

A Randomized, Double-Blind, Placebo-controlled Study of Growth Hormone in the Treatment of Fibromyalgia

Robert M. Bennett, MD, Sharon C. Clark, PhD, Jacqueline Walczyk, MS

PURPOSE: The cause of fibromyalgia (FM) is not known. Low levels of insulin-like growth factor 1 (IGF-1), a surrogate marker for low growth hormone (GH) secretion, occur in about one third of patients who have many clinical features of growth hormone deficiency, such as diminished energy, dysphoria, impaired cognition, poor general health, reduced exercise capacity, muscle weakness, and cold intolerance. To determine whether suboptimal growth hormone production could be relevant to the symptomatology of fibromyalgia, we assessed the clinical effects of treatment with growth hormone.

METHODS: Fifty women with fibromyalgia and low IGF-1 levels were enrolled in a randomized, placebo-controlled, double-blind study of 9 months' duration. They gave themselves daily subcutaneous injections of growth hormone or placebo. Two outcome measures—the Fibromyalgia Impact Questionnaire and the number of fibromyalgia tender points—were evaluated at 3-monthly intervals by a blinded investigator. An unblinded investigator reviewed the IGF-1 results monthly and adjusted the growth hormone dose to achieve an IGF-1 level of about 250 ng/mL.

RESULTS: Daily growth hormone injections resulted in a prompt and sustained increase in IGF-1 levels. The treatment (n = 22) group showed a significant improvement over the placebo group (n = 23) at 9 months in both the Fibromyalgia Impact Questionnaire score ($P < 0.04$) and the tender point score ($P < 0.03$). Fifteen subjects in the growth hormone group and 6 subjects in the control group experienced a global improvement ($P < 0.02$). There was a delayed response to therapy, with most patients experiencing improvement at the 6-month mark. After discontinuing growth hormone, patients experienced a worsening of symptoms. Carpal tunnel symptoms were more prevalent in the growth hormone group (7 versus 1); no other adverse events were more common in this group.

CONCLUSIONS: Women with fibromyalgia and low IGF-1 levels experienced an improvement in their overall symptomatology and number of tender points after 9 months of daily growth hormone therapy. This suggests that a secondary growth hormone deficiency may be responsible for some of the symptoms of fibromyalgia. *Am J Med.* 1998;104:227-231. ©1998 by Excerpta Medica, Inc.

Fibromyalgia is a common syndrome of widespread musculoskeletal discomfort that is readily differentiated from other causes of rheumatic pain (1). Individuals with fibromyalgia probably represent one end of the spectrum of widespread pain that has been reported in 12% to 16% of subjects responding to population surveys (2). There is increasing evidence that fibromyalgia is an example of a central pain state (3). Two well-studied pathophysiological correlates of this phenomenon are an upregulation of NMDA (N-methyl-D-aspartate) receptors at spinal synapses and a dysregulation of substance P production (4). The central pain sensitization state causes amplification of normally innocuous sensations (5). Thus the aches and pains of everyday existence become magnified and adversely affect the quality of life (6). In

some patients the resulting psychological distress causes changes in sleep, endocrine rhythms, psyche, and behavior (7,8). It has been known for 20 years that patients with fibromyalgia have an abnormal sleep pattern involving stages 3 and 4 of non-REM sleep (9). As growth hormone is secreted predominantly during stages 3 and 4 of non-REM sleep, it was hypothesized that fibromyalgia may be associated with impaired secretion of growth hormones (10). About one third of patients with fibromyalgia have low IGF-1 levels (11).

Growth hormone deficiency in adults has been associated with symptoms that are similar to those described by patients with fibromyalgia: low energy (12), poor general health (13), reduced exercise capacity (14), muscle weakness (15), cold intolerance (12), impaired cognition (16), dysthymia (12), and decreased lean body mass (17). Furthermore, growth hormone is important in maintaining muscle homeostasis (18), and it was theorized that suboptimal levels may be a factor in the impaired resolution of muscle microtrauma in fibromyalgia (19). To test the hypothesis that impaired growth hormone secretion contributes to symptoms of fibromyalgia, we studied the effects of administering growth hormone to patients with fibromyalgia who have low levels of IGF-1.

From the Department of Medicine, Oregon Health Sciences University, Portland, Oregon.

Supported in part by a research grant from Genentech, Inc., San Francisco.

Requests for reprints should be addressed to Robert Bennett, MD, Department of Medicine (L329A), Oregon Health Sciences University, Portland Oregon 97201.

Manuscript submitted March 6, 1997 and accepted in revised form September 13, 1997.

METHODS

This study was approved by the ethics committee of the Oregon Health Sciences University and performed according to their guidelines. All subjects gave their informed written consent.

Patient Population

Only women with fibromyalgia were studied. All patients fulfilled the 1990 American College of Rheumatology diagnostic criteria (1) and had an IGF-1 level <160 ng/mL. Other inclusion criteria were duration of fibromyalgia of 5 years or greater, absence of known pituitary disease, no previous growth hormone therapy, and ability and willingness to give written informed consent. Exclusion criteria included any serious medical condition that would require changes in drug therapy during the study, major depression, malignancy or history of malignancy, any other endocrine disorder including diabetes mellitus, and receipt of any other investigational therapy within 3 months of this study. Patients who were pregnant or were contemplating pregnancy during the study period were also excluded.

Medication

Growth hormone in the form of Nutropin was supplied in 5-mg vials containing sterilized lyophilized powder. (Nutropin is a recombinant protein with a 191 amino acid sequence identical to human pituitary derived growth hormone.) Excipients were mannitol, glycerin, USP for isotonicity, and phosphate for pH balance. The vial contents were reconstituted with bacteriostatic water for injection, USP (benzyl alcohol preserved). Placebo was lyophilized excipient having an appearance identical to the active drug. Excipient vials contained mannitol, glycerin, and sodium phosphate; they were reconstituted, stored, and administered in an identical fashion to growth hormone. Patients were taught to give their own subcutaneous injections.

Randomization and Blinding

Patients were randomly assigned to receive growth hormone ($n = 25$) or placebo ($n = 25$). Randomization was performed by the biostatistics department at Genentech, Inc., prior to the shipment of the treatment vials. Each treatment vial was assigned to contain either growth hormone or placebo, according to a randomization table, and vials were numbered anonymously in a sequential fashion. The randomization code was made available only to an unblinded investigator.

The vials containing either growth hormone or placebo were identical in appearance, and the code number was anonymous as to the contents. The investigator who evaluated the patients and recorded the outcome measures was blinded to the treatment group of the patients. The investigator who reviewed the IGF-1 levels and made adjustments to growth hormone doses was unblinded

and did not interact with patients. For every dosage change in a treated patient, a placebo patient was instructed to change the injected volume by a similar amount to maintain the simulation of receiving active drug.

Dose Adjustments

The dose of growth hormone was 0.0125 mg/kg daily for the first month. This relatively low initial dose was designed to minimize the development of early side effects, as a strategy for keeping the study double blinded. The dose was adjusted by the unblinded investigator at monthly intervals to maintain an IGF-1 level of about 250 ng/mL. If side effects such as edema, arthralgia, or carpal tunnel symptoms occurred, the dose was reduced to 0.0125 mg/kg per day until the problem subsided.

Outcome Measures

Two primary outcome measures were used to evaluate the effectiveness of the treatments. The *Fibromyalgia Impact Questionnaire* is a 10-item instrument that measures physical functioning, pain, depression, anxiety, fatigue, morning tiredness, stiffness, work record, job difficulty, and overall well-being (6). The instrument has been shown to have good reliability and validity (20). A lower score indicates improvement; the maximum possible score is 100. *Fibromyalgia tender points* were examined using the protocol described by Wolfe et al (1) employing 18 standardized locations. The number of tender points could range from 11 to 18 at enrollment and from 0 to 18 at follow-up visits. In addition, at the end of the study, patients were asked whether they had experienced a worthwhile global improvement.

Follow-Up Evaluations

Patients were seen monthly for evaluation of weight, heart rate, blood pressure, peripheral edema, carpal tunnel syndrome symptoms, adverse reactions, IGF-1 levels, and antibodies to human growth hormone. At baseline and at months 3, 6, and 9 patients completed the *Fibromyalgia Impact Questionnaire*, were evaluated for fibromyalgia tender points, and had a complete blood count, chemistry screen, and urinalysis.

Serological Tests

All blood samples were drawn between 10.00 AM and 4.00 PM. IGF-1 was measured on serum samples that had been acid/ethanol extracted to remove IGF-1 binding proteins. The assay was performed at Endocrine Sciences (Calabas Hills, California), as previously described (11). The inter-assay and intra-assay coefficients of variation were 7.3% and 5.4%, respectively. Antibodies to growth hormone were measured by a radioimmunoassay performed at Genentech.

Statistical Analysis

Based on the previous work (21), it was estimated that a sample size of 40 would be sufficient to detect a change in

Table 1. Demographics of Patient Population

	Control Group	Growth Hormone Group
Number starting study	25	25
Number finishing study	23	22
Meeting criteria for CFS	18	11
Age	47.9 ± 6.6	46.5 ± 6.4
Weight (kg)	84.8 ± 15.8	84.0 ± 22
Height (inches)	64.8 ± 2.0	64.1 ± 2.9
Initial IGF-1 level (ng/mL)	106 ± 35	100 ± 31
Taking NSAIDs	8	12
Taking tricyclics	9	11
Taking estrogens	19	12

CFS/chronic fatigue syndrome; IGF/insulin-like growth factor; NSAIDs/nonsteroidal antiinflammatory drugs.

Fibromyalgia Impact Questionnaire scoring of 10 and tender point scoring of 3, with an alpha of <0.05 and a power of 80%. Fifty subjects were enrolled in the study to allow for drop-outs. Analysis was based on the intention-to-treat principle. Prior to using parametric tests, we tested for normality using a Kolmogorov-Smirnoff test. If this failed, nonparametric distributions were compared with a Wilcoxon rank sum test or Kruskal-Wallis ANOVA on ranks test. Within-group comparisons from baseline to 9 months employed *t* tests or Wilcoxon rank sum tests. Between-group comparisons used analysis of variance (ANOVA), with Dunnett's test for assessment of individual differences. A chi-square analysis with Yates' correction was used to compare categorical variables. All *P* values were based on a two-tailed distribution, and 95% confidence intervals (CI) were estimated.

RESULTS

Fifty patients were enrolled according to the protocol guidelines. Forty-five patients completed all 9 months of study. The two treatment groups were similar in all major demographic features (Table 1). Eighteen subjects in the placebo group and 11 patients in the growth hormone group fulfilled modified criteria for the chronic fatigue syndrome (22). Three patients in the growth hormone group were discontinued, 2 for medical reasons and 1 for noncompliance. Two patients receiving placebo were discontinued, 1 for medical reasons and 1 for noncompliance. There was an abrupt increase in IGF-1 levels within the first month in all 25 patients receiving growth hormone injections; this was sustained throughout the 9-month treatment period. The placebo group showed no increase in IGF-1 levels (Figure 1). Antibodies to growth hormone were not found at any point during the study.

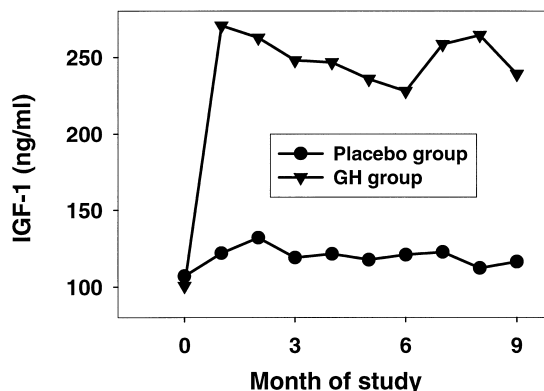


Figure 1. Mean IGF-1 levels in patients tested with growth hormone or placebo.

Between-Group Analysis

There was a significant improvement in the growth hormone treated group compared with the placebo group (Figure 2) at the 9-month evaluation for both the Fibromyalgia Impact Questionnaire Score (*P* <0.04) and the

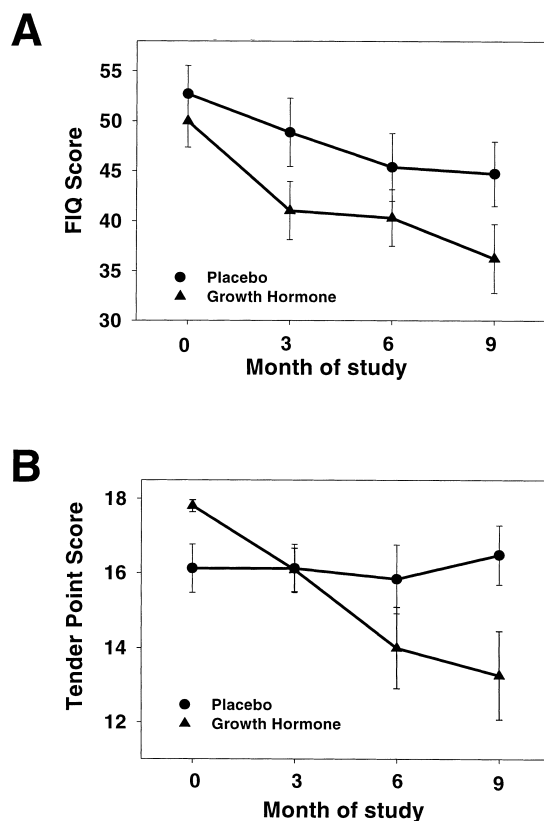


Figure 2. Mean (SD) scores on the Fibromyalgia Impact Questionnaire (graph A) and the number of fibromyalgia tender points (graph B) in patients treated with growth hormone or placebo. Scores at 9 months are significantly different (*P* <0.05) in the two groups.

fibromyalgia trigger point score ($P < 0.03$). The mean differences in questionnaire scores (growth hormone - placebo) were -2.7 (95% CI: -10.5 to $+5.1$) at baseline, -7.8 (95% CI: -16.8 to $+1.2$) at 3 months, -4.1 (95% CI: -9.8 to $+8.4$) at 6 months, and -8.5 (95% CI: -18.0 to -1.1) at 9 months. The mean differences in tender point scores were $+1.7$ (95% CI: $+3.0$ to -0.34) at baseline, -0.04 (95% CI: -1.8 to -1.7) at 3 months, -1.8 (95% CI: -4.7 to $+1.1$) at 6 months, and 3.3 (95% CI: -6.1 to -0.4) at 9 months.

Within-Group Analysis

The growth hormone group achieved a significant improvement between baseline and 9 months in the Fibromyalgia Impact Questionnaire score of -13.8 (95% CI: -5.3 to -22.3); the mean change in the tender point score was -4.5 (95% CI: -0.21 to -6.8). The placebo subjects failed to achieve a significant improvement between baseline and 9 months (Table 2). Fifteen subjects in the growth hormone group and 6 in the control group experienced a worthwhile global improvement at the end of the study ($P < 0.02$).

Eleven patients in the growth hormone group and 18 patients in the placebo group also fulfilled criteria for the chronic fatigue syndrome. The mean change in tender points between baseline and 9 months in the growth hormone group was 5.5 (95% CI: -2.3 to -8.7 , $P = 0.002$). In the placebo group the mean change was -1.8 (95% CI: -4.7 to $+1.1$, $P = 0.222$). There was a nonsignificant improvement in the Fibromyalgia Impact Questionnaire score in the growth hormone group ($P = 0.08$) compared with the placebo group ($P = 0.1$).

Adverse Reactions

No unexpected adverse reactions that could be attributed to the growth hormone injections were encountered. Two patients in the growth hormone group who had to discontinue the study for serious problems (a sciatic nerve tumor and cardiomyopathy) had early symptoms of these problems prior to entering the study. There were no significant changes in weight, blood pressure, or glucose levels in patients taking growth hormone. Carpal tunnel symptoms occurred in 7 growth hormone patients compared with 1 control. Symptoms were treated by lowering the dose of growth hormone and the provision of night-time wrist splints. They were usually seen in the early stages of therapy; none of the growth hormone treated patients were experiencing carpal tunnel symptoms at the end of the study.

DISCUSSION

We assessed the efficacy of recombinant human growth hormone in the treatment of fibromyalgia patients. The treated group experienced significant improvement after

Table 2. Change in Primary Outcome Measures from Baseline to Finish

	Baseline	Finish	<i>P</i> value
Placebo Group			
FIQ	52.7 ± 14.3	46.6 ± 17.8	0.19
T. point	16.12 ± 3.23	16.48 ± 4.76	0.76
Growth hormone group			
FIQ	50.0 ± 13.1	36.2 ± 16.6	0.0025
T. point	17.79 ± 0.83	13.26 ± 5.71	0.0037

FIQ/fibromyalgia impact questionnaire (range 0–100); T. point/tender point score (range 0–18).

9 months of treatment in symptoms, as measured by the Fibromyalgia Impact Questionnaire, and signs, as measured by the tender point score. No patient had a complete remission of symptoms, although several patients experienced an impressive improvement in their functional ability. In general there was a lag of about 6 months before patients started to note improvement. It is probably pertinent that the reported effects of growth hormone on improving muscle strength and exercise performance describe a benefit at about 3 months, with progressive improvements thereafter (14,23). Such a time course would be unusual for a placebo response.

The beneficial changes that patients remarked upon were not precisely captured by the standard fibromyalgia outcome measures used in this study. A common observation was an initial increased sense of well-being followed by the ability to sustain increased levels of activity without the usual increase in muscle pain. All patients who experienced improvement with growth hormone experienced a reversion of symptoms over a period of 1 to 3 months after stopping growth hormone treatment. However, this observation must be interpreted with caution, as the posttreatment period was not blinded.

Growth hormone therapy in adults has been reported to improve quality of life and energy level (16), enhance cognitive psychometric performance (24), augment stroke volume (25), and improve exercise capacity and muscle strength (14,23). Formal testing has shown that the many patients with fibromyalgia have an impaired exercise capacity (26) and low aerobic fitness (27), and thus the beneficial effects on work capacity that were subjectively reported by many patients on growth hormone in the current study may have a physiological explanation. Most patients with fibromyalgia report flares of pain in muscles that have been overused. It has been suggested that this is the result of muscle microtrauma (19)—the usual cause of postexertional pain (28). However, this pain is exaggerated in fibromyalgia, both in terms of severity and the period for recovery. We have hypothesized that the prolonged recovery of muscle microtrauma in patients with fibromyalgia would be worsened by growth

hormone deficiency (11). The results of this study lend some support to this notion.

Growth hormone deficiency in fibromyalgia appears to be an epiphenomenon that occurs in a subset of patients secondary to hypothalamic-pituitary secretory dysfunction (29). An analogous "stress"-related disturbance of growth hormone secretion has recently been described in abused children (30). We hypothesize that suboptimal growth hormone secretion in patients with fibromyalgia adversely affects the symptoms of fatigue, poor exercise tolerance, dysthymia, and postexertional muscle pain. Because 1 month of therapy with growth hormone costs about \$1,500, the cost-benefit ratio prohibits its use in the treatment of patients with fibromyalgia and low levels of IGF-1.

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