REVIEW ARTICLE

Julie R. Ingelfinger, M.D., *Editor*

Pathogenesis and Diagnosis of Growth Hormone Deficiency in Adults

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In a landmark 1962 review of growth hormone, Raben wrote, "Pituitary growth hormone is distinctive in causing growth of almost all tissues and in increasing size without advancing maturation . . . ."[1] Written in an era of hormone bioassays, before the introduction of peptide sequencing, his description has remained accurate with the subsequent development of rigorous growth hormone assays and the introduction of recombinant growth hormone for clinical use. This review discusses the production and action of growth hormone, the pathogenesis and diagnosis of adult growth hormone deficiency states, and the safety of growth hormone in adults.

Growth Hormone Synthesis

Circulating growth hormone, a 191-amino-acid polypeptide secreted by anterior pituitary somatotrophs, has anabolic and growth-promoting properties. Differentiated, cell-specific growth hormone transcription is determined largely by the POU1F1 transcription factor, as well as by chromatin-interacting enhancer elements.[2] The growth hormone gene cluster, located on chromosome 17q24.2, expresses predominantly an alpha-helix 22-kDa peptide and a less abundant 20-kDa variant, as well as other related peptides.[3] Peripheral tissues such as placenta, breast, colon, and lymphatic tissue also express growth hormone, in a tissue-specific autocrine or paracrine manner.[4]

Control of Growth Hormone Secretion

Growth hormone secretion is regulated primarily by hypothalamic signals and by complex gut, liver, and gonadal signals. Growth hormone–releasing hormone (GHRH) and somatostatin traverse the hypothalamic–pituitary portal system to induce or suppress growth hormone production, respectively, by signaling through specific somatotroph cell-surface G protein-coupled receptors.[5] Gastric-derived ghrelin also stimulates growth hormone production and synergizes the action of GHRH.[6] Insulin-like growth factor 1 (IGF-1), the peripheral target hormone for growth hormone, suppresses growth hormone by exerting negative feedback and regulating paracrine growth hormone receptor trafficking.[7] Neuropeptides, neurotransmitters, and amino acids modulate coordinated hypothalamic release and the actions of GHRH, somatostatin, or both, orchestrating pulsatile growth hormone secretory patterns, which are largely determined by age, nutritional status, and sex.[8]

Growth hormone pulses occur mainly at night and account for most (>85%) of the daily growth hormone production. Nadir growth hormone levels occur mainly during the daytime when levels are mostly undetectable, especially in elderly or obese persons. Episodic growth hormone release is augmented by exercise and

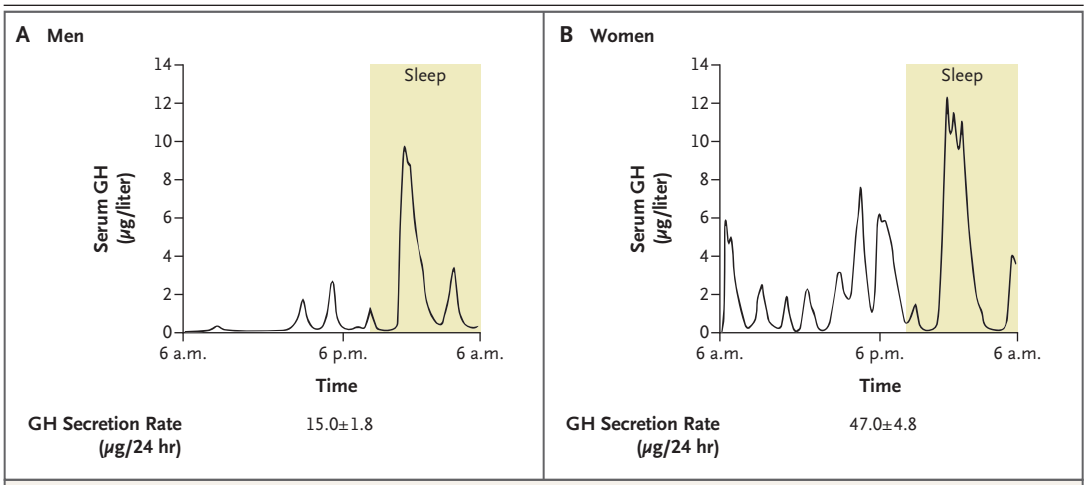

Figure 1. Growth Hormone Secretion Patterns in Adults.

Physiologic patterns of adult growth hormone (GH) secretion in men (Panel A) and women (Panel B) are shown (adapted from Jessup et al.[13]). GH secreting profiles in men and women were assessed by deconvolution analysis. Plus–minus values, which are derived from van den Berg et al.,[14] are means ±SE.

blunted by normal aging and visceral adiposity.[9-11] For each unit increase in the body-mass index, secretion of growth hormone drops by 6%.[10] Growth hormone release is suppressed by glucose loading and stimulated by insulin-induced hypoglycemia. Glucose loading suppresses the serum growth hormone level to less than 0.70 μg per liter in women and to less than 0.07 μg per liter in men, whereas malnutrition or hypoglycemia leads to increased growth hormone levels. Insulin-induced hypoglycemia stimulates growth hormone release within 45 minutes, during the induced glucose trough. Single amino acids (arginine and leucine) administered intravenously induce growth hormone secretion.

Both growth hormone secretion profiles and tissue growth responses are sexually dimorphic. Women have more disorderly growth hormone release, more growth hormone secreted per pulse, higher basal growth hormone levels, and more growth hormone resistance than men, and estrogen augments growth hormone responses to GHRH. The circulating growth hormone half-life is about 14 minutes. Production peaks during midadolescence; levels decline after growth ceases, remain stable until midadulthood, and wane progressively with aging by about 14% per decade, most likely because of decreasing output of GHRH[12] (Fig. 1). In the elderly, low physiologic growth hormone levels may overlap with values observed in younger, truly growth hormone–deficient patients.[11]

GROWTH HORMONE ACTION

The constitutively dimeric growth hormone receptor, a 70-kDa, class I cytokine receptor, is expressed on multiple tissues, especially liver, cartilage, muscle, fat, and kidney tissue (Fig. 2). The growth hormone ligand–growth hormone receptor complex[17] triggers intracellular signal transduction to regulate JAK2 (Janus kinase 2) tyrosine kinase phosphorylation and STAT (signal transducer and activator of transcription) proteins, which in turn regulate target genes, primarily hepatic IGF-1 production.[18] Growth hormone also signals through non-STAT pathways. Both chondrocyte proliferation and linear growth require growth hormone and IGF-1, as well as thyroid hormone and sex steroids. Suppressors of cytokine-signaling proteins and phosphatases down-regulate growth hormone receptor signaling.

Growth hormone–activated STAT5β induces hepatic IGF-1 synthesis,[19] mediating growth hormone–induced somatic growth and adipocyte and metabolic functions. Growth hormone–mediated postnatal growth, adipocyte functions, and the sexual dimorphism of the hepatic actions of growth hormone are regulated by STAT5β. The critical role of STAT5β transduction of the growth hormone signal and IGF-1 production is exemplified by short stature in patients who have inactivating STAT5β mutations and low IGF-1 levels with insensitivity to injected growth hor-

mone.[20] Growth hormone may also act independently of IGF-1.[21]

Secretory patterns,[22] levels of circulating hormone, and degree of adiposity,[23] as well as the IGF-1 receptor,[24] determine transduction of the growth hormone signal and tissue-specific responses to growth hormone receptor activation. Chondrocyte proliferation and childhood linear growth require both growth hormone and IGF-1. Although growth hormone is required for linear growth during childhood, metabolic functions unrelated to growth are maintained by growth hormone throughout adulthood. These include potent anabolic effects,[25] as well as antagonism of insulin action, which decreases adipocyte glucose uptake while increasing hepatic glucose production. Growth hormone directs amino acids toward muscle protein synthesis[26] and induces lipolysis, with loss of mainly visceral adipose tissue, and release of free fatty acids, as well as lowering of cholesterol and apolipoprotein B levels, with increased high-density lipoprotein levels.[27] Since growth hormone enables lipolysis in the fasting state, the net metabolic actions of growth hormone appear to confer homeostatic energy metabolism, whereas in the malnourished state, tissue resistance to growth hormone is manifested.[28] Growth hormone induces osteoblast differentiation and proliferation and bone formation, dampens osteoclast activation, and increases renal sodium absorption.[29] IGF-1 is required, in particular, for maintenance of cortical bone repair and remodeling.

ACQUIRED GROWTH HORMONE DEFICIENCY IN ADULTS

CAUSES

Suppression of growth hormone production in adults may be caused by structural insults, such as an expanding intrasellar mass compressing somatotroph function, damaged hypothalamic–pituitary neuroendocrine pathways, or local vascular compromise resulting from surgery, radiation therapy, or head trauma (Fig. 2). Survivors of childhood cancers are at risk for the development of growth hormone deficiency in adulthood, especially if they received radiation therapy to the head or neck.[30] In persons with normal pituitary function who do not have such conditions, age-adjusted growth hormone levels are invariably within normal limits.

DIAGNOSIS

An accurate biochemical diagnosis is required to confirm acquired adult growth hormone deficiency, since affected patients do not have a short-stature phenotype (Table 1). The symptoms are usually nonspecific yet common, and growth hormone replacement is approved only for patients with a true deficiency of growth hormone. Accordingly, since validated growth hormone deficiency is rarely encountered, the challenging diagnostic evaluation should be undertaken only if pituitary dysfunction is apparent. Thus, it is prudent to first determine the likelihood that a given patient does, in fact, have compromised growth hormone secretion. Assessment is not indicated without evidence of a pituitary or parasellar mass lesion or a history of a hypothalamic–pituitary insult, such as surgery, radiation therapy, head trauma, brain tumor, or stroke.

Because growth hormone secretion is pulsatile, relying on a single random measurement of the circulating (serum) growth hormone level is insufficient; rather, an accurate reflection of pituitary function is obtained by measuring secretory reserve in response to validated provocative pituitary-function tests, each of which has advantages and disadvantages (Table 2).[33] Such testing is indicated for patients in whom pituitary deficiency due to hypothalamic–pituitary defects is suspected, as outlined in Figure 2, especially for those with central obesity, loss of muscle mass, and hyperlipidemia. Retesting of the growth hormone axis is required in adults who received growth hormone during childhood to increase linear growth. Establishing a biochemical diagnosis is challenging. Provocative testing should be avoided in patients with commonly encountered, generalized, nonspecific symptoms of weakness, frailty, or obesity, since a misleading diagnosis of adult growth hormone deficiency may be made in some patients with these symptoms who actually have normal pituitary function.

Establishing an accurate diagnosis may also be challenging owing to the variable results of different growth hormone stimulation tests. Distinguishing patients with growth hormone deficiency from those with intact pituitary function requires a blunted growth hormone response to at least two validated provocative tests that elicit growth hormone release. Insulin-induced hypoglycemia (insulin-tolerance test) is the reference standard for making the diagnosis of adult growth

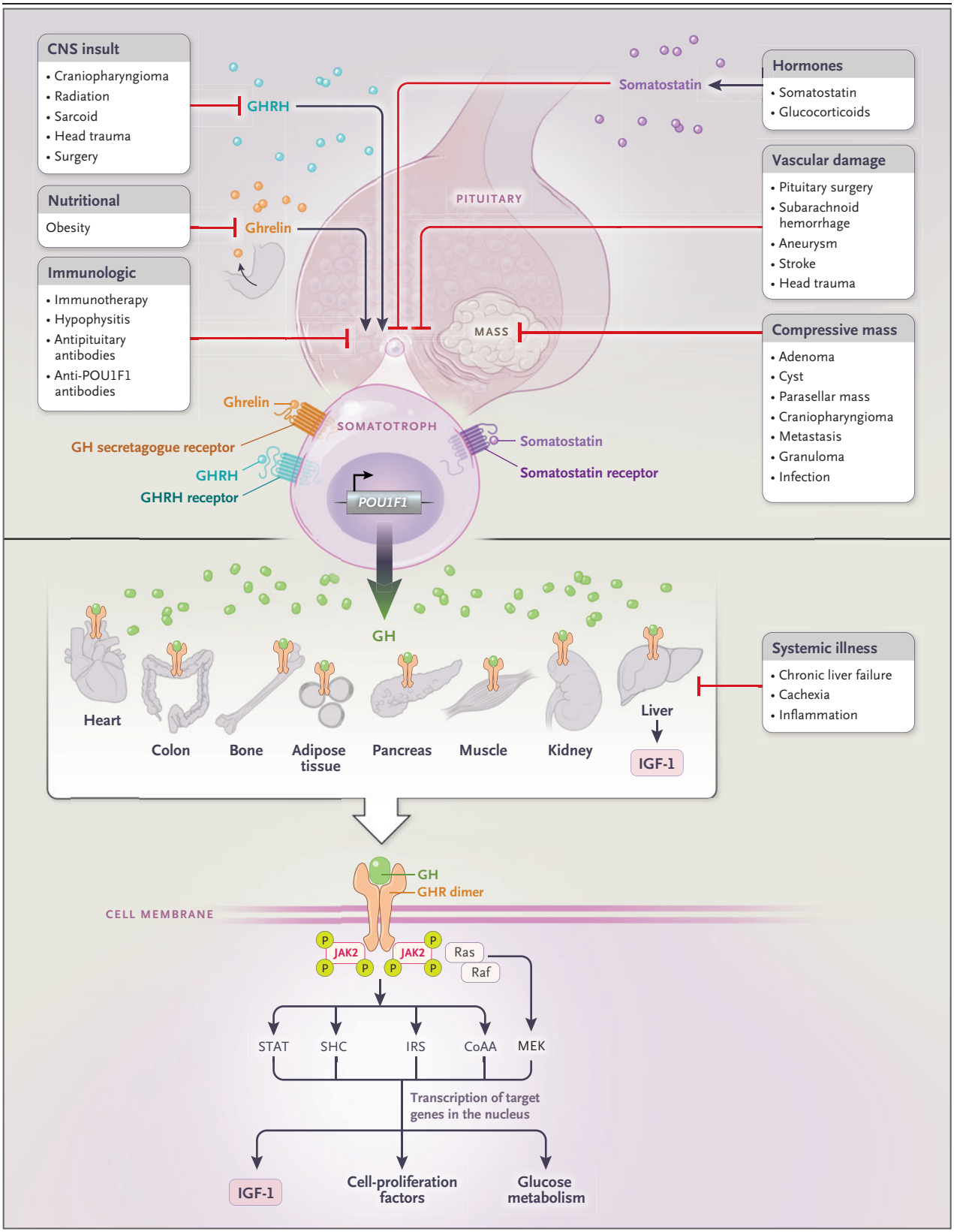

Figure 2 (facing page). Causes of Acquired Adult GH Deficiency.

Differentiated pituitary GH production, determined largely by POU1F1, is induced by GH-releasing hormone (GHRH) and ghrelin and is suppressed by somatostatin by means of signaling through cognate somatotroph surface receptors. GH binds the preformed GH receptor (GHR) dimer. Internal dimer rotation results in Janus kinase 2 (JAK2) phosphorylation (P) and signaling by JAK2-dependent and JAK2-independent pathways. GH targets include insulin-like growth factor 1 (IGF-1), cell-proliferation factors, glucose metabolism, and cytoskeletal proteins. GHR internalization and translocation may directly induce nuclear proproliferation genes.[15] GHR signaling may be abrogated by suppressors of cytokine signaling proteins and by phosphatases. GH production may be suppressed by a range of conditions.[16] GH action targets pleiotropic tissues mainly in the organs depicted. A model of GH bound to the GHR dimer is shown. CNS denotes central nervous system, and IRS insulin receptor substrate.

Table 1. Caveats for Assessing Growth Hormone Deficiency in Normal-Height Adults.*

Growth hormone measurements have several confounders
Growth hormone and IGF-1 assays have not been rigorously standardized and have poor reproducibility
Pulsatility of growth hormone secretion precludes single-measurement interpretation
Postprandial growth hormone levels are suppressed
"Normal" adult baseline values for growth hormone levels are inadequate
Provocative testing is required to rigorously assess the adequacy of growth hormone production
Awareness of physiologic and pathologic phenotypic growth hormone suppressors is crucial
Normal aging is associated with declining growth hormone levels
Obesity, central adiposity, and elevated body-mass index suppress growth hormone levels
Hyperglycemia or uncontrolled diabetes dysregulates growth hormone production
Elevated free fatty acid levels suppress growth hormone levels
Chronic illness is associated with suppressed growth hormone levels
Intact hypothalamic–pituitary function usually precludes diagnosis
Pituitary mass ruled out by MRI
No history of hypothalamic–pituitary disease
Reproductive, thyroid, and adrenal function intact

* IGF-1 denotes insulin-like growth factor 1, and MRI magnetic resonance imaging.

hormone deficiency.[34] As an alternative test, intravenous GHRH plus arginine or injectable glucagon can be used (Table 2). Most likely by suppressing somatostatin, arginine potentiates growth hormone secretion induced by GHRH[35]; the mechanism for the action of glucagon on growth hormone secretion is unclear. With the insulin-tolerance test, adult growth hormone deficiency is diagnosed if the elicited peak growth hormone level is less than 5 μg per liter.[36] Specificity and sensitivity are enhanced by using an even lower growth hormone level as the cutoff point.[33] In a randomized study comparing induced growth hormone levels with arginine stimulation and with the insulin-tolerance test in 69 patients, the peak growth hormone level was 3.67 μg per liter with arginine stimulation (79% sensitivity and 95% specificity), corresponding to a peak level with the insulin-tolerance test of 3 μg per liter.[37]

False positive (i.e., blunted) growth hormone responses may result in misdiagnosis of adult growth hormone deficiency, especially in obese patients and those older than 60 years of age. For example, the peak growth hormone levels induced by the test of arginine-stimulated GHRH have been found to be blunted by 1 μg per liter for each 1-cm increase in waist circumference.[10] Since GHRH is largely unavailable in the United States, a glucagon stimulation test has been used, with a cutoff value of less than 3 μg per liter.[38] Macimorelin, an orally active ghrelin mimetic, binds the GHS-R1a receptor with an affinity similar to that of ghrelin and stimulates growth hormone secretion. When used to provoke growth hormone secretion, macimorelin has a diagnostic accuracy similar to that of the insulin-tolerance test, with 92% sensitivity and 96% specificity, thereby offering a method with no risk of hypoglycemia and a lower likelihood of false positive results.[32]

Multiple measurements of growth hormone levels in the same sample may vary by more than 10%, and guidelines therefore suggest harmonization of growth hormone measurements across laboratories with the use of a uniform reference standard.[39] Since some growth hormone is protein-bound and some is free, the balance may affect assay results. In addition, assays are poorly standardized, and except for well-validated assays, sensitivity values are inconsistent.[40] Patients with three or four documented pituitary-axis deficiencies (thyroid, adrenal, gonadal, and vasopressin deficiencies) invariably have growth hormone deficiency (elicited growth hormone level,

Table 2. Provocative Testing for the Diagnosis of Growth Hormone Deficiency in Adults.*

Test	Diagnostic Cutoff Level	Considerations
	per liter of serum	
Insulin-tolerance: insulin, 0.05–0.15 U/kg, intravenous	5 μg	Hypoglycemia symptoms may occur, precluding use in patients with epilepsy or ischemic heart disease, pregnant women, and patients >65 years old; test requires close medical supervision
GHRH–arginine: GHRH, 1 μg/kg (maximum, 100 μg), intravenous; and arginine, 0.5 g/kg (maximum, 30 g), intravenous infusion	11 μg if BMI <25 8 μg if BMI 25–30 4 μg if BMI >30	Not available in the United States; hypothalamic disease may not be accurately diagnosed
Glucagon: 1 mg (1.5 mg if body weight >90 kg), intramuscular	3 μg	Nausea, vomiting, headache, and delayed hypoglycemia may occur
Ghrelin receptor agonist: 0.5 mg/kg, oral solution	2.8 μg	Avoid concomitant use with drugs known to prolong QT interval; hypothalamic disease may not be accurately diagnosed
IGF-1: random serum level	Below the level in age-matched controls	Useful if patient has ≥3 pituitary hormone deficits; values may be normal in adult growth hormone deficiency

* Data are from Yuen et al.[31] and Garcia et al.[32] Lower cutoff values may improve sensitivity and specificity, especially in obese patients. The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. GHRH denotes growth hormone–releasing hormone.

<3 μg per liter) and may not require growth hormone stimulation testing.[41] In such persons, obtaining a validated low IGF-1 value is reassuring, given the costly commitment of long-term daily growth hormone injections.[42,43] Borderline-low IGF-1 values should be interpreted with caution.[43] Isolated IGF-1 measurements are of limited diagnostic use because levels in adults with growth hormone deficiency may still be within normal limits, and isolated low IGF-1 levels are more commonly due to aging or catabolic illness than to adult growth hormone deficiency.

CLINICAL FEATURES

Rigorously documented adult growth hormone deficiency is associated with central obesity, loss of lean muscle mass, decreased bone mass, and a variable effect on the quality of life (Fig. 3).[44,45] Fat mass is increased, as are levels of cholesterol, low-density lipoproteins, triglycerides, and apolipoprotein B, and lean body mass is decreased. Although growth hormone antagonizes insulin action, adult growth hormone deficiency may also be associated with hyperglycemia and diabetes, probably aggravated by the central obesity that is typically present in such patients.[46] Left ventricular function and exercise capacity are reduced. Bone mineral density and bone turnover are decreased, leading to osteopenia, skeletal fragility, and moderate parathyroid hormone insensitivity, features that are associated with an increased risk of skeletal fracture.[29] Indeed, in a prospective series of 40 patients with growth hormone deficiency (median age, 44 years), 12 patients (30%) had incident vertebral fractures at 6 years of follow-up.[47]

GROWTH HORMONE REPLACEMENT FOR GROWTH HORMONE DEFICIENCY

BENEFITS

The often nonspecific features of adult growth hormone deficiency, including central obesity and osteoporosis, may be reversed or ameliorated with sustained daily growth hormone replacement therapy. Growth hormone replacement at physiological doses is approved for adults with proven pituitary growth hormone deficiency, including those with well-documented, childhood-onset growth hormone deficiency.[36,42,48-50]

Although the results of growth hormone replacement therapy are widely variable, most studies have shown increased lean body mass and exercise capacity and reduced fatigue. Whether physiological growth hormone replacement in adults with growth hormone deficiency conclusively reduces mortality remains unresolved, since it has proved challenging to ascribe increased mortality in association with hypopituitarism solely to growth hormone deficiency, without account-

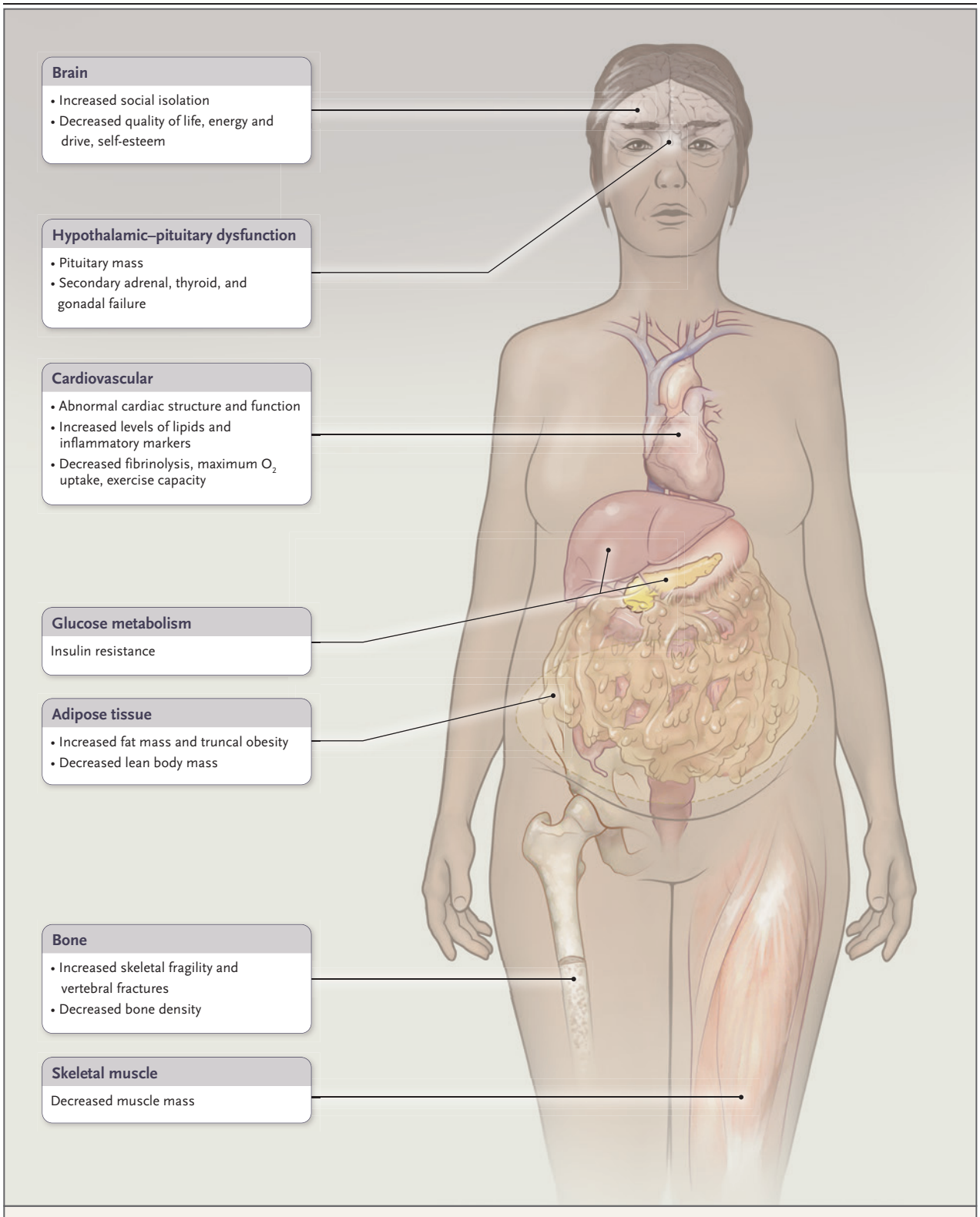

Figure 3. Clinical Features of GH Deficiency in Adults.
Shown are the most prominent clinical features of GH deficiency.

ing for adequate adrenal, thyroid, and sex hormone replacement. The difficulty of recruiting participants for a long-term, placebo-controlled study of growth hormone replacement precludes assessment of a growth hormone–specific reduction in mortality.

SAFETY

Growth hormone replacement may unmask underlying hypothyroidism or hypoadrenalism,[42] and side effects of growth hormone therapy, observed in about 30% of patients, include dose-dependent joint and muscle pain, soft-tissue swelling, paresthesia, carpal tunnel syndrome,[51] sleep apnea, hypertension, insomnia, and hyperglycemia.[52] In rare cases, features of acromegaly have developed in patients.[53,54] Despite improvement in cardiac risk factors, metabolic syndrome, diabetes, and hypertension may develop over a period of 10 years.[55] On the basis of observational studies, the incidence of new cancers, recurrent pituitary adenoma, diabetes, or cardiovascular events is not elevated in patients with pituitary deficiencies who are receiving physiological growth hormone replacement.[56,57] In a case–control study of growth hormone replacement for a median of 10 years after pituitary adenoma resection, progression-free survival did not differ significantly between the 121 patients who received growth hormone replacement and the 114 controls.[58] However, after a median of 5.9 years of surveillance in a group that received active treatment, an increased risk of a second neoplasm was evident among patients with childhood-onset growth hormone deficiency (standardized incidence ratio, 10.4; 95% confidence interval [CI], 5.9 to 16.9) as compared with those who had adult-onset growth hormone deficiency.[59] Since radiation exposure was more likely in the childhood-onset cohort, further vigilant surveillance is required. Pregnancy outcomes in women with adult growth hormone deficiency are not adversely affected by growth hormone replacement.

GROWTH HORMONE IN PATIENTS WITHOUT GROWTH HORMONE DEFICIENCY

Off-label use of growth hormone has not been proved to be efficacious. There is no compelling evidence from controlled studies that growth hormone is beneficial (except for acute fat loss) in otherwise healthy adults without a rigorously established diagnosis of growth hormone deficiency.[36,42,60] Growth hormone has been tested for the treatment of catabolic states, osteoporosis, and fracture healing and as an adjuvant for in vitro fertilization, with inconsistent outcomes.

HUMAN IMMUNODEFICIENCY VIRUS–ASSOCIATED CACHEXIA

Growth hormone responses to secretagogues are blunted in persons with human immunodeficiency virus (HIV) infection. Growth hormone therapy, which is approved for treating HIV-associated cachexia,[61] induces a positive nitrogen balance and muscle mass, with decreased fat. The development of diabetes in HIV-infected patients treated with growth hormone is of concern, especially in patients receiving concomitant protease-inhibitor therapy.[62] A GHRH analogue administered for 6 months appears to be effective in reversing visceral adiposity and modestly reduces liver fat,[63] but long-term mortality results in controlled studies are not yet available.

ATHLETIC PERFORMANCE

Listed by the World Anti-Doping Agency as a prohibited substance, the use of growth hormone to enhance athletic performance is illegal, in accordance with federal statute 21 U.S.C. §333(e), and is not ethically or scientifically justified.[60] Nevertheless, growth hormone has been improperly used by athletes attempting to achieve a competitive performance advantage,[64] although studies have not shown clinical benefits. In a randomized, controlled trial, growth hormone did not specifically enhance rotator-cuff healing,[65] and a double-blind, placebo-controlled study involving 96 trained recreational athletes receiving growth hormone (2 mg per day) for 8 weeks showed that muscle strength, power, and endurance were unchanged, although sprint capacity was increased by 5.5% in male participants.[66] A systematic review of 27 randomized, controlled trials involving a total of 303 young men showed that high growth hormone doses (mean dose, 2.5 mg daily) were associated with increased fat-free body mass, but strength and exercise performance were unchanged.[67] Up to 44% of the participants reported side effects, including arthralgia, edema, carpal tunnel syndrome, and sweating. A comprehensive meta-analysis of 11 placebo-controlled trials in-

volving 254 healthy participants confirmed that growth hormone decreased fat mass (by about 1.2 kg on average) but also showed an increase in free fatty acid levels, with no change in muscle strength or exercise capacity.[68] Specific growth hormone efficacy cannot be rigorously deduced from interpreting the results of these few randomized, controlled trials, given the variations in study duration, dosing schedules, and clinical end points.[64] In addition, since many athletes take concomitant hormonal supplements, including testosterone, clear validation of anecdotal effects attributed to growth hormone is elusive. Testosterone augments the effects of growth hormone on muscle mass and potentiates growth hormone–induced sprint capacity,[66] and testosterone may also amplify levels of circulating growth hormone biomarkers.[69] Thus, the clinically modest and largely short-lived effects of growth hormone should be placed in the context of the potential side effects, including diabetes and, ultimately, in the spectrum of coexisting conditions associated with growth hormone excess and acromegaly.[5,53,54,70]

Since exogenous recombinant human growth hormone is identical to endogenous, pituitary-derived growth hormone, detecting growth hormone abuse by means of immunoassays is challenging. The short circulating growth hormone half-life precludes implementation of a rigorous testing protocol. To discriminate endogenous from exogenous growth hormone bioactivity, unique circulating growth hormone biomarkers, including IGF-1 and procollagen type III N-terminal extension peptide, are measured for up to 2 weeks after growth hormone injection.[71] A second type of assay relies on the observation that exogenous, injected growth hormone is monomeric (22 kDa), whereas endogenous pituitary growth hormone comprises several isoforms. Although injected growth hormone elicits negative pituitary feedback, suppressing endogenous isoform production,[40] this measurement must be performed within 36 hours after an injection of growth hormone, making universal implementation to screen for growth hormone abuse challenging.

AGING

Aging is associated with obesity, loss of lean body mass, and decreased energy, and growth hormone may decrease fat mass in persons with normal pituitary function.[72] Given the age-related decline in levels of growth hormone, especially after 60 years of age, some have advocated the use of growth hormone as a "fountain of youth" for rejuvenating the frail elderly. Improper growth hormone use has sometimes been justified by relying on the results of an unvalidated test for diagnosing adult growth hormone deficiency or by omitting such testing. Short-term, randomized, controlled trials have shown that in healthy elderly patients, combined use of growth hormone and testosterone may improve selective muscle strength and oxygen uptake.[73] However, systematic reviews of trials evaluating the safety and efficacy of growth hormone in healthy elderly persons have shown only small changes in body composition and inconsistent strength and exercise-capacity outcomes.[74-76] Epidemiologic studies have largely been inconclusive, especially since data are lacking from rigorous studies accounting for sex-specific growth hormone pulsatility, the tissue specificity of growth hormone action, and the role of nutrition in determining specific clinical outcomes.

Several lines of experimental and clinical evidence derived from models that start with unicellular organisms and extend to humans show that abrogated growth hormone and IGF-1 signaling may slow aging.[77-79] In experimental models, low growth hormone levels promote longevity by providing protection against chronic illnesses associated with aging, enhancing insulin sensitivity, and providing protection against diabetes and cancer, thereby extending the lifespan.[80-82] Evidence supporting the protective effects of low growth hormone levels include induction of the NLRP3 inflammasome and aging-associated genes by growth hormone, IGF-1, or both[83] and an association of longevity with low IGF-1 levels.[77] Notably, in persons with mutant growth hormone receptors, low IGF-1 levels have been identified as markers of longevity, conferring about 10 added years to the lifespan.[84] Furthermore, in familial-longevity cohorts, growth hormone secretion entropy is decreased, and 24-hour growth hormone production is diminished by 28%.[85]

A meta-analysis of 23 studies showed a standardized incidence ratio of 1.5 (95% CI, 1.2 to 1.8) for cancer incidence in patients with acromegaly.[86] The oncogenic potential of growth hormone receptor signaling[15] has been supported by studies showing that excess circulating growth hormone

levels, as well as the actions of paracrine growth hormone and IGF-1, can participate in neoplastic initiation and progression.[4] Evidence that autocrine growth hormone promotes breast-cancer stem-cell phenotypes[87] and that the amount of tumor growth hormone correlates strongly with the clinical outcomes of breast, endometrial, and liver cancer is consistent with these observations.[88] In patients with acromegaly, colon mucosal tumor suppressors are attenuated, and blocking of growth hormone receptor signaling induces growth suppressor pathways. Thus, excess growth hormone appears to contribute to the proliferative microenvironment sustaining the growth of colon polyps.[89] This hypothesis is supported by evidence that growth hormone induces an epithelial-to-mesenchymal transition.[90] That attenuated growth hormone secretion and action favor an antiproliferative phenotype is strongly exemplified by the observation that cancer does not develop in persons with genetically determined growth hormone deficiency and short stature.[91]

Since growth hormone may have unacceptable adverse effects in otherwise healthy persons with normal pituitary function,[54,92] guidelines do not recommend growth hormone as an antiaging therapy.[36,42,93,94]

CONCLUSIONS

A rigorous biochemical diagnosis of adult growth hormone deficiency is required to distinguish pathologically attenuated growth hormone levels from diminished levels due to normal aging. Growth hormone replacement may be beneficial for persons with proven adult growth hormone deficiency, but randomized, controlled trials are needed to refine individualized efficacy markers and determine survival benefits. With respect to growth hormone for frail elderly patients with normal pituitary function, trials are needed to determine when and how the action of growth hormone on tissue undergoes a programmed switch from beneficial effects in younger persons to detrimental effects for longevity in older persons.[80]

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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