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The Role of Oral Growth Hormone Secretagogues in Anti-Aging Therapy

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BACKGROUND

Based on the increasing body of evidence that adults with human growth hormone (hGH) deficiency exhibit signs of impaired health, many countries have approved the use of hGH (somatotropin) as a replacement therapy in deficient adults. The results and efficacy of hGH therapy are strikingly consistent. Untreated hGH deficient adults are shown to have increased cardiovascular mortality, reduced skeletal muscle strength, reduced exercise capacity, reduced glomerular filtration and renal plasma flow, defective thermo-regulation and sweat secretion, reduced energy expenditure and basal metabolic rate, reduced myocardial function, clinical signs of premature atherosclerosis, and abnormal thyroid metabolism. Body composition has been found to be abnormal in these patients, as evidenced by decreased lean body mass, increased fat mass, visceral obesity, reduced bone mineral content, and reduced extracellular fluid volume, while independent groups have reported impaired psychological well being. Somatotropin deficiency has distinct clinical consequences, all of which can be totally or partially alleviated by rhGH replacement therapy.

Safety and cost considerations associated with growth hormone replacement have generated interest in several research studies focused on oral growth hormone releasers, also known as hGH secretagogues. This class of compounds works by directly stimulating the pituitary to release hGH and by affecting contiguous endocrine organs, like the hypothalamus. There are several known factors that affect hGH release and response, including insulin regulation, somatotroph receptors, GHRH, somatostatin, liver function, and IGF-1 receptor sites.[8,10,17] Pharmacologically correlating these factors with the action of the anterior pituitary peptides, a sequenced glycoamino acid complex, and botanical regulators of insulin and IGF-1 has led to the development of Symbiotropin®, which promotes hGH release and IGF-1 formation. Clinically, the efficacy of Symbiotropin® has been evaluated through IGF-1 measurements and patient self-assessments.

Somatotropin is one of several endocrine hormones, like testosterone, estrogen, progesterone, and DHEA - that decline in circulation as we age. While many of these hormones are replaced to deter some of the effects of aging, somatotropin goes far beyond the effect of any of these other hormones, to not only inhibit biological aging, but to significantly reverse many of the effects of aging. Research has demonstrated that rhGH therapy can reverse the biological markers of aging by as much as twenty years within six months of therapy. [7, 13]

Somatotropin is secreted by somatotrophs located in the anterior portion of the pituitary gland. Somatotropin secretion peaks during adolescence when accelerated growth occurs. After age 30, secretion decreases by about 14% per decade.

Decline of hGH with Age

Daily release of growth hormone averages about 500 mcg at age 20, then declines to 200 mcg at age 40, and 25 mcg at age 80. hGH secretion is regulated primarily by the hypothalamus, which releases Growth Hormone Releasing Hormone (GHRH) through a negative feedback regulatory process from the pituitary to release hGH.
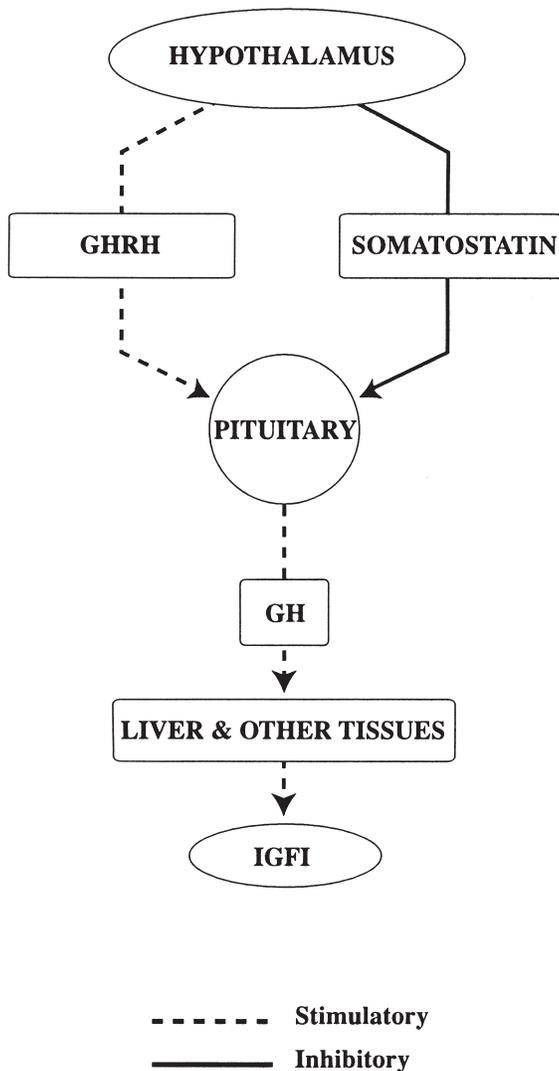
It is known that the aging pituitary somatotroph cells are capable of secreting as much hGH as the young somatotroph cells when they are adequetly stimulated. The primary influences on age-related production of GHRH and increased production of somatostatin, the hypothalamic inhibitor of hGH release.

Research has shown that aging leads to reduced responsiveness of the precursor hormone GHRH to signals from the hypothalamus. Research also suggests that overall metabolic response to available hGH diminishes due to decreased sensitivity of cellular receptor sites. Some hGH secretagogues work by stimulating GHRH, inhibiting somatostatin, and/or affecting pituitary receptors that are not yet clearly defined.[5,8,9]

The physiological effects associated with hGH are now assessed through the evaluation of IGF-1. Circulating hGH (1/2 life = 20 minutes) stimulates the liver to release IGF-1 (1/2 life = 20 hours). Serum IGF-1 levels are more sustained, and therefore a more practical indicator of growth hormone status.

hGH improves utilization of fat as a source of energy by stimulating lipolysis and fat oxidation. The significance of these effects is reflected in the finding of increased adiposity in hGH deficiency and reduced fat mass in acromegaly. Studies under fully controlled conditions in vitro have indicated that cortisol and insulin facilitate lipid accumulation by expressing lipoprotein lipase (LPL). hGH and testosterone inhibit expression of LPL which markedly stimulates lipolysis.[16]

hGH affects protein metabolism in a manner that increases lean body mass through stimulation of protein synthesis, and reduction of protein oxidation. It does not inhibit protein catabolism.[21]

Long term IGF-1 deficiency affects carbohydrate metabolism, leading to insulin resistance and exacerbated obesity. These effects can be reversed with hGH therapy. hGH increases glucose turnover, making it more readily available metabolically as a primary fuel.[21]

HYPOTHALAMUS

GHRH

SOMATOSTATIN

PITUITARY

GH

LIVER & OTHER TISSUES

IGFI

- - - - - Stimulatory
———— Inhibitory

CHARACTERISTICS OF GH DEFICIENCY

Anabolic Tone
- Reduced lean body mass and/or skeletal muscle mass
- Reduced skeletal muscle strength
- Reduced exercise performance
- Increased total body fat
- Increased abdominal and visceral fat

Lipid Effects
- Elevated LDL cholesterol
- Decreased HDL cholesterol
- Elevated apolipoprotein-B

Bone Effects
- Osteopenia (lack of bone)

Metabolic Effects
- Insulin resistance (in obese people)
- Hypoglycemia
- Possible abnormal resting metabolic rate
- Reduced T4 to T3 conversion

Protein Synthesis
- Thin skin
- Lack of collagen
- Decreased size of organs
- Decreased nail and hair growth

Dehydration
- Reduced glomerular filtration and renal plasma flow
- Reduced sweating – inability to thermoregulate
- Reduced cardiac output (potentially)
- Increased vein resistance

Mental Health
- Reduced energy
- Emotional instability
- Poor memory and concentration
- Depression
- Lack of social interaction
- Lack of purpose
- Reduced sex drive

Action of Secretagogues

Functional studies have demonstrated that GHRH and secretagogues act through different mechanisms, and distinct receptor sites. Somatotrophs stimulated with secretagogues release hGH in response to both GHRH and the secretagogue. Efficacious secretagogue peptides, work at the level of the hypothalamus, to affect hGH releasing factors, and at the level of the pituitary to release stored hGH in a synergistic fashion. Pituitary receptors have been identified that respond to specific hGH releasing peptides.[10,17]

Since somatostatin increases with age to lower levels of hGH, it is important for effective secretagogue peptides to inhibit the action of this hormone. Hypothalamic receptors have been identified that respond to peptides that inhibit somatostatin and stimulate GHRH.

Many studies have evaluated the effectiveness of oral amino acids and peptides. Oral absorption studies have demonstrated very erratic absorption rates. Orally ingested peptides must be formulated in a delivery system that will endure the acid pH of the stomach in order to be absorbed effectively and arrive at appropriate receptor sites. Absorption of the hGH molecule has been examined through various means of delivery, e.g. mucosal surfaces, the mouth and nose. These studies have demonstrated very ineffective absorption rates of around 5-10%. Studies indicate that absorption rate and efficacy of amino acid secretagogues are enhanced when administered in a carbonated solution.[1,2,3]

Management of hGH secretion through the use of peptides and other synergistic compounds have been shown to increase the amplitude and frequency of hGH release within age-related physiologic boundaries.

Clinical Results

Thirty-six individuals were evaluated clinically for changes in existing symptomatology and serum IGF-1 levels over a period of 12 weeks while being administered Symbiotropin®, a combination of anterior pituitary peptides, sequenced glycoamino acid complex, pharmaceutical saccharides, and botanical regulators of insulin and IGF-1. Initial

IGF-1 measurements ranged from 21 to 276. Patients were instructed to take two Symbiotropin® effervescent tablets dissolved in water four hours after last meal and prior to retiring. This schedule was maintained in five-day cycles, with two days separating each cycle for a term of twelve weeks.

IGF-1 levels were measured before the onset of Symbiotropin® therapy and then at four week intervals. Patient self-assessments were performed every four weeks throughout the twelve week term. Additional clinical observations were made during routine office visits.

Patient self-assessments in areas of endurance and body composition, hair and skin, sexual function, healing and immunity, and mental function reflect significant improvement in all 23 areas of evaluation, with range of 21%-74% of patients reporting improvements in these areas. Additional clinical observations reflect significant improvements in blood sugar management in diabetic patients, lowered prostate-specific antigen (PSA), improved cardiac and pulmonary function, blood pressure management, and improvement in menopausal symptoms.

Areas of IGF-1 Activity
• Synthesized by Leukocytes
• Restores Lymphoid Organ size
• Stimulates Proliferation of Leukemic Blasts and T Lymphocytes
• Increases Uptake and Degradation of LDL by Macrophages
• Estrogens Influence Formation of IGF-1 and IGF-1 BPs
• Nitrogen Retention/Sodium Excretion
• Parathyroid-Vitamin D axis
• Increased Circulating Osteocalcin
• Increased Urinary Hydroxyproline Secretion
• IGF-1 Levels Do Not Exhibit Diurnal Variations
• IGF-1 Measurements Reflect Integrated GH Secretion and Bioactivity Method

Patients % Reported Improvement with Symbiotropin

Area of Assessment	Month Three
Endurance & Body Composition	
Muscle Strength	58%
Muscle Size	42%
Fat Reduction	68%
Overall Energy	74%
Exercise Tolerance	58%
Exercise Endurance	68%
Hair & Skin	
Skin Texture	47%
Skin Thickness	32%
Skin Elasticity	26%
Wrinkle Disappearance	37%
New Hair Growth	47%
Healing & Immunity	
Healing of old injuries	26%
Healing of other injuries	21%
Healing Capacity	21%
Back & Joint Flexibility	37%
Resistance to Common Illness	47%
Sexual Function	
Sexual Potency/Frequency	32%
Duration of Penile Erection	44%
Frequency of Nighttime Urination	66%
Mental Function	
Mental Energy & Clarity	53%
Emotional Stability	42%
Attitude Toward Life	37%
Memory	47%

The results of patient self-assessments indicate symptomatic response to Symbiotropin® within the first four weeks in all patients, with continued improvement between the fourth and twelfth week. Improved energy, endurance, and body composition were among the most frequently reported improvements within the first four weeks. New hair growth, restoration of hair color, thickening of skin, and disappearance of skin discoloration generally occurred between the eighth and twelfth weeks, with continued improvement beyond the twelve week term. It should be noted that the results of this patient self-assessment are not adjusted for areas that did not apply to each individual.

No side effects were observed that could be attributed to Symbiotropin®.

One female patient was removed from the study due to a citric acid allergy that was aggravated by Symbiotropin. IGF-1 measurements indicate an overall increase in IGF-1 throughout the twelve week term. Measurements taken during the first four weeks indicate increases of over 200% and averaging over 18%. Eight week measurements indicate increases of over 100% and averaging 24%. Twelve week measurements indicate a 30% average increase in IGF-1. Rate of symptomatic response occurred independent of the rate of IGF-1 increase such that fluctuations in IGF-1 measurements were associated with concurrent symptomatic improvements, even when IGF-1 levels are decreased.

Case Studies

In the case of a 46 year old male, after 6 months of therapy with Symbiotropin®, significant reductions in total cholesterol and triglycerides were observed. HDL was also increased by nearly 10%. A 10% increase in HDL, has been shown to correlate to a reduction on cardiovascular mortality by 35%.

Case Study
Blood Lipid Profile with Symbiotropin
Male, Age 46

	Cholesterol	Triglycerides	HDL	LDL
Initial	211	396	37	94
3 months	164	145	35	100
6 months	162	117	40	98

In this 41 year old male, significant reductions in elevated liver enzymes were observed with four months of therapy.

Case Study
Liver Profile with Symbiotropin
Male, Age 41

	GGT	SGPT	SGOT	LDH
Initial	187	39	26	146
2 months	200	35	23	162
4 months	54	16	17	134

In the case of a 52 year old female, the left ventricular ejection fraction (LVEF) improved from 15% to 45% after 3 months of therapy. LVEF was evaluated with color Doppler echocardiography.

Case Study
Ventricular Ejection Fraction with Symbiotropin
Female, Age 52

|	VEF
Initial	15%
3 months	45%

In a 58 year old female with chronic primary biliary cirrhosis – liver function tests, LDLs, and blood pressure all improved with ten months of therapy.

Case Study

Female   Age 58

Diagnosis:
Chronic Primary Billiary Cirrhosis, unknown origin. Slight high blood pressure.

Clinical Values:	Initial	10 Months
Alk. Phos	431	218
LDH	217	157
SGOT	82	36
SGPT	153	43
GCT	408	136
Cholesterol	284	271
Triglycerides	87	104
HDL	91	97
LDL	176	153
Blood Pressure	142/88	120/76

*Patient exhibits increased energy and strength and improved digestion*

IGF-1 and Prostate Cancer

A recent study presented by Cass Terry, M.D., analyzed the relationship of IGF-1 levels and prostate cancer in 749 men. Because IGF-1 is mitogenic, and may effect cell differentiation, its role in increasing prostate cancer was evaluated. The incidence of prostate cancer increases with age, whereas blood levels of IGF-1 decline significantly with age, at about 14% per decade after the age of thirty.

Relationship Between Age & PSA

Frequency Histogram of IGF-1 Blood Levels

	20	94	168	241	315	369	463
■ Frequency	1	10	44	52	24	5	2
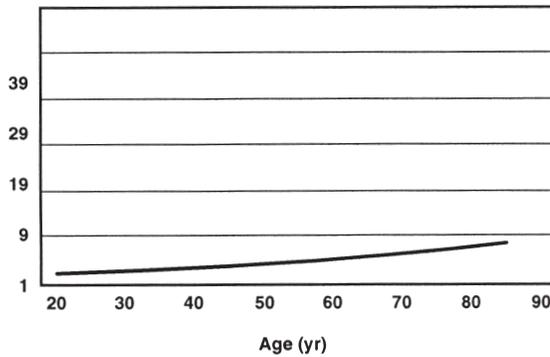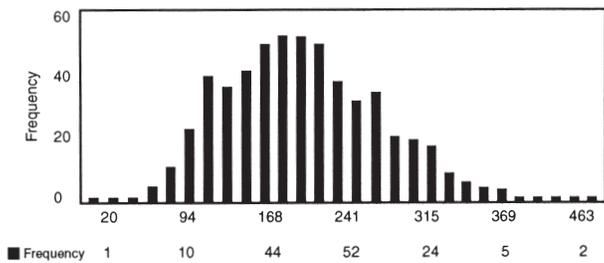
This frequency histogram of IGF-1 blood levels of 593 patients aged 22 to 86 years many of whom were on hGH injections. The dosage ranged from 4-10 IUs per week, in twice daily injections. Mean age of all men was 55.1 years.

Median PSA Levels in IGF-1 Quartile Ranges

|	25%1c	50%1c	75%1c	100%1c
Mean IGF1 (ng/ml)	122	187	239	331
Range	(20-159)	(100-211)	(212-271)	(272-518)
Median PSA (ng/ml)	1.1	0.9	1.0	1.1
Range	(0-61.7)	(0.2-27.5)	(0-8.6)	(0-25.2)
Sample Size	138	133	138	135

This table demonstrates no correlation between IGF-1 and median PSA levels, when comparing the highest and lowest quartiles.

**Mean IGF-1 Levels in Normal and Abnormal PSA Ranges**

	PSA >4.0	PSA <4.1
Mean IGF1 (ng/ml)+SEM	218+12.6	219+3.5
RANGE	(20-156)	(22-518)
MEDIAN PSA (ng/ml)	6.0	0.9
Range	(4.1-61.7)	(0-4.3)
Sample Size	59	536

This table grouped PSA levels greater than 4.0 ng/ml, and PSA levels less than 4.1 ng/ml. There was no correlation between PSA and IGF-1 levels in the group of men with a PSA of less than 4.1. In the group of men with PSA levels greater than 4.0 there was a negative correlation between PSA and IGF-1 levels. A significant finding was that the mean IGF-1 levels were essentially the same in both groups, but the median PSA in the group who had PSA levels greater than 4.0 – had median PSA levels that were greater than 6 times higher than the group with values less than 4.1.

Relationship Between PSA's >4.0 & IGF-1 Levels
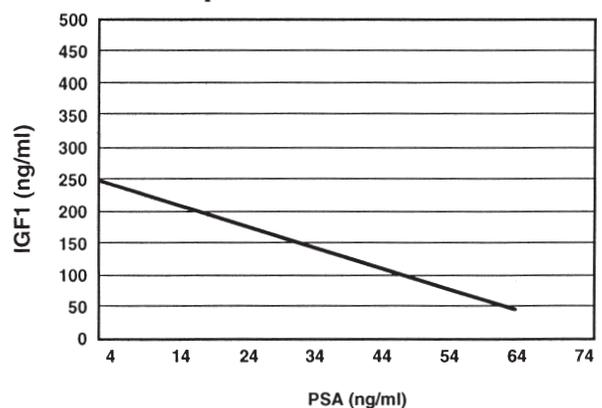
This graph demonstrates the negative correlation of IGF-1 levels with PSA levels greater than 4.0.

Relationship Between PSA's <4.1 & IGF-1 Levels
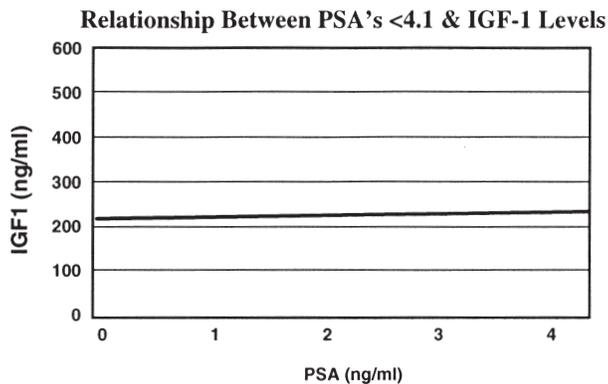
This graph demonstrates no correlation of IGF-1 and levels of PSA less than 4.1 ng/ml.

In this study, circulating IGF-1 levels had no relationship to PSA levels, or prostate cancer. Dr. Terry also reports that in a patient population of approximately 3,000, no increase in prostate cancer, or any other malignancy have been observed in those receiving long-term hGH injections.

Conclusion IGF-1, PSA, and Risk for Prostate Cancer

- PSA levels were found to increase with increasing age.
- As PSA levels increase to levels greater than 4.0 ng/ml, there is a negative correlation of PSA and IGF-1 levels. The PSA levels in this group are greater than 6 times higher than those with levels of PSA less than 4.1 ng/ml. Higher PSA levels correlate with lower IGF-1 levels.
- In those patients with PSAs less than 4.1 ng/ml, there is no correlation of IGF-1 levels and PSA.

Conclusion:
Oral Secretagogues as an Adjunct to Growth Hormone Injections

Many physicians in the United States and abroad are using rhGH injections concomitantly with oral secretagogues. In combination, patients have been able to use lower doses of rhGH, and have reported clinical improvements beyond what they had previously experienced with injections alone.

In some cases, rhGH injections are associated with a decrease in IGF-1 as lean body mass increases. Some of these patients have had to increase the daily dose of rhGH in order to maintain their clinical response as well as IGF-1 levels. These inconsistencies in response to rhGH therapy are thought to be related to developed resistance and receptor site sloughing.

hGH therapy has been typically monitored by laboratory analysis with IGF-1. To date, IGFs 2-7 have been identified, but the relative significance of these other insulin growth factors – as they relate to longevity assessments and their individual functions – has not been fully elucidated. Due to the lack of consistent correlation between IGF-1 and symptomatic improvement, patient assessments may allow clinicians to make clearer discernments about therapeutic recommendations to patients.

As an oral secretagogue, Symbiotropin® has been found to be a safe and effective hGH therapy capable of improving many of the clinical signs and symptoms associated with the process of aging. It has been found to be profoundly efficacious as a single therapy and as an adjunct to rhGH injections.

There are several known factors that effect hGH release and response, including insulin regulation, somatotroph receptors, GHRH, somatostatin, liver function, and IGF-1 receptor sites. Pharmacologically correlating these factors with the action of the anterior pituitary peptides, a sequenced glycoamino acid complex, and botanical regulators of insulin and IGF-1 has led to the development of an effective growth hormone secretagogue therapy. Clinically, the efficacy of Symbiotropin® has been verified through IGF-1 measurements and patient assessments.