Introduction

The parenteral administration of human growth hormone (HGH) has become an intervention of great significance in anti-aging medicine. There is now frenetic interest in using reliable GH secretagogues in the form of peptides, such as GHRP-2. Although age-related sarcopenia is related to HGH deficiency, the use of HGH for the building of “lean body mass” has been questioned, especially in young adults. Growth hormone administration has precipitated ethical concerns and controversies concerning its use in medical practice. There are many Food and Drug Administration (FDA)-approved brands of HGH, and their use is governed by federal law that has been in place for approximately two decades. Criminal use of HGH involves anyone who “knowingly distributes or possesses with the intent to distribute human growth hormone for any use in humans other than the treatment of a disease or other recognized medical condition where such use has been authorized by the Secretary of Health and Human Services (i.e., FDA) and pursuant to the order of a physician” (21 USC s33 [e]).

The consequences of violating these laws that govern HGH use may involve imprisonment for a period of up to five years (or longer). State licensing authorities have taken disciplinary action (with irrevocable license suspension) against physicians who have used HGH in a “non-approved” manner. In these instances, the prescribing of HGH has most often been for cosmetic or “body building” initiatives and, in some cases, “anti-aging practices.” Adverse consequences of deviation from laws that govern the use of HGH have gone beyond federal or state criminal prosecution to allegations of malpractice with attendant civil liability. While some physicians have argued that their use of HGH is quite legitimate, “anti-aging therapy” has not been considered a valid use of HGH, according to US law.

While arguments prevail about legitimate indications for the use of HGH injections, credible bodies of opinion reject the common practice of testing for insulin growth factor (IGF-1) levels as an adequate basis for the diagnosis of growth hormone deficiencies. The diagnostic criteria accepted for the presence of growth hormone deficiency involve the demonstration of a subnormal response to GH stimulation tests (peak GH < 5ng/L) or the clear identification of pituitary insufficiency with notable GH deficiency, as a consequence of pituitary or central nervous system disease or trauma or pituitary ablation by surgery or radiation therapy. An unequivocal and acceptable indication for GH treatment is established GH deficiency in children with dwarfism or retarded growth. The diagnostic criteria to be applied to the use of GH are not stated with clarity in the federal or state laws, and a difference of opinion exists in clinical practice.

In brief, there are many disincentives to use GH injections in any clinical context, other than those that have been defined as clearly acceptable or perceived by regulators as part of “usual and customary medical care.” The putative side effect profile of GH administration and an incomplete understanding of the safety and effectiveness of prolonged administration of GH have pushed many practitioners of anti-aging medicine to seek alternative options for the regulation of HGH. It is against this background that practitioners of Integrative Medicine are evaluating the use of GH secretagogue technology, as a potentially viable alternative to HGH injection therapies.

Growth Hormone Release

Many stimuli promote GH secretion, but most act by neural mechanisms. Several centers in the brain control growth hormone release, including the limbic system, the arcuate nucleus, and the ventromedial nucleus (Table 1). These controls recruit different neurotransmitters. These central nervous system (CNS) controls result in the elaboration of
growth hormone releasing hormones (GHRH), which act on the anterior pituitary to release GH. Somatostatin can inhibit GH release.

Control of GH secretion is quite complex and still not completely understood. Factors such as stress, exercise, and protein depletion release GH, whereas circumstances such as obesity, corticosteroid administration, progesterone, and elevated levels of free fatty acids inhibit GH release (Table 1). Glucose plays a special role in controlling GH secretion. If GHRH peptides are administered with glucose, the GH release is attenuated as a consequence of high blood sugar promoting somatostatin secretion.

There is a family of peptides that cause growth hormone release (GHRP). These peptides are chemically related to met-enkephalin. Chemical modifications to several GHRP molecules have resulted in increased GH-releasing potency. The most effective GHRP has been identified as GHRP-2. Of great interest is the ability to use GHRP-2 in a non-invasive manner by oral or intranasal routes, perhaps providing a way of increasing GH levels by obviating the need for HGH injections in some circumstances.

Aging in humans is associated invariably with decreases in activity of the functional axis involving GH and IGF-1. Overall, there is a tendency for GH levels to fall with age, and patterns of GH secretion show reduced frequency and amount of GH secretion. There is approximately a 10-15% fall in growth hormone levels or actions in each decade of advancing age (Figure 1). This results in a circumstance where an individual in the seventh or eighth decade of life may have approximately only five percent of the HGH that was present during youth. Such reductions in GH secretion are notable in the presence of insulin resistance (Metabolic Syndrome X) and obesity.

The decline in the actions of growth hormone that is noted with age has been identified as contributing to reduced musculoskeletal mass, obesity, and reductions in cognitive function in the elderly. The amino acid L-arginine - and other amino acids used in combination - promote GHRH-stimulated GH release, and amino acids have been used as secretagogues in several dietary supplements, but their effects may not be as potent or predictable as the use of a GHRP, such as GHRP-2. Exercise can have major effects on blood GH levels, and anaerobic exercise promotes GH secretion. Factors that promote growth hormone release or its inhibition are summarized in Table 1, by reference to principle anatomic regions that are involved. There are major gender differences in the controls of GH release. Women tend to have higher concentrations of GH compared with age-matched men. It would appear that estrogen plays a role in increasing the sensitivity of GH-releasing mechanisms to the many stimuli that promote growth hormone secretion. These circumstances lead to the strong inference that women in the post-menopausal transition of life may have compromise of GH secretion, secondary to lack of estrogen. Anti-aging physicians are increasingly applying GH with sex hormone replacement therapy.

Investigation of the GH/IGF-1 Axis

Conventional medicine does not recognize the need for routine screening for HGH deficiency in adults because of the fixed notion that HGH therapy has discreet and finite indications. Integrative Medicine often takes a different perspective with an increasing belief that growth hormone has great therapeutic potential as an anti-aging or "metabolic-enhancing" strategy. This notion is supported by landmark studies that imply that GH replacement therapy in adults with known GH deficiency results in beneficial effects on abnormalities in body composition and physical performance that are often encountered with increasing age.

Some studies have implied that HGH replacement beyond the boundaries of conventional application has the disadvantage of potential adverse outcome that is not balanced by therapeutic benefit, but arguments prevail. While it is accepted that normal blood levels of IGF-1 are reasonable indicators of adequate activity of HGH, low levels of IGF-1 are not reliable predictors of HGH deficiency in humans. It is important to reiterate that the...
GH Secretagogues

"gold standard" of diagnosis for GH deficiency involves use of one or more provocation tests with measurements of growth hormone responses. In the practice of anti-aging medicine, some physicians may fail to recognize the effect that hypothyroidism or suppression of adrenal function may have on growth hormone responses. The same reasoning applies often to sex hormone deficiencies in the "integrative" medical mode of care.

Two provocative types or categories of testing are applied most often. One involves the induction of hypoglycemia with insulin followed by subsequent measurements of GH release. The other categories of testing may utilize GH-releasing peptides (GHRP-2), infusions of arginine, administration of L-Dopa, sleep, vigorous exercise, or clonidine administration. While these latter types of provocative testing for growth hormone release are safer than insulin tolerance tests, the results of such testing may be less accurate for the diagnosis of HGH insufficiency.

Unfortunately, no single test that measures GH release to provocative stimulus is completely accurate, and endocrinologists may apply more than one type of provocative testing before they accept a "cast-iron diagnosis" of HGH deficiency. The interpretation of these provocative types of testing may vary among physicians.

The diagnostic dilemmas that are present in states of variable GH deficiency are worthy of significant discussion. These circumstances reinforce the complexity of the interplay of factors that control HGH secretion. It appears that intermittent secretion of somatostatin exerts major inhibitory effects on the output of HGH, and even the diagnostic accuracy of provocative testing with GHRH peptides (GHRP-2) is perceived to be inconsistent in its results. It is important to note that provocative testing cannot uncover minor degrees of dysregulation of GH release. This has led to a proposal for even more detailed assessments such as the use of 24-hour integrated GH secretory responses that require serial blood sampling over a 24-hour period. Arguably, there are no attorneys or practice regulators that can interpret GH provocative testing results better than an experienced physician, and all laboratory tests must be interpreted in the clinical context of the presentation of the patient.

Actions of Growth Hormone

The major end-product of GH administration is the stimulation of the production of IGF-1 or IGF-2, mainly in the liver. The GH/IGF-1 axis is responsible for stimulation of body growth, and it exerts major effects on body metabolism. Overall, the physiological effects of GH are biphasic. The acute administration of GH exerts insulin-like effects where there are notable increases in glucose uptake in muscle and adipose tissue, with concomitant stimulation of amino acid uptake and protein synthesis in muscles and the liver. A major acute response to GH injections is lipolysis, but a number of hours after the administration of HGH, these metabolic effects cease and more complex biochemical events occur in the body.

In these secondary phases of response to GH, GH activity becomes antagonistic to the actions of insulin, with inhibition of glucose uptake, resulting in hyperglycemia and increased lipolysis. This results in an elevation of circulating free fatty acids. Fasting induces a rise in blood levels of HGH, and this adaptation is a response to acute starvation. In this regard, HGH works in concert with other hormones that cause a rise in blood glucose (epinephrine, glucagon, and cortisol) to support the availability of CNS function (an adaptation response in the harmony of life). In addition, GH tends to diminish fat stores to provide alternative energy sources for the body, especially during periods of fasting.

The actions of HGH are complex. Some studies imply that HGH has effects independent of IGF-1 and IGF-2 production (old nomenclature in the US: somatomedin C, etc. or growth stimulating end-products). Some studies imply that adipocytes and chondrocytes may show increased responsiveness to IGF after

Figure 1: Growth Hormone Declines with Age.

Presented in a schematic that was provided in marketing information to the National Products Association by Biocentrics, Brentwood, Tennessee, and other companies that manufacture amino acid combinations that are used as "growth hormone boosters." (Source of data not disclosed.)

Growth Hormone Decline

![Graph showing the decline of growth hormone with age.](image-url)
initial exposure to GH, and certain metabolic responses in renal tubular epithelium occur as a consequence of GH stimulation in a manner that is not observed in the presence of IGF-1 or IGF-2 in high concentrations.\textsuperscript{30,33} While several theoretical “risks” are proposed with prolonged HGH administration, the proponents of GH replacement therapy describe few substantial side effects. The adverse effects of chronic GH administration are most often related to fluid retention, which occurs in an intermittent, dose-dependent circumstance.\textsuperscript{28,38} However, the antagonistic actions of GH on insulin actions and the potential promotion of the growth of cancer or cellular proliferation (a function of growth factors) present serious, residual concerns. It would appear that the chronic administration of high dosages of GH in some individuals has resulted in a clinical syndrome that is substantially similar to acromegaly. Such observations have been reported, often in an anecdotal manner, in the extreme aerobic enthusiast or “elite athlete” who may develop a form of “dependence” on their perceived need for body contouring to achieve their “aesthetic” ambitions. Mixed abuse of anabolic steroids with GH in some body-building enthusiasts clouds the clinical picture (“Droid Boys and Girls”).

While growth hormone is diabetagenic overall, it is worrisome that insulin-like growth factors are potent mitogens and proliferative factors for several cell types, including breast, colon, and prostate epithelial cells. Anti-aging physicians have tended to reject these concerns, but well-constructed clinical trials show a relationship between IGF-1 levels and the promotion of breast or prostate cancer. Increased values of IGF-1 have been associated with an increased risk of prostate cancer (and perhaps benign prostatic hyperplasia) in two studies.\textsuperscript{39,40} The relationship between IGF-1 and breast cancer is somewhat conflicting, but in vitro studies show that IGF-1 is a potent stimulator of cell division in breast cancer cell lines. In a Scandinavian study of premenopausal women with elevated levels of IGF-1, a significant correlation was observed between increased IGF-1 levels and breast cancer.\textsuperscript{41} The potential association of chronic GH administration with persistent high levels of IGF-1 has led to proposals that frequent monitoring of free testosterone levels, blood PSA levels, estrogen levels, and mammography is required variability to assess risks of cancer development in men or women who are receiving GH therapies.

**Adult GH Deficiency Syndromes**

There have been attempts to define symptoms and signs that permit the recognition of “adult HGH deficiency,” and it has been argued strongly that there is approval to treat this syndrome in general medical practice, provided that this syndrome is documented with provocative testing of GH secretion (perhaps using two different provocative testing methods?). Other bona-fide recommendations for GH therapy include Turner’s Syndrome and body wasting due to AIDS. In brief, symptoms and signs that are attributable to adult HGH deficiency include prominent wrinkling of the skin, sagging cheeks and neck tissues, hair loss with thinning of lips and facial bones, pseudogynecomastia, pot belly, sarcopenia, fatigue, and behavioral change. Unfortunately, this constellation of symptoms and signs is quite non-specific, but coexisting laboratory abnormalities may include reduced IGF levels, abnormal blood cholesterol, impaired thyroid function, high fibrinogen, and raised blood levels of osteocalcin.

Descriptions of adult GH deficiency syndrome seem to bear substantial resemblance to symptoms and signs that are encountered in Metabolic Syndrome X,\textsuperscript{42} where a major conundrum exists. In Syndrome X, there is a relationship between hyperinsulinemia and cancer that may be best explained by the growth-promoting effects of IGF-1.\textsuperscript{42} Therefore, I recommend strongly that individuals with Metabolic Syndrome X be identified and treated for their specific constellation of problems, before clinical plans move towards GH “replacement therapy.” This circumstance is an under-explored area of clinical practice, but the clinician must understand that the prevalence of Metabolic Syndrome X is much higher than that of adult GH deficiency. It is estimated that up to 70 million Americans have the Metabolic Syndrome X.\textsuperscript{4} The diatheses of the Metabolic Syndrome X and adult GH deficiency may often co-exist, and they are both strongly associated with the development of atherosclerosis and increased cardiovascular disability or mortality and other causes of premature death and disability.\textsuperscript{34,39,42}

There are many compelling studies that imply beneficial effects of GH treatments in aging individuals.\textsuperscript{43} Demonstrated GH deficiency that remains untreated in adults is clearly associated with abnormal body composition, decreased extracellular water and bone mineral content, and enhanced cardiovascular disease and mortality.\textsuperscript{2} This body of medical literature has prompted several popular, well-written accounts of the use of growth hormone in anti-aging medicine.\textsuperscript{34–38} In brief, the clinical benefits associated with increasing HGH levels in the presence of HGH deficiency in adults are summarized in Table 2, which is adapted from the popular work of R. Klatz, R. Goldman, and C. Kahn.\textsuperscript{34,35}

**Is HGH Parenteral Therapy an Acceptable Anti Aging Strategy?**

In a review, published in the *Annals of Internal Medicine* in 2007,\textsuperscript{29} the safety and efficacy of GH therapy in healthy individuals was examined. This review concluded that HGH injections may not be cost-effective or beneficial in routine anti-aging clinical practice. The conclusions were based largely upon meta-analysis studies, but such statistical manipulations of
compiled data are notoriously difficult in their ability to reach portable conclusions. The selection of studies that are "thrown into the statistical mix" in a meta-analysis study exerts a major influence on the reported outcomes.

In the aforementioned negative systematic review of GH use, it appears that a large proportion of the selected studies involved the investigation of patients who had received either large dosages of HGH or poorly described dosage schedules. Dosages of HGH used in the treatment of dwarfism or Turner's Syndrome tend to be large because the desired clinical outcome is significant growth and enhanced stature from bone elongation. These dosage regimens of HGH are much higher than those used in routine anti-aging practice, where many physicians use more modest dosages of HGH of the order of 1-2.5 IU. In fact, dose-response information on the treatment of adult GH deficiency is not readily available, and it has not been fully researched.

General consensus would support initial dosage in correction of adult GH deficiency to be up to 0.9 IU per day with gradual increases in dosage at approximate monthly intervals to achieve the required outcome, which must be closely monitored. It appears that dose requirements for HGH decline with age, and maintenance dosage of GH injections, in this context, require approximately 3 IU per day, or less. Most physicians agree that measurements of blood IGF-1 are useful as guidance for the titration of the administered dosage of HGH, but careful clinical monitoring is of great importance. The adverse clinical outcomes of HGH administration, noted in the systematic review, included edema, joint discomfort, and abnormal glucose tolerance tests, but there is some suggestion that such side effects are not encountered with any frequency at lower dosages of GH that are currently used in anti-aging medicine.

There have been some allegations that negative reporting about the use of anti-aging interventions with HGH is fueled by individuals with vested interests. Clearly, our current level of scientific knowledge still casts some degree of doubt on the routine acceptance of HGH therapy as a cost-effective anti-aging strategy, with an acceptable risk/benefit. These debates continue.

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Table 2: Many Actions of GH Replacement Therapy Have Been Described in Popular Literature.
These data are based upon positive interpretations of peer-reviewed medical literature. Data has been presented in many formats, as found in references 34-37.

Potential Positive Actions Associated with Increases in HGH Levels in States of GH Deficiency

- Enhanced muscle mass (>8% after six months)
- Decreased body fat (>14% after six months)
- Increased energy level
- Enhanced sexual performance
- Reversal of age-related shrinkage of certain organs (heart, liver, spleen, kidneys, thymus, etc.)
- Greater cardiac output
- Enhanced immune function
- Improvement in kidney function
- Enhanced exercise performance
- Blood pressure reduction
- Improvement in blood cholesterol (increased HDL, reduced LDL)
- Improved bone strength
- Increased rapidity of wound healing
- Improvement in skin texture and thickness
- Regrowth in thinning hair or hair loss
- Wrinkle reduction
- Cellulite reduction
- Improved vision
- Elevation of mood
- Improved cognitive function and memory
- Enhanced sleep

Reviewing HGH Secretagogues

Several nutritional formulae have been proposed as dietary supplements to stimulate the release of HGH and the consequential production of IGF-1. Several of these formulae have been proposed as effective, cost-advantageous ways of stimulating GH release. They have been proposed as an alternative to parenteral GH administration, which may cost up to 50,000 USD per year.34,37 These formulae most often use amino acids in variable combinations to promote GH release. Selected amino acids or chemical secretagogues include L-arginine, L-lysine, L-glutamine, L-ornithine, L-dopa, GABA, glycine, etc. There is some suggestion that combinations of amino acids are more effective than the use of single amino acids alone, but there is major inter- and intra-individual variation in GH secretagogue responses.34,35,37

Dosages of the order of 15-20 grams per day or more of mixed amino acid formulations, taken over periods of several weeks, have been shown to increase IGF-1 concentrations in small patient samples, in open-label clinical studies. It has been suggested that effervescent powdered formulations of amino acids are more effective than other formulations,34,38 but the evidence for these and other statements of advantage remain unclear. Marketing organizations have suggested that putative HGH-releasing formulae should be given to any individual with an IGF-1 <350ng/ml, but this would include the bulk of the population over the age of 40 years.51 While research on dietary supplement formulae of amino acids that may release GH is sparse, a significant body of evidence exists that amino acids can effectively release growth hormone.52,55

The most recent innovations in the use of dietary supplements to stimulate GH secretion involve the use of GHRP, most notably GHRP-2. A deficiency of GHRH peptides is one of several factors that have been implicated in the reduction of GH secretion that has been documented in elderly individuals.56 Other factors...
that variably operate include a reduction in the functional capacity of GH-secreting cells in the pituitary, including a deficiency of the hormone ghrelin and increases in somatostatin secretion that have an inhibitory effect on GH release.

A large body of evidence has accrued that GHRP-2 is a highly effective way of increasing GH levels in many individuals. Peptides that release GH belong to a family of synthetic chemicals that have a polypeptide sequence of five to seven amino acids. Such peptides were originally synthesized as copies of metenkephalin peptides. A number of laboratory and clinical studies imply that these peptides act on both the pituitary and hypothalamus, but GHRP-2 binds to pituitary receptors that are quite separate from opiate receptors and GHRH-receptors.

It is important to note that stimulation of GH release in elderly individuals may result in levels of GH that are encountered in young adults. Furthermore, the administration of GHRP-2 in combination with GHRH or L-arginine can result in substantial increases in GH levels. The hormone ghrelin may play a major role as a GH secretagogue, and increases in blood levels of the orexigenic hormone ghrelin are sometimes noted in individuals with sleep deprivation. This is a contrarian observation, because deep sleep is associated with stimulation of GH secretion. Again, the complexities of GH secretion and the actions of GH appear repeatedly in scientific literature.

It is noted that GHRPs have greater GH-releasing actions than GHRH, and GHRP-2 can be administered by oral or intranasal routes with evidence of GH-releasing actions of a significant magnitude. It is proposed that GHRPs, most notably GHRP-2, are able to be made available as dietary supplements. In order for this position to be tenable, GHRPs should have been available in the food chain prior to 1994 with some precedent of use for a health benefit (to conform to the US Dietary Supplement and Health Education Act of 1994). In fact, GHRPs have been arguably present in the food chain, but GHRP-2 is a synthetic molecule. However, there are several dietary supplements that are synthetic molecules that have gained acceptance as dietary supplements, e.g., ipriflavone, which occurs only in very small quantities in the food chain. Obviously, these circumstances are not completely clear, but manufacturers of GHRP-2 have taken the position that they can sell releasing peptides as dietary supplements, but they have preferred to limit their dispensation through health care givers.

There is no doubt whatsoever that oral GHRP-2 can be expected to be effective in releasing growth hormone in humans, with some degree of variable response. The use of these potent secretagogues has become very popular in recent times, and good clinical outcome has been described among anti-aging physicians in a national forum. A major advantage has been perceived with the use of secretagogues for the promotion of GH release, because there is a reliance on the pituitary to perform its usual and customary function. Some physicians have suggested that this approach is more natural than attempts to titrate growth hormone injections in anti-aging treatment protocols. In other words, the use of GH releasers fit with body homeostatic mechanisms, in comparison with HGH injection therapy. However, long-term outcome of the administration of GH secretagogues remains under-explored, in the same way that the long-term administration of GH injections in adult GH deficiency syndrome or elderly subjects remains a matter of incomplete understanding.

Recommendations for Staged Anti-Aging Strategy

Protagonists of hormone replacement in anti-aging medicine conclude that the optimization of hormonal status in the aging individual requires careful supervision and expert application to achieve optimal outcome. One expert in the field stated, “The first thing we should remember is that we should not be rushing to throw hormones at people. Hormone optimization is the finishing touch.” The author echoes these comments strongly and considers hormone therapy to be “icing on the cake of anti-aging medicine.” In the July of 2008 Townsend Letter, the author provided a review of a bio-integrative approach to anti-aging interventions that focused on the role of holistic care as the first-line option for anti-aging. The author of this article has rejected the notion that there are “true bioidentical hormones,” but he does accept the notion of bio-similarity with its putative enhancement of safety (and perhaps efficacy?). That said, recent information seems to indicate that the timing of the administration of certain hormone supplements in the chronology of altered body composition with age, especially sex hormones, may be quite critical in overall clinical outcome in anti-aging medicine. I must sound the warning that all clinicians who recommend hormone replacements must educate themselves in the legal considerations that govern the use of controlled hormone substances, including GH and sex hormones.

An excellent summary of legalities in hormone use are to be found in the recent presentations of Rick Collins, Esq.

Conclusion

There seems to be a good reason to reappraise how GH deficiency can be approached in clinical practice. If regulations permit the use of releasing peptides or secretagogues, as seems to be the case at this juncture, then arguably this approach represents the first-line option in attempts to increase GH levels in those individuals with documented deficiency of GH. Clearly, a number of issues remain unresolved, but the use of GH in anti-aging medicine has become established on a global basis, despite continuing controversies.
concerning its safety, effectiveness, and widespread availability. It seems quite problematic that the use of GH appears to be legislated in a manner that removes a physician's judgment as to whether or not to apply this therapy as an anti-aging tactic.

Notes

Stephen Holt, MD, is a clinician, researcher, and bestselling author. He is a Knight of Grace of the Holy Order of St. John and the recipient of many honors and awards for medical teaching and research. He is a scientific advisor to Natural Clinician LLC, Little Falls, NJ, a company that sells health care products. Dr. Holt is regarded as a pioneer of Integrative Medicine, and he is the President of the World Organization of Natural Medical Practitioners (www.womnpus.com).


Dear Tenant,

Effective immediately, you may no longer reside in my intestine.

Sincerely,

The Landlord