

Shouldn't Adults with Growth Hormone Deficiency Be Offered Growth Hormone Replacement Therapy?

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Growth hormone as therapy for adults with growth hormone deficiency has not been universally accepted by endocrinologists who treat adult patients. The following are addressed in this commentary: the evidence on safety and efficacy in the literature supporting the idea that growth hormone should be offered as replacement therapy to adults who are growth hormone deficient; common concerns of the average prescribing endocrinologist, including the purported association between insulin-like growth factor-I and malignant neoplasms and quality-of-life issues with long-term therapy; and controversial subjects, such as differences

in dosing for adults versus children and diagnostic issues. This analysis should encourage reluctant practitioners to at least consider growth hormone replacement therapy for patients with definite growth hormone deficiency—that is, patients with symptomatic panhypopituitarism.

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In August 1966, the U.S. Food and Drug Administration approved the use of growth hormone as replacement therapy for adults with growth hormone deficiency. Since that time, such therapy has been widely discussed, but according to industry data, relatively few adults with growth hormone deficiency actually receive the therapy. There are many reasons for this, including lack of awareness of the efficacy of this hormone for replacement in patients with growth hormone deficiency; perceived difficulties in diagnosis, in part due to a lack of diagnostic standards; the paucity of guidelines on monitoring; and issues related to cost, such as inadequate reimbursement for the physician's time and expertise and the insurer's unwillingness to pay for this expensive therapy.

WHY SHOULD ADULTS RECEIVE REPLACEMENT THERAPY WITH GROWTH HORMONE?

An important report by Rosén and Bengtsson in 1990 (1) raised awareness of the health risks for adults who are growth hormone deficient. These authors observed that adults with growth hormone deficiency were at increased risk for cardiovascular mortality. Although growth hormone deficiency in the patients in that study was not directly proven, the diagnoses were probably accurate because the patients had associated deficiencies of all other pituitary hormones (that is, panhypopituitarism). Since that report, three other studies (2-4) have confirmed increased mortality in adult patients with growth hormone deficiency, but not all of these studies concluded that the increased mortality was due to cardiovascular disease (4). A more recent report, in abstract form (5), suggested that mortality in adults with growth hormone deficiency was increased but that the increase was unrelated to the deficiency. Another report (6) suggested that growth hormone therapy decreased the risk for mortality to that of unaffected persons.

Growth hormone deficiency also contributes to morbidity through its effects on bone. Several studies have

confirmed that growth hormone deficiency results in osteopenia, with an associated increase in fracture rates (7, 8). This seems to be true for adults with several pituitary hormone deficiencies as well as for those with isolated growth hormone deficiency (7). The fact that adults with isolated deficiency have an increase in fracture rates casts doubt on the suggestion that overreplacement of glucocorticoids or inadequate replacement of sex steroids may cause the decreased bone density in patients with panhypopituitarism. Colao and colleagues (9) have demonstrated a close correlation between degrees of growth hormone deficiency and decrease in bone density. Moreover, Rosén and coworkers (7) have demonstrated an increase in fracture rates in both men and women who had growth hormone deficiency, regardless of gonadal function. ter Maaten and colleagues (10) found that after a mean of 7.5 years following discontinuation of growth hormone replacement therapy, patients who had had growth hormone deficiency since childhood had decreased bone density at all evaluated sites, including the spine and hip, compared with healthy controls. Several studies have confirmed the efficacy of growth hormone replacement on bone density.

The physiologic effects of growth hormone therapy are unique. Growth hormone activates bone-remodeling units, beginning with increased resorption followed by increased formation. The effects of growth hormone differ from those of other therapies designed to improve bone density (for example, bisphosphonates and sex steroids), which act solely as antiresorptive agents (11). In growth hormone therapy, bone resorption occurs before bone formation; thus, bone density appears to decrease in the first 6 to 8 months after initiation of therapy. This is followed by a return to baseline at 12 months, an increase over baseline at 18 months, and a continuing increase thereafter. Caregivers who are unaware of this early decrease after initiation of growth hormone may find it difficult to respond to third party payers who request proof of improvement as early as 3 to 6 months after initiation of therapy. Repeating measurement of bone density too early can actually show a

decrease, thereby discouraging continuation of therapy and jeopardizing continued reimbursement. Experience with growth hormone replacement therapy in adults has been insufficient to demonstrate a decrease in fracture rates (12), but increases in bone density would be expected to lead to that outcome.

Bone is not the only body component affected in adults with growth hormone deficiency; other potentially important changes in body composition include increased fat mass and decreased muscle mass (13–16). Body mass index may not increase in patients with growth hormone deficiency, but careful evaluation, using techniques such as dual-energy x-ray absorptometry, demonstrates a disproportionate increase in fat mass, especially an increase in visceral fat, which is a known risk factor for cardiovascular disease. Although risk factors for cardiovascular disease, such as total and low-density lipoprotein cholesterol levels, are significantly increased in adults with growth hormone deficiency (6, 18–20), mildly elevated low-density lipoprotein cholesterol values are not usually problematic. Carotid intima-media thickness increases substantially with growth hormone deficiency (21, 22); however, these arterial changes have been shown to revert to a control population level as soon as 6 months after initiation of growth hormone therapy (23), and the improvements are maintained for as long as 10 years (24). Thickening resolves despite modest or minimal changes in blood lipid levels (25). A growing body of evidence suggests that atherosclerotic damage may partly result from inflammation and that growth hormone therapy may return various inflammatory markers to their normal range (26). For example, Sesmilo and colleagues (27) have reported a decrease in inflammatory markers with growth hormone therapy in adults with growth hormone deficiency. A study by Serri and colleagues (26) found that pretreatment plasma concentrations of cytokines, tumor necrosis factor- α , and interleukin-6 were significantly higher in adults with growth hormone deficiency than in controls but were reduced within 3 months of initiation of growth hormone replacement therapy. The immune system generally seems to be disturbed in adults with growth hormone deficiency but improves with therapy (28–30).

Although improving quality of life by using growth hormone replacement is not a major issue for children with growth hormone deficiency, this issue becomes important in affected adults and may be the primary reason that such patients continue replacement therapy. Burman and colleagues (31) studied quality-of-life changes in a placebo-controlled study of adult patients with growth hormone deficiency. Using three different quality-of-life questionnaires, they demonstrated a significant improvement in self-reported quality of life in the respondents who were using growth hormone replacement therapy. More dramatic, however, were the improvements perceived by spouses or family members, who were also blinded.

Central nervous system effects of growth hormone re-

placement are reflected in changes in cerebrospinal fluid neurotransmitter concentrations after growth hormone therapy (32). Verhelst and colleagues (33) reported the pragmatic, economic effect of growth hormone therapy. These investigators observed a decreased number of sick days after replacement therapy was begun, from 12 days in 6 months at baseline to 7 days in 6 months of therapy, 3 days in 12 months, 0.4 days in 18 months, and 3 days in 24 months (33). These findings may be important in defining the ratio of socioeconomic costs to benefits for prolonged growth hormone replacement therapy in adults with growth hormone deficiency.

Improved exercise capacity has also been reported with growth hormone replacement. In a 3-year study, Johannsson and colleagues (34) demonstrated an increase in muscle strength from using bicycle ergometry, and Nass and colleagues (35) demonstrated an increase in maximal oxygen consumption and maximal power output, perhaps related to an associated increase in muscle mass. ter Maaten and colleagues (10) studied 38 young men with growth hormone deficiency since childhood who had discontinued use of growth hormone for a mean of 7.5 years. They found a sustained increase in exercise performance with growth hormone replacement over a 6-month period, as measured by maximal workload (watts) and maximal oxygen uptake (VO_2 max [mg/kg per minute]) achieved during bicycle ergometry.

CONFUSION ABOUT LABORATORY DIAGNOSIS

Clinicians who are convinced that the syndrome of adult growth hormone deficiency warrants treatment have been confused about how best to make the laboratory diagnosis of this condition. In children, the diagnosis of growth hormone deficiency is supported by auxologic data, that is, growth characteristics. In adults with epiphyseal fusion, lack of vertical growth, of course, is not diagnostic. Instead, various tests of growth hormone stimulation are used to make the diagnosis. A positive result on stimulation testing for pituitary growth hormone release is currently required for reimbursement of therapy by third party payers. Several provocative tests have been extensively studied, including insulin-induced hypoglycemia—a stressful, complicated, and potentially dangerous test that many physicians are reluctant to use in their offices. The insulin-induced hypoglycemia test has been recommended as the test of choice by the Growth Hormone Research Society (36). Many physicians are unaware that less demanding tests are available—for example, arginine or L-dopa infusion, or a combination of arginine and growth hormone-releasing hormone—and that these tests can verify disease in patients whose diagnosis is almost certain (that is, in patients with demonstrated severe hypopituitarism and a low concentration of insulin-like growth factor [IGF]-I).

Hartman and Crowe (37) have suggested that if three or four other anterior pituitary hormones are known to be

deficient and the IGF-I concentration is below 84 ng/mL, the patient has a 98% chance of having growth hormone deficiency. I have three criteria for diagnosing growth hormone deficiency in adults: 1) a reasonable cause, such as the presence of a pituitary tumor or pituitary trauma; 2) a low serum IGF-I level measured by using an assay that has standards for age and sex; and 3) lack of response to an appropriate, standard, provocative stimulation test. Because low serum IGF-I concentrations may be observed in liver or renal disease, this test cannot be used in isolation. Moreover, patients with poor protein and calorie intake may have low IGF-I concentrations, but these patients respond normally to provocative stimuli. Finally, obesity may be associated with failure to release growth hormone normally on stimulation testing, but obesity itself is not associated with a low serum IGF-I level. As noted, a potentially dangerous test for growth hormone reserve—that is, insulin-induced hypoglycemia—is not necessary to confirm cases of adult growth hormone deficiency when the diagnosis is obvious, as in the setting of panhypopituitarism and a low serum IGF-I level. In this scenario, an easy-to-perform and safe test, such as arginine or L-dopa infusion, should suffice. When the diagnosis is in question, such as in adults with a history of head trauma and symptoms of poor quality of life or established pituitary disease without demonstrable loss of other hormones, the diagnosis should be confirmed with a more strenuous test for growth hormone reserve, such as arginine plus growth hormone-releasing hormone or insulin-induced hypoglycemia; these tests yield fewer false-positive results. The diagnosis should be considered in any patient with known pituitary disease. It has been estimated that any patients with some form of pituitary insult have a 25% chance of being growth hormone deficient, even if the other pituitary hormones are intact (38). This percentage increases exponentially if other hormone levels are depleted.

FEAR OF ADVERSE EFFECTS OF GROWTH HORMONE

Despite the demonstration of severe pituitary disease and panhypopituitarism, including growth hormone deficiency on laboratory testing, many patients are not being prescribed replacement with growth hormone by their endocrinologists. Why? A recent report suggesting that growth hormone may be associated with adverse outcomes, including increased mortality, when used as an anabolic agent in intensive care settings appears to have fueled the fires of concern (39). However, the dosages of growth hormone used in this intensive care study ranged from 4000 to 8000 $\mu\text{g}/\text{d}$ —amounts that far exceed the dosages used for replacement therapy in adults, which range from 200 to 1000 $\mu\text{g}/\text{d}$. No increases in mortality have been observed in persons taking growth hormone replacement therapy at these lower dosages; on the contrary, initial studies with replacement therapy in adults have suggested a favorable effect on mortality (6). Further concern has been raised

about the possibility that growth hormone therapy may cause neoplasms. This fear has resulted from epidemiologic studies that suggest an increase in prostate, lung, and colon cancer in normal persons with high-normal serum IGF-I concentrations and reduced levels of IGF-I binding proteins, resulting in elevated free IGF-I concentrations (40–43). However, experiments of nature, such as acromegaly, have not been associated with an increase in cancer (44), suggesting that high-normal IGF-I concentrations may be a marker for cancer but are not causally related to induction or growth of cancer.

Appropriate growth hormone replacement therapy is associated with normalization, not elevation, of serum IGF-I concentrations. In addition, levels of binding proteins are concomitantly increased with growth hormone replacement, along with levels of IGF-I, resulting in normal, not elevated, free IGF-I concentrations (45).

Finally, many endocrinologists are still unconvinced of the efficacy of growth hormone replacement therapy for adults with growth hormone deficiency and are waiting for studies that more convincingly demonstrate improved health outcomes. For growth hormone replacement therapy, those outcomes will probably include improved mortality and quality of life or decreased fracture rates. Although the body of literature on this subject can be interpreted as convincing in the aggregate, no single study has yet provided unequivocal evidence of improved health outcomes. The high cost of growth hormone has further limited interest in replacing growth hormone in adults.

CONFUSION ABOUT DOSING AND MONITORING

Dosing guidelines have changed considerably in the past 10 years. When growth hormone was first prescribed for adults, doses were arbitrarily chosen to be only slightly lower than those for children on a per-weight basis. These estimates proved far too high, resulting in such side effects as edema, joint and muscle pain, and the carpal tunnel syndrome. Doses that were half those used for children also turned out to be too high. It was eventually determined that doses of 10% to 20% of childhood requirements were the proper dosing levels for adults (46).

Learning how to monitor the safety and efficacy of growth hormone replacement therapy has also taken some time. When to measure bone-density, for example, and appropriate use of dual-energy x-ray absorptiometry with special software to obtain body composition, especially adipose tissue, have become clear only in recent years.

REIMBURSEMENT AND COST ISSUES

Some insurance companies have decided that growth hormone therapy for adults is still experimental, despite evidence to the contrary and approval by the Food and Drug Administration. Because adults require only approximately 10% to 20% of the doses required for children and because the drug is given on the basis of weight, the cost in

adults is proportionally lower than that in children. All manufacturers that produce an approved form of growth hormone have financial-assistance programs for patients who cannot afford therapy.

WHY ISN'T GROWTH HORMONE THERAPY BEING PRESCRIBED FOR ADULTS WITH GROWTH HORMONE DEFICIENCY?

Growth hormone is not prescribed for adults with growth hormone deficiency for many reasons, including the various controversial issues discussed here. The major reason, however, appears to be individual physicians' reluctance to confirm the diagnosis and initiate therapy. This reluctance seems to exist even in the most obvious cases of growth hormone deficiency and therefore affects the patients who may benefit the most (47). Industry-sponsored surveys have suggested that physicians do not prescribe growth hormone replacement because of the complexity and inconvenience of provocative testing and uncertainty about proper adult dosing, as well as the cost of therapy, including product cost and lack of adequate physician reimbursement. Physicians are, in fact, financially constrained in the application of this new therapy. Initiation of growth hormone therapy in a new patient appears to require approximately 6 to 8 hours of the physician's and nurse's time combined, which includes the time needed for stimulation testing, patient education, and paperwork. It remains to be seen whether these impediments to initiating and monitoring growth hormone therapy will change significantly in the near future. In the meantime, many patients who could and should be helped are being deprived of its benefits.

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