Retrospective Analysis of the Effects of Low Dose, High Frequency Human Growth Hormone on Serum Lipids and Prostate Antigen

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ABSTRACT

Background. Elevated serum total cholesterol (TC) and triglycerides (TG) are risk factors for atherosclerosis and aschemic heart disease. Adult growth hormone deficiency (AGHD) is associated with elevated TC and TG. Many treatment protocols for AGHD use relatively high doses of growth hormone (GH) given at low frequency, which is associated with increased incidences of edema, joint pains, and carpal tunnel syndrome. We have treated > 2200 patients using a low-dose high frequency (LDHF) dosing regimen of GH and Total Hormone Replacement Therapy which results in similar beneficial subjective responses, and fewer of the side-effects associated with the higher-dosage treatment at a substantial cost savings. Clinically, in addition to increased insulin-like growth factor 1 (IGF-1), we observed lower TG and TC levels and no elevation of prostate specific antigen levels in treated patients.

Methods. A retrospective analysis of IGF-1, TG, TC and PSA data from our patient population was performed to test our hypothesis that positive objective responses of IGF-1, TG, and TC occur and that elevation of PSA does not occur in response to LDHF dosing regimen of GH. The mean duration of treatment of the analyzed data ranged from 181 to 259 days.

Results. The mean plasma IGF-1 level rose significantly ($p<.00001$) to a level 37% greater than baseline with treatment. TC and TG decreased significantly ($p<.001$) in those patients with elevated baseline values, and did not change significantly in those with normal baseline values. PSA concentrations decreased non-significantly during treatment, and few cases of edema, joint pain, or carpal tunnel were reprted.

Conclusions. Treatment of AGHD using the LDHF dosing regimen of Total Hormone Replacement Therapy resulted in significant increases in IGF-1, significant reductions in

TC and TG levels in patients with elevated baseline values, no increase in PSA concentrations, and fewer side effects than other dosing regimens.

INTRODUCTION

Hypercholesterolemia and hypertriglyceridemia are important risk factors for atherosclerosis. An increases risk of ischemic heart disease (IHD) can be detected when the cholesterol level is higher than 200 mg/dL. The National Cholesterol Education Program has suggested that cholesterol levels greater than 240 mg/dL should be considered high risk development of IHD[1].

Adult growth hormone deficiency (AGHD) appears to be associated with a lipid profile known to be related to premature atherosclerosis and cardiovascular disease[2]. Elevated total cholesterol (TC), and low density lipoprotein have been observed in a substantial proportion of patients with AGHD compared with the predicted range or to age- and sex-matched controls,[3-5] and triglyceride (TG) levels are higher compared to healthy controls [5-7]. A reduction in TC has been reported in six double blind placebo controlled trials of growth hormone replacement (GHR), [3-5,8-11] while no reduction was reported in one double placebo contolled, [12] and one non-placebo controlled trial.[13] None of these trials reported a significant reduction in TG levels, however there was a tendency for lower TG with GHR in patients with elevated baseline TG in one study.[12]

The dose of GH in the above trails was 0.25 IU/kg•week with the exceptions of the third study,[8] in which patients were treated with 0.5 IU/kg•week, and the eighth study[13] in which the dose was guided by insulin-like growth factor 1 (IGF-1, also known

as somatomedin C is an indirect measurement of growth hormone secretion) plasma levels and averaged 0.23 IU/kg•week. The dosing frequency of the above studies was three times per week.

Since 1994, one of us (EC) has administered lower doses of GH to AGHD patients in a manner that more closely mimics the normal daily pulsed pituitary secretion of GH. Typically 0.06 to 0.12 IU/kg•week was self-administered subcutaneousley in 12 divided doses, injected once upon rising, and once at bedtime, six days per week. Previously published clinical observations of over 1000 patients using this low-dose, high frequency GH regimen included increased IGF-1 levels, and many subjective improvements including increase in muscle strength, exercise endurance, sexual drive and performance, energy levels, emotions, memory, and loss of body fat.[14] Following that publication, it was noticed that normalization of hypercholesterolemia and hypertriglyceridemia occurred in patients following this regimen. We therefore retrospectively analyzed our latest objective TC, TG, and IGF-1 data from our >2200 patient pool, and present the results herein. A recent study concluded that there was a strong positive association between IGF-1 levels and prostate cancer risk.[15] Our study of our patients we also observed that serum prostate specific antigen (PSA) levels remained the same, and in some cases decreased in our patient population, PSA data were also analyzed and are presented.

MATERIALS AND METHODS

Subjects and HGH Therapy

Subjects were male and female Palm Springs Life Extension Institute clinic patients diagnosed with AGHD (defined by plasma IGF-1 level <350 ng/mL). Patients were instructed to self administer growth hormone subcutaneously. Recombinant human growth hormone (brand was left up to patient, however most prescriptions were filled with Genotropion, manufactured by The Upjohn Company, Kalamazoo, MI, or Humatrope, manufactured by Eli Lilly and Company, Indianapolis, IN) 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. This schedule resulted in a weekly GH dose of 3.6 to 8.4 IU.

Data Analysis

Data from a computerized database of the above patient were analyzed retrospectively. For data to be included, the patient must have been treated with subcutaneous growth hormone for a minimum of 1 month. Data for plasma IGF-1, serum prostate specific antigen (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 intra- or post-treatment values existed, the most recent value was included, and others disregarded. Using the above criteria plasma IGF-1 data from 349 patients, serum PSA data from 142 patients, serum triglyceride data from 191 patients, and serum cholesterol data from 215 patients were analyzed.

P values based on two-tailed, matched pair t-tests were calculated for the comparisions betweenans the intr- or post-therapy values using Microsoft Excel software.

Measurements

During routine clinical follow up, plasma IGF-1, TC, TG, 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 TG, 120-240 mg/dL for TC, and 0-4 mcg/L for PSA. Other hormones as described by The Total Hormone Replacement Therapy patent were checked and balanced per patented procedures.

RESULTS

Clinical Observations

Clinical observations were much the same as we had previously reported.[14] Most patients reported increase in muscle strength, muscle size, exercise tolerance and endurance, and a loss of body fat. Skin texture and elasticity improved, and many patients reported new hair growth, and reduction in skin wrinkling. A majority of patients reported increased sexual potency, energy level, emotional stability, and memory. Also reported were increased healing capacity, and resistance to common illness.

Laboratory Data

A significant 37% increase in IGF-1 levels was seen compared to baseline levels (Table 1). Fasting serum TG and TC levels were significantly lower after treatment

compared to baseline values. When subsets of normal and abnormal baseline TG and TC values were analyzed, it was found that there was a significant reduction in both TG and

TC in the patients with abnormally high baseline levels and a non-significant increase in both TG and TC values in the normal baseline subsets (Table 2,3). Stratification of the IGF-1, TG, and TC data into groups treated for different durations (30-120, 121-210, 211-300, and >301 days) revealed: 1) a significant increase in IGF-1 levels in all groups (Table 4); 2) a significant decrease in Tg levels in all groups (Table 5); 3) a significant reduction in TC levels in the two groups treated for 30-120, and 121-210 days, and 4) a non-significant reduction in TC levels for the groups treated for longer than 211 days (Table 6).

There was a non-significant trend toward decreases PSA values (Table 7). Only one out of twenty patients with an elevated PSA baseline value had an increase on treatment, while 18 had a reduction, and one remained the same. Interestingly, one patient, previously diagnosed with intracapsular carcinoma of the prostate experienced a dramatic decrease in PSA (33-0.2) after 11 months of treatment with GH without any other treatment for the prostate cancer.

DISCUSSION

We describe here a retrospective analysis of IGF-1, TC, TG, and PSA data culled from the records of AGHD patients treated with GH using a low-dose, high frequency dosing regimen. This regimen results in usage of ½ to ¼ the GH described in other clinical trials, therefore reducing the cost of therapy accordingly.

The analysis of these data revealed that treatment using LDHF GH regimen resulted in a significant increase of IGF-1, an indirect indicator of circulating GH levels. The analysis also demonstrated that this treatment schedule resulted in a reduction of TG

and TC in patients with elevated baseline values, and that there was not an unwanted decrease in TG and TC levels in patients with normal baseline values. We do not know whether the growth hormone itself, or another secondary factor, such as increased exercise was the prime force in reducing TC and TG in this pool of patients. The not result however, was a significant reduction in serum concentrations of two major indicators of IHD and atherosclerosis in patients with elevated TG and TC. We believe this is the first report of GH lowering Tg levels in AGHD patients.

We also demonstrated that there was no increase in PSA associated with long term (mean 256 days, range to 752 days) usage of GH, indicating no association for risk of prostate cancer with the use of GH. These data, on the surface may appear to contradict the recent report of a strong positive association between IGF-1 levels and prostate cancer risk.[15] However, IGF-1 parallels GH levels in the blood, but the two molecules do not behave similarly. GH exerts immunostimulatory effects,[16] while IGF-1 possesses mitogenic and anti-apoptotic qualities. An elevated IGF-1 plasma level without concomitant elevation of plasma GH level, as was the case in study 15, allows for the negative effects of IGF-1 to be manifest without the positive immunostimulatory effects of GH. In this study, the IGF-1 and Gh levels rose together, and may explain why there was no increase in PSA in our data.

Although this study was not double-blinded, or placebo controlled, it does contribute valuable information to those treating AGHD in the clinical setting.

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