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Growth hormone in the aging male

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Abstract

Secretion of growth hormone (GH) and IGF-1 levels decline during advancing years-of-life. These changes (somatopause) are associated with loss of vitality, muscle mass, physical function, together with the occurrence of frailty, central adiposity, cardiovascular complications, and deterioration of mental function. For GH treatment to be considered for anti-aging, improved longevity, organ-specific function, or quality of life should be demonstrable. A limited number of controlled studies suggest that GH supplementation in older men increases lean mass by ~2 kg with similar reductions in fat mass. There is little evidence that GH treatment improves muscle strength and performance (e.g. walking speed or ability to climb stairs) or quality of life. The GHRH agonist (tesamorelin) restores normal GH pulsatility and amplitude, selectively reduces visceral fat, intima media thickness and triglycerides, and improves cognitive function in older persons. This report critically reviews the potential for GH augmentation during aging with emphasis on men since women appear more resistant to treatment.

Keywords

growth hormone; insulin-like growth factor I; longevity; dwarfs; sarcopenia; muscle weakness; tesamorelin; ghrelin

Introduction

Treatment with growth hormone (GH) has long been considered as a possible “fountain of youth” to promote improved function during aging. Growth hormone production and secretion, GH binding protein, and insulin-like growth factor-1 (IGF-1) levels decline with aging, which is often referred to as the “somatopause”. These decrements provide the basis for speculation that these anabolic hormones are related to the body composition, metabolic, and functional changes that occur with aging. After puberty, GH levels decrease exponentially.¹ Production is reported to decline by 14% per decade² and may decline by up to 50% every seven years for adult men.³ Elderly men may produce as little as 50 µg/day compared with pubertal boys who produce 1.0–1.5 mg/day.⁴ In men 60 years-of-age or older, 35% were GH-deficient.⁵ Similarly, serum IGF-1 levels progressively decline through the 8th and 9th decades of life and 85% of healthy 59–98 year-old men had low serum IGF-1 levels below the 2.5th percentile for younger men.⁶

This “somatopause” may be associated with age-related loss of vitality and vigor, muscle mass (sarcopenia), physical function and activities of daily living, together with the occurrence of frailty, central adiposity, accelerated risks for cardiovascular complications, and deterioration of mental function. The hope is that GH supplementation would slow these

processes and improve health during aging. However, treatment with rhGH has adverse effects and could impair survival if it hastens development of certain cancers (e.g. via IGF-1) or insulin resistance which accelerates the metabolic syndrome. In animal models, alterations in GH/IGF-1 signaling with reductions in these somatotrophs appear to increase life span. This paper examines a body of laboratory and clinical research that investigate effects of GH/IGF-1 on longevity and common health problems that plaque the elderly, with a focus on older men where possible.

Effects of GH/IGF-1 on longevity

Animal models

Studies in invertebrates such as *Caenorhabditis elegans* and *Drosophila melanogaster* along with laboratory rodents including Ames dwarf, Snell dwarf and GH receptor knockout mice and Lewis rat models suggest that low IGF-1 and GH levels beneficially affect longevity (Table 1). See review by Sonntag for additional citations for this section.⁷

Ablation or attenuation of DAF-2 signaling via its receptor (analogous to IGF-1 receptor) in invertebrates significantly increases their life span. The most compelling data emanates from rodent models. Knockout of Pit-1 producing Snell dwarfs⁸ and prop-1 producing Ames dwarfs⁹ which results in GH and IGF-1 deficiency, respectively, and Knockout of GH receptor in other strains¹⁰ significantly increases life span. In Ames dwarfs, occurrence of cancer is significantly reduced, in part explaining their increased longevity.¹¹ Similarly, in Lewis dwarf rats (deficient in GH and IGF-1) risk of carcinogen-induced mammary cancer is reduced two-fold and probably explains their increased longevity.¹² Whereas, over-expression of GH in transgenic mice results in shortened survival.¹³

There are conflicting effects of GH and IGF-1 deficiency on how they might increase life span. Laron dwarf mice (GH receptor mutation), which are GH-resistance with decreased IGF-1 levels, have increased longevity¹⁴; these animals have lower insulin, preserved subcutaneous adipose tissue, and increased adiponectin levels, all of which should be cardioprotective. Yet, some effects of adequate GH and IGF-1 appear beneficial. Administration of IGF-1Eb (mechanogrowth factor) stimulates proliferation of myoblasts and induces muscle hypertrophy. Increases in GH and IGF-1 during adolescence are beneficial for brain and cardiovascular function during the aging process and GH administration during adolescence is vasoprotective and increases life-span.¹⁵

Age of onset of GH/IGF-1 deficiency may be critical to longevity in animals. Treatment of Ames dwarfs with GH from week 3-to-16 weeks of life completely reverses their increased life-span. Further, the degree of impairment in GH/IGF-1 status may affect outcomes. In GH-deficient (GHD) dwarf rats, modest reductions of 40–50% in IGF-1 have no effect on longevity but attenuate the occurrence of cancer. Thus, in dwarf animals and GH receptor knockout models, impairments of developmental programming may affect critical cellular regulatory systems (e.g. differentiation of important longevity related tissues, response to stress, metabolism, energy balance) that determines their lifespan. These animal models suggest that GH/IGF-1 deficiency in early life imprints a favorable effect on longevity.

Humans

The importance of physiologic GH and IGF-1 status during the aging process has been widely inferred by researchers, practitioners and lay public from studies of GH or IGF-1 administration which improves protein synthesis, lean body mass, immunity, cardiovascular function, and neurocognition and decreases upper body obesity. It may be that low levels of GH and IGF-1 protect some age-related tissues but increase risks of others. Therapies that augment GH status may cause increased insulin resistance and risk for metabolic syndrome

or possibly increased risk for certain cancers. Unfortunately, there have been limited clinical studies with most lacking adequate statistical power or duration to assess the effects of GH status or treatment on longevity and causes of death.

Studies relating GH and IGF-1 status to longevity provide inconsistent evidence as to whether decreased (somatopause) or high levels (e.g. acromegaly) of these hormones are beneficial or detrimental to longevity. Laron Syndrome dwarfs with GH gene deletion and low IGF-1 levels have signs of early aging including wrinkled skin, insulin resistance and diabetes, but lack endothelial dysfunction and have long life-spans often reaching 80–90 years.¹⁶ Laron Syndrome dwarfs in one Brazilian cohort of 222 subjects had no malignancies compared to 9–24% of family members who had cancer.¹⁷ A small subset ($n = 22$) of Brazilian patients with Laron Syndrome had increased abdominal obesity, elevated LDL-C and C-reactive protein (CRP) but lacked increases of carotid intima media thickness (cIMT) or abnormalities with stress echo-cardiograms.¹⁸ Reductions in malignancy and atherosclerosis may explain prolonged survival in this population. Finally, natural mutations in the IGF-1 receptor producing cellular resistance to IGF-1 have resulted in short stature and extended longevity. These mutations have been over-represented in centenarians.¹⁹

Ecuadorians with GH receptor mutations, IGF-1 deficiency, and cellular protection from oxidative damage have stunted growth, lower incidence of diabetes and cancer but do not have increased longevity. These Ecuadorians may actually have shorter life-spans and two thirds die by 65 years-of-age.²⁰ In patients with Hereditary Dwarfism based on a 7.6 kb deletion of the GH gene resulting in isolated GHD live substantially shorter life-spans compared to family siblings,²¹ as do adults with untreated GH deficiency and hypopituitarism.²²

Several longitudinal studies provide additional glimpses of the potential effects of GH and IGF-1 on aging. In a report from the Netherlands of 2694 adults with GHD who were treated and followed for an average of 6.1 years, there were 95 deaths.²² The standardized mortality rate was no greater in men but was significantly increased in women due to cardiovascular disease (CVD). An 8-year longitudinal study of 376 older men (73–94 years-of-age) showed that men in lowest quartile of IGF-1 bioactivity had a 1.8-fold (95%CI = 1.2–2.8) increased mortality versus the highest quartile.²³

Summary

It is difficult to reconcile the largely protective effects of GH/IGF-1 deficiency on longevity in animals with the inconsistent or deleterious effects of low levels or declining GH/IGF-1 during human aging. Further, the beneficial and adverse regulatory effects of IGF-1 and GH on various organ-specific tissues and aspects of metabolism is incompletely understood and must be investigated to understand pathophysiology that affects longevity and co-morbidities in advanced years (Table 2).

Effects of GH/IGF-1 on organ-specific tissues

Much of the optimism for treatment of somatopause with GH or possibly even IGF-1 stems from observations of the effects of GH deficiency on certain physiologic functions and tissues (Table 3) along with studies of GH replacements in adults with GHD due to pituitary disorders.

Brain function and cognition

In the US, dementia is predicted to increase from 5 million persons by almost 3-fold over the next 3 decades (US Census Bureau). In both animals and humans, age-associated deficits in learning and memory have been linked to synaptic loss and dysfunction. Both GH and IGF-1

appear to be important for normal cognitive function since IGF-1 improves neurogenesis, neurite out-growth, synaptic complexity, brain angiogenesis and blood flow, and is neuroprotective against oxidative stress and toxicity of beta amyloid. Plus, IGF-1, as with insulin, improves glucose metabolism in the brain. For citations in this section, see articles by Deak and Sonntag²⁴ and Baker.²⁵

In animals, GH and IGF-1 decrements with aging are related to impairments in spatial and working memory. Although IGF-1 is synthesized locally in the brain, especially in response to neuronal injury, systemic IGF-1 readily crosses the blood brain barrier, binds to receptors throughout the brain. Blood levels have been directly related to overall cognitive performance, including perceptual motor performance, fluid intelligence, processing speed – possibly mediated by CNS signaling of the IRS-PI3K-Akt pathway, which appears necessary for optimal neuronal function. If IGF-1 levels are increased in the hippocampus by treatment with GH or IGF-1, deficits in these functions are corrected. Further, deficits of NMDA in post-synaptic receptors in learning and memory impaired models are reversed by treatment with IGF-1, apoptosis is reduced, and neuronal death prevented.

In humans, decreases in somatotrophic hormones are associated with impaired short term memory and executive function. Deficiencies of IGF-1 in aging due to attenuated pulsatile release of GH (low amplitude, low area under the curve) are postulated to be causally related to neurodegeneration and dementia. These decreases are also associated with greater pathologic abnormalities in patients with Alzheimer's disease. Treatment with GH or GH-mimetics in older persons with cognitive impairment or risk for dementia (reviewed later) supports the importance of IGF-1 in preserving normal cognitive function.

Cardiovascular performance and atherosclerosis

Aging is closely associated with hypertension, progressive atherosclerosis, myocardial infarction and stroke, as well as peripheral artery disease (arterial aneurysms, local ischemia and infarction). During aging, abdominal obesity with increased visceral adipose tissue (VAT), insulin resistance, and pro-coagulants are also expected to increase CVD risks. As will be reviewed below, deficiencies in GH and IGF-1 appear to be important mediators in CVD risks; see Higashi et al. for citations in this section.²⁶

Growth hormone deficiency and low systemic levels of IGF-1 are associated with greater risk for endothelial dysfunction, increases in cIMT, impaired coronary blood flow, coronary artery disease, congestive heart failure, heart attack and ischemic stroke. In a population based study in Rotherdam, subjects with a wild type 192 base pair allele had not only lower serum IGF-1 levels (18% reduction) but had significantly greater occurrence of heart attack, left ventricular hypertrophy, hypertension and increased cIMT. Finally, Laron dwarfs have impaired left ventricular function and cardiac output during exercise but both improve during treatment with IGF-1.

From animal models and *in vitro* studies, physiologic IGF-1 levels appear necessary for integrity of patent arteries in the systemic circulation and central nervous system, and for normal endothelial function and cardiac performance. IGF-1 inhibits atherogenesis by reducing inflammation associated with oxidative stress from reactive oxygen species (ROS) which increases foamy macrophages and plaque in vessels, and reverses endothelial dysfunction in IGF-1 depleted states. Importantly, there are large numbers of IGF-1 receptors in cardiac myocytes, vascular smooth muscle cells, and endothelial cells. IGF-1 attenuates apoptosis in these cells, further emphasizing the importance of the somatotroph in controlling the integrity and function of the vascular system.

To better understand these divergent findings, 102 normal and overweight obese persons without hypopituitarism were studied for GHD using GHRH-arginine stimulation to detect peak GH levels $4.2 \mu\text{g/L}$.²⁷ Low peak GH was significantly associated with low IGF-1 levels, greater cIMT and obesity, elevated CRP, high LDL-C and fasting triglycerides, higher fasting glucose, and low HDL-C and adiponectin, all of which are expected to increase CVD risks.

Muscle mass, strength and physical performance

Sarcopenia, a common complication of aging, may progress to weakness, frailty, impaired activities of daily living, social isolation and eventually depression. These morbidities may advance relentlessly from disability to institutionalization to death. The relationship of these co-morbidities with soma-topause is uncertain. Further, declines in testosterone and resistance to insulin adversely affect muscle and may contribute to sarcopenia in older men. In this section, potential mechanisms for sarcopenia are examined; see review by Giovannini for citations.²⁸

Molecular considerations

IGF-1 is a primary mediator of muscle repair and growth, both from GH stimulated IGF-1 release from liver and from its paracrine-autocrine secretion in muscle. Two different spliced-variants of IGF-1 regulate these processes. Mechanogrowth factor (MGF, IGF-1Ec) is produced locally in response to damage, stretch and over-load and increases myofibrillar protein synthesis and hypertrophy. In response to a hypertrophic stimulus, IGF-1Ea is released locally and stimulates satellite cell proliferation which donates nuclei to the myofibrillar nuclear domain. IGF-1 promotes delivery of amino acids to muscle, suppresses proteolysis, protects against damage after vigorous muscle contraction by attenuating inflammation and fibrosis, and facilitates muscle recovery after damage or injury.

Effects of aging on muscle

Studies suggest that age-related loss in muscle mass is largely due to atrophy associated reduction of fast twitch type 2b fibers. However, a 12-year study in older humans, showed that both type 1 and type 2 fibers were lost.²⁹ It is possible that IGF-1 impaired signaling is contributing to loss of myofibrillar motor neurons since treatment with IGF-1 promotes neuronal sprouting and repair of damaged axons. Yet, aging muscle shows plasticity to some hypertrophic stimuli.

In observational studies in older persons, the relationship between IGF-1 levels with sarcopenia, muscle strength, and self-reported disability are conflicting. Some studies show no relationship but others show a significant relationship between low serum IGF-1 levels and impairments in voluntary muscle strength, physical function and mobility. Finally, there may be a relationship between chronic inflammation which inhibits IGF-1 secretion resulting in low levels and weakness in older persons.

Effects of IGF-1/GH on lipid and carbohydrate metabolism

The observation that GH replacement for GHD patients reduces body fat, lowers serum triglycerides, and increases insulin resistance suggests that GH is beneficial for lipid metabolism but detrimental to glycemic control. These effects are due to a complex relationship of GH and IGF-1 working through their receptors and interactions with other hormones controlling substrate metabolism. Indeed, studies indicate that during fasting (e.g. sleep) and catabolic stress, GH increases lipolysis and lipid oxidation sparing carbohydrate and protein metabolism. See review by Vekayakumar for citations in this section.³⁰

Lipid metabolism

Growth hormone is lipolytic and releases free fatty acids (FFAs) from largely visceral adipose tissue and less so from subcutaneous fat by increasing hormone sensitive lipase (HSL). Lipoprotein lipase (LPL) induced systemic breakdown of triglycerides to FFAs and their uptake by adipose tissue is not affected by GH. Whereas, GH stimulates uptake of FFAs by the liver via LPL and hepatic lipase. Further, GH maintains triglyceride storage in liver by either inhibiting triglyceride lipolysis via HSL or oxidation by PPAR γ . Finally, GH stimulates triglyceride uptake into skeletal muscle via LPL for energy during muscle contraction or storage as intramyocellular lipid.

Glucose metabolism

GH-induced release of FFAs from adipose tissue into the systemic circulation may lead to insulin resistance. FFAs impair insulin signaling and transport of Glut-4 to the cell surface by inhibiting insulin receptor substrate associated PI3K via its p85 α subunit, or more simply by FFA oxidation leading to decreased uptake of glucose. Further, GH may cause insulin resistance by its effects on the adipokine, resistin, although GHD individuals may have lower adiponectin levels suggesting that physiologic GH might actually be protective against insulin resistance. Growth hormone may also contribute to insulin resistance by increasing hepatic glucose output by promoting glycogenolysis and gluconeogenesis in the liver. It is also possible that local production of FFAs may lead to accumulation of intramyocellular lipid both of which have been associated with insulin resistance. Finally, expression of suppressor of cytokine signaling (SOCS) family of proteins, which down-regulate insulin signaling, is induced by GH.

Treatment to enhance GH/IGF-1 status and improve performance in aging men

During advanced aging, skeletal muscle strength and performance decline, which may lead to frailty, often occurring together with accumulation of central adiposity, onset of impairments in cardiac and neurocognitive function, and worsening quality of life. Whether these manifestations are due to age-related declines in GH/IGF-1 status or are the consequences of sedentary life style, years of exposure to dyslipidemia, elevated blood pressure, insulin resistance, depression or other hormonal abnormalities (e.g. declining testosterone in men) is uncertain. A meta-analysis in 2005 that examined a Medline database of 1924 citations produced only 8 controlled studies of GH versus no GH in ostensibly healthy older persons.³¹ These and several studies reported since then examining effects of GH supplementation via rhGH, GH-secretagogues or GHRH analog are reviewed below with the focus on older men.

Diagnosis and treatment

Diagnosis and treatment considerations of idiopathic GHD is challenging in older men who are prone to upper body obesity, which per se is associated with impaired GH secretion and lower IGF-1 levels. Even though systemic IGF-1 levels are relatively stable during the day and may be lower than in younger persons, they are often normal even with documented GHD. Further, IGF-1 may be depressed during catabolic conditions (e.g. rheumatoid disorders) or liver disease without overt GHD. To justify treatment with GH or one of its secretagogue and to obtain third party reimbursement, a provocative stimulatory test such as with arginine plus GHRH should be done to determine if peak GH levels are below 4.1 μ g/L. Still, uncertainty of the long-term effectiveness and safety of GH treatment for symptoms of somatopause, even if the stimulatory tests are abnormal, raises risk-to-benefit issues.

Sarcopenia and frailty

Perhaps the greatest interest in GH supplementation in older persons is for treatment or prevention of sarcopenia and physical weakness. The concept was supported by observation that 2-years of treatment in GHD adults restored muscle strength but effects were greater in younger recipients.³² Table 4 shows a series of studies to augment GH in older men. In a landmark report, 21 men 61–81 years-old were assigned to treatment with biosynthetic GH three-times weekly or no treatment for 6 months.⁵ Treatment produced an 8.8% increase in body cell mass (BCM) using total body potassium counting. In eight other studies, total lean body mass (LBM) increased 1.4–4.8 kg by different methods. In six of these studies, there was no change in muscle strength or performance, although knee extensor strength increased by 21.3% in one and knee torque by 14.5% in another. Despite lack of improvement in quadriceps strength, leg power, or muscle fiber CSA, in one study, myosin heavy chain 2X isoform increased significantly suggesting that GH rejuvenated the effects of IGF-1 on skeletal muscle³³ by increasing local expression of the IGF-1Ea spliced-variant and mechanogrowth factor mRNA. Treatment with the GH-secretagogue ghrelin to augment GH pulsatility and IGF-1 levels produced similar modest increases in lean mass but no change in upper or lower body muscle strength after 12 months.

Differences in dosing and duration of therapy, lack of consistent evidence of GH deficiency, relatively small sample sizes, and different tests of physical function, make these studies difficult to compare. Yet, they suggest that GH supplementation modestly improves lean tissue mass.

GH therapy combined with other treatment strategies

Interaction of GH and testosterone supplementation—Growth hormone treatment has been hypothesized to augment effects of testosterone supplementation in older men. In one study, there was no benefit to GH treatment or positive interaction of the two hormones on LBM or muscle performance.³⁴ In a study by Blackman, muscle performance did not improve with either rhGH or testosterone treatment alone (100 mg biweekly), but 1-repetition maximum (1-RM) strength and aerobic capacity by VO_2max increased significantly with the combination.³⁵ In a third study, 112 (65–90 year-old) community-dwelling men were randomized to placebo, 3 or 5 $\mu\text{g/kg/day}$ of rhGH or transdermal testosterone gel (5-or-10 g/d) for 16 weeks.^{36,37} Total and appendicular LBM were enhanced by addition of rhGH. For men who achieved at least 1.5 kg increases in total and 0.8 kg increases in appendicular LBM, there were significant increases of 30% in 1-RM strength. Aerobic endurance improved substantially during treatment with both hormones. These latter two studies suggest that rhGH may indeed enhance the effects of testosterone administration on muscle performance.

Interaction of GH treatment with resistance exercise—There is also interest in the potential of GH treatment when combined with exercise to augment strength and function in older men (Table 4). Taaffe and colleagues showed in 18 men 65–82 years-of-age with low IGF-1 levels and who had completed 14 weeks of progressive resistance training (PRT), addition of rhGH (0.02 mg/kg/day) for 10 weeks did not increase type I or II muscle fiber CSA or strength compared to placebo during continued PRT, although fat free mass (FFM) increased for those receiving GH.³⁸ Yarasheski et al. showed in 23 sedentary 67 ± 1 year-old men with low IGF-1 levels assigned to concurrent PRT and randomized to rhGH (12.5–24 $\mu\text{g/kg/day}$) or placebo for 16 weeks, total FFM increased more with GH, but increments in vastus lateralis protein synthesis rates and training specific isotonic and isokinetic strength were similar in both groups.³⁹ These results are similar to the study by Hennessey which showed no benefits of the addition of GH to RRT.⁴⁰ In these studies, PRT may have provided a maximal stimulus for muscle hypertrophy as demonstrated in animal models. In

addition, testosterone levels may have been suboptimal, thereby limiting the effects of GH treatment as suggested earlier.

Summary

These data provide convincing evidence that rhGH augments total LBM but limited evidence that it meaningfully increases in muscle strength, power, aerobic endurance, or physical function after short treatment periods. A number of these studies assessed muscle and lean tissue by DEXA which over interprets hydration as lean tissue, as may occur with increases in intramyocellular water due to synthesis of non-contractile muscle proteins or extremity edema from rhGH, which may have artificially suggested that muscle mass was increased.

Cardiovascular disorders—In humans, cIMT is an excellent surrogate of coronary atherosclerosis. In adults with hypopituitarism who have increased atherosclerosis, rhGH replacement improves IMT of major arteries and endothelial function after several years of treatment compared to progression of cIMT in GHD untreated patients, which progressed at a similar rate as matched controls without GHD.⁴¹ The reductions in cIMT may occur as early as three months after initiating rhGH treatment. In a recent study of the GHRH analog (tesamorelin), 12 months of treatment (2 mg/d subcutaneously) in 60 abdominally obese volunteers with peak GH stimulation 4.2 µg/L significantly decreased cIMT, VAT, CRP and triglycerides compared to placebo.⁴² It's not clear whether the treatment benefits on cIMT were due to direct effects of IGF-1 (increased by 86 ± 21 µg/L) on the vasculature or reductions in VAT, C-reactive protein or triglycerides. Regardless, the composite cardiometabolic risk profile was markedly improved.

Metabolic syndrome components—Because VAT and dyslipidemia are central to cardiovascular complications in older men, GH has been studied because of its fat oxidizing and lipolytic actions. The potential for treatment of obesity was demonstrated in one placebo- controlled investigation of 30 relatively healthy men 48–66 years-old with abdominal obesity and low serum IGF-1 levels⁴³(Table 5). Treatment with rhGH (9.5 µg/kg/day) for nine months resulted in significant reductions in total body adipose tissue of $9.2 \pm 2.4\%$ by ⁴⁰K counting and VAT of $18.1 \pm 7.6\%$ by computed tomography. These changes were associated with significant reductions in total cholesterol, fasting triglycerides, fibrinogen and diastolic blood pressure; fasting glucose, insulin levels, and systolic blood pressure were unchanged. The glucose disposal rate (GDR) during a hyperinsulinemic euglycemic clamp decreased modestly after six weeks but was identical to the GDR in the placebo group at 9 months. Other studies (Table 5) involving only men at least 55 years-of-age and without pituitary disease also reported significant decreases in fat mass by 0.8–3.2 kg.

A meta-analysis of rhGH for treatment of simple obesity without endocrinopathies in adults showed significant but only modest reductions in VAT (-22.8 cm²) and LDL-C (-9 mg/dL).⁴⁴ Age, gender, body mass index, dose, and duration of treatment differed broadly in these studies, and most did not report effects of rhGH on dynamic tests of glycemic control or insulin sensitivity. In adult patients with hypopituitarism and GHD, insulin resistance often increases in the first several months but generally returns to baseline after 6–12 months of treatment, possibly due to reductions in fat mass.

With the GHRH (tesamorelin) analog, GH secretion is stimulated and physiologic nocturnal pulsatile rhythm is restored. These effects are inhibited by IGF-1 feedback, which conceptually should reduce risks for GH excess and adverse events. In the study of GHRH analog described earlier,⁴² tesamorelin reduced VAT by -16 ± 9 cm² versus a 19 ± 9 cm²

increase in placebo recipients. There was no change in subcutaneous adipose tissue (SAT) but CRP and triglycerides were significantly reduced. There was no change in glycated hemoglobin or 2-h glucose levels.

Cognitive impairment and dementia—Treatment studies have shown conflicting effects of augmenting GH and IGF-1 for improving neurocognition in humans. In one study of older patients treated with GH, performance on Tails B test was improved but in a different study of facial recognition and word recall from a list, GH treatment produced no improvements.⁴⁵ Use of a more physiologic stimulus of IGF-1 release (GHRH peptide, tesamorelin), showed promising results. In older adults with normal neurocognitive function and those with minimal cognitive impairment, treatment for up to 5 months significantly improved measures of executive function (problem solving, attention, planning) and verbal memory, although the magnitude of these effects was small.²⁵ In a study of Alzheimer's disease (AD), treatment with a GH secretagogue (MK-677, similar to ghrelin) for 12 months did not arrest disease progression.⁴⁶ The lack of benefit in the latter study may have been related to the more advanced neurodegenerative state with AD, perhaps lack of plasticity of AD, or lower levels of IGF-1 achieved with the ghrelin analog (77% increase) versus those with GHRH (117% increase).

Accelerated aging and visceral adiposity in patients with HIV—With more than 30 anti-retroviral drugs (ART) available to treat HIV, patients are living regularly into their 6th and 7th decades and even longer. Aging appears to be occurring at an accelerated pace in these individuals who often have increased cardiometabolic risks at younger ages than persons without HIV. Abdominal obesity was treated with rhGH in several studies shortly after these manifestations first burst onto the scene when combinations ART became available and prolonged survival. In one study, 245 men were randomized to placebo or 4 mg/day or 4 mg every other day for 12 weeks, followed by re-randomization for an additional 12 weeks.⁴⁷ All groups had significant reductions in abdominal VAT and SAT, and non-HDL cholesterol but no change in fasting triglycerides. Insulin area under curve during a 2-h oral glucose tolerance test increased after 12 weeks but was no different than baseline at 24.

Tesamorelin was tested in a randomized, double blind study of 2 mg/day subcutaneously versus placebo for 26 weeks in 412 HIV patients (86% men) with abdominal obesity.⁴⁸ VAT decreased by 15.2% versus with tesamorelin versus 5% increases with placebo and fasting triglycerides decreased by 50 mg/dL versus 9 mg/dL increases, respectively ($p < 0.001$ for both). There was no evidence of impaired glucose tolerance and adverse events were similar in both groups. In these patients with lipodystrophy including lipatrophy, there was no loss of limb fat or abdominal SAT with tesamorelin. Two subsequent pivotal phase III licensure studies of 806 total HIV infected patients produced nearly identical findings. Tesamorelin thus appears highly effective in reducing VAT and safe in HIV patients.

Athletic performance—Much public attention has been given to abuse of GH by professional athletes and Olympic performers. Risk for serious adverse health outcomes and potential for unfair performance advantages are concerning. It is possible that recreational and Master Athletes who perform into their 7–9th decades could also abuse GH.

In one study of rhGH (2 mg/d) or placebo for eight weeks in adult recreational athletes, GH administration increased LBM by increasing extracellular water but did not increase BCM, muscle strength, power or aerobic endurance in men.⁴⁹ In a meta-analysis of almost 4500 studies, there were only 8 randomized controlled studies that reported muscle performance outcomes.⁵⁰ Although there were demonstrable benefits on body composition and

metabolism in GH treated participants compared to no therapy, GH treatment did not increase biceps or quadriceps strength, improve VO₂max, bicycling speed, and power output but was associated with greater lactate production and fatigue. In this meta-analysis, treatment was relatively short (3 months) and doses may not have reflected those used during doping or the effect of concomitant use of other anabolic hormones (e.g. testosterone or insulin). These studies suggest that treatment with GH alone generally does not improve physical strength or endurance. It is possible that small improvements, for example, in aerobic endurance, that would not be quantifiable in clinical studies could confer an athletic advantage. There is little reason to believe that the effects would be different in older men with marginally lower GH/IGF-1 status than these younger study participants.

Summary

Despite enthusiasm for treatment of somatopause and projections that many tens of thousands of persons are using GH as an anti-aging therapy, there is little evidence to support its use to extend longevity or restore youthful health. A limited number of studies suggest that GH supplementation in older men does increase total LBM modestly by about 2-kg with a similar reduction in fat mass. These effects appear gender specific as women are generally more resistant to the effects of GH, with more modest increases in IGF-1 at similar doses and they often do not show improvements in LBM or fat mass.³¹ However, there is little controlled evidence that treating older men with GH alone improves voluntary muscle strength or performance (e.g. walking speed or ability to climb stairs) or importantly quality of life. In addition, GH administration frequently causes adverse events including edema, arthralgias, carpal tunnel syndrome and early insulin resistance. Yet, treatment with a GHRH agonist (tesamorelin) can restore normal GH pulsatility and amplitude, increases IGF-1 to upper physiologic ranges, and selectively reduces VAT, cIMT, CRP, and triglycerides, and improves cognitive function in some older persons. Despite the fact that most reviews and commentaries suggest that existing data do not warrant GH supplementation as an anti-aging therapy, recent observations that tesamorelin benefits important age-related processes affecting CVD morbidity and mental function without substantive increases in risk for toxicity or insulin resistance suggests that the “fat lady may not have sung” yet, at least for the older guys.

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Practice points

- There is no compelling data that empiric treatment of older men with rhGH improves muscle strength or performance (walking speed or ability to climb stairs) or quality of life. Thus, it is unlikely to benefit patients with sarcopenia or frailty.
- Consideration of treatment for idiopathic GHD should be based on presence of signs and symptoms consistent with adult onset GHD.
- Treatment should not be initiated without evidence of impaired GH stimulation by provocative testing (e.g. GHRH-arginine stimulation) since patients may have GH deficiency even with normal serum levels of IGF-1.
- Adverse events with rhGH are not frequent with appropriate physiologic dosing but there remain increased risks for arthralgias, carpal tunnel syndrome, fluid retention, increases in blood pressure, and insulin resistance along with other unforeseen effects including potential for increased cancer risk from IGF-1 stimulation.
- Practitioners need to be alert to abuse of rhGH by even older recreational athletes or those desiring to experiment with it as an anti-aging antidote.

Research points

- The GHRH analog, tesamorelin, should be further tested in non-HIV populations (both men and women) to evaluate its effects on reducing abdominal visceral adipose tissue in patients with metabolic syndrome along with those at increased risk for major vessel atherosclerosis and as a potential therapy to treat and prevent dementia, especially in abdominally obese persons.

Table 1

Longevity in growth hormone and IGF-1 deficient animal models.

Animal model	Mechanism	Outcomes	Citations
Ames dwarf mice	Knockout prophet gene (Prop-1) GH/GH-1 deficiency	↑ longevity; reduced somatic growth. ↓ adenocarcinoma of lung	Ikeno Y, 2003
Snell dwarf mice	Knockout of Pit-1 GH deficiency	↑ longevity ↓ body weight	Flurkey K, 2001
Little mutation (Ghrhr ^{lit/lit})	GHRH-receptor insensitive	↑ longevity marked ↓ in body weight	Flurkey K, 2001
Laron dwarf mice	Mutation of GH receptor GH, IGF-1, IGFBP-3 deficiency	↑ longevity ↓ weight, insulin, IGF-1 levels	Coschigano K, 2003
GHR-KO mice ("Laron" dwarfs)	GH receptor knockout, IGF-1 deficiency	↑ longevity; ↓ in neoplasms; ↑ SQ ^a fat, ↑ adiponectin	Bonkowski MS, 2006 Berryman DE, 2004
Lewis dwarf rats	Mutation causing ↓ GH synthesis, IGF-1 ↓ 50%	↑ longevity; resistance to carcinogen-induced cancer	Ramsey MM, 2002

^a Subcutaneous.

Table 2

Effects of GH and IGF-1 deficiency and excess on longevity in humans.

Mechanism	Clinical outcomes	Longevity effects	Citations
Growth hormone deficiency			
Ecuadorians – GH receptor mutation	↑ insulin sensitivity, ↓ incidence of diabetes and cancer	No ↑ 2/3 die by 65 years-of-age	Guevara-Aguirre J, 2011
Laron Syndrome – GH gene deletion	Early aging – wrinkled skin, insulin resistance, osteopenia but normal endothelial function	May be ↑ to 80–90 years	Laron Z, 2004; Schechter M, 2007
Hereditary Dwarfism – 6.7 kb deletion in the GH gene – untreated GHD	Small stature and heart problems	Shortened versus unaffected sibs	Besson A, 2003
Laron Syndrome (<i>n</i> = 222)	No malignancies versus 9–24% in family members	Expected to be ↑	Shevah O, 2007
Isolated GHRH-receptor mutation; Brazilian dwarfs (untreated)	Obesity, ↑ LDL-C; no insulin resistance or premature CVD	Not shortened	Menezes-Oliveira JL, 2006,
IGF-1 deficiency			
Ashkenazi Jewish centenarians	Short stature, over-representation of mutations in the IGF-1 receptor gene (females only)	Prolonged	Suh Y, 2008
Polymorphic variants of IGF-1 path (IGF-1r, PI3K, IRS-1, FOXO1A)	↓ IGF-1 and variants over-represented in long-lived persons	Prolonged	Bonafe M, 2003
GH excess or GH treatment			
Acromegaly	↑ diabetes, CVD, heart failure, colon cancer; tumors have increased IGF-1 receptors	Shortened	Bartke A, 2008 Sacca L, 2003
Pituitary extract treatment; United Kingdom cohort	↑ incidence of colon cancer and Hodgkin's disease	Shortened	Swerdlow AJ, 2002
Pituitary extract treatment; United States cohort	↑ deaths due to hypoglycemia and adrenal insufficiency	Death rate ↑ 4-fold	Mills JL, 2004
Treatment – children with GHD (<i>n</i> = 6928, 17 years later)	No ↑ cancer (except bone) but CVD outcomes increased; ↑ risk if dose 50 mg/kg/day	↑ mortality	Carel J-C, 2012
Treatment – adults with GHD (<i>n</i> = 2694; 13,000 treatment years)	Rates of cancer not ↑; mortality ↑ in women (CVD events)	Not affected in men	Van Bunderen 2011

Table 3

Manifestations of growth hormone deficiency in adults.

Body composition
↓lean body tissue
↓skeletal and myocardial muscle
↑total and trunk fat mass
Osteopenia and osteoporosis
Dry thin skin, wrinkles
Metabolism
↓total whole protein synthesis
↓lipolysis and fat oxidation
Insulin resistance
↑total and LDL-cholesterol
↑fibrinogen and PAI-1
Function
↑blood pressure
↓cardiac stroke volume
↓skeletal muscle strength
Anemia, ↓oxygen carrying capacity
↓aerobic exercise capacity
↓vitality and vigor
↓quality of life (depression, isolation)

Table 4
Effects of growth hormone therapy on lean tissue mass and muscle performance in older men.

Study	Age (years)	N=	Dose of GH (mg/kg/week)	Length of therapy	Effects on LBM (total and regional)	Effects on strength, power and aerobics	Effects on bone
Rudman ^a 1990	61–81	21	0.09	12 months	↑8.8% (↑3.7 kg)	NR ^b	↑1.6% lumbar spine BMD ^c
Welle ^a 1996	62–74	10	0.09	3 months	↑3.3 ± 0.7 kg (LBM) ^d ↑3.3 ± 1.1 kg (muscle)	↑14 ± 5% knee torque	NR
Papadakis ^a 1996	70–85	52	0.09	6 months	↑4.3%	NC ^g in hand grip, knee torque, VO ₂ max	↑0.9% in total BMC ^e
Blackman ^a 2002	71 ± 1.7	34	0.09	6 months	↑3.1 kg	NC in 1-RM strength ↑8.3% in VO ₂ max	↑osteocalcin, pro-collagen peptide
Lange ^{a,f} 2002	74 ± 1.0	14	0.05	3 months	↑2.46 ± 0.51 kg NS Δ in leg CSA ^g	NC in isokinetic quad strength or leg power	NC in BMC
Hennessey ^{a,f} 2001	71 ± 1.3	9	0.015	6 months	↑type I/II fibers	↑21.3% in knee ext	NR
Taaffe ^{a,f} 1996	65–82	18	0.14	10 weeks	↑1.4 kg (↑3.3%)	NC in 10 strength exercises	NR
Yarasheski ^{a,f} 1995	67 ± 1	23	0.09–0.17	16 weeks	↑4.8 ± 0.6 kg FFM ↑2.3 ± 0.2 kg	NC in 9 strength exercises	NR
Giannoulis ^a 2006	65–80	32	0.7–8.4 ^h	6 months	↑2.0 ± 0.5 kg	NC in VO ₂ max, knee strength, hand grip	NR
Nass ^a 2008	60–81	25	ghrelin 25 mg/day	12 months	↑1.1 (CI = 0.7–1.5) kg ↑0.5 (CI = 0.8–0.8) kg	NC in shoulder or knee flexion strength	↓femoral neck BMD

^aControlled study; sample size includes placebo or no treatment.

^bNot reported.

^cBone mineral density.

^dLean body mass.

^eBone mineral content.

^fWith resistance exercise.

^gCross-sectional area.

^hmg/week to achieve IGF-1 levels of 141–252 ng/mL.

Table 5

Effects of growth hormone therapy on fat mass, metabolism, neurocognitive measures in older men.

Study ^a	Adipose tissue	Insulin sensitivity	Lipids	Cognitive function
Rudman 1990	↓14.4% (↓2.4 kg)	Hyperglycemia in 3	NC ^b cholesterol NC triglycerides	NR ^c
Papadakis 1996	↓13.1%	NR	NR	↑Trails B; NC in MMS ^d / DSS ^e
Blackman 2002	↓3.2 kg ↓21 cm ² in VAT	↓glucose tolerance in 7; diabetes in 2	NR	
Lange 2002	↓2.27 ± 0.54 kg	NR	NR	NR
Taaffe 1994	↓0.8 kg (12.3%)	NR	NR	NR
Yarasheski 1995	↓2.6 ± 0.8 kg	NR	NR	NR
Johannsson ^f 1997	↓9.2 ± 2.4% ↓18 ± 7.6% VAT	NC in GDR ^g	↓cholesterol ↓triglycerides	NR
Giannoulis 2004	NC	NC in insulin or glucose	↓Apo B; NC LDL-C or triglycerides	NR
Nass 2008	↑VAT 8.4 (CI = 1.6–15) cm ² , ^h ↑limb fat 1.1 kg	↑HgbA1C and QUICKI ⁱ	NC	NR

^aSee Table 4.^bNo change.^cNot reported.^dMini Mental Status test.^eDigital Symbol Substitution test.^fSubjects aged 48–66 years.^gGlucose disposal rate.^hNon-significant versus placebo ($p > 0.05$); qualitative insulin sensitivity check index.