

GH HAS DIRECT ANABOLIC ACTIONS ON MUSCLE INDEPENDENT OF IGF-1.

Contributed by Robbie Durand
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"GROWTH HORMONE IS NO MUSCLE BUILDER." This is headline that appeared in many recent newspapers and newswires this month. The newspapers and media tend to vilify anything that builds muscle, the press has jumped all over a recent meta-analysis (a collection of previous research findings) published in this month's journal of the Annals of Internal Medicine¹ that reported GH has little benefits for building muscle or improving quality of life. The article went on to explain how although growth hormone (GH), which has been reported to build muscle and reduce bodyfat, GH is nothing more than snake-oil! The meta-analysis also noted that GH causes a host of unhealthy side effects, including joint pain, soft tissue swelling, carpal tunnel syndrome, and a heightened risk of diabetes. The article did acknowledge that GH administration did increase lean muscle mass by more than two kilograms (four pounds) and decreased fat mass by roughly the same amount but noted that the side effects associated with GH usage was not worth the small changes in body composition. The lead author also claimed that the small increases in lean mass could easily be accomplished by starting a resistance exercise program. So is GH as worthless for building muscle as the media is portraying it to be? Don't believe the hype, GH is an important muscle builder. A few days after the GH bashing study was published, Ronald M. Klatz, M.D., President of the American Academy of Anti-Aging Medicine responded to the article with the following,

"Absorb what is useful, reject what is useless"

— Bruce Lee

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"The American Academy of Anti-Aging Medicine has reviewed the findings of the meta-analysis concerning adult growth hormone (GH; HGH) replacement therapy published in the January 15, 2007 issue of the Annals of Internal Medicine, and refutes the paper's findings. The meta-analysis is flawed, as it is based on an incomplete compilation of clinical studies of GH replacement in healthy adults. The American Academy of Anti-Aging Medicine submits that thousands of published studies on hundreds of thousands of patients have demonstrated the clear benefits of adult GH replacement therapy, when utilized under proper clinical guidelines and at proper physiological dosages. Real-world results must take precedence over academic hypotheses as to benefits and risks."

GH Works Synergistically With Other Anabolic Hormones

GH has become a very controversial drug over the years in the medical field, but it has become even more controversial among the exercise world in terms of its effect on building muscle. A number of animal studies have shown that GH is not essential for exercise induced muscle hypertrophy; however, this does not mean that GH has no role to play in building muscle. GH works synergistically with other anabolic hormones such as IGF-1 and testosterone. Research with various muscle wasting disorders have shown that a combination of GH and testosterone or GH plus IGF-1, work better than if each is used separately^{3, 10, 12, 22, 29}. Both GH and IGF-1 directly increase whole body protein synthesis, but unlike GH, IGF-1 reduces muscle tissue breakdown³¹. It is well acknowledged that GH is not as anabolic as testosterone, but GH does play an essential role in the grand scheme of building muscle. Testosterone is the king of building muscle, but testosterone can also increase both GH and IGF-1 levels, mainly thru aromatization of estrogen. Interestingly, if testosterone is administered with an aromatase inhibitor (tamoxifen), there are no increases in GH or IGF-1. It seems overwhelming clear that GH by itself is only a mild anabolic agent at best, but when combined with other anabolics, it's clear that GH produces an additive effect. For example, Gibney et al.²¹ compared the effects of GH alone or GH plus testosterone treatment. GH increased IGF-1 levels; however, co-administration of GH and testosterone induced an even greater rise in IGF-1 levels. In another study, researchers examined the effects of GH alone or GH plus testosterone on protein synthesis. GH increased protein synthesis by itself, but a combination of GH and testosterone had an even greater effect on increasing protein synthesis³⁰. One of the pioneers in GH research Bill Kraemer once said at the American College of Sports Medicine that, "GH responses to exercise are essential and more importantly, the anabolic hormone response that occurs with resistance exercise is like a symphony and GH is an important part of that symphony along with testosterone, IGF-1, MGF, and other anabolic hormones." Think of GH as being the drummer of your band, by itself a drum solo will probably suck, but combine him with the guitar player (IGF-1), and a good singer (testosterone) and you have one kick ass band.

So if GH is as worthless for building muscle as the media portrays it to be, let's look at some of the research studies examining the anabolic actions of GH. Here are a few highlights of some of the actions in which GH contributes to building muscle by itself and in conjunction with other anabolics:

- One study reported that GH administration results in a reduction in myostatin expression in muscle and resulted in an increase in lean muscle mass. Additionally, when researchers administered pegvisomant, (a drug that blocks the actions of GH binding to its receptor) myostatin protein was significantly increased².
- GH increases protein synthesis thru the mTOR pathway (an important stimulator of muscle protein synthesis) ³³.
- When the effects of GH or a combination of GH and testosterone on lean muscle mass and fat mass were compared, a combination of GH and testosterone resulted in superior increases in lean muscle mass and reduced fat mass compared to GH or testosterone alone. The effects of GH and testosterone on lean body mass appeared additive, suggesting that both GH and testosterone are synergistic yet increase muscle hypertrophy thru different mechanisms^{3,10}.
- MGF (a powerful local growth factor) in skeletal muscle is increased with GH administration⁴.
- GH has direct actions on skeletal muscle that are independent of IGF-1¹⁸.
- A single dose of GH has been shown to increase IGF-1 mRNA (a growth factor) in muscle²⁶
- GH stimulatory effects on muscle protein synthesis may be in part due in part to GH's direct effects on satellite cells¹⁸
- A combination of GH and IGF-1 injections was found to be superior for increasing muscle mass compared to GH or IGF-1 alone^{12,22}.
- Acute and chronic hormonal responses to resistance training were evaluated in 11 college men who completed 12 weeks (33 sessions) of high volume resistance training. Significant correlations existed only between absolute mean GH increases over the training sessions and the degree of muscle fiber hypertrophy for type I and type II fibers⁷.

RESEARCH UPDATE: GH HAS DIRECT ANABOLIC ACTIONS ON MUSCLE INDEPENDENT OF IGF-1

The anabolic action of GH has been exploited to increase lean body mass and protein synthesis however; the mechanisms of GH anabolic actions on skeletal muscle are not fully understood. The growth-promoting actions of GH are thought to be mediated by circulating or locally produced insulin-like growth factor 1 (IGF-1), which is a critical agent involved in muscle growth^{5,6}. Acute resistance exercise has been shown to increase blood levels of both GH and IGF-1 which may be an important physiological adaptation to building muscle⁹. For example, in one study, the GH responses during exercise and during the recovery period in trained and sedentary young men were compared. The GH levels were higher during exercise and in recovery in trained athletes compared to the sedentary controls. This increase of GH in the trained athletes may represent an important endocrine adaptation to training and building muscle. Additionally, studies have reported that GH is taken up directly by human skeletal muscle during exercise²³. This direct uptake of GH may contribute to the acute increases in muscle protein synthesis that occurs during exercise as GH acutely stimulates muscle protein synthesis in muscle. In this month's journal of Clinical Endocrinology and Metabolism, researchers examined how GH affects protein synthesis when produced in excess and what happens when GH is suppressed. They compared patients with pituitary disorders whom produce excess GH (Gigantism) and compared them to normal people. Patients with excess GH had increased rates of protein synthesis compared to normal people but protein breakdown was the same between the groups. This is similar to a previous research reporting that GH stimulates muscle protein synthesis yet has no effect on muscle tissue breakdown. Interestingly, researchers examined protein synthesis rates in the gigantism patients undergoing GH suppression therapy to control excess GH and found that GH suppressive therapy resulted in a reduction in protein synthesis and lean mass with GH suppressive therapy³¹.

For a long time, many researchers have attributed the anabolic effects of GH to increases in circulating IGF-1 levels, but new research has reported direct anabolic effects of GH on muscle. In this month's journal of Proc. Natl. Acad. Sci. U S A researchers reported that GH has direct anabolic actions on muscle independent of IGF-1¹⁸. The researchers reported that GH leads to an increased muscle fiber number, indicating that GH has direct actions of muscle. GH was found to increase the size of muscle fibers by acting on a specific feature called muscle cell fusion (the process of turning immature muscle fibers develop into mature muscle fibers). In conclusion, a few important findings were reported: 1.) GH has direct anabolic actions on muscle 2.) GH and IGF-1 muscle enhancing effects are additive and rely on different signaling pathways. Taken together, the data reveals that GH has specific function in the control of muscle cell fusion, an essential process for muscle growth.

Growth Hormone Receptor Regulation

It's now clear that GH is having some direct effects on muscle itself that are acting independently of IGF-1. Furthermore, the direct effects of GH on muscle have been documented as a single dose of GH can lead to an increase in mRNA IGF-1 expression (a powerful local muscle growth factor)²⁶. As mentioned previously, GH seems to work best when combined with other anabolics such as IGF-1. For example, when researchers want to test how anabolic an agent is they put mice on what's called hindlimb suspension (This is equivalent to putting a human leg in a cast, it's a model that produces rapid muscle atrophy or loss). Researchers placed rats in hindlimb suspension and then had them contract their leg muscles and administered GH, IGF-1, or a combination of GH and IGF-1. The group that received both GH and IGF-1 effectively prevented muscle atrophy compared to either group alone¹². The rise in GH that occurs during exercise may be important for GH receptor regulation as GH receptors are found in muscle and may be an important adaptation to increasing muscle mass. In fact age-related reductions of GH binding proteins levels, which reflect diminished GH receptor status has been observed in older adults¹³. One study reported that in healthy older men, the two biggest factors that contributed to reduced muscle mass in healthy older men was increased muscle myostatin levels (myostatin suppresses muscle growth) and reduced GH receptor number in muscle¹⁷. In a similar study to the previous study mentioned above, researchers put mice with their legs on hindlimb suspension and looked specifically at the GH receptor in muscle. GH receptor in muscle was increased in muscle by 406% in type I muscle and 90% in type II muscle after 7 days of muscle unloading. The researchers speculated that the increase in GH receptor concentration was due to prevent further atrophy and increase anabolic activity in muscle. So what happens after you damage muscle tissue when you go to the gym? GH receptor increases in regenerating muscle cells after muscle damage, as GH is

important for the early phase of muscle regeneration^{24, 25, 27}. So now that you know that GH has direct actions on muscle, there is no better way to increase GH than hardcore training.

SEEING LITTLE BIRDS AFTER A SET = GOOD GH SECRETION

Want to know if you are getting a good increase in GH during exercise without taking blood samples? If you feel like the last set you did was going to make you pass out from exhaustion then chances are you have a good spike in GH. Here is a cool little research study where researchers reported that GH levels during exercise are related to work perception or how hard you feel like you are working. Kjaer et al¹⁵ investigated the mechanisms responsible for the regulation of GH secretion during exercise in healthy male subjects. So how do you alter someone's perception of how hard they are working out in the gym? The researchers administered a drug which weakened skeletal muscle contractions by blocking muscle nerve transmission! Basically, it makes lifting the barbell feel like you were maxing out!! The authors report that the GH level is closely related to perceived exercise intensity (how hard you feel you are working out) and not to the actual workload carried out. Makes sense, as the GH responses to short, high intensity resistance exercise with moderate weights which produce large increases in lactic acid, produce greater GH responses than maxing out with singles, heavier weight, and longer rest periods. Additionally, the use of forced reps which allows a person to perform a greater than normal workload has been shown to increase GH to a greater extent than performing a regular set...so crank up your intensity to increase your GH.

Repeated Bouts of Exercise Period without Sufficient Rest Blunts GH Responses

A few years ago a book called the Bulgarian Burst System was printed which was supposed to give the training secrets of the Bulgarians weightlifters. It went on to explain how the Bulgarian weightlifters trained 6 times a day with short, high intensity sessions that lead to explosive increases in muscle growth and strength. It made sense that short high intensity sessions several times a day would increase GH and lead to higher increases in anabolic hormones, but according to the newest research this is just not the case. In this month's journal of Medicine & Science in Sports & Exercise, researchers reported that GH responses were suppressed in response to high intensity exercise with a recovery period less than 3 hours. In this interesting study, research subjects were divided into three groups: 1.) resistance exercise only 2.) an all out bicycle sprint session followed by a 60-minute rest period followed by resistance exercise 3.) An all out sprint session followed by a 3 hour-rest period followed by resistance exercise. You may be wondering why the researchers had the subjects perform a all-out exhaustive sprint session before the resistance training session. An all out sprint session produces large increases in GH, the researchers wanted to see if the high intensity resistance exercise program also would produce large increases in GH with a different recovery times (60 minute rest and 3 hour rest periods). Results of the study concluded that after each intense sprint sessions there were large increases in GH, however performing a resistance training session after a 3 hour rest period only resulted in a small GH response, furthermore performing a resistance training session with less than a hour rest period resulted in a blunted GH response to resistance exercise. So much for the Bulgarians training six times a day with high anabolic hormone responses...seems like a recipe for overtraining! Although the actual role of GH in muscle growth remains unclear, combinations of high GH and local growth factors produced in muscle (MGF, IGF-1) would activate anabolic processes in muscle. Therefore, a blunted GH response to exercise might have an undesirable effect if one is trying to produce maximal increases in muscle mass. Based on the research, if you are going to train with multiple training sessions make it early morning and later in the afternoon with sufficient rest periods.

It's Not Growth Hormone but Growth Hormones!

We commonly think of GH as a single hormone, but it is well recognized now that there are over 100 molecular isoforms of GH that exist in human circulation^{11,16}. GH should no longer be regarded as a single hormone, but rather a

“family of related GH peptides.” Exercise is one of the most potent physiological stimulators of pulsatile GH secretion and thus increases the concentration of IGF-I. Factors such as the training status, age, exercise 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 GH secretion, which is equally important for the GH-regulated secretion of IGF-I. Future research is currently underway to determine the exact role of the different GH isoforms and their effect on muscle hypertrophy and performance.

In conclusion, contrary to the media printing articles reporting GH is not important for building muscle, it is!! GH works synergistically with other hormones (testosterone and IGF-1) to increase protein synthesis and muscle mass. GH has direct anabolic action on muscle that occurs independently of IGF-1 and is essential for building muscle.

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