

Update on Acromegaly

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Acromegaly is a rare disorder, with over 95% of cases due to excessive secretion of growth hormone (GH) by a benign pituitary tumor. These adenomas result from a monoclonal proliferation of pituitary somatotroph cells, leading to increased GH secretion. At the liver, GH stimulates secretion of insulin-like growth factor-1 (IGF-1). IGF-1 mediates many of the peripheral somatic effects of GH.

In addition to the classic somatic changes in acromegaly such as enlargement of the hands and feet (*Figure 1*), this disorder is associated with significant medical comorbidities including sleep apnea, hypertension, Type II diabetes, and hypertrophic cardiomyopathy. Sleep apnea is found in over 50% of patients with acromegaly. All of these comorbidities improve with biochemical control of the disorder. In addition, acromegaly is associated with an increased risk of premature mortality. Studies have shown that control of acromegaly, with GH and IGF-1 normalization, results in a mortality rate no different from the general population. This demonstrates the clear benefit of biochemical control on long-term health in such patients.

The diagnosis of acromegaly is based on three key findings: 1) clinical features, 2) demonstration of an elevated IGF-1 level, and 3) inability to suppress serum GH to less than 1 ng/ml following an oral glucose challenge (OGTT). Following biochemical confirmation of the disorder, a head MRI is performed. In most patients, a macroadenoma (>1cm) will be found, but some patients may have microadenomas or no clear lesion.

Because it is a rare disorder and development of the clinical features is typically insidious, patients often have acromegaly for many years before the diagnosis is made. In some cases, the diagnosis may be obvious based on clinical evaluation. However, in others, the disease may be subtle, particularly in early stages of the disorder. It is prudent to ask about other symptoms of acromegaly in patients with new onset hypertension, sleep apnea, carpal tunnel syndrome and diabetes, as this may be a treatable cause of such morbidities.

The primary mode of therapy for acromegaly is usually transsphenoidal surgery to reverse mass effect and attempt biochemical cure. Surgical cure is dependent on surgical skill and experience (see next article in this Bulletin) as well as the size and location of the tumor. Cure, defined as normalization of IGF-1 levels and normalization of the GH response to an OGTT, is demonstrated in up to 88% of patients with microadenomas (<1cm) if performed by an expert pituitary surgeon. In contrast, surgery is curative in only 50-65% of acromegalic patients with macroadenomas, in the best centers. Residual disease following transsphenoidal surgery is therefore common, and patients with persistent disease require further therapy.

Medical management is a highly useful adjuvant therapy for patients with acromegaly. Dopamine agonists have the advantages of being oral medications and being the least expensive medical option. However, high doses are usually needed, and despite increasing doses, which may produce side effects, bromocriptine (Parlodel) is not effective in most patients.



Figure 1. Hand of a 39 year old woman with acromegaly (R) next to the hand of a healthy woman of the same age and height (L), demonstrating the classic hand enlargement in acromegaly. In addition to such external manifestations of the disease, most patients also have systemic morbidity.

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This medication only successfully normalizes GH and IGF-1 levels in <10% of patients. The longer acting dopamine agonist, cabergoline (Dostinex), is often better tolerated than bromocriptine, and may have better efficacy compared to bromocriptine in acromegaly. In one study, cabergoline administration resulted in normal IGF-1 levels in 39% of subjects. Patients with more modest biochemical activity and hyperprolactinemia appear to be the most sensitive to cabergoline. Thus, this may be a reasonable option to try in patients with mildly elevated IGF-1 levels.

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Somatostatin analogs, such as octreotide, are more effective than dopamine agonists in the medical management of acromegaly. Octreotide administration results in a decrease in GH and IGF-1 levels in a majority of patients, with up to 60% attaining normalization of IGF-1 levels, indicating biochemical remission. Tumor size and level of GH hypersecretion are important prognostic factors, as well as the presence of somatostatin receptors on tumor cells. Most patients note a marked improvement in symptoms of acromegaly soon after starting octreotide therapy, including headaches, joint pains and diaphoresis. The most significant adverse effect of somatostatin analogs is the development of gallstones. However, the frequency of development of symptomatic gallstones varies widely among studies, and the need for

serial ultrasounds is controversial. Other side effects include gastrointestinal disturbance with nausea, abdominal pain and diarrhea which often occur upon initiation of therapy, but usually resolve within one to two weeks.

Octreotide is administered in the majority of cases as Sandostatin LAR (long acting release formulation of Sandostatin). Sandostatin LAR is available in three doses: 10 mg, 20 mg, and 30 mg; the long-acting preparation allows it to be administered just once a month via intramuscular injection. Another depot formulation of the somatostatin analog lanreotide is available in Europe and a new somatostatin analogue is under investigation in the United States.

A different mechanism of action is represented by the growth hormone antagonist, pegvisomant (Somavert). Pegvisomant is a human GH molecule that has been altered to compete with natural GH for binding to its receptor and, additionally, to prevent receptor activation. Rather than acting at the pituitary tumor, pegvisomant blocks hepatic production of IGF-1. This lowering of IGF-1 levels occurs without decreasing GH (levels of GH actually rise, but it is blocked at the receptor). In a double-blind, placebo-controlled study, pegvisomant was administered as nightly subcutaneous injections to 112 patients with acromegaly for three months. IGF-1 levels normalized in 90% of subjects. This included patients resistant to somatostatin analogs. In an open label extension protocol, pegvisomant was administered for up to two years in more than 90 subjects. In this study, normal IGF-1 levels were achieved in 97% of subjects. In another study in patients with acromegaly and diabetes, pegvisomant was effective in lowering endogenous insulin and glucose levels. In this study, oral hypoglycemic agents were discontinued in some patients as glucose management improved. Therefore, pegvisomant is a highly effective medication, useful in patients resistant to other acromegaly medications, and may be particularly useful in patients with concomitant diabetes. Side effects of pegvisomant include hepatitis and the potential risk of tumor growth. Serial liver tests and MRI monitoring are therefore very important during treatment.

Radiation therapy is a potential adjuvant therapy for patients with residual disease, however, there is a long waiting period until it is effective. In patients treated with conventional radiation, it takes up to ten years for over half of subjects to attain GH levels <5 ng/ml and normalization of IGF-1 is more difficult to achieve. Hypopituitarism is a significant complication of radiation therapy, and there is a small (1-2%) risk of secondary neoplasia developing in the radiation field. There are data suggesting that targeted radiotherapy using stereotactic techniques such as gamma knife or proton beam modalities may lead to

more rapid biochemical control, with less risk of hypopituitarism. However, further studies are necessary to confirm such claims. Therefore, in most patients not cured with surgery, medical management is necessary in lieu of, or in combination with, radiation.

In summary, an operation by an expert pituitary surgeon is the first line of treatment of acromegaly. In those patients not cured, there is a strong role for adjuvant medical therapy for acromegaly. Both dopamine agonists and somatostatin analogs act at the level of the pituitary adenoma, and are effective at lowering GH and IGF-1 levels in a large number of patients. Pegvisomant acts in the periphery by blocking the effects of GH and preventing production of IGF-1 by the liver, and is effective in the majority of patients. More clinical experience is necessary to determine the precise roles of these medical options in the therapy of acromegaly.

References

1. Freda PU, et al. *J Clin Endocrinol Metab.* 2004; 89:495-500.
 2. Ho KY, et al. *Ann Int. Med.* 1990; 112:173-81.
 3. Serri O, et al. *J Clin Endocrinol Metab.* 1985; 61:1185-9.
 4. Swearingen B, et al. *J Clin Endocrinol Metab.* 1998; 83:3419-26.
 5. Attanasio R, et al. *J Clin Endocrinol Metab.* 2003; 88:3105-12.
 6. Trainor PJ, et al. *NEJM.* 2000; 342(16):1171-7.
 7. van der Lely AJ, et al. *Lancet.* 2001; 358(9295):1754-9.
 8. Biermasz NR, et al. *J Clin Endocrinol Metab.* 2004; 89:2789-96.
 9. Rose DR, Clemmons DR. *Growth Horm & IGF Res.* 2002; 12(6):418-24.
 10. Clemmons DR, et al. *J Clin Endocrinol Metab.* 2003; 88:4759-67.
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The Importance of Experience in Surgical Treatment of Pituitary Tumors

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INTRODUCTION With the exception of prolactinomas, which can be treated medically, most pituitary tumors and other sellar masses of >1cm are treated surgically. The usual approach is through the sphenoid sinus (transsphenoidal), utilizing an operative microscope. Because pituitary adenomas are rare, most surgeons do not perform transsphenoidal surgery frequently. Some surgeons perform this operation only every few years, whereas at several centers in the United States, transsphenoidal surgery is performed several times every week. The question as to whether surgical experience in transsphenoidal surgery affects the results in patients with pituitary masses can be addressed by examining the volume outcome relationship.

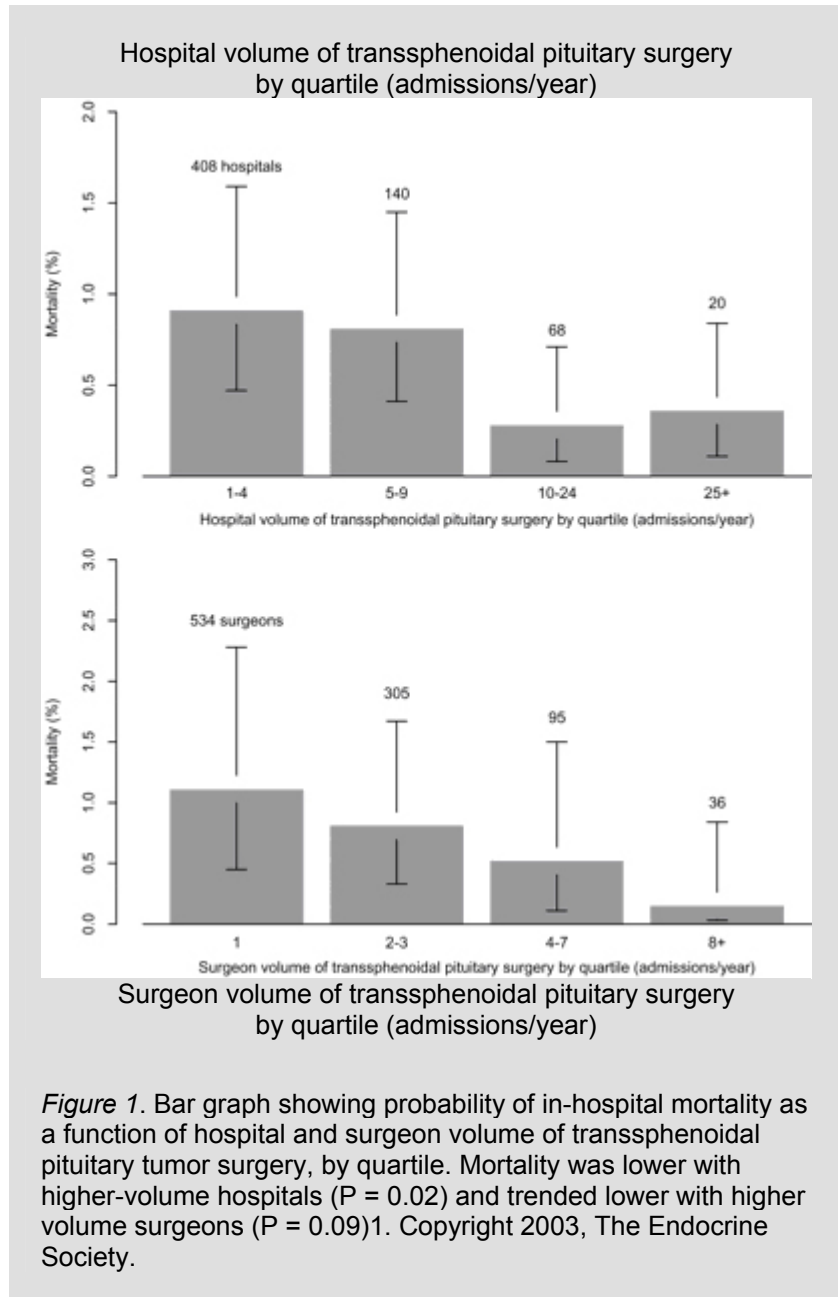
The volume outcome relation is the commonsense notion that results improve with experience. It is a major topic in medical economics literature, and this relation has been found to hold true for coronary artery bypass grafting, coronary artery stenting, complex cancer surgery, and AIDS management. The Leapfrog group (www.Leapfrog.com), a coalition of major health insurers, labor unions, and businesses, has been evaluating these data to direct health care consumers to high-quality physicians and institutions. We investigated whether the link between more experience and favorable outcome also holds true for pituitary surgery¹.

Several studies have already been published showing the importance of having transsphenoidal surgery performed by a highly experienced surgeon. Data from the United Kingdom showed that surgical results for acromegaly improved significantly when the procedures were performed by only one designated surgeon, as opposed to multiple surgeons. This research also demonstrated that the surgical remission rates from a single surgeon improved over time²⁻⁴. We took a systematic approach, by looking at outcomes in the United States after pituitary surgery, as demonstrated in the federal administrative database, the Nationwide Inpatient Sample. This database is derived from the discharge coding obtained from a selected subsample from 20% of all non-federal hospital discharges in a given year. The individual

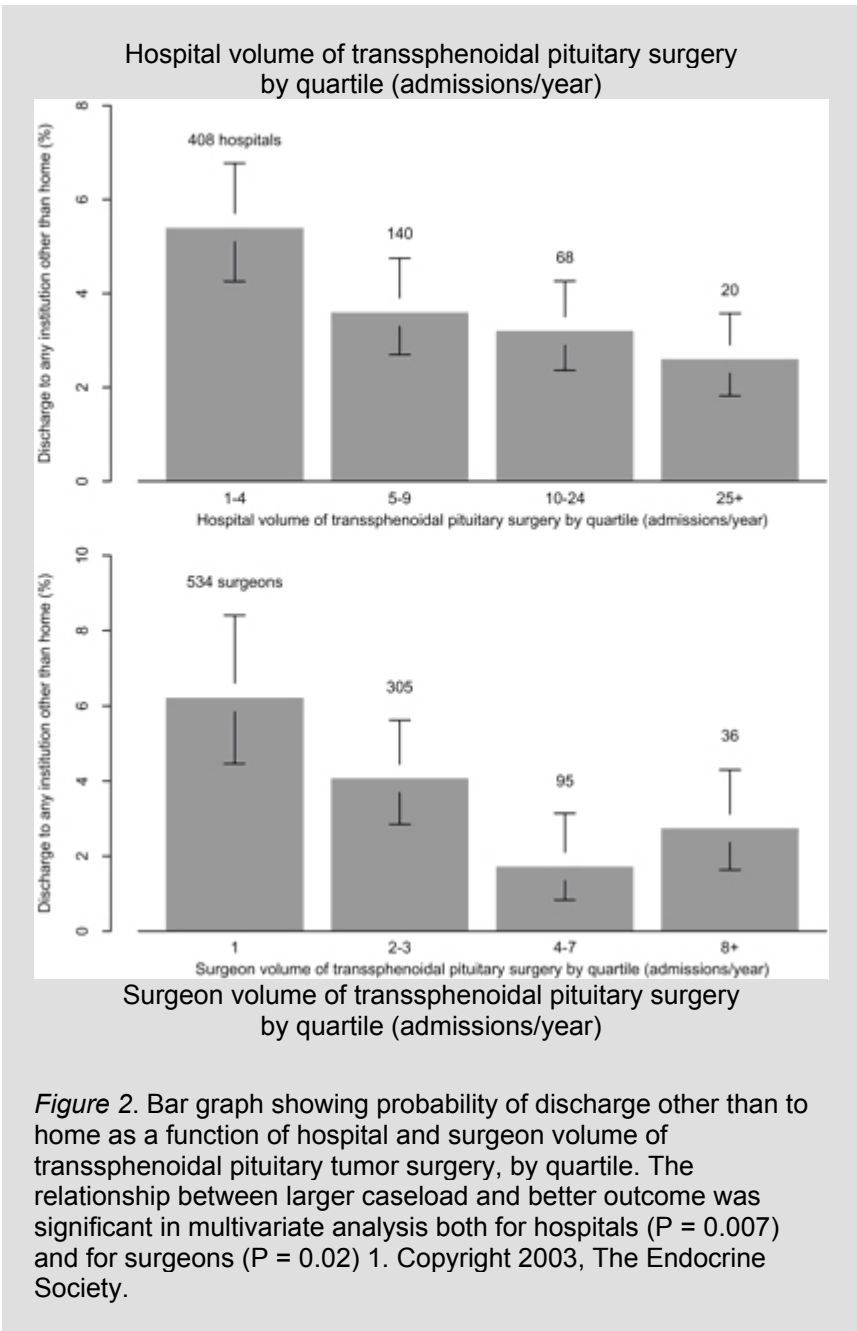
surgeon was identified in about half of the cases and the institution identifiable in all cases. Although there are no data regarding biochemical cure in this database, available endpoints include in-hospital mortality, discharge disposition (skilled nursing facility, long-term care, or home), the presence or absence of various medical complications, length of stay, and hospital charges. These outcome measures were evaluated with appropriate statistical analysis (multivariate logistic and ordinal logistic regression) to investigate whether these outcomes could be correlated with surgeon and/or institutional experience.

RESULTS

For the years 1996 to 2000, there were 5497 patients at 538 hospitals who were discharged following pituitary surgery. Since this is a 20% sample over a five-year period, it suggests that about 5500 patients undergo transsphenoidal operations every year. The mean age was 50 years, with 53% of patients being female and 68% Caucasian. Eighty-two percent of these procedures were done after a routine admission. The overall in-hospital mortality rate was 0.6%. The vast majority of patients (96.3%) were discharged home, 0.9% to a long-term care facility, and 2.1% to a short-term care facility. The relationship between mortality and the number of transsphenoidal cases both at a particular hospital and by an individual surgeon is shown in Figure 1. The data demonstrate that approximately one-quarter of all patients had their procedures done by a surgeon who performed only one pituitary operation that year. This group had the highest mortality; the mortality rate for low-volume surgeons was approximately 1.2%, as opposed to 0.2% for those surgeons who performed eight or more procedures in a given year (p value for this trend 0.09). When comparing institutional volume to mortality, similar findings were seen, with a statistically significant difference between institutions with low pituitary surgery volume compared with those institutions at which many pituitary operations are performed each year (p=0.02). When discharge disposition was compared with surgeon and institutional volume, more experience was related to a higher likelihood of being discharged to home. Figure 2 demonstrates that patients operated on by low-volume surgeons or at low-volume institutions were more likely to be discharged to locations other than home (p=0.007 and p=0.02 respectively).



It was difficult to determine the incidence of postoperative complications, given the administrative nature of this database. Discharge codes were entered every time the patient had a single electrolyte abnormality, or a single episode of diabetes insipidus. It cannot be determined whether these complications were temporary or permanent. Defining a complication in this fashion will tend to artificially inflate the true incidence of postoperative problems. Nonetheless, even with this very loose definition of complication, a negative correlation was seen between surgeon and institutional volume and complication rate. Higher volumes were associated with lower rates of complications. This is illustrated in Figure 3. In addition, complications were seen more commonly in patients with Cushing's disease, and in patients with other medical co-morbidities. Finally, we were able to demonstrate that low-volume hospitals serve primarily non-white, non-privately insured patients. Notably, the length of stay was shorter with high-volume hospitals and surgeons and there was a trend towards lower total charges at high-volume institutions. The median length of stay in the US database in year 2000 was four days. In contrast, the typical length of stay at Massachusetts General Hospital for transsphenoidal surgery, where this operation is performed several times each week, is currently 36-48 hours.



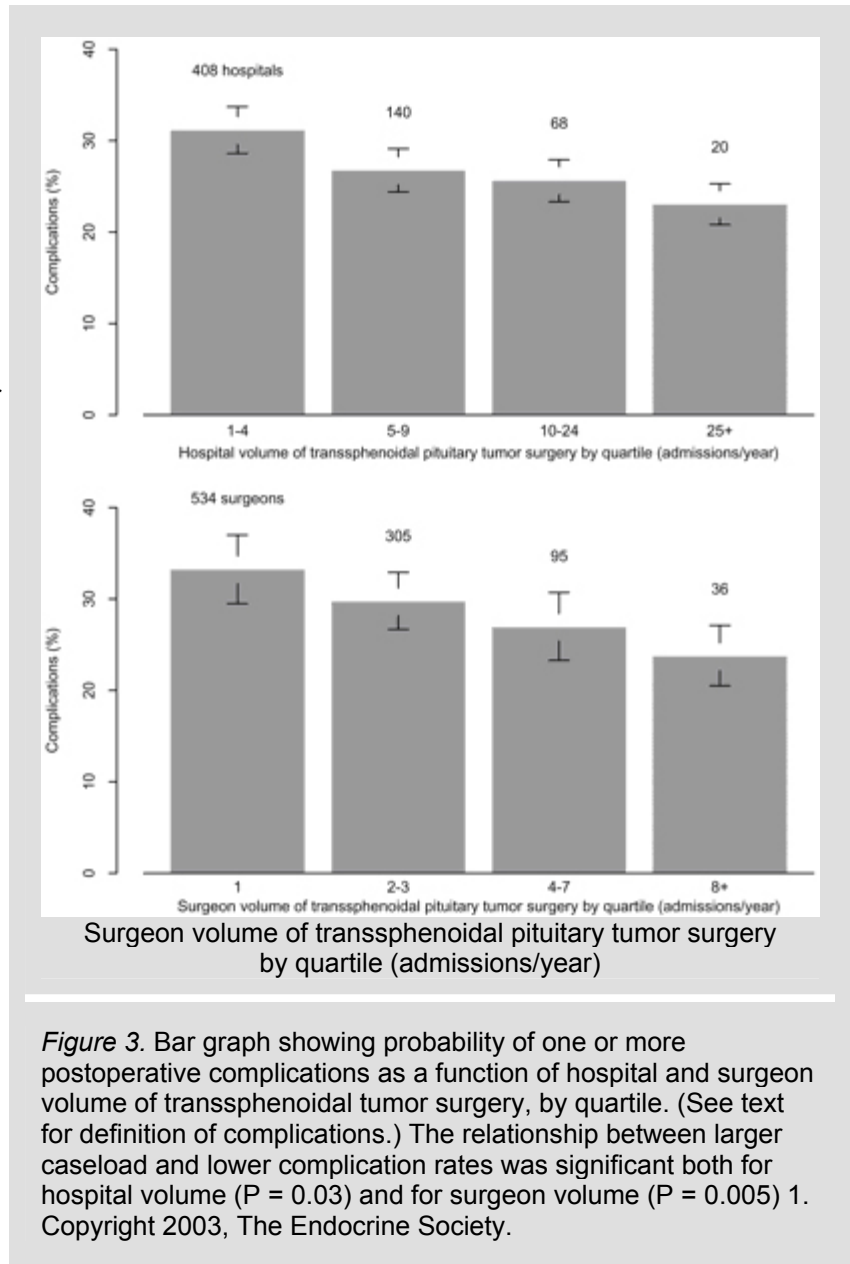
Hospital volume of transsphenoidal pituitary tumor surgery by quartile (admissions/year)

SUMMARY

There are a number of potential problems with this analysis. The data are based upon an administrative database without clinical input from physicians. There are no data regarding cure of the pituitary adenoma. There is no distinction between temporary and permanent complications, as coding occurs at the time of discharge. Although we attempted to correct for the presence of other medical comorbidities, it is theoretically possible that young and healthy patients with a better prognosis, undergoing elective pituitary surgery, could select high-volume surgeons and institutions, and thereby skewing the data to the advantage of these institutions. Nonetheless, it does appear that the volume outcome relationship holds for pituitary surgery, and that patients with pituitary tumors would be advised to seek out institutions and surgeons with special expertise in the field.

References

1. Barker FG, et al. J Clin Endocrinol Metab 88:4709-19, 2003.
2. Gittoes NJ, et al. QJM 92:741-5, 1999.
3. Ahmed S, et al. Clin Endocrinol (Oxf) 50:561-7, 1999.
4. Clayton RN, et al. BMJ 319:588-9, 1999.



Strategies for the Diagnosis of Adult Growth Hormone Deficiency (GHD)

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Since 1996, growth hormone (GH) replacement in adults has been approved by US Food and Drug Administration. Growth hormone replacement in adults has been shown to improve body composition, bone density, cardiovascular risk markers, and quality of life. The current indications for the use of GH in

adults include either a history of pituitary disease or a history of childhood onset growth hormone deficiency (GHD) which persists in adulthood. The goal of diagnostic testing for GHD is to determine which patients are truly deficient and might benefit from replacement, and which patients continue to make normal amounts of GH despite their pituitary disease, therefore having no need for GH replacement.

Consensus guidelines by the Growth Hormone Research Society and the American Association of Clinical Endocrinologists indicate that the diagnosis should be established in patients with an appropriate clinical history by demonstrating a peak GH concentration of less than 3-5 mcg/L following insulin-induced hypoglycemia (insulin tolerance test, ITT)^{1,2}. However, the ITT is not frequently performed in the United States because it is labor intensive, has potential risks, and is contraindicated in some patients. A recent study of over 800 patients being tested for adult GHD showed that only 11.4% were evaluated with insulin tolerance tests³. A multi-center study was designed to determine whether another stimulation test might have the same diagnostic accuracy as the ITT without the associated risk.

This study, conducted at Massachusetts General Hospital, Oregon Health Sciences University, University Hospital of Cleveland, Cedars Sinai Medical Center, and New York University Medical Center evaluated five stimulation tests for the diagnosis of GHD⁴. Thirty-nine patients with adult onset hypothalamic-pituitary disease and multiple pituitary hormone deficiency were compared with 34 control subjects carefully matched for age, sex, body mass index, and estrogen use. Subjects underwent stimulation testing on five separate mornings approximately a week apart including ITT, arginine (ARG), L-dopa, ARG + L-dopa, and ARG + growth hormone releasing hormone (GHRH). Blood was sampled for GH every 20-30 minutes for 2.5 hours and samples were measured in a central laboratory.

Cut points were chosen to allow three different diagnostic options. A cut point was chosen which provided 95% sensitivity, another was selected to afford 95% specificity, and an additional cut point termed CART was chosen to minimize misclassification of patients in either direction. The results showed that the ARG-GHRH test achieved the same diagnostic accuracy as the ITT. Receiver operating characteristic (ROC) curves for peak serum GH responses to ITT and ARG-GHRH are shown in Figure 1. A perfect test, one which would discriminate completely between diseased and normal subjects, would demonstrate a line along the left side and upper part of the box, coinciding with the left upper corner, and would be associated with a ROC area of 1.0. In contrast, a test that is unable to discriminate between diseased versus normal groups would result in a diagonal line from the left lower to the right upper corner of the box, corresponding to a ROC area of 0.5. Both the ITT and the ARG-GHRH test demonstrate excellent discrimination between groups, with ROC areas under the curve of 0.962 and 0.968 (NS) respectively. The superscripts a, b and c denote cut points which provide CART (minimization of misclassification), 95% sensitivity, and 95% specificity values, respectively.

The ARG-GHRH test represents an ideal alternative to the ITT in making the diagnosis of GHD in most adults.

In contrast, the ROC curve for the L-dopa test shows a significantly lower ability to discriminate between the patients and the normal subjects, with a substantially lower ROC area under the curve of 0.906, compared with ITT or ARG-GHRH. In addition, this test was not able to achieve 95% specificity, so there is no cut point labeled c.

The choice of a high sensitivity versus a high specificity cut point may depend on the clinical setting. In patients with panhypopituitarism, a number of studies have demonstrated a very high probability of GHD. For example, patients who are deficient in 3 or 4 other pituitary hormones have been shown to have a greater than 95% probability of being deficient in GH^{5, 6}. In such patients, clinicians might prefer to use a test with at least 95% sensitivity, thereby limiting the chance of a false negative result, in order not to misclassify a deficient patient as having normal GH secretion. Because patients with panhypopituitarism have such a high probability of GHD, some insurance companies have approved GH replacement without requiring stimulation testing. In contrast, in a patient with no other pituitary hormone deficiencies, the risk of GHD is less than 50%. In such a patient, a clinician is likely to seek high specificity. Choosing a cut point with high specificity would limit the chance of a false positive test, which would be important for avoiding the

unnecessary use of GH replacement in someone with adequate GH production. Alternatively, the cut points derived by CART analysis provide a balance between high sensitivity and specificity, and might be preferred by some clinicians.

While insulin-like growth factor-1 (IGF-1) is diagnostically useful for the GH excess state of acromegaly, it is not as accurate in the diagnosis of GHD. This is because there is substantial overlap at the low end of the normal range between normal people and patients subsequently confirmed to have GH deficiency. Thus, IGF-1 has low sensitivity for the diagnosis of GHD when it is in the lower half of the normal range. It has been suggested that an IGF-1 level below a certain cut point might be useful for the diagnosis of GHD, particularly in childhood onset or younger adult-onset GHD patients 7, 8. Because serum IGF-1 levels decline with age, the diagnostic utility of this measurement is particularly low in older patients 9,10. Several studies have shown specific IGF-1 levels below which normal subjects almost never fall. These levels have typically been in the 70-80 mcg/L range 3, 4. However, choosing a specific IGF-1 cut point below which all subjects are classified as GHD must take into account other variables that affect IGF-1 such as nutrition, liver disease, and the IGF-1 assay employed. It may be clinically useful to measure an IGF-1 as a screening test in patients with possible GHD. If the level returns very low, in the absence of other causes of low IGF-1, the diagnosis may be established if the patient is also deficient in three or more other pituitary hormones. Some insurance companies have accepted this combination of panhypopituitarism and a frankly low IGF-1 as sufficient for the diagnosis of GHD. However, it is important to note that if a screening IGF-1 level returns in the lower half of the normal range, this does not exclude the possibility of GHD, and further stimulation testing should be performed. If a screening IGF-1 is in the high end of the normal range for age and sex, then the probability of GHD is quite low, and clinical judgment should be used as to whether to pursue stimulation testing.

In summary, the ARG-GHRH test represents an ideal alternative to the ITT in making the diagnosis of GHD in most adults. There are several caveats regarding clinical situations where this test may not be accurate. Patients who have had recent radiation, and may have hypothalamic damage (but not yet pituitary dysfunction), may have a falsely normal response to GHRH. The same situation may be seen in patients with other sources of hypothalamic GHD including childhood-onset subjects without organic disease. In such patients, an alternative test, such as ITT or ARG + L-dopa with a more stringent cut point (such as 0.25 mg/L, 95% specificity) might be advisable. The use of clinical history, including the presence of panhypopituitarism and a low IGF-1 may also assist in making the diagnosis of growth hormone deficiency. Establishing the presence or absence of GHD using accurate diagnostic tests will allow replacement therapy to be offered to the appropriate patients.

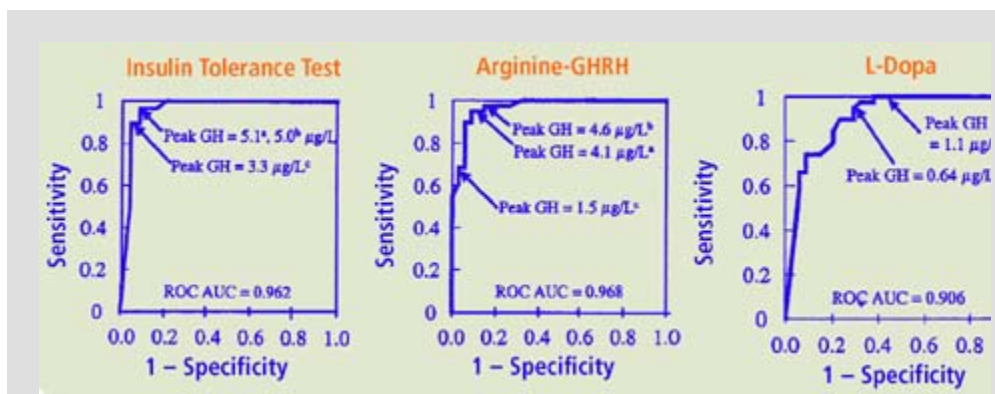


Figure 1. Receiver-operating characteristic (ROC) curves for peak serum GH responses to ITT, ARG-GHRH, and L-DOPA. The ROC curve plots the true positive rate (sensitivity) against the false-positive rate (1-specificity) for different cut-points. A test with perfect discrimination between multiple pituitary hormone deficiencies (MPHD) patients and matched control subjects (100%

sensitivity and 100% specificity) would coincide with the left upper corner of the box, and be associated with a ROC area of 1.0. In contrast, a test providing no discrimination between groups would result in a diagonal line from the left lower to the right upper corner of the box (sensitivity = 1-specificity), and correspond to a ROC area of 0.5. The arrows and superscripts indicate the location on the ROC curves of the three diagnostic cut-points defined as follows: a, minimize misclassification of MPHD patients and control subjects; b, 95% sensitivity for GHD; and c, 95% specificity for GHD. The area under the curve (AUC) for each ROC curve is shown. The ITT and ARG-GHRH tests are statistically equivalent for diagnostic accuracy. Reprinted with permission from The Endocrine Society.

References

1. American Association of Clinical Endocrinologists. *Endocr Pract.* 1998; 4:165-73.
2. Growth Hormone Research Society *J Clin Endocrinol Metab.* 1998; 83:379-81.
3. Hartman ML, et al. *J Clin Endocrinol Metab.* 2002; 87:477-85.
4. Biller BMK, et al. *J Clin Endocrinol Metab.* 2002; 87:2067-79.
5. Aimaretti G, et al. *J Clin Endocrinol Metab.* 1998; 83:1615-8.
6. Toogood AA, et al. *Clin Endocrinol.* 1994; 41:511-6.
7. Hilding A, et al. *J Clin Endocrinol Metab.* 1999; 84:2013-9.
8. Span JP, et al. *J Endocrinol Invest.* 2001; 22:446-50.
9. Ghigo E, et al. *Eur J Endocrinol.* 1996; 134:352-6.
10. Toogood AA, et al. *J Clin Endocrinol Metab.* 1996; 81:460-5.