# Review on the Merits and Demerits of Growth Hormone as Anabolic Agent

**Mohammad Shohel*, Biplab Kumar Das, M. Mahfuzur Rahman and Asif Zaman**

Department of Pharmacy, North South University, Dhaka-1229, Bangladesh

**Abstract**

This review was performed to determine the effects of growth hormone therapy as an anabolic agent. The prime intention was to assess the effects of growth hormone on basal metabolism, body composition, strength and exercise capability. Moreover, indication on adverse actions associated with growth hormone in the healthy patients was blended. A systematic review of randomized controlled trials, that growth hormone certainly have some dominant effects on fat and carbohydrate biotransformation, commonly accepted as the anabolic effect and, in particular, promotes the metabolic application of adipose tissue. Nevertheless, net protein retention is promoted in adult connective tissue.

**Keywords:** Growth hormone, Anabolic agent, Somatropin, Somatotropin and Randomized control trial.

## Introduction

Growth hormone is a peptide hormone comprising of about 190 amino acids which stimulates growth, cell reproduction and regeneration in humans. It is secreted from the anterior hypophysis, underneath the hypothalamus in the brain. GH secretion is maximal during periods of human growth, mostly in adolescence; then both the periodicity and amplitude of GH secretion falls at a relatively low rate. The secretion of GH typically occurs at night, although it can be stimulated during the day by high protein foods, particularly those containing arginine, and by exercise of both the aerobic and resistance types. Exercise is the most potent physiological stimulus of GH secretion apart from sleep and even though it is well characterized, the basic mechanisms are still mostly unknown (Rennie, 2003).

Anabolic agents are those which are primarily responsible for protein synthesis ensuring the promotion of muscle growth and the growth of other complex living tissue in the body. Testosterone for instance, is an anabolic agent that promotes muscle growth, as are human growth hormone and insulin. An anabolic agent also obstructs the function of catabolic hormones such as cortisol, progesterone etc. Both anabolic and catabolic hormones are required by the human body to sustain homeostasis, or regulation of a stable inner environment. Anabolic hormones are manufactured into anabolic steroid supplements. They can be either natural or synthetic and are generally administered in pill form or by injection.

Human growth hormone (HGH) is an anabolic agent on which every organ of the human body relies for growth. It is used clinically for conditions relating to growth deficiency and in cases where people cannot produce it on their own. HGH has beneficial clinical uses and is only available through doctors. Besides increasing height in children and teenagers, growth hormone has numerous other effects on the body such as - increasing calcium retention and strengthen the mineralization of bones, boosting muscle mass through sarcomere hyperplasia, amplifying protein synthesis, promoting lipolysis, enhancing the growth of all internal organs apart from the brain, reducing liver uptake of glucose, gluconeogenesis in the liver, contributing to the maintenance and function of pancreatic islets, stimulating the immune system. Growth hormone is also an inhibitor of myostatin, a cytokine that selectively and effectively inhibits myogenesis, thus resulting in the increase of lean body mass and enhanced aerobic performance (Liu *et al.*, 2003).

The use of GH as an anabolic agent has been approved by the FDA for quite a few indications. This indicates that the drug has adequate safety in light of its

* Correspondence to: Mohammad Shohel, Department of Pharmacy, North South University, Dhaka-1229, Bangladesh.
E-mail: sohelustc@yahoo.com

benefits when used in the approved way. But like every drug, there are some side effects caused by GH. Among them, some are common and some are rare. Injection-site reaction is very common. More rarely, patients can experience joint swelling, joint hurting, carpal tunnel syndrome etc. (Liu *et al*.., 2007). Other side effects can comprise less sleep needed after dosing. In a few cases, patient can develop an immune response against GH.

The main objective for conducting this review is that, the evidence for use of GH as an anabolic agent in adults is very poor. Moreover, there is good confirmation that chronic high serum concentrations of GH diminish performance and may even cause acute metabolic changes in the short term that are likely to reduce the capacity for tough physical activity. Conceivably, high dose of chronic HGH administration in typical adults may lead to metabolic alterations that are related to a number of harmful side effects, e.g. cardiac instability, hypertension, and the development of insulin resistance and possibly type 2 diabetes, many of which are experienced by patients who produce too much of growth hormone as a result of pituitary tumors—namely, acromegaly - and by patients receiving rHGH in an effort to combat wasting caused by HIV/AIDS (Rennie, 2003).

*Aims and Objectives:* The objective was to perform a systematic review of randomized controlled trials to determine the effects of growth hormone therapy as an anabolic agent in healthy, physically fit or diseased young adults and/or elderly patients. The primary aim was to evaluate the effects of growth hormone on body composition, strength, basal metabolism, and exercise capacity. Additionally, evidence on adverse effects associated with growth hormone in healthy young and the quality of the published literature was assessed.

## Methods

*Data sources*: An individual search strategy was developed in consultation with co-workers, to identify potentially relevant studies from the MEDLINE, HighWire Press, EMBASE, PubMed, Google Scholar, Springerlink, EBSCO, and Wolters Kluwer Health databases. English-language reports were sought, which were indexed through May 15, 2011. Bibliographies of retrieved articles for additional studies were also searched.

***Study selection criteria*:**

*i) Inclusion:* Fully published randomized controlled trials (RCTs) or systematic reviews of RCTs were included. Additionally, crossover trials and cohort studies were also integrated. Indicators of a systematic review included: explicit search strategy, inclusion criteria, data extraction and assessment of quality. Where judged necessary and appropriate, the inclusion of evidence was considered from other non-randomized studies. In brief, those studies were chosen which (a) evaluated at least 5 participants, (b) enrolled only large variety of participants, (c) assessed participants with a mean or median age between 13 and 45 years, and (d) evaluated growth hormone as treatment for a specific illness (for example, adult growth hormone deficiency or fibromyalgia).

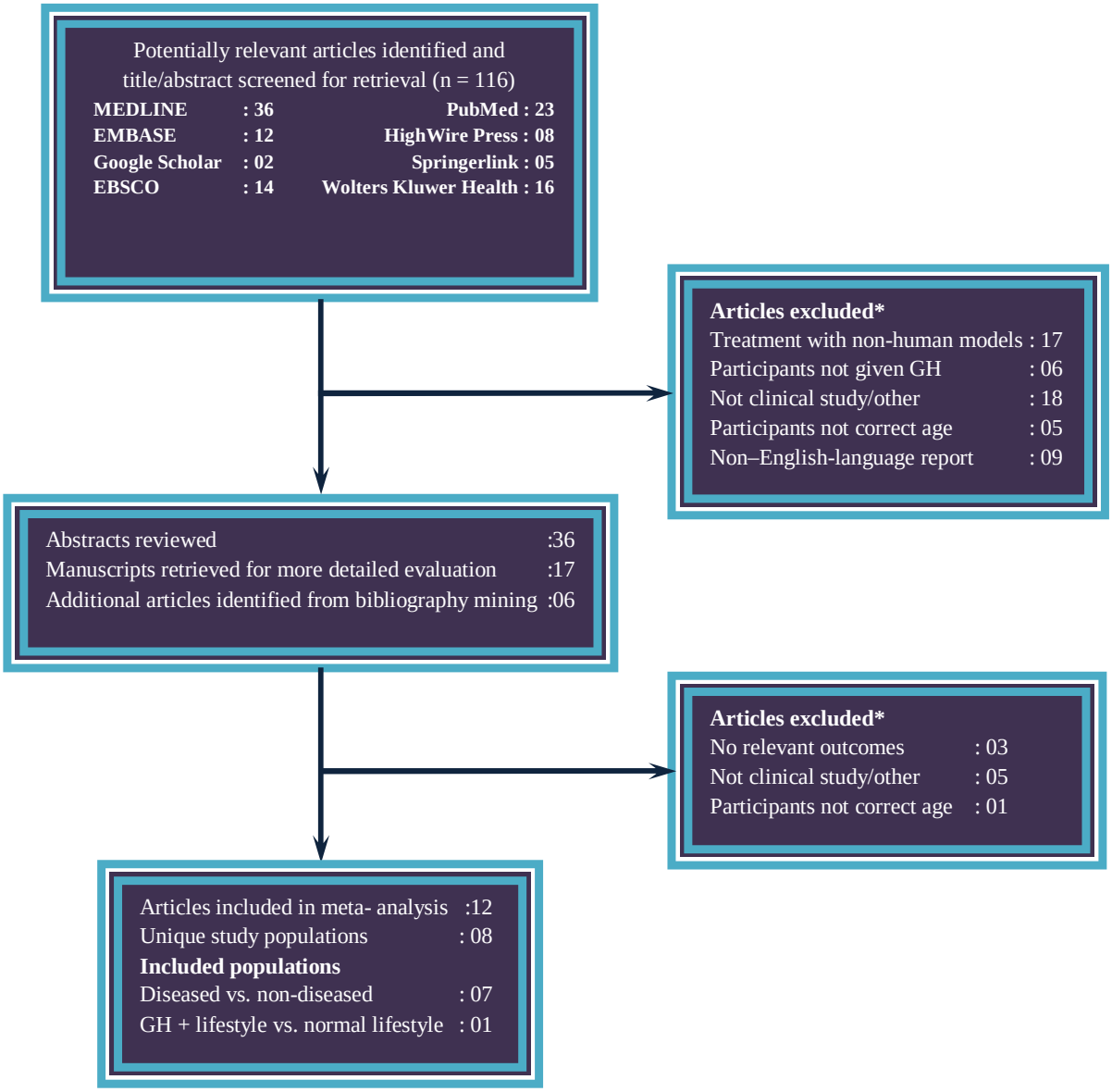
*ii) Exclusion:* The studies were excluded which (a) focused solely on evaluating growth hormone secretagogues, (b) explicitly included animal models and children subjects, (c) not written in English language.

*Keywords used in searching*: The searching was based on the words resembling ‘growth hormone’, ‘anabolic agent’, ‘somatropin’, ‘somatotropin’ and, ‘randomized control trial’.

*Data extraction*: Two authors reviewed the titles and abstracts of articles identified through the search and retrieved potentially relevant studies. Abstraction differences were resolved by repeated review and consensus. If a study did not present data necessary for analysis or mentioned results but did not illustrate any data, additional information from authors was searched. If multiple studies presented findings from the same cohort, these data were used only once in the final analysis. At each stage, any discrepancy was resolved by discussion, with involvement of a third reviewer where necessary.

## Results

The following figures summarize the results of the literature searches. A total of 116 titles were reviewed from the MEDLINE, HighWire Press, EMBASE, PubMed, Google Scholar, Springerlink, EBSCO, and Wolters Kluwer Health databases. Then from the search, 36 abstracts were reviewed in detail and 19 articles were retrieved for full-text evaluation. Moreover 5 additional studies were identified through searches of bibliographies. Multiple articles were often published on the same study sample. Thus finally 8 articles met the inclusion criteria.




*Sum may be greater than total number excluded because some studies had multiple reasons for exclusion

Figure 1. Study selection flow diagram.

**Table 1. Characteristics of the selected studies & target population**

| Reference | Study characteristics | Demographic Data |
|---|---|---|
| Byrne *et al.*, 1993 | Prospective, controlled clinical trial | Age: 45.3±4.4 yrs./ Sex: 5/5 (M/F) |
| Jones *et al.*, 1998 | Randomized, double-blind, placebo-controlled trial | Age: 49.3±1.8 yrs./ Sex: 6/6 (M/F) |
| Pupim *et al.*, 2005 | Randomized crossover study | Age: 42.4 ±15.6 yrs./ Sex: 5/2 (M/F) |
| Healy *et al.*, 2003 | Double-blind, placebo-controlled study | Age: 31±8 yrs./ Sex: 11/0 (M/F) |
| Bechtold *et al.*, 2010 | Prospective longitudinal evaluation | Age: 12.19±2.7 yrs./ Sex: 5/7 (M/F) |
| Lucidi *et al.*, 1997 | Randomized, double-blind study | Age: 26±16.7 yrs./ Sex: 6/0 (M/F) |
| Kopple *et al.*, 2008 | Prospective, double-blind, multicenter, randomized clinical trial | Age: ≥18 yrs./ Sex: 1250/1250 (M/F) |
| Esposito *et al.*, 2005 | Randomized, double blind, placebo-controlled crossover trial | Age: 43.9±7.2 yrs./ Sex: 27/0 (M/F) |

**Table 2. Clinical indication for anabolic use.**

| Reference | Indication | Dose |
|---|---|---|
| Jones *et al.*, 1998 | Adult onset GH deficiency | 0.018 U/kg/day (0.006mg/kg/day) for the 1st month, followed by 0.036 U/kg/day (0.012mg/kg//day) for the 2nd month |
| Byrne *et al.*, 1993 | GI dysfunction requiring long-term specialized nutritional support | 0.14 mg/kg per day |
| Pupim *et al.*, 2005 | Patients with chronic hemodialysis | 75µg/kg per day |
| Healy *et al*., 2003 | Endurance-trained adult athletes at-rest and during & after exercise | 0.067mg/kg per day |
| Esposito *et al*., 2005 | Patients with HIV-associated wasting | 6mg per day |
| Kopple *et al.*, 2008 | Hypoalbuminemic maintenance hemodialysis patients | 20µg/kg per day |
| Lucidi *et al.*, 1997 | Severe GH-deficient adults | 3.3 or 2µg/kg per day |
| Bechtold *et al.*, 2010 | Patients with Juvenile Idiopathic Arthritis (JIA) | 0.047mg/kg per day |

**Table 3(a). Quantitative summary of clinical effects,**

| Reference | Timeline | Clinical effects | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Body weight (kg) | | BMI* (kg/m$^2$) | | Height (cm) | | LBM** (kg) | | IGF-I^ (mmol/L) | |
| | | Placebo | Study | Placebo | Study | Placebo | Study | Placebo | Study | Placebo | Study |
| Jones *et al.*, 1998 | 0 month | 79.7±4.0 | 76.8±7.5 | 28.1±1.5 | 26.1±1.7 | NA | NA | 45.0±2.6 | 48.0±5.6 | 16.2±2.0 | 18.1±2.7 |
| | 2 month | 80.5±4.4 | 78.6±7.7 P < 0.05 | 28.4±1.6 | 26.7±1.7 | | | 47.1±3.0 | 51.7±6.3 P < 0.05 | 14.6±1.9 | 42.7±5.5 P <0.005 |
| Byrne *et al.*, 1993 | ------- | 57.7±2.2 | 54.7±2.0 | NA | NA | 175±2.0 | 171±4.0 | NA | NA | NA | NA |
| Healy *et al*, 2003 | Baseline | 74.9±3.4 | 74.4±1.1 | NA | NA | NA | NA | 61.6±2.5 | 57.6±1.1 | 25.8±2.7 | 24.6±3.0 |
| | 4 weeks | 74.7±3.3 | 77.9±1.6 P < 0.05 | | | | | 61.8±2.4 | 61.0±1.2 P < 0.05 | 25.2±2.6 | 106.3±16.4 P < 0.001 |
| Bechtold *et al.*, 2010 | Baseline | NA | 30.68±7.0 | NA | 16.42±1.6 | NA | 135.7±12.7 | NA | NA | NA | NA |
| | Final | 52.58±9.9 | 46.46±6.5 | 19.9±2.5 | 18.13±2.2 | 162.0±10.9 | 160.14±8.7 | | | | |
| Pupim *et al.*, 2005 | Before HD^^ | NA | NA | NA | NA | NA | NA | NA | NA | 31.7±4.89 | 43.2±6.55 |
| | After HD | | | | | | | | | 30.4±5.15 | 41.3±6.68 |

* BMI: body mass index; ** LBM: lean body mass; NA: Not Applicable; ^^ HD: hemodialysis; ^ IGF-I: insulin-like growth factor I;

**Table 3(b). Quantitative summary of clinical effects.**

| Study, year | Clinical variables | Placebo Group | | Study Group | |
|---|---|---|---|---|---|
| | | Baseline | Endpoint | Baseline | Endpoint |
| Jones *et al.*, 1998 | C-peptide, nmol/l | 0.40±0.12 | 0.43±0.13 | 0.23±0.06 | 0.46±0.07 P < 0.05 |
| | * NEFA, mmol/l | 0.57±0.04 | 0.58±0.04 | 0.47±0.06 | 0.63±0.04 P < 0.05 |
| Byrne *et al.*, 1993 | ** CHI | 78.5±10.5 | | 79.2±7.5 | |
| | Grip strength (kg of force) | 31.5±8.7 | | 29.9±2.7 | |
| Healy *et al*, 2003 | Total Body fat (kg) | 9.8±1.9 | 10.1±2.0 | 11.4±1.5 | 11.6±1.7 |
| | Insulin (mU/liter) | 6.0±0.3 | 9.3±2.4 | 7.9±1.6 | 16.0±9.3 P < 0.05 |
| Pupim *et al.*, 2005 | Fat oxidation, P < 0.05 (mg.kgFFM$^{-1}$.min$^{-1}$) | 0.78±0.13 | 1.05±0.06 | 1.24±0.22 | 1.65±0.20 |
| | Amino acid oxidation, P < 0.05 (mg.kgFFM$^{-1}$.min$^{-1}$) | 0.35±0.04 | 0.27±0.03 | 0.67±0.15 | 0.38±0.05 |
| Bechtold *et al.*, 2010 | Forearm length (cm) | 236.15±17.9 | | 203.75±27.31 | 237.92±22.8 |
| | Relative muscle area (%) | 71.22±10.0 | | 73.68±11.6 | 62.13±7.8 P < 0.05 |
| | Relative fat area (%) | 23.39±10.7 | | 20.79±11.9 | 32.02±8.6 P < 0.05 |
| | Relative bone area (%) | 5.40±1.3 | | 5.5±0.7 | 5.8±1.2 |
| Esposito *et al.*, 2005 | ^ TBW (liters) | 44.4±1.5 | 0.4±0.5 | 43.9±1.2 | 4.4±0.7 |
| | ^^ BCM (kg) | 36.9±1.4 | 0.3±0.5 | 36.3±1.2 | 3.2±0.6 P < 0.001 |

* NEFA, nonesterified fatty acids; ^ TBW, Total body water; ** CHI, creatinine height index; ^^ BCM, Body cell mass;

**Table 4. Outcomes of Growth Hormone as anabolic Agent.**

| Study, year | Benefits | Risks |
|---|---|---|
| Lucidi *et al.*, 1997 | - Increase in the rates of protein synthesis and lipolysis. | - Requires alertness is GH-induced insulin resistance. |
| Kopple *et al.*, 2008 | - Increase in LBM and serum transferrin and high density lipoprotein-cholesterol, a fall in serum homocysteine.<br>- Improved signs associated with better clinical effect in adult MHD patients, including LBM and serum protein levels.<br>- Enhancement in anabolism associated with an increase in insulin dosage. | - Reduced insulin sensitivity during conditions of stress or food deprivation.<br>- Increased left ventricular hypertrophy in GH-deficient adults without kidney failure.<br>- Cancer or promote cancer proliferation. |
| Esposito *et al.*, 2005 | - Anabolism in patients with HIV-associated wasting.<br>- Favorable changes in aerobic capacity and functional status. | - Arthralgia<br>- Headaches<br>- Cerebrovascular accidents |
| Byrne *et al.*, 1993 | - Increased accumulation of the protein-containing component of the lean mass.<br>- Deposition of protein in stable adult patients undergoing aggressive nutritional rehabilitation is accelerated. | - Nitrogen retention is affected. |
| Bechtold *et al.*, 2010 | - Increase in muscle and decrease in fat CSA. | - No risk found |
| Jones *et al.*, 1998 | - Increase in efficiency of leucine removal from the circulation. | - No risk found |
| Healy *et al.*, 2003 | - Increase in muscle mass. | - Physical strength reduced. |

## Discussion

The use of GH as anabolic agent is widespread and has been advocated in popular articles and in scientific literature. However, this review of the limited published literature suggests that although growth hormone may alter body composition, it has minimal effect on key athletic performance outcomes and may, in fact, be associated with poor exercise capacity. Administration of r-HGH to endurance-trained athletes exerts a protein anabolic effect both at rest and through submaximal exercise. GH increases whole body protein synthesis in normal subjects, but not in weightlifters which might signify a differential response in resistance-trained subjects. Muscle that is already hypertrophied might have less potential to further increase. Despite an increase in muscle mass, physical strength is abridged rather than increased (Healy *et al.*, 2003).

Also from the studies, most striking findings are the significant increases in muscle CSA (cross-sectional area) and total bone CSA. With GH treatment, there has been a modification in body composition with an increase in muscle and a decrease in fat CSA. In case of the GH-treated patients, in parallel to a significant increase in muscle CSA and its normalization at final height, reduction or stabilization in fat CSA occurs (Bechtold *et al.*, 2010).

GH administration increase the accumulation of the protein-containing component of the lean mass compared with the STD (standard nutritional therapy) hypercaloric nutritional therapy. GH-treated patients tend to gain more protein than those patients receiving STD. It is also suggested that substrate oxidation and storage are modified by GH, allowing for maximal protein gain without increasing $CO_2$ production or fat deposition. GH administration accelerates the deposition of protein in stable adult patients undergoing aggressive nutritional rehabilitation. IGF-1 is thought to mediate a component of the GH anabolic response and is synthesized mainly in the liver. As a result, an alteration in liver function may impair IGF-1 or hepatic synthesis and, therefore, either directly or indirectly affects nitrogen retention (Byrne *et al.*, 1993).

GH may increase the efficiency of leucine removal from the circulation which is maintained in the postprandial state after GH treatment. Since GH has been shown to have a role in regulating amino acid transporters in the gut, it is likely that GH has a similar effect in peripheral tissues (Russel *et al.*, 1998). It demonstrates significant and simultaneous increase in the rates of protein synthesis and lipolysis. However, it requires alertness is GH-induced insulin resistance (Lucidi *et al.*, 1997). On the other hand, rHGH treatment induced anabolism in patients with HIV-associated wasting. This effect is followed by favorable changes in aerobic capacity and functional status, as a result of rHGH anabolic action (Esposito *et al.*, 2005).

Patients treated with GH exhibit a considerable increase in LBM (lean body mass) and serum transferrin and high density lipoprotein-cholesterol with a fall in serum homocysteine (Pupim *et al.*, 2005). It improves

signs associated with better clinical effect in adult MHD (maintenance hemodialysis) patients, including LBM and serum protein levels. An enhancement in anabolism associated with an increase in insulin dosage was considered a potential benefit of GH treatment. On the other hand, it reduces insulin sensitivity during conditions of stress or food deprivation. GH-deficient adults without kidney failure have increased left ventricular hypertrophy after treatment. GH may stimulate isolation of β-cell lymphoid precursors, and IGF-I may promote cancer growth in vitro. Hence, there is concern that GH might induce cancer or promote cancer proliferation (Kopple *et al.*, 2008).

**Limitations**

There was not enough information on the experiment carried out on the Opportunity™ Trial (Kopple *et al.*, 2008). No comprehensive experimental data was included in the paper on the hemodialytic effect of growth hormone. Not all the trials were randomized and almost all of them included a very small number of subjects. In addition, some of the studies were conducted in a very short window of time, so the outcomes of those trials are not entirely satisfactory. On the other hand, this review covered a vast area of therapeutic outcomes, which made it very difficult to summarize appropriately.

**Suggestions**

Many of the side effects (i.e. diabetes, fluid retention, joint and muscle pain, carpal tunnel syndrome and high blood pressure) of administration of GH were seen in studies that used much higher doses of human growth hormone than are now used in elderly people. So these studies should use lower doses alone or in combination with modest doses of anabolic steroids which may illustrate a positive ratio of benefits to side effects. Well controlled clinical trials are required to explore the potential uses of human growth hormone in aged people and of its other potential utilization as an anabolic agent (Hintz, 2004). As far as, this topic should have been more specific i.e. a particular clinical condition should have been chosen, which might have helped more to confine the benefits and risks of GH use as anabolic agent.

**Conclusion**

It is difficult to draw definite conclusions from the present analyses which directly compare GH therapy with lifestyle interventions and disease conditions, given the small size of the studies and their relatively short duration. However, their findings highlight the important need for additional research to evaluate the differential effects of GH on body composition. It is also clear from this review that growth hormone does indeed have powerful effects on fat and carbohydrate metabolism, commonly acknowledged as the anabolic effect, and in particular promotes the metabolic use of adipose tissue. However, there is no proof that net protein retention is promoted in adults, except possibly of connective tissue. The over-exaggeration of the effects of growth hormone in anabolic action is effectively promoting its abuse and thereby encouraging common people to expose themselves to increased risk of disease for small benefit (Rennie, 2003).

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