Urinary Growth Hormone
Clinical Value and Applications
by Brett Jacques, ND

Background
Growth hormone (GH) is arguably the most important anti-aging hormone. It consists of approximately 191 amino acids with molecular masses between 20-22,000 Daltons (20-22kDa). There are several (some researchers claim 7) principal variants of GH, 22kDa-GH, 20kDa-GH, a glycosylated form (hGH-V), dimers and biologically active peptides derived from 22kDa-GH. The release of growth hormone is controlled by growth hormone releasing hormone (GHRH) and growth hormone releasing peptides such as Ghrelin secreted by the stomach. GH is released in pulsatile fashion with the greatest output occurring between 12 pm and 4 am. Other stimuli for GH release include intense physical exercise, fasting and hormones such as testosterone. Additionally, stimulation of neurotransmitters receptors by neurotransmitters or compounds that bind to them can also stimulate GH release. Somatostatin inhibits the action of GHRH and cortistatin and other peptides homologous to somatostatin inhibit the binding of growth hormone releasing peptides. GH exerts a negative feedback on the hypothalamus and pituitary to also regulate growth hormone release. Growth hormone, like all other hormones, declines with age at a rate of about 14% per decade after age 20. This results in an 80 year old man having about 5% of the amount of GH that he did at age 20.

Growth hormone binding protein (GHBP) is thought to regulate plasma growth hormone, however, some researchers dispute this. There are 2 types of GHBPs, a high affinity and a low affinity. Little is known about the low affinity binding protein and its biological significance. The high affinity GHBP appears to enhance GH activity by prolonging half-life and increasing growth hormone receptor sensitivity. GHBP levels have been found to correlate with growth hormone receptor activity especially in the liver—probably because GHBP is a proteolytically cleaved portion of the growth hormone receptor. Growth hormone receptors (GHR) most likely exist in all tissues. When GH binds to GHR, it induces a dimerization that appears to be necessary for biological action. After binding to the receptor, GH induces signal transduction by many pathways, allowing expression of GH action.

Growth hormone almost certainly exerts the majority of its action via insulin-like growth factors (IGF-1, 2, etc.). GH stimulates the production of IGFs and also the production of insulin-like growth factor binding proteins (IGFBPs). Many hormones other than GH can stimulate IGFs production such as thyroxin and prolactin. IGFs production increases in the presence of insulin despite the absence or low levels of GH. GH and IGFs have many similar and different effects. For instance, GH is thought to induce cellular differentiation where IGFs are believed to promote cellular multiplication. IGFs are also called somatomedins and the primary one, IGF-1 (Somatomedin C), circulates as a ternary complex consisting of IGF-1, IGFBP3 and an acid labile subunit (ALS). ALS prolongs the half-life of the IGF-1/IGFBP complex and IGFBP3 prolongs the half-life of IGF-1. This invariably improves the biological action of IGF-1. IGF-1 is part of the negative feedback system with GH by influencing the release of GH through its effect on the hypothalamus and pituitary. All IGF levels decline with age and this decline usually corresponds to the decline in GH levels.

Biological Effects of Growth Hormone and IGF-1
Research has not adequately distinguished the different biological actions of GH and IGF-1. This extensive list of physiological actions includes: increase in protein synthesis, DNA synthesis, neurite outgrowth, myelin synthesis, production of sex steroids, testosterone release and keratinocyte formation. GH was shown to exert insulin-like effects (now known to be caused by IGF-1 binding to insulin receptors) and anti-insulin effects (long term administration of GH led to decreased glucose tolerance). Some distinctions between GH and IGF-1 that recent research has shown are that GH does not stimulate muscle growth and IGF-1 does. GH can stimulate bone growth at the epiphysial plate whereas IGF-1 stimulates type 1 collagen formation, and GH increases water, sodium, potassium and phosphorus retention but IGF-1 does not seem to influence water or mineral retention except possibly calcium.

GH increases cellular differentiation and IGF-1 induces cellular multiplication but there is evidence that IGF-1 can induce chondrocyte differentiation. IGF-1 also inhibits apoptosis of certain cell lines especially hematopoietic and neuronal precursor cells. There are other proposed biological effects of GH/IGF-1 and some of them were revealed when studying GH/IGF-1 related diseases. More were discovered after changes were noted from supplementation with GH and IGF-1.

Lifestyle Factors and Growth Hormone
Many lifestyle factors can exert significant influence on the production and release of GH and IGF-1. The
critical lifestyle factors are stress, sleep, diet, exercise and body fat percentage. Prolonged stress has a negative impact on GH output. The rise in cortisol associated with prolonged stress inhibits growth hormone release. It can also diminish testosterone levels and suppress luteinizing hormone (LH). The loss of normal gonadotropin stimulation and testosterone further reduces the reduction in GH release. It is interesting to note that acute stress can initially raise GH levels but if prolonged, it leads to a decline in release. Urinary cortisol and 17-hydroxycorticoids can easily be measured in the same sample as growth hormone to evaluate the impact of hormonal stress.

Endogenous GH is usually released during the first 30-90 minutes of sleep, the slow wave portion of sleep. Decreased sleep, especially slow wave sleep, causes an increase in cortisol and a decrease in GH and testosterone. It also alters insulin sensitivity. Alteration in sleep also disturbs melatonin rhythm and this disruption reduces GH release. Research at AAL with urinary GH measurement has been consistent with these findings demonstrating low levels in chronic and acute insomnia in otherwise healthy individuals.

The effect of diet on GH production and release is somewhat controversial. Higher protein levels correlate with higher growth hormone levels but in high protein food there is an abundance of fat. High fat intake stimulates somatostatin release. Carbohydrates on the other hand stimulate insulin release and insulin antagonizes GH and furthermore, high blood glucose levels inhibit GH release. Short term fasting can increase GH but decrease IGF-1 levels. It appears that GH can be either anabolic or catabolic. In the presence of sufficient calories and protein, GH is anabolic leading to the production of IGF-1 and IGFBP3. In the absence of adequate calories especially protein, GH is catabolic where it induces lipolysis and spares blood glucose. Lastly, research has shown that alcohol intake especially at night suppressed GH and testosterone release and elevated cortisol levels. Urinary GH measurement has been shown to be sensitive to dietary manipulations. The relationship between exercise and GH is also controversial. Anaerobic exercise such as weight training stimulates the production and release of growth hormone to a much greater degree than aerobic exercise. The intensity of exercise correlates directly with the release of GH, the higher the intensity, the greater the output of GH. However, when beginning an exercise program either for the first time or after a long layoff, any exercise type will induce GH release. As you become more fit less GH is released per exercise bout. The volume of training is important because the longer you train per exercise session the lower the GH output and the higher the cortisol release. Cortisol inhibits GH release. Exercising too frequently may also hinder GH release. In our research with urinary GH, we have found that intense anaerobic training dramatically increases GH release.

Obese people generally have normal to high IGF-1 levels and low GH. They also appear to have altered GHR activity and are less responsive to GH therapy until there is body fat reduction. Research has demonstrated that GH therapy works better in obese subjects undergoing calorie restriction. When weight training was included with GH therapy with or without calorie restriction, the response to treatment was significantly better. Invariably, a 100% of our test subjects who were obese, had extremely low urine GH.

Growth Hormone and Cancer

Due to the fact that GH stimulates growth, there is concern that GH may cause cancer or at least increase the risk of neoplasms. In diseased states where there are prolonged elevations of GH and or IGF-1 such as acromegaly, one would expect higher levels of cancers but in fact the reverse is true. There is also a statistical association between high levels of IGF-1 and breast or prostate cancer. In light of facts that IGF-1 stimulates cellular reproduction and inhibits apoptosis of certain cell lines, then this would seem to be a logical correlation. Again the research is not conclusive and as Ron Rothenberg, MD has stated in his 2000 presentation at the American Academy of Aging’s 8th International Conference on Aging, the GH/IGF-1 and prostate cancer connection may be guilt by association. It must be remembered that GHBP and IGFBP are regulators of GH and IGF-1 and that these 2 binding proteins induce tumor suppressor protein p53. Therefore, it is important to have normal levels of the binding proteins as part of the normal checks and balances of the body. However, there exists a possibility that GH through IGF-1 may increase the risk of cancer if the person has a familial history, poor diet and lifestyle, low binding protein levels and the GH replacement therapy is supraphysiological.

GH/IGF-1 and Other Hormones

The relationship of all hormones to each other is critical to understand in order to achieve the best possible clinical outcomes. Certainly, GH interacts with many hormones and these relationships have significant physiological effects. Many of these are not known but through supplementation of a hormone and observing its effect on GH (or vice versa) helps to establish clues to hormonal interrelationships.

Acute excess dosing of cortisol will initially raise GH but if prolonged, it will suppress GH output. Estrogens may stimulate GH release but it is well known that oral estrogens decrease
Urinary Growth Hormone

IGF-1 levels. This decrease is overcome by concomitant supplementation with progesterone. Interestingly, IGF-1 has been shown to activate the estrogen receptor. Insulin antagonizes GH actions yet supports the production of IGF-1 or possibly decreases IGFBPs. Melatonin increases GH production, as does testosterone. Thyroid hormones, especially T3, increases GH release and increases GHR and IGF-1 receptor activity. Excess levels of thyroid depress GH release. These are the most common interactions of GH with other hormones. Understanding these relationships necessitates using a diagnostic method that enables the physician to evaluate and track as many hormones as possible such as a comprehensive 24-hour urine hormone profile featuring growth hormone.

Growth Hormone Assays
The challenge for the clinician has always been the diagnosis of adult growth hormone deficiency. Random serum samples reveal nothing due to the pulsatile secretion and relatively short half-life of GH. The gold standard is the insulin tolerance test (ITT). However, this provocative test is contraindicated in patients with cardiovascular disease, seizure disorders and diabetes. An experienced endocrine unit in a hospital best performs this procedure. Other provocative tests are also employed but they are less effective in obese patients, have unpleasant side effects and fail to account for the negative feedback caused by IGF-1. Furthermore, provocation tests do not predict whether the patient will respond favorably to GH therapy. Another hospital-based procedure is frequent serum samplings. This and the previous procedure are totally impractical for the practicing clinician.

The measurement of biomarkers of GH action such insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein 3 (IGFBP3) are relied on for the diagnosis of adult GH deficiency. The measurement of IGFs and in particular IGF-1 was at one time the best method for the determination of growth hormone status. We now know that there is a better way, urinary growth hormone. An example of why IGF-1 does not necessarily reflect GH status can be found in obese people. Obese people generally have normal to high levels of IGF-1 and very low GH. Furthermore, thyroid disease, diabetes, liver pathology and malnutrition alter IGF production making IGF-1 less reliable. Because a large portion of the known GH action is mediated through IGF-1, measuring IGF-1 and its primary regulator IGFBP3 are very valuable and should be part of every physician’s battery of baseline and follow up tests. Whether or not the inclusion of the acid labile subunit in this measurement is still open to discussion. The research is unclear whether there is value and most clinicians are also unsure of its value.

Based on these clinical challenges and multiple requests from practicing physicians, AAL Reference Laboratories developed a method for measuring growth hormone in a 24-hour urine sample. The measurement of urinary growth hormone levels has been in use for research purposes for about 20 years. Reliable methods of 24-hour urinary GH measurements have been strongly correlated with serial serum measurements and provocation tests. This was not found to be true with single overnight urine samples. Many researchers feel that urinary growth hormone reflects the central release of the hormone and also the changes in plasma GH during the 24-hour period of collection. AAL Reference Laboratories offers a

Signs & Symptoms of Growth Hormone/IGF-1 Deficiency and Excess
The signs and symptoms of adult growth hormone deficiency include:

**Signs**
- Negative nitrogen balance
- Decreased de Novo protein synthesis
- Decreased lean body mass
- Decreased bone mass
- Negative calcium balance
- Decreased joint cartilage
- Decline in glucose tolerance
- Increased insulin resistance
- Decreased cardiac endurance
- Decreased cardiac ejection fraction
- Decreased B, T and NK cell function
- Decreased rate of wound healing
- Decrease in sleep and sleep quality
- Sagging cheeks

**Symptoms**
- Fatigue worse after midnight
- Loss of recovery capacity
- Loss of self confidence
- Anxiety
- Excessive emotionality
- Sharp verbal retorts
- Increased social isolation
- "Grumpy old man" syndrome
- Depression

The signs and symptoms of adult growth hormone excess are:

**Signs**
- Edema of hands and feet
- Hypertrophy of forehead, nose, chin
- Hypertension
- Hyperglycemia
- Hypercalcemia
- Hypertriglyceridemia
- Hyperphosphatemia
- Arthralgias

**Symptoms**
- Parathesias nose fingers and feet
- Carpal tunnel syndrome
- Behavioral disturbances
- Nausea and vomiting
- Headaches
- Visual disturbances
- Fatigue
unique, reliable and reproducible method of measuring growth hormone in a 24-hour urine sample. We had the opportunity to measure the 24-hour urinary growth hormone levels of a person with a GH-secreting pituitary tumor and found the results were in excess of 3 times the upper limit of our range. Conditions that can elevate or reduce urinary GH levels are listed below.

**Therapeutics**

Therapeutic approaches in treating GH deficiency have encompassed 3 basic premises: increase endogenous production, GH secretagogues and GH administration. There are 2 primary methods of increasing endogenous production of GH, dietary changes and exercise. Dietary manipulations attempt to remove negative influences on GH release such as hyperinsulinemia from excess carbohydrate consumption and to maximize protein consumption and utilization thereby increasing the building blocks for GH production. The typical diet is one of high protein, high fat and low carbohydrate though several variants of the diet exist. For the most part, these have met with moderate success. Exercise definitely influences GH release especially brief, highly intense exercise bouts. However, the research is mixed when studying aging adults and understandably there is great controversy regarding study design when trying to determine exercise effects on GH release in older adults.

It is speculated that the reason that exercise therapy in aging adults does not increase GH release is due to decreased somatostatin tone. The research in support of this does not control for enough variables to conclusively support this idea. Nevertheless, diet and exercise can contribute to increased GH release.

Secretagogues are compounds that increase the release of GH and include drugs that induce slow wave sleep, neurotransmitter receptor analogs, growth hormone releasing hormone analogs, amino acids, peptidomimetic compounds and synthetic growth hormone releasing peptides. The majority of these compounds do not work. Amino acid therapy does not consistently raise GH levels in adults older than 40 years of age. There are side effects when using the synthetic peptides and hypnotics (that induce slow wave sleep). The peptidomimetic compounds and synthetic growth hormone releasing peptides do work but they are unavailable for the most part. There is a topical growth hormone releasing analog currently available that can raise urinary and plasma GH levels but it does not seem to increase IGF-1 levels. More research needs to be done on why this occurs and whether or not this is a problem or a benefit.

The use of GH has spanned oral preparations, GH recovered from cadavers and recombinant GH. Oral preparations simply do not work because their molecular mass prevents sublingual absorption and they are easily broken down in the GI tract. Homeopathic GH and IGF-1 preparations do not have any valid research supporting manufacturer’s claims. Recycled GH from cadavers has been associated with significant clinical problems such as Creutzfeldt-Jakob disease.

Recombinant GH appears to be the best choice for treating GH deficiency. Dosing regimes, timing and injection sites are subjects of frequent debate. GH injection can induce lipolysis at the site of injection, which could influence site choice. Abdominal injections take longer to reach peak levels than injecting into the thigh. Some clinicians feel that giving GH in the morning eliminates suppression of endogenous release at night. One study has shown that a twice-daily injection regime has fewer side effects that single nightly dosing. It has also been recommended that GH not be given directly after exercise so that there is no interference with exercise-induced GH release. Dr. Thierry Hertoghe believes that balancing all other hormones prior to GH therapy affords the practitioner the luxury of using smaller doses of GH. The side effects from recombinant GH therapy are minimal if physiological dosages are used. Some of the signs and symptoms of excess therapy include edema, arthralgias, parasthesias and glucose intolerance. These can be easily mitigated by decreasing GH dose and by implementing complementary therapies to address symptoms. The absolute contraindications of GH therapy are active malignancy, intracranial hypertension and proliferative retinopathy.

A combination of exogenous GH and endogenous enhancement methods provides the optimum GH treatment strategy. Tracking GH therapy is probably best achieved by measuring urine growth hormone every 2 months coupled with serum

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<td>Aging adults</td>
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<td>Hypopituitarism</td>
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<td>Prader-Willi Syndrome</td>
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<td>Malnutrition</td>
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<td>Cushing’s Syndrome</td>
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<td>Chronic Disease</td>
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<th>High Urinary Growth Hormone</th>
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<tbody>
<tr>
<td>Children and Adolescents</td>
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<tr>
<td>Young Adults</td>
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<tr>
<td>Gigantism</td>
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<td>Acromegaly</td>
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<td>Pituitary Tumors</td>
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<td>Laron-type Dwarfism (low IGF-1)</td>
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Urinary Growth Hormone

IGF-1 and IGFBP3 levels. We have found that urinary GH levels rise in correspondence to the amount of injected GH. A crucial point to keep in mind is that GH has a short half-life therefore; collect the 24-hour urine on the day of the injection. We have found that measuring urinary GH after 48 hours of the last injection results in levels similar to baseline.

There are several options available to treat GH excess. The 2 drug classes used to treat GH excess are somatostatin analogs or high doses of dopamine agonists. Other methods employed are pituitary radiotherapy and surgery.

Conclusion

Our research has shown that lifestyle factors play a significant role in growth hormone output as measured in the urine. We have found that intense exercise bouts increase output, chronic or acute (3 days duration) insomnia decreases output, and a diet of simple carbohydrates for 72 hours significantly reduces output and all of the obese people that we have measured have low GH output. Furthermore, urine GH levels correspond to the amount of injected GH, making urinary GH an excellent method to track and tailor therapy.

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AAL Reference Laboratories, Inc offers comprehensive urine hormone panels featuring growth hormone. These panels represent a level of sophistication unsurpassed by any other method. The information obtained is truly state of the art. This is 21st century laboratory medicine for healthcare practitioners looking to provide cost efficient, comprehensive endocrine analysis.

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