

Growth Hormone Replacement in Older Men

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Discussion in this article is limited to hyposomatotropism of aging. For more information on adult growth hormone deficiency (GHD)

The decrease in lean body mass and increase in adipose tissue that occurs with aging have been suggested to be partly due to the age-associated decrease in growth hormone (GH) secretion and insulin-like growth factor-1 (IGF-1), also known as somatomedin C, which is produced by the liver and other tissues in response to GH. This decline in the secretory activity of the GH-IGF-1 axis has been termed somatopause or hyposomatotropism of aging. Whether this decrease in GH secretion should be treated is debatable.^[1, 2, 3, 4, 5, 6, 7, 8, 9, 10]

Pathophysiology

GH secretion

GH is released from the anterior pituitary gland in a pulsatile manner. Two hypothalamic hormones control GH secretion: Growth hormone-releasing hormone (GHRH) stimulates GH secretion, and somatostatin inhibits it. The majority of GH secretion occurs at night during slow-wave sleep, when somatostatin release is diminished.

GH stimulates production of IGF-1 in the liver and other tissues. IGF-1 circulates through the bloodstream bound to 6 specific binding proteins in several combinations. The major serum IGF-binding protein is insulinlike growth factor binding protein-3 (IGFBP-3). Both GH and IGF-1 have important metabolic actions in several tissues.

A single measurement of plasma GH levels is difficult to interpret because of the pulsatile secretion of GH. Levels of IGF-1 vary little during the day; therefore, assays of IGF-1 have been used as a better screening indicator of the status of the GH-IGF-1 axis.

Effect of age on GH secretion

Several studies have shown that the amplitude of GH pulses is reduced with aging both in men and women.^[11] In aging men, GH secretion declines by 50% every 7 years after age 18-25 years. The negative effect of age on 24-hour mean serum GH is twice as much in men as in premenopausal women. Estrogens may have a protective effect that limits the rate of decline of GH secretion with aging.

IGF-1 and IGFBP-3 levels also decrease with aging. This decline of the GH-IGF-1 axis is probably caused by altered hypothalamic regulation (ie, decrease in GHRH and increase in somatostatin), rather than a decreased capacity to secrete GH.

The pathophysiology of the somatopause is confounded by several variables that can contribute to the decline in GH secretion associated with aging. These variables include the following:

- **Adiposity:** Individuals who are moderately to markedly obese have profound suppression of GH secretion at any age.
- Decreased production of sex steroid hormones: Falling levels of testosterone in men and estrogens in women affect GH secretion.
- Decreased physical fitness: A strong correlation exists between aerobic capacity and 24-hour serum GH concentration.
- Fragmented sleep: GH secretion can be affected by altered sleep patterns because it occurs predominantly during slow-wave sleep.

- Malnutrition: Poor nutritional status negatively affects IGF-1 synthesis and action.

Epidemiology

Frequency

United States

Incidence is unknown because somatopause may be part of normal aging rather than a disease.

Age

In aging men, GH secretion declines by 50% every 7 years after age 18-25 years.

History

GHD in adults causes changes in body composition that are similar to those occurring with normal aging.

- Decrease in lean body mass
- Increase in total and abdominal fat
- Decrease in muscle strength
- Decrease in bone mineral density

Causes

The pathophysiology of somatopause is confounded by several variables that can contribute to the decline in GH secretion associated with aging: adiposity, decreased production of sex steroid hormones, decreased physical fitness, fragmented sleep, and malnutrition (see Pathophysiology).

Differential Diagnoses

- [Hypopituitarism \(Panhypopituitarism\)](#)
- [Obesity](#)
- [Sleep Disorders](#)

Laboratory Studies

A single measurement of plasma GH levels is difficult to interpret because of the pulsatile secretion of GH. Levels of IGF-1 vary little during the day; therefore, assays of IGF-1 have been used as a better indicator of the status of the GH-IGF-1 axis. Plasma IGF-1 levels decrease with aging, and an inverse correlation exists between age and IGF-1 levels. A cutoff IGF-1 level cannot be used for diagnostic purposes because the GH-IGF-1 axis is influenced by other factors besides aging (see Pathophysiology). Furthermore, evidence of an association between IGF-1 levels and measures of muscle strength, body composition, and physical functioning in older adults is lacking.

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According to 2007 consensus guidelines for the diagnosis and treatment of adults with GH deficiency,^[12] the following patients should be considered for testing for growth hormone deficiency (GHD):

- Patients with signs and symptoms of hypothalamic-pituitary disease
- Those who have received cranial irradiation or tumor treatment
- Those with traumatic brain injury or subarachnoid hemorrhage

In these patients, a low IGF-1 concentration increases the likelihood of GHD. Further testing may include a stimulation test, such as the insulin tolerance test (ITT), GHRH + arginine testing, GHRH + GHRP testing, or a glucagon stimulation test. The ITT is contraindicated in patients with ischemic heart disease or seizure disorders, and many authorities prefer not to use the ITT in patients older than 60 years.^[13] Patients who are deficient in at least 3 pituitary hormones and have an IGF-I level below the reference range have a greater than 97% chance of being GH deficient. For more details on how to diagnose GHD, see [Hypopituitarism \(Panhypopituitarism\)](#).

Medication Summary

According to a 2011 systematic review, [GH replacement](#)^[14] is effective in reversing some of the changes that occur in older adults (aged >60 y) with GH deficiency secondary to hypopituitarism. The effects of GH replacement in these patients include the following:

- Decreased waist circumference (by about 3 cm) and waist-to-hip ratio without changing BMI; GH increased lean body mass and decreased total fat mass in 4 studies but not in another 2.
- Reduction in total cholesterol level by 4-8% and low-density lipoprotein cholesterol (LDL) by 11-16% but no change in HDL and triglycerides
- Improvement in quality of life
- No consistent improvement in blood pressure or bone mineral density; additionally, no data are available on GH-deficient patients older than 80 years.

Growth hormones

Class Summary

Most studies of GH supplementation in healthy older people (not GH deficient) have shown that in both men and women, GH increases muscle mass and decreases body fat, but it does not improve strength. In a 6-month study, the combination of testosterone and GH also increased total body isotonic strength and aerobic capacity in older men.^[15] GH reduced serum leptin and LDL-C and increased triglycerides, with no effect on HDL.^[16] Common side effects were arthralgias and carpal tunnel syndrome.

One month of a small dose of GH (ie, 6.25 mcg/kg/d) alone or in combination with transdermal testosterone did not improve strength, flexibility, or percentage of body fat, but it improved certain measures of balance and physical performance in healthy older men. At such a small dose, there were no significant adverse events. In another study, GH did not enhance the positive effect of exercise on muscle strength.^[17, 18]

A systematic [review](#) of randomized trials of GH therapy in 220 older men and women reported that GH therapy decreased fat mass and increased lean body mass without change in weight. Despite the improvement in body composition, persons treated with GH were significantly more likely to develop soft tissue edema, arthralgias, carpal tunnel syndrome, and gynecomastia. The authors concluded that GH cannot be recommended as antiaging therapy.^[6]

GH secretagogues that would produce a more physiological increase in circulating GH levels are under investigation. These include GHRH and the growth hormone releasing peptides (GHRPs) and their analogs. Six months treatment with daily GHRH improved performance in cognitive tests compared to placebo in healthy older adults. An orally active GH secretagogue, MK-0677, was studied in older adults with recent hip fractures.^[19] Although it increased serum IGF-1, it did not improve functional performance measures significantly.^[20]

GH treatment in frail older people

In a placebo-controlled trial of patients aged 64-99 years who were malnourished, GH caused a rise in circulating IGF-1, an average weight gain of 2.2 kg, and an increase in nitrogen

retention.^[21] Older individuals are more sensitive to GH replacement than children and young adults; therefore, the dose of GH must be lower. Treating older adults with the amount of GH produced in healthy puberty (ie, 23-35 mcg/kg/d) can cause glucose intolerance, arthralgias, fluid retention, carpal tunnel syndrome, and, rarely, papilledema.

Complications

Adverse effects of growth hormone replacement

- Carpal tunnel syndrome
- Gynecomastia
- Glucose intolerance
- Arthralgias
- Myalgias
- Peripheral edema
- Papilledema (rare)

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