

Editorial: Diagnosis of GH Deficiency in Adults—How Good Do the Criteria Need to Be?

The availability of recombinant human GH has made it possible to treat not only children with impaired growth due to GH deficiency (GHD) but also adults with GHD. Information from a large number of studies has resulted in the description of a GHD syndrome in adults, and many studies have shown that several aspects of this syndrome can be reversed with GH treatment (for reviews see Refs. 1–5). However, in many subjects, the benefits cannot be clearly quantitated and the treatment remains quite costly. The average retail price for GH is about \$40 per milligram at present. Average maintenance doses (based on achieving an IGF-I near the age-adjusted normal mean) for men and for women who are not receiving estrogen or who are receiving transdermal estrogen are about 0.3–0.4 mg/d, and for women receiving oral estrogen the dose is about double that (6–8). The maximum dose used usually does not exceed 1 mg/d (9). Thus, the yearly cost for GH therapy ranges from about \$4,400 to about \$14,600 for the GH plus any costs for syringes, *etc.*

Fortunately, GH treatment of adults with GHD is safe (10). Although there has been some concern about an increased risk of cancer, reviews of existing, well-maintained databases of treated patients have shown this theoretical risk to be nonexistent (10). Nonetheless, current labeling states that active malignancy is a contraindication for GH treatment. Adverse effects such as fluid retention, carpal tunnel syndrome, and arthralgias are dose dependent, and recent studies show that they can be largely avoided if a low dose is used initially with slow titration upward based on IGF-I levels and clinical symptoms (4). Thus, the major concerns regarding GH treatment center around the balance between efficacy *vs.* cost plus the relative inconvenience of having to give daily sc injections. The controversies regarding efficacy relate, in part, to initially making the diagnosis of GHD and patient selection.

Who is GH deficient?

Acquired GHD secondary to structural lesions or trauma. Studies of patients with large, clinically nonfunctioning adenomas (11–14), of patients following transphenoidal surgery for pituitary adenomas (11–14), and of patients who have had irradiation of pituitary tumors or other head/neck/brain tumors (15, 16) all show that GH is generally the first hormone lost. Several studies have shown that there is an increasing likelihood of GHD in a patient, the greater the number of deficits occurring of the other pituitary hormones (17–20). In this issue of *JCEM*, Hartman *et al.* (21) report a similar analysis using the extensive database that Eli Lilly & Co. has generated for the follow-up of patients treated with

Humatrope (Hypopituitary Control and Complications Study). They used a stimulated GH level of less than 2.5 $\mu\text{g}/\text{liter}$ (with an immunochemiluminometric assay that generally gives levels half those of a polyclonal RIA) as being diagnostic of GHD and a variety of stimulation tests. With this stimulated GH cutpoint, they analyzed patients stratified by the number of other pituitary hormones that were deficient, finding that with zero, one, two, three, and four hormones lost the proportions who turned out to be GH deficient were 41%, 67%, 83%, 96%, and 99%, respectively. An IGF-I level of less than 84 $\mu\text{g}/\text{liter}$ (a level obtained from an earlier pilot study) also had the very strong positive predictive value of 96%. They have shown that the presence of either three or four pituitary hormone deficiencies or an IGF-I of less than 84 $\mu\text{g}/\text{liter}$ had a positive predictive value of 95%, with a specificity of 89% and a sensitivity of 69%, and propose that such patients do not require GH stimulation testing. However, when both three or four deficiencies were present and the IGF-I was less than 84 $\mu\text{g}/\text{liter}$, the positive predictive value and the specificity increased to 100%, but the sensitivity was low at 30%.

Adult GHD in patients who had had prior childhood GHD. These patients can be divided into three categories: 1) those with structural lesions or trauma with associated other hormone deficiencies generally have been found to have persistent GHD as adults (22, 23); 2) those with GHD due to gene defects causing structural alterations in the GH molecule, alterations in the GH and GH-releasing hormone receptors, or alterations in transcription factors, such as Pit-1 and Prop-1, continue to have GHD as adults (3); and 3) those found to have idiopathic GHD as children; retesting of these patients usually shows that only about 30–50% can be shown to have GHD as adults (22, 23).

What are the criteria for GHD?

GH criteria. A number of criteria have been proposed for documentation of GHD using a variety of tests. Attention has generally not been paid to the “normal” decline in GH levels that occurs with aging so that the criteria have not been age adjusted. An example of studies that have addressed the issue of what criteria should be used is that of Hoffman *et al.* (24), who assessed 17 patients with structural lesions and other multiple hormone deficiencies and 3 patients with idiopathic hypopituitarism and multiple hormone deficiencies and compared their responses with those of normal controls using the insulin tolerance test (ITT). In this study, none of the hypopituitary patients had GH levels greater than 3 $\mu\text{g}/\text{liter}$ with the ITT whereas all 25 of the age-, sex-, and body mass index-matched controls had GH responses greater than 5 $\mu\text{g}/\text{liter}$ (24). According to the *Consensus Guidelines for the Diagnosis and Treatment of Adults with GH Deficiency* (9), the

Abbreviations: BMD, Bone mineral density; GHD, GH deficiency; ITT, insulin tolerance test; SMR, standardized mortality ratio.

ITT is the diagnostic test of choice and the criterion for diagnosing GHD severe enough to warrant therapy is a peak GH of less than 3 $\mu\text{g}/\text{liter}$. In patients with contraindications to the ITT, the combined arginine/GHRH test is best. The United States Food and Drug Administration defines GHD as a stimulated GH level of less than 5 $\mu\text{g}/\text{liter}$. These numbers are based the standard polyclonal GH RIA, and values 50% of these are used if an immunochemiluminometric assay is used. It must also be remembered that if two or three ITTs in normal individuals are performed, there is very poor concordance of responses, although in one recent study all of the GH responses to three separate tests in young normal men were greater than 20 $\mu\text{g}/\text{liter}$ (25). The concordance rates in subjects who might have some limitation of GH reserve are fairly good (25, 26), but in one series of patients with hypothalamic/pituitary disease there was a considerable discrepancy in the two GH peaks and in 3 of 26 patients the difference was such that GH treatment would be indicated by the results of one test but not by those of the second test (26). In another series in which the GH responses to hypoglycemia were compared with responses to arginine in patients with hypothalamic disease, the concordance rates between these two tests (percentage of patients in whom both tests confirmed or refuted the biochemical diagnosis of severe GHD) was 100%, 76.8%, 66.6%, 83.3%, and 92.3%, respectively, in controls and those with loss of zero, one, two, and three other pituitary hormones (27).

What about IGF-I? The definition of GHD is based on a decreased GH response, as noted above. What about IGF-I levels? Most studies show that about one third of patients with GHD diagnosed by stimulated GH levels have IGF-I levels in the normal range (7, 19, 20, 24, 28, 29). The *Consensus Guidelines* state that "In adults, a normal serum IGF-I does not exclude the diagnosis of GH deficiency" (9). However, during therapy GH dose increases are titrated against IGF-I levels, and "... values should be kept in the age-related normal range" (9). Thus, the values can be normal to begin with, and yet that is the goal of therapy. This would seem to be internally inconsistent conundrum. I think that part of the problem here is that not a lot of GH is needed to get normal IGF-I levels. When a very sensitive ELISA is used, a considerable overlap is found between normal individuals and "hypopituitary" individuals with respect to 24-h integrated GH secretion with high correlations between the integrated GH concentration with IGF-I levels in both groups (30). Thus, what GH level is truly normal or abnormal with respect to IGF-I or other aspects of GH action is not clear. I think that we should be using the IGF-I level as a true integrated reflector of GH action at the low end of GH levels just as we do at the high end in patients with acromegaly.

What are the benefits of GH treatment in GH-deficient adults? Some, but not all, studies have shown that there is an increase in overall mortality in patients with hypopituitarism, specifically in the categories of cardiovascular, respiratory, and cerebrovascular causes (31–35). It has been suggested that this increased mortality is due to GHD and, therefore, GHD should be treated (5, 31, 33). However, in several of these studies sex hormone replacement was not done routinely

and, in women, less than 20% received estrogen replacement (31, 33). In a recent study, untreated gonadotropin deficiency was associated with a significant increase in mortality [standardized mortality ratio (SMR) of 2.97]; treatment with sex-steroid replacement was associated with a significant reduction in SMR to 1.42 (35). In addition, T_4 therapy is not monitored by titrating the dose against TSH levels and, therefore, many patients may have been taking too little or too much T_4 and there is an increased mortality associated with subclinical hyperthyroidism (36). Similarly, many of these patients were likely taking too much glucocorticoid replacement, and it is known that Cushing's syndrome is associated with increased mortality (37). It is now known that the true adult secretion rate of cortisol is only about one half that suggested by earlier studies (38, 39). Finally, in these studies many of the patients were treated with cranial irradiation, and irradiation may increase the risk of stroke as much as 2-fold (40). Two recent series of patients with hypopituitarism in which the history of cranial irradiation was half those in the prior studies showed no excess mortality (32, 34). In the recent series by Tomlinson *et al.* (35), the aspect of cranial irradiation was specifically addressed and those irradiated had a SMR of 2.32 compared with 1.66 in those not having undergone irradiation. Interestingly, those patients in this last series with two or more hormone deficiencies, a feature known to correlate with GHD (see above), had no greater increase in mortality than those with one deficiency (35). In that series, 111 patients were tested for GHD and there was no difference in SMR between those with and without GHD (35). Thus, the case that the excess cardiovascular and other mortality found in patients with hypopituitarism is due to GHD is far from proven. There are no prospective studies showing an effect of GH therapy in decreasing this mortality. It is possible that the data currently being collected by the various pharmaceutical companies that market GH preparations may eventually allow this question to be answered. It is very unlikely that long-term, prospective, placebo-controlled, randomized studies designed to address this issue will ever be done.

There is a wealth of studies that have looked at cardiac risk factors in patients with GHD (reviewed in Refs. 1–5 and 41). To summarize briefly, patients with adult onset GHD compared with age-matched controls in most studies have been shown to have decreased muscle mass, increased fat mass, increased intra-abdominal fat, increased insulin resistance, mild increases in low-density lipoprotein cholesterol, lipoprotein(a), apolipoprotein B, and triglycerides, and mild decreases in high-density lipoprotein cholesterol, and most studies have shown that these changes can be reversed with GH therapy (1–5, 41). In two studies, carotid intima thickness has been shown to be increased in patients with GHD compared with matched controls (42, 43), and in one study the intima thickness decreased after 1 yr of GH treatment (44). Based on the rapidity of this response, it is likely that changes in the vascular endothelium were being assessed rather than progressive atherosclerosis, and the relationship of changes in intima thickness to long-term cardiovascular disease outcomes remains to be proven.

Many studies have shown reduced left ventricular mass, systolic function, ejection fraction at rest and after exercise,

stroke volume, and cardiac index in adults with GHD, and some, but not all, studies show improvement of many of these parameters with GH therapy in many patients (reviewed in Refs. 1, 2, 4, and 41). Changes in $\text{VO}_{2\text{max}}$ that appear to increase with GH therapy when expressed per total body weight become insignificant when expressed per kilogram of lean body mass, suggesting that the change was due primarily to the change in the ratio of lean body mass to fat mass (45). Some placebo-controlled studies have shown an increase in exercise capacity and duration (46) but others have not (47, 48). In a recent, placebo-controlled study, Woodhouse *et al.* (49) found no change in muscle strength with GH therapy of GH-deficient adults but found that there was a decrease in the oxygen cost of walking at normal and fast speeds with a functional improvement in walking ability. This may account for the perception of increased fatigue and impaired physical performance in GH-deficient subjects with improvement in these parameters with GH treatment. Whether these changes affect every day exercise capacity and endurance or long-term cardiac outcomes in a clinically meaningful way is also not known.

Bone mineral density (BMD) is decreased in patients with GHD. Although short-term studies have tended to show a further decrease, studies lasting more than 18 months have shown an increase in BMD in most studies, especially in men (reviewed in Refs. 1–5).

Many, but not all, studies have shown GH-deficient subjects to have a decreased quality of life using a variety of questionnaires (reviewed in Refs. 2–5). Using placebo-controlled designs, again some, but not all, studies have shown improvement with GH therapy (2–5), and the validity of a specific questionnaire designed to assess quality of life in adults with GHD has recently been called into question (50).

Conclusions

Adult GHD is clearly a hormone deficiency syndrome. We must be honest, however, regarding what benefits can be achieved with GH therapy, which is very expensive and requires daily injections. No data yet exist with regard to reduction of mortality and/or serious morbidity by GH treatment. Certainly, therapy would have to be virtually lifelong for this to be potentially beneficial to the individual. Although the lean body mass to fat ratio is clearly improved, clinically meaningful improvements in strength and endurance have been difficult to demonstrate. Quality-of-life data are somewhat murky. It is certainly cheaper and likely more effective to treat mild dyslipidemias with a statin and osteoporosis with a bisphosphonate. All studies purporting benefit of GH therapy in GH-deficient adults acknowledge variability in responsiveness. Clearly, some patients benefit with clinically significant improvements in exercise capacity and reduction in fatigue, but it would be nice to know ahead of time who those people are. Thus, I think much of the problem we have in clearly finding clinically meaningful benefits of GH therapy is in defining the proper population to treat. Most patients found to have GHD will be those with organic disease of the pituitary/hypothalamus and other hormonal deficits, and true idiopathic, isolated GHD must be

very rare. Therefore, I believe the criteria used to define GHD should be changed.

The stimulated GH levels currently used are somewhat arbitrary and are based on relative cutoffs between normal and abnormal populations. I think the time has come to develop criteria for GHD based on outcomes. Outcome data based on the responses of patients who have been treated with GH are already available. A level of GH after stimulation that has been associated with clear clinical benefits in a majority of patients should be able to be found from an analysis of already existing databases. Similarly, an analysis could be done of clinical responses to GH based on IGF-I levels at the onset of GH treatment. For each clinical response, a specific level of change could be found that is clinically meaningful based on other independent data. Examples might be the change in BMD that results in a significant reduction in fracture risk from the osteoporosis literature or a change in muscle strength or $\text{VO}_{2\text{max}}$ that would result in a clinically meaningful increase in exercise capacity or endurance. Each clinical response could then be analyzed separately and together with respect to GH and IGF-I cutoffs. It may turn out that these GH and/or IGF-I cutoffs are quite similar. In this fashion, outcomes-based criteria could be derived to determine the best candidates for GH therapy.

In summary, I am dubious about using only the GH response to a provocative test as the criterion for labeling patients as having GHD. There are sufficient databases available to determine whether IGF-I levels are useful and whether certain GH cutoffs yield better clinical responses. Because the cost of treatment is so high, I would not like to treat the 5% of patients who are false-positive who would not be tested because of having deficiencies of three or four other pituitary hormones, as Hartman *et al.* (21) would have us do. I like the comfort of his 100% specificity when the low IGF-I is added.

Pending the development of outcomes-based criteria, I think it is reasonable to keep an open mind on treatment and offer GH therapy to those individuals with clearly low GH values on stimulation and who also have other hormone deficiencies. I, myself, restrict GH therapy to patients with low or borderline IGF-I values as well. A 6- to 12-month trial of GH therapy is warranted in such patients with a period of at least 6 months after normalization of IGF-I levels. Some objective measures of improvement should be carried out, such as exercise duration or amount. Patients who feel no better and who show no improvement in objective measures probably should not then continue on treatment. If sustained-release GH preparations requiring only monthly injections, oral GH-mimetics, or oral GH-releasing agents become available at lower cost, then this decision to treat may become easier.

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