Review

Growth hormone and connective tissue in exercise

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Over the last few years, growth hormone (GH) has become increasingly popular as doping within different sports. However, the precise mechanisms behind the ergogenic (performance enhancing) effects of GH in athletes are still being debated. Besides a well-documented stimulatory effect of GH on carbohydrate and fatty acid metabolism, and a possible anabolic effect on myofibrillar muscle protein, we suggest a role for GH as an anabolic agent in connective tissue in human skeletal muscle and tendon. Given the importance of the connective tissue for the function of skeletal muscle and tendon, a strengthening effect of GH on connective tissue could fit with the ergogenic effect of GH experienced by athletes.

This review examines the endogenous secretion of GH and its mediators in relation to exercise. Furthermore, we consider the effect of endogenous GH and administered recombinant human GH (rhGH) on both myofibrillar and connective tissue protein synthesis, thus offering an alternative explanation for the ergogenic effect of GH. Finally, we suggest a possible therapeutic role for rhGH in clinical management of the frequently suffered injuries in the connective tissue.

The last year’s news media coverage of the abuse of growth hormone (GH) by professional athletes, and of the arrests of athletes possessing GH, has brought full attention onto GH-doping as an increasing problem in professional sports. Furthermore, several anecdotal reports from track and field athletes (Brandt, 2000), bodybuilders (Dickerman et al., 2000), baseball and American football players (Smith, 1991; Verducci, 2002) and even high school students (Rickert et al., 1992) suggests a widespread abuse of GH, from amateurs to professionals, within a range of different sports.

Because of the nature of endogenous GH secretion during exercise (Wallace et al., 2000a) and stress (Armanini et al., 2002) and because of the amino acid sequence identity between the majority of endogenous GH and exogenous recombinant human GH (rhGH), it is a challenge to document use of rhGH (Wallace et al., 1999, 2001a; Ehrnborg et al., 2003), and currently no valid test for proofing rhGH-doping is available. This fact and a general agreement in athletic communities that GH possesses powerful ergogenic (i.e. performance enhancing) effects, presumably make GH the “drug of choice” for many athletes. This raises the obvious question of whether there is scientific evidence for effects of GH on the human body that can explain its postulated ergogenic effect.

Besides the well-documented stimulatory effect of GH on carbohydrate (Rosenfalck et al., 2000; Lange et al., 2002b) and fatty acid metabolism (Lange et al., 2001a, 2002b) and a possible muscle anabolic effect (Fryburg et al., 1991; Fryburg & Barrett, 1993; Welle et al., 1996), a role for GH as an anabolic agent in connective tissue in human skeletal muscle and tendon is suggested (Verducci, 2002; Rennie, 2003).

The major role of connective tissue in muscle and tendon is to provide a matrix for transmission of force from individual muscle fibers to the bone. Thus, a strengthened connective tissue would give a stronger and more strain-resistant muscle and tendon and this could, in part, fit with the claimed effect of rhGH on athletic performance. Furthermore, an anabolic effect of rhGH in connective tissue could also suggest a potential for rhGH in treatment of muscle and tendon injuries, which are common problems in many sports.

The following review will focus on exercise-induced secretion of GH (and mediators of GH actions) and effects of GH/rhGH in muscle and tendon connective tissue during exercise, and thus offer an alternative explanation for the popularity of rhGH-doping, and evaluate the potential for the use of rhGH-supplementation in treatment of sport injuries.

Exercise, GH and connective tissue

Collagen is an important strength-carrying part of the connective tissue i.e. extracellular matrix (ECM)
and influences the function of the muscle–tendon unit, which is constantly challenged during athletic performance. Exercise has been shown to stimulate collagen synthesis in the ECM (Langberg et al., 1999; Miller et al., 2004) and although the precise mechanisms regulating the increase in synthesis during exercise are not accounted for, it is based on in vitro data indicating very likely that the GH/insulin-like growth factor-I (IGF-I) axis plays an important role in the regulation of collagen metabolism (Abrahamsen et al., 1991a, b; Banes et al., 1995).

A more complicated model of GH-endocrinology has, over the last few years, replaced the traditional concept of a top–down GH/IGF-I system with GH at the apex. GH has been shown to have powerful, IGF-I-independent effects on peripheral tissues (Izumi et al., 1995; Waters et al., 1999), and furthermore GH production is also found in extra pituitary tissues with possible paracrine and autocrine effects (Waters et al., 1999). Also, the different IGF-I isoforms identified are now divided into two main groups. Class-1 isoforms, which are produced locally in muscle and tendon tissue and presumably act in an autocrine–paracrine manner, and class-2 isoforms, produced in hepatocytes with systemic actions on myocytes and fibroblasts (Harridge, 2003; Hameed et al., 2004). Finally, the peripheral actions of IGF-I will be regulated via coupling of IGF-I, IGF-binding protein-3 (IGFBP-3) and acid-labile subunit (ALS) into a ternary complex, in a mechanism only partly understood, and this fact adds further complexity to the system (Baxter, 1994; Laursen et al., 2000; Borst et al., 2001).

However, pulsatile endogenous GH secretion from somatotrophs in the pituitary gland and concomitant elevation of IGF-I concentrations in target tissues are closely associated with exercise and is believed to stimulate fibroblasts to synthesize collagen (Ehrnborg et al., 2003).

**GH and IGF-1 axis during exercise**

Pituitary GH secretion and plasma concentrations of IGF-I ternary complex are affected by several interacting physiological and endocrinological factors. Exercise is one of the most potent physiological stimulators of pulsatile GH secretion (Weltman et al., 1992; Pritzlaff et al., 1999) and thus increases the concentration of IGF-I and its binding proteins (Wallace et al., 1999; Ehrnborg et al., 2003). Factors such as the training status and age of the individual, duration and peak intensity of the exercise bout and the total workload performed will influence not only the average GH secretion but also the pulsatile pattern of secretion, which is equally important for the GH-regulated secretion of IGF-I (Isgaard et al., 1988; Izquierdo et al., 2001b). Also, vigorous exercise changes the relative serum concentrations of GH-isofoms, with a more pronounced increase in non-22 kDa isoform concentration compared with the 22 kDa isoform (Wallace et al., 2001b). The 20 kDa isoform and other non-22 kDa isoforms have an extended half-life compared with the 22 kDa isoform, and it is suggested that vigorous exercise increases the bioactivity of GH by a change in the concentration of different GH isoforms (Wallace et al., 2001b; Nindl et al., 2003). Therefore, differences in exercise and assay protocols will greatly influence results and conclusions regarding the GH response to exercise.

Exercise has an acute stimulatory effect on pituitary GH secretion both in trained athletes (Kjaer et al., 1988; Wallace et al., 1999; Ehrnborg et al., 2003) and in recreationally active persons (Kjaer et al., 1988; Pritzlaff et al., 1999; Wallace et al., 2001a, 2001b). In a study by Ehrnborg et al. (2003), a single maximal exercise bout performed by competitive athletes resulted in a fourfold increase in serum concentrations of total GH and 22 kDa GH isoform. In active men, an increase in levels of both 22 kDa GH and in total GH following vigorous exercise is reported (Wallace et al., 2001a, b), and interestingly, Pritzlaff et al. (1999) report a linear dose–response relationship between exercise intensities and serum level of GH in active male subjects.

Kjaer et al. (1987) investigated the mechanisms responsible for the regulation of GH secretion during exercise in healthy male subjects. By varying both the actual exercise intensity and the perceived exercise intensity (the latter achieved by weakening skeletal muscles by curarization) the authors report that the GH level is closely related to perceived exercise intensity and not to the actual workload carried out (Kjaer et al., 1987). These results lead to the conclusion that GH secretion is regulated via activity in motor centers in the brain (“central command”) that simultaneously stimulate skeletal muscle and endocrine centers (Kjaer et al., 1987).

In an elegant intervention study, Weltman et al. (1992) randomized untrained women to one year of training at either low or high intensity, with a third group of sedentary control subjects. Compared with the sedentary and low-intensity training group, the high-intensity training group exhibited significantly increased plasma GH, with regard to peak height, peak area and 24 h GH concentration, but no changes in the number of GH peaks were observed (Weltman et al., 1992). These results show that training increases plasma GH concentration and suggest that changes in peak GH concentration, rather than changes in the number of GH peaks, are important to target tissues. Taken together, there is a strong positive correlation between vigorous and chronic exercise and the serum level and pulsatile secretion of GH (Fig. 1).
Fig. 1. Twenty-four-hour serum growth hormone (GH) concentration in a subject at baseline and after 1 year of training. GH concentration in an untrained female subject (a), and GH concentration in the subject after 1 year of regular training at high intensity (b), illustrating that endurance training at high intensity amplifies the pulsatile release of GH. Redrawn from (Weltman et al., 1992).

The acute GH response to exercise is blunted in middle-aged and older individuals, and several authors report data suggesting that the training response to exercise in this group is blunted as well (Hakkinen et al., 1998; Kraemer et al., 1999; Izquierdo et al., 2001a). This further suggests that with aging, larger doses of GH may be needed in order to observe similar doping responses as seen in younger individuals.

Several studies have demonstrated increased concentrations of IGF-I, IGFBPs and ALS in relation to exercise (Wallace et al., 1999; Borst et al., 2001; Manetta et al., 2002; Ehrnborg et al., 2003). In a study of 120 competitive athletes, Ehrnborg et al. (2003) found transient increases in circulating IGF-1, IGFBP-2+3 and ALS in response to a maximal exercise test, and interestingly, serum markers of collagen synthesis were also increased with exercise in this study. In 17 trained adult males, similar results are reported, with transient increased serum levels of IGF-I, IGFBP-1+3 and ALS after 30 min of high-intensity exercise (Wallace et al., 1999).

In human and animal studies, resistance training and mechanical overload increase mRNA expression of locally produced class 1 IGF-I isoforms in skeletal muscle (Owino et al., 2001; Hameed et al., 2004). Of the different class 1 IGF-I isoforms identified in skeletal muscle, upregulation of the IGF-IIEc/mechano growth factor (MGF) isoform is positively correlated with mechanical load (Owino et al., 2001; Hameed et al., 2004). A resistance training period of five weeks increased MGF mRNA expression by approximately 200% in a group of elderly men (Hameed et al., 2004). Furthermore, when training was combined with rhGH administration, expression of MGF mRNA increased by approximately 400%, suggesting an additive effect of rhGH and training (Hameed et al., 2004). The other IGF-IIEa isoform examined in this study responded to rhGH administration rather than to exercise, and no additive effect of rhGH and exercise on IGF-IIEa mRNA expression was observed for that isoform, suggesting that different class 1 IGF-I isoforms respond differently to stimuli such as exercise and exogenous rhGH supplementation (Hameed et al., 2004). Despite a more pronounced rise in mRNA for MGF in the trained group receiving rhGH compared with the trained group not receiving rhGH, there was no difference in maximal muscle force and volume between groups (Hameed et al., 2004). This illustrates that the relative importance of systemic and local IGF-I isoforms with respect to exercise, GH-level and muscle function remains to be elucidated.

New perspectives of the physiologic roles of IGFBPs (the IGFBP superfamily) have been introduced, including a more complex regulation of IGF-I bioactivity and IGF-I-independent actions of IGFBPs in cell growth and metabolism (Rosenfeld et al., 1999). Comparing trained and previously untrained individuals, Rosendal et al. (2002) report that prolonged physical training resulted in increased IGFBP-3 proteolysis in previously untrained persons only, suggesting a different training effect on IGFBPs between trained and untrained persons.

Of the several endocrinological factors known to regulate GH secretion, some are influenced by exercise (de Vries et al., 2002, 2003; Kraemer et al., 2004; Schmidt et al., 2004). In healthy male subjects, the effect of exercise on the levels of growth hormone-releasing hormone (GHRH), somatostatin and GH was investigated (de Vries et al., 2002, 2003). It was reported that the elevated GH secretion in response to exercise can partly be explained by an exercise-induced change in plasma levels of GHRH and somatostatin (de Vries et al., 2002, 2003). Growth hormone-releasing protein (ghrelin), on the other hand, does not seem to be involved in GH regulation during exercise, and two studies report that exercise increased GH and IGF-I levels, without having any effect on the level of ghrelin (Kraemer et al., 2004; Schmidt et al., 2004) (Fig. 2).

Effect of rhGH supplementation on myofibrillar muscle protein

The effect of GH on myofibrillar protein anabolism and muscle strength is controversial. The increase in muscle mass and strength argued by rhGH-abusers in athletic and bodybuilding communities and by several researchers is challenged by scientific controlled studies reporting no such effect in healthy individuals. This area has recently been reviewed (Rennie, 2003) and is briefly summarized in the following.

There are several studies reporting a positive correlation between GH supplementation and myo-
fibrillar protein synthesis (Cuneo et al., 1991a, b; Fryburg et al., 1991; Fryburg & Barrett, 1993; Welle et al., 1996, 1998; Lucidi et al., 2000; Mauras et al., 2000). Studies of rhGH administration in GHD children and adults (Cuneo et al., 1991a, b; Lucidi et al., 1998, 2000; Mauras et al., 2000) and studies of GHD and animals not fully grown (Daugaard et al., 1998; Molon-Noblot et al., 1998) uniformly report a significant effect of GH supplementation on muscle growth, strength and performance. Furthermore, in healthy adults and athletes, wholebody measurements of nitrogen balance (Butterfield et al., 1997) and whole-body protein synthesis (Mauras, 1995; Healy et al., 2003) and even specific measurements of muscle protein synthesis (Fryburg et al., 1991; Fryburg & Barrett, 1993; Butterfield et al., 1997), suggest a myofibrillar anabolic effect of GH supplementation. However, increasing GH level in healthy subjects via GH supplementation is not necessarily comparable with a situation in which normalization of GH level is achieved by GH-treatment in GHD. Furthermore, whole-body measurements are obviously not always very conclusive regarding the local myofibrillar protein. The studies measuring local human myofibrillar synthesis as a response to a single GH administration in healthy adult subjects included relatively few subjects and have lately been challenged by large, placebo-controlled studies, examining the effect of long-term GH treatment (Yarasheski et al., 1992; Lange et al., 2002a). In a double-blinded study in which 47 healthy elderly men and women received either placebo or rhGH for a 12-week-period, no difference in muscle strength, muscle power and muscle hypertrophy was observed (Lange et al., 2002a). Moreover, in a study of exercising young men, no effect of GH on muscle protein turnover, limb circumferences and muscle mass was reported (Yarasheski et al., 1992). In agreement with these results, a study including experienced male weight lifters showed no effect of rhGH supplementation on muscle protein synthesis (Yarasheski et al., 1993).

**Growth hormone and connective tissue in exercise**

In *in vitro* studies of collagen tissue indicate that IGF-I plays an important role in promoting collagen synthesis on a cellular level (Abrahamsson et al., 1991a, b; Banes et al., 1995). In avian tendon fibroblasts, IGF-I supplementation led to a dose-dependent increase in DNA synthesis, which is indicative of cell division (Banes et al., 1995). Interestingly, although mechanical load alone did not increase DNA synthesis, IGF-I and mechanical load, increased DNA synthesis synergistically (Banes et al., 1995). Moreover, in rabbit tendon explants the rate of fibroblast cell division and collagen synthesis, determined via incorporation of labeled thymidine and hydroxyproline, respectively, was significantly increased in medium with rh IGF-I vs medium without rhIGF-I (Abrahamsson et al., 1991a, 1991b). Thus, IGF-I promotes collagen synthesis in tendon *in vitro*.

In *in vivo* studies in animals support *in vitro* findings and suggest that GH/IGF-I increases collagen synthesis. Following Achilles tendon transection in rats, treatment with local IGF-I injection resulted in a faster functional recovery compared with controls (Kurtz et al., 1999). Studies of GH-deficient dwarf rats showed a significant increase in collagen turnover in knee tendon and ligaments following 14 days of rhGH supplementation (Kyparos et al., 2002). Moreover, GH injection increased mRNA for IGF-I and collagen in skeletal muscle of dwarf rats (Wilson et al., 1995).

In patients with clinical conditions of altered GH activity, the plasma GH/IGF-I level is associated with pathological changes in connective tissue (Colao et al., 1998, 1999a, b; Baroncelli et al., 2000; Lange et al., 2001b; Scarpa et al., 2004). In acromegalic patients, GH hypersecretion is associated with periarticular soft-tissue hypertrophy and excess cartilage synthesis, causing arthropathy (Colao et al., 1998, 1999b; Scarpa et al., 2004). Suppression of circulating GH and IGF-I levels with somatostatin analogous is standard medical treatment in acromegalic individuals (Colao et al., 1998; Colao et al., 2004). Thus, suppressing the secretion of GH for 6 months in prior untreated acromegalic patients improved articular mobility and significantly decreased periarticular soft-tissue mass and cartilage thickness.
(Colao et al., 1998, 1999b). These findings strongly suggest that increasing of GH level for a period of time, which is often for a period of several years in late diagnosed acromegalic patients (Colao et al., 2004), causes excess connective tissue deposition, which is only partly reversed following 6 months of GH-suppressing treatment (Colao et al., 1998, 1999b).

In growth hormone-deficient (GHD) children and adults, hyposecretion of GH and low IGF-I level in plasma causes a decreased connective tissue deposition compared with healthy counterparts (Colao et al., 1999a; Baroncelli et al., 2000; Lange et al., 2001b). Jensen and colleagues (1991) observed a significant positive correlation between GH supplementation, IGF-I level in plasma, and soft-tissue collagen synthesis in GHD (Jorgensen et al., 1988). Similar results were found in a study, in which GH administration to GHD patients exhibited increased IGF-I, IGFBP and collagen synthesis in soft tissue and this provides further support for this notion (Bollerslev et al., 1996). Thus, decreased connective tissue deposition observed in GHD individuals seems to be reversible by GH supplementation, again pointing toward a close positive correlation between the level of GH and collagen synthesis in connective tissue.

In studies of healthy humans treated with rhGH, a similar increase in plasma IGF-I level and markers of whole-body collagen synthesis is observed (Longobardi et al., 2000; Wallace et al., 2000). In a large placebo-controlled study, rhGH administration increased whole-body soft-tissue collagen synthesis dose-dependently (Longobardi et al., 2000). Moreover, in a study of healthy active males, comparing the effect of exercise and rhGH supplementation vs exercise and placebo, a significantly higher collagen synthesis was reported in the rhGH group compared with the control group (Wallace et al., 2000). This suggests that GH not only has a stimulating effect on collagen synthesis in GHD humans and animals but also has a stimulating effect in normo-endocrine human subjects. A large number of studies report that systemic GH supplementation increases serum levels of the IGF-I ternary complex (Lange et al., 2000; Lange et al., 2001a; Lange et al., 2002a, b). Recently, Olesen et al. (2004) showed that mRNA levels of class 1 IGF-I isoforms and IGFBP-3 were correlated to a concomitant rise in collagen in the tendon and muscle of exercising rats, suggesting a role for the IGF-I-ternary complex in mediating exercise-induced collagen synthesis in tendon and muscle. This finding is further supported by another study in rats, reporting elevated IGF-I expression and increased tendon healing following shock wave treatment (Kurtz et al., 1999).

A measurement of collagen synthesis is only indicative of the complete collagen metabolism, and without any concomitant information on collagen breakdown, no conclusions regarding overall collagen metabolism can be made. Unfortunately, no reliable method for determination of collagen breakdown is currently available.

Thus, investigations on animals, healthy persons and patients with altered GH secretion report a close positive relationship between (1) the level of GH in plasma, (2) the concentrations of systemic and local tissue effectors and (3) collagen synthesis in connective tissue in muscle and tendon.

In conclusion, supraphysiological doses of GH do not seem to increase synthesis of myofibrillar protein; however, it is possible that a supraphysiological GH level has an effect on the connective tissue. A possible explanation is that the scaffold structure of connective tissue in skeletal muscle is more “exposed” to changes in the concentration of hormones in plasma, and thus, to greater extents than that seen in myofibrillar protein of skeletal muscle, reacts to increased concentrations of GH and IGF-I (Fig. 3).

**GH-supplementation: ergogenic effect and perspectives in injury treatment**

From the scientific literature it is not obvious why GH-doping has gained such popularity. There is not
one single study that provides evidence of improved athletic performance in healthy individuals as a result of GH administration, and furthermore, a large group of controlled studies report no performance-enhancing effect of rhGH administration in healthy adults (Yarasheski et al., 1992, 1993; Deyssig et al., 1993b). It has been argueed that the beneficial effect of rhGH supplementation and the main reason for GH abuse is because of its lipolytic effect, allowing athletes to lose weight while keeping their muscle mass intact (Kraemer et al., 2002; Biddlemaier et al., 2003). Others argue that increased muscle size observed in GH abusers is because of fluid retention rather than actual increase in contractile protein concentration, thus creating a false impression of a stronger muscle (Rennie, 2003). The results from studies in animals, acromegalic patients and healthy human subjects presented in this review strongly suggest a role for GH in maintaining and increasing the strength of primarily connective tissue in muscle and tendon. To our knowledge, there is unfortunately no study investigating the precise effect of GH on the synthesis of intra-muscular and intra-tendinous connective tissue, in exercise and non-exercise conditions in humans.

Tendons heal faster in GH-supplemented animals (Kurtz et al., 1999), and anecdotal reports from bodybuilders (http, 2004) and baseball players (Verducci, 2002) suggest that GH prevent tendon and muscle rupture, especially in those with a concomitant abuse of anabolic androgenic steroids (AAS). Tendon and especially the myotendinous junction are considered a “weak link in the chain” in those with fast-growing muscles (AAS and/or heavy strength training) and in athletes training at high intensities. Thus, it is possible that rhGH supplementation allows the athlete to train at a higher intensity and/or reduce the necessary recovery time between exercise bouts, without running the risk of getting injured.

Clinical use of rhGH treatment is currently standard in childhood and adult onset GHD (Cunco et al., 1991a; Lucidi et al., 1998, 2000; Mauras et al., 2000) and in Turner syndrome patients (Gault et al., 2003). In treatment of burns and bone fractures and in treatment of intensive care patients, rhGH supplementation has also been attempted (Suman et al., 2003; Bach et al., 2004; Carroll et al., 2004). The effect of GH in connective tissue in humans could be suggestive for GH treatment after muscle and tendon injury. However, no studies have, to our knowledge, investigated the potential of rhGH supplementation either in injury prevention or in promoting healing of human muscle and tendon. The lack of such studies can possibly be explained by ethical concerns regarding possible side effects of high-dose rhGH administration or because of concerns of increasing abuse of ergogenic substances.

Side effects of rhGH administration are an extremely serious aspect of GH abuse. Observations in rhGH-supplemented human subjects and acromegalic patients, including carpal tunnel syndrome and pitting edema (Lange et al., 2001a), increased bone growth (Kraemer et al., 2002), myocardial hypertrophy and cancer (Colao et al., 2004), are suggestive of the potential risk of rhGH abuse. Furthermore, because of the high cost of rhGH (annual costs of up to 36,000 USD according to bodybuilder-steroid-homepages (Berardi, 2004)), the use of cadaveric pituitary derived GH is still widespread on the black market, with abusers running the hazardous risk of getting the fatal Creutzfelt–Jacobs disease (Deyssig & Frisch, 1993a; Ehrnborg et al., 2000; Dean, 2002). However, extrapolating observations from studies in human subjects, receiving relatively small doses of GH, and from acromegalic patients, with years of elevated GH-level, are at best indicative for which side effects are to be expected in abusing athletes. Unfortunately, because of a lack of communication between physicians and abusing communities, there is so far very little knowledge available of the side effects of short- or long-term GH abuse.

It is concluded that endogenous and exogenous GH does in fact possess a strong potential for affecting synthesis of connective tissue during exercise. At high levels of plasma GH, the effect on connective tissue synthesis by far exceeds the very moderate effect on myofibrillar muscle protein and it is very likely that this effect, in part, can explain the popularity of GH doping among athletes. Future research exploring GHs potential as a possible treatment of muscle and tendon injuries is needed, and furthermore, experiments in healthy young individuals and patients with altered GH secretion will contribute to an increased understanding of the regulatory role of GH.

Key words: insulin-like growth factor-I, myofibrillar protein, collagen, doping, performance enhancing.

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