Treatment of the Adult and Transitional Patient

Gary Owens, MD; Donald Balfour, MD, FACP; S. Thomas Bigos, MD; Jay Cohen, MD, FACE; James Grua, MD, PhD, FACE; Wynter Kipgen, MD; Rajendra Ratnesar, MD; Kenneth L. Schaecher, MD; Mary Lee Vance, MD; and David E. Wilcox, MD, FACEP

Once the hurdles associated with testing and diagnosing adults with growth hormone deficiency (GHD) have been crossed, the challenge of determining which adult patients should be treated with growth hormone (GH) replacement therapy remains. In 1996, the US Food and Drug Administration (FDA) approved recombinant human growth hormone (hGH) for the treatment of adult GHD secondary to pituitary disease from known causes—pituitary tumor, pituitary surgical damage, hypothalamic disease, irradiation, trauma, and reconfirmed childhood GHD.[1] This indication encompasses most adult patients with GHD. In addition, hGH is now also indicated for the management of acquired immunodeficiency syndrome–related cachexia. Interest abounds in using hGH for a host of other indications, such as chronic fatigue syndrome, fibromyalgia, obesity, and enhanced athletic performance, none of which has FDA approval. The potential for fad, unproved, and even cosmetic use of hGH has forced many payers to implement precertification requirements for all patients who are about to undergo therapy with hGH.[1] All of the currently marketed hGH products are made using recombinant deoxyribonucleic acid processes, eliminating the risk of contamination or disease transmission found with natural products.

For patients with documented GHD, hGH therapy is the standard of care. However, economic considerations greatly influence the initiation of treatment. Clinicians may be reluctant to prescribe treatment for GHD because it requires substantial physician time and staff support to diagnose and justify reimbursement. Patients may also be reluctant to undergo a treatment that is expensive, time consuming, and inconvenient. The patient out-of-pocket costs may be significant, resulting in a choice not to pursue therapy. This is especially true in benefits that require coinsurance without an annual out-of-pocket cap. Patients should be told the goals of hGH therapy have specific and attainable end points, such as improved lipid profile, increased bone mineral density, decreased fat mass, improved quality of life (QoL), and reduced mortality. The patient should understand that the therapeutic benefits of hGH are gradually achieved from several months to more than a year after treatment. Accepted patient groups that should receive treatment include young adults transitioning from pediatric care and young and middle-aged adults with recent-onset GHD. Patients older than 60 years of age may glean only minimal benefits. In fact, because of preexisting medical conditions, older patients may be more susceptible to hGH side effects, such as fluid retention, the appearance of glucose intolerance, or worsening glycemic control in patients with diabetes. Generally, older adults are more susceptible to the side effects of hGH therapy compared with young patients, especially at the start of treatment. Lower starting doses will help minimize adverse events in the older population. Starting therapy as a young adult decreases the duration of GHD (ie, decrease time to accrue consequences that may not be significantly reversible) and reduces the comorbid diagnosis. In the young adult patient, the medication is generally better tolerated and there is a better chance to prevent or reverse the degenerative consequences of GHD. Waiting until the

Table. Adult GHD: Effect of Long-term GH Therapy on Serum Lipids Versus Untreated Patients

	GH Treated		Not Treated	
	Baseline	10 year	Baseline	10 year
Total cholesterol (mg/dL)	228 ± 15.5	232 ± 15.5	220 ± 11.6	255 ± 27
Triglycerides (mg/dL)	186 ± 44.3	239 ± 70.8	195 ± 0.2	310 ± 79.7
HDL cholesterol (mg/dL)	30.9 ± 3.9	54.1 ± 3.9*	30.9 ± 3.7	46.4 ± 3.9*
LDL cholesterol (mg/dL)	159 ± 11.6	130 ± 7.7†	143 ± 11.6	146 ± 19.3

Values are mean ± standard error of mean.
*P <.01 vs baseline.
†P <.05 vs baseline.
GHD indicates growth hormone deficiency; GH, growth hormone; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
Adapted from Gibney J, et al. *J Clin Endocrinol Metab.* 1999;84:2596-2602.

patient's condition progresses raises the potential for more advanced degenerative consequences and a greater number of comorbid diagnoses. The potential gain may be less in the population with a higher risk of potentially serious side effects. Clinical judgment is critical when it comes to starting treatment with hGH, and greater caution is needed when evaluating older patients who have more complicated health profiles. The following case provides an example of the effects of adult GHD and the restorative actions of hGH therapy.

> ***Case study:*** A 47-year-old man was in a car accident and suffered a head injury. He experienced central nervous system bleeding and was unconscious and placed on a ventilator for 3 weeks. He lost 30 lb in 3 weeks and was unable to be taken off the ventilator. Diagnosed with panhypopituitarism, the patient was treated with hormone replacement therapy (glucocorticosteroids, thyroid hormone, androgens). Within 48 hours he was taken off the ventilator, he entered rehabilitation for 7 days, and then returned home. Several weeks after he was discharged, he returned to work; however, his physical condition worsened and he was extremely fatigued. He tried an exercise program but was unable to sustain a simple regimen. This scenario continued for months without any improvement, despite treatment with antidepressants and continued attempts at graded exercise. Although he was in his mid-40s, the patient felt like a frail octogenarian. An endocrinologist evaluated the patient. Provocative GH stimulation testing was performed revealing GHD, and he was prescribed hGH therapy. His ability to read and retain material returned completely. As the months progressed, his strength returned, the depression resolved, and he felt as if he had regained the energy level he had before the car accident.

In a small, 10-year study that included 10 adults with GHD, hGH treatment increased lean body mass, improved lipid profiles (**Table**), reduced carotid artery thickness, and enhanced the patient's sense of well-being (**Figure 1**).[2] Moreover, in a 2-year study of 148 adults with GHD, hGH replacement treatment significantly reduced the need for sick leave and hospitalizations and also bolstered QoL measures. These beneficial effects were maintained throughout the 2-year treatment period.[3]

In children and adults with GHD, hGH treatment has been shown to significantly improve both high-density lipoprotein (HDL) serum concentrations and HDL/low-density lipoprotein (LDL) ratios (**Figure 2**).[4]

In addition, hGH treatment in adults with GHD reverses the increases in carotid artery intima media thickness seen in untreated patients (**Figure 3**).[5] In a study that includ-

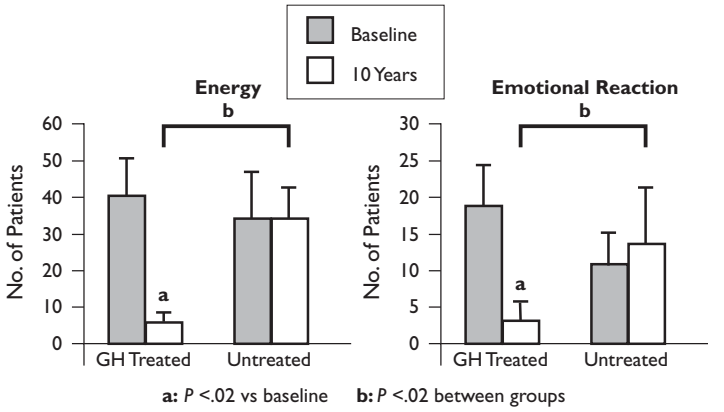
ed 11 men with GHD and carotid intima thicknesses that significantly exceeded those of control subjects, hGH treatment normalized intima thickness after 6 months of treatment. These findings illustrate that hGH treatment in adults with GHD can reverse early harmful morphologic changes to the vasculature and perhaps reduce cardiovascular risks.

Treatment with hGH has also been shown to reverse the attenuation in bone mineral density seen in GHD. In a randomized, placebo-controlled, 18-month study of 32 men with adult-onset GHD, treatment with hGH increased bone density and turnover in addition to increasing lean body mass.[6] Thus, hGH therapy may prevent bone loss in adults with GHD and possibly reduce the fracture risk. In the transitional patient, hGH has also been shown to improve bone mineral density, body composition, and lipid profiles.[7]

Together, these clinical findings strongly demonstrate that adult and transitional patients with GHD can gain meaningful clinical benefits from hGH replacement therapy, and that this form of treatment should be a standard of care for those with legitimate replacement needs.

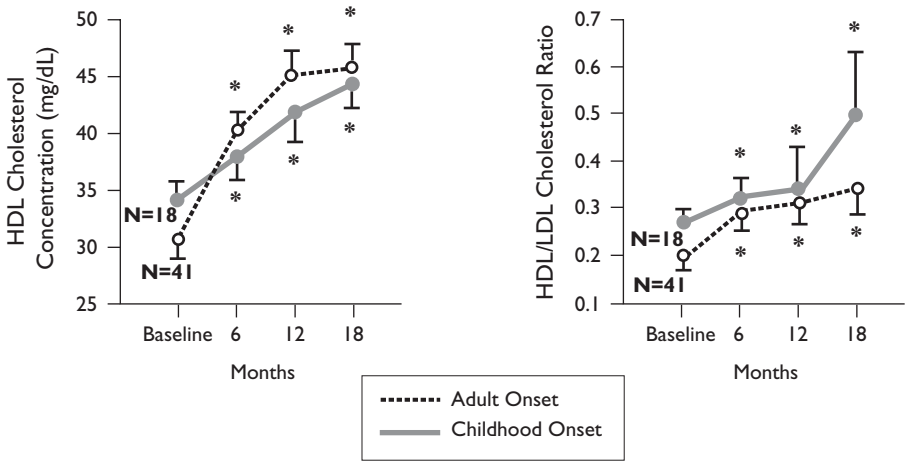
The initial adult hGH dose is 0.1 to 0.3 mg/day, which can be titrated monthly to achieve target insulin-like growth factor 1 (IGF-1) levels and symptom reduction. Typical maintenance doses are 0.3 to 1.0 mg/day; dose adjustments for weight are not usually necessary. Older patients may be treated with 50 µg/day to minimize adverse effects. Women have greater GH requirements than men, especially women receiving oral estrogen therapy.[8,9] The time to reach maintenance dose level in terms of IGF-1 response typically varies from 3 to 6 months, but can be longer. Body composi-

Figure 1. 10-year Effect of GH Treatment on Quality of Life



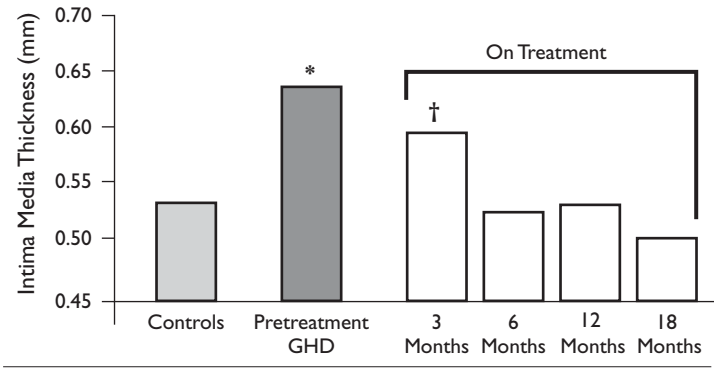
N = 21 growth hormone deficient adults.
GH indicates growth hormone.
Source: Gibney J, et al. *J Clin Endcrinol Metab.* 1999;84(8):2596-2602.

Figure 2. Change in Cholesterol with GH Treatment



*P <.02 vs baseline values. Values mean ± standard error of mean.
GH indicates growth hormone; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
Source: Attanasio AF, et al. *J Clin Encrinol Metab.* 1997;82:82-88.

Figure 3. Carotid Artery Thickness Changes



*P <.001 vs controls.
†P <.01 vs controls.
N = 11 GHD men; age: 24 to 49 years.
GHD indicates growth hormone deficiency.
Source: Pfeifer M, et al. *J Clin Endocrinol Metab.* 1999;84:453-457.

tion should improve with therapy, but total body weight may not substantially change. During treatment, side effects may dictate the final hGH dose.

Although 90% of cases of GHD are caused by pituitary adenomas, irradiation, surgery, infiltrative disease, infection, or trauma, 10% are idiopathic and have normal radiographic studies. Isolated GHD is being diagnosed with greater frequency over time. This condition is more difficult to diagnose and explain. Therefore, payer guidelines may not include criteria or guidelines specific for approval of isolated GHD.

Case study: A 54-year-old white man reports a 3-year history of not feeling well, increased abdominal girth, decreased muscle mass and strength, moodiness, decreased libido, and anhedonia. The patient has a medical history significant for hyperlipidemia and erythrocytosis. He is currently taking pravastatin sodium, aspirin, venlafaxine hydrochloride, niacin extended-release tablets, dehydroepiandrosterone, and a multivitamin. His social history includes consuming no alcohol, using smokeless tobacco for 20 years, and lifting weights regularly. He is married and a college graduate. His physical examination revealed that he is 6 ft, 3 in tall and weighs 231 lb. His blood pressure is 126/92 mm Hg, his pulse is 80 bpm with flat affect, and he has minimal abdominal obesity. The patient's baseline laboratory values are: IGF-1, 213 mg/L (90-360); LDL cholesterol, 131 mg/dL; HDL cholesterol, 61 mg/dL; normal testosterone, prostate specific antigen, thyroid-stimulating hormone (TSH), free triiodothyronine (T3), and prolactin. The work-up for GHD included an arginine stimulation test with the following results: 0.1 mg/mL at 0 minutes, 0.4 mg/mL at 30 minutes, 0.3 mg/mL at 60 minutes, 0.3 mg/mL at 90 minutes, 0.3 mg/mL at 120 minutes, and 0.1 mg/mL at 150 minutes. His pituitary magnetic resonance imaging test is normal. A decision was made to treat based on the physical examination and the failed arginine stimulation test. His insurance company denied the claim because a destructive lesion of pituitary was not present and he did not display childhood-onset GHD. In this case, the patient did not meet the payer guidelines for the use of hGH in adults, even though GHD was supported by provocative testing. After an appeals process, therapy was initiated. The patient responded to therapy with increased stamina and is being monitored for improvement in his hyperlipidemia.

Patients who have reached epiphyseal fusion and who complete pediatric indications for hGH represent a special category referred to as "transitional patients." These patients are typically in their mid-teens to early 20s; however, a precise interval has not been established between the completion of hGH therapy in childhood and the initiation of testing or continued hGH therapy in adolescence. These patients, especially those with idiopathic GHD, should undergo retesting to establish whether GHD has persisted into adulthood, although the presence of a structural pituitary defect, such as a craniopharyngioma in childhood, makes it likely that GH deficiency will continue into adulthood. In those transitional patients with idiopathic GHD in childhood, however, the hypothalamic-pituitary unit may mature, thereby restoring normal GH levels in some patients.[1]

Case study: A 20-year-old man with panhypopituitarism secondary to surgery at age 7 for craniopharyngioma has not received GH for several years. He receives testosterone

(luteinizing hormone and follicle-stimulating hormone were 0 when testosterone was low), thyroxin (TSH 0 regardless of thyroid dose), and hydrocortisone. He is not treated with desmopressin acetate and his current IGF-1 is 15 mg/dL (normal is 180-780 mg/mL).

The question remains as to whether this transitional patient should be treated with GH now that his bone growth is complete. The results of a 2-year study of transitional patients demonstrated that these individuals are at risk for the same metabolic disturbance that afflicts adult GHD patients and that resumption of hGH treatment can ameliorate these effects.[7] Those transitional patients with no other pituitary deficiencies whose initial childhood diagnosis was partial GHD may need no further testing than IGF-1. If this test is normal, it can be assumed that GH levels are also normal. Alternatively, if IGF-1 levels are low, provocative testing should be considered. Those patients with multiple pituitary deficiencies and a low IGF should continue receiving GH long term without the need for stimulation testing.

Transitional patients typically require larger doses of hGH than older patients with GHD.[7] A Canadian/American study revealed that 25 µg/kg/day affords better results in terms of bone density and body composition than lower doses. This converts to 1.75 mg/day for a 70-kg patient and 2.5 mg/day for a 100-kg patient. This dose, although well tolerated by younger patients, may be less tolerated by older patients.[8] For the transitional patient, the American Association of Clinical Endocrinologists guidelines recommend a starting dose of 0.4 to 0.8 mg/day, with increments of 0.2 to 0.4 mg/day every 4 to 6 weeks until maintenance doses of 1.2 to 2.0 mg/day are achieved. These maintenance doses are much higher than the 0.2- to 0.5-mg/day dose recommended for a 50-year-old man and the 0.4- to 1.0-mg/day dose recommended for a 50-year-old woman.[1]

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