RETROSPECTIVE ANALYSIS OF THE EFFECTS OF LOW-DOSE, HIGH FREQUENCY HUMAN GROWTH HORMONE ON SERUM LIPIDS AND PROSTATE SPECIFIC ANTIGEN

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ABSTRACT

Background. Elevated serum total cholesterol (TC) and triglycerides (TG) are risk factors for atherosclerosis and ischemic 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 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 I (IGF-I), we observed lower TG and TC levels and no elevation of prostate specific antigen levels in treated patients.

Methods. A retrospective analysis of IGF-I, TG, TC, and PSA data from our patient population was performed to test our hypothesis that positive objective responses of IGF-I, 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-I 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 reported.

Conclusions. Treatment of AGHD using the LDHF dosing regimen of GH resulted in significant increases in IGF-I, 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 increased 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 for 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 blind placebo controlled,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 trials 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 study¹³ in which the dose was guided by insulin-like growth factor I (IGF-I, also known as somatomedin C is an indirect measurement of growth hormone secretion) plasma levels and averaged 0.23 IU/kg•week. The

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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 subcutaneously 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-I 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-I data from our patient pool, and present the results herein. Because a recent study concluded that there was a strong positive association between IGF-I levels and prostate cancer risk,¹⁵ and it was 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-I 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 Genotropin, 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 patients 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-I, 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-I 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 comparisons between the baseline and the intra- or post-therapy values using Microsoft Excel software.

Measurements

During routine clinical follow up, plasma IGF-I, 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-I, 30-150 mg/dL for TG, 120-240 mg/dL for TC, and 0-4 mcg/L for PSA.

RESULTS

Clinical Observations

Subjective and objective clinical improvements were much the same as previously reported.¹⁴ There were few side effects. Less than 7% of the patients experienced edema, fewer than 3% reported new onset of joint pains, and less than 1.5% of patients experienced carpal tunnel syndrome. In most cases the side effects resolved with a reduction in GH dose.

Laboratory Data

A significant 37% increase in IGF-I 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 (Tables 2,3). Stratification of the IGF-I, TG, and

Table 1. Results of IGF-I Data Analysis

Age and Duration of Treatment; n=345	
Median Age (range)	53 (25-96)
Mean duration of treatment in days (range)	216 (30-790)
Plasma IGF-I levels (ng/mL)	
Base line mean $\pm$ SD	201 $\pm$ 65
Intra- or post-mean $\pm$ SD	277 $\pm$ 89**

**p<.00001

Table 2. Results of Triglyceride Data Analysis

Age and Duration of Treatment		
Median Age (range)		
54 (31-80)		
Mean duration of treatment in days (range)		
181 (30-752)		
Fasting Serum Triglyceride Levels (mg/dL)		
	Base line mean $\pm$ SD	Intra- or post-mean $\pm$ SD
All triglyceride data; n=186	191 $\pm$ 128	150 $\pm$ 107**
Base line triglyceride >150; n=98	280 $\pm$ 119	194 $\pm$ 125**
Base line triglyceride < or + 150; n=88	96 $\pm$ 31	101 $\pm$ 50*

*p=.38; **p<.001

TC data into groups treated for different durations (30-120, 121-210, 211-300, and >301 days) revealed: 1) a significant increase in IGF-I 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

Table 3. Results of Cholesterol Data Analysis

Age and Duration of Treatment		
Median Age (range)	54 (31-80)	
Mean duration of treatment in days (range)	202 (30-784)	
Fasting Serum Triglyceride Levels (mg/dL)		
	Base line mean ±SD	Intra- or post-mean ±SD
All cholesterol data; n=210	224±50	209±47**
Base line cholesterol >200; n=154	245±41	222±45**
Base line cholesterol < or =200; n=56	168±211	173±32*

*p<.38; **p<.001

*p=.38; **p<.001

Table 4. Results of IGF-I Analysis Comparing Groups Treated for Different Durations

Treatment duration (days)	n=	Pre-treatment (ng/mL)	Post- or Intra- Treatment (ng/mL)	p value
30-120	137	207±75	274±89	<.0001
121-210	73	212±80	294±89	<.0001
211-200	33	207±72	290±76	<.0001
301-	102	205±72	278±91	<.0001

Table 5. Results of Triglyceride Analysis Comparing Groups Treated for Different Durations

Treatment duration (days)	n=	Pre-treatment (ng/mL)	Post- or Intra- Treatment (ng/mL)	p value
30-120	39	270±131	195±160	<.05
121-210	31	271±78	183±30	<.001
211-200	12	315±82	194±31	<.01
301-	16	288±110	195±82	<.05

Table 6. Results of Total Cholesterol Analysis Comparing Groups Treated for Different Durations

Treatment duration (days)	n=	Pre-treatment (ng/mL)	Post- or Intra- Treatment (ng/mL)	p value
30-120	70	249±50	218±46	<.001
121-210	35	240±32	214±35	<.001
211-300	17	255±38	240±49	=.31
301-	32	240±26	230±50	=.37

Table 7. Results of Serum Prostate Specific Antigen (PSA) Data Analysis

Age and Duration of Treatment; n=142	
Median Age (range)	57 (22-83)
Mean duration of treatment in days (range)	259-(30-752)
PSA Levels (mcg/L)	
Base line mean ± SD	2.4±3.8
Intra- or post-mean ± SD	2.2±3.1*

*p=.64

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 decreased 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-I, TC, TG, and PSA data culled from the records of AGHD patients treated with GH using a low-dose, high-fre-

quency 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 the LDHF GH regimen resulted in a significant increase of IGF-I, 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. The reduction in TG concentration was sustained while the TC concentration reduction was transient. TC concentrations were not significantly lower than baseline after 211 days in the time-stratified data. Others have reported lower TC in GH treated males for periods up to nine months (274 days).¹⁵

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 net result however, was a significant reduction in serum concentrations of two major indicators of IHD and atherosclerosis in patients with elevated TG and TC, albeit transient in the case of 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-I levels and prostate cancer risk.¹⁶ However, IGF-I parallels GH levels in the blood, but the two molecules do not behave similarly. GH exerts immunostimulatory effects,¹⁷ while IGF-I possesses mitogenic and anti-apoptotic qualities. An elevated IGF-I plasma level without concomitant elevation of plasma GH level, as was the case in study 15, allows for the negative effects of IGF-I to be manifest without the positive immunostimulatory effects of GH. In this study, the IGF-I 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 information to those treating AGHD in the clinical setting.

REFERENCES

1. Bierman, EL: Atherosclerosis and other forms of arteriosclerosis, in Harrison's Principles of Internal Medicine, edn 12, edited by Wilson, JD, Braunwald, E, et al, New York, McGraw-Hill, Inc, 1991, pp. 996-998.
2. Carroll, PV, Christ, ER, Bengtsson BA, et al: Growth hormone deficiency in adulthood and the effects of growth hormone replacement: A review. J. Clin. Endocrinol. Metab., 83:382-395, 1997.

3. Attanasio, AF, Lamberts, SWJ, Matranga, AMC, et al: Adult growth hormone-deficient patients demonstrate heterogeneity between childhood onset and adult onset before and during human GH treatment. *J. Clin. Endocrinol. Metab.*, 82:82-88, 1997.
4. De Boer, H, Blok, GJ, Voerman, HJ, Phillips, M, and Schouten, JA: Serum lipid levels in growth hormone-deficient men. *Metab. Clin. Exp.*, 43:199-203, 1994.
5. Cuneo, RC, Salomon, F, Watts, GF, Hesp, R, and Sonksen, PH: Growth hormone treatment improves serum lipids and lipoproteins in adults with growth hormone deficiency. *Metab. Clin. Exp.*, 42:1519-1523, 1993.
6. Rosen, T, Eden, S, Larson, G, Wilhelmsen, L, and Bengtsson, BA: Cardiovascular risk factors in adult patients with growth hormone deficiency. *ACTA Endocrinol. (Copenh.)*, 129:195-200, 1993.
7. Johansson, JO, Landin, K, Tengborn, L, Rosen, T, and Bengtsson, BA: High fibrinogen and plasminogen activator inhibitor activity in growth hormone-deficient adults. *Arterioscler. Thromb.*, 14:434-437, 1994.
8. Salomon, F, Cuneo, RD, Hesp, R, and Sonksen, PH: The effects of treatment with recombinant human growth hormone on body composition and metabolism in adults with growth hormone deficiency. *N. Engl. J. Med.*, 321:1797-1803, 1989.
9. Russell-Jones, DL, Watts, GF, Weissberger, A, et al: The effect of growth hormone replacement on serum lipids, lipoproteins, apolipoproteins and cholesterol precursors in adult growth hormone deficient patients. *Clin. Endocrinol. (Oxf)* 41:345-350, 1994.
10. Beshyah, SA, Henderson, A, Niththyananthan, R, et al: The effects of short and long-term growth hormone replacement therapy in hypopituitary adults on lipid metabolism and carbohydrate tolerance. *J. Clin. Endocrinol. Metab.*, 80:356-363, 1995.
11. Weaver, JU, Monson, JP, Noonan, K, et al: The effect of low dose recombinant human growth hormone replacement on regional fat distribution, insulin sensitivity and cardiovascular risk factors in hypopituitary adults. *J. Clin. Endocrinol. Metab.*, 80:153-159, 1995.
12. Eden, S, Wiklund, O, Oscarsson, J, Rosen, T, and Bengtsson, BA: Growth hormone treatment of growth hormone-deficient adults results in a marked increase in Lp(a) and HDL cholesterol concentrations. *Arterioscler. Thromb.*, 13:296-301, 1993.
13. Rudman, D, Feller, AG, Nagraj, S, Hoskote, S, et al: Effects of human growth hormone in men over 60 years old. *N. Engl. J. Med.*, 323:1-6, 1990.
14. Terry, LC, and Chein, E: Human growth hormone replacement therapy in aging adults at the Palm Springs Life Extension Institute, in *Growing Young With HGH*, edited by Klatz, R, New York, Harper Collins, 1997, pp. 62-73.
15. Svensson J, Bengtsson B, Taskinen M, Wiklund O, Johannsson G A nine-month, placebo-controlled study of the effects of growth hormone treatment on lipoproteins and LDL size in abdominally obese men. *Growth Horm IGF Res* 2000 Jun;10(3):118-126
16. Chan, JM, Stampfer, J, Meir, J, et al: Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. *Science*, 279:563-565, 1998.
17. Bozzola, M, Valtorta, A, Moretta A, et al: In vitro and in vivo effect of growth hormone on cytotoxic activity. *J. Pediatr.*, 117:596-602, 1990.