A Nanoliposomal - Amino Acid Complex as a Potent Growth Hormone Secretagogue; a Second Look.

Journal of Anti Aging Protocology, Vol. 3, No. 4, March 2008. Gordon, ML. Gordon, EF, Gordon, AM.

Abstract

The recognition and acceptance of amino acid complexes as potent growth hormone secretagogues has been less than positive due to a number of real and perceived limitations.

First, past research data has largely been based upon small test groups of individuals that were given large quantities of Amino Acid Complexes (AAC) designed to enhance growth hormone production and release. Although many of these complexes demonstrated an elevation in the GH/IGF-1 axis, some were also associated with the development of osmotic diarrhea. This side-effect is detrimental to the promulgation of secretagogue technology, even in light of the nutritional benefits and hormonal enhancing property.

Second, delivery of amino acids by mouth is at high risk of inactivation by the stomach's hydrochloric acid. This chemical reaction can be significantly reduced by suspending the AAC in a liposomal matrix. Not only does this protect the product from inactivation but it also allows for a smaller quantity of each component since the need for compensation is reduced. The volume of the product becomes smaller (dropping from 13 grams to 1.5grams) thereby allowing for an alternative means of delivery without the associated osmotic diarrhea.

Third, since a secretagogue does not alter the natural hormonal homeostasis, the ability to time a blood test to measure its effect on GH and/or IGF-1 is random at best. Frequently, the peak pulsed production of GH (from the secretagogue), is achieved within 90 minutes, which is frequently at bedtime thereby obviating documentation of this peak response until morning. Since GH has a 20 minute half-life, morning testing cannot substantiate the beneficial increase in its production. Nonetheless, if the product is consistently capable of increasing the production of growth hormone, then over time, the use of IGF-1 to monitor the response, due to its longer half-life of 20 hours, becomes the obvious choice. (**Note:** IGF-1 has an 8 minute half life when in the free state and a 20 hr half-life when bound to IGFBP3. IGFBP3 has a 24 hour ± 4 hour half life when unbound to IGF-1 [47]).

Fourth, as the circulating level of IGF-1 increases it induces an up-regulation in the hepatic production of IGFBP-3 (IGF Binding Protein 3). The measurable increase in BP-3 is a *sine qua non* indicator of an up-regulation in the GH/IGF-1 Axis.

Summary

After a 12 month testing period, the AAC was shown to increase circulating levels of IGF-1 to a physiological and therefore therapeutic level. This was based upon the study participants using 0.2cc of the oral preparation in the morning and 0.4cc at bedtime. This volume represents about one-tenth of the amount of components that would normally be used in a powder formulation (10-13 grams). Laboratory testing was performed prior to starting the preparation and at 1, 3, and 6 months during continuous product use. There were no complaints or side-effects encountered during testing. A subjective inventory was obtained at each office visit to address the participant's perceptions of psychological, physiological and physical changes.

Introduction

As issues of cost and legal restrictions make the availability of Human Growth Hormone less accessible, the need for a cost effective and efficacious alternative becomes *mandatory*.

Aside from human recombinant growth hormone (hrGH) there are other products such as Sermorelin[1-2], an injected 29 amino acid growth hormone releasing hormone that directly stimulates the anterior pituitary to increase the production of GH from somatotrophs; Insulin-like Growth Factor-1 (IGF-1), an injectable product which by-passes GH to interact with cell wall receptors to stimulate intracellular events; and Amino Acid Complexes (AAC); whose composition has the ability to both stimulate the production of GH from the anterior pituitary, and also stop production of Somatostatin from the supraoptic nuclei which has a suppressive effect on the Anterior Pituitary's production, and release, of GH.

History

Amino Acids as Growth Hormone Secretagogues

Ornithine

Ornithine is derived from the amino acid arginine. High doses of oral Ornithine have successfully raised growth hormone levels. Bucci, et al, investigated the effect of 40, 100 and 170 mg/kg of oral L-Ornithine HCl. Twenty-five percent of the subjects experienced a significant increase in their serum growth hormone level at the two lower doses, while fifty percent of the subjects showed an increase in growth hormone at the highest dose. Growth hormone levels increased up to four times the baseline level. [3]

Arginine

The ability of oral arginine to raise growth hormone has been investigated in numerous studies with conflicting results. For example, in one study, subjects given 6 grams of oral arginine experienced a 100% increase in plasma levels of arginine without any growth hormone release. [4] Other researchers administered oral arginine to 12 young and 5 elderly non-obese adults, all of whom had a body mass index (BMI) less than 30. The subjects participated in three trials: resistive weight-lifting exercise with no placebo; 5 grams of oral L-arginine only; and 5 grams of arginine supplementation prior to exercise.

When arginine was consumed at rest, it did not significantly raise GH levels, compared with baseline values, in either the young or the old subjects. In fact, GH levels in those consuming arginine at rest were significantly lower than during the exercise-only trial. Consuming arginine before exercise did not significantly raise the GH concentrations in either the old or the young subjects, compared to exercise only. Surprisingly, the amount of GH secreted in the exercise-plus-arginine trial was 20% less than during exercise only in the young subjects, indicating arginine may actually blunt growth hormone production, particularly in the young. [5]

Other researchers drew the same conclusion in a study of 16 young men during an acute episode of resistive weight lifting. After 3 grams of oral arginine and lysine, the subjects experienced a peak GH response to exercise approximately 15% lower than during exercise without supplementation. [6] One group of researchers, after reviewing the evidence, wrote, "These results suggest that oral arginine, unlike intravenously infused arginine, does not appear to be an effective means of enhancing GH secretion." [5]

Researchers suspect that arginine may only act as a growth hormone secretagogue at night, rather than prior to exercise or during non-exercise daytime conditions. When researchers administered 250 mg/kg/day of oral arginine aspartate to five healthy subjects aged 20 to 35 for seven days, the rise in GH that occurred during slow wave sleep was approximately 60% higher in the subjects after arginine aspartate administration than in the control period. These same results were not obtained with a lower dose of 100 mg/kg/day. [7]

Another group of researchers achieved promising results when treating 12 normal adults with one large, 37.5-gram dose of arginine aspartate, administered orally. The treatment caused a small but significant release of serum growth hormone in these subjects. [8]

In a more contemporary study, arginine was found to stimulate growth hormone secretion by suppressing endogenous somatostatin secretion. So in an indirect manner, growth hormone production and release is enhanced when there is a reduced tone to shut off its production via Somatostatin. [11]

Arginine and Ornithine

When administered together, arginine and Ornithine do appear to offer anabolic benefits. These benefits appear to be caused by growth hormone release, but this remains unproven. In a double-blind study of 22 adult males participating in a 5-week progressive strength-training program, half the subjects orally consumed a combination of 2 grams of L-arginine and 1 gram of L-Ornithine; the other half consumed a placebo. Following a short-term strength program using progressively higher intensities, subjects taking the arginine-Ornithine combination scored significantly higher in total strength and lean body mass and excreted less urinary hydroxyproline (found in collagen and its excretion is a marker of catabolism) than subjects on placebos. In reviewing the study, one group of researchers wrote, "It was concluded that arginine and Ornithine taken in prescribed doses can, in conjunction with a high-intensity, strength-training program, increase total strength and lean body mass in a relatively short time".

The researchers suggested that the lower hydroxyproline levels were an indication that arginine and Ornithine aided in recovery from chronic stress by alleviating tissue breakdown. The reviewers hypothesized that these changes were due to increases in growth hormone release, although GH was not measured. [10-11]

Ornithine-alpha-ketoglutarate (OKG)

Ornithine alpha-ketoglutarate (OKG) is formed of two molecules of ornithine and one molecule of alpha-ketoglutarate. OKG is a promising anti-catabolic agent that promotes wound healing and protein synthesis. Researchers have hypothesized that OKG fulfills these functions by encouraging the secretion of insulin and human growth hormone, and by upregulating glutamine and arginine production. When fed enterally to trauma patients, OKG significantly increased both IGF-1 and growth hormone levels. [12-17]

Although few, if any, oral studies exist on OKGs ability to release growth hormone in normal subjects, studies do show that in healthy subjects OKG does increase tissue levels of glutamine and arginine, which are regulators of protein synthesis. In fact, animal studies show that ornithine alpha-ketoglutarate (OKG) generates more glutamine in the systemic circulation

than glutamine itself when these substances are given orally.[17-18] Oral glutamine has been shown to release growth hormone. [19]

Arginine Pyroglutamate and Lysine

Arginine and lysine may work synergistically to release growth hormone. In a study of 15 healthy male subjects, separate consumption of arginine pyroglutamate or lysine, as single nutrients, did not significantly increase growth hormone compared to baseline. In another study of normal young males, oral administration of 1,200 mg of L-lysine did not raise serum growth hormone levels. [20]

Studies indicate, however, that these two amino acids can work together to increase the release of growth hormone. In 15 healthy male subjects aged 15 to 20 years old, 1200 milligrams of arginine pyroglutamate combined with L-lysine hydrochloride significantly elevated biologically active growth hormone from two to eight times the baseline value at 30 to 120 minutes after consuming the amino acids. [20]

Another study indicated arginine and lysine may act to increase growth hormone--but only under specific conditions. Sixteen men randomly completed four trials. Trial A consisted of a performance of a single bout of resistance exercise preceded by placebo ingestion (vitamin C). Trial B involved ingestion of 1,500 mg L-arginine and 1,500 mg L-lysine, followed by exercise as in Trial A. In Trial C, subjects consumed arginine and lysine as in Trial B, but with no exercise. In Trial D, subjects consumed a placebo and did not engage in exercise. There was no difference in growth hormone concentrations between the placebo-supplemented subjects and the amino acid-treated subjects. However, in Trial C, during resting conditions, growth hormone was significantly elevated 60 minutes after consumption of arginine and lysine compared with the placebo trial. The researchers concluded that ingestion of 1,500 mg arginine and 1,500 mg lysine before resistance exercise did not alter exercise-induced changes in GH in young men. When the same amino acid mixture is ingested under resting conditions, however, acute GH secretion is increased. [21]

Unfortunately, not all studies investigating the use of arginine and lysine have resulted in positive findings. One study investigated whether oral arginine/lysine could be used to increase basal IGF-I and GH levels in non-obese elderly men to values similar to those of untreated young men. Researchers gave two groups of 8 healthy elderly men either 1.5 grams of arginine plus 1.5 grams of lysine or a placebo twice daily for 14 days. The researchers also administered the amino acid combination to young men during the same time period and measured GH and IGF-1

levels. The researchers found that arginine and lysine administration did not significantly alter basal or sleep-related GH levels or serum IGF-I, either in the elderly or young subjects. Our data suggest that oral arginine/lysine is not a practical means of chronically enhancing GH secretion in old men, the researchers reported. [21] Another group of researchers suggested the lack of GH release in this study may be due to the low doses used. [5]

Glycine

Glycine is a nonessential amino acid contained in gelatin protein and is an important component of collagen. Although much of the early research revolved around glycine's ability to increase strength in athletes, more recent studies have documented that oral glycine can indeed raise growth hormone levels in humans. In fact, researchers have hypothesized that the reason glycine has been found to increase muscle strength in many studies, (with females experiencing a 22% increase and men a 32% increase in cycle ergometry workloads after ingestion of 5 to 12 grams of glycine daily) may be the result of its growth-hormone-boosting capabilities. [23]

One study clearly illustrated glycine's ability to act as a GH secretagogue. When 19 normal, non-obese subjects consumed 6.75 grams of glycine orally, growth hormone levels significantly increased for 3 hours, reaching a maximum of 3 to 4 times that of baseline at 2 hours. Interestingly, the only group of subjects not deriving a growth-hormone-boosting benefit from glycine was non-obese diabetics. According to the researchers, glycine is one of the stimulatory agents inducing the pituitary gland to secrete hGH. [24]

On the other hand, another study of eight men revealed that six or twelve grams of glycine daily for 10 weeks could increase urine creatine levels, but did not improve grip strength. These same disappointing results were upheld in a double-blind, crossover study of 33 football players given a placebo or 5 grams of glycine daily. After consuming glycine for 21 days, the subjects did not experience any noticeable benefit to work output. [26]

After reviewing the above studies, one group of researchers hypothesized that the reason glycine showed no effect in the later trials is because glycine enhances growth hormone levels already produced during a whole-body resistance training program and during anaerobic or intermittent exercise. In subjects performing endurance exercise where growth hormone release is low, glycine would not show any benefit because this amino acid only enhances effects of growth hormone already produced. The researchers concluded, acute ingestion of large p.o. doses of glycine appears to stimulate release of growth hormone and increase creatine synthesis rates. Both of these attributes are desirable for persons undergoing progressive weight training. [27]

More recent research lends support to the above hypothesis. In a randomized, double-blind, crossover study published in December 2000, 13 human subjects were given a supplement consisting of glycine and an L-arginine or a placebo over 23 days. Treatment with arginine and glycine increased the subjects' mean resistance to fatigue up to 28% over the controls during acute exhaustive high-intensity anaerobic isokinetic exercise. The subjects taking glycine and arginine also experienced an overall gain in total muscle work of 10.5% more than controls. [28]

GLUTAMINE

Glutamine is the most abundant amino acid in human muscle and plasma, directly regulating both the production and wearing-down of protein, as well as immune cell activity. [29-30] When 9 healthy subjects consumed two grams of oral glutamine 45 minutes after a light breakfast, 8 of the 9 subjects experienced elevated plasma growth hormone within 90 minutes. These findings demonstrate that a small oral glutamine load is capable of elevating plasma growth hormone.[31-33] In the small intestine, glutamine is converted into citrulline, which in turn triggers the synthesis of arginine, an amino acid shown to release growth hormone in some studies. Moreover, glutamine is converted into glutamate, which can directly enhance growth hormone secretion. [34-36]

GABA

Gamma-aminobutyric acid (GABA) is the brain's major inhibitory neurotransmitter. Studies have shown it is responsible for both the rise of growth hormone (when at rest) and the inhibition of growth hormone (when exercising).[37] Oral GABA supplementation has increased growth hormone levels in humans. In one study, a single oral dose of 5 grams of gamma aminobutyric acid administered to 19 subjects significantly elevated plasma growth hormone levels compared to placebo-treated controls. [38-39]

MUCUNA PRURIENS

This contains high concentrations of levodopa, a direct precursor of the neurotransmitter dopamine. It has long been used in traditional Ayurvedic Indian medicine for diseases including Parkinson's Disease.[40] In doses as large as 30g, it has been shown to be as effective as pure levodopa/carbidopa in the treatment of Parkinson's disease, but no data on long-term efficacy and tolerability is available.[41]

COMPARISON OF STUDY RESULTS

Amino Acids	Study Results

Intravenous Ornithine	Produced a five-fold increase in serum GH within 90 minutes.
Ornithine	Increased serum GH up to four times the baseline level.
Arginine	250 mg/kg/day of oral arginine aspartate (20 grams) for seven days caused a 60% rise in GH.
Arginine and Ornithine	In a double-blind study, adult males participating in a 5-week progressive strength-training program who consumed 2 grams of L-arginine and 1 gram of L-Ornithine experienced significantly higher total strength and lean body mass scores and excreted less urinary hydroxyproline than placebo-treated subjects.
Ornithine Alpha-ketoglutarate (OKG)	Significantly increased IGF-1 and growth hormone levels in trauma patients. In healthy subject, OKG increased tissue levels of growth-hormone-releasing glutamine.
Arginine and lysine	In 15 to 20 years old participants, 1200 milligrams of arginine pyroglutamate combined with L-lysine hydrochloride elevated GH levels from two to eight times the baseline value.
Arginine and lysine	1,500 mg arginine and 1,500 mg lysine increased GH in young men only during resting conditions.
Glycine	In non-obese subjects, 6.75 grams of glycine increased GH levels 3 to 4 times that of baseline.
Gamma Amino butyric Acid (GABA)	An oral dose of 5 grams of GABA significantly elevated GH levels compared to placebo-treated controls.
Glutamine	Two grams of oral glutamine resulted in elevated plasma GH levels.

THE LIPOSOMAL DELIVERY TECHNOLOGY

A liposome is a spherical vesicle composed of a bilayer membrane. In biology, this specifically refers to a membrane composed of a phospholipid and cholesterol bilayer. Liposomes can be composed of naturally-derived phospholipids with mixed lipid chains (like egg phosphatidylethanolamine), or of pure surfactant components like DOPE (dioleoylphosphatidylethanolamine). Liposomes, usually but not by definition, contain a core of aqueous solution; lipid spheres that contain no aqueous material are called micelles, however, reverse micelles can be made to encompass an aqueous environment. [43]

Liposomes were first described by British hematologist Dr Alec D Bangham FRS in 1961, at the Babraham institute, Cambridge. They were discovered when Bangham and R. W. Horne were testing the institute's new electron microscope by adding negative stain to dry phospholipids. The resemblance to the plasmalemma was obvious, and the microscope pictures served as the first real evidence for the cell membrane being a bilayer lipid structure. [43]

Liposomes are used for drug delivery due to their unique properties. A liposome encapsulates a region of aqueous solution inside a hydrophobic membrane; dissolved hydrophilic solutes can not readily pass through the lipids. Hydrophobic chemicals can be dissolved into the

membrane, and in this way liposome can carry both hydrophobic molecules and hydrophilic molecules. To deliver the molecules to sites of action, the lipid bilayer can fuse with other bilayers such as the cell membrane, thus delivering the liposome contents. By making liposomes in a solution of DNA or medication (which would normally be unable to diffuse through the membrane) they can be (indiscriminately) delivered past the lipid bilayer. [43]

Liposomes can also be designed to deliver drugs in other ways. Liposomes that contain low (or high) pH can be constructed such that dissolved aqueous drugs will be charged in solution (i.e., the pH is outside the drug's pI range). As the pH naturally neutralizes within the liposome (protons can pass through some membranes), the drug will also be neutralized, allowing it to freely pass through a membrane. These liposomes work to deliver drug by diffusion rather than by direct cell fusion. Another strategy for liposome drug delivery is to target endocytosis events. Liposomes can be made in a particular size range that makes them viable targets for natural macrophage phagocytosis. These liposomes may be digested while in the macrophage's phagosome, thus releasing its drug. Liposomes can also be decorated with opsonins and ligands to activate endocytosis in other cell types. [43]

The Lipotropin Study

INITIAL RESEARCH OF 2001

In 2000, the Millennium Health Centers, Inc. was approached by Lifetech Resources of Los Angeles California, to assist in the development and testing of a product containing a number of select amino acid complexes encapsulated by the newest Nanoliposomal technology.

In 2001, a finished product was made available for clinical testing. The original study's protocol was designed to assess the product's ability to produce a measurable increase in the level of IGF-1 (Insulin-like growth factor-1) within a 30 day trial period. At the time, a number of retail products were available claiming the ability to increase the IGF-1 level but, only after 3 to 6 months. Additionally, these manufacturers failed to perform their own efficacy studies relying on inferences taken from Dr. Daniel Rudman's study on injectable growth hormone as a ***de facto*** equivalent.

The clinical study started with twenty healthy male and female participants who were selected at random from a group of volunteers. After a history questionnaire, physical examination, and laboratory testing the participants were placed on the original test product identified as ***Lipotropin.*** ™ A total of 16 individuals completed the 30 day clinical trial; 5

females and 11 males. During the testing, each participant was instructed to take 0.33 cc of Lipotropin under the tongue in the morning and 0.66 at bedtime. They were to hold the solution under the tongue for 30 seconds before swallowing the product. At the end of 30 days (one full bottle of the product) they returned to the office and had a repeat IGF-1 level, weight, percent body fat, BMI and responded to a subjective questionnaire. .

Initial Study Results 2001

Initials	Gender	Age	Weight (lbs)	Initial IGF-1 ng/ml	Final IGF-1 ng/ml	▲IGF-1 ng/ml	▲IGF-1 %
MM	M	53	218	93	215	122	131%
BB	M	40	196.5	159	271	112	70%
PM	M	49	174.5	101	169	68	67%
DR	F	46	139	170	271	101	59%
JMO	F	37	131.5	204	315	111	54%
WB	F	45	135	178	230	52	29%
CD	M	57	184	155	192	37	24%
SW	F	38	118	118	141	23	19%
MS	F	37	194	262	295	33	13%
MS2	M	39	150.5	246	245	-1	0%
MS3	M	40	249.5	173	169	-4	-2%
AE	M	48	218	282	275	-7	-2%
DM	M	51	168	210	204	-6	-3%
KB	M	59	260.5	261	242	-19	-7%
DC	M	37	205.5	215	162	-53	-25%
JT	M	41	215	238	171	-67	-28%
Avg.		**45**	**185**	**192**	**223**	**31**	**25%**

The results of this study were sent out for an independent analysis. The results of this independent assessment helped to adjust the formulation, and use, of this initial product.

The conclusions made by the reviewer were; the product was found to influence the level of IGF-1 greatest in those test subjects that had initially low levels of IGF-1. Overall, in those test subjects that had initially high levels of IGF-1, there was a reduction or suppression of the IGF-1 level. Weight was also found to influence the response to the secretagogue. Those subjects with the greatest percentage of body fat had the least response from the secretagogue.

During the six years following this study, fresh science has become available which helped to categorically explain these initial findings. This allowed for a more refined second study to be designed. What we now know is that IGFBP-3 must be monitored concurrent with

any measurement of IGF-1. Additionally, the individual's percent body fat, more than their overall weight, negatively influenced the production and release of GH which invokes the cellular production of IGF-1. [44]

The Second Secretagogue Study – The Betatropin Study

RESEARCH DESIGN 2007

In the original study, the measurable response from the secretagogue was based upon measured changes in the level of IGF-1. Subsequent to this initial study we learned that the laboratory's measurement of IGF-1 represented only the free IGF-1 and not the total amount of IGF-1. Our technology then and now is unable to measure both the bound and free IGF-1. We did not know that there was possible a considerable proportion of IGF-1 that could become bound to the carrier Insulin-like Growth Factor Binding Protein -3 (IGFBP-3). So if there was a testing interim increase or decrease in the amount of the IGF Binding Protein the measurement of an IGF-1 response while using the test product could be inaccurate.

In reflecting upon the original study's results, when the level of IGFBP-3 increased it caused a relative decrease in the amount of measurable free IGF-1. Thereby, giving the perception that the secretagogue did not increase the IGF-1 levels and possibly decreased the level. This inverse relationship, between the serum levels of IGFBP-3 and IGF-1, must be taken into account when performing testing for response to the secretagogue in order not to conclude that the product was ineffective.

Stimuli to the increase in IGFBP-3 are; elevation in growth Hormone (GH), IGF-1, estrogens [45], and Quercetin®.

STUDY

Fifty patients were taken at random to test the Secretagogue for a period of 12 months. This consisted of males and females, medically and non-medically challenged, all age groups, and none of whom had been on any prior growth hormone product for at least 12 months prior to admission into this study protocol.

CONCURRENT STUDY 1

Another question that arose was; can a patient switch from injectable growth hormone to the Secretagogue and get a reasonable response measurable by IGF-1 levels? So a parallel study was started where patients on GH were started on the Secretagogue and followed along the same protocol as the base study. (Results due in late 2008).

CONCURRENT STUDY 2

Finally, a number of articles have appeared suggesting that DHEA has a central effect on the production of Growth Hormone. As a Neurosteroid produced in the brain, DHEA exerts an influence on the health of the hypothalamus, as well as on neuronal connectivity. It appears that DHEA, at healthy physiological levels, improves upon sleep and thereby enhances or improves upon the nocturnal, pulsatile production of Growth Hormone. With this understanding a number of patients have agreed to have all their deficient hormones corrected save Growth Hormone.

INITIAL LABORATORY SCREENING

Upon admission into the study, each patient had a comprehensive history and physical exam, and laboratory testing to screen for Growth Hormone Deficiency/Insufficiency.

LABORATORY TESTING

Abbreviation	Full name	Family
IGF-1	Insulin-Like Growth Factor-1	Growth Factor
IGFBP-3	Insulin-Like Growth Factor Binding Protein - 3	Growth Factor Carrier
t(T)	Total Testosterone	Androgen
F(T)	Free Testosterone	Androgen
DHT	Dihydrotestosterone	Androgen
DHEA	Dehydroepiandrosterone	Androgen
E1	Estrone	Estrogen
E2	Estradiol	Estrogen
SHBG	Sex Hormone Binding Protein	Gender Hormone Carrier
TSH	Thyroid Stimulating Hormone	Thyroid
fT4	Free T-4 (Tetraiodothyronine)	Thyroid
fT3	Free T-3 (Triiodothyronine)	Thyroid
NA	Cortisol	Corticosterone

Results

Of the initial 50 study participants, 35 continued on the program for at least 6 months.

	Age	BMI	Pre BT	BP3	Post BT	BP3	Post BT	BP3
1	33	23.0	149.0	4393	187.9	4623	227.4	4485
2	37	27.6	107.0	4197	140.0	4140	237.7	4653
3	48	31.3	115.0	2674	167.0	3872	211.0	4319
4	45	29.9	122.0	5450	290.0	6527	276.2	6233
5	63	28.7	77.0	4490	123.0	4659	187.0	4709
6	57	20.0	92.0	4090	219.0	4485	232.1	4573
7	54	24.9	114.0	4280	197.7	4917	220.8	5290
8	50	26.7	190.0	4485	233.8	4572		
9	56	32.2	58.0	2743	104.0	2984	122.3	3738
10	40	30.3	99.0	2487	196.9	4227	207.6	4312
11	37	37.0	199.2	5175	197.7	4543		
12	39	26.3	123.0	3791	176.2	4169	202.3	4427
13	55	29.8	156.9	4370	123.8	4284	169.0	4198
14	62	30.7	116.0	3120	149.0	3750	196.3	3827
15	48	27.9	145.5	7361	227.4	6943		
16	47	26.1	122.0	5520	236.9	5233	220.0	5463
17	28	23.6	154.0	2830	240.0	3882	290.8	3767
18	40	22.2	223.0	4993	265.0	5376	247.7	5607
19	53	25.4	171.0	4850	286.9	4600	262.3	5377
20	50	20.7	99.0	4130	213.0	5147	267.0	5262
21	54	24.0	118.0	4210	213.8	4370	234.3	4193
22	42	30.1	163.1	4313	253.7	4528		
23	30	34.7	217.0	4138	256.0	4322		
24	52	31.3	91.0	3824	150.8	5237	177.4	5514
25	59	32.1	154.0	3139	136.0	4664	167.0	4832
26	53	25.8	109.0	5430	167.7	4514	213.5	4768
27	71	23.8	145.0	4785	166.0	4140	223.0	4385
28	50	34.1	156.2	4629	197.0	4893		
29	44	21.4	177.0	4330	225.0	5031	205.4	4715
30	47	25.5	116.0	3156	287.0	5704		
31	69	28.8	121.0	3241	125.0	3720	125.4	3278
32	51	22.4	163.2	5549	206.2	4428	213.1	4227
33	58	24.9	135.0	3659	177.0	4387	236.0	4427
34	43	28.9	147.0	4950	226.4	5567		
35	43	30.6	172.0	4420	247.3	4732		

DISCUSSION:

These results clearly show an over-all increase in IGF-1 and IGFBP-3 over the series of serum samples. The most marked increases occurred within the first 30 days of use of the nanoliposomal, amino acid complex secretagogue.

A comment about the significance of an increased level of IGFBP-3 is that this occurs only in response to increases in GH, IGF-1, and Estrogen. Looking down the list of responses, there are noted participants who achieved a measurable elevation in IGFBP-3 while the level of IGF-1 was negligible or decreased. As discussed above, the change in concentration of IGFBP-3 has an inverse effect on IGF-1's measurable level and more so represents a recent increase in GH and IGF1 levels precipitated by the secretagogue.

Since secretagogues work within the natural homeostatic regulatory system, once the levels of GH and/or IGF-1 are perceived by the neuoregulatory system to be above the level physiologically necessary, Somatostatin is released by the supra optic nuclei, and the release of GHrH by the hypothalamus is decreased in order to down-regulate GH release from the Anterior Pituitary.

Accounting for the wide range of responses to this secretagogue is difficult, at best, because of the number of variables that existed during testing. We considered a number of factors that have already been shown in the literature to influence the inherent production of GH from the pituitary and considered all of them to be enhancers to any response that we anticipated from the secretagogue. These factors are age, Body Metabolic Index (BMI), weight, percent body fat, supplementation with vitamins, Insulin-like Growth Factor Binding Protein 3, Dehydroepiandrosterone (DHEA), pregnenolone, cognitive amino acids, exercise, and nutrition.

At the time this study was designed, it was and still is the conviction of the designer (Mark L. Gordon, M.D.) that in order to achieve optimal benefits, all hormones must be within physiological parameters. It is becoming more apparent that the ultimate responses obtained from the supplementation of any hormone are predicated by the presence of physiological levels of all the hormones. This is due to the complex synergy of interactions amongst all the hormones where in order for any one specific hormone to produce an optimal response all the other hormones need to be present at a physiological level. Therefore, to obtain the optimal treatment response in each patient both major and minor hormones need to be assessed and maintained at physiological levels in order to gain the most benefits.

Additionally, there are studies that show that the full effectiveness of any product on the modulation of hormone production, augmentation or even reduction is based upon a comprehensive balance of all neurosecretory and neurosteroids being of physiological levels. That is to say, if we just corrected a portion of the neuron-hormonal milieu there would be a biochemical deficiency that would impede the optimal response from other neurogenic stimuli.

Whether that stimulus is to reduce a hormone's release, or to increase its production and release (i.e. Somatostatin versus GHrH) the effectiveness of that response can be attenuated by a tangential deficiency.

Neuroendocrinology research has published a number of articles showing there is a positive influence of DHEA on the anterior pituitary production of GH.[46]. When DHEA was supplemented in women on daily growth hormone injections their IGF-1 increased significantly enough to allow for a reduction in the dose of GH [47].

CONCLUSION

The ability of this amino acid complex to elevate the production and release of Growth Hormone is defined by the change in both IGF-1 and IGFBP-3 levels. The diverse range of increases observed was comparable to the wide range of IGF-1 elevations seen in patients using rhGH. In both groups there are, as of yet, unknown biochemical and hormonal interactions that appear to influence the quality of responsiveness to said products. The quality of the response is also influenced by the peripheral recognition of the Growth Hormone molecule at functional receptors (Laron's Syndrome). We are finding that there are a number of genetically precipitated receptor abnormalities that can alter the optimal production of IGF-1. Thereafter, the ability of IGF-1 to be recognized at its own receptor-site (as well as at the insulin receptors) has a bearing on the ultimate benefits.

Nearly five years ago, it became apparent that the relationship between IGF-1 and IGFBP-3 was important enough to investigate beyond the superficiality of it being just a carrier. At that time, we were not aware of the laboratory limitations of IGF-1 testing in that the technology was only able to measure the Free-IGF-1 and not the Total-IGF-1. Frequently we never measured the IGFBP-3 levels thinking that they were non-functional in terms of benefiting our patient's care. Frequently, we chased IGF-1 levels due to a poor response from injecting 1 IU of GH a day. Had we been more diligent and understanding of the limitations of our laboratory technology, at the time, we would not have chased the IGF-1 levels with more Growth Hormone.

In over 10 years of treating patients with rhGH and secretagogues, one commonality has come forward as being a cornerstone to achieving an optimal response; this being the need to correct all hormones, not just some. As man is not an island, neither is any one of the hormones we produce in our body. There is a symphony going on that can produce beautiful responses if we only provide all the instruments of health.

Furthermore, although this study produced positive results, it must be taken with clinical objectivity and the understanding that there is a need to monitor the patient prior to and during treatment with this amino acid secretagogue. Therefore, the acquisition and use of this nanoliposomal secretagogue product will be restricted to physicians who will perform the recommended laboratory testing prior to initiation of treatment and subsequently based upon the protocol listed below.

RECOMMENDED PROTOCOL

Initial	Subsequent	Abbreviation	Hormone
√	√	IGF-1	Insulin-Like Growth Factor-1
√	√	IGFBP-3	Insulin-Like Growth Factor Binding Protein - 3
√		F(T)	Free Testosterone
√		DHT	Dihydrotestosterone
√	√	DHEA	Dehydroepiandrosterone
√		E1	Estrone
√	√	E2	Estradiol
√		TSH	Thyroid Stimulating Hormone
√		fT4	Free T-4 (Tetraiodothyronine)
√		fT3	Free T-3 (Triiodothyronine)

Finally, due to the significant increase in the GH/IGF-1 axis, this product will only made available to physicians and will not be sold on the internet, to retail outlets, or muti-level marketing programs. Due to the potential health benefits that healthy physiological levels of Growth hormone and IGF-1 have demonstrated in thousands of research reports, Secretropin Rx will only be available through:

UNIVERSITY COMPOUNDING PHARMACY

Acknowledgement

The Millennium Health Centers, Inc. would like to thank Dr. John Crisler for his medical and technical support and Ms. Alicia Vidor for her literary skills in the production of this study presentation.

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04-12-2008