Growth Hormone and Maintaining Optimal Health

Research has demonstrated repeatedly that lifestyle changes can reduce the risk of diseases and health-compromising conditions. Not smoking, drinking alcohol moderately, lowering total and low-density lipoprotein (LDL) cholesterol levels, lowering high blood pressure, maintaining a healthy body weight, consuming a variety of healthy foods, engaging in regular physical activity, reducing stress, and ensuring sufficient sleep can help individuals optimize their health. Inadequate intake of several vitamins has also been linked to chronic diseases.¹

Ample evidence additionally exists to show that maintaining optimal levels of the body’s hormones is critical for vigor and vitality in the later years. Serum levels of many hormones decline with normal aging. Though the changes seen with aging are multifactorial, ample scientific data suggest that this normal hormonal decline is intimately involved. Specifically but not exclusively, growth hormone (GH) replacement therapy in aging adults has been shown to increase quality of life and prolong years of health.² Multi-year studies, well beyond the typical 6–12 month study protocols, have supported the positive benefits of growth hormone.³,⁴ Research studies have documented that GH therapy can positively affect many of the changes seen with aging. Physiological supplementation has been shown to decrease weight, body fat mass, and fracture rate; increase lean body and muscle mass, exercise capacity, strength, and cognitive function; and improve bone density, poor sleep, sense of well being, and immune function.⁵–¹¹

When combined with a comprehensive lifestyle and behavioral modification program, hormone optimization—the maintenance of hormone levels close to the levels of young adulthood when measures of health peak—including GH has the potential to maximize a broader preventative and maintenance therapy approach to a patient’s health. Skepticism, however, remains over the benefits of growth hormone treatment. This article does not represent an exhaustive review of the literature; rather, it offers an environmental scan of hormone replacement therapy issues.

Growth Hormone Helps Chronic Disease

Growth hormone has been reported to assist patients better manage diseases including chronic bronchitis,¹² heart disease,¹³⁻¹⁵ diabetes,¹⁰⁻¹² depression,¹³,¹⁴ anxiety,¹⁵ rheumatism,⁹,¹⁰ and wasting syndromes.¹¹

Cancer. Researchers and physicians have been concerned that GH could trigger undetected cancer cells to divide more rapidly and pro-
mote the growth of a tumor. While the question of whether GH increases the possibility of cancer is still unanswered, little in the literature supports this hypothesis. On the contrary, there are reasons to believe that GH replacement therapy given to cancer patients reduces cancer recurrence and mortality, as well as increases survival time. In one study, long-term GH therapy (60 months) reduced the increased cancer risk and mortality of GH-deficient patients by half.

Growth hormone therapy raises the levels of both insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3). A high serum IGF-1 has been found to be associated with a reduced prostate cancer risk, and a high serum IGFBP-3 has been associated with a reduced prostate cancer risk (~30%) and recurrence.

History of Growth Hormone
In the 1920s, GH was purified from pig and cow pancreases for the treatment of type 1 diabetes. However, because of the significant variations in molecular structure between pig, cow, and human GH, pig and cow GH was not effective for humans.

In 1958, Dr. Maurice Raben, a pioneering endocrinologist at the New England Medical Center in Boston, purified enough GH from human pituitary glands to successfully treat a GH-deficient boy. A few endocrinologists began to help parents of severely GH-deficient children make arrangements with local pathologists to collect human pituitary glands after removal at autopsy.

Supplies of this “cadaver growth hormone” were limited and only the most severely deficient children were treated. From 1963 to 1985, about 7,700 children in the United States and 27,000 children worldwide were given GH extracted from human pituitary glands to treat severe GH deficiency. In the late 1960s, about 100 physicians trained in the new specialty of pediatric endocrinology around the world provided most of this care.

It took thousands of cadaver brains to obtain the few drops of the hormone that could be injected into children’s tissue. Most cadaver brains came from Africa and were shipped to commercial drug manufacturers where the hormone would be extracted from pituitary glands. Since heating the hormone would destroy it, the manufacturers sterilized the extract through a kind of pasteurization.

However, by the 1980s, when children were taking GH extracts developed the same rare disease (Creutzfeldt-Jakob disease), the US Food and Drug Administration (FDA) ordered the distribution of the human GH drug stopped. With the cadaver source lost, a GH drug had to be synthesized from scratch.

Scientific Mechanism of Recombinant Growth Hormone
The anterior pituitary gland produces GH, which is a polypeptide consisting of 191 amino acids. Fashioning a molecule that size in a laboratory is a monumentally difficult task. In 1977, through new genetic engineering technology, Eli Lilly made a 191-amino acid GH that was identical—physically, chemically, and biologically—to the one made by the human pituitary.

Insulin-like growth factor-1. The pituitary gland releases GH in a pulsatile manner throughout the day. Having a very short half-life, GH only remains in the bloodstream for a few minutes. In the liver, GH stimulates the synthesis and release of growth factors (including IGF-1, also known as somatomedin C) and their binding proteins (including IGFBP-3).

The messenger that promotes most of the actions of GH, IGF-1 also has a longer half-life in the blood (being detectable for more than 12 hours) compared with GH whose half-life is less than 30 minutes. The largest release of GH occurs at night shortly after a person falls asleep. This makes accurate determination of peak levels difficult at best. Because of these reasons, IGF-1, rather than GH, is used as an indirect measure of GH secretion.

The clinical presentation of adult GH deficiency (AGHD) relates to findings, such as sarcopenia, increased body fat, osteoporosis, anxiety, fatigue, a diminished sense of well-being, and an unhealthy cholesterol profile.

Possibly due to the difficulty of accurately measuring GH levels, the laboratory diagnosis of AGHD has traditionally relied on a negative stimulation test (e.g., insulin, arginine). However, there is some validity to diagnosing AGHD through documentation of low IGF-1 levels, since in a sense it is the “active hormone” and because it is the levels of IGF-1 present in the blood rather than the pituitary’s potential ability to release GH (as reflected in a stimulation test) that is important. Similarly, one makes the diagnosis of diabetes through blood sugar and insulin levels, not through a pancreatic stimulation test.

Two main factors directly regulate the release of GH. One is GH-releasing hormone, which stimulates its release, and the other is somatostatin, which inhibits its release through a negative feedback loop that may involve GH itself. Exercise and dieting enhance GH release, while obesity and free fatty acids inhibit GH release.

Numerous studies support the relationship of healthy aging to IGF-1 levels, although it is a complex topic.

Cellular rejuvenation. Until recently, one of the few ways we could limit damage to DNA was by taking antioxidant supplements, such as vitamins C and E, to bolster our own defenses and neutralize DNA-damaging intracellular free radicals. Growth hormone and IGF-1 act like carriers, bringing cells the raw materials needed for renovation and repair. Insulin-like growth factor-1 launches the delivery of the building blocks of the nucleic acids, DNA and RNA, right into the cell nucleus, where DNA resides. This allows for the efficient repair of damaged DNA and the stimulation of normal cell division.

Growth hormone also initiates the transport of amino acids, the building blocks of protein, and nucleic acids into the cytoplasm of the cell, the area outside the nucleus. This includes the cell membranes and intracellular organelles, such as the mitochondria. In this way, GH and IGF-1 do not just minimize the damage to the DNA and cellular structures; they also help repair the cell and the DNA. Growth hormone is probably the body’s most important hormone of repair.
The supplementation of GH either by injections or by the use of GH secretagogues (amino acids, such as arginine, that may boost GH release) rejuvenates the cell’s ability to repair itself and helps correct disturbances in homeostasis. Improved homeostasis means less disease and a healthier life span.

Diagnosing AGHD Syndrome

The AGHD syndrome is a documented deficiency disease. Most patients age 60 and older have total 24-hour human GH secretion rates indistinguishable from those of hypopituitary patients with organic pituitary gland lesions. Growth hormone production by the pituitary declines by 1%–3% after the early 20s. By the time many adults reach 40 years, their GH levels have declined markedly regardless of the underlying etiology. If a mean IGF-1 of 300 ng/mL is normal for 20–30 year olds, this means that almost all men and women over the age of 40 have an IGF-1 deficit and therefore might qualify for hormone replacement therapy. In a similar manner, when a man’s testosterone levels decline to a significant degree, he is diagnosed with hypogonadism and treated with testosterone supplementation.

Symptoms of AGHD, such as increased body fat, decreased lean body mass, decreased bone density, impaired cardiac function, and other parameters, may be sufficient for a clinical diagnosis of AGHD syndrome. As previously discussed, the current laboratory diagnosis of AGHD through stimulation testing, though noteworthy, may not accurately reflect the clinical condition.

Growth Hormone Replacement Therapy in Adults

Since the 1990 publication of an article by Rudman et al suggesting that a short course of recombinant GH therapy could reverse aging-related changes in body composition in otherwise healthy men, GH use has increased rapidly in the United States and worldwide.

The exact number of people who currently use GH is unknown. Some have reported that 20,000–30,000 people used GH in the United States as an anti-aging therapy in 2004, a more than 10-fold increase since the mid-1990s. Others claim that more than 100,000 people received GH without a prescription in 2002.

Hundreds of studies since the seminal Rudman study have documented the value of GH replacement in otherwise healthy adults who have low IGF-1 levels.

Adult growth-hormone deficiency therapy. While a recently published meta-analysis by Liu et al concluded that GH cannot be recommended as an anti-aging therapy, we excluded studies that evaluated GH as a treatment for a specific illness, including AGHD syndrome.

Hernberg-Stahl et al tallied the number of doctor visits and hospital and sick-leave days from patients included in a pharmaco-epidemiological survey of hypopituitary adults with GH deficiency (for 6 months before GH treatment and 6–12 months after the start of treatment). Assistance required with normal daily activities was recorded at baseline and after 12 months of GH therapy. Quality of life (assessed using a disease-specific questionnaire, QoL-Assessment of Growth Hormone Deficiency in Adults) and satisfaction with physical activity during leisure time were assessed. For the total group (n = 304), visits to the doctor, number of days in the hospital, and amount of sick leave decreased significantly after 12 months of GH therapy. Patients needed less assistance with daily activities (significant only for men). Quality of life improved after 12 months of GH treatment, and both the amount of physical activity and satisfaction with level of physical activity improved after 12 months.

Murray et al administered a low-dose GH regimen to 67 adults with GH deficiency. Significant improvements in total cholesterol, LDL, triglycerides, and ratio of total cholesterol to high-density lipoprotein (HDL) were seen.

Molitch et al found that GH therapy offers benefits in body composition, exercise capacity, skeletal integrity, and quality of life measures and that the risks of GH treatment are low.

Side effects. Additional studies have found that GH therapy in adults is tolerated with minimal or no side effects. Huang et al, for example, cited the benefits of low-dose GH without mention of side effects.

In a single-center study of 118 adults with AGHD, Goetherstrom et al examined the effects of 5 years of GH replacement on body composition, bone mass, and metabolic indices. The mean initial GH dose was 0.98 mg/day. The dose was gradually lowered, and after 5 years, the mean dose was reduced to 0.48 mg/day. The mean IGF-1 SD score increased from -1.73 at baseline to 1.66 at study end. A sustained increase in lean body mass and a decrease in body fat were observed. The GH treatment increased total body bone mineral content as well as lumbar (L2–L4) and femur neck bone mineral contents. Body mass density in lumbar spine (L2–L4) and femur neck were increased and normalized at study end. Total and LDL cholesterol decreased, and HDL cholesterol increased. At 5 years, serum concentrations of triglycerides and hemoglobin A (1c) were reduced compared with baseline values. The study concluded that 5 years of GH substitution in adults with GH deficiency is safe and well tolerated. The effects on body composition, bone mass, and metabolic indices were sustained. The effects on body composition and LDL cholesterol were seen after 1 year, whereas the effects on bone mass, triglycerides, and hemoglobin A (1c) were first observed after years of treatment.

Gillberg et al evaluated the safety and effects of a fixed low dose of GH, 0.17 mg/day for 3 months, on glucose metabolism, serum lipids, body composition, and cardiac function in 53 adults with GH deficiency. At 3 months, serum levels of IGF-1, IGFBP-3, and lipoprotein (a) and lean body mass increased. Total and LDL cholesterol levels and fat mass were reduced. There was a small but significant increase in the serum glucose value at 120 minutes after an oral glucose tolerance test (performed at 3 months). No other changes in glucose metabolism or cardiac function were noted. This fixed low-dose regimen resulted in improvements in body composition and lipid profile without causing serious side effects. Other studies have noted that altered blood sugar levels return to normal after 6–12 months.
Ahmad et al. recommended the use of low-dose GH therapy after finding that it improves body composition and quality of life as early as 1 month after commencement, with beneficial effects continuing at 3 months, and that these changes occur in the absence of side effects.

No deaths or permanent life-threatening morbidities have been reported as a result of GH use by adults with GH deficiency who are otherwise healthy.

Clinical Applications and Pathways

Physical examinations and tests. In addition to the general physician workup, including a history and physical, blood cholesterol (LDL, HDL, and total), blood glucose, and blood pressure, some of the following tests should be conducted prior to instituting hormone replacement therapy at 1 month after therapy commencement and every 3 months thereafter once key biomarker hormone levels are stable.

Level 1. Overall body function. Biomarkers on the physiological level of overall functioning are listed in Table 1.

Table 1
Biomarkers on the Physiological Level of Overall Functioning

- Muscle mass/body fat ratio
- Weight
- Flexibility
- Bone density
- Forced vital capacity (measure of lung function)
- Aerobic capacity
- Tactile response time
- Forced expiratory volume
- Blood pressure and heart rate

Level 2. Laboratory analysis. Biomarkers, including biochemical assays of key biomarker hormones, should be checked and optimized as part of a comprehensive health program; these hormones, however, are not affected by GH treatment. In addition to IGF-1 and IGFBP-3, levels of the hormones listed in Table 2, which also have been found to decline as part of normal aging, should be monitored and treated as needed.

Level 3. DNA analysis. Biomarkers on the chromosomal level are currently being developed and include telomere position and DNA strand breakage rates. A breakthrough blood test can track damage to the DNA to assess the effect a GH regimen is having on reducing damage to DNA.

Assessment of Growth Hormone Deficiency in Adults Questionnaire. The Assessment of Growth Hormone Deficiency in Adults Questionnaire can be a useful complement to the clinical evaluation of patients with GH deficiency.

Proper dosage. The aim of wellness-oriented physicians is to help their patients with GH deficiency optimize levels of essential hormones. Customizing the proper dosage for each individual patient is accomplished through regular clinical examinations and laboratory testing. The final decision to treat adults with GH-deficiency requires thoughtful clinical judgment with a careful evaluation of the benefits and risks specific to the individual.

When the correct physiologic dosage is properly determined and monitored by a qualified physician, adverse effects of GH replacement therapy in adult patients are minor and self-limited (side effects disappear by decreasing the dosage or ceasing treatment). The side-effect profile generally does not apply to clinical treatment where low doses are used initially and doses are slowly ramped up or decreased if side effects occur. Also, when the same total dose is divided daily over a week (instead of administered 3 days a week), side effects are diminished or absent.

One approach to titrating the dosage to an individual’s optimal level is to use end-results based on patient symptomatology (e.g., patient’s energy, physique, mood, cardiovascular measures, blood pressure, cholesterol) and monitor IGF-1 levels to be sure they remain within a physiological range. Hopefully, in the future, IGF-1 levels will be monitored during an individual’s prime years as a means of determining his or her personal ideal IGF-1 level.

Route of administration. Individual patients typically self-administer approximately 1 unit of GH in the subcutaneous tissue of the anterior thigh or lower abdomen via an insulin syringe every evening (or 6 nights a week) at bedtime.

Regulatory Issues

Physicians can legally prescribe GH to patients who have a deficiency of this hormone. The definition of “deficiency” has been open to interpretation. As mentioned, stimulation tests are commonly utilized for this purpose; however, one can be led astray by treating a lab result rather than the patient’s clinical symptoms.

History. Synthetic anabolic steroid hormones, such as those abused by some professional athletes and body builders looking for an “edge,” have
Conditions being investigated for the effects of GH include bone loss in men, GH deficiency, GH deficiency in young adults age 18–35 years, cardiovascular risk, traumatic brain injury, adults with low GH who survived childhood cancer where treatment caused low bone density, and fibromyalgia. Five clinical trials for patients with HIV infection were designed to investigate the effects of human GH therapy on the following conditions: HIV infections, lipodystrophy, insulin resistance, metabolic syndrome X, body weight changes, and diabetes.

Only 1 of the 24 studies addresses the elderly population. This study will evaluate the independent effects and interaction of human GH and testosterone in 108 men age 65–90 years who were identified as being deficient in those two hormones. This clinical trial began enrolling subjects in September 2002 at Tufts University (Boston, Mass) and Washington University School of Medicine (Saint Louis, Mo) and was scheduled for completion in April 2007 but still is listed on ClinicalTrials.gov as recruiting subjects.

We repeated the search on ClinicalTrials.gov in August 2008 using the same terms. Interestingly, there are now 373 clinical trials registered using the term “human growth hormone.” The repeated search using the term “adult human growth hormone deficiency” resulted in 41 studies of which 22 studies are recruiting children and adolescents only and 2 studies were limited to the elderly population.

Additional research. Prospective, randomized, multicenter, clinical trials that enroll and follow large numbers of adult and elderly patients who are hormone deficient over the course of many years are needed to overcome limitations of previous studies (most notably short duration and inadequate or incomplete follow-up) and to resolve remaining contradictory research findings and scientific disputes with respect to the effects of human GH on health outcomes.

A team of internationally renowned research scientists has already assembled to complete a full clinical research protocol to further study human GH on adults. The trial’s design will include randomization, treatment comparison groups, uniform study eligibility criteria, evidence-based diagnostic measures, and standardized outcome variables. The study will be conducted under proper regulatory oversight and abide by the Code of Federal Regulations (Title 21 CFR). Protected health information will be assessed in accordance with the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA), Title 45, US Code of Federal Regulations 164.501, 164.508, and 164.512.

Conclusion

Although human GH is not “a fountain of youth,” it has tremendous promise for treating adults whose pituitary glands release insufficient amounts of GH. This includes people in the fastest growing segment of the population—those over 65 years of age. Replacing essential hormones that decline with age may be as important as replacing insulin for people with diabetes. The benefits of GH therapy, moreover, can be maximized when included in a broader, comprehensive treatment program that includes balancing other hormones as well as modifying diet and physical activity based on each patient’s unique medical profile.
While studies, new and old, provide convincing evidence that GH enhances health and quality of life, skepticism remains with respect to the benefits of GH treatment. To provide reassurance that GH can be a safe and necessary form of hormone replacement therapy for adults with GH deficiency, the accumulation of long-term treatment data is required.

A new clinical trial whose methodological design will allow for a large enough sample size and a long enough follow-up period will help develop objective answers to some remaining scientific disagreements on the value of human GH for adults.

**References**


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