

Review of Growth Hormone Therapy

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Abstract

Hormone replacement therapy (HRT) is a well studied and accepted means of preventing disease and the symptoms associated with aging.¹ In addition to a reduced production of the hormones estrogen, progesterone, dehydroepiandrosterone (DHEA), and testosterone, the production of growth hormone declines with age.² Associated with the decline in these hormones is an increase in incidence of cardiovascular disease, osteoporosis and diabetes.³ In addition, an increased tendency towards central obesity and a decline in total muscle mass are associated with the aging process.² New research is providing evidence of a protective effect of growth hormone replacement in aging individuals against the aforementioned diseases and body changes.^{4,5} Adverse effects of excess growth hormone have also been documented. These include an increased rate of proliferation of breast and prostate epithelial cells.^{6,7} Research is needed to determine the lowest possible dose of growth hormone that can be used to obtain benefit from this therapy and to limit the adverse effects.

Background

Growth hormone (GH) is one of the seven hormones produced in the anterior portion of the pituitary gland. Growth hormone (somatotropin) is produced in the somatotrope cells (which make up 30-40% of the cells) of the anterior pituitary gland. The secretion of GH by the anterior pituitary is controlled by growth hormone releasing hormone (GHRH) and growth hormone inhibitory hormone (somatostatin) secreted by the hypothalamus. Normal secretion of GH occurs in a diurnal rhythm, and varies with exercise, sleep, stress and nutritional status. Unlike the other hor-

mones secreted by the pituitary gland, GH has no single target gland; rather, it has a more universal effect.

Growth hormone has been used for over thirty years for the treatment of children suffering from a GH deficiency. It was extracted from the hypophyses of cadavers in Africa; however, this practice resulted in an outbreak of Creutzfeld-Jakob disease in a small number of children undergoing treatment. In the 1980s Eli Lilly developed and patented a recombinant-DNA version of human GH, (rhGH), which has been utilized ever since for the treatment of GH deficiency. This form of GH is supplied in an injectible form.

It is recognized that associated with aging there is a natural decline in hormone production (estrogen, progesterone, dehydroepiandrosterone (DHEA), testosterone, and GH).⁴ With advancing age, an increase in incidence of osteoporosis, heart disease, and diabetes, as well as the development of central obesity and muscle wasting occur.⁸ Studies are demonstrating a causal relationship between the decline in hormones and the increased incidence of the aforementioned diseases, and body changes.^{2,9} In hormone replacement therapy, estrogen and progesterone are given to postmenopausal women as preliminary studies indicate a protective effect of these hormones against these age-related changes.¹ DHEA and testosterone replacement is currently being studied, and initial results reveal a protective effect of replacing these hormones against age-associated diseases as well.^{10,11}

Via genetic engineering techniques, prokaryotic microorganisms are able to synthesize identical-to-human forms of GH, making GH therapy safer and less expensive for patients. The reduced cost and improved safety have led to a surge of interest in GH and its potential "anti-aging" effects.¹² Studies are necessary to determine

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the efficacy and safety of GH replacement in preventing and treating age-associated diseases and symptoms such as cardiovascular disease, osteoporosis, diabetes, obesity, and muscle wasting. Clinical trials are currently under way to determine the impact of GH replacement on the aforementioned diseases and symptoms. Initial results of the clinical trials are promising,^{5,13-14} and in the future we may see GH replacement as a part of a standard hormone replacement program (estrogen and progesterone), along with DHEA and testosterone.

Laboratory Analysis

Growth hormone production increases in children with age. The serum values of GH measured in children range from undetectable to 16ng/mL.¹⁵ Normal serum values of GH decline with advancing age and range from 0-5 ng/mL and 0-10 ng/mL in men and women respectively.¹⁵ GH must be measured at consistent times (6-8 a.m.), due to the diurnal rhythm.¹⁵

GH stimulates the liver to form small proteins called somatomedins; of the four different somatomedins isolated, somatomedin-C is believed to closely reflect the secretion of growth hormone.¹⁵ Somatomedin-C promotes the transport of glucose through membranes, and thus has been referred to as insulin-like growth factor (IGF-1).¹⁶ Plasma IGF-1 is measured as an indirect indicator of GH status.¹⁵ Normal values of IGF-1 (plasma) decline with advancing age and range from 43-178 ng/mL and 24-253 ng/mL in men and women respectively.¹⁵

Biological Effects of Growth Hormone

GH enhances growth at the cellular level by promoting cell mitosis and causing differentiation of certain types of cells (in particular osteoblasts and myocytes).^{17,18} Enhancing cellular growth may be beneficial in the treatment of osteoporosis, cardiovascular disease, and muscle wasting. However, enhancing cellular growth may

not be desirable in many disease states, particularly cancer.

GH is bound weakly to plasma proteins in the blood, and has a very short half-life. IGF-1 binds tightly to plasma proteins, resulting in a prolonged half-life. Due to its enhanced half-life, IGF-1 extends the effects of GH in the body.

GH enhances transport of amino acids through the cell membrane to the interior of the cells resulting in increased protein synthesis within the cell. In addition, intercellular protein synthesis is increased by up-regulation of RNA translation and DNA transcription.¹⁵ This provides a sparing effect on the rest of the body cells by decreasing the breakdown of protein within the cells.

The structure of IGF-1 is similar to that of insulin, having 43% sequence homology with human proinsulin.¹⁹ Administration of GH to hyperglycemic patients has resulted in an improvement in blood glucose, and other measures of glucose regulation.²⁰

Age-Related Decline

GHRH,²¹ GH secretion, IGF-1 levels and Growth Hormone Binding Protein (GHBP)²² are reduced and somatostatin is increased in healthy older people.²³ It has been suggested that this somatopause may be in part responsible for the symptoms and diseases associated with natural aging. Supplementing aging individuals with hGH to the physiologic levels of GH found in that of the younger population are being studied.²⁴

The age-related decline in GH production (somatopause) can be likened to the age-related decline in estrogen and progesterone (menopause) in women and the decline in DHEA and testosterone (andropause) in men. Hormone Replacement Therapy (HRT), supplementation with both estrogen and progesterone to women in order to achieve premenopausal levels, is a well-studied and accepted form of preventive medicine.¹ Supplementation of men with DHEA and testosterone is currently

being investigated, and may become as commonplace as standard HRT in women. By comparison, supplementation with rhGH to elevate plasma IGF-1 levels to that of a pre-somatopausal level, may be a part of a preventive HRT regime in the future. Adverse effects have been associated with standard HRT (an increase in both uterine and breast cancer), as have adverse effects with GH (an increase in both uterine and prostate cancer). It is necessary for practitioners to evaluate each patient's personal and family history to determine the safety of HRT and to assess the benefits versus the risks of this therapy. Monitoring the levels of GH/IGF-1 is essential in order to maintain patients' levels within a physiologic range.

Osteoporosis

Biological Effects

GH has multiple effects on bone including an increased conversion of chondrocytes into osteogenic cells, increasing activity of the chondrocytic and osteogenic cells, and stimulation of the osteoblast cells.^{17,25,26} These cellular changes are important in the regulation of growth of long bones, and in the maintenance of bone density. In addition to its cellular effects, GH (via IGF-1) stimulates renal 25-hydroxyvitamin D-1alpha-hydroxylase activity, thereby enhancing calcium and phosphate absorption in the intestine.²⁶

GH/IGF-1 and Bone Density

Studies provide support for a relationship between plasma IGF-1 and bone mineral density in healthy elderly.²⁷⁻²⁹ It has been suggested that an impairment of IGF-1 production is involved directly in the pathogenesis of osteoporosis.³⁰

Clinical trials of GH therapy have revealed increases in laboratory measures of both bone formation and bone resorption in postmenopausal women.^{31,32} When a low dose of IGF-1 was administered relative to a high dose of IGF-1 this provided the ben-

efit of increasing the measures of bone formation, while only minimally increasing the measures of bone resorption.³³ This supports the growing trend in research towards a lower dose of hormone replacement therapy.

Injections of GH (20 mcg/kg/day) have been administered to increase IGF-1 concentrations from an (aging) low normal baseline, to that of a young normal level, and significant increases in total hip bone mineral density of 1-2% were observed.³⁴ Further study is necessary to determine the safety and efficacy of GH in the prevention of postmenopausal osteoporosis and to determine the effects of standard HRT on these results.³⁵

Hormone Replacement Therapy

Estrogen and progesterone administration is being utilized for the prevention and treatment of postmenopausal osteoporosis.³⁶ Some studies have revealed an inhibition of serum somatomedin and an increase in serum GH levels in response to estrogen replacement.³⁷ Future hormone replacement regimes may consider utilizing measures of IGF-1 and GH in addition to serum estradiol and progesterone in order to provide a more complete program of osteoporosis prevention.

Cardiovascular Association

Blood Lipid Levels

Adults suffering from GH deficiency suffer from hypercholesterolemia and an increase in cardiovascular mortality.³⁸ Substitution of these adults with GH results in a decrease in total and LDL cholesterol levels, and an improvement in body mass index.³⁹

Studies of healthy adults reveal an inverse relationship between IGF-1, body mass index, and lipid levels (in particular HDL levels).⁴⁰ It is suggested that the cardiovascular benefits reported with the use of standard HRT may be mediated via the effect of estrogen on GH levels.⁴⁰

Cardiac Function

GH stimulates myocyte hypertrophy and contractility.¹⁸ A rat model of impaired cardiac performance (following experimentally induced myocardial infarction) was used to study the impact of GH therapy. Utilizing physiologic doses of GH, there was a significant improvement in systolic function without evidence of cardiac hypertrophy.⁴¹

Vascular Density

GH and IGF-1 play a role in vascular maintenance and remodeling. Studies of rats have indicated improved vascularity with increasing plasma IGF-1.⁴² Neurodegenerative changes associated with aging have been linked to a decline in cerebral blood flow. Increasing IGF-1 may prevent this disease process.

An increased risk of cardiovascular disease occurs when IGF-1 is measured outside of the normal range (either excess or deficiency). It has been suggested that replacement doses of GH (maintaining IGF-1 within the physiologic range) in the elderly will provide the cardiovascular benefits desired of GH therapy.⁴³ However, it is necessary to monitor GH therapy (via plasma IGF-1) to insure the safest dose, as increasing beyond the physiologic range may lead to adverse cardiovascular effects.

Body Mass Index

Aging is associated with a decline in growth hormone production, and an accumulation of body fat. A negative association exists between plasma IGF-1 and BMI.⁴⁴

A study of healthy elderly men supplemented with hGH resulted in an increase in lean body mass of 8.8%, a decrease in adipose tissue of 14.4% and an increase in bone density of 1.6% ($p < 0.05$ for all parameters).⁴⁵ Elderly women (age 66-82) given rhGH revealed an increased nitrogen balance after one week of treatment, indicative of an increase in whole body and muscle protein synthesis.⁴⁶

A study of 83 healthy elderly men re-

sulted in an increase in lean body mass to 106% of baseline and a decrease in adipose to 84% of baseline. The body composition responses after 12 months of treatment were larger in men whose mean IGF-1 level was 0.5-1.0 units/mL than they were in those whose mean IGF-1 level was 1.0-1.5 units/mL, and the side effects were fewer in this lower range.⁴⁷ This lends support to an optimal dosing range, within physiologic range, above which side effects are noted and below which the therapy is of decreasing benefit. Future study is necessary to determine the optimal range of therapy to provide beneficial results and safety.

Immune System Effects

Research indicates a partial deficiency in growth hormone production, which develops with age.¹² On average GH production declines by 14% with each decade in normal adults after 20 years of age. An increase in immune related disease including cancer and herpes zoster occurs with age, and may be associated with a decreased production of GH/IGF-1. With age, abnormalities in certain neutrophil functions occur. In vitro administration of GH to these neutrophils normalizes function.⁴⁸ Studies have revealed a reversal of other abnormal parameters of immune system function in aging humans and primates with supplementation of GH and/or IGF-1.⁴⁹

Muscle wasting is a serious complication of cancer. Growth hormone could potentially limit muscle loss, and improve immune function, however studies are necessary to determine if growth hormone will promote tumor growth. Initial studies in a tumor-bearing animal model indicate a reduction in metastasis and an improvement in host body weight.⁵⁰ The benefits and risks of GH therapy in cancer treatment will likely be tumor-dependent as suggested by varying levels of IGF-1 receptors in different tumor types.⁶

Breast and Prostate Cancer

Insulin-like growth factors are known to be mitogenic and influence proliferation of many cell types, including breast epithelial cells.^{51,52} Interventions designed to reduce circulating IGF-1 levels are currently under investigation. In addition to direct effects, IGF-1 has been shown to synergize with estrogen in stimulating the growth of breast cancer cells in vitro. Tamoxifen, a drug with known antagonism to estrogen receptors has demonstrated increased efficacy when plasma levels of IGF-1^{53,54} and GH were reduced.^{55,56}

Initial studies in an aging model indicate an increase in mammary gland size and epithelial cell proliferation directly associated with GH and IGF-1 supplementation.⁵⁷ Due to the potential induction of carcinogenesis by both GH and estrogen, and the additive effect of the two hormones, safety of these hormones must be evaluated on an individual basis.

IGF-1 is a potent mitogen for prostate epithelial cells. In prostatic tissue, androgens may stimulate epithelial growth by an interaction with the IGF system.^{7,58} Plasma IGF-1 levels have been found to positively correlate with risk of prostate cancer.⁵⁹⁻⁶¹ Finasteride exerts an antiproliferative effect, beneficial for the treatment of benign prostatic hyperplasia (BPH) and has been shown to inhibit both IGF-1 and the expression of IGF-1 receptors in the prostate.⁶²

Treatment of rats with IGF-1 led to increased growth in prostatic epithelial cells.⁶³ The treatment of "andropause" with DHEA and testosterone is a new form of preventive medicine. Because of the potential of these hormones to promote an androgen dependent cancer, it is necessary to measure these hormones (serum DHEA-S and serum testosterone) in addition to other laboratory measures of disease (prostate specific antigen (PSA)). In addition because of the potential of GH to promote prostatic epithelial cell growth, the use of this hormone in the treatment of andropause will require close moni-

toring of the plasma IGF-1 levels.

Diabetes

The structure of IGF-1 is similar to that of insulin and can induce metabolic effects through the insulin receptors. Because of the structural similarity of IGF-1 to insulin, GH administration may provide benefit in the treatment of hyperglycemia and insulin resistance in diabetes.⁶⁴ Clinical trials are currently evaluating GH and IGF-1 supplementation, and provide evidence of beneficial results.⁶⁵

Conclusion

It is necessary to determine optimal levels of IGF-1 for an aging population in order to take advantage of the beneficial effects of GH and to avoid the adverse effects associated with elevated levels of GH. As with standard HRT supplementation, GH may have adverse effects and the risks need to be evaluated and monitored by a health care practitioner. Maintaining IGF-1 within a physiologic range may provide the patient with a safe and efficacious means of monitoring GH therapy.

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