Review article

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Interval training and the GH-IGF-I axis – a new look into an old training regimen

Abstract: Interval training is a commonly used training method known to improve both aerobic and anaerobic capabilities, and is one of the popular techniques used in training young athletes engaged in both anaerobic- and aerobic-type sports. This occurs although anaerobic glycolytic capacity is less efficient in the child and becomes increasingly more effective with age. The endocrine system, by modulation of anabolic and catabolic processes, plays a major role in the physiological adaptation to exercise training. In recent years, changes in circulating components of the growth hormone-insulin-like growth factor-1 axis, a system of growth mediators that control somatic and tissue growth, have been used to quantify the effects of training. Interestingly, exercise is also associated with remarkable changes in inflammatory cytokines, and the exercise-related response of these markers can also be used to gauge exercise load. The balance between these two seemingly antagonistic systems is believed to determine the effects of exercise. This review will summarize current knowledge on the balance of anabolic hormones and inflammatory mediators following anaerobic, interval exercise and training and its implication to young athletes.

Keywords: anabolic; exercise; growth hormone; interval training.

Introduction

Training efficiency depends on the intensity, volume, duration, and frequency of exercise as well as on the athlete’s ability to tolerate it. An imbalance between the training load and the individual’s tolerability may lead to under- or overtraining. As a consequence, many efforts are made to develop objective measures to quantify the fine balance between training load and the athlete’s tolerance. The endocrine system, by modulation of anabolic and catabolic processes, plays a major role in the physiological adaptation to exercise training (1). Changes in the testosterone/cortisol ratio, as an indicator of the anabolic-catabolic balance, have been used for many years, to try and determine the physiological strain of training, with very limited success (2). Therefore, in recent years, changes in circulating components of the growth hormone-insulin-like growth factor-1 (GH-IGF-I) axis, a system of growth mediators that control somatic and tissue growth (3), have been used to quantify the effects of training (4). Interestingly, exercise is also associated with remarkable changes in inflammatory cytokines, and the exercise-related response of these markers can also be used to gauge exercise load (5–7). Therefore, it was suggested that the evaluation of changes in these antagonistic, anabolic, and catabolic circulating mediators, and the balance between them, may assist in gauging the effects of different types of single exercise bouts as well as the effects of exercise training and recovery modalities.

The effect of exercise on the GH-IGF-I axis was studied mainly during aerobic and resistance training. In recent years, several studies have suggested that anaerobic-type training also affects the GH-IGF-I axis. This review will summarize the known effects of anaerobic exercise, particularly interval training, on components of the GH-IGF-I axis, with an emphasis on the unique relations between the exercise-related anabolic response and exercise-associated change in inflammatory mediators. In addition, we will try to demonstrate how these interval training-induced changes may be used by young elite athletes and their coaches to evaluate the training load during different types of interval...
trainings, and the recovery from such training, throughout the competitive season in a “real life” setting.

**Interval training**

Interval training is a method that involves a repeated series of exercise work bouts interspersed with rest periods. This training method is popular among athletes, as it allows them to exercise at a higher relative intensity during the work interval than that possible with a longer-duration, continuous training. Interval training programs can also be designed to improve speed and anaerobic endurance, as well as aerobic endurance, simply by modifying the exercise intensity and the length of the work and rest intervals (8, 9). Interval training is one of the popular techniques used in training young athletes engaged in both anaerobic- and aerobic-type sports. This occurs despite evidence from changes in glycolytic enzyme activity and lactate production during exercise indicating that anaerobic glycolytic capacity becomes more effective with age (10). Studies have shown that the glycolytic enzyme activity of phosphofructokinase, pyruvate kinase, and lactate dehydrogenase increase by 30%–60% between ages 4 and 18 years (11, 12). Lower concentrations of blood lactate are found in children compared with adults at all levels of exercise intensity. There is an increase of about 50% in lactate level between ages 4 and 16 years following maximal exercise, resembling the increase in glycolytic enzyme activity. The exercise-induced maximal lactate increase occurs uniformly during the childhood years, suggesting that this difference between children and adults is not related to pubertal hormonal changes (13).

The intensity of interval training depends on the running distance (sprint vs. long-distance repetitions), running speed (expressed as percentage of maximal speed), number of repetitions, and length of the rest interval between runs. In addition, coaches and athletes very often change the style of the interval training and use constant running distances (e.g., 6×200 m), increasing-distance interval session (e.g., 100-200-300-400 m), decreasing-distance interval session (e.g., 400-300-200-100 m), or different combinations of increasing-/decreasing-distance interval session (e.g., 100-200-300-200-100 m). While the overall distance may even be similar, these modifications may involve different physiological demands and impose different stress levels on the exercising young athlete. For example, in the increasing-distance protocol, metabolic demands (e.g., lactate levels) increase gradually and are highest toward the end of the session, while in the decreasing-distance protocol the metabolic demands are higher from the beginning of the session (14).

**GH-IGF-I axis**

The GH-IGF-I axis is composed of hormones, growth factors, binding proteins (BPs), and receptors that regulate essential life processes, such as growth and development, reparative processes, and aging, and also plays an important role in the adaptation to exercise training. Understanding of the axis must consider both its individual components and the interaction between them, under physiologic as well as pathological conditions.

The axis starts at the hypothalamus, which synthesizes GH-releasing hormone (GHRH), known to stimulate the anterior pituitary to synthesize GH, and somatostatin, which inhibits GH secretion. GH is the major product of the axis. One of the most important functions of GH is the stimulation of hepatic IGF-I synthesis. However, some effects of GH on metabolism, body composition, and tissue differentiation are IGF-I independent. Tissue GH bioactivity stems from an interaction between GH and its receptor. The GH receptor is composed of intra- and extracellular trans-membrane domains. The extracellular domain is identical in structure to GH binding protein (GHBp) (15). Thus, uniquely, GH receptor number and activity can be determined by measurements of circulating GHBp levels.

IGF-I, one of the insulin-related peptides, can act as a hormone, and its effects are GH dependent; however, the majority of its actions occur owing to paracrine or autocrine secretion and regulation, which are only partially GH dependent. IGF-I is responsible for most, but not all, anabolic and growth-related effects of GH. IGF-I inhibits GH by a negative feedback mechanism (16).

The bulk of circulating IGF-I is bound to several IGFBPs. The most important circulating BP is IGFBP-3, which is synthesized mainly in the liver. When bound to IGF-I, the IGBP complexes with an acid-labile subunit to form a circulating ternary complex that carries most of the IGF-I in the serum. Some IGFBPs are GH dependent (e.g., IGFBP-3); however, others, such as IGFBP-1 and IGFBP-2 are insulin dependent (being high when insulin level is low and vice versa). The interaction between IGF-I and its BPs is even more complicated as some BPs stimulate (e.g., IGFBP-5), while others inhibit (e.g., IGFBP-4), IGF-I anabolic effects (17).

Some hormones in the GH-IGF-I axis (i.e., GH) have a pulsatile secretion pattern, and this pulsatility is significantly important for accelerated growth rate (18). In contrast, IGF-I and IGFBP levels are relatively stable throughout the day.

Several components of the axis are age dependent. GHRH, GH, GHBp, IGF-I, and IGFBP-3 reach their peak circulating levels during puberty (19), and decrease with aging (20). These changes are partially sex hormone
mediated. Nutritional state also has a remarkable influence on the GH-IGF-I axis. For example, fasting and malnutrition increase GH secretion; however, despite elevated GH, IGF-I levels are reduced owing to the lower level of GH receptors (21). In contrast, obesity reduces GH secretion (22). All these factors must be taken into account when studying the effect of exercise on the GH-IGF-I axis.

**Anaerobic exercise**

The effect of aerobic exercise on the GH-IGF-I axis was studied extensively (4). In recent years, major progress in the understanding of the effects of anaerobic exercise on the GH-IGF-I axis has occurred. This may be particularly important not only for young athletes but also for the non-athletic children, as spontaneous physical activity in this age is characterized by brief, often intense exercise bursts. Stokes et al. (23) were the first to study the effect of a single supra-maximal 30-s sprint on a cycle ergometer against different levels of resistance. They found that the increase in GH levels was significantly greater when resistance was 7% (faster cycling) and not 9% (slower cycling) of body mass. Consistent with this, Headley et al. (24) demonstrated that faster weight lifting was associated with more total work and higher IGF-I levels. The possible implication for athletes is that lower levels of resistance and faster anaerobic efforts may better stimulate the GH-IGF-I axis, and are thus preferred by coaches and athletes.

Interval training is one of the most frequent training methods used in anaerobic- and aerobic-type sports (8). Recently, we were the first to demonstrate a significant increase in GH and IL-6 levels following a typical constant-distance (4×250 m) interval training in young male handball players (7). Consistent with previous findings in aerobic exercise, changes in the GH-IGF-I axis following the brief sprint interval exercise suggested exercise-related anabolic adaptations. The increase in IL-6 probably indicates its important role in muscle tissue repair following anaerobic exercise. We suggested that changes in the anabolic/catabolic/inflammatory balance can be used as an objective tool to gauge the training intensity of different types of anaerobic exercises and training periods as well.

The interval training had no effect on circulating IGF-I levels. IGF-I plays a central role in the exercise-induced muscle adaptation (25, 26). Previous reports suggested that very short supra-maximal exercise efforts (e.g., 90 s) (27) lead to increases in IGF-I levels. Therefore, it is possible that increases of IGF-I following anaerobic exercise depend on exercise intensity.

The interval training was associated with an increase in IGFBP-3, known to stimulate IGF activity, and with a decrease in IGFBP-1, known to inhibit IGF effects, supporting an anabolic effect of the interval training as well. Moreover, the results support the notion that exercise-related effects on IGF-I may not be mediated only by alteration in IGF-I levels per se, but also rather by the effect on its BPs. The mechanism for the increase in IGFBP-3 following the interval training session was not clear. Although IGFBP-3 synthesis is GH dependent, both GH and IGFBP-3 peaked at the same time (immediately after the fourth 250-m run), indicating that a GH-mediated increase of IGFBP-3 is unlikely (Figure 1). We speculate that the increase in IGFBP-3 resulted from a release from more available vascular marginal pools, or owing to an increase of the proteolytic activity of IGFBPs (5, 28).

![Figure 1](image-url)
As mentioned earlier, the interval session was associated with an increase in IL-6 levels, and levels remained significantly elevated 1 h after the end of the exercise (Figure 1). However, there was no significant change in other pro- and anti-inflammatory markers, such as IL-1β, IL-1ra, and IL-10. Previous studies found increases in IL-6, IL-1β, and IL-1ra following intense prolonged endurance-type exercise sessions (5, 29, 30). Therefore, our finding of an increase of only IL-6 following anaerobic-type exercise suggests, probably, that IL-6 is the most sensitive inflammatory cytokine to exercise, or that anaerobic exercise may lead to a different hormonal catabolic environment. IL-6 is believed to play an important mediatory role in the inflammatory response needed for the exercise-associated muscle damage repair (31, 32). This may explain why in the present study, levels of IL-6 remained elevated during the recovery period from the anaerobic-type exercise as well. It was previously demonstrated that IL-6 may alter IGF-I activity through a variety of mechanisms, including direct inhibition of IGF-I production (33). Thus, it is possible that the prolonged exercise-related increase in IL-6 prevented an increase in IGF-I following the sprint interval exercise.

More recently, we also evaluated the effect of increasing-distance (100-200-300-400 m) and decreasing-distance (400-300-200-100 m) sprint interval training protocols, two other common types of sprint interval training, on the balance between anabolic, catabolic, and inflammatory mediators in young handball players (14). Running speed (80% of maximal speed based on 100 m running times) and resting times between runs were similar in both sessions. Both types of sprint interval trainings led to a significant increase in lactate and the anabolic factors GH and IGF-I. Both types of sprint interval sessions led to a significant increase in the circulating pro- and anti-inflammatory mediators IL-1, IL-6, and IL-1ra. Interestingly, the lactate and GH area under the curve was significantly greater in the decreasing-distance session. Thus, despite similar running distance, running speed, and total resting period in the two interval training sessions, the decreasing-distance interval was associated with a greater metabolic (lactate) and anabolic (GH) response (GH and IL-6 shown in Figure 2). In contrast, the rate of perceived exertion (RPE) was higher in the increasing-distance session. The fact that metabolic and anabolic responses were not accompanied by an increase in RPE suggests that physiological and psychological responses to interval training do not necessarily correlate. When the athletes were asked to explain why the increasing-distance training protocol was perceived as more intense, they replied that the fact that the longest and hardest run (400 m) was only at the end of the session was very difficult to tolerate. Coaches and athletes should be aware of these differences, and as a consequence, of the need for specific recovery adaptations after the different types of interval training sessions. Differences in physiological and psychological responses to competitive sport training, and their influence on the training course and recovery process and final performance, should also be addressed.

Recently, a similar significant concurrent increase of GH and IL-6 was also demonstrated following a typical 1-h volleyball practice in adolescent male and female elite volleyball players (34). The main part of the typical practice consisted of an interval-like session including seven consecutive sprints from the back of the volleyball court to the net, maximal jump, and a hit of the volleyball over the net at the end of each sprint. Each repetition lasted about 1.5 min with 1-min rest (to collect the balls) between repetitions. The results suggest that anabolic and inflammatory changes may serve as an objective, quantitative tool to monitor training intensity in team sports with anaerobic characteristics as well.

Finally, in contrast to the observation that both aerobic and anaerobic exercise require a high metabolic demand in order to stimulate GH secretion, we previously demonstrated a small but significant GH response to an exercise input that was perceived as difficult by the participants (i.e., 10 min of unilateral wrist flexion; a small and relatively unused muscle group), but had no effect on heart rate or circulating lactate levels (35, 36). This suggests that factors, such as the individual’s perceived
exertion and associated psychological stress play an important role in the activation of the hypothalamic-pituitary axis and GH release even in exercise protocols involving relatively small muscle groups.

The concomitant antagonistic exercise response (anabolic and inflammatory mediators) probably emphasizes the importance of optimal adaptation to the stimulation of exercise. The very fine balance between the anabolic and inflammatory/catabolic response to exercise will determine the effectiveness of exercise training and the health consequences of exercise. If the anabolic response dominates, exercise will probably ultimately lead to increased muscle mass and improved fitness. A dominant catabolic response, especially if it persists for a long duration, may lead to overtraining. Therefore, changes in the anabolic-catabolic hormonal balance and in circulating inflammatory cytokines can be used by athletes and/or their coaches to gauge the training intensity in individual and team sports. The response of these mediators to different types of sports, training sessions, or training protocols can be used as an objective tool to monitor the training load and to better plan training cycles throughout the competitive season (Figure 3).

The development of methods to enhance the recovery of elite athletes from intense training and/or competition has been a major target of athletes and their accompanying staff for many years. Recently, it was shown that bicarbonate supplementation before high-intensity interval training attenuated the GH response (37). The authors suggested that acidosis increases the GH response to interval training, and that these findings might be relevant to the selection of active or passive recovery. While active recovery between intervals improves lactate clearance, reduces acidosis, and allows longer training, its effect may attenuate the GH response to training. Therefore, this information has to be accounted for by the athletes and coaches when planning interval training.

Cryotherapy is used widely to treat sports-associated traumatic injuries and as a recovery modality following training and competition that may cause some level of traumatic muscle injury (38, 39). However, evidence about the effectiveness, and appropriate guidelines for the use of cryotherapy are limited. Recently, we evaluated the effect of cold-ice-pack application following a brief sprint interval training on the balance between anabolic, catabolic, and circulating pro- and anti-inflammatory cytokines in 12 male elite junior handball players (40). The interval practice (4×250 m) was associated with a significant increase in GH and IL-6 levels. Local cold-pack application was associated with significant decreases in the anabolic hormones IGF-I and IGFBP-3 during the recovery from exercise (Figure 4), supporting some clinical evidence for possible negative effects on athletic performance. These results, along with the previously reported evidence for some
negative effects of ice application on athletic performance, and no clear effect on muscle damage or delayed onset muscle soreness, may suggest that the use of cold packs should probably be reserved for traumatic injuries or used in combination with active recovery and not with complete rest. However, this is an example of how exercise-induced changes in the GH-IGF-I axis and inflammatory markers may fit into the puzzle of optimizing competitive training. Further studies are needed to explore the beneficial use of the measurement of anabolic, catabolic, and inflammatory markers in many other aspects of recovery from exercise.

Lastly, several studies suggested that the timing of nutritional supplementation may affect the training-associated response of the GH-IGF-I axis in aerobic training (25). The effect of nutrition on the GH-IGF-I response to interval training is understudied. A combination of post-exercise essential amino acid and carbohydrate supplementation (compared with carbohydrate only or placebo) during 3 weeks of high-intensity interval training was accompanied by significant increases in free IGF-I (41), suggesting a potential role for this supplementation in improving athletic performance.

In summary, anaerobic glycolytic capacity becomes increasingly more effective with age (13). Despite that, anaerobic training, and in particularly interval training, is very common among children engaged in sports. Recent advancements in sports endocrinology indicate that changes in the balance of anabolic hormones and inflammatory mediators following aerobic, and as demonstrated in the present review also following anaerobic, exercise and training, may help young athletes and their coaches in developing an “optimal” training program. This is particularly important for adolescent athletes, due to the unique combination of rapid growth, high levels of physical activity, and the natural puberty-related increase in anabolic hormones (GH, IGF-I, and sex steroids) that suggests a possible integrated mechanism linking exercise with anabolic responses. However, unsupervised participation of athletes at this age in intense competitive training, especially if associated with inadequate caloric intake, may attenuate growth potential (42).

Thus, further studies are needed to clarify the complex relation between hormonal response, nutritional supplementation, different types and phases of anaerobic training, and optimal performance in competitive sports.

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References


