

# **GH improves growth and clinical status in children with cystic fibrosis – a review of published studies**

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## **Abstract**

Children with cystic fibrosis (CF) have problems with poor linear growth and inadequate weight gain. Nutritional augmentation has been the mainstay of therapy for improving both weight and height in CF; however, inadequate growth continues to be a problem. Furthermore, protein catabolism has been documented even in non-acutely ill adults and children with CF, and could adversely affect longitudinal growth. Human recombinant GH has positive effects on nitrogen balance, and multiple studies have demonstrated improved height and weight in children treated with GH. The purpose of this article is to summarize studies evaluating GH use in children with CF.

All published studies of GH use in children with CF have demonstrated significant improvement in height velocity and height Z score. All studies but one, in which subjects were treated only three times per week with GH, have demonstrated improvement in weight as reported by weight velocity and/or weight Z score, and one trial has demonstrated a substantial improvement when GH was used to augment nutritional therapy. Several reports suggest that GH treatment results in improved forced vital capacity, and multiple studies have found improved clinical status as measured by decreased hospitalizations and courses of intravenous antibiotics. Furthermore studies to date also suggest that GH results in improvement in exercise tolerance and bone accumulation. To date significant side effects, including glucose intolerance, have not been reported. Thus mounting evidence suggests that human recombinant GH provides safe and effective therapy in children with CF.

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## **Poor growth is common in cystic fibrosis (CF)**

Children with CF have difficulty gaining weight and struggle to attain normal linear growth. The most recent North American CF Foundation Annual Report (1) documented that 26% of CF children are below the 10th percentile for weight and 29% are below the 10th percentile for height. Unfortunately, the growth deficit is not corrected during puberty. Previous studies (2, 3) have documented that patients with CF have delay in attainment of pubertal maturation. These same studies also document blunting of maximal growth velocity once puberty ensues. Adults with CF have lower than average final adult heights. Adult males with CF reach an average height of 172.8 cm (36th percentile) and females 160.4 cm (38th percentile) (North American annual CF registry, unpublished data). Furthermore, 34% of CF adults were below the 85th percentile of ideal body weight (1).

Multiple studies have demonstrated the association between poor weight gain and worsened clinical status (4, 5) and much emphasis has been placed on improving nutrition in these patients. However, improvement of longitudinal growth may be important independently of the issue of improved weight gain. Two independent groups have documented an association

between poor linear growth and later worsened pulmonary function (6, 7). These groups have hypothesized that better longitudinal growth allows more lung mass resulting in better lung function. Improvement of linear growth has typically focused on improvement of nutritional intake. However, studies have suggested that stunted linear growth in children with CF can occur independently of poor nutritional intake (8–10). Our group reviewed the relationship between weight gain and linear growth by reviewing the Epidemiologic Study of CF database (ESCF, Genentech, Inc., South San Francisco, CA, USA) and found poor correlation between the two (11). Thus, nutritional supplementation alone may not be the best means for improving short stature in CF. Human recombinant growth hormone (GH) stimulates accrual of linear height, and has been used to improve weight gain in chronic illness (12–14). Multiple studies have documented its efficacy in children with CF.

## **Published studies of GH treatment in CF children**

### **Anthropometric data**

Early case reports of GH use in CF reported improved height; however, weight was not evaluated (15).

A retrospective analysis (16) of 24 CF patients treated with daily GH and whose data were maintained by the National Cooperative Growth Study (NCGS), demonstrated increased height velocity, height Z scores and weight for height standard deviation. Two patients, who were pubertal, developed glucose intolerance; however, there was no indication of prescreening for diabetes prior to initiation of GH treatment.

Several non-randomized prospective trials have been conducted. Sackey *et al.* (17) reported improved height velocity, height Z score and weight velocity in seven prepubertal children treated daily with GH. Huseman *et al.* (18) conducted a study of nine children treated with GH three times per week and reported improved height velocity and height Z scores; however, weight velocity did not statistically improve; weight Z score was not reported. Our group (19) studied nine prepubertal children treated daily with GH and found improved height velocity, height Z score, weight velocity and weight Z score. Skin-fold thickness decreased despite increased body weight, suggesting improved lean tissue mass (LTM). Alemzadeh *et al.* (20) studied GH effects in very young children (6 months–5.2 years) with CF, and reported improved height and weight Z scores. The first randomized prospective trial was conducted by our group (21) in which we studied 19 prepubertal children (10 received GH at 0.3 mg/kg per week). Although no differences existed between the groups at baseline, at 1 year the GH-treated group demonstrated significantly higher height and weight Z scores and height and weight velocity. Hutler *et al.* (22) conducted a similar study in Europe and found nearly identical effects on growth (Table 1). Both our group and Hutler evaluated LTM and found it was significantly higher in the treated group (Table 1). Our group recently completed a study of GH used as adjunctive therapy for enteral supplementation (23). We found that GH plus enteral supplementation resulted in greater height and weight gain than enteral

**Table 1** This table depicts the anthropometric data from the two published randomized controlled trials of Hutler *et al.* (22) and Hardin *et al.* (21) and demonstrates clear evidence that GH treatment results in improved height, weight and lean tissue mass in prepubertal children with CF. TX, treatment.

	Hardin <i>et al.</i> (21) 1 year (19 subjects)	Hutler <i>et al.</i> (22) 6 months (10 subjects)
Height		
NonTX	3.8±1.2	5.1±1.1
GHTX	8.2±1.3	9.0±0.9
Weight		
NonTX	2.2±1.1	1.4±1.0
GHTX	4.2±1.1	5.0±0.7
LBM		
NonTX	1.8±1.2	1.8±1.1
GHTX	4.1±1.1	5.4±0.9

**Table 2** The data are taken from our randomized trial (21), and our publication on the use of GH to augment overnight gastrostomy-tube (G-tube) feedings (23). GH provided a significant benefit to patients receiving nutritional supplementation. We also compare the results to our patients who took GH alone. FVC, forced vital capacity; FEV1, forced expiratory volume in 1 min.

	G-tube	G-tube+ GH	GH only
Height velocity (cm/year)	3.3±1.1	10.3±2.03*	8.2±1.3
Weight velocity (kg/year)	3.2±1.1	9.9±1.9*	4.2±1.1
FVC (change from baseline in 1 year, l/min)	0.05±0.2	0.43±0.2*	0.40±0.3
FEV1 (change from baseline in 1 year, l/min)	-5.4±0.3	+0.34±0.2*	0.36±0.2

\**P* < 0.05 compared to G-tube only group.

supplementation alone (Table 2). In the only study to date of teenagers, we found GH resulted in significant improvement in height, weight and LTM (24).

### Clinical status (pulmonary function, hospitalizations and exercise tolerance)

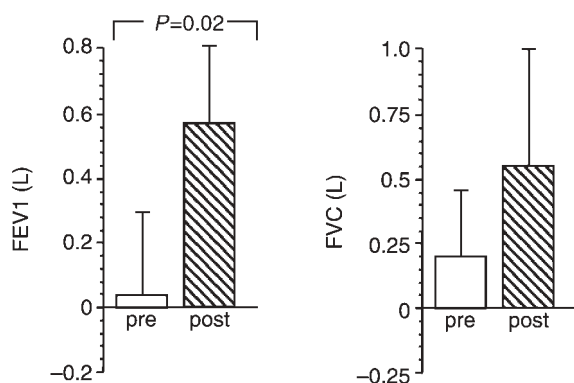
As previously stated, poor nutritional status is associated with worsened clinical status. One way to assess the clinical status of CF patients is to measure pulmonary function (forced expiratory volume in 1 min (FEV1) and forced vital capacity (FVC)). These can be expressed as absolute values or as percent predicted. Although percent predicted FEV1 is typically used as a surrogate marker for clinical status in people with CF, it is important to realize that the normalization to achieve percent predicted is derived by height matching. For example, a very short child can have relatively poor absolute pulmonary function, but appear to have normal percent predicted values because his/her values are 'matched' to those of a younger, shorter child who has less lung mass. Thus percent predicted pulmonary function is probably not the best surrogate for clinical outcome in a rapidly growing child.

Sackey *et al.* (17) evaluated FEV1 percent predicted and did not find statistical improvement. Huseman *et al.* (18) noted a 'trend towards' an increase in absolute FVC, but no change in FVC percent predicted. Alemzadeh *et al.* (20) were unable to assess pulmonary function secondary to the young age of the children. In our non-randomized trial (19), we found that percent predicted FVC and FEV1 increased during the year of GH treatment in all but two subjects, who remained the same. These results were clinically significant because all of the patients had declining pulmonary function the year prior to study. In our randomized controlled trial (21), we demonstrated improved absolute FVC, but no change in percent predicted FVC. We also found improved peak inspiratory and expiratory pressures, measures used to estimate pulmonary muscle strength. There was no significant change in absolute FVC at 6 months, and neither absolute nor percent predicted FEV1 were significantly different at

any time point. In our adolescent study (24), we found improvement in both FVC and FEV1 (Fig. 1).

Another way of estimating clinical status is to measure the number of hospitalizations or antibiotic courses. The study by Sackey *et al.* (17) demonstrated a decrease in the number of courses of antibiotic therapy during GH compared with pretreatment data. We collected data on intravenous antibiotic use in our first prospective trial (19) and found a decrease with GH. As part of our randomized controlled trial (21), we documented the effect of GH on clinical status by recording the number of hospitalizations and outpatient intravenous antibiotic courses for each subgroup as compared with the year prior to study. The GH-treated group demonstrated significant reduction in both, while there was a slight increase in hospitalizations in the non-treated group. We have found a similar decrease in hospitalizations in our adolescent study (24). Table 3 depicts the data from each study.

Exercise tolerance is yet another way of assessing clinical status. The study by Sackey *et al.* was the first study to assess this measure. They demonstrated (17) an initial decline in exercise capacity at 6 months, followed by significant improvement over baseline after 12 months of GH treatment. We evaluated (19) muscle strength by kinetic measurements of knee flexion and extension using a Cybex dynamometer in our non-randomized prospective trial. Strength significantly improved with GH; however, when strength was normalized for body weight, there was no difference between baseline and GH-treatment values. These results suggest improved muscle strength was related to body weight, most probably LTM. Hutler *et al.* (22) evaluated exercise tolerance using cycle ergometry and noted significant improvement in peak power output and  $VO_{2\text{peak}}$  by 6 months. The latest group to assess exercise tolerance was Schibler (25). They conducted a trial of 20 patients who varied in age from 10 to 23 years. Subjects were assigned to GH treatment or no treatment by age and gender matching. Maximal workload and  $VO_{2\text{max}}$  (both



**Figure 1** Pulmonary function improvement in GH-treated adolescents.

**Table 3** Compiled data on decreased hospitalisation and courses of i.v. antibiotics. Data derived from Sackey *et al.* (17), Hardin *et al.* (19, 21, 24). TX, treatment.

Author	No. of subjects treated with GH	Decrease in hospitalizations		Decrease in i.v. antibiotic use (occurrences in 12 months)	
		PreTX	GHTX	PreTX	GHTX
Sackey <i>et al.</i> (17)	7		NA	13	6*
Hardin <i>et al.</i> (19)	9		NA	3.5±4	1.4±3*
Hardin <i>et al.</i> (21)	10	1.8±1.0	0.9±0.9*	0.9±1.7	0.7±0.8
Hardin <i>et al.</i> (24)	19	2.1±0.8	0.69±0.75*		NA

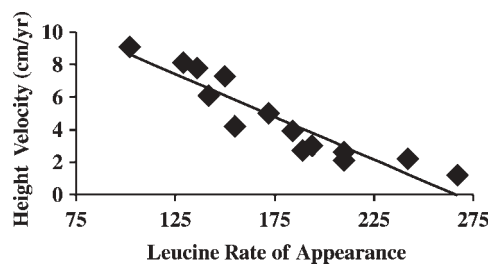
\* $P < 0.05$  as compared to baseline.

assessed by cardiopulmonary exercise testing unit) significantly increased in the GH-treated group, but did not change in the non-treated group. This study also noted a significant increase in LTM in the treated group.

## Other beneficial effects of GH

### Whole-body protein turnover (WBPT)

Many studies have documented increased WBPT and higher rates of protein breakdown in people with CF. Protein catabolism has been found both in malnourished (26) and non-malnourished groups (27, 28). Our group has found a correlation between negative protein balance and lower growth velocity in CF patients (Fig. 2), as well as in other chronically ill children. Several investigators (29, 30) have studied nutritional intervention in CF. Although they document good weight gain, improvement of linear growth is modest. These studies have also found that nutritional augmentation improves protein synthesis, but does not affect protein catabolism. Using oral [ $^{15}\text{N}$ ]glycine, Huseman *et al.* (18) were the first to evaluate the effect of GH on WBPT in CF. All subjects had a negative nitrogen balance (were protein catabolic) at baseline and all demonstrated improvement after 12 months of GH. Our group utilized the stable isotope of leucine to obtain an estimate of protein breakdown and synthesis (28). When compared with age-matched

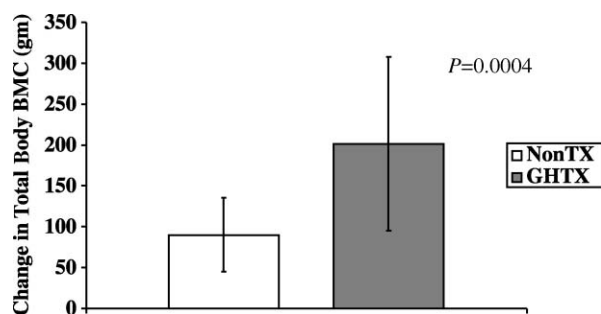


**Figure 2** This depicts the association between protein catabolism (leucine rate of appearance) and growth velocity in children with CF participating in our clinical trials. The more catabolic the child, the worse the growth velocity.

normals, the CF children were protein catabolic. Treatment with GH resulted in significantly lower protein catabolism, suggesting that improvement in weight and LTM was in part due to improved efficiency of whole-body protein kinetics. Interestingly, we did not find improvement in protein synthesis, a finding commonly reported in short-term studies of non-chronically ill GH-deficient children. We have hypothesized that the effects on protein catabolism noted in our CF children were principally secondary to improving their clinical status and to improvement in insulin-like growth factor-I (IGF-I) levels. Improvement of growth by improving IGF-I levels has been demonstrated in other types of chronic illness (13, 14, 31) and in protein-calorie malnutrition). Low IGF-I levels (28, 32) and high levels of cytokine tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) (33) have been reported in both adults and children with CF. Our group has documented (28) significant increase in IGF-I levels, as well as decreased levels of TNF- $\alpha$ , with GH treatment.

Osteoporosis is common in CF, occurring in an estimated 33% of adults and 8–20% of children with CF (34). The pathophysiology of osteoporosis is both excessive stimulation of osteoclasts (possibly from cytokines) (35), as well as decreased osteoblast function. GH increases osteoblast activity and long-term study of GH in GH-deficient adults has demonstrated improvement in bone density with GH (36). Schnable *et al.* (37) studied bone metabolism in 12 children using markers of bone formation and breakdown, as well as measuring bone density by quantitative catscan. They found bone density to be normal in these prepubertal patients, but also noted an increase in total bone density in 8 of the 12 children treated with GH. There was no change in the non-treated children. Our group recently completed an evaluation of GH effects on bone in children with CF and found significantly better accrual of bone mineral in GH-treated children (Fig. 3).

Although glucose intolerance is a significant problem in patients with CF (38), to date glucose intolerance has been documented in only one published study of GH in CF. In this retrospective study (16), the two patients who demonstrated glucose intolerance were pubertal and no prescreening for diabetes was indicated. Glucose



**Figure 3** Increased bone accrual in GH-treated prepubertal children. BMC, bone mineral content.

intolerance occurs most often in adults and pubertal patients (38); therefore, these two patients may have already had the problem prior to the initiation of GH. No other study has documented glucose intolerance or any other side effect of GH.

## Summary

All published studies of GH use in children with CF have demonstrated significant improvement in height velocity and height Z score. All studies but one, in which subjects were treated only three times per week with GH, have demonstrated improvement in weight as reported by weight velocity and/or weight Z score, and one trial has demonstrated a substantial improvement when GH was used to augment nutritional therapy. Several reports suggest that GH treatment results in clinical improvement of FVC; however, this may simply be a result of improved longitudinal growth. Multiple studies have found improved clinical status as measured by decreased hospitalizations and courses of intravenous antibiotics, and thus far evidence also suggests that GH results in improvement in exercise tolerance and bone accumulation. Thus mounting evidence suggests that human recombinant GH provides safe and effective therapy in children with CF. Our group is currently conducting a large randomized prospective trial which should help identify which children (poorly growing or moderately growing) with CF would benefit most from the drug. This very large study will also help to improve our understanding of whether GH results in better pulmonary function, beyond the effect of growth.

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