GROWTH HORMONE (GH): USAGE AND ABUSE

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Abstract

Growth hormone is essential for body growth but it also modulates metabolic pathways as well as neural, reproductive, immune, cardiovascular, and pulmonary functions. Numerous beneficial effects of growth hormone have led to its expanded therapeutic use in both children and adults. There are several officially approved applications of human growth hormone and many more proposed applications that resulted from huge number of clinical studies on GH therapy.

Growth hormone abuse includes improper or excessive use. Over the last decade GH has become one of the most commonly abused drugs in sport due to the fact that its administration is currently undetectable. Enormous doses that are injected and frequent simultaneous abuse of other substances such as other anabolic steroids (testosterone) lead to frequent side effects that may be fatal.

In spite of numerous beneficial effects of growth hormone the true physiological impact of GH replacement therapy on various metabolic parameters may be confounded by the dose and route of administration of GH so accurate physicians' monitoring during GH therapy is needed.

Key words: growth hormone, therapeutic use, abuse

Introduction

Growth hormone (GH) is a polypeptide hormone secreted by the pituitary gland in a pulsatile manner every two hours with a mean daily secretion of 0.5 mg. The predominant form has a molecular weight of 22kDa and half-life in plasma of 15-20 min after secretion or intravenous injection (1). After subcutaneous or intramuscular injection, blood concentration of GH reach the peak between 1 and 3 h after injection and drop to undetectable levels 24h after administration. When administered by mouth GH is completely digested to its constituent amino acids (2). After secretion GH may be found in the system circulation in the "free" state or bind to GH binding protein (GHBP). Growth hormone receptors are present on all cells in the body. One GH molecule binds two receptors and leads to their dimerisation. This process is essential for initiation of intracellular signaling (3). The circulating GH is removed from the blood stream through receptor-mediated degradation, predominantly in the liver and kidney. The liver and kidney internalize GH receptor complex and completely degrade it to its basic amino acids. Only small quantities of GH appear in the urine(1).

Growth hormone secretion is controlled by two hypothalamic peptides: growth hormone releasing hormone-GHRH and somatostatin (SS) which are final mediators of numerous neuroendocrine, metabolic, nutritional and immune influences on GH secretion (4). The precise mechanism that mediates the effects of physiological factors on GH secretion in humans may be difficult to determine. The most important stimuli of GH secretion in humans are sleep, exercise and stress (5). The sleep-related GH secretion occurs most during the phase of deep slow-wave sleep in the early hours of sleep. In circumstances where sleep pattern is disturbed GH secretion is impaired. Results of numerous studies showed that acute physical exercise increase GH secretion within 10-20 minutes of aerobic exercise, peak at the and of exercise and remain elevated for approximately one to two hours (6). Ageing is associated with decreased concentrations of GH. In man, each decade of increasing age is associated with a 14% decline in 24 hour GH production rates (7). The total amount of GH secreted during 24 h in normal adults over the age of 65 is, in the majority of cases, concurs with people with organic GH deficiency secondary to pituitary pathology. There is, thus, evidence of the development of functional GHD with increasing age, the so called "somatopause". The majority of middle-aged and elderly normal subjects may be considered incompletely GHD.

Growth hormone is essential for body growth but as normal growth occurs over relatively short period of time and GH secretion continues through life it is not surprising that GH has many other functions that regulate body composition, fluid homeostasis, glucose and lipid metabolism, bone metabolism, exercise performance and cardiac function (8). These actions improve the quality of life of adults and confer beneficial effects when used appropriately.

Growth hormone increases protein synthesis (9). Studies of Florini and al. (10) showed that GH increased the number and activity of ribosomes and increased RNA polymerase in rat muscle suggesting that GH may control synthesis at the translation level. Growth hormone may also reduce urea synthesis increasing the availability of nitrogen for protein synthesis. When GH is replaced protein synthesis rates in the postabsortive and postprandial state

are increased which leads to protein accretion and increase in lean body mass (LBM). The effects of GH on postabsortptive glucose metabolism are more subtle. Though muscle utilisation of glucose is already low the further suppression of glucose uptake is typically seen after GH exposure. Large dose of GH were reported to decrease postabsorptive glucose output acutely, compatible with increased glucose uptake while in vitro experiments have shown increased gluconeogenesis (11). It is still beyond doubt that GH contributes to the overall insulin resistance of type 1 diabetes and also acts as initiator of the vicious circles leading to acute metabolic derangement (12).

Figure 1.1. Growth hormone molecule bound to two growth hormone receptors (Biotechnology: Science, Engineering and Ethical Challenges for the 21st Century 1996: Joseph Henry Press)

Growth hormone stimulates lypolisis. Pulsatile and continuous administration of more moderate amounts of GH 70-400 micrograms to healthy postabsortive humans reveals clear dose-dependent stimulation of lypolysis, circulation levels of free fatty acids (FFA) and glycerol and increased lipid oxidation rates (13).
All these metabolic effects influence body composition increasing LBM and decreasing fat body mass (13).
Several independent studies showed that GH is capable of affecting cardiac function by modulating preload, after load and contractility through direct and indirect mechanism (14). Some studies showed that administration of GH and IGF I reduce peripheral vascular resistance (15). Studies on animals showed that GH directly stimulates myocyte growth (14).

Growth hormone use

These numerous beneficial physiological effects of growth hormone led to extended application of the hormone in both children and adults.

The therapeutic application of human growth hormone was first demonstrated 45 years ago in the treatment of pituitary dwarf. At first, the quantities were limited and originated from cadaver pituitaries. Ever since, the number of proposed applications of human growth hormone has grown. Biosynthetic GH initially became available for prescription use in the United States in 1985. Data indicated that the first therapeutic application in 1985 was followed by clinical complications. Three young men developed Creutzfeldt-Jakob disease caused by contaminated material (16). Today, recombinant GH with amino acid sequence identical to GH of human pituitary origin is produced by several pharmaceutics companies. Growth hormone preparations that contain minimum impurities, are apparently safe and readily available.
The officially approved uses of human growth hormone vary from country to country, but generally include :

in pediatric conditions :

- *children with growth hormone deficiency or insufficiency*
  This is the most important indication for GH therapeutic application (17). The cause for the GH insufficiency is particularly important in determining appropriate treatment. Because of its pronounced anabolic effects, GH is contraindicated in children with an active malignant condition.

- *Turner syndrome*
  Growth hormone may be used in the cases of short stature induced by Turner syndrome (18). Because the growth in these patients varies the decision whether and when to treat with GH should be made on the basis of each patient's height and growth velocity.

- *poor growth due to chronic renal insufficiency (CRI)*
  Growth delay in children with CRI, resulting from numerous physiological derangements including acidosis, secondary hyperparathyroidism, malnutrition or zinc deficiency, is an important indication for GH use (19). Also, there are some pediatric conditions for which GH therapy is under investigation:
- *Idiopathic, genetic or primordial short stature* in children who are more than 2.5 standard deviations below mean. Numerous clinical trails have documented the capacity of GH to induce growth acceleration in such cases but several reports suggest that it may enhance pubertal development and may reduce the duration of growth during puberty (20).
- *constitutional delay of growth and development*
  This clinical state is characterized by normal prenatal growth followed by growth deceleration during infancy and childhood. This causes significant psychosocial adolescent stress. Of note, the use of GH in these cases will result in permanent closure of epiphysis precluding further growth (20).

- *intrauterine growth retardation and Russell-Silver syndrome*
  The children whose growth has not caught up by the age of 4 may benefit from GH therapy, as some studies have suggested (21).

- *skeletal dysphasia's*
  Growth hormone therapy was tried in several skeletal dysphasia's associated with abnormally short stature (22). Much of the experience in treating these conditions was gained in management of achondroplasia.
- osteogenesis imperfecta
  Some studies showed that this condition may be effectively treated with GH. In particular, with such treatment patients may experience improved bone mineralization and improved growth (23).

- *Prader-Willi syndrome*
  Preliminary findings suggest that GH treatment in some patients with Prader-Willi syndrome accelerates growth, reduces hyperphagia, appreciably affects lypolysis and decreases obesity (24).

- *Down syndrome and the other syndromes associated with short stature*
  Because short stature is a characteristic of many syndromes GH therapy has been attempted in several conditions including Down syndrome (25), Fanconi syndrome, Bloom syndrome.

in adults (who have completed their statural growth)

In spite of these beneficial effects AACE Guidelines for growth hormone use, list approved use of GH in adults only in cases of:

- *adult growth hormone deficiency (GHD)*
  This is the most important indication for GH replacement in adults (20). Importance of GHD in adulthood as a disease first became apparent in the late 1980s. Studies estimated total of 35000 adults with GHD in USA and approximately 6000 new cases that occur each year. GHD adults have several abnormal clinical features including increased adiposity, reduced muscle strength and exercise capacity, and impaired psychological well-being. Some of these features are normal signs of aging so certain specific biochemical criteria remain necessary for diagnosis.

- *AIDS related wasting*
  HGH may also play a role in immune reconstitution (26) and body composition improvement in AIDS patients. In addition to these generally accepted therapeutic applications of human growth hormone many proposed applications have not been established as yet. The anabolic actions of human GH made it attractive as a potential agent for catabolic problems in wide range of clinical conditions including:

- *severally catabolic patients in an intensive care environment (27)*
- *chronic catabolic states (16)*
- *burns (28)*
- *cystic fibrosis (29)*
- *inflammatory bowel disease (30)*
- *infertility short-gut syndrome (30)*
- *obesity (31)*

GH Therapeutic use in Cardiovascular Medicine

A number of animal studies have shown that therapeutic use of GH could be beneficial in experimental model of heart failure with growth promoting and positive inotropic actions. Studies by Duerr and Yang (32) demonstrated beneficial effects of exogenous administration of insulin-like growth factor (IGF-I) and GH in the rat model of post-infarction heart failure. Some studies showed remarkable enhancement of cardiac function following GH therapy in GHD patients with severe dilated cardiomyopathy (33). Following these findings, several investigations by independent groups have confirmed the efficacy of GH in more advanced stages of heart failure. Large placebo controlled trails to confirm these data are currently ongoing. Recent evidence also showed that GH secretion may be impaired in patients with less advanced stages of heart failure.

Growth Hormone Abuse

Growth hormone abuse includes improper or excessive use (34). There are a lot of scientific debates on what type of GH applications may be labeled as abuse.
Over the last decade GH has become one of the most common drugs in elite sport. For the first time it was discovered in possession of cyclists during Toure de France in 1998 (35). Since that period the abuse of recombinant human growth hormone in sports is considered to be a widespread phenomenon. Its popularity lies in the fact that it possesses marked ergogenic properties. Although growth hormone is listed as prohibited class E substance in Appendix A to the Olympic Movement Anti Doping Code no official test for the detection of GH abuse is implemented (35). Several tests are currently under study.
Although the abuse has been reported in competitive athletes, the largest groups by far that abuse GH are competitive and recreational body builders. In both groups, usually, GH is self-administered without any medical supervision (35). Enormous doses injected and frequent simultaneous abuse of other substances such other anabolic steroids (testosterone) lead to frequent side effects which may be fatal (36).

Application of human GH to increase height in children who already attained normal height should also be considered abuse (16).

Another common form of abuse of human GH is to reverse the effects of aging as it's considered to be the "fountain of youth".

There are a lot of advertisements in printed media and on the internet which promote the use of growth hormone or agents touted as increasing human growth hormone levels.Although anabolic effects and changes in body composition have clearly been associated with the application of human GH, little or no evidence exists of important positive functional effects on the process of aging in elderly people (34). Finally, the decision to treat healthy older people with GH or GH secretagogues will inevitable evoke certain ethical considerations.

Conclusion

In spite of numerous beneficial effects of growth hormone the true physiological impact of GH replacement therapy on various metabolic parameters may be confounded by the dose and route of administration so accurate physicians' monitoring during GH therapy is needed.

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