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Growth Failure and Treatment in Cystic Fibrosis

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Abstract

Poor growth has long been a characteristic feature of cystic fibrosis (CF) and is significantly linked to lung function and overall health status. Improvements in pulmonary and nutrition care for patients with cystic fibrosis (CF) have resulted in better growth outcomes; however, height gains have not paralleled the improvements in weight in children with CF, and patients with more severe CF mutations remain significantly more affected. Many factors affect the growth hormone-IGF-1 axis and the growth plate of the long bones, including the chronic inflammatory state associated with CF. There are also increasing data on the direct effects of CFTR on bone and implications for CFTR modulators in attaining optimal growth. Treatments aimed at improving growth in CF are also reviewed here.

Keywords

growth; short stature; cystic fibrosis; growth delay

1. Background

Growth is a key indicator of health status in children with cystic fibrosis (CF) and is strongly linked with CF outcomes such as nutrition and pulmonary function (1-5). While monitoring growth and nutrition status at every visit is a standard component of optimal CF care, particularly critical times for meticulous attention to growth include the 12 months after initial diagnosis, whether made prenatally, through newborn screening, or later diagnosis,

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and the peripubertal period (6). Lower weight-for-age and height-forage during the toddler years are associated with subsequently lower pulmonary function (2), and weight-for-age <50th percentile (4) and lower height (1) are risk factors for early mortality by young adulthood. Stunting, defined as <5th percentile for height, is an independent risk factor for mortality after adjusting for factors such as *CFTR* genotype, FEV1, exocrine pancreatic insufficiency, or bacterial colonization (7). Early intervention to improve growth can mitigate this risk; for infants with CF who attain weight z-score at or above birth weight by age 2 years, lung function is significantly better at age 6 years (3), and higher weight-for-age at age 4 years is associated with improved pulmonary function, height, and pubertal progression (5).

The advent of newborn screening for CF has allowed for earlier implementation of pancreatic enzyme replacement therapy, and other aggressive nutritional interventions have resulted in overall better growth (8, 9). However, improvements in height have continued to lag behind improvements in weight. In a cohort of infants diagnosed on newborn screening, 23.9% of infants remained below 10th percentile of length for age at 1 year of age, compared with only 13.6% below the 10th percentile of weight- for- age (9). In a 2012 analysis of another cohort of children diagnosed with CF by newborn screening, only 32% had attained predicted mid-parental height by puberty (10), while data from the CF Foundation registry that year indicated that 54% of children were at goal of 50th percentile for body mass index (BMI) (11). Of note, because the calculation of BMI is dependent on height, in instances of stunted linear growth, BMI would provide an incomplete assessment of growth status, as weight gain without linear growth would still result in higher BMI. Indeed, in children with CF and a BMI between the 25th and 50th percentiles, 16.8% had weight-for-age below the 10th percentile and 26.6% had height- for- age below the 10th percentile (12).

2. Mechanisms and Pathophysiology

The hypothalamic – pituitary – growth axis is the main determinant of postnatal growth. In response to hypothalamic signals, growth hormone (GH) is secreted by the anterior pituitary gland, thereby increasing production of insulin-like growth factor −1 (IGF-1) from both the liver and target tissues. In combination with GH, IGF-1 acts on the cartilaginous growth plates of the long bones to effect linear growth (13). Normally, growth rates are highest *in utero*, during infancy, and during puberty, with an intervening period of slower growth in childhood (14). At pubertal onset, there is a slowing of growth velocity prior to a pubertal acceleration; estrogen and particularly testosterone transiently stimulate pituitary GH secretion and growth acceleration, with peak height velocity occurring during mid- to late puberty, slightly earlier in girls than boys (15). Many chronic illnesses of childhood are associated with pubertal delay and impaired growth; children with CF can demonstrate this decrease in pubertal peak height velocities (16, 17) and delayed pubertal growth spurt, with greater delays in those with more severely affected lung function (16). Accordingly, patients with CF may display more severe growth impairment during puberty than in the prepubertal years (beyond infancy) (18-20).

2.1 *CFTR*, linear growth, and the GH-IGF-1 axis

Contributors to poor growth in CF are illustrated in Figure 1. *CFTR* mutation class continues to demonstrate a relationship between the severity of mutation and growth impairment that becomes more prominent over time (11). The CF Foundation Patient Registry Data Report for 2017 indicates that for infants under 24 months of age, those with the most severe mutations (class I-III) continue to have lower weight and substantially lower length percentiles than those with class IV and V mutations; with median weight percentile of 41.8 for I-III versus 51.4 for IV-V, and median length percentile of 29.5 for I-III versus 35.5 for IV-V(11). For children aged 2 to 19 years, the differences in mutation severity become more pronounced with the median weight percentile of 44.6 for class I-III compared with 61.0 for class IV-V, and a dramatic difference in median height percentile of 35.5 for class I-III versus 51.6 for Class IV-V (11).

The relationship between *CFTR* mutations and impaired growth may be partially explained by exocrine pancreatic insufficiency (PI), which is highly linked to genotype (21). Within the first 6 weeks of life, up to 85% of infants with class I-III mutations are already pancreatic insufficient (22), with 100% progression to PI by age 12 months in infants with class I and II mutations (23). Deficiency of pancreatic lipases results in macronutrient malabsorption, with particularly high caloric losses from fat malabsorption, leading to poor growth through worsening malnutrition.

The GH-IGF-1 axis is suppressed in states of malnutrition and inflammation, as seen in other chronic pro-inflammatory conditions of childhood such as juvenile idiopathic arthritis, inflammatory bowel disease, and also CF (24). However, growth impairment has also been reported in individuals with CF without substantial malnutrition or inflammation. For example, several studies have demonstrated that birth weight is already lower in neonates with CF (9, 25-27) prior to the onset of chronic lung infections or malabsorption, with subsequent faltering in length by age 12 months despite maintenance of adequate correction of weight with nutritional management (9), thus implicating a more direct role for CFTR mutations in growth impairment. Birth length has also been reported to be lower in neonates with CF (18), although not consistently (9). Hypotheses regarding the etiology of *in utero* growth failure include increased energy requirements and energy expenditure due to meconium ileus, which could shunt energy balance away from growth (27), despite the lack of dependence on the gut for nutrition during fetal life, and possible effects of defective CFTR expressed in placental tissue. The finding that placental CFTR may mediate placental aquaporin activity (28) raises the question of the role of impaired amniotic fluid and nutrient solute exchange as a factor in impaired prenatal growth. However, data to support these hypotheses remain limited.

Whether CFTR dysfunction may directly affect the GH-IGF-1 axis is also unknown. Lower IGF-1 levels are noted in both children and adults with CF (29, 30) and has previously been attributed to malnutrition, but has also been noted to be already lower in the neonatal period in both humans and animal models. Specifically, IGF-1 levels measured from blood spot newborn screening samples indicated that newborns with CF (n=23) already have a small but statistically significant reductions in IGF-1 when compared to newborns without CF (n=41) (31). At birth, CFTR-null ($CFTR^{-/-}$) pigs demonstrate decreased pituitary GH

release (from pituitary cell cultures), lower serum IGF-1 levels, and decreased bone mineral content compared to non-CF controls, despite non-significantly lower weight (31). Lower IGF-1 concentrations have also been found in CF-mice, although not until 3 weeks of postnatal life (28), indicating some interspecies variability of impairments in the GH-IGF axis in the context of CF.

Despite consistent reports of lower IGF-1 concentrations in both humans and animal models of CF (28-32), some controversy exists over the adequacy of GH hormone production in CF. Whereas some studies have suggested a decreased production of GH and IGF-1 in individuals with CF, other studies imply normal GH and/or IGF-1 concentrations in CF (33-35). Further complicating our understanding of the etiology of GH axis dysfunction in CF, in a single study of patients with CF and significant growth failure who underwent provocative testing for GH deficiency (n=18), two-thirds of subjects met standard diagnostic criteria for GH deficiency (36). Thus, CF may demonstrate significant variability along the GH-IGF-1 axis at multiple levels, and CF-related growth impairment and may have features both similar to and distinct from other states of GH deficiency or impaired GH-IGF-1 action.

CFTR is expressed in human bone and has been identified in neonatal osteoblasts, osteocytes, and osteoclasts (37). CFTR-deficient mice, CFTR-deficient rats and neonatal $CFTR^{-/-}$ pigs have all demonstrated reduced bone length in addition to diminished bone quality (31, 32, 38). CF rats revealed both reduced bone thickness and reduced IGF-1 levels when compared to wild-type controls (32). Taken together, these data suggest multiple mechanisms for direct effects of CF mutations on poor growth, which are distinct from and additive to the effects of malabsorption-related malnutrition.

The presence of CFTR in human bone (37) raises the possibility of an intrinsic defect in linear growth related to CFTR mutations; as the linear growth from the growth plate involves a multitude of cellular interactions that could be impacted either directly or indirectly by CFTR. Furthermore, differences have been demonstrated in the growth plates—specifically of the hypertrophic zone—of CF rats compared to wildtype littermates (32). Perhaps poor linear growth is a combination of intrinsic factors, hormonal influences, and biochemical influences all interrelated to overall bone health and linear growth in the CFTR deficient state.

2.2. Inflammation and glucocorticoids

The chronic pro-inflammatory state of CF is associated with increased levels of the pro-inflammatory cytokines IL-1β and TNFα, resulting in a smaller growth plate from decreased chondrogenesis (39) and increased chondrocyte apoptosis (40). IL-1β and TNFα inhibit the growth of metatarsal bones in culture and have synergistic effects on growth reduction when applied in combination (41). The mechanism for these effects may be related to impaired intracellular signaling along the GH-IGF-1 axis, as IL-1β has been shown to inhibit GH signaling in hepatocytes, resulting in GH resistance in the liver (42) and impairment of IGF-1 downstream signal activation in myoblasts (43). However, data to support this hypothesis in chondrocytes remain limited. Thus, in addition to the low IGF-1 levels as outlined above, there may be a component of inflammation-induced GH resistance through

impaired signaling along the GH axis, resulting in decreased GH-IGF-1 action and further exacerbating the poor growth seen in patients with CF.

Glucocorticoids adversely affect growth through interactions with the GH-IGF-1 axis and through direct actions on chondrocytes at the growth plate. Glucocorticoid receptors are present in the human growth plate (44), and glucocorticoids are well known to have several adverse effects on bone with chronic systemic use, ranging from suppression of growth to osteoporosis. Systemic glucocorticoid use is associated with decreased GH secretion, decreased IGF-1, and direct inhibition of growth plates through increased chondrocyte apoptosis and decreased chondrocyte proliferation and differentiation (24, 45). The use of inhaled corticosteroids, although at a significantly lower dose than systemic steroids, may still present potential concerns. In children with asthma, daily doses of inhaled corticosteroids (ICS) have been shown to temporarily reduce prepubertal growth velocity and reduce mean adult height by a small but statistically significant 1.2 cm when compared with unexposed control subjects (46). A recent Cochrane analysis of 25 trials studying the effects of ICS on growth in children with asthma concluded that use of ICS results in a mean reduction of 0.48 cm/yr in growth velocity, with the maximal impact noted during the first year of treatment with ICS and attenuated thereafter (47). In patients with CF and features of asthma requiring ICS, this relatively small effect may still represent a concern when considered in the context of overall growth impairment and its relationship to other CF outcomes.

3. Diagnostic Work Up

Careful assessment of height and weight gain remains essential to initial evaluation of growth failure. This is particularly true in the first year after diagnosis of CF, and during the peripubertal years. Length (for supine measurements) and height (standing) which is more than 2 standard deviation scores (SDS) below the mean for age, or below the 5^{th} percentile for age, are concerning predictors of mortality (1, 7). Height velocity should be assessed and is concerning if less than 4-5 cm per year for prepubertal children; decline in height velocity can identify growth failure earlier than may be detected by height percentiles alone. When assessing growth as the patient nears the age of pubertal onset, assessment of pubertal status with Tanner staging is indicated, and is concerning for pubertal delay if there are no signs of puberty by age 12-13 years in girls or age 14 years in boys. The reader is referred to the Delayed Puberty, Article 11 **in this issue**, for further details. Bone age x-ray of the left hand may assist in quantifying the degree of bone maturation and / or pubertal delay, if present. Other causes of growth failure should be ruled out such as thyroid disorders, liver / kidney disease, or celiac disease (as celiac disease and cystic fibrosis tend to affect the same population of individuals of Northern European descent). Declining growth may be an early sign of development of cystic fibrosis related diabetes seen 1-2 years before the diagnosis of CFRD (48, 49).

Due to the pulsatile nature of GH secretion, which can include undetectable GH levels in between pulses in non-GH-deficient children, random GH levels are uninterpretable for diagnosing GH deficiency; provocative testing with agents (insulin, arginine, levodopa, clonidine, or glucagon) to stimulate a peak level of GH response are often used in

diagnosing GH deficiency (50). However, these tests are imperfect even in patients without CF, due to variability in GH assays, poor reproducibility, and the non-physiological nature of the testing conditions (50). In patients with CF, given that GH deficiency is not the only underlying cause of growth failure for the mechanistic reasons outlined above, a “normal” response to GH with peak levels above 10ng/mL may be of little clinical utility. Since a normal response on provocative testing may indicate that there is no evidence of classic GH deficiency, but still does not account for other causes of poor linear growth intrinsic to CF, provocative GH testing remains controversial in patients with CF and should not be undertaken routinely in patients with CF and growth failure.

4. Routine Management

For optimal growth, nutritional and pulmonary status should be optimized, and if necessary, CFRD should be diagnosed and treated. Growth-impairing medications such as ICS should be reduced to the minimum dose and duration necessary. At this point, other pharmacologic agents may, in some individuals, be considered.

4.1 Recombinant human growth hormone

Recombinant human growth hormone (rhGH) has been studied for effects not only on growth but also on pulmonary function, bone health, and lean body mass. In the most recent update of a Cochrane review of randomized controlled trials of rhGH treatment in patients with CF, eight trials (age range, 5-23 years, n=291) were included, with rhGH dose for most studies of 0.3mg/kg/week and total treatment time of 1 year (51). Height velocity was significantly increased with rhGH treatment compared with placebo (52-55), along with improved lean body mass (46, 52-54, 56). FEV1 was improved in some trials (54, 55) but not in others (56-58). Data on bone mineral content, exercise tolerance and quality of life suggest improvement with rhGH treatment (52, 56, 57, 59), but data remain limited. A retrospective analysis of patients with CF treated with rhGH for 1 year suggests reduction in delayed puberty as compared with controls (60). Due to the known increase in insulin resistance associated with GH, theoretical concerns of inducing hyperglycemia with rhGH treatment have been raised, but there was no difference in development of impaired glucose tolerance or CFRD in rhGH-treated patients compared with control (55) and no differences in fasting plasma glucose levels (53, 55, 58). Other potential side effects regarding rhGH include increased intracranial pressure, which has been reported in 1 patient with CF (55), and scoliosis, which has not been reported in CF patients. Also, CF is not a currently approved indication for rhGH by the Food and Drug Administration (US) or the European Medicines Agency (Europe), and there are no data regarding a cost-benefit analysis of rhGH in CF.

4.2 Oxandrolone

Oxandrolone is an orally administered weak androgen with anabolic effects that has been used to enhance growth in multiple conditions. A meta-analysis of oxandrolone-rhGH combination treatment in children with Turner Syndrome indicated greater height velocity than with rhGH alone(61). Potential side effects of oxandrolone of particular concern in females include deepening of the voice, hirsutism, acne, and clitoromegaly, which appears to

be dose-dependent (61). Published data on oxandrolone use in CF are limited; in a retrospective study of patients with CF aged 8.5-14.5 years (3 male, 2 female), treatment with oxandrolone 2.5mg daily for at least 8 months resulted in improved height velocity and BMI z-score, with no adverse effects reported (specifically, neither female subject developed hirsutism, clitoromegaly, or other hyperandrogenism) (62).

4.3 Recombinant IGF-1

A single double-blind placebo-controlled study of 6 months of recombinant IGF-1 treatment in seven prepubertal children with CF did not show differences in growth velocity, weight gain, lean body mass, or FEV1 when compared with placebo (63); no additional studies of recombinant IGF-1 have been undertaken in CF.

Other agents that have been studied for growth effect in CF include insulin and CFTR modulators. Other agents used in instances of growth failure may have differential results on weight versus height improvement, depending on whether they are intended to stimulate appetite or have direct effects on linear growth, and are summarized in Table 1. Overall, published data on safety and efficacy of appetite stimulants in CF remain limited (64).

5. Potential Impact of CFTR Modulation

The advent of CFTR modulators, which target specific defects in the CFTR protein, have drastically altered the outlook for the future of CF care. The CFTR potentiator ivacaftor improves CFTR function in those with *G551D-CFTR* mutations (65) and has been shown to improve lung function, weight, and BMI, along with decreasing resting energy expenditure and gut inflammation (66-68). In an analysis of data pooled from 83 prepubertal children treated with ivacaftor in 2 clinical trials, height and weight z-scores along with height velocity increased significantly from baseline (69). In comparison to those treated with placebo, there was an improvement of +1.08cm/year in the treatment group when compared over 48 weeks (69). Thus, there are encouraging signs that improvement of CFTR function may provide additional benefits in linear growth and bone health through correction of the underlying defect.

6. Future Directions

Studies of the CFTR modulators ivacaftor and the lumacaftor/ivacaftor combination for the very young child, under 5 years of age, are underway (70-73). Ongoing follow up of patients already treated with CFTR modulators will provide additional longitudinal information on the effect of CFTR modulators on the growth patterns of peripubertal children with regard to pubertal growth acceleration and mid-pubertal peak growth velocity. Ivacaftor provided dramatic improvements in CFTR activity for individuals with G551D genotypes (74). New combination therapies are on the horizon which have the potential to provide similar improvements for a wider range of CF individuals. The impact of these therapies on linear growth will provide a better understanding of the pathogenesis of growth restriction in CF. Due to the increased burden of care associated with daily subcutaneous injections of rhGH, there has been ongoing interest in the development of longer acting growth hormone formulations, through the development of rhGH fusion proteins with longer half-lives or

through microencapsulation of the molecule for slower release (75), but currently these agents remain investigational.

7. Clinical Practice Points

- Careful attention to both height percentile and height velocity are indicated along with meticulous assessment of weight status at each visit for patients with CF, as height has additional prognostic significance in CF outcomes.
- Optimization of nutrition status remains a cornerstone of a treatment plan for poor growth, but may still be inadequate to attain adequate improvement in height.
- Inhaled corticosteroids should be used at the minimum effective dose and duration of treatment to reduce the impact on linear growth.
- Critical times to assess growth are during the first year after initial diagnosis, whether in the neonatal period or with later diagnosis, and at the time of expected pubertal onset.
- Delayed puberty or poor pubertal progression can have significant impacts on both peak growth velocity at mid-puberty and final adult height and should be addressed as part of a complete evaluation for growth failure.
- Screening for CF-related diabetes with an oral glucose tolerance test should be performed, as early glucose abnormalities may contribute to growth failure.
- Consider early referral to endocrinology if growth velocity is faltering during infancy, slower than expected during the childhood years (less than 4-5cm/year), or with delayed pubertal onset (no signs of breast bud in girls by age 12 years, no increase in testicular size by age 14 in boys, although family history and timing of pubertal development must also be considered), or height less than −2 SDS.

8. Summary

Careful ongoing measurement of both height and weight are critical in ensuring optimal growth for patients with CF. Improvements in linear growth have lagged behind improvements in weight despite earlier diagnosis of CF and earlier pulmonary and nutrition interventions. Because CFTR appears to have direct effects on linear growth and the GH-IGF-1-growth plate axis, treatments aimed directly at the GH axis and CFTR may better address suboptimal linear growth and improve height-related CF outcomes.

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Highlights

- Careful attention to both height and weight at each visit for patients with CF, is important, as height has additional prognostic significance in CF outcomes.
- Optimization of nutrition status may still be inadequate to attain improvement in height.
- Consider early endocrinology referral at any time that growth velocity is faltering.

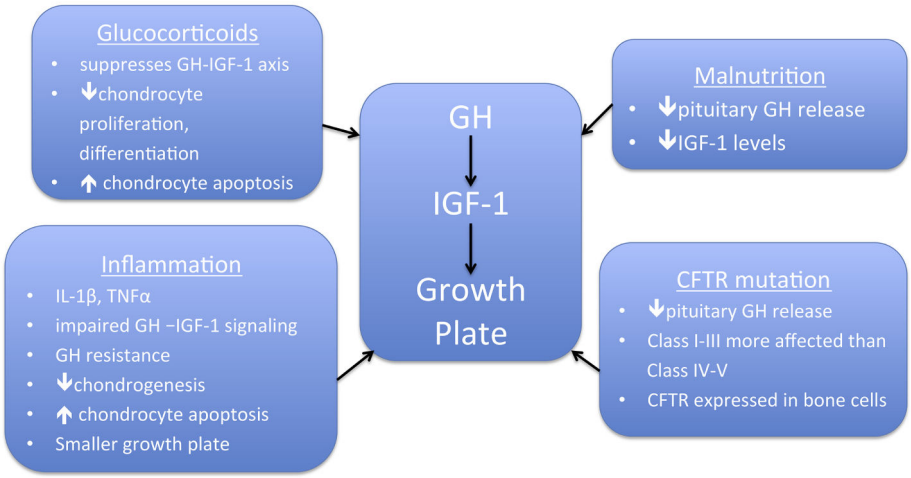

Figure 1. Contributors to Poor Growth in CF.

Multiple factors are implicated in poor growth in CF affect the GH-IGF-1-growth plate axis and can impair growth through actions on GH-IGF-1 signaling and through direct effects on the growth plate.

Table 1.

Pharmacologic Agents Studied for Effects on Growth and Nutrition in CF.

Drug	Mechanism of Action	Dosage	Adverse Effects
Megestrol acetate	Appetite stimulant, ↑neuropeptide Y	400-800mg/day or 7.5-15mg/kg/day	Glucose dysregulation, insomnia, hyperactivity, irritability, adrenal suppression, concern for increased fat vs lean body mass (76, 77). There are no data regarding a safe duration for long-term use.
Cyproheptadine	Appetite stimulant, antihistamine and serotonin agonist	4mg BID-QID or 0.5mg/kg/day	Transient mild sedation, pill fatigue (78)
Dronabinol	Appetite enhancement via central cannabinoid receptors	2.5mg daily - 5mg BID	Anxiety, confusion, euphoria, somnolence (79)
Olanzapine	Appetite stimulant, atypical antipsychotic	5-20mg daily	Liver dysfunction, sleepiness, hyperglycemia (80)
Mirtazapine	Appetite stimulant, antidepressant - central presynaptic $alpha_2$-adrenergic antagonist, potent antagonist of 5-HT_2 and 5-HT_3 serotonin receptors and H_1histamine receptor	15-45mg daily	Mild sedation, dry mouth, somnolence (81)
Oxandrolone	Anabolic steroid, ↑protein synthesis and skeletal muscle growth	0.03-0.075mg/kg/d, once daily, max 2.5mg per day for children >9-10yrs	Hepatic dysfunction, androgenic effects in females when used at high doses, rapid progression of puberty in males in high doses (61, 62)
rhGH	Anabolic agent, stimulates linear growth of linear bone, skeletal muscle	0.3-0.5 mg/kg/week dose, given as a daily SQ injection	Potential for hyperglycemia (not found to be clinically significant to date), increased intracranial pressure, additional treatment burden due to requirement for daily injections(51-55)
Ivacaftor	Potentiates epithelial cell chloride ion transport of defective (G551D mutant) cell-surface CFTR protein	150mg every 12 hours for age 6 years and up	Skin rash / hypersensitivity reaction, transaminitis, cough(82)