Scand J Med Sci Sports 2012: 22: e1–e7
doi: 10.1111/j.1600-0838.2012.01459.x



SCANDINAVIAN JOURNAL OF
MEDICINE & SCIENCE
IN SPORTS

Review

# GH/IGF-I axis and matrix adaptation of the musculotendinous tissue to exercise in humans

**K. M. Heinemeier, A. L. Mackey, S. Doessing, M. Hansen, M. L. Bayer, R. H. Nielsen, A. Herchenhan, N. M. Malmgaard-Clausen, M. Kjaer**

[1]*Institute of Sports Medicine, Department of Orthopedic Surgery M81, Bispebjerg Hospital, Copenhagen, Denmark, and Centre of Healthy Ageing, Faculty of Health Sciences, University of Copenhagen, Denmark*
*Corresponding author: Katja M. Heinemeier, Institute of Sports Medicine, Department of Orthopedic Surgery M81, Bispebjerg Hospital, Bispebjerg Bakke 23, Building 8, 1 Floor, 2400 Copenhagen, Denmark. Tel: +45 35316089, Fax: +45 3531 2733, E-mail: katjaheinemeier@gmail.com*

Accepted for publication 21 February 2012

**Exercise is not only associated with adaptive responses within skeletal muscle fibers but also with induction of collagen synthesis both in muscle and adjacent connective tissue. Additionally, exercise and training leads to activation of the systemic growth hormone/insulin-like growth factor I axis (GH/IGF-I), as well as increased local IGF-I expression. Studies in humans with pathologically high levels of GH/IGF-I, and in healthy humans who receive either weeks of GH administration or acute injection of IGF-I into connective tissue, demonstrate increased expression and synthesis of collagen in muscle and tendon. These observations support a stimulatory effect of GH/IGF-I on the connective tissue in muscle and tendon, which appears far more potent than the effect on contractile proteins of skeletal muscle. However, GH/IGF-I may play an additional role in skeletal muscle by regulation of stem cells (satellite cells), as increased satellite cell numbers are found in human muscle with increased GH/IGF-I levels, despite no change in myofibrillar protein synthesis. Although advanced age is associated with both a reduction in the GH/IGF-I axis activity, and in skeletal muscle mass (sarcopenia) as well as in tendon connective tissue, there is no direct proof linking age-related changes in the musculotendinous tissue to an impaired GH/IGF-I axis.**

The growth hormone/insulin-like growth factor I (GH/IGF-I) axis plays a vital role for the growth and maturation of children and adolescents, and is also a major regulator of substrate metabolism and insulin sensitivity (Moller & Jorgensen, 2009). Several studies have focused upon the importance of the GH/IGF-I axis in the human locomotor system, e.g., bone and skeletal muscle development with regard to growth and metabolism. However, only very few studies have tried to investigate the role of the GH/IGF-I axis in relation to connective tissue matrix adaptation within tendon and skeletal muscle. The matrix of tendon and skeletal musculature plays an essential role in the transmission of force from the individual contracting muscle cell to the skeletal structures, resulting in limb and body movement. Thus, the investigation of matrix regulation in the musculotendinous tissue is of importance for understanding its structure and function. This review will focus on the role of the GH/IGF-I axis in matrix biology in tendon and skeletal muscle.

## Exercise-induced regulation of GH/IGF-I in blood

Both circulating GH and IGF-I will increase in response to exercise (Roth et al., 1963; Bang et al., 1990). Circulating GH responds to exercise in tight relation to the exercise intensity, and the GH level is related to the central effort in the brain to perform exercise. This view is supported by an experiment where the use of partial neuromuscular blockade, in order to raise the central effort to complete a certain exercise bout, resulted in a greater GH response compared to that of control individuals without blockade (Kjaer et al., 1987). The IGF-I response to exercise is always less pronounced than the GH response (Wallace et al., 1999), and is not necessarily just a direct result of GH release. This is indicated by the fact that the rise in IGF-I sometimes occurs earlier than is predicted from the time of GH release (Schwarz et al., 1996). In addition, it has been shown that circulating IGF-I can rise in response to exercise in patients with pituitary insufficiency (Bang et al., 1990).

Repeated exercise and regular training leads to a chronic elevation in circulating levels of GH and IGF-I, and it has been demonstrated that training is associated with an increased capacity to secrete GH from the pituitary gland. This has been shown both in athletes who have trained for many years (Kjaer et al., 1984), and in subjects who carried out intense training over a period of 1 year (Weltman et al., 1992). Similarly, other hormonal

responses, e.g., epinephrine release capacity from the adrenal medulla, are enhanced by training (Kjaer & Galbo, 1988).

## Local changes in IGF-I in response to mechanical stimulus

Several studies indicate that not only circulating levels of IGF-I increase in response to exercise, but also local levels of IGF-I can be induced in tissues subjected to loading. Thus, increased expression of IGF-I mRNA in human skeletal muscle has been shown in response to both long- and short-term loading (e.g., Bamman et al., 2001; Hameed et al., 2004; Heinemeier et al., 2011), and animal data indicate that the loading-induced IGF-I expression in muscle happens independently of pituitary GH release (Yamaguchi et al., 2006). Similarly in tendon tissue, rat studies show that loading of the tendon leads to higher local expression of IGF-I on both protein and mRNA levels (Hansson et al., 1988; Olesen et al., 2006; Heinemeier et al., 2007b). In young men however, no elevation in IGF-I expression was found in the patella tendon in response to moderate endurance-type kicking exercise (Heinemeier et al., 2011), indicating perhaps that loading was insufficient in this model and/or that human tendons might be less responsive to mechanical stimuli than rat tendons.

The induction of IGF-I expression in skeletal muscle in response to loading has traditionally been linked to the hypertrophic response of muscle fibers. However, there are several indications that the GH/IGF-I system may be more related to the regulation of the connective tissue of the muscle-tendon unit (discussed below).

## Mechanical regulation of matrix synthesis

The dominating component of tendon and muscle connective tissue is collagen, primarily type I and III fibrillar collagen. The total collagen content represents 80–90% of the tendon tissue organic mass, whereas in muscle the percentage is 5–10%, primarily located around the muscle fibers (endomysium, perimysium) or surrounding the entire muscle (epimysium) (Light & Champion, 1984). Type I and III pro-collagen molecules are composed of three polypeptide chains [type I collagen of two $\alpha$1(I) chains and one $\alpha$2(I) chain; type III collagen of three $\alpha$1(III) chains] that are coupled in a triple helix. Following removal of C- and N-terminal pro-peptides from pro-collagen, the collagen molecules self-assemble extracellularly and form collagen fibrils (Myllyharju & Kivirikko, 2001).

Mechanical stimuli of cells/tissue appears to be a major regulatory factor in collagen homeostasis, and many *in vitro* studies demonstrate enhanced collagen expression and synthesis in response to mechanical loading (reviewed by Chiquet et al., 2009). Similar to this, mechanical loading through exercise/training can induce collagen synthesis in both the loaded tendon and muscle tissue of humans. This is shown by local changes in type I collagen pro-peptide levels (Langberg et al., 1999; Crameri et al., 2004) and by increases in incorporation of amino acid tracers (Miller et al., 2005). Additionally, short-term strength training in rats leads to increased mRNA expression of collagen I and III in both tendon and muscle tissue (Heinemeier et al., 2007a). A number of *in vitro* studies suggest that this mechanical stimulation of collagen expression and synthesis depends on the auto/paracrine action of certain growth factors, including IGF-I (Hansson et al., 1988; Abrahamsson & Lohmander, 1996; Butt & Bishop, 1997; Schild & Trueb, 2002; Yang et al., 2004; Nakama et al., 2006). Thus, it may be speculated that mechanical loading via exercise leads to induction of GH/IGF-I systemically and locally, and that this is related to regulation of matrix production in tendon and muscle tissue.

## GH/IGF-I in stimulation of collagen synthesis

A stimulatory action of IGF-I on collagen synthesis in connective tissue is supported by several *in vitro* and animal studies. Thus, *in vitro* studies on human fibroblasts and rabbit tendon explants show robust increases in collagen synthesis in response to IGF-I (Goldstein et al., 1989; Abrahamsson et al., 1991; Bird & Tyler, 1994; Abrahamsson & Lohmander, 1996) and overexpression of IGF-I in striated muscle in mice leads to elevated levels of collagen in heart muscle (Delaughter et al., 1999). Furthermore, administration of rhGH to GH-deficient dwarf rats results in an upregulation of local IGF-I and collagen (I/III) mRNA expression in skeletal muscle (Wilson et al., 1995), as well as a higher collagen turnover in knee tendon and ligaments (Kyparos et al., 2002).

Similarly in humans, considerable evidence for a connection between GH/IGF-I and collagen production exists. Thus, acromegalic patients who have high concentrations of GH and IGF-I display increased formation of collagen-rich tissues such as bone (Ezzat et al., 1993). In line with this, a more recent study demonstrated higher levels of collagen and IGF-I mRNA in local musculotendinous tissue in adult acromegalic patients compared to adult GH-deficient patients (Doessing et al., 2010b), as well as a tendency towards a higher collagen protein synthesis rate (Doessing et al., 2010b). Furthermore, supplementation with GH in hypo-pituitary resulted in a rise in mRNA for both IGF-I and collagen in skeletal muscle (Sjogren et al., 2007). Similarly, in healthy young individuals subjected to 2 weeks of GH injections (with doubling of normal circulating IGF-I), it was found that IGF-I mRNA, collagen I mRNA, and collagen protein synthesis was elevated in both tendon and muscle, whereas muscle myofibrillar protein synthesis was unaffected (Doessing et al., 2010a) (Fig. 2). These results

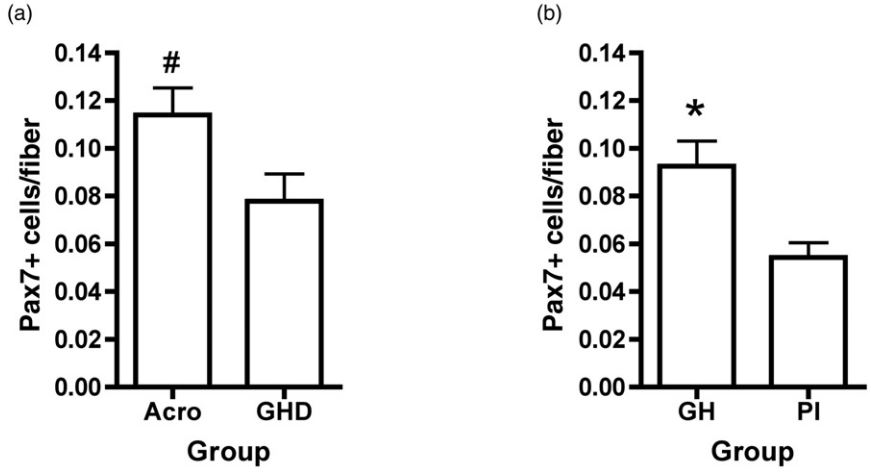


*Fig. 1.* Differing numbers of satellite cells (Pax7+) under conditions of high and low growth hormone in (a) skeletal muscle biopsies from acromegalic (Acro)- and growth hormone-deficient (GHD), and (b) growth hormone (GH)- and placebo (Pl)-treated individuals. Mean +/− SEM error bars; #$P = 0.06$ Acro vs GHD. *$P < 0.01$ GH vs PI; Mann–Whitney test.

support a collagen-stimulating role of GH/IGF-I in human connective tissue and indicate that GH/IGF-I is more important in strengthening of the matrix tissue than for muscle cell hypertrophy in adult human musculotendinous tissue (further discussed below).

The above-mentioned studies do not clearly conclude whether GH or IGF-I plays a dominating role in stimulation collagen synthesis. However, both systemic and local administration of IGF-I in animals was shown to increase tendon collagen content, and also to improve the strength of the tendon (Dahlgren et al., 2002; Provenzano et al., 2007). In line with this, a coupling between local IGF-I and healing of skin has been demonstrated (Dunaiski & Belford, 2002). The direct link between IGF-I and collagen synthesis is further supported by a recent human study, where IGF-I was injected directly into the patella tendons, resulting in an increase in local collagen synthesis relative to control tendons injected with saline (Hansen et al., 2012). These observations indicate that IGF-I in itself is at least sufficient to induce collagen production, and it seems likely that IGF-I dominates over GH in regulation of collagen homeostasis.

The signaling pathway for IGF-I-mediated induction of collagen synthesis has not been described in detail, although *in vitro* studies on human fibroblasts suggest that IGF-I induces collagen production through the IGF-I receptor (Goldstein et al., 1989; Bird & Tyler, 1994). Data on fetal lung fibroblasts suggests that this signaling is propagated through the PI-3 kinase pathway (Chetty et al., 2006), while results from human hepatic stellate cells indicate that IGF-I-mediated collagen stimulation is dependent on both PI-3 kinase and ERK (Svegliati-Baroni et al., 1999). Finally, results from human dermal fibroblasts indicate that the IGF-I-mediated stimulation of collagen expression may be a secondary result of and induction of TGF-β1 synthesis, which in turn leads to increased collagen synthesis (Ghahary et al., 2000).

## GH/IGF-I as mediators of loading-induced collagen synthesis

Taking into account the evidence of loading-induced increases in circulating GH/IGF-I, and local IGF-I, combined with the stimulating effect of IGF-I on collagen synthesis, it seems that GH/IGF-I may well play a mediating role in mechanically induced stimulation of matrix production. As mentioned earlier, prolonged training leads to an increased capacity to secrete GH in humans (Kjaer et al., 1984; Weltman et al., 1992) and at the same time, an increased Achilles tendon cross-sectional area is found in long-term runners (Rosager et al., 2002). Although it is tempting to believe that increased circulating levels of GH/IGF-I could contribute to these training-induced adaptations, it is unlikely to be the full explanation. The most important determinant for tendon growth and size in adult humans is most likely the degree of mechanical loading on the individual tendon. In support of this, runners and jumpers not only had thicker Achilles tendons compared to untrained counterparts, but also compared to elite-trained kayakers who carried out a less weight-bearing sports (Kongsgaard et al., 2005). Furthermore, studies of male athletes competing in sports with a pronounced side-to-side difference (badminton and fencing) showed a greater cross-sectional area of the patella tendon in the leading leg compared to the non-leading leg (Couppe et al., 2008). Whereas these finding do not support an effect of circulating levels of GH/IGF-I, it seems likely that local concentrations of IGF-I could influence the adaptation. In support of IGF-I

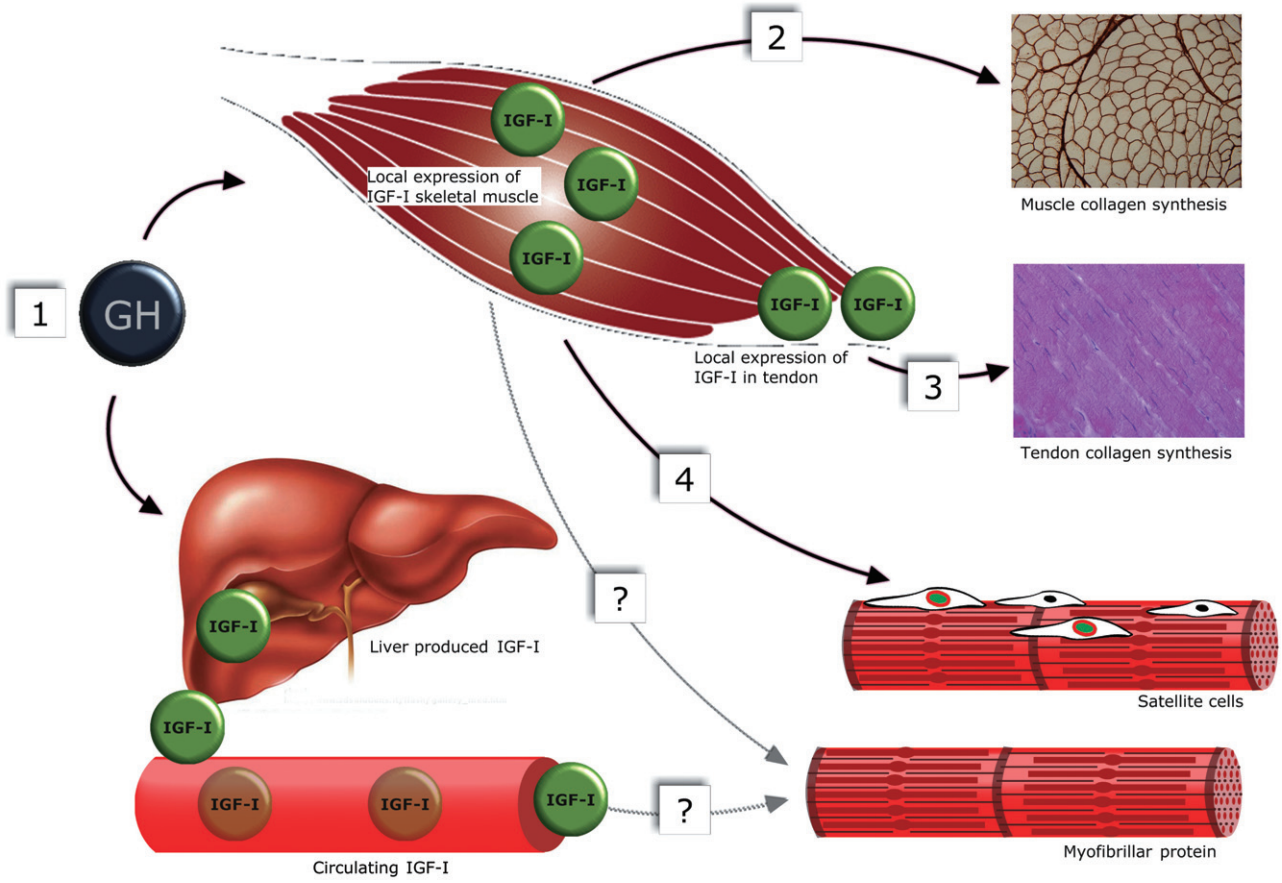


*Fig. 2.* Effect of growth hormone (GH) supplementation on muscle and tendon tissue. GH supplementation (1) leads to increased circulating levels of IGF-I and to increased local expression of IGF-I in skeletal muscle and tendon tissue. This is concurrent with increased expression of fibrillar collagen in muscle (2) and tendon tissue (3) as well as increased satellite cell numbers (4). Myofibrillar protein synthesis appears unaffected by the increased levels of both circulating and local IGF-I levels (gray arrows; modified from Doessing & Kjaer, Physiology News, Autumn 2010).

playing such a role, it has been shown that loading of the rat tendon muscle unit leads to increased local expression of IGF-I mRNA in parallel with collagen mRNA in both muscle and tendon tissue (Olesen et al., 2006; Heinemeier et al., 2007a, b).

## GH-IGF-I, skeletal muscle, and its stem cells

Although a positive correlation exists between circulating GH levels and whole-body protein synthesis, studies on GH supplementation to both young and elderly healthy individuals have not been able to demonstrate any enhancing effect of GH on muscle mass or muscle strength either *per se* or as an addition to muscle strength training (Yarasheski et al., 1992; Lange et al., 2002). This view is further supported by data indicating that a functional IGF-I receptor is not crucial for overload muscle hypertrophy in mice (Spangenburg et al., 2008). In addition, recent studies on young men found equal acute and long-term muscle anabolic responses to strength training whether this was done at high or low GH/IGF-I environments (West et al., 2009, 2010). In contrast, GH administration has been shown to have an enhancing effect upon muscle growth, strength and performance in GH-deficient children and adults (Cuneo et al., 1991; Lucidi et al., 1998; Mauras et al., 2000) and also in immature animals (Molon-Noblot et al., 1998). Importantly, it has recently been shown in mice that IGF-I only induces muscle hypertrophy in growth situations (Shavlakadze et al., 2010). This illustrates that in healthy adult skeletal muscle, no additional growth will be achieved with GH/IGF-I administration, and that GH/IGF-I in relation to skeletal muscle is mostly of importance for early development and growth. In support of this, 2 weeks of GH administration did not result in any rise in muscle myofibrillar contractile protein synthesis (Doessing et al., 2010a) nor could any difference in muscle protein synthesis be detected between acromegalic and adult growth hormone deficiency patients despite a twofold difference in circulating GH and IGF-I levels (Doessing et al., 2010b). Interestingly, in those two human studies, the detection of human pax-7 positive satellite cells (muscle stem cells) in skeletal muscle showed that the number of

satellite cells per muscle fiber was elevated in GH-treated young men vs nontreated, and also in acromegalic patients vs growth hormone deficient (Fig. 1). The association between IGF-I levels and stem cell activity is supported by a recent study on mice, in which an increase in the number of pax-7 positive cells observed in skeletal muscle in response to viral-mediated IGF-I gene transfer (Stevens-Lapsley et al., 2010). In addition, previous mouse data indicated that satellite cell activation was an important part of IGF-I-mediated muscle hypertrophy in mice (Barton-Davis et al., 1999). In adult humans, the stimulatory effect of GH/IGF-I on myofibrillar protein synthesis seems absent (Doessing et al., 2010a); however, our data indicate that the stimulatory effect of GH/IGF-I on satellite cell activity does exist in human skeletal muscle (Fig. 1). This finding, in combination with the enhancing effect of GH/IG-I on matrix production, adds support to the suggestion that IGF-I is an important factor in regeneration of injured muscle tissue (Charge & Rudnicki, 2004).

## Matrix in tendon and muscle: Potential effect of GH-IGF I in ageing

Ageing is associated with a decrease in both GH and IGF-I plasma levels (somatopenia) (Zadik et al., 1985), but whether this decline in the GH/IGF-I axis is directly related to any changes of matrix in tendon or skeletal muscle is unknown. The collagen content in human tendon has only recently been determined and compared in young and old individuals (Couppe et al., 2009). Here, it was found that the collagen content was approximately 30% lower in old vs young tendon (Couppe et al., 2009). This finding supports the possibility that reduced activity in the GH/IGF-I axis in older individuals could result in lower collagen content in elderly human tendon. In skeletal muscle, very few studies have been carried out in relation the effect of age on the collagen-rich connective tissue. Some studies find indications of increased relative amounts of collagen in skeletal muscle of animals with ageing (Kovanen & Suominen, 1989), as well as indications of higher collagen synthesis rates in skeletal muscle of old compared to young men (Babraj et al., 2005). On the other hand, a more recent human study demonstrated no difference in collagen content between young and old skeletal muscle (Haus et al., 2007). Thus, no clear picture exists, with regard to ageing-associated changes in muscle collagen, and the existing data do not support the view that impaired IGF-I contributes significantly to the age-associated changes in the matrix regulation.

In summary, current data show that elevated circulating GH/IGF-I, concomitant with increased local IGF-I, leads to stimulation of collagen expression and synthesis in the connective tissue of the muscle-tendon unit in both humans and animals (Fig. 2). Given the induction of local IGF-I observed simultaneously with increased collagen expression in response to mechanical loading of the muscle/tendon tissue during exercise, it is suggested that IGF-I may mediate loading-induced collagen synthesis. However, no causal relationship linking IGF-I to the exercise-induced regulation of connective tissue synthesis has yet been verified, and further studies are needed to confirm this connection. In addition, the association between high GH/IGF-I activity and satellite cell number could indicate a link between GH/IGF-I and stem cell function in adult human skeletal muscle.

## Perspectives

The stimulatory effect of GH/IGF-I on collagen synthesis may hold clinical perspectives in relation to traumatic musculoskeletal injuries, where the collagen matrix is damaged. In animals, local and systemic application of IGF-I has been shown to improve tendon collagen content and strength in relation to both overuse and acute injuries (Dahlgren et al., 2002; Provenzano et al., 2007), but in humans further studies are needed to determine the potential of using GH/IGF-I in treatment of musculoskeletal injury.

**Key words:** insulin-like growth factor, growth hormone, tendon, skeletal muscle, collagen, myofibrillar, mechanical loading.

## Acknowledgements

Financial support from The Danish Medical Research Council (09-063546), Lundbeck Foundation, Novo Nordisk foundation and Nordea Foundation (Healthy Ageing grant) is greatly appreciated.

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