Journal of Advancement in Medicine
Volume 12, Number 3, Fall 1999

# *Clinical Experiences Using a Low-Dose, High-Frequency Human Growth Hormone Treatment Regimen*

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*ABSTRACT:* Clinical experiences with more than 2000 patients using a low-dose high-frequency dosing regimen of human growth hormone are described. Results of a questionnaire revealed subjective positive effects of the treatment, and lower than expected incidences of adverse side effects reported by others using higher dose regimens. Retrospective analysis of patient laboratory results revealed that this treatment regimen resulted in lower levels of serum cholesterol and triglycerides, significant elevations of plasma insulin-like growth factor 1, and no increase in serum prostate specific antigen levels.

## Introduction

In 1990 Rudman et al. (1) reported several positive effects of human growth hormone (hGH) replacement therapy in aging adults. These positive effects included increased lean body mass, decreased adipose-tissue mass, increased average lumbar vertebral bone density, and increased skin thickness. The high-dose, low-frequency (HD) hGH replacement regimen described in that study (5 to 5.5 units of hGH injected s.c. three times weekly) is commonly used today for hGH replacement therapy.

In addition to the above-mentioned positive effects, decreases in blood lipids and improved psychological well-being and quality of life assess-

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ments have also been reported with HD hGH replacement therapy (2). The most commonly reported side-effects of HD hGH replacement therapy are fluid retention, arthralgias, and carpal tunnel syndrome (3).

In 1994 we began treating aging adults with hGH using a different treatment regimen. We chose a low-dose, high-frequency (LD) hGH replacement regimen that more closely mimics the natural rhythm of hGH release by the pineal gland. Our hypothesis was that patients could receive the same benefits of the hGH replacement therapy with fewer side effects and at a lower cost.

Herein we report our clinical experiences with treating more than 2000 patients with adult growth hormone deficiency (AGHD) using our LD hGH replacement regimen. Results of self-assessment side effects, beneficial effects, and cancer incidence surveys and retrospective analyses of pre- and post-treatment plasma IGF-I, total serum cholesterol, serum triglycerides, and serum prostate specific antigen (PSA) concentrations are presented and discussed.

## Patients and Dosing Regimen

### *Patients*

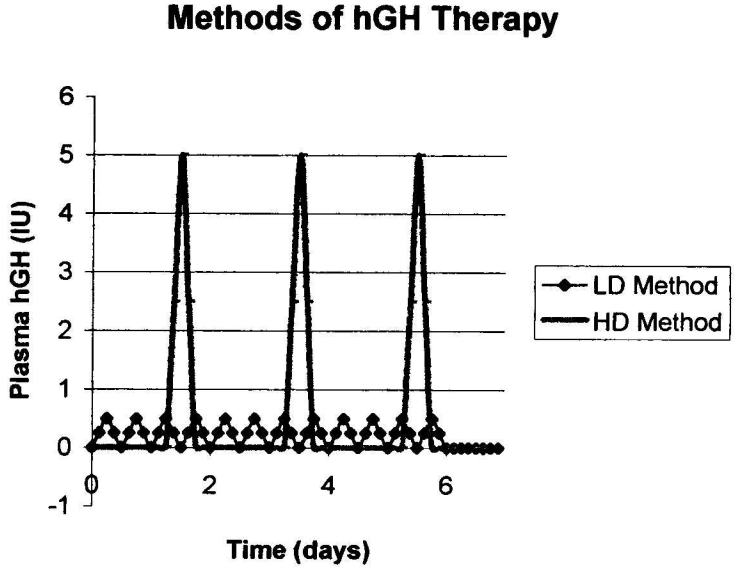
This report is based on Palm Springs Life Extension Institute clinic patients diagnosed with AGHD (defined by plasma IGF-1 level <350 ng/mL) from 1994 through 1998. Patients were instructed to self administer growth hormone subcutaneously. Recombinant human growth hormone 0.06 to 0.12 IU/kg·week was self administered subcutaneously in 12 divided doses, injected once upon rising, and once at bedtime, six days per week. Most prescriptions were filled with Genotropin, manufactured by The Upjohn Company, Kalamazoo, MI, or Humatrope, manufactured by Eli Lilly and Company, Indianapolis, IN. This schedule resulted in a weekly growth hormone dose of 3.6 to 8.4 IU. A comparison of the theoretical blood levels of hGH using our LD vs. the HD dosing regime is illustrated in Figure 1.

### *Data Analyses*

Data from a computerized database of the patients' laboratory results were analyzed retrospectively. Only data from patients treated with subcutaneous growth hormone for a minimum of 1 month were included. Data for plasma IGF-1, serum PSA, triglycerides, and cholesterol were included if a baseline and at least one intra- or post-treatment value were in the database. For cases in which multiple

**FIGURE 1**

**Theoretical plasma levels of hGH using high-dose, low-frequency (HD) and low-dose, high-frequency (LD) treatment regimens.**




intra- or post-treatment values existed, the most recent value was included and others disregarded. Using the above criteria, plasma IGF-1 data from 345 patients, serum PSA data from 142 patients, serum triglyceride data from 186 patients, and serum cholesterol data from 215 patients were analyzed.

*P* values based on two-tailed, matched pair t-tests were calculated with Microsoft Excel software for the comparisons between the values before and after therapy.

*Measurements*

During routine clinical follow up plasma IGF-1, and serum total cholesterol, triglycerides and PSA levels were determined by Pinnacle Labs, Inc., Salt Lake City, Utah. Non-age/sex-specific reference values were 71–290 ng/mL for IGF-1, 30–150 mg/dL for triglycerides, 120–240 mg/dL for total cholesterol, and 0–4 mcg/L for PSA.

## Experiences and Discussion

### *Plasma IGF-1 Levels*

One goal of the LD hGH replacement regimen was to obtain plasma IGF-1 levels between 290 and 350 ng/ml, the range Rudman et al. (1) found optimal for increasing lean body mass, bone marrow density and skin thickness while decreasing body fat. Measured IGF-1 levels before and after therapy varied among individuals. Some patients showed significant increases in plasma IGF-1 concentrations after one month of treatment, while others responded to therapy more slowly. In the case of slow responders, hGH dose was gradually increased until a response was observed. Average plasma IGF-1 concentrations before and after therapy are given in Table 1.

Males responded to hGH more quickly at lower doses than females (data not shown). The reduced response in females may be due to estrogen, which decreases hepatic IGF-1 production. The mean increase in plasma IGF-1 levels for men was roughly 75 ng/ml per month. The value in females was similar once their hGH doses were increased to compensate for their increased requirements. Typically females were given 2 to 4 units of hGH per week more than men.

There are some caveats that need to be considered when examining plasma IGF-1 measurements. There are variations in laboratory methods and reference ranges; moreover, IGF-1 concentrations reported for a given plasma sample varied among different laboratories by as much as 100 ng/ml. Another caution is that we have seen diurnal variations in plasma IGF-1 concentrations. Therefore, all blood samples used for data analysis here were drawn between 1 PM and 2 PM. These precautions allowed for accurate comparisons of IGF-1 levels for a given patient.

### *Cholesterol and Triglycerides*

Significant reductions were seen in serum concentrations of total cholesterol ($n=202$, $p<.001$) and triglycerides ($n=186$, $p<.0001$). Data are summarized in Table 1.

### *Cancer Incidence / PSA*

Increased cancer incidence is a concern with growth hormone therapy because some believe it can cause undetected cancer cells to proliferate more rapidly. Among our patients who have had growth hormone replacement therapy for six months or longer, only four have

**TABLE 1**

| | Before Treatment | After Treatment |
|---|---|---|
| Fasting Serum Cholesterol Levels (mg/dL), n = 215, mean duration of treatment in days 202, median age 54. | 224 | 209<br>p<.001 |
| Fasting Serum Triglyceride Levels (mg/dL), n = 186, mean duration of treatment in days 181, median age 54. | 191 | 145<br>p<.0001 |
| Plasma IGF-1 levels (ng/mL), n = 345, mean duration of treatment in days 216, median age 53. | 201 | 277<br>p<.00001 |
| Serum PSA levels (mcg/L), n = 142, mean duration of treatment in days 259, median age 57. | 2.4 | 2.2<br>p = .64 |

reported newly diagnosed cancer. Two of the four developed squamous cell carcinoma of the skin. They both had high exposures to sunlight. A third patient had a squamous cell cancer of the tonsil. A fourth patient developed plasma cell cancer one month after treatments began. It is unlikely that this plasma cancer developed as a result of the treatments because of the short treatment duration. We have not seen any cases of newly diagnosed prostate cancer in our patient population. There was a non-significant decrease in serum PSA levels in evaluable patients (n = 142, Table 1). These data on the surface appear to contradict the recent report of a strong positive association between IGF-1 levels and prostate cancer risk (4). IGF-1 parallels growth hormone levels in the blood; however, the two molecules do not behave similarly. Growth hormone exerts immunostimulatory effects (5) while IGF-1 possesses mitogenic and anti-apoptotic qualities. An elevated IGF-1 plasma level without concomitant elevation of plasma growth hormone level, which may have been the case in reference 4, allows for the negative effects of IGF-1 to be manifest without the positive immunostimulatory effects of growth hormone. IGF-1

concentrations in our patient population rose in response to GH levels. This may explain why there was no overall increase in serum PSA concentrations found in our data.

### *Subjective Benefits of Growth Hormone Replacement Therapy in Adults*

Self-assessment forms to assess benefits of LD hGH replacement therapy were provided to 1000 patients; 308 responded. The assessment forms asked patients to check one of three responses for each category: no improvement; slight improvement; marked improvement. The respondents were 3:1 females to males.

Self-assessment data collected at a mean assessment time of 180 days after therapy are given in Table 2. Greater than eighty percent of the respondents reported slight to marked improvements in strength, exercise capacity, and body fat reduction. Patients also reported improvements in sexual function, skin quality, healing, mental attitude, energy level, and memory. The same benefits seen with HD hGH replacement therapy were seen in our patient population.

### *Subjective Side Effects of Growth Hormone Replacement Therapy in Adults*

Self-assessment side effect reporting forms were provided to 1000 patients; 282 responded. The assessment forms asked patients to check one of three responses for each category: no side effect, mild side effect, severe side effect. Fluid retention was the most commonly reported side effect. This problem was transient, however, and could be eliminated by reducing the dose of human growth hormone initially and then gradually increasing the dose. Growth hormone's effect on activity in the sebaceous glands also gave rise to acne in some cases. Acne, like fluid retention, could be eliminated by adjustment of the hGH dose. Some patients also reported hair growth, joint pain, and carpal tunnel syndrome. A detailed list of reported side effects is in Table 3. Three patients developed prostatitis, though this may have been due to concomitant use of testosterone replacement. One diabetic patient had a temporary increase in blood sugar, which was corrected by reducing the hGH dose temporarily.

The incidence of side effects reported by respondents in this survey is lower than that reported in studies using HD hGH replacement therapy. One such study reported 60% of patients had side effects and 30% required dose adjustments due to the severity (6).

**TABLE 2**

**Patient Self-Assessment: Effect of hGH Administration in 202 Patients**

| Attribute | Percent Reporting Improvement |
|---|---|
| Strength, Exercise, and Body Fat | |
| Muscle Strength | 88% |
| Muscle Size | 81% |
| Body Fat Loss | 72% |
| Exercise Tolerance | 81% |
| Exercise Endurance | 83% |
| Skin and Hair Quality | |
| Skin Texture | 71% |
| Skin Thickness | 68% |
| Skin Elasticity | 71% |
| Wrinkle Disappearance | 51% |
| New Hair Growth | 38% |
| Healing, Flexibility, and Resistance | |
| Healing of Old Injuries | 55% |
| Healing of Other Injuries | 61% |
| Healing Capacity | 71% |
| Back Flexibility | 53% |
| Resistance to Common Illnesses | 73% |
| Sexual Function | |
| Sexual Potency/Frequency | 75% |
| Duration of Penile Erection | 62% |
| Frequency of Nighttime Urination | 57% |
| Hot Flashes | 58% |
| Menstrual Cycle Regulation | 39% |
| Energy, Emotion, and Memory | |
| Energy Level | 84% |
| Emotional Stability | 67% |
| Attitude Toward Life | 78% |
| Memory | 62% |

**TABLE 3**

**Patient Self-Assessment: Side Effects of hGH Administration in 282 Respondents**

| Side Effect | Number Reported | Percent Reporting |
|---|---|---|
| Fluid Retention | 13 | 4.6 |
| Acne | 12 | 4.3 |
| Increased Hair Growth | 8 | 2.8 |
| Joint Pains or Discomfort | 7 | 2.5 |
| Carpal Tunnel Syndrome | 5 | 1.8 |
| Prostatitis | 3 | 1.1 |
| Oily Skin | 2 | 0.7 |
| Hot Flashes (males) | 2 | 0.7 |
| Flushed Skin | 1 | 0.4 |
| Thicker Skin | 1 | 0.4 |
| Increased Blood Sugar (diabetic) | 1 | 0.4 |

## Summary

Our clinical experience with LD hGH replacement therapy for more than 2000 AGHDS patients has been that it provides the same benefits of HD hGH replacement therapy with fewer side effects and at a lower cost. This regimen results in usage of ½ to ¼ the hGH described in other clinical trials, therefore reducing the cost of therapy accordingly. Our patients, most of who were between forty-five and sixty-five years old, showed significant increases in IGF-1 levels, along with decreases in cholesterol and triglyceride levels, after treatment. Moreover, many of them reported improvements in quality of life, including increased exercise duration, sexual performance, energy levels, and muscular strength. Side effects reported by the patients were minimal and could be reversed by temporarily decreasing the hGH dose. Data analysis also showed that there was no increase in PSA associated with long term (mean 256 days) LD hGH replacement therapy. Our clinical experiences and data reported in this report suggest that LD hGH replacement therapy is a viable alternative to HD hGH replacement therapy.

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