

Growth Hormone Therapy for Adults: Not Ready for Prime Time?

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Human growth hormone is now readily available and approved for treatment of the growth hormone deficiency syndrome in adults. However, physicians have been slow to adopt this therapeutic modality. Reasons for skepticism about the use of growth hormone for the growth hormone deficiency syndrome include doubts about whether growth hormone deficiency causes increased morbidity and mortality in patients with hypopituitarism; availability of highly efficacious, easier to use, and less expensive agents for certain aspects of the growth hormone deficiency syndrome, especially cardiovascular disease; and concerns about pos-

sible toxicity in adults. Long-term studies in patients receiving appropriate comprehensive management for other hormonal deficiencies and for concomitant abnormalities will be required to convince physicians of the utility and safety of growth hormone replacement therapy.

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The availability of human growth hormone from recombinant DNA technology has led to a virtually limitless supply of this once scarce and rationed substance. Growth hormone therapy was once limited to use in short children with clearly defined growth hormone deficiency; however, in recent years, a newly defined clinical syndrome associated with growth hormone deficiency has emerged (1), along with advocacy of growth hormone injections for adult patients with this condition (2).

Four questions need to be answered in assessing the validity of this therapy. First, does such a phenotypic syndrome (the growth hormone deficiency syndrome) exist? Second, is growth hormone deficiency necessarily the cause of this constellation of symptoms and signs? Third, does growth hormone therapy improve the components of the growth hormone deficiency syndrome, and specifically, is it likely to be safe and to reduce morbidity and mortality? Finally, is growth hormone therapy likely to be cost-effective in treating the components of the growth hormone deficiency syndrome?

EXISTENCE OF THE GROWTH HORMONE DEFICIENCY SYNDROME

The growth hormone deficiency syndrome has been defined as a condition associated with weight gain, abnormal body composition (increased fat mass and decreased lean body mass), decreased bone mass, an atherogenic lipid profile, and increased cardiovascular risk in patients with documented growth hormone deficiency (1). What is the evidence that such a syndrome actually exists?

Arguments for the existence of this syndrome often begin with the issue of increased mortality, particularly cardiovascular mortality, in patients with hypopituitarism. Several retrospective studies that have used age-matched control data have suggested increased mortality in persons with hypopituitarism (Table 1) (3–7). Growth hormone deficiency has often been assumed to be the cause of this excess risk because these patients have usually been receiving conventional therapy for other hormonal abnormalities. Not all studies have observed excess atherosclerotic disease in these patients (3, 4, 6); in fact, one study actually

noted a decrease in vascular death (6). Furthermore, many patients in these studies received cranial irradiation, which is known to affect deleteriously cerebral vasculature (8).

Advocates of growth hormone therapy usually assume that patients with the growth hormone deficiency syndrome have excess atherosclerotic cardiovascular disease (9). This excess is generally thought to be caused, in part, by components of the metabolic syndrome (abnormal accumulation of body fat resulting in central obesity, decreased insulin sensitivity, and dyslipidemia) (10). Patients with the growth hormone deficiency syndrome generally have increased fat mass and decreased lean body mass compared with sex-, age-, height-, and weight-matched controls (11–13). Obesity and, in particular, increased central adiposity are common in persons with this condition (11, 14), as are insulin resistance (15); dyslipidemia (16–19); and other metabolic, inflammatory (20), and vascular factors (21, 22) associated with accelerated atherogenesis. Studies in these patients have generally used age-matched control data or population data for comparison. Some (23, 24) but not all (25) have observed abnormal cardiac function (both diastolic and systolic) in patients with hypopituitarism who have not received growth hormone therapy.

In summary, there does appear to be a clinical syndrome matching the components of the growth hormone deficiency syndrome in patients with hypopituitarism. Premature death may not necessarily be related to accelerated atherosclerosis, despite the presence of increased cardiovascular risk factors in such patients.

EVIDENCE THAT GROWTH HORMONE DEFICIENCY IS THE CAUSE OF THE GROWTH HORMONE DEFICIENCY SYNDROME

Whether this constellation of symptoms is related to growth hormone deficiency specifically, hypopituitarism generally, or some other factor is open to question. The studies of patients with hypopituitarism that have attributed excess mortality to growth hormone deficiency have been plagued by difficulties. Some of the patients in these studies received their diagnosis before the availability of

Table 1. Studies on Hypopituitarism and Mortality

Study (Reference)	Country	Total Patients Assumed To Have Hypopituitarism	Patients Identified as Having GHD/Patients Tested for GHD	Patients Not Tested for GHD	Patients with Cranial Irradiation	Odds Ratio for Mortality in Patients with Hypopituitarism (95% CI)	Effect on Causes of Mortality	Predictors of Mortality
		<i>n</i>	<i>n/n</i>	<i>n</i>				
Rosén and Bengtsson (3)	Sweden	333	53/53	280	158	Not reported	Increased vascular	–
Bates et al. (4)	United Kingdom	172	94/98	74	96	1.73 (1.28–2.28)	–	Age at diagnosis, hypogonadism
Bülow et al. (5)	Sweden	344	61/62	282	304	2.17 (1.8–2.51)	Increased cerebrovascular, cardiovascular	Age at diagnosis, sex
Bates et al. (6)	United Kingdom	348*	Unknown	Unknown	99	1.2 (0.95–1.55)	Decreased vascular	Age at diagnosis
Tomlinson et al. (7)	United Kingdom	1014	100/111	903	353	1.87 (1.62–2.16)	Increased cardiovascular, respiratory, cerebrovascular	Age at diagnosis, sex, craniopharyngioma, untreated gonadotropin deficiency

* 92 patients did not have adequate records; 10 of 243 patients had normal results on pituitary function testing. GHD = growth hormone deficiency.

hormonal assays for definitive diagnosis of one or more hormonal deficiencies. Most of the patients in these studies were not proven to have growth hormone deficiency (Table 1). However, given the natural history of pituitary hormone loss (26), an assumption of growth hormone deficiency is probably not unreasonable. Many patients in these studies received cranial irradiation, which is known to have deleterious effects on the cerebral vasculature (8, 27). Statistical analyses generally have not identified growth hormone deficiency as the major cause of increased mortality. Gonadotropin deficiency and age at diagnosis have been found to predict increased mortality in some studies (4–7). Although excess mortality rates have usually been attributed to vascular disease, clinical events—even nonatherosclerotic events, such as pulmonary embolism, congestive heart failure, and cerebrovascular disease—are sometimes included, clouding the analysis.

Another limitation of the mortality studies in patients with hypopituitarism concerns the appropriateness of using mortality data on age-matched controls. Some patients with hypothalamic or pituitary disease may be chronically ill as a result of tumors or therapy (for example, surgery or radiotherapy), which can contribute to adverse changes in body composition (central obesity with decreased lean body mass) if lack of activity due to illness is accompanied by caloric excess. Moreover, some of these patients may have hypothalamic abnormalities, resulting in increased appetite and body fat (28). This scenario is certainly plausible in patients with craniopharyngiomas, hypothalamic tumors, or a history of large pituitary tumors. Ideally, a better control sample would comprise growth hormone-sufficient patients with central nervous system disease and prolonged survival who have received surgery or radiotherapy. However, such a control group is not readily available.

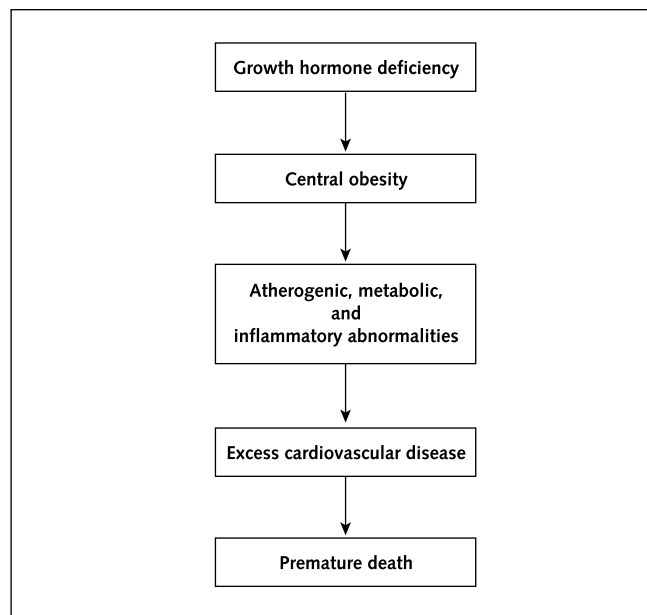
Because patients with the growth hormone deficiency

syndrome have generally received “standard replacement therapy” for other hormonal deficiencies, the lack of growth hormone is usually assumed to be the cause of the clinical syndrome and the increased mortality. But is “standard replacement therapy” optimal for other hormonal deficiencies? Recent work suggests that reducing glucocorticoid replacement doses in patients with hypopituitarism can improve insulin sensitivity and reduce risk for glucose intolerance (29). Many patients may be overtreated with standard therapy, which can cause abnormal body composition (central obesity and decreased lean body mass), attendant metabolic abnormalities, and osteopenia (30, 31). Thyroid hormone replacement is less precise in patients with hypopituitarism whose thyrotropin does not respond to titrated L-thyroxine therapy. Patients treated with excess thyroid hormone are at increased risk for atrial fibrillation (32) and osteopenia (33). Undertreated patients would be more likely to be obese and have an increased level of low-density lipoprotein cholesterol (34).

The doses of testosterone replacement that have been administered to men with hypopituitarism have often been suboptimal (35). Long-acting testosterone esters given monthly to men with hypogonadism leave the patients temporarily with low androgen levels. Newer cutaneous testosterone preparations do not have this disadvantage (36) but have not been available for a sufficient period to allow assessment of long-term effects.

The question of hormone replacement for women, particularly at older ages, is even murkier. In some of the studies on mortality, estrogen replacement was relatively uncommon. There is now considerable controversy about hormone replacement and cardiovascular and cerebrovascular risks in normal women (37, 38). On balance, when used in normal women of nonadvanced age, estrogen therapy probably decreases cardiovascular risk (39). However,

Figure 1. A growth hormone deficiency paradigm to explain excess death rates in patients with hypopituitarism.



two recent studies found that in women with hypopituitarism treated with conventional hormone replacement, lipid profiles, including low-density lipoprotein particle size, often worsened (18, 19). Whether such changes are related primarily to growth hormone deficiency is unknown (19). Androgen levels are decreased in women with hypopituitarism (40). No therapeutic trials have assessed the effects of androgen replacement on body composition, metabolic variables, and vasculature in women with hypopituitarism. Dehydroepiandrosterone (DHEA) benefits body composition and bone mineral density in normal elderly patients with a low baseline level of DHEA sulfate (41).

Optimal glucocorticoid and sex steroid replacement (adrenal androgens and testosterone in men and estrogens, adrenal androgens, and testosterone in women) needs to be clarified. To conclude at this time that growth hormone deficiency causes the growth hormone deficiency syndrome would be premature. Data on the existence of the growth hormone deficiency syndrome in patients who are otherwise healthy and have no pituitary deficiencies other than growth hormone would be far more compelling.

Figure 1 shows the pathophysiological paradigm for the growth hormone deficiency syndrome assumed by advocates of growth hormone treatment. However, a more accurate paradigm may be that shown in Figure 2. Perhaps the growth hormone deficiency syndrome would be more appropriately labeled “the hypopituitary syndrome.”

EVIDENCE THAT GROWTH HORMONE THERAPY REVERSES ASPECTS OF THE GROWTH HORMONE DEFICIENCY SYNDROME

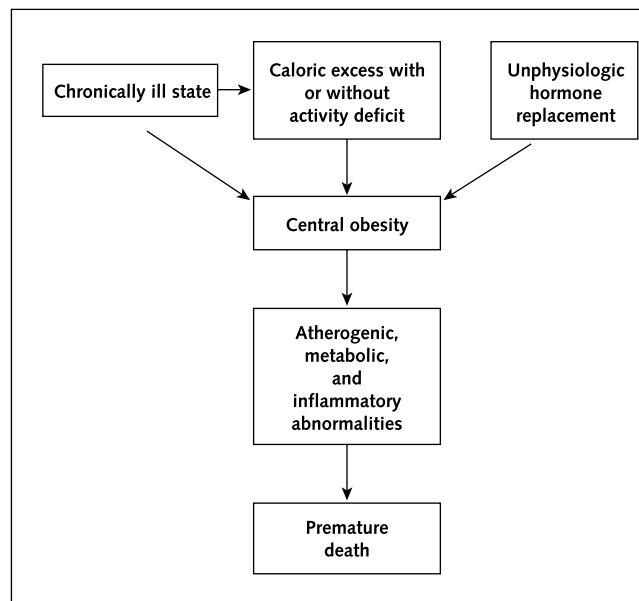
Human growth hormone therapy given for a relatively short time (usually < 1 year) to patients with rigorously

defined growth hormone deficiency and conventionally treated concomitant hormonal deficiencies has been associated with improved body mass composition (decreased fat mass and increased muscle mass), lipid variables (decreased low-density lipoprotein cholesterol level), and bone density (42, 43). However, many of the reports summarized in these reviews were not blinded or placebo-controlled studies. Table 2 lists the effects of growth hormone treatment on body composition and lipid levels in placebo-controlled, double-blind studies that have lasted at least 6 months. Of interest, improvements in high-density lipoprotein cholesterol and triglyceride levels have been inconsistent. One would expect that if growth hormone deficiency were the direct cause of the metabolic syndrome in patients with the growth hormone deficiency syndrome, the two major components of the characteristic dyslipidemia, a low level of high-density lipoprotein cholesterol and a high level of triglycerides levels, would improve.

The benefits of growth hormone on cardiovascular risk factors and cardiac performance (systolic function) were recently highlighted (52, 53). Lipoprotein(a), another atherosclerotic risk factor, is often markedly increased in patients who received growth hormone treatment (20, 54). Recent work showed a reduction in inflammatory markers in patients with growth hormone deficiency who received growth hormone therapy (20). Inflammatory markers correlate with risk for cardiovascular events (55).

Recent reviews have emphasized (2) or minimized (56) the effects of growth hormone on muscle performance; the evidence for minimized effects has primarily come from placebo-controlled trials. Barkan and colleagues (56) have correctly noted a significant placebo effect in patients in

Figure 2. An alternative paradigm to explain excess death rates in patients with hypopituitarism.



Not all inciting factors will be present in all patients.

Table 2. Effects of Growth Hormone Replacement on Lipids and Body Composition in Patients with Growth Hormone Deficiency in Controlled Trials*

Study (Reference), Year	Patients	Duration of Therapy	Dosage	Effect on Lean Body Mass	Effect on Fat Mass	Effect on LDL Cholesterol Level	Effect on HDL Cholesterol Level	Effect on Triglyceride Level
	<i>n</i>	<i>mo</i>	$\mu\text{g}/\text{kg per day}$					
Salomon et al. (11), 1989	12	6	26	Increase of 5.5 kg	Decrease of 5.7 kg	Decrease†	No change	No change
Whitehead et al. (12), 1992	14	6	26	Increase of 7%	Decrease of 10%	No change	No change	No change
Cuneo et al. (44), 1993	24	6	26	–	–	Decrease of 13%	Increase of 8%	No change
Bengtsson et al. (13), 1993	10	6	12.5–25	Increase of 2.5 kg	Decrease of 6.1 kg	Decrease†	–	No change
Edén et al. (45), 1993	9	6	13–26	–	–	No change	Increase of 15%	No change
Beshyah et al. (46), 1995	40	6	Variable	Increase of 1.1 kg	Decrease of 0.5%	–	–	–
Beshyah et al. (47), 1995	20	6	Variable	–	–	No change	No change	No change
Hansen et al. (48), 1995	29	12	Variable	Increase of 3.3 kg	Decrease of 4.9 kg	–	–	–
Weaver et al. (49), 1995	22	6	Variable	Increase of 5.7 kg	Decrease of 1.5 kg	No change	–	No change
Baum et al. (50), 1996	32	18	10	Increase of 2.5 kg	Decrease of 3.6%	–	–	–
Johannsson et al. (51), 1996	68	6	12	Increase of 2 kg	Decrease of 2.7 kg	–	–	–
Attanasio et al. (17), 1997	52 with adult onset	6	12.5	Increase of 3.5 kg	Decrease of 4.9%	Decrease of 11%	Increase of 23%	–
Attanasio et al. (17), 1997	32 with childhood onset	6	12.5	Increase of 3.7 kg	Decrease of 5.5%	Decrease of 5%	Increase of 12%	–

* Double-blind, placebo-controlled trials lasting at least 6 months. HDL = high-density lipoprotein; LDL = low-density lipoprotein.

† Decrease in total cholesterol level.

placebo-controlled trials, especially for a substance like growth hormone. Some studies have shown a positive effect on exercise performance as assessed by maximum oxygen uptake in patients with growth hormone deficiency who were undergoing treatment (57, 58). However, after changes in oxygen consumption were corrected for changes in lean body mass, no increase from baseline was seen (12, 58).

Are the putative positive effects a direct effect of growth hormone? Improvements in body composition (increased muscle mass and decreased fat mass) and reductions in levels of low-density lipoprotein cholesterol may be related to increased levels of triiodothyronine in patients receiving growth hormone (13). Furthermore, growth hormone therapy may reduce the adverse effects of excess glucocorticoid replacement by increasing cortisol degradation (59). It is unclear whether different strategies for thyroid and adrenal replacement would have salutary effects equal to those of growth hormone replacement.

Few long-term studies have been conducted. After initial improvement at 6 months, Sesimalo and colleagues (20) observed that lipid levels returned to baseline values. An open-label, 5-year study of 118 patients with growth hormone deficiency given a mean initial dosage of growth hormone of 0.98 mg/d that was reduced to 0.48 mg/d by year 5 (on the basis of serum insulin-like growth factor I levels) saw little improvement in body composition after the first year; however, some measures of bone health and

lipid variables improved through the last year of the study (60). A recently reported 7-year study of patients treated for growth hormone deficiency noted long-term benefits only for body composition compared with untreated controls, with no positive changes in lipid levels, cardiac dimensions, echocardiographic diastolic function, or exercise tolerance (61). Perhaps the benefits of growth hormone on most components of the growth hormone deficiency syndrome are experienced only over the short term. Furthermore, some of the effects may be related to a pharmacologic dose (rather than replacement) of growth hormone. Dose reductions of administered growth hormone have not been unusual in some of the longer-term studies.

What about the safety of growth hormone given to adults? Although persons with growth hormone deficiency are already insulin resistant (62), presumably because of increased central adiposity, growth hormone therapy has been associated with decreased insulin sensitivity and modestly increased blood glucose levels (61, 63). However, not all studies have observed increased glucose levels. Because recent epidemiologic studies have shown that hemoglobin A_{1c} level is a continuous variable for predicting mortality (64), any deterioration in glucose tolerance, even within the normal range, may have deleterious effects. At present there does not appear to be an increase in rates of cancer in adult patients who have received growth hormone therapy

Table 3. Cost Data for Human Growth Hormone, Common Cardiovascular Therapeutics, and Bisphosphonates*

Drug (Reference)	Dosage	Annual Cost, \$
Growth hormone	0.15 to 0.6 mg/d	3000 to 10 000
Simvastatin (58)	20 to 40 mg/d	1499
Ramipril (62)	10 mg/d	131
Alendronate (67)	70 mg/wk	711

* The data for costs were reported in reference 78. Costs are presented in U.S. dollars.

(65). However, long-term surveillance studies will be necessary to verify this finding.

Growth hormone therapy, like all medications, has side effects. Edema, arthralgias, or myalgias are not uncommon (43). In early trials that used 25 $\mu\text{g}/\text{kg}$ per day, as many as 40% of participants required a reduction in dose of growth hormone therapy because of adverse medication effects (2). The risk for serious side effects has been markedly decreased by reducing the initial dose of growth hormone and by reducing the dose to maintain insulin-like growth factor I levels within the normal range (2).

Although some components of the growth hormone deficiency syndrome improve with therapy, improved survival with treatment has yet to be demonstrated. Short-term safety of growth hormone therapy in adults has been shown, but the long-term effects in significant numbers of patients are still being determined.

COST-EFFECTIVENESS OF GROWTH HORMONE THERAPY

Practitioners should ask how much “pain” (physical and financial) is necessary to realize the aforementioned “gain,” particularly compared with other possible therapies. Compared with statins, which markedly decrease the risk for coronary heart disease, growth hormone therapy modifies lipid levels only modestly (66–68). Modern optimal cardiovascular management with statins, antiplatelet agents (69), and angiotensin-converting enzyme inhibitors (70) and treatment of other cardiovascular risk factors (71) have appreciably reduced the toll of cardiovascular disease. In addition to affecting lipid levels, statins can reduce markers of inflammation (72). Furthermore, statins are cheaper and easier to use than growth hormone.

Bone density is decreased and the fracture rate is increased in patients with growth hormone deficiency (73). Growth hormone therapy may increase bone mineral density (74), although its effect on fracture rates is unknown. Bisphosphonates increase bone mass and reduce fracture rates (75, 76) and are cheaper and easier to use than growth hormone. The recent advent of once-weekly bisphosphonate therapy makes this therapy especially attractive (77). **Table 3** compares cost data for growth hormone and cardiovascular and bone therapies. The development of generic drugs in these classes, including growth hormone, could significantly alter any cost-effectiveness analysis.

The major benefit attributed to growth hormone ther-

apy is altered body composition, that is, diminished fat mass and increased muscle mass. Such changes are unlikely to be achieved with other active pharmacologic interventions, although improper glucocorticoid and sex steroid replacement may cause an insulin-resistant phenotype to develop. From a pure cost-effectiveness standpoint, one could question whether money spent on supervised exercise training would produce greater health benefits in most patients with growth hormone deficiency than money expended on growth hormone therapy.

SUMMARY

Although the growth hormone deficiency syndrome exists, it is unclear whether growth hormone deficiency is the primary etiologic factor of this syndrome. Treatment with growth hormone has proven benefits for body composition, surrogate markers for cardiovascular disease, and bone health, although some of the benefits are modest and more long-term studies are required. Replacement therapy with growth hormone is more akin to renal replacement therapy than to thyroid hormone replacement in terms of cost and ease of use. Other drugs that are simpler to use and less expensive may have greater salutary effects. Long-term studies with patients receiving appropriate concomitant medications for related conditions and optimal hormonal replacement for other deficiencies will be necessary to show that growth hormone provides “better living” with prolonged survival.

The first rule of medicine is “Primum non nocere” (First, do no harm). It remains to be seen whether the use of growth hormone will harm patients over the long term (43, 56). The first rule of 21st century medicine is “Remember that resources are finite. Use them wisely.” For the practicing physician, allocation of resources using traditional means for prevention of cardiovascular and bone disease and promoting health and general well-being (appropriate nutrient intake, exercise, positive social interactions, proven pharmacologic intervention) is likely to produce meaningful results. Long-term benefits and the risks of growth hormone treatment are still largely unknown. Although the science of growth hormone replacement is interesting and investigations should continue, for most patients growth hormone therapy is not quite ready for prime time.

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