

A PRELIMINARY STUDY OF GROWTH HORMONE THERAPY FOR CROHN'S DISEASE

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ABSTRACT

Background Crohn's disease is a chronic inflammatory disorder of the bowel. In a preliminary study, we evaluated whether the administration of growth hormone (somatropin) as well as a high-protein diet would ameliorate the symptoms of the disease.

Methods We randomly assigned 37 adults with moderate-to-severe active Crohn's disease to four months of self-administered injections of growth hormone (loading dose, 5 mg per day subcutaneously for one week, followed by a maintenance dose of 1.5 mg per day) or placebo. We instructed all patients to increase their protein intake to at least 2 g per kilogram of body weight per day. Patients continued to be treated by their usual physicians and to receive other medications for Crohn's disease. The primary end point was the change in scores on the Crohn's Disease Activity Index from base line to month 4. Scores can range from 0 to 600, with higher scores indicating more disease activity.

Results At base line, the mean (\pm SD) score on the Crohn's Disease Activity Index was somewhat higher among the 19 patients in the growth hormone group than among the 18 patients in the placebo group (287 ± 134 vs. 213 ± 120 , $P=0.09$). Three patients in the placebo group withdrew before their first follow-up visit and were not included in the data analysis. At four months, the Crohn's Disease Activity Index score had decreased by a mean of 143 ± 144 points in the growth hormone group, as compared with a decrease of 19 ± 63 points in the placebo group ($P=0.004$). Side effects in the growth hormone group included edema (in 10 patients) and headache (in 5) and usually resolved within the first month of treatment.

Conclusions Our preliminary study suggests that growth hormone may be a beneficial treatment for patients with Crohn's disease. (N Engl J Med 2000; 342:1633-7.)

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CROHN'S disease is a debilitating multisystem disorder whose cause is uncertain. It is characterized by inflammation of the bowel, which usually begins during adolescence or early adulthood and often leads to catabolism.¹ To reduce the inflammation and induce remission, patients with Crohn's disease are treated with immunosuppressive and antiinflammatory drugs that often have severe side effects and that, in some cases, enhance the catabolic process. Attempts to counteract the effects of the disease through the use of high-

protein diets have been partially successful.² The effect of regulatory peptides such as growth hormone³ and insulin-like growth factor I⁴ on intestinal growth and repair has received increasing attention in recent years, and the results of trials of growth hormone in patients with short-bowel syndrome have been encouraging.⁵ We assessed whether the administration of growth hormone in patients with Crohn's disease who are following a high-protein diet would counteract the catabolic process of the disease and reduce morbidity.

METHODS**Patients**

Between March 1997 and May 1998, patients 20 to 55 years of age in whom moderate-to-severe active Crohn's disease had been diagnosed for at least two years were recruited for the study. The diagnosis of Crohn's disease was based on a combination of radiologic and histologic criteria. Patients were excluded if they had a tumor or a history of tumor, were pregnant, or had kidney disease or diabetes or other types of endocrine disease. Because we initially had difficulty recruiting patients from local physicians, we began to recruit patients by radio advertisements. The majority of the 597 respondents did not meet the criteria. Ultimately, 142 patients were screened, 105 of whom were excluded: 70 lived too far away to return for the required frequent follow-up visits, the diagnosis of Crohn's disease could not be confirmed in 24, and 11 did not want to give themselves daily injections. Therefore, 37 consecutive patients who met the entry criteria were enrolled.

Study Design

The study was double-blind and placebo-controlled. After completion of the base-line evaluation of eligibility, the 37 patients were randomly assigned by the hospital pharmacy, with use of a permuted-block design, to receive growth hormone (in the case of 19 patients) or placebo (in the case of 18). Patients continued to be treated by their usual physicians and to receive other medications for Crohn's disease at the discretion of their physicians. The protocol was approved by the institutional review board of the hospital, and all patients provided written informed consent.

Treatment

The growth hormone group received a loading dose of 5 mg of growth hormone (somatropin, Humatrope, Eli Lilly, Indianapolis) per day subcutaneously for the first week (for example, a 70-kg patient received 0.5 mg per kilogram of body weight per week), followed by a maintenance dose of 1.5 mg per day for the remaining 16 weeks of the study (for example, a 70-kg patient received 0.15 mg per kilogram per week). Patients in the placebo

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group received an equivalent volume of diluent. Growth hormone and placebo were supplied by Eli Lilly as lyophilized powders containing 5 mg of growth hormone and placebo, respectively, for reconstitution in 1 ml of diluent. The placebo was identical in appearance to the growth hormone. Patients were taught how to prepare and inject the solution, and were asked to administer it in the morning.

Evaluation of Efficacy

The primary end point was an improvement in the clinical condition, as defined by a decrease in the score on the Crohn's Disease Activity Index between base line and four months. For one week before the initiation of therapy and for one week at the end of each month of therapy, patients used a diary card to score the Crohn's Disease Activity Index.⁶ This index assesses the severity of disease on the basis of eight clinical variables: the number of liquid or very soft stools per day, the severity of abdominal pain, general well-being, the presence or absence of an abdominal mass or extraintestinal manifestations of disease, the use of antidiarrheal drugs, hematocrit, and weight. These variables yield a composite score that ranges from 0 to approximately 600, with higher scores indicating greater disease activity. Patients were assessed one and two weeks after the initiation of therapy and again at the end of each month of the four-month study. Laboratory tests performed after an overnight fast before and at the end of four months included measurements of plasma glucose, insulin, insulin-like growth factor I, insulin-like growth factor-binding protein 3, and growth hormone-binding protein; hemoglobin; hematocrit; erythrocyte sedimentation rate; serum iron, ferritin, cholesterol, triglycerides, prealbumin, urea, and creatinine; and creatinine clearance and urinary urea nitrogen. Biochemical variables were measured in the hospital laboratory, and hormones were assessed by radioimmunoassay at Endocrine Sciences (Calabasas Hills, Calif.).

Dietary Recommendations

The dietary intake of each patient was estimated by a computerized analysis (Food Processor, version 7.1, Salem, Oreg.) of a three-day food diary before the initiation of therapy and during the last week of each month of treatment. Patients were instructed to increase their protein intake to at least 2 g per kilogram per day. This was achieved by increasing their intake of foods that were high in protein or by taking a high-protein dietary supplement.

Statistical Analysis

Analysis of efficacy was performed according to the intention-to-treat method and included all patients who received at least one dose of growth hormone or placebo and who had at least one follow-up visit. Three patients in the placebo group who did not return for the first follow-up visit and withdrew from the study within the first two weeks after starting therapy were not included in the analysis of data. Comparisons of changes in scores on the Crohn's Disease Activity Index and biochemical variables between the placebo group and the growth hormone group were analyzed with use of Student's *t*-test. Changes in the use of other drugs for Crohn's disease were assessed with use of Fisher's exact test with Yates' correction.⁷ All data are expressed as means \pm SD unless otherwise indicated, and all *P* values were two-tailed.

RESULTS

The base-line characteristics of the two groups are listed in Table 1. At base line, the mean scores on the Crohn's Disease Activity Index were somewhat higher among patients in the growth hormone group than among those in the placebo group (287 ± 134 vs. 213 ± 120 , $P=0.09$). The mean scores and the change from the base-line value at the end of each month of therapy are shown in Table 2. The decrease in scores

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	PLACEBO (N=18)	GROWTH HORMONE (N=19)
Age — yr		
Mean	41.1 \pm 9.8	39.0 \pm 9.4
Range	27–54	20–52
Sex — M/F	11/7	13/6
Weight — kg		
Mean	69.7 \pm 14.9	65.1 \pm 9.4
Range	45–99	45–83
Years since diagnosis		
Mean	15.9 \pm 8.6	17.6 \pm 9.4
Range	3–34	3–36
Crohn's Disease Activity Index†	213 \pm 120	287 \pm 134
Disease site — no. (%)		
Small intestine	17 (94)	17 (89)
Large intestine	13 (72)	15 (79)
Both	12 (67)	14 (74)
Bowel resection — no. (%)	13 (72)	13 (68)

*Plus-minus values are means \pm SD.

†Scores on the Crohn's Disease Activity Index can range from 0 to approximately 600. Higher scores indicate more disease activity.

was significantly greater in the growth hormone group than in the placebo group by the end of the first month of therapy ($P=0.02$), with further decreases occurring during the next three months of the study. At the end of the four months, 14 of the 19 patients in the growth hormone group (74 percent) had a decrease of more than 90 points in the score. Of these patients, eight had a decrease of more than 150 points, and four had a decrease of more than 300 points. Two patients in the growth hormone group had no clinical improvement: one had no change in scores, and the other had an increase, indicating more disease activity. Patients in the placebo group did not have a significant improvement in their condition ($P=0.72$).

By the end of month 4, three variables assessed by the Crohn's Disease Activity Index had significantly improved in the growth hormone group but not in the placebo group: the number of liquid or very soft stools per day ($P=0.002$), the severity of abdominal pain ($P<0.001$), and well-being ($P=0.03$); values for the other five variables were not significantly different from the base-line values. Improved well-being was associated with a marked increase in patients' energy levels.

Although there was a significant decrease in the use of other medications for Crohn's disease, this change was not reflected in the scores on the Crohn's Disease Activity Index, since the only drug included in the variable for the use of antidiarrheal drugs is atro-

TABLE 2. CHANGES FROM BASE LINE IN THE CROHN'S DISEASE ACTIVITY INDEX SCORES DURING FOUR MONTHS OF TREATMENT WITH GROWTH HORMONE OR PLACEBO.*

MONTH	PLACEBO			GROWTH HORMONE			P VALUE†
	NO. OF PATIENTS	SCORE	CHANGE FROM BASE LINE	NO. OF PATIENTS	SCORE	CHANGE FROM BASE LINE	
0 (base line)	15	206±126	—	19	287±134	—	
1	15	202±115	-5±76	19	186±107	-100±135	0.02
2	15	235±109	29±77	18	172±110	-116±139	0.001
3	15	204±140	-3±91	17	148±123	-139±159	0.006
4	15	187±163	-19±63	17	145±124	-143±144	0.004

*Plus-minus values are means ±SD. Only the 15 patients in the placebo group for whom follow-up data were available were included in the analysis. Higher scores on the Crohn's Disease Activity Index indicate more disease activity.

†P values are for the comparison of the changes in scores between the two groups.

TABLE 3. USE OF OTHER DRUGS AT BASE LINE AND AT THE END OF THE STUDY.

DRUG	PLACEBO (N=15)		GROWTH HORMONE (N=17)	
	AT BASE LINE	AT THE END OF STUDY	AT BASE LINE	AT THE END OF STUDY
	no. of patients			
Prednisone	6	8 (dose increased in 2 and decreased in 1)	7	3 (dose decreased in 3)
Immunosuppressive drugs	5	5 (dose increased in 1)	6	3
Mesalamine	11	10	13	6 (dose decreased in 2)
Narcotics	3	3	6	2 (dose decreased in 2)
Total no. of drugs*	25	26	32	14

*Some patients were taking no drugs, and some were taking more than one type of drug.

pine-diphenoxylate (Lomotil), which is no longer commonly used to treat Crohn's disease. At the end of the four months, patients in the growth hormone group had reduced their drug requirements, with 56 percent of the drugs being discontinued, as compared with a 4 percent increase in the placebo group (P=0.002) (Table 3). By the end of the study, 50 percent of the patients in the growth hormone group who still required medication had reduced the dose; in contrast, 11 percent of the patients in the placebo group who still required medication had had an increase in the dose (P=0.003). The decrease in drug use in the growth hormone group included four types of drugs used for Crohn's disease: prednisone, immunosuppressive drugs (mercaptopurine, azathioprine, and methotrexate), mesalamine, and narcotics. Since the study was only four months in duration we were unable to analyze the outcome of growth hormone therapy for longer periods.

The changes in mean plasma glucose, insulin, and

insulin-like growth factor I values before and at the end of the trial are given in Table 4. Base-line values in the placebo and growth hormone groups did not differ significantly. After treatment there were no significant differences in the changes between groups, except for a significant increase in insulin-like growth factor I levels in the growth hormone group (P=0.01). There was no significant association between insulin-like growth factor I levels in individual patients and their Crohn's Disease Activity Index scores (P=0.75). There were no significant changes in hemoglobin levels, the hematocrit, the sedimentation rate, plasma insulin-like growth factor-binding protein 3 or growth hormone-binding protein, or serum iron, ferritin, prealbumin, cholesterol, or triglycerides in either group (data not shown). Despite the increased protein intake of all patients, there were no significant changes in serum urea, creatinine, creatinine clearance, or urinary urea nitrogen (data not shown).

TABLE 4. CHANGES IN PLASMA BIOCHEMICAL VALUES FROM BASE LINE TO THE END OF THE STUDY.*

VARIABLE	NORMAL RANGE	PLACEBO			GROWTH HORMONE			P VALUE†
		BASE LINE	END OF STUDY	CHANGE FROM BASE LINE	BASE LINE	END OF STUDY	CHANGE FROM BASE LINE	
Glucose (mg/dl)	65–118	80.7±13.2	82.0±10.7	1.3±13.6	88.7±14.4	88.4±13.3	-0.3±16.9	0.77
Insulin (μU/ml)	5–20	6.5±4.0	7.7±7.7	1.3±7.9	7.8±6.1	7.8±5.3	0.03±4.6	0.56
Insulin-like growth factor I (ng/ml)	160–367	176.3±52.0	179.0±78.0	2.7±63.0	166.2±76.0	247.1±131.0	80.9±94.2	0.01

*Plus-minus values are means ±SD. Measurements were made after an overnight fast. To convert values for glucose to millimoles per liter, multiply by 0.05551. To convert values for insulin to picomoles per liter, multiply by 7.175. To convert values for insulin-like growth factor I to nanomoles per liter, multiply by 0.1307.

†P values are for the comparison of the changes in values between the two groups.

The most frequent side effects in the growth hormone group were edema (in 10 patients) and headache (in 5) during the first one to two weeks after the initial loading dose. However, both edema and headache resolved in most patients after two to three weeks of the maintenance dose. Seven patients in the placebo group had edema, and four had headache. Among the patients in the growth hormone group, arthralgia developed in one, enlarged tender lymph nodes that responded to a reduction in the dose of growth hormone occurred in another, and breast tenderness that persisted despite a reduction in the dose of growth hormone occurred in one woman. No patient in either group withdrew from the study because of side effects.

Although the patients had been asked whether they had a tumor or had a history of tumors, tumors were identified during the study in two patients receiving growth hormone and one receiving placebo. The first patient in the growth hormone group had had persistent intestinal bleeding for which he had undergone bowel resection before enrolling in the study. When the bleeding persisted during the study, an abdominal computed tomographic (CT) scan was obtained before further bowel resection was scheduled. This coincidentally detected a well-circumscribed renal tumor, which was subsequently found to be an adenocarcinoma. The second patient in the growth hormone group had had pain in the right arm for two years, which was shown on CT scanning to be due to a benign schwannoma impinging on the spine. Growth hormone therapy was discontinued in these two patients after two months and one month, respectively. The patient in the placebo group underwent an upper gastrointestinal endoscopy during the fourth month of therapy that demonstrated precancerous cells of the esophagus and a benign polyp of the stomach.

DISCUSSION

The cause of Crohn's disease remains unclear. Some have suggested that exposure to an enteric infection

or toxin alters the permeability of the gut, inducing an immune response against a luminal or tissue antigen or both.⁸ The persistence of this immunologic response is presumed to cause chronic intestinal inflammation.⁹ Others have suggested that an inherited defect in permeability may predispose persons to chronic inflammation.¹⁰ Crohn's disease is characterized by relapses that require intense medical treatment and, at times, surgical intervention. Medical therapies that are directed at attenuating the inflammatory and autoimmune aspects of the disease have potentially severe side effects. Recently, infliximab, a chimeric monoclonal antibody (cA2) against tumor necrosis factor α , has been shown to have considerable healing potential.¹¹ However, infliximab also has a number of serious side effects.¹² The way in which growth hormone may benefit patients with Crohn's disease is unclear. Growth hormone enhances the uptake of amino acids¹³ and electrolytes¹⁴ by the intestines, decreases intestinal permeability, and increases intestinal protein synthesis in animals.¹⁵ Supplemental protein was provided to all our patients, since protein has been shown to enhance the synthesis of protein by muscles and overall.¹⁶ The beneficial effect of supplemental protein on the intestinal tract is further enhanced when growth hormone is administered.¹⁷

In our study, patients in the growth hormone group had significant improvement by the end of the first month, with further improvements during the subsequent three months of therapy. Clinical improvement was accompanied by a marked reduction in the amount of medications used by the patients for Crohn's disease.

In studies in which growth hormone was administered to adults, an initial low dose, with a gradual increase to a therapeutic dose, has been recommended.¹⁸ Inoue et al.¹³ found that high doses of growth hormone, but not low doses, enhanced the uptake of amino acids by the small intestine. Consequently, we reversed the usual practice and started with a high

loading dose the first week and then switched to a moderate maintenance dose for the remainder of the study. This maintenance dose was higher than the dose used in adults with growth hormone deficiency (0.5 mg per day)¹⁸ but considerably lower than that used for adults with short-bowel syndrome (6.5 mg per day).⁵

The increase in insulin-like growth factor I in patients in the growth hormone group was consistent with that seen in adults with other diseases that are treated with growth hormone.¹⁹ However, our findings do not support the possibility that the beneficial effect of growth hormone is due to the action of insulin-like growth factor I on the bowel,²⁰ since the degree of clinical improvement in individual patients was not correlated with their levels of insulin-like growth factor I.

In our study, the side effects of growth hormone therapy, such as transient edema and headache, were similar to those observed in other studies of growth hormone in adults.¹⁹ The possibility that treatment with a growth factor may induce the development of tumors in adults is a concern. Despite careful questioning of each patient before the initiation of therapy, during the course of the study we found that three patients had a tumor, two in the growth hormone group and one in the placebo group. In the two patients in the growth hormone group, the tumors were detected during the first and second months of therapy. Although we cannot be certain, we believe that these tumors were not related to growth hormone therapy.

Our preliminary study demonstrates that growth hormone may be beneficial in the treatment of patients with chronically active Crohn's disease. We did not study whether growth hormone therapy would be beneficial at the onset of Crohn's disease. A larger multicenter study should be conducted to confirm these results and to address many issues, including the best dose of growth hormone and the length and frequency of therapy that are necessary to produce and maintain clinical remission. Intestinal biopsies and radiologic studies should help clarify the mechanism of the effect of growth hormone.

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