}}$: + 795 ± 156%, P<0.0005), TNFα ($\mathbf{\Delta}_{\text{TNF-}\alpha}$: + 30 ± 12%, P<0.05), and IL-1β ($\mathbf{\Delta}_{\text{IL-1}\beta}$: + 286 ± 129%, P<0.034) were also observed; as well as increases in IGFBP-1, a binding protein that is often associated with reduction in IGF-I bioactivity. According to Nemet et al [5], these data demonstrate that an intense exercise set of wrestling in young athletes led to a reduction in anabolic mediators and a great increase in cytokine levels, resulting in a predominantly catabolic response. To these authors, the effects of these alterations on growth/development of adolescents are not yet fully understood.

Additionally, Nemet et al [6] analysed the effects of a water polo training session on GH/IGF-I axis, cytokines levels, and immunological function in adolescent girls. The sport was chosen due to its high physical demand, intermittent characteristics, and high popularity amongst American high school girls. In summary, the study demonstrated that a typical water polo training session led to substantial changes in some growth mediators, cytokines, and cellular components of the immune system. The reduction in insulin levels and the high increase in IL-6 and IGFBP-1 levels observed are consistent with the hypothesis that acute exercise in female adolescents leads to a predominantly catabolic response. Although the pattern of changes in IGF-I levels observed in female water polo athletes had been quantitatively similar to that observed in the adolescent wrestlers, there was no significant changes in IGF-I levels in this study.

Eliakim et al [16] suggested that exercise associated to high levels of cytokines lead to a reduction in IGF-I levels at the start of a training program (first weeks of training). In order to test the hypothesis that cytokines can affect GH/IGF-I axis behaviour in response to stimuli from training sessions, Scheett et al [15] analysed the effects of a 1h30min football session on pre-pubertal children. Football practice led to a significant increase in circulating TNFα ($\mathbf{\Delta}_{\text{TNF-}\alpha}$: + 18 ± 7%, P<0.05) and IL-6 ($\mathbf{\Delta}_{\text{IL-6}}$: + 125 ± 35%, P<0.05). IGF-I levels decreased to a lesser degree ($\mathbf{\Delta}_{\text{IGF-I}}$: -6.4 ± 3.2%, P<0.05) and IGFBP-1 levels increased markedly ($\mathbf{\Delta}_{\text{IGFBP-1}}$: 156 ± 40%, P<0.001). To the authors, the increase in circulating cytokine levels triggered by the training sessions can significantly alter IGF-I bioactivity by affecting its concentration and that of its binding proteins.

A close correlation exists between cytokine levels, especially IL-6, and the intensity and duration of exercise (i.e. the greater the duration and intensity of exercise, the greater the circulating levels of cytokines) [18, 19], as demonstrated by Pedersen [18], who reported that IL-6 levels increase up to 100 times in runners after a marathon. According to Bruunsgaard et al

[20], the highest levels of cytokines can be seen at the eccentric phase of the movement and there is a strong correlation (r = 0.725) between plasma IL-6 and creatine kinase (CK) enzyme levels. However, increases in circulating cytokines are not only related to muscle damage or repair (adaptive microtrauma) [18, 20]. According to Steinacker, Reissnecker, and Liu [20], muscle glycogen content influences the extent of IL-6 release during exercise. When glycogen stock is close to being depleted, glycogenolysis is reduced, glucose transporters are down-regulated in the muscle and liver, and there is a reduction in IGF-I production. Furthermore, transitory insulin resistance develops during exercise under glycogen depletion conditions [21]. Therefore, Steinacker, Reissnecker, and Liu [20] believe that glycogen deficiency is associated with increases in local cytokine expression (IL-6 in muscles), reduction in glucose transporters, increase in cortisol, reduction in insulin secretion, and β adrenergic stimulation; and that cytokines act as indicators to the hypothalamus, which in turn acts on the release of GH and thus leads to a reduction in IGF-I levels.

By analysing the effects of a Taekwondo fight simulation (three 6min fights with 30min interval in between) on serum concentrations of IGF-I, LH, FSH, testosterone (considered anabolic hormones) and cortisol (catabolic) in adolescent fighters from the national sport elite (10 boys and 10 girls aged between 12 and 17 years), it could be observed a significant (P<0.05) reduction in IGF-I levels ($\Delta_{\text{IGF-I masculine}}$: – 27.1 ± 25.6; $\Delta_{\text{IGF-I feminine}}$: – 22.4 ± 36.3ng/ml), LH ($\Delta_{\text{LH masculine}}$: - 0.7 ± 1.2; $\Delta_{\text{LH feminine}}$: - 2.3 ± 3.3 U/L), and FSH ($\Delta_{\text{FSH masculine}}$: - 0.9 ± 0.5; $\Delta_{\text{FSH feminine}}$: - 1.5 ± 1.1 U/L) associated to a significant (P<0.05) increase in cortisol levels ($\Delta_{\text{Cortisol masculine}}$: - 141.9 ± 30.1; $\Delta_{\text{Cortisol feminine}}$: - 64.1 ± 30.6 µg/dL) in both genders. The fight protocol also significantly reduced (P<0.05) testosterone levels ($\Delta_{\text{Testosterone masculine}}$: - 190 ± 160; $\Delta_{\text{Testosterone feminine}}$: - 20 ± 6 ng/dL) [17]. In summary, the authors conclude that the stimuli from the protocol of Taekwondo fights led to a hormonal response typically catabolic. The authors further state that such hormonal responses may not only affect the muscular system but also other systems (immune, cardiorespiratory) and thus, the hormonal responses analysed in the study can be used as a complimentary tool to improve the training cycles of fighting sports as well as to monitor training load.

Steinacker, Reissnecker, and Liu [20] go as far as to state that the understanding of hormonal and cytokine function and of the regulatory effect the muscular system can have during exercise practice will be fundamental for better understanding of the complex adaptation mechanism of the body to exercise and physical training.

Contrary to studies that have reported GH/IGF-I axis suppression after a training session, Tourinho et al. [22], in a study with nine Jiu-Jitsu fighters from the Brazilian sport elite, observed no significant reduction in IGF-I levels. Blood samples were collected in the beginning and at the end of a training session composed by a warm up, a main part divided between the improvement of techniques (20min), and a sequence composed of six Brazilian Jiu-Jitsu fights (total of 45 minutes of effort). An acute elevation in plasma CK activity was recorded but no changes in LDH, IGF-I, and IGFBP3 concentrations were observed. The ab¬sence of a reduction in IGF-I and IGFBP-3 levels in the second measurement in this study was probably due to the training status of the Jiu-Jitsu fighters, who were in their maximum level of perfor¬mance in the season. These authors also suggest that the responses of GH/ IGF-I axis components to exercise can be used as training status mark¬ers in fighting sports.

Chronic effects of exercise on the GH/IGF-I axis

Some authors have speculated whether the GH/IGF-I axis could have a two phases behaviour during a training season – one catabolic phase, which would occur at the first 3 to 5 weeks of training; and another anabolic, which could be seen at 5 to 6 weeks from the start of the training [7, 8, 13, 23]. Eliakim et al. [13] suggested that the catabolic phase was accompanied by a reduction in GHBP levels, a GH binding protein that can reflect the levels of GH receptor (GHR), followed by an anabolic adjustment of the GH/IGF-I axis after 5 weeks based on the nutritional state and energy balance of each athlete. This behaviour has been hypothesized in the literature by several authors as a "two phases theory" [7, 8, 13, 14, 23].

Increases in IGF-I levels after a longer training period (4 to 9 weeks) was supported by animal model studies, which showed increase in IGF-I gene expression in the skeletal muscle [24] and in circulating IGF-I [25]. However, it remained unclear whether the changes in GH/IGF-I axis behaviour, from a catabolic to an anabolic phase, also occurred in humans subjected to prolonged training periods [23].

In order to demonstrate the biphasic behaviour of the GH/IGF-I axis (two phases theory), Tourinho Filho et al. [10] conducted a study with adolescent swimmers during a training season. These authors observed a significant reduction in IGF-I levels during the intensive phase and an increase in these levels at the tapering phase. Thus, it was possible to observe for the first time, IGF-I catabolic and an anabolic phases in humans during a training season. Increases in serum IGF-I and IGFBP-3 concentrations coincided with increases in Peak and Average Force at the tapering phase, even though this was not accompanied by an increase in lean body mass. These findings indicate that tapering is often used when trying to achieve the best athletic performances in the training season, in preparation for the main competitions of the year.

The effects of four weeks of training on the aptitude, self-evaluation of physical condition, and circulating IGF-I levels were determined in elite Israeli handball players during training for the Junior World Handball Championship. The program consisted of two weeks of intense training followed by two weeks of lighter training (tapering). Circulating IGF-I reduced significantly after the two first weeks of training and returned to basal level after the four weeks of training [26].

In order to study the effects of a football-training program on GH and IGF-I levels, Mejri et al. [27] evaluated 13 young football players (19 ± 1 years) using a submaximal test on a cycle ergometer at the beginning, middle, and end of the training season; which extended from October to May. Data analysis revealed that GH levels increased with exercise during the submaximal test. However, significant responses were greater at the start rather than at the middle and end of the season, differently from the results reported by Tourinho Filho et al. [10] in adolescent swimmers. In the study by Mejri et al. [27], it was not possible to test the "two phases theory" regarding GH/IGF-I axis behaviour.

Tourinho et al. [28] evaluated eleven male adolescent players, aged between 14 and 15 years, throughout a 7-month football-training season and observed that IGF-I showed biphasic behaviour during the championship. Serum GH, IGF-I, and IGFBP-3 concentrations were determined before and after standardized training sessions (STS) at different stages of the 7-month championship: initial, middle (4^{th} month), and final phase (7^{th} month). The catabolic phase was characterized by a reduction in IGF-I levels after STS at the final phase (461±95 vs. 429±87; P=0.04), while the anabolic phase was marked by an increase in IGF-I levels after STS at the middle phase (460±68 vs. 519±115; P=0.05). IGFBP-3 levels were significantly higher, both before (4.9±1.0 vs. 4.6±1.0 mg/l; P=0.03) and after STS (5.5±1.7 vs. 4.5±0.8 mg/l; P=0.04), in the middle than in the final phase.

Eliakim et al. [26], Mejri et al. [27] (2005), Tourinho Filho et al [28], and Tourinho Filho et al [10] all reported increases in GH/IGF-I levels, even if at different times of the training season; however, Eliakim et al. [13] and Rosendal et al. [23] observed a negative effect on circulating IGF-I. According to these studies, the effects of intense training on IGF-I differ between trained and untrained individuals, with more pronounced changes in IGF-I levels present in non-trained individuals subjected to intense training.

Eliakim et al. [13], to test whether physical activity increased IGF-I levels, followed 38 adolescents who were randomly distributed into control and trained groups, with the later performing activities for 5 weeks. Thigh muscle volume was measured before and after intervention by magnetic resonance and serum GH, GHBP, IGF-I, and IGFBPs 1-5 recorded. Trained individuals showed a significant increase in thigh volume, greater energy expenditure when compared to controls, and no evidence of weight loss. In contrast, trained individuals showed a significant decrease in IGF-I (Δ_{IGF-I}: - 12 ± 4%, P<0.005). The training program significantly reduced GHBP (Δ_{GHBP}: - 21 ± 4%, P< 0.005) and increased IGFBP-2 levels ($\Delta_{IGFBP-2}$: + 40 ± 16%, P< 0.008). According to the authors, the 5-week training program increased muscle mass in the adolescents and, surprisingly, influenced not only IGF-I levels but also GHBP and IGFBP-2 in a manner typically seen at the catabolic stage [13]. The mechanism that surrounds this process seem paradoxical, for at the same time that a fall in circulating GH and IGF-I reflect a catabolic state, it is possible to observe increases in muscular mass as well as improvement in the cardiorespiratory condition of individuals.

In a study that evaluated trained (n = 12) and untrained youngsters (n = 7) that were subjected to the same intense 11-week physical training program, it was hypothesized that any potential changes in IGF-I levels would be more pronounced in untrained individuals due to their lower physical capacity [23]. The data obtained confirmed the hypothesis, as the intense training program resulted in a marked influence on the IGF-I system and its binding proteins, with greater changes being observed in the group of untrained youngsters. These results indicate that intense training affects the behaviour of the GH/IGF-I axis of trained and untrained individuals differently. In both groups, total IGF-I levels were significantly reduced, especially after four weeks of training (samples were collected at the start, four weeks, and at the end of the 11-week intense training). Although the study identifies a state typically catabolic in both groups, it was also possible to observe a significant increase in VO2peak in untrained individuals while no change was detected in trained youngsters.

According to Rosendal et al. [23], the presence of a significant reduction in circulating IGF-I levels does not exclude the possibility of increased IGF-I levels in tissues, and that an autocrine/paracrine action could take place and thus explain the improvement of VO2peak observed in one of the groups; or that an increased number of IGF-I receptors (or altered sensitivity) could be responsible for the more pronounced local anabolic response.

The cause of the reduction in IGF-I levels during periods of intense training and what should be an adequate elevation of this hormone during the tapering phase and reduced training remains controversial. However, it is believed that the inability to increase circulating IGF-I levels before an important competition must be seen as red flag for athletes and coaches, as it could indicate that the athlete is not at its best athletic state [14]. Furthermore, according to Eliakim and Nemet [14], sampling and recording of basal levels and changes in GH/IGF-I axis behaviour for comparison with responses obtained in previous seasons and with the knowledge and experience of previous successes can be an important parameter in the preparation of young athletes.

The use of IGF-IGFBPs system as biomarkers of training status is supported by a review by Nindl and Pierce [29], in which there is scientific evidence that IGF-I is an important metabolic biomarker associated with a variety of health and exercise-related outcomes.

Thus, it can be suggested that these components of the GH/IGF-I axis may be used as important markers of the training condition of young athletes during their preparation throughout a season.

Conclusions

Even though GH/IGF-I axis has been well studied, several of its physiological aspects are yet to be fully understood, including its relationship with physical exercise.

In children and adolescents, the combination of fast growth and development, high levels of physical activity, and spontaneous increase of anabolic hormones related to puberty (GH, IGF-I, and sex steroids) suggest integrated mechanisms linking exercise to several anabolic/catabolic responses that must be better understood.

Bearing in mind the relationship between training status and physical activity and stimulation or inhibition of the GH/IGF-I axis, which in turn could affect both anabolic or catabolic state in children and adolescents exposed to physical exercise programs, it is preconized that evaluation of changes in IGF-I and its binding proteins are of great interest, as the behaviour of these variables can:

a) directly interfere with the performance of young athletes,

b)and their growth and development process, and

c)Very likely reflects the state of training overload in which young athletes finds themselves at specific times of their preparation, and can be used as sensitive markers of overtraining and nutritional status.

In summary, recent studies have contributed to a substantial progress in the filed of exercise endocrinology. Furthermore, changes in anabolic/catabolic balance and inflammatory mediators, followed by different types of training sessions and programs at different times in the season, can aid coaches and athletes in planning of training to better improve performance and health indexes.

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