Growth Hormone and Aging

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KEYWORDS

• Growth hormone • Human aging • GH resistance • GH deficiency • Somatopause

KEY POINTS

- In adults, growth hormone (GH) contributes to maintaining cardiac function, glucose homeostasis, bone mineralization, appropriate balance of adipose lipogenesis and lipolysis, and skeletal muscle anabolism.
- GH secretion decreases with aging, a process known as somatopause.
- GH deficiency (GHD) because of organic pituitary disease presents with more marked physical features compared with somatopause, such as increased risk and bone fragility, unfavorable fat/lean mass ratio, reduced muscle strength, and psychological deficiencies.
- Although extended longevity has been observed in GH deficient- (GHD) or GH-resistant mice, this statement could not be applied to untreated human GHD.
- The relative deficiency in GH that occurs with normal aging (somatopause) has been proposed to have a possible causal association with age-related changes, but a causative role in aging is yet to be established. Therefore, GH treatment as anti-aging therapy is not recommended

BACKGROUND

The number of people aged 60 and older outnumbers children younger than 5 years.[1] For the first time in history, life expectancy exceeds 60 years worldwide.[1] The United Nations General Assembly has declared the upcoming decade as a decade of healthy aging to improve older people's lives. An increasing number of anti-aging methods have been proposed to halt or slow senescence. These methods aim to establish a healthy life with a functional capacity that enables well-being in older age. One particular area of interest has been somatopause, a term that describes the expected decline in growth hormone (GH) secretion that occurs with age. Today, with the availability of recombinant GH, restoring GH to youthful levels in otherwise normal older adult populations has been an area of focus for many health care researchers. This study aims to elucidate the current knowledge and novel advances of GH in the aging population.

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DISCUSSION

Physiology of Growth Hormone

GH (somatotropin) is produced by somatotroph cells in the anterior pituitary gland. The GH gene (*GH1*) is located on chromosome 17q22 (OMIM: 139250, NBCIgeneID: 2688). Mutations or deletions in this gene result in congenital GHD. The arcuate nucleus in the hypothalamus stimulates GH secretion via GH-releasing hormone (GHRH) transported through the hypothalamo-hypophyseal portal system targeting the GHRH receptor (GHRHR) in the pituitary. The GH secretion is inhibited by somatostatin (GH-inhibiting hormone) produced by neuroendocrine neurons in the ventromedial nucleus of the hypothalamus. A third hormone (ghrelin), secreted mainly by the enteroendocrine cells of the gastrointestinal tract (predominantly in the stomach), induces GH secretion. GH has a distinctive pulsatile secretion that is mostly mediated by a reduction in tonic inhibition by somatostatin.[2] GH is secreted mostly at night, starting shortly after the onset of sleep in association with the first phase of slow-wave sleep (SWS) (stages III and IV). GH's sleep-related secretion primarily depends on the increased release of GHRH.[3] GH is also produced in non-pituitary cells, mainly in the colon and the breast, with a possible role in regulating local cell proliferation.[4] Some effects of GH are direct, whereas others are indirectly mediated by systemic (primarily produced in the liver) or locally produced insulin-like growth factor I (IGF-I). Circulating IGF-I inhibits GH secretion by the pituitary somatotroph cells with a negative feedback loop.[5]

GH acts by binding to the GH receptor (GHR), a class 1 cytokine receptor with 638 amino acids forming three domains.[6] Upon attaching to GH, the extracellular domain undergoes a conformational change, followed by phosphorylation and activation of STAT5 through Janus kinase 2.[7,8] The GHR gene consists of nine coding exons and several additional exons in the 5′ UTR. Of note, two major isoforms of GHR differ by the absence of exon 3 encoding the extracellular domain of GHR. Its absence gives rise to GHR lacking 22 amino acids in the extracellular domain.[9,10]

In healthy adults, GH increases lipolysis and lipid oxidation, stimulates protein synthesis, antagonizes the effect of insulin, and causes phosphate, water, and sodium retention.[11] In addition, it can maintain cardiac function, glucose homeostasis, bone mineralization, appropriate balance of adipose lipogenesis and lipolysis, and skeletal muscle anabolism.

After growth is completed, the secretion of GH decreases over time, starting early in adult life.[12,13] Effectively, the daily secretion of GH in adults falls by about 50% every 7 years after turning 18 to 25 years.[14] This reduction seems to be due to the loss of nocturnal sleep-related GH pulses.[15] In addition, a decline in pituitary responsiveness to GHRH and pituitary or hypothalamic responsiveness to ghrelin is observed with aging.[16] The reduction in GH secretion parallels an increase in adiposity with aging.[17] The decrease in sex steroid hormones, physical fitness, sleep quality, and nutritional status that occur during aging are all correlated with a decline in GH secretion, without proof of causality. Consequently, somatopause remains hard to define as it occurs as part of the normal aging process.

GH decrease is associated with (but not necessarily caused by) significant changes in body composition. However, one cannot help noticing that the physiologic changes seen with aging are similar to those observed in young individuals with organic GHD. Most studies on somatopause focus on a few markers, such as lean body mass, total fat, muscle strength, and bone mineral density. Although musculoskeletal impairment has been associated with aging, extreme cases are seldom seen in normal somatopause.[18] Similarly, the temporal association between somatopause and increased

adiposity remains a central topic of interest with a significant lack of established causal–effect relationships. Aging is associated with a modified body fat distribution and a decreased lipolytic responsiveness to GH, while GH release can be reduced by the increased amount of abdominal fat, creating a vicious cycle of increased fat mass that promotes reduction in GH in older adults.[19]

GH has effects on bone, either directly or mediated by IGF-I, stimulating osteoblast proliferation as well as osteoclast differentiation.[20] Although bone loss associated with aging is multifactorial, the age-related decline in GH contributes to reduced bone turnover. Replacing GH may not necessarily improve bone density with age-related bone loss, but in a therapeutic context (meaning in adults with proven GH deficiency), it has shown signs of possible protective effect, with a decrease in the risk of fracture and osteopenia.[21]

GH, through IGF-I, has a role in maintaining cognitive function. Several positive associations in healthy older individuals between the circulating levels of IGF-I and different neuropsychological tests of intelligence have been demonstrated.[22–24] However, the detailed roles of GH and IGF-I in the adult human brain remain unclear as the overall effects of somatopause on learning and memory are still unidentified.

Although somatopause is a naturally occurring phenomenon, it remains important to distinguish it from true GHD caused by hypothalamic or pituitary pathologic processes, such as tumors, infarcts, inflammation, head trauma, or radiation. Most acquired GHD cases present more severe physical defects than normal aging, such as increased cardiovascular risk and bone fragility, unfavorable fat/lean mass ratio, reduced muscle strength, and psychological deficiencies (impaired quality of life, social isolation).[25] Therefore, if suspected, GHD should be ruled out via measurement of serum IGF-I or GH provocative testing. It is vital to notice that although a low serum IGF-I (<−2.0 standard deviation score) in the appropriate clinical scenario is strongly suggestive of GHD (particularly if additional pituitary hormone deficits are present), a normal IGF-I level does not rule it out, particularly in men. Therefore, GH stimulation tests are often needed to establish the diagnosis of GHD. Such tests can use different stimuli and their interpretation (notably depending on body mass index) requires knowledge of the performance, accuracy, and limitations of each secretagogue. A review of the available GH stimulation tests and their interpretation and cutoff points are given in **Table 1**.[26]

Mice Model of Growth Hormone Deficiency or Resistance

In 1929, George D. Snell published the first description of dwarf mice, later proven to be caused by a point mutation in the pituitary-specific transcription factor-1 (Pit1) gene.[27] Pit1 regulates the differentiation of the anterior pituitary and activates the GHRHR expression.[28] Consequently, these mice were widely studied to understand GH's various actions. In 1961, Robert Schaible and J.W. Gowen described phenotypically similar mice, *Ames* dwarf, later shown to have a point mutation in the transcription factor Prophet of Pit-1, essential for developing cell lineages in the anterior pituitary gland, including the somatotrophs.[29] Since then, several other mice have been described in the literature, some with isolated GHD (IGHD). These include the naturally occurring *Little* mouse, with a point mutation in the GHRHR gene, the GHRH knockout, and GH knockout mice.[28,30] Finally, a GHR knockout mouse (GH resistant) was developed. These mice all shared delayed sexual maturation, decreased fertility, reduced muscle mass, increased adiposity, small body size, and increased insulin sensitivity. However, one particular area of interest showed unexpected results. In 1996, Brown-Borg first reported that the *Ames* dwarf mice live significantly longer than their normal siblings.[31] Conversely, transgenic mice with chronic

Table 1
Recommended peak growth hormone cutoff points (ng/mL) for growth hormone stimulation tests

		Recommended Peak GH Cutoff Points (ng/mL) for GH Stimulation Tests[a]				
Test	**Method**	**GRS '07**	**AACE '09**	**ES '11**	**AACE '19**	**Characteristics**
Insulin tolerance	0.05–0.15 U/kg, IV	3.0	5.0	3.0–5.0	5.0	Accurate (gold standard), and available in the USA
GHRH + Arginine						
BMI <25	GHRH, 1 μg/kg, IV; arginine, 0.5 g/kg, IV	11.0	11.0	11.0	N/R	Accurate, safe, and simple. GHRH not available in the USA
BMI 25–30		8.0	8.0	8.0		
BMI >30		4.0	4.0	4.0		
Glucagon						
BMI <25	1 mg (1.5 mg if > 90 kg), IM	3.0	3.0	3.0	3.0	Safe and available in the USA
BMI 25–30		3.0	3.0	3.0	3.0 or 1.0	
BMI >30		3.0	3.0	3.0	1.0	
Macimorelin	0.5 mg/kg, oral	N/A	N/A	N/A	2.8	Accurate, safe, simple, fast, available in USA, and expensive
Arginine	0.5 g/kg, IV	N/R	0.4	N/R	N/R	

Abbreviations: BMI, body mass index in kg/m^2; GHRH, growth-hormone releasing hormone; N/A, not available; N/R, not recommended.
[a] *Data from* Refs.[26,81,82]

high GH showed accelerated aging.[32] These findings came at a time when D. Rudman first noted that GH might improve muscle mass in older humans, establishing an ongoing debate on the effect of GH and anti-aging.[33]

It is now established that regardless of the mouse model, disruption of GH signaling leads to a remarkable longevity extension in rodents, maintaining cognitive function into advanced age. In contrast, pathologic sustained and unregulated excess of GH has been associated with learning and memory impairments.[34–36] The extended longevity in GHD and GH-resistant mice may stem from multiple mechanisms. The lack of GH signaling leads to hypoinsulinemia, increased insulin sensitivity, and decreased pancreatic mass and function of beta cells.[37–40] The GHD mice demonstrate an increased antioxidant enzyme activity, decreased oxidative damage to macromolecules, decreased reactive oxygen species, resistance to cytotoxic, metabolic, and oxidative stressors, and increased humanin (a secreted mitochondrial-encoded peptide with neuroprotective effects), which are all essential to an increase in health span.[41–44] In addition, improved mitochondrial function, increased fatty acid oxidation, food and oxygen consumption, lower core body temperature, alterations in thermogenesis, and shift in energy from growth to repair could be crucial to the increased lifespan.[45–47] Furthermore, an increased stress resistance with a shift from pro-inflammatory to anti-inflammatory cytokines and decreased chronic inflammation have been reported.[48] The mechanisms likely include several other factors such as a delayed immune-senescence, decreased NLRP3 inflammasome, decreased IGF-I and mTOR signaling, maintenance of protective local IGF-I, improved genome maintenance, altered expression of numerous genes and miRNA, and increased number of stem cells.[40,49,50]

Opposite effects were shown in GH overexpressing transgenic mice, with symptoms of decline in cognitive function via a significant turnover of hypothalamic neurotransmitters and decreased body weight, graying of hair, and an increased cancer incidence.[32,40,51]

Establishing the evolutionary etiology of GH's effect on longevity stems from the variable impact of GH on aging at different stages of life history.[40] Evidence of delayed puberty, reduced fertility, and extended lifespan of GHD and GH-resistant mice fits the concept of antagonistic pleiotropy proposed in the literature. Simply stated, genes selected for sexual maturation show evolutionary fitness even though they might have detrimental effects on disease risk and survival.[34]

These studies did not stop at mice but were further extrapolated to rats, domestic cats, horses, and domestic dogs, with strong evidence that adult body size, positively correlated with GH levels, is negatively correlated to longevity.[40]

Human Models of Congenital Growth Hormone Deficiency or Resistance

The extrapolation of results from animal models to human senescence is not clear. Several human models of GH resistance or IGHD exist. The Laron syndrome, an autosomal recessive disorder characterized by resistance to GH due to mutations in the GHR gene, was first described by Amselem and colleagues in 1989.[52] Families with mutations in the GH1 and GHRHR genes are models of IGHD.

A small Swiss cohort of patients with IGHD from a homozygous mutation in the GH1 gene was reported to have a shortened lifespan.[53] Yet, in an Ecuadorian-kindreds population with Laron's dwarfism (GH resistance), rates of cancer and (self-reported) diabetes were reported to be lower than the matched non-affected population.[54] Similarly, a group of Croatian patients with dwarfism and deficiencies in GH, among other pituitary hormones, from a PROP1 gene mutation did not show premature death or increased incidence of diabetes mellitus and had delayed gray hair appearance.[55]

In the Brazilian Itabaianinha kindred, the largest cohort ever described of untreated subjects with congenital IGHD (due to a GHRHR gene mutation), we reported that these IGHD individuals (never managed with GH replacement) have, throughout life, high serum total and low-density lipoprotein cholesterol and C-reactive protein, with a mild increase in systolic blood pressure, without evidence of cardiac hypertrophy or increase in carotid intima-media thickness, or premature coronary and abdominal aortic atherosclerosis, and have normal cerebrovascular reactivity.[56] Accordingly, the risk of death of GHD subjects was not different from their normal-statured siblings. Although the life span in IGHD individuals is shorter than the general population, this is due to a high frequency of deaths in female individuals aged 4 to 20 years. There is, however, no significant difference in lifespan in participants who reached age 20 years.[57]

On the opposite spectrum of GHD, acromegaly is a condition with multiple comorbidities, such as hypertension, diabetes, and cancer, resulting in reduced life expectancy.[58] In addition, a possible inverse association between height-increasing alleles and extreme longevity in normal adults has been hypothesized.[59] For instance, a Japanese ancestry study demonstrated that shorter people live longer, yet this remains less obvious and controversial, with multifactorial causes that need further elaboration.[60,61] However, studies in taller populations are controversial as an interplay of multiple interacting mechanisms leads to aging.

The GH status in late adulthood has few genetically apparent components. Most new-onset GHD cases in older adults are due to tumors, surgery, and radiation to the pituitary or hypothalamus, or traumatic brain injuries. Nevertheless, it is vital to distinguish age-related declines in GH from a pathologic process regardless of the etiology.

Growth Hormone Replacement

In adult patients with GHD (whether congenital or acquired), GH replacement therapy (GHRT) is recommended. GHRT should be individually tailored, started at low doses, and up-titrated according to the clinical response, side effects, and IGF-I levels. The treatment goals should be an adequate clinical response and achievement of IGF-I levels within the normal range for age while minimizing side effects.[25,62,63]

The situation is different in healthy older individuals. In 1990, Rudman and colleagues showed in a small number[12] of healthy men aged from 61 to 81 years that a 6 month GH treatment (with a high dosage of 0.03 mg/kg 3 days per week) can reverse some body composition changes observed with aging.[35] The mean plasma IGF-I level rose into the youthful range resulting in an 8.8% increase in lean body mass, a 14.4% decrease in fat mass, and a 1.6% increase in vertebral bone density. In addition, skin thickness increased by 7.1%.[35] These individuals were selected because of low serum IGF-I levels, without any proof that this was caused by low GH secretion. In a similar study, 6 months of the same dose GH treatment reduced fat mass by 13.1% and increased lean body mass by 4.3%.[64] However, these changes did not improve functional ability in this study population.[18] Positive effects on body composition were also found in a 10 wk study in 18 healthy older adults when strength training was combined with GH treatment.[65] Interestingly, the effects of GH on body composition seem to be more marked in male than in female individuals. Indeed, a 6 month treatment with GH (0.02 mg/kg/d) in older men and women caused a significant decrease in subcutaneous abdominal fat only in men.[66] The discrepancy between muscle mass and function could stem from the fact that GH causes an increase in tubular sodium reabsorption in the distal nephron, accompanied by an increase in plasma renin activity and a decrease in B-type natriuretic

peptide.[6,67,68] Therefore, the increase in lean mass may be due to an increase in extracellular water rather than an intracellular mass increase. A meta-analysis of 31 studies of GH administration in healthy older adults showed that despite a significant increase in serum IGF-I, an average reduction of fat mass by 2.08 kg, and an average increase in lean body mass by 2.13 kg, there were no beneficial effects on function or strength.[18,69] Papadakis and colleagues showed no GH effect on knee flexor and extensor and hand grip muscle strength in healthy older male adults (>69 years), although this may have also been due to a ceiling effect.[64] Taaffe and colleagues showed no improvement in strength and exercise capacity compared with exercise training without GH supplements in men of the same age group.[65] Multiple side effects were noted in all studies: soft-tissue edema, arthralgias, carpal tunnel syndrome, and gynecomastia.[70] In addition, a few participants had new onset of diabetes mellitus (DM) and impaired fasting glucose, likely due to GH's counter-insular effect.[69,70]

As for brain function, Vitiello and colleagues administered 6 months of treatment with GHRT in older healthy adults demonstrating improvement in several cognition functions.[71] In terms of sleep, the chronology of aging of GH secretion follows a pattern remarkably similar to that of SWS.[72] However, administrating GH in several trials demonstrated contradictory reports of deep sleep either failing to improve or even worsening with unaffected or even increased sleep fragmentation and reduced total sleep.[73,74] A lack of a unified questionnaire makes determining the cognitive function effect after GH treatment difficult to interpret.

Regarding lipid metabolism, a systematic review of 11 studies showed that treatment with GH in those older than 60 years decreases total and low-density lipoprotein cholesterol levels but did not change high-density lipoprotein or triglyceride levels.[75] The GH did not affect body mass index (BMD), or blood pressure, but decreased waist circumference, increased lean body mass, and decreased total fat mass while consistently improving quality of life.[75] Few data on the efficacy and safety of GH treatment exist in patients older than 80 years.[6]

More robust information on the effect of GH treatment in older adults may be generated by a meta-analysis. Liu and colleagues analyzed 31 articles published before 2005 and showed an overall fat mass decrease and an overall lean body mass increase with a weight that did not change significantly.[69] The total cholesterol levels decreased but were not significant after adjustment for body composition changes. Other measures, such as bone density, did not change. In addition, persons treated with GH were more likely to experience soft-tissue edema, arthralgias, carpal tunnel syndrome, and gynecomastia. They were also more likely to experience the onset of DM and impaired fasting glucose. Although most studies had a small sample size and many outcomes were infrequently measured (a total of 107 person-years for 220 participants), the authors concluded that GH as an anti-aging treatment could not be recommended.[69]

Another potential strategy to reverse somatopause could be relying on treatments that increase endogenous GH secretion rather than GH administration. Such an approach could be safer than GH replacement, as one could predict a reduced response of the somatotroph cells to exogenous stimuli when IGF-I is elevated due to its negative feedback mechanism. White and colleagues published the results of a multicenter randomized, double-masked, placebo-controlled study on the effect of an oral ghrelin receptor agonist (capromorelin, also known as MK677) in older adults with mild functional limitation.[73] A significant number of participants (n = 395) of both sexes aged 65 to 84 years were randomized for a 2-year treatment of four doses of capromorelin or placebo. The study was terminated early according to predetermined treatment effect criteria, but 315 individuals completed 6 months of treatment and 284

completed 12 months. As expected, capromorelin caused a dose-related increase in peak nocturnal GH and serum IGF-I. At 6 months, capromorelin caused an increase in lean body mass and improved muscle function assessed by tandem walk. By 12 months, stair climbing was also enhanced. In addition, the capromorelin-treated arm observed a slight increase in fasting glucose, glycosylated hemoglobin, and indices of insulin resistance. Although this study put forth a credible case for a careful reappraisal of the potential role for enhancement of GH secretion in older adults with functional decline, no GH treatment studies have delved deeper into the beneficial effect on muscle strength.[76] As far as the authors can find, capromorelin has not been further studied in older adults.

GH treatment as an anti-aging treatment has been widely advertised. The so-called "fountain of youth" has been widely advertised and marketed today via Internet sites and anti-aging groups. As this review notes, considering treatment with GH or GH secretagogues as anti-aging is premature at this time. Most information on reversing aging features comes from uncontrolled and short studies and lacks long-term data. Importantly, GH is the only legal drug whose off-label prescription is illegal in the USA (although this is rarely, if ever, enforced). Despite this, the use of GH for anti-aging and athletic enhancements accounted for 30% of prescriptions in the USA in 2003,[77] and it is possibly higher nowadays.

SUMMARY

The U.S. Food and Drug Administration approved recombinant GH in 1985 as replacement therapy for adults with hypothalamic–pituitary disease and confirmed GHD on biochemical testing. Thirty years ago, an editorial in the New England Journal of Medicine that accompanied the Rudman article wondered about the potential benefits of GH in older subjects without proven GHD.[78] Although anti-aging medicine has become a multimillion-dollar industry with significant economic, health, and societal costs, at present, there is no evidence of long-term beneficial effects of GH treatment in healthy older adults, and GH should only be prescribed for clinically approved indications.[79,80]

CLINICS CARE POINTS

- Serum IGF-I is not a sensitive test to assess the GH secretory status.
- GH stimulation tests can be used, but they can be affected by body mass index.
- Testing subjects with no history of pituitary or hypothalamic pathology for GHD is not generally advisable.
- True IGHD is an extremely rare disorder.
- GH replacement in older adults without pituitary disease is not currently advisable.

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