

Guidelines for the Diagnosis and Treatment of Adult Growth Hormone Deficiency

Cenegenics® Medical Institute

By

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Background

Because human growth hormone (hGH) has been the subject of controversy and legal limitations, a clinician must carefully consider how, when, and on what basis to prescribe the drug. Although the Food and Drug Administration has broad authority to oversee the efficacy and safety of drugs, it does not generally oversee the practice of medicine by regulating off-label use of drugs by individual physicians. However, federal law treats hGH differently than other drugs and limits the distribution of hGH to indicated uses and imposes criminal sanctions on those who violate the law.

These guidelines are not intended to address the legal aspects of hGH prescribing or distribution. Suffice it to note the safest course is for physicians to prescribe hGH in adults *only* for FDA approved uses as indicated in the package insert and PDR i.e. adults with growth hormone deficiency. The package insert further states that adult growth hormone deficiency syndrome (AOGHD or GHD) must be confirmed through provocative testing. Provocative testing is achieved through pituitary stimulation in a controlled environment. The FDA has clearly stated that it is unlawful to use hGH for anti-aging purposes, for the purpose of muscle building, or for the enhancement of athletic performance.

Cenegenics® recognizes that aging is inevitable; our mission is to improve quality of life and reduce risks for disease. When we encounter a patient at our initial evaluation that we suspect has insufficient growth hormone levels based on our clinical and laboratory findings we correct their other hormonal deficiencies and start them on a closely supervised nutrition and exercise program. If after 2 months this patient is unable to increase his or her endogenous production of growth hormone we bring them back to our clinic for pituitary stimulation testing to prove or disprove our suspicions of GHD. hGH supplementation is only initiated if they fail the stimulation testing. ⁽¹⁾

These guidelines summarize some of the science underlying the use of hGH and provide assistance to clinicians for the diagnosis of GHD and for use of hGH to treat such deficiencies. Importantly, the role of hGH in medical practice continues to change as new research creates additional medical science. Thus, like any summary of medical science in an evolving field, these guidelines capture

a snapshot and provide a summary of the current state of knowledge regarding hGH. These guidelines are not intended to establish a standard of care or to be an unalterable mandate for treating any individual patient. Each clinician must base treatment decisions for each patient on the clinician's independent judgment, knowledge of the patient's circumstances, and continuing developments in the field.

Adult Growth Hormone Deficiency

The Society of Endocrinology has described the consequences of adult growth hormone deficiency as follows ⁽²⁾:

<http://www.endocrinology.org/policy/docs/gh.html>

Symptoms

- Decreased energy levels
- Social isolation
- Lack of positive well being
- Depressed mood
- Increased anxiety

Clinical features

- Increased body fat, particularly central adiposity.
- Decreased muscle mass.
- Decreased bone density, associated with an increased risk of fracture.
- Increased LDL cholesterol and Apo B. Decreased HDL cholesterol.
- Decreased cardiac muscle mass (especially in childhood onset somatotrophin deficiency)
- Impaired cardiac function.
- Decreased total and extracellular fluid volume.
- Decreased insulin sensitivity ⁽³⁾ and increased prevalence of impaired glucose tolerance.
- Increased concentration of plasma fibrinogen and plasminogen activator inhibitor type I ⁽⁴⁾.
- Accelerated atherogenesis ^(5,6).

The above metabolic changes are known to increase the risk of atheromatous cardiovascular disease and decrease physical performance. This is borne out by retrospective analyses of epidemiological data which show that hypopituitary patients have approximately double the risk of cardiovascular death ^(7,8). Conclusive evidence that this is due to somatotrophin deficiency is, however, lacking although therapy with somatotrophin reverses most of the metabolic changes associated with increased cardiovascular risk.

Diagnosis and Provocative Testing

Until 1986 human growth hormone was harvested from cadavers for the treatment of deficiency states and, as such, carried a risk for transmission of disease to its recipients. The Insulin Tolerance Test (ITT) and other stimulation tests were, therefore, developed to help select only those individuals with the poorest ability to secrete growth hormone as candidates to receive this drug. Since 1986, however, growth hormone has been commercially produced in the laboratory with recombinant gene technology and issues concerning disease transmission are no longer applicable.

Several researchers consider IGF-1 a reliable diagnostic and therapeutic marker of growth hormone deficiency ^(11,14,15,16,17). The Growth Hormone Research Society (<http://www.ghresearchsociety.org/bin/Default.asp>) published their consensus statement in the *Journal of Clinical Endocrinology and Metabolism*. The Society concluded that in association with appropriate clinical signs and symptoms and in conjunction with proper laboratory evaluation, an accurate clinical diagnosis can be made in the absence of ITT ⁽²²⁾. They also point out that GHD may even be associated with IGF-1 values near the statistical mean. At least one leading endocrinology textbook comes to the same conclusion. In *Williams Textbook of Endocrinology*, the authors point out that IGF-1 levels may be “low or normal” in adult deficiency states ⁽²³⁾.

This may be akin to recent developments in the prevention of coronary artery disease where statistically average values for cholesterol were correlated with an increased risk of disease. In response to the evolving research that has demonstrated that low LDL levels are associated with a decrease in plaque formation and can even result in plaque reversal, the medical community has rethought what levels of cholesterol and lipids should be recommended as “normal” and what levels triggered prescribing statins and lifestyle changes.

Stimulation Testing

The ITT test has been the stimulation test used by most endocrinologists to diagnose growth hormone deficiency in adults. ITT, however, has inherent danger of serious risks that include seizures or unconsciousness due to neuroglycopenia. It is also contraindicated in patients with known or who are at risk for coronary artery disease or in patients with a history of seizures ⁽⁹⁾. Murray, et al, describes all GH stimulation tests as “plagued by poor reproducibility” and “being labor intensive” ⁽¹⁰⁾. He goes on to say that there is little data available that indicates whether stimulation tests can reliably separate growth hormone deficient individuals from normal subjects.

For these reasons along with a growing criticism surrounding the validity, reliability, and safety of ITT many investigators and clinicians now reject ITT and other stimulation tests as the gold standard for diagnosing adult growth hormone deficiency (11,12,13,14,15, 16, 17, 18,). Indeed, several recent studies have demonstrated the clinical usefulness of growth hormone supplementation without the requirement of “failing” an ITT (19,20,21).

However, in spite of all the controversy over the best method to diagnose GHD, the FDA and hGH manufactures have maintained their positions that stimulation testing is necessary and required for the accurate diagnosis of adults with growth hormone deficiency. For this reason, Cenegenics® has implemented pituitary stimulation testing as a prerequisite for diagnosing GHD in our patients.

See appendix A for a more detailed explanation on our current protocol for Glucagon Stimulation Testing

Growth Hormone and Health

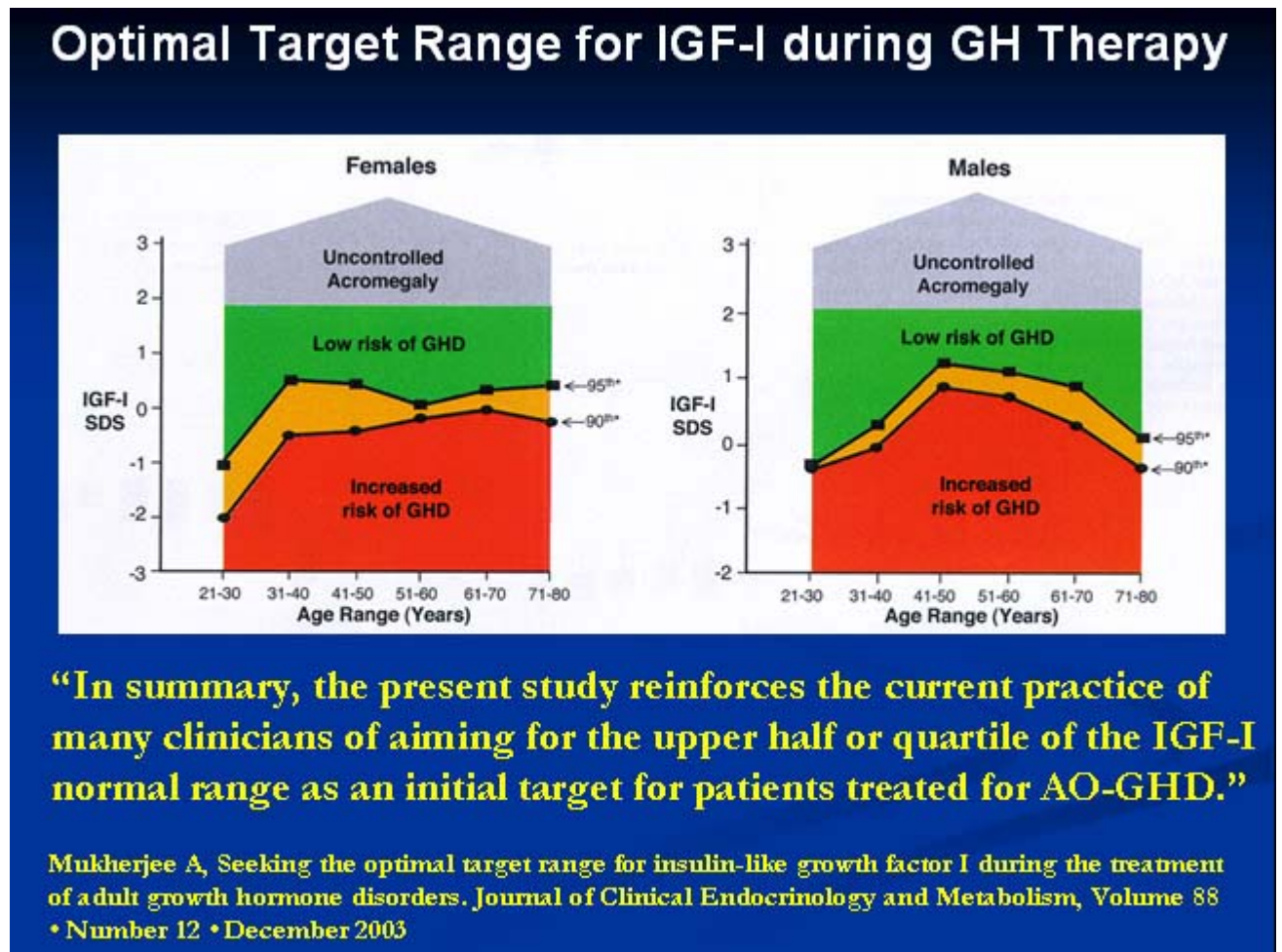
As in many disease states, there are varying levels of severity of growth hormone deficiency in affected patients. (10, 24) It has been reported by several researchers (10,25,26,27,28) that there are patients with less severe GH deficiency and that these patients, like their counterparts with severe GH deficiency, suffer from the same sequelae such as, dyslipidemia, altered body composition, cardiac dysfunction and insulin resistance. There is mounting evidence that adults with GH deficiency or insufficiency (29) with impaired health improve with GH replacement therapy.

The following paragraphs discuss evidence-based, peer-reviewed scientific literature that demonstrate the value of GH therapy and optimizing levels of IGF-1 in adults diagnosed with GH deficiency or insufficiency in preventing or modulating significant disease processes that are the major cause of morbidity and mortality in America today.

Drake discusses the clinical importance of maintaining IGF-1 levels between the statistical mean for a patient’s age and two standard deviations above that mean to maintain optimal health (30). Maintaining an IGF-1 level in this range appears to be an appropriate clinical goal for GH supplementation therapy in adults with growth hormone deficiency.

Mukherjee evaluated the relationship between IGF-1 and GH levels from a different point of view. Instead of using IGF-1 to diagnose deficiency, she looked at what IGF-1 level would be sufficient to “avoid a deficiency state.” Her findings reinforce the current practice of setting the goal for GHD therapy as achieving IGF-1 levels in the upper half or quartile for an individual’s

normal age-related range. Dr. Mukherjee found that her 95% sensitivity measurement for “adequately” treating GHD with GH therapy was achieving IGF-1 levels above the age-related mean as described in her following chart (31):



Roubenoff and Cappola each separately point out the inverse association between IGF-1 levels and mortality risk. Both researchers found that patients with lower IGF-1 levels were at generally increased risk for mortality compared to an otherwise matched cohort (32, 33).

These studies use IGF-1 as an objective marker of actuarial risk. This use of IGF-1 establishes a direct relationship between its measurement and patient outcomes in the same way clinicians use other well-established markers of morbidity and mortality risk.

Roubenoff’s study followed subjects who were part of the Framingham Heart Study over a 22-year period and found a 13% lower mortality rate for IGF-1 values in the upper two quartiles (all subjects above the mean) versus those in

the lower two quartiles⁽³²⁾. This was independent of all other risk factors and remained consistent when adjusted for the presence of other risk markers. In other words, low IGF-1 levels predicted higher mortality rates when the outcomes were adjusted for smoking history, lipids, and other risk factors.

In a study similar to Framingham, the Rancho Bernardo Study which consisted of an on-going community-based investigation was performed on healthy adults for extended intervals. Over a 13-year follow-up span, IGF-1 levels again were inversely associated with both total mortality and cardiovascular disease rates. For every 40ng/mL decrease of IGF-1 below the mean, there was a 38% increase in total mortality. This study also was controlled for any potential effect of IGF-1 on any specific type of mortality. Increased IGF-1 was not associated with any elevation of risk for any other subject mortality. The authors concluded that low baseline levels of IGF-1 are associated with increased risk for heart disease mortality among patients⁽³⁴⁾.

Elderly people have four to five times the case rate of cancer, tuberculosis, and herpes zoster and six to seven times the fatality rate from pneumonia compared to young adults⁽³⁵⁾. This is thought to be due to a decreased GH and IGF-1 production along with decreased immune function⁽³⁵⁾. By age 60 most adults have a 24-hour GH secretion rate indistinguishable from those of hypopituitary patients with organic lesions in their pituitary gland^(36, 42). The fall in GH secretion seen with aging is accompanied by changes in body composition, lipid metabolism, immune function and a progressive loss of muscle mass⁽³⁷⁾, power⁽³⁸⁾ and physical performance⁽³⁹⁾ which leads to the frailty and loss of independence seen in adults with GH deficiency. The increase in body fat that is associated with falling levels of GH and IGF-1 is mostly made up of metabolically active abdominal fat⁽⁴⁰⁾ and this fat results in an increase in the markers for cardiovascular risk.

The similarity between the negative features of the adult GH deficiency syndrome and aging has led several investigators to speculate that the GH-deficient state of normal later life may have a causal relationship to the undesirable physiological changes associated with aging⁽⁴¹⁾. Savine et al believe GH therapy may be an effective approach to promote and maintain health in old age and points out the need for long-term studies in our aging population⁽⁴²⁾.

hGH Therapy & Cardiovascular Disease

Conti et al recently described the increasing evidence that IGF-1 protects against endothelial dysfunction, atherosclerotic plaque development, metabolic syndrome, plaque instability, and ischemic myocardial damage⁽⁴³⁾. They concluded that low IGF-1 levels may represent an additional independent risk factor for cardiovascular disease and the measuring of circulating IGF-1 may add valuable information to the current assessment

of cardiovascular risk. They further state that individuals with low IGF-1 levels might develop disease even in the absence of traditional risk factors and individuals with traditional cardiovascular risk factors but normal or elevated IGF-1 levels may be protected, at least in part, against disease ⁽⁴⁴⁾.

It appears clinically important that the relation between serum IGF-1 levels and protection against heart disease (identified in several prospective studies) remains significant even after adjustment for body mass index, smoking, hypercholesterolemia, menopause, alcohol intake, physical activity, gender, age, social class, previous diabetes, family history of ischemic heart disease, self-evaluated health, use of antihypertensive agents, and circulating IGFBP-3 levels (which lower IGF-1 bioavailability due to increase protein binding and lower free levels) ^(44, 45, 46).

hGH Therapy & Stroke

In 2004, Denti studied the connection between IGF-1 levels and stroke outcome in elderly patients. Outcomes were stratified as to both mortality risk and “quality.” This study found a potent inverse relationship between IGF-1 levels and outcome quality as well as mortality risk. For each 20 ng/mL increase in IGF-1 levels seen in stroke patients, the mortality risk was reduced by 30%. The investigators concluded that low levels of circulating IGF-1 may predict poorer clinical outcomes of stroke in elderly patients ⁽⁴⁴⁾.

hGH Therapy & Cancer Risk

There is concern among the lay public as well as many health-care providers that GH replacement therapy may put individuals at an increased risk for developing a malignancy. The literature, however, does not support this notion. Current clinical guidelines for AACE ⁽⁹⁾ and The Endocrine Society ⁽⁴⁷⁾ state there is no evidence that the incidence of intra or extracranial tumors is increased by GH therapy. The Consensus Guideline for the Diagnosis and Treatment of Adults with Growth Hormone Deficiency II published in 2007 states that “There is no evidence that GH replacement in adults increases the risk of *de novo* malignancy or recurrence ⁽⁴⁸⁾. Dr. Shlomo Melmed, editor of *Williams Textbook of Endocrinology*, also supports this view in an editorial ⁽⁴⁹⁾ where he states that “**No increased cancer occurrence has been observed in surveillance studies of GH replacement in pituitary-deficient adults.**”

In 2001, The Growth Hormone Research Society ⁽⁵⁰⁾ extensively reviewed the question of whether GH therapy is associated with tumor genesis and their conclusion was that GH therapy is **not** associated with the promotion of pituitary tumor recurrence or the development of any other neoplasm. They even went so far as to state that for patients receiving GH therapy “**No additional monitoring for other malignant tumors (such as tumors of the prostate, breast, or colon) is currently suggested**

beyond the accepted standard of care for the patient's age and sex."

GH replacement therapy that is carefully monitored with periodic IGF-1 levels to assure healthy levels does not put individuals at an increased risk for cancer.

hGH Therapy & Obesity

It is well known to everybody today that obesity in America has reached epidemic proportion. The health risks associated with obesity are closely correlated with central fat (abdominal or visceral), rather than a gluteal-femoral fat pattern. Visceral fat causes metabolic syndrome which is associated with serious metabolic disorders including silent inflammation, heart disease, cancer, stroke, insulin resistance, diabetes, and Alzheimer's disease. These complications are thought to be a result of increases in portal vein free fatty acid levels caused by the visceral fat⁽⁵¹⁾. Visceral adiposity is also recognized to be associated with a decrease in IGF-1 and deficits in GH secretion^(52, 53).

A study published in a 2007 *Journal of Clinical Endocrinology and Metabolism* showed that GH therapy in non-GH-deficient adult men with visceral adiposity did reduce visceral fat, although the magnitude of the effect on adiposity was less than what was expected from studies that examined replacement therapy in GH-deficient adults⁽⁵⁴⁾. Another study published in the *Journal of Clinical Endocrinology and Metabolism* in April 2008 demonstrated that low-dose GH therapy in GHD women decreased total and visceral adipose tissue, and improved cardiovascular disease markers with a relatively modest increase in IGF-1 levels without worsening insulin resistance⁽⁵⁵⁾.

Numerous studies of GH replacement therapy have found that GH treatment decreases fat mass and increases lean body mass^(56,57). Studies using computed tomography imaging have shown that much of this decrease in fat mass is derived from the visceral fat pool^(58, 59). Several studies also show that GH therapy improves lipid profiles⁽⁵⁶⁾.

hGH Therapy & Exercise Capacity

GH therapy can have a positive impact on the declining exercise capacity observed in individuals with low levels of GH and IGF-1. A recent article published in the *Journal of Clinical Endocrinology and Metabolism* in January 2008 showed that GH replacement therapy in adults with deficiency will improve maximal oxygen consumption (aerobic exercise capacity) and maximal power output independently of dosing regimen or physical activity⁽⁶⁰⁾.

hGH Therapy & Diabetes

GH deficiency in adults is associated with a reduction in muscle mass and an increase in fat mass, particularly around the abdomen leading to metabolic syndrome. This accumulation of abdomen fat appears to be important in the development of insulin resistance.

Observation of the effects of GH replacement therapy has helped our understanding of the role of GH in glucose metabolism. In the short term, there is an increase in insulin resistance. However, as lean body mass (muscle) increases and fat mass is reduced, long-term insulin sensitivity gradually improves with an associated reversal of metabolic syndrome.

Metabolic syndrome is a cluster of features including abdominal obesity, hypertension, insulin resistance, and glucose intolerance – precursors to Type 2 diabetes. There are similarities in the clinical features of metabolic syndrome and untreated GH deficiency. They suggest that the reduction in GH concentrations may be important in the development of metabolic syndrome. The correction of GH concentrations may have beneficial effects. When GH is administered to abdominally obese men, it leads to a reduction in abdominal fat, and a corresponding improvement in insulin sensitivity. ⁽⁶¹⁾

When IGF-1 is given to people with Type 1 diabetes, there is an improvement in blood glucose control and a reduction in the insulin dose required to maintain normal glucose control. Similar results, together with a reduction in fat mass, are seen in people with Type 2 diabetes who receive larger doses of IGF-1. ⁽⁶²⁾

Correcting GH & IGF-1 Deficiencies and Insufficiencies through Lifestyle Changes

IGF-1 synthesis is not only regulated by GH but also by nutrient supply and other hormones ⁽⁶³⁾. Serum IGF-1 levels fall rapidly with fasting and return to normal following a balanced intake of protein and calories ⁽⁶⁴⁾. A high fat, low carbohydrate diet reduces GH secretion by 30% ⁽⁶⁵⁾. On the other hand, protein and fat increase IGF-1 levels ⁽⁶⁴⁾. Amino acids such as arginine stimulate GH secretion ⁽⁶⁶⁾. Positive correlations have also been shown between serum IGF-1 and the intake of micronutrients such as calcium, iron, potassium, magnesium, niacin, phosphorus, riboflavin, thiamine, and zinc ^(67, 68).

GH secretion measured over 24 hours is negatively correlated with abdominal adiposity ⁽⁶⁹⁾. Caloric restriction and weight loss restore normal GH secretion rates, suggesting that the decrease in GH secretion in obese subjects is a result of, rather than the cause of the obesity ⁽⁷⁰⁾.

Exercise can play a significant role in GH secretion. About 10-20 minutes of aerobic exercise causes a rise in serum GH levels that peak at the end of that period and are sustained for up to 2 hours ⁽⁷¹⁾. The intensity and duration of the exercise is important with a threshold required before GH is released from the pituitary ⁽⁷²⁾. Chronic training above the lactate threshold produces a 2-fold increase in GH secretion, an increase not seen in individuals exercising below the lactate threshold ⁽⁷³⁾. Increasing levels of aerobic fitness are positively correlated with 24-hour GH secretion ^(74, 75).

Sleep

Growth hormone release from the pituitary occurs mostly during sleep. The major GH pulse coincides with early sleep and there are marked reductions in the magnitude of this pulse as individuals age. ⁽⁷⁶⁾ Strategies to prevent or limit decrements of sleep quality in midlife and late life offer an indirect form of hormonal therapy with beneficial health consequences. Quality sleep is essential for maintaining healthy GH levels.

Signs and Symptoms of Adult Growth Hormone Deficiency & Related Disease Risk Factors

<ul style="list-style-type: none"> ○ Low IGF-1 ○ QOL AGHDA Score ○ Beck Depression Inventory Score ○ Fatigue ○ Metabolic Syndrome ○ Truncal/Visceral Obesity ○ Decreased Bone Mineral Density ○ Decreased Muscular Strength ○ Muscle Wasting ○ Hypoandrogenism ○ Decreased Energy and Vitality ○ Hypothyroidism ○ Hyperinsulinemia ○ Dyslipidemia ○ Depression ○ Abnormal Fasting Glucose ○ Obstructive Sleep Apnea ○ Insulin Resistance ○ Menopause ○ Obesity ○ Hx Head Injury 	<ul style="list-style-type: none"> ○ Perimenopause ○ Overweight ○ Family Hx CAD ○ Memory Loss ○ Family Hx Diabetes ○ Sleep Disturbance ○ Family Hx Cancer ○ Increased CRP ○ Family Hx Osteoporosis ○ Hypersomnia ○ Family Hx Alzheimer's Disease ○ Poor Cognitive Stability Index ○ Cardiac Decompensation ○ Hypertension ○ Reduced Exercise Capacity ○ Decreased Libido ○ Endothelial Dysfunction ○ Sarcopenia ○ Adverse Cardiovascular Risk Profile ○ Elevated Estradiol in Men

Reference Ranges, Normal Ranges, and Optimal Ranges

Many clinicians believe that laboratory reference ranges are, in fact, normal ranges. Federal regulations require all federally-approved (Medicare-approved) laboratories to publish their reference ranges for all tests performed in their laboratory. These reference ranges are usually based on a large number of patients assumed to be essentially normal for the particular test being performed. It is easy, therefore, to understand why many think reference ranges are the same as normal ranges. There are in fact very few “normal” ranges in medicine today that are supported by appropriate laboratory data. The Framingham Study is an example where we have a good understanding of the ideal and normal ranges for cholesterol. These values are considerably different than the reference ranges we used prior to the Framingham Study. The mean cholesterol level in the reference range was 250 mg/dL, but we now understand that patients with values of 200 or greater are at increased risk of cardiovascular disease.

The dilemma of reference ranges vs. normal ranges becomes an even greater problem when it comes to infrequently performed tests like IGF-1. Most laboratories are forced to use a small group of apparently normal individuals, i.e. those without obvious evidence of growth hormone deficiency, to determine their reference ranges. Quest Diagnostics recently (February 2010) established new reference ranges for IGF-1.

Males & Females

Adult Reference Ranges for IGF-1, LC/MS:

Age	(ng/mL)
18-19.9 Years:	108-548
20-24.9 Years:	83-456
25-29.9 Years:	63-373
30-39.9 Years:	53-331
40-49.9 Years:	52-328
50-59.9 Years:	50-317
60-69.9 Years:	41-279
70-79.9 Years:	34-245
>80 Years:	34-246

The reference ranges listed above provide information regarding IGF-1 levels for healthy men and women at various stages in their life span. Deficiencies in hGH and the commensurate fall in IGF-1 levels are now known to play a pivotal role in the decline of quality of life and increased incidence of age-related disease. Studies suggest individuals that maintain IGF-1 levels in the range of 1 to 2 standard deviations above the mean for their age are less likely to experience these declines in quality of life and are able to improve body fat distribution (specifically visceral fat) and improve muscle mass, strength, and endurance resulting from sarcopenia; prevent or reverse metabolic syndrome; improve serum lipoprotein profiles; reduce cardiac risk; improve glucose

tolerance and insulin sensitivity; improve vitality; and avoid many of the other age related diseases^(30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46).

Summary of disorders associated with adult growth hormone deficiency and insufficiency

1. Low IGF-1 levels. IGF-1 levels less than 1 SD above the mean for a patient's age and gender are now considered by recent research studies to adversely impact quality of life and increase risk for age related diseases. Low IGF-1 levels are also considered to be an independent risk factor for cardiovascular disease. IGF-1 levels can be low or normal in adult deficiency states.
2. Deficiencies in other hormones.
3. Quality of life issues as identified by the Quality of Life Adult Growth Hormone Deficiency Assessment Questionnaire.
4. Beck Depression Inventory scores of 10 or greater.
5. Borderline or impaired performance on Cognitive Stability Index testing.
6. Impaired muscular strength, muscular endurance, flexibility, agility, or cardiovascular endurance.
7. Reduced bone mineral density greater than -1 SD.
8. Truncal/Visceral Obesity
9. Reduced muscle mass leading to sarcopenia
10. Endothelial Dysfunction
11. Adverse cardiovascular risk factors
12. Other signs and symptoms of adult onset growth hormone deficiency and related disease risk factors such as those listed above.

Cenegenic's contraindications to hGH therapy

1. Provocative testing not performed or if performed, their pituitary response was satisfactory
2. Pregnancy
3. Malignancy
4. Past history of malignancy (exception basal cell carcinoma)
5. Diabetic proliferative retinopathy
6. Sclerosing diseases of the liver and lungs
7. Benign intracranial hypertension
8. Uncontrolled diabetes

Growth Hormone Dosing Strategies

Growth hormone requirements can be affected by various factors in the GH deficient/insufficient patient. In general, younger patients will need a higher dose as will women on oral estrogens. Older patients, diabetics, and women discontinuing oral estrogens will typically need a lower dose. Patients under thirty years of age can typically be started at 0.4 – 0.5 mg/day, patients from 30 to 60 years of age need to be started at 0.3mg/day and those over 60 years of age, and those with diabetes or glucose intolerance, seem to do best if started at 0.1 – 0.2 mg/day.

No two patients will have the same absorption or GH sensitivity so each must be titrated individually in a stepwise approach. Six to 8 weeks after initiating treatment, the dose may be increased by 0.1 to 0.2 mg/day based on clinical response and IGF-1 levels as well as individual considerations such as glucose intolerance and any side effects that may be present. Edema or joint pain rarely develop after treatment is initiated, but if this should occur, decrease the dose by one half and once symptoms have abated resume a gradual stepwise increase in dosage as tolerated. Laboratory monitoring every six months once maintenance dosage is reached should include lipids, IGF-1, fasting glucose, HbA1c and thyroid levels.

Growth hormone replacement can lower free T4 levels and also inhibit 11- beta hydroxysteroid dehydrogenase resulting in an increase in cortisone production and subsequent decreases in cortisol production. These are small changes and typically are not clinically significant however it is possible that secondary hypothyroidism and hypoadrenalism may be unmasked in susceptible patients. Those patients already on thyroid and cortisol replacement due to pituitary insufficiency will need to be monitored closely for signs and symptoms indicating a need for increased dosages of these hormones.

Discussion

Growth hormone deficiency and insufficiency are disorders that are known to be associated with significant morbidity. Many studies support the notion that IGF-1 levels of less than 1 SD above the mean for men and women at various ages in their life can be used in the context of a patient's total clinical assessment as an indication of GHD. This clinical assessment should include other independent lab markers of disease, signs and symptoms of growth hormone deficiency, a complete medical history, concomitant medical issues, current complaints, an in-depth review of systems, a complete physical exam, cognitive stability index testing, quality of life assessment testing, testing for body composition (lean mass, fat mass, bone mineral density), strength, endurance, flexibility, agility, cardiovascular endurance, and vascular health.

If GHD is suspected after considering all of these factors we, at Cenegenics®, believe patients should be given an opportunity to improve their endogenous production of growth hormone through correction of their other hormone deficiencies and maximizing their diet, nutraceutical supplementation, and exercise programs. If, at a patient's 6- to 8-

week follow up blood draw and evaluation, IGF-1 levels remain low and their signs and symptoms of GHD have not improved, we will consider performing a stimulation test to prove or disprove our suspicions of GHD. If the provocative testing demonstrates an inadequate pituitary response to stimulation we consider initiating hGH therapy and discuss in detail the pros and cons with the patient.

When prescribed and monitored properly, GH treatment is very safe and has the potential to greatly improve quality of life and reduce the incidence of morbidities associated with untreated GHD. Gone are the days of cadaveric GH with its associated risks. The supply of GH is safe, available and easy to administer. Unfortunately GH is expensive, though the costs of preventing the morbidities associated with untreated GHD over the lifetime of the patient far outweigh this expense.

DRAFT

**CENEGENICS MEDICAL INSTITUTE RECOMMENDATIONS REGARDING
THE ADMINISTRATION OF GROWTH HORMONE IN GROWTH HORMONE
DEFICIENT ADULTS**

1. Carefully review outside medical records, labs, and diagnostic studies such as sleep study etc, at the time of the initial EHE.
2. Make sure any underlying sleep disorder at the time of the EHE is being treated. If not, initiate successful treatment before next blood draw.
3. Re-evaluate the patient in two months with follow-up labs, which should include an IGF-1 as well as other hormones levels and risk factors for disease.
4. Repeat the Quality Of Life AGHDA Questionnaire at the two-month follow-up visit.
5. Repeat the Beck Depression Inventory Questionnaire at the two-month follow-up visit.
6. Repeat CSI Vital Signs Cognitive Study
7. Repeat abdominal girth or DEXA for body composition and assessment of visceral fat at the two-month follow-up visit.
8. Repeat the energy/strength/fitness questionnaire at the two-month follow-up visit.
9. If, after a critical review of the clinical, diagnostic, and laboratory data, you still believe the patient has remained clinically growth hormone deficient, consider performing a provocative stimulation test to prove or disprove AOGHD.

All Cenegenics' patients receiving hGH must be followed closely with repeat blood draws every 4 to 5 months to assure IGF-1 levels are in the range of 1 to 2 standard deviations above the mean for the patient's age and not higher. Follow-up annual visits are required and should include the following:

CENEGENICS RECOMMENDED FOLLOW-UP OF PATIENTS BEING TREATED WITH EXOGENOUS GROWTH HORMONE.

ALL PATIENTS CURRENTLY RECEIVING GROWTH HORMONE THERAPY FOR ONE YEAR OR MORE SHOULD HAVE THE FOLLOWING DOCUMENTED IN THEIR MEDICAL RECORD ON A YEARLY BASIS.

- Physical Exam
- QOL AGHDA score.
- Beck Depression Inventory II score
- Percent Body Fat & Visceral Fat as determined by DEXA scanning to assess gains or losses.
- Muscle mass (DEXA) and strength testing to assess gains or losses.
- Bone mass (DEXA) to assess gains or losses.
- Lipid profile (VAP Test if indicated) to assess improvements or worsening.
- HbA1c, Fasting Insulin, & Cardio CRP to assess changes.
- Carotid ultrasound study to assess changes in intima-media thickness, plaque character, and stenosis.
- Endothelial testing to assess endothelial functional changes.
- VO2 max to assess changes in cardiovascular fitness.
- CNS Vital Signs Cognitive testing to assess changes.
- Energy status questionnaire to assess changes over previous year.
- Carefully document all findings in the medical record.

Note: These guidelines are not intended to dictate the treatment of a particular patient. Treatment decisions must be made based on the independent judgment of the physician and each patient's individual circumstances.

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Appendix A

Glucagon Stimulation Testing (GST)

The Glucagon stimulation test is currently our provocative test of choice for the diagnosis of GHD. It is readily available and simple to perform. Studies to date have suggested that it is accurate and reproducible, though further validation studies will be necessary for this test to supplant the ITT as the gold standard. It is much safer than the ITT, with hypoglycemia being very uncommon. The only contraindications are in the malnourished or those who have not eaten in the previous 48 hours.

The entire test takes a total of 3 hours from IM injection to final blood draw, with GH levels being measured at 0, 90, 120, 150 and 180 minutes. Any GH response above 3 ug/L is considered to be an indicative of pituitary sufficiency and NOT consistent with a diagnosis of adult onset growth hormone deficiency.

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