Adult Growth Hormone Deficiency: A Higher Compliance Delivery System

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ABSTRACT

Growth hormone deficiency (GHD) is a complex endocrine syndrome, which is most commonly known to affect the pediatric population. However, adults also suffer from GHD, and it is often seen as part and parcel of the aging phenomenon. Adult GHD is accompanied by changing body composition with decreased lean muscle mass and increased total body fat, demineralization of bone resulting in osteoporosis, loose skin which translates to wrinkles, and decreased quality of life, which includes decreased energy, decreased libido, poor sleep patterns, generalized malaise, and fatigue. However, research presented in this manuscript shows that monthly human growth hormone injections can promote reversal of some of these changes.

Keywords: Growth Hormone; Growth Hormone Deficiency (GHD); Insulin-Like Growth Factor-1 (IGF-1); Growth Hormone Replacement Therapy; Recombinant Human Growth Hormone

INTRODUCTION

Growth hormone deficiency (GHD) is a complex endocrine syndrome, which is most commonly known to affect the pediatric population. In children, growth failure is often apparent by the end of the first or second year of life. Infants may experience hypoglycemic seizures or prolonged jaundice, and male infants may suffer from micropenis and undescended testes. One in every 4,000 school-age children is estimated to have GHD.

PEDIATRIC GROWTH HORMONE DEFICIENCY

Linear growth velocity may be as slow as 3 cm per year and growth velocity of < 4 to 5 cm per year is common. A significant number of these affected children fail to undergo puberty at the appropriate age unless treated. Children treated properly with human growth hormone (HGH) supplementation are capable of achieving 5-10 cm per year growth. Diagnosis of GHD in children is often straightforward with a reduced linear growth velocity and the maximal growth hormone value of provocation of less than 7 ng/ml. A provocation value in excess of 10 ng/ml excludes the diagnosis of growth GHD. The treatment of GHD with HGH in children has not been linked to any oncogenic potential.

The Kabi International Growth Study (KIGS) is a long-term surveillance study of pediatric patients being treated for GHD since 1987. Adverse effects of HGH supplementation have been followed by mandatory prospective data collection.

The most common tumor associated with the etiology of growth hormone deficiency is craniopharyngioma. In comparing patients who received supplemental growth hormone and patients who did not, the data revealed that the reoccurrence rate is dramatically less in the supplemental group. In fact, KIGS seems to suggest an argument against growth hormone having oncogenic potential of significance. Another recent study conducted at Memorial Sloan-Kettering Cancer Center further concluded that growth hormone therapy does not appear to carry any additional risk of disease reoccurrence or death in survivors of childhood cancer.

ADULT GROWTH HORMONE DEFICIENCY

In contrast, the diagnosis of adult GHD is complex. Adult GHD is part and parcel of the aging phenomenon, and is elegantly described by this chapter's lead author as the "pause theory of aging". In the pauses associated with aging, there are measurable objective parameters that are consistent, valid, and interpretable in every decade of life. However, often by the time the deficits are usually noted, degenerative changes have already taken hold.

Adult GHD is accompanied by changing body composition with decreased lean muscle mass and increased total body fat, demineralization of bone resulting in osteoporosis, loose skin which translates to wrinkles, and decreased quality of life, which includes decreased energy, decreased libido, poor sleep patterns, generalized malaise, and fatigue.

Figure 1. IGF-1 Levels As Individuals Age

Starting value	IGF-1 levels fall from 500-1000ng/ml
At age 30	IGF-1 levels typically drop to 400ng/ml
At age 40	IGF-1 levels typically drop to 300ng/ml
At age 50	IGF-1 levels typically drop to 200ng/ml
At age 60	IGF-1 levels typically drop to 100ng/ml
At age 70	IGF-1 levels typically drop to 50ng/ml
On average, at death (assuming approximately at age of 80)	IGF-1 levels typically drop to 0 (zero) ng/ml

Since aging is a multifactorial neuroendocrine disorder, multiple hormone deficiencies coexist. Each of the hormonal systems has to be evaluated independently with laboratory and clinical biomarkers. Direct measurement of growth hormone level does pose a significant challenge because of its pulsatile nature. Plasma Insulin-like Growth Factor 1 (IGF-1) level concentrations decline with advancing age in healthy adults paralleling the growth hormone decline (Figure 1). After a great deal of debate, a consensus has been reached to use IGF-1 as an indirect marker for growth hormone level.

In spite of the ongoing debates, we as clinicians require practical working solutions. A general consensus is in place that the low IGF-1 value appears diagnostic of GHD [<100ng/ml]; however, the caveat is that the normal IGF-1 level does not exclude the diagnosis of GHD. As clinicians in the real world, we treat the patient not the lab test. There is a subgroup of physicians and third-party payors who insist upon growth hormone stimulation tests such as insulin tolerance test (Clonodine or L-Dopa stimulation test) with peak growth hormone <9ng/ml as the gold

standard. Most of us agree with a consensus standard that an IGF-1 level below 100ng/ml is a clear indication for replacement.

Laboratory values are usually based upon normograms, which indicate sub-therapeutic, therapeutic, and supra-therapeutic. Sub-therapeutic defines deficiency and supra-therapeutic defines toxicity. Toxicity has been suggested to be an increased risk of oncogenic potential in the past. In the PATH Medical population, it has been noted that patients (e.g., pro basketball players) with pituitary tumors can have elevated IGF-1 levels above 900 without supplementation and to date have not demonstrated any increase in the development of adenomas. Major medical textbooks have stated that specific tumors, such as prostate, kidney, and breast may elevate IGF-1 levels. However, when the elevation arises from the pituitary there is no association with an increase in tumors. A large survey of patients with acromegaly revealed no increase in malignant neoplasms. Notable is that growth hormone is fairly similar in composition and structure to insulin and diabetics are known to take insulin for 20-40 years without an increased incidence in adenomas or other tumors.

GROWTH HORMONE REPLACEMENT THERAPY

Our current knowledge base on growth hormone replacement allows us to conclude that human growth hormone is a safe medication for supplementation. This is underscored by the fact it is considered a schedule V drug, which is one step above an over-the-counter agent. It has been put in the same classification as an antibiotic.

One must be aware of the multifactorial nature of aging and its accompanying degenerative changes. Multiple hormone supplementations invite poor compliance in the best of patients. We have chosen to use a long-acting form of recombinant human growth hormone, which has a long history of use within the pediatric population. This reduces the frequency of injections from every night to once a month. Few adverse reactions have been noted at the injection site: a small nodule the size of a pea, redness, pain, tenderness at the injection site, and an even more rare complaint of transient edema post injection. These reactions are minimal and diminish with time.

In this chapter, we present a case study of 23 patients who have benefited from this therapy (Figure 2). Patients received dosages ranging from 13.5mg to 36mg, with an average of 22mg for a 70kg (150lb) patient. Statistical analysis revealed a clinically relevant P value of <0.005 for the IGF-1 level; as well as a notable P value of <0.010 for total cholesterol and <0.005 for change in total body weight.

Figure 2. Effect of growth hormone therapy on IGF-1 levels, cholesterol levels, and body weight.

Measure	*# Patients*		*Mean*	*Std Dev*	*Std Error*	*Minimum*	*Maximum*	*P Value*
IGF-1	23	Baseline	203.000	100.703	20.998	13	376	
		Post Tx	296.130	177.942	37.103	90	600	
		Increase	93.130	136.331	28.427	-123	340	P<0.005
Cholesterol	17	Baseline	209.471	34.522	8.373	153	275	
		Post Tx	184.412	33.783	8.193	132	246	
		Decrease	25.059	34.635	8.400	-18	95	P<0.010
Body Weight	22	Baseline	164.091	30.276	6.455	123	252	
		Post Tx	158.136	27.777	5.922	126	233	
		Decrease	5.955	7.332	1.563	-10	19	P<0.005

CONCLUSIONS

Our clinical experience demonstrates that monthly human growth hormone injections can sustain elevated levels of IGF-1, and promote reversal of pause phenomena in areas such as total cholesterol and total body weight.

This is just the beginning to the benefits that this treatment modality can offer. We anticipate that the field would follow our footsteps in providing such an efficacious treatment and promoting its positive outcomes for patients.

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