

# Anabolic Effects of Growth Hormone Treatment in Young Children with Cystic Fibrosis

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**Key words:** cystic fibrosis, growth hormone, malnutrition, growth failure

**Background:** Malnutrition is commonly found in children with Cystic Fibrosis (CF) and is characterized by poor weight gain and linear growth. Almost one-third of children with CF are below 5th percentile for weight and height. Intensive nutritional supplementation may not result in sustained improvement in weight gain and linear growth.

**Objective:** To evaluate the anabolic effects of GH, Humatrope (Eli Lilly, 0.05 mg/kg/day) was administered to five children with CF (3 males/2 females) for an average period of 2 years.

**Methods:** All patients were maintained on caloric intake of 1.3–2.0 times the recommended daily allowance. Patients underwent standard growth hormone (GH) stimulation studies and measurement of IGF-1 and IGFBP-3.

**Results:** The mean  $\pm$  SE for age and skeletal age were  $3.2 \pm 0.85$  years and  $2.0 \pm 0.45$  years, respectively. Growth was assessed by determining both weight and height, which were normalized for age and sex by calculating Z scores using HANES I reference data. Differences in Z scores between clinic visits ( $\Delta Z$ ) were calculated for both weight and height to determine changes in growth velocity. The mean Z scores for weight and height were markedly attenuated in CF children as compared with healthy children ( $-1.95 \pm 0.23$  and  $-2.8 \pm 0.27$ , respectively). The mean  $\pm$  SE for maximum stimulated GH value, IGF-1 and IGFBP-3 were  $9.2 \pm 1.2$  ng/dl,  $67 \pm 6$  ng/ml, and  $1.7 \pm 0.22$  mg/L, respectively. GH treatment improved weight and height Z scores ( $-0.11 \pm 0.05$  and  $-0.94 \pm 0.18$ ,  $p < 0.01$ ) significantly. The  $\Delta Z$  scores for weight and height were significantly increased during first and second year of GH treatment ( $p < 0.02$ ). Also, the average values of IGF-1 and IGFBP-3 were significantly increased as compared to pretreatment values ( $186 \pm 37$  ng/ml and  $3.0 \pm 0.22$  mg/L,  $p < 0.01$ ).

**Conclusions:** GH treatment significantly improves weight and linear growth in young patients with CF. These data suggest that anabolic effects of GH may be beneficial for treatment of malnutrition in children with CF.

## INTRODUCTION

Cystic Fibrosis (CF) is the most common lethal genetic disease in the United States with an incidence of 1 in 2500 live births [1,2]. CF was believed to be a generalized disease of the exocrine glands [2]. However, it has been recognized that the disturbed chloride transport across cell membrane is primarily due to abnormalities of the cystic fibrosis transmembrane conductance regulator (CFTR) [1]. The thick mucous secretions in many organs are associated with a) chronic obstructive lung disease with predominant airway obstruction and recurrent, persistent infections; b) exocrine pancreatic insufficiency with steatorrhea; c) intestinal obstruction in neonates and older patients; d) infertility, especially in males; e) abnormally high

levels of sodium and chloride sweat, resulting from the failure of salt resorption in sweat gland ducts [3]. Most patients develop initial symptoms before the age of 2 years [1].

Protein calorie malnutrition and poor growth continue to be a significant problem for children with CF as 40% are below the 5th percentile weight age [4,5]. Poor weight gain, weight loss, and suboptimal nutrition seems to result primarily from reduced energy intake, increased energy loss, and increased energy expenditure. The energy imbalance responsible for development of malnutrition in patients with CF are believed to be due to disease factors such as chronic respiratory infections, malabsorption of nutrients [5], and possible increased metabolic rate [7].

Actual energy intakes in patients with CF have not been

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well documented. It is well recognized that their energy intakes should exceed normal requirements, and estimates have suggested that CF patients require 120% to 150% of the recommended dietary allowance (RDA) [8]. The few studies evaluating energy intake of patients with CF have found that most patients were consuming about 80 to 100% of RDA of energy for healthy individuals [9]. Furthermore, in a recent study of calorie intake of school age children with CF, it was found that they consumed an average of 106% RDA for energy and this was significantly more calories than consumed by their healthy peers (93% of the RDA for energy) [10]. However, this level of energy intake can result in deficits of up to 50% of the RDA for patients with CF and lead to deterioration of lung function, decreased total body nitrogen and growth [11,12]. Additionally, nutrient losses in stool contribute to the energy imbalance in CF. It has been shown that children with CF have increased rates of energy expenditure [13]. In general, increased energy expenditure is believed to be due to increased respiratory effort; however, the degree of increased work has not been well documented [14].

While timely and optimal delivery of nutritional support is known to be beneficial to patients with CF, intensive nutritional support alone does not always appear to meet the energy demands of some children with CF. In recent years, growth hormone (GH) use in patients with burn injuries, trauma, and chronic renal insufficiency has been shown to enhance nitrogen retention and protein synthesis [15]. GH therapy has also been demonstrated to stimulate protein synthesis during hypocaloric parenteral nutrition in both healthy and critically ill individuals [16]. Furthermore, GH treatment has been beneficial in children with renal insufficiency by improving weight gain and linear growth [17]. Theoretically, if protein synthesis and total body nitrogen can be increased in children with CF by the use of supraphysiologic doses of GH, this may be beneficial for the nutritional rehabilitation and treatment of growth failure in these patients. To date, three published studies [18–20] have evaluated the effects of GH in children with CF. All three reports have noted increase in height with varying rates of increase in weight gain. In the present study, we examined the effect of GH therapy on the rate of weight gain and growth velocity in a small group of very young CF children with growth failure over a 2-year period.

## **MATERIALS AND METHODS**

### **Patients**

Five prepubertal (Tanner stage I) Caucasian children, ages 6 months to 5.2 years, with CF who had pancreatic insufficiency and marked growth failure were recruited from the pulmonary clinic at the University of Tennessee Medical Center. Cystic Fibrosis was diagnosed based on duplicate sweat tests with chloride and sodium secretion greater than 60 mEq/L. All

children were heterozygous for  $\Delta F508$  mutation (cf/F<sub>508</sub>) [1]. Diagnosis of pancreatic insufficiency was based on 72-hour stool collection for fecal fat analysis with absorption of 90% or less.

### **Evaluation**

The clinical data from five patients with CF (3 males, 2 females) were collected over a 2- to 3.5-year period (July 1993 to December 1996). The mean  $\pm$  SE for chronologic age was  $3.2 \pm 0.85$  years before GH treatment. Each child was evaluated at 3-month intervals. At each clinic visit, patients underwent a complete physical examination and the following determinations were made: 1) length (ages 0 to 23 months) was measured using an infantometer (O'Leary lengthboard, Ellard Instrumentation Ltd., Seattle WA), 2) height (ages 2 years and older) was determined by using a stadiometer (Harpender), and 3) weight was measured with a standard electronic scale (Seca delta, model 707). Length/height and weight measurements done for each office visit were normalized for age and sex calculating individual Z score using HANES I reference data [21]. The Z score was determined by using the following formula [22]: actual value – mean value of the population/standard deviation of the population. Previous growth data of each child were assessed retrospectively by reviewing his/her medical records. Growth velocity and weight gain were determined by difference in Z score ( $\Delta Z$ ) for both height and weight between clinic visits.

### **Nutritional Assessment**

All patients and their families underwent regular nutritional counseling by our registered dietitian. The caloric requirements of each patient were evaluated approximately every 6 to 9 months and 24-hour recalls and calorie counts were obtained in order to assess the adequacy of caloric intake. All patients were prescribed diets of 1.3–2.0 times the RDA with high protein content and without dietary fat restriction. The available reported dietary intake from each patient was analyzed by a computer nutrition program (Nutritionist IV) for the following: 1) total energy intake and 2) distribution of major dietary components (carbohydrate, fat and protein). Data for total calories and protein were expressed as a percentage of the 1989 RDA guidelines [23].

### **Laboratory Testing**

Prior to the initiation of GH therapy, each subject underwent two standardized GH stimulation tests utilizing clonidine [24] and glucagon [25]. All subjects underwent thyroid function studies performed at the University of Tennessee Medical Center Laboratory. Growth hormone levels were measured with a monoclonal antibody-based immunoradiometric assay (HGH, Hybritech, Nichol's Laboratory). The assays of IGF-1 and IGFBP-3 were analyzed by standard double-antibody

methods at Nichol's Laboratory (San Juan Capistrano, CA). Finally, bone age was determined at baseline and every 12 months by method of Greulich and Pyle from a left hand radiograph [26].

### Pulmonary Function Studies

Determination of pulmonary function test were attempted in three patients during episodes of respiratory exacerbations and following recovery. The pulmonary function tests evaluated functional vital capacity (FVC), forced expiratory volume in 1 second (FEV<sub>1</sub>), and peak expiratory flow rate (PEFR). However, baseline measurements could not be obtained due to the young age of our patients.

### Medications

Recombinant human growth hormone (Humatrope, Eli Lilly) was administered at a dose of 0.05 mg/kg/day subcutaneously 6 times per week. The dose was adjusted for change in weight at each 3-month clinic visit. An informed consent was obtained from each patient's parent(s). The compliance with the GH injections were monitored by a home health nurse visiting the family once a month.

The following drugs were permitted to be administered routinely: multivitamins and vitamins A, D, E and K supplements, pancreatic enzyme (pancrease) replacement, prophylactic inhalational antibiotic therapy with gentamicin and clindamycin, inhalational steroids and bronchodilator (i.e., Albuterol) as clinically indicated.

### Statistical Methods

The primary analysis was based on results at baseline as compared to 12 months and 24 months after GH therapy. Descriptive statistics are presented as mean  $\pm$  SE. One-way analysis of variance was used to analyze differences between means of all growth variables and growth factors before and during GH treatment.

## RESULTS

The results of provocative GH stimulation tests revealed normal maximum stimulated GH response with mean  $\pm$  SE of  $9.2 \pm 1.2$  ng/dl (normal  $>7.0$  for Hybritech assay). Table 1 shows the clinical characteristics of patients with CF at baseline, 12 months and 24 months following the initiation of GH therapy. The weight and height Z scores were markedly attenuated as compared to National Center for Health Statistics (NCHS) standards (HANES I) [19]. The bone age and height age of children at baseline were modestly delayed as compared to their respective chronologic age. The baseline serum IGF-1 and IGFBP-3 were in low-normal range for age. GH treatment resulted in significant increase in both weight and height Z scores over a 2-year period. This was accompanied by modest maturation of bone age without significant change in their bone age to chronologic age ratio. Similarly, there was no significant change in bone age to height age ratio. Also, the mean values of IGF-1 and IGFBP-3 were significantly increased as compared to pretreatment values ( $p < 0.01$ ).

Table 2 demonstrates the estimated average caloric intake before and during first and second year of GH treatment that could be retrieved from the patients' charts. Reported caloric intake of children with CF were estimated at an average of 145% of RDA with high dietary content of protein estimated at more than 500% of RDA for age. During GH treatment, the average estimated caloric intakes and distribution of dietary macronutrients were comparable to estimated caloric intake before initiation of GH therapy. The review of available pulmonary function data did not reveal any significant change over the 2-year period of GH treatment (data not shown).

Fig. 1 shows the pattern of weight and height progression before and during GH therapy. GH treatment resulted in significant improvement of both weight and height Z scores during first and second year of GH treatment as compared to pretreatment weight and height Z scores ( $p < 0.02$ ). Fig. 2 demonstrates  $\Delta Z$  scores for weight and height before and during first and second year of GH treatment. There was a

**Table 1.** Clinical Characteristics of Children with Cystic Fibrosis

Characteristics	Pre-treatment	Post-treatment	
		12 months	24 months
Chronologic age (years)	$3.2 \pm 0.85$	$3.9 \pm 0.64$	$5.1 \pm 0.94$
Weight Z score	$-1.95 \pm 0.23$	$-0.97 \pm 0.25^*$	$-0.11 \pm 0.05^{*\dagger}$
Height Z score	$-2.80 \pm 0.27$	$-1.56 \pm 0.27^*$	$-0.94 \pm 0.18^{*\dagger}$
Bone age (years)	$2.0 \pm 0.45$	$2.9 \pm 0.47$	$3.6 \pm 0.58$
Height age (years)	$1.9 \pm 0.50$	$3.0 \pm 0.76$	$4.3 \pm 0.65$
BA:CA ratio	$0.75 \pm 0.08$	$0.76 \pm 0.06$	$0.79 \pm 0.07$
BA:HA ratio	$1.25 \pm 0.2$	$0.94 \pm 0.10$	$0.83 \pm 0.07$
Serum IGF-1 (ng/dl)	$67 \pm 6$	$130 \pm 17^*$	$186 \pm 37^{*\dagger}$
Serum IGFBP-3 (mg/L)	$1.7 \pm 0.22$	$2.2 \pm 0.14$	$3.0 \pm 0.22^*$

Data were analyzed by one-way analysis of variance. Data are expressed as mean  $\pm$  SE.

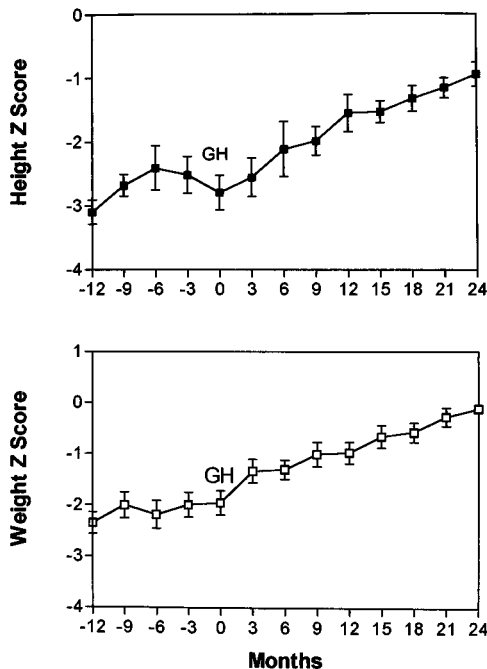
\* Significantly different from pretreatment ( $p < 0.01$ ).

† Significantly different from 12 mo ( $p < 0.02$ ).

**Table 2.** Estimated Mean Caloric Intakes before and during rhGH Treatment

	Pre-treatment	12 months	24 months
Calories			
(kcal/kg/day)	153 ± 19	151 ± 16	145 ± 20
Calories % RDA	160 ± 10	173 ± 18	195 ± 26
Protein			
(g/kg/day)	6.5 ± 1.9	6.0 ± 0.8	5.8 ± 0.7
Protein % RDA	479 ± 117	512 ± 106	594 ± 138
% CHO	49 ± 7	46 ± 3	47 ± 3
% FAT	34 ± 6	38 ± 4	37 ± 3
% PRO	17 ± 5	16 ± 2	16 ± 2

Data are expressed a mean ± SE.

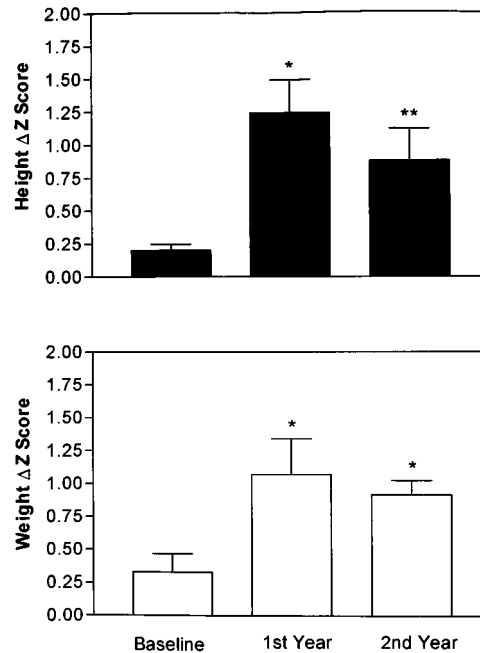


**Fig. 1.** Top—Height Z score profiles of children with CF before and during GH treatment. Data are expressed as mean ± SE and are plotted against period (months) before and after initiation of GH treatment. Bottom—Weight Z score profiles of children with CF before and during growth hormone treatment. Data are expressed as mean ± SE and are plotted against period (months) before and after initiation of GH treatment.

marked increase in weight gain during 2 years of GH therapy ( $p < 0.01$ ). This was accompanied by significant improvement in height  $\Delta Z$  scores ( $p < 0.02$ ).

**DISCUSSION**

In this study, we have shown that GH treatment of a group of very young children with CF and growth failure resulted in marked improvement in their rate of weight gain and growth. This was accompanied by significant increase in the circulating



**Fig. 2.** Top—Height  $\Delta Z$  score of children with CF before (baseline) and during first and second year of GH treatment. Data are expressed as mean ± SE. Bottom—Weight  $\Delta Z$  score profiles of children with CF before and during growth hormone treatment. Data are expressed mean ± SE. \*Significantly different from baseline ( $p < 0.01$ ). \*\*Significantly different from baseline ( $p < 0.02$ ).

growth factors: IGF-1 and IGFBP-3, without significant advancement of skeletal maturity. Additionally, the review of available nutritional data did not reveal any significant change in estimated nutrient intakes for age during GH treatment.

While it has been widely recognized that intensive nutritional intervention in patients with CF results in significant reduction in morbidity and mortality [27,28], this strategy has not always been effective in preventing growth failure and delayed puberty in these children [29]. This is because the nutritional problems in CF are multifactorial. These include intestinal losses due to malabsorption, suboptimal caloric intake, and increased energy expenditure secondary to intercurrent respiratory exacerbations/infections [6,7]. Therefore, disturbances in metabolic and energy balance appears to be mainly responsible for poor rate of weight gain and linear growth in children with CF. Furthermore, it has been shown that growth failure in CF children is 2 to 3 times higher during the periods of rapid growth (0 to 2 and 10 to 18 years) when the energy and nutrient requirements are high [30].

Maintenance of an appropriate metabolic balance is primarily under endocrine control through agents such as GH and IGF-1 [31]. Major effects of GH include reduced protein catabolism, enhancement of protein synthesis, fat mobilization and conversion of fatty acids to acetyl coenzyme A, while enhancing glycogen deposition [32,33]. The anabolic effects of

**Table 3.** GH Treatment Effect in Children with CF: Demographic and Clinical Data from Three Previous Studies and Present Study

Studies	Patient number	CA range (years)	BA range (years)	Sex	Weight velocity (kg/year)				Height velocity (cm/year)			
					Pretrial	0–12 months	12–24 months	P	Pretrial	0–12 months	12–24 months	P
Stackey et al <sup>†</sup> (1995)	4	7.0–11.6	NA	2M/2F	2.8 ± 0.5	4.78 ± 1.3	–	NS	4.83 ± 0.63	7.05 ± 0.82	–	0.05
Huseman et al (1996)	9	5.5–9.8	4.5–9.0	6M/3F	2.7 ± 0.45	3.2 ± 0.2	–	NS	5.7 ± 0.2	7.8 ± 0.4	–	0.05
Hardin et al NCGS (1997)	24	1.6–15.8	NA	16M/8F	NA	NA	NA	–	3.7 ± 0.5	7.7 ± 0.3	6.5 ± 0.2	0.02
Present study*	4	2.0–5.2	1.5–3.2	4M	1.8 ± 0.43	2.6 ± 0.34	3.5 ± 0.6*	0.05	5.0 ± 0.73	7.3 ± 0.45	9.0 ± 0.85*	0.02

Data are expressed as mean ± SE, data and statistical analysis were reproduced from published article (references 18–20). The following abbreviations were used: CA=chronologic age; BA=bone age; NA=not available; P, significant level of difference between pretrial and post-treatment weight or height velocity; NS=not significant.

\* Excluded one patient age 6 months.

<sup>†</sup> Excluded three patients ages 3.5 to 11.1 years treated for only 6 months.

GH are mediated by somatomedins, principally IGF-1 [34], which acts on muscle to suppress protein degradation while it increases amino acid uptake and cellular proliferation [35]. The endocrine effects of IGF-1 are modulated by Insulin-like growth factor binding proteins (IGFBP)-1 and -3 [36]. IGFBP-3 prolongs serum IGF-1 half-life and potentiates IGF-1 activity. IGF-1 levels appear to be inversely related to GH levels. Also, IGFBP-1 is believed to regulate the access of IGF-1 to cell receptors. Furthermore, it has been shown that the growth enhancing effect of GH and IGF-1 are influenced by nutritional factors. Malnutrition results in elevation of GH levels that promote lipolysis and fat oxidation while its anabolic effects are diminished due to reduced plasma IGF-1 [37,38], that is proportionate to the degree of nutritional depletion in many pathologic conditions [39]. Serum IGF-1 concentrations increase in response to protein-calorie repletion and has been used as an index of nutritional recovery [40].

The known anabolic effect of GH in promoting protein synthesis and tissue growth is expected to improve nitrogen balance in malnourished and hypercatabolic patients with cystic fibrosis. Table 3 summarizes the clinical data from three previous studies and our study. Stackey et al and Huseman et al evaluated the effect of rhGH in CF children 5 years and older for only 1 year, whereas the paper by Hardin et al reviews a 2-year NCGS database from a multicenter experience in children ages 1.6 to 15.8 years. In our study, our patients ranged in age from 6 months to 5 years and were treated for 2 years. Similar to other studies, our patients had suboptimal rates of weight gain and linear growth prior to the initiation of GH therapy. The observed growth failure in these young children occurred during the period of rapid growth when the energy and nutrient requirements are high [30]. This was associated with modest delay in skeletal age and low-normal serum IGF-1 and IGFBP-3 levels. Linear growth velocities increased without any significant advancement of skeletal maturity. While the rate of weight gain appeared to increase in all studies, it reached statistical significance only in NCGS database and our patients. The increased rates of weight gain and growth in our subjects was associated with elevation of plasma IGF-1 and IGFBP-3

and did not appear to be due to increased caloric intake during the GH treatment period. There was no apparent change in pulmonary function tests in those patients evaluated, although we did not have adequate baseline pulmonary function data to provide a valid assessment of pulmonary function during GH therapy.

In summary, we observed that rhGH treatment of a small group of young CF children with growth failure resulted in a marked acceleration of weight gain and growth rates over a two-year period. The observed rate of weight gain and growth in these children suggests that anabolic effects of rhGH may be beneficial in treatment of malnutrition in children with CF. Moreover, longitudinal studies in a larger group of children with CF is required to assess the effect of rhGH on pulmonary function. The beneficial effect of GH on nutritional status of CF children is expected to improve or stabilize pulmonary function and lessen disease-related morbidity.

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