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Approach to the Patient

Approach to the Peripubertal Patient With Short Stature

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Abstract

Context: The assessment and treatment of children with growth retardation is increasingly complex, and due to availability of targeted genetic sequencing, an ever-expanding number of conditions impeding growth are being identified. Among endocrine-related etiologies of short stature amenable to hormonal treatment, defects in the growth hormone (GH)–insulin-like growth factor I axis remain pre-eminent, with a multiplicity of disorders causing decreased secretion or insensitivity to GH action. Sex steroids in puberty increase epiphyseal senescence and eventual growth plate closure. This is mediated mostly via estrogen receptor (ER)α in males and females, effects that can greatly limit time available for growth.

Evidence Acquisition: Extensive literature review through PubMed and other search engines.

Evidence Synthesis: Therapeutic strategies to be considered in peripubertal and pubertal children with disordered growth are here discussed, including daily and weekly GH, low-dose sex steroids, gonadotropin hormone releasing hormone (GnRH) analogues in combination with GH, aromatase inhibitors (AIs) alone and in combination with GH in boys. When used for at least 2 to 3 years, GnRH analogues combined with GH can result in meaningful increases in height. AIs used with GH permit puberty to progress in boys without hindrance, selectively decreasing estrogen, and resulting in taller height. With more than 20 years of cumulative experience in clinical use of these medications, we discuss the safety profile of these treatments.

Conclusion: The approach of growth retardation in the peripubertal and pubertal years must consider the sex steroid milieu and the tempo of bone acceleration. Treatment of affected children in this period must be individualized.

Key Words: puberty, short stature, growth hormone, GnRH analogue, aromatase inhibitor, growth

Abbreviations: ALS, acid labile subunit; CDC, Centers for Disease Control; CDGM, constitutional delay of growth and maturation; CNP, C-type natriuretic peptide; DXA, dual-energy x-ray absorptiometry; FDA, Food and Drug Administration; FGFR3, fibroblast growth factor receptor 3; GH, growth hormone; GHRH, growth hormone releasing hormone; GnRH, gonadotropin hormone releasing hormone; IGF-1, insulin-like growth factor 1; IGFBP, insulin-like growth factor binding protein; ISS, idiopathic short stature; NPR2, natriuretic peptide receptor 2; PAPPA-2, pregnancy-associated plasma protein A2; SGA, small for gestational age.

Short stature, commonly defined as height at or below −2.0 SDS below the mean according to the Centers for Disease Control (CDC) standards, is one of the most common reasons for referral to pediatric endocrinologists. Genetic and nutritional factors, the prenatal environment, postnatal factors, and hormones, alone and combination, play a role in the maintenance of normal linear growth. The perception, especially in Western cultures, that taller height is better, is also an increasingly important societal factor that drives families to seek consultation, particularly in male individuals. The evaluation of children who present with short stature in the peripubertal years presents unique challenges, as the expected development of puberty may limit the time available to enhance growth. In this article, we briefly review the physiology of linear growth, the main causes of short stature, and diagnostic approach to these children when they present in the peripubertal years; we also discuss current therapeutic approaches and possible future treatments under investigation.

Physiology of Growth

Linear growth in children is a complex process principally orchestrated by the interaction of the hypothalamic-pituitary-bone and hypothalamic-pituitary-gonadal axes. In normal growth, growth hormone (GH) production is a result of the synchronized release of hypothalamic peptides, GH releasing factor (GHRH), and somatotropin release inhibitory factor (somatostatin) secreted out of phase with each other to produce a GH pulse. GH production from the somatotropes, under the regulation of GH gene (1) is highly pulsatile (ultradian), the amplitude of those pulses much higher at night. Once released, GH travels in plasma protein bound to GH binding protein (GHBP) which is homologous to the extracellular domain of the GH receptor. GH then binds and activates the GH receptor in the GH-sensitive tissues, generating a complex cascade of events, activating the JAK/STAT signaling system, resulting in the generation of insulin-like growth factor (IGF)-1 and IGF binding protein-3 (IGFBP-3). Downstream signaling pathways, including PI3/Akt and MAPK/Erk, ultimately lead to cell proliferation and other metabolic effects, some of which are not IGF-1 mediated. IGF-1 in turn travels in plasma mostly protein bound, particularly with IGFBP-3 and the acid labile subunit (ALS) which together form a ternary complex that transports IGF-1 to the tissues to bind its cognate receptor. The liver is the source of approximately 75% of plasma IGF-1, as proven by organ-specific gene

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targeting studies (2). Pregnancy-associated plasma protein A2 (*PAPPA-2*), encodes a metalloproteinase responsible for cleavage of IGFBP-3 and IGFBP-5, a required step in the production of free IGF-1 to be available in the GH-sensitive tissues, including bone (3, 4). GH, IGFBP-3, and ALS can also have major effects modulating IGF-1 concentrations. C-type natriuretic peptide (CNP) is another player in this cascade which stimulates bone growth by activating natriuretic peptide receptor 2 (NPR2) which leads to endochondral bone growth (5). Reduced expression, mutations or deletions of genes encoding for these proteins can result in severe impairment of linear growth, including dwarfism (6, 7).

GH production is also impacted by a host of other factors including nutrition (8), and the inflammatory milieu of chronic disease states such as hypothyroidism, inflammatory bowel disease, chronic liver, kidney and cardiac disease can adversely affect GH release and/or function.

Puberty, Sex Steroids, and Growth

Puberty marks a time of rapid growth and culmination of linear growth with maximum plasma IGF-1 production (9), a process that is largely GH dependent, with more than doubling of GH production rates during that period (10, 11). The pubertal phase is characterized by a growth spurt of 8 to 14 cm per year due to the synergistic effects of increasing sex steroids and GH (10-13). On average, girls reach their peak height velocity around the age of 10 to 11 years and finish growth around 14.5 years, boys peak height velocity around the age of 12 to 13 years and complete growth at 16.5 to 17 years (14). GH, in conjunction with sex steroids and also insulin—all of which physiologically increase in this period—produce a protein-anabolic milieu that results in rapid linear growth, increased muscle mass, and increased bone mass accrual, leading to a whole-body transformation into a physically and sexually mature individual (15, 16).

Estrogens and Growth

Approximately 87% of an individual's final adult height is achieved prior to the onset of puberty, and the end of linear growth period is determined by closure of the growth plates. Hence, the peripubertal/early pubertal years (8-12 years in females, 10-14 years in males) are a critical window to investigate children with poor growth and to assess the need of intervention with growth-promoting therapies. Sex steroids have a dual effect on growth, causing a doubling of GH production rates in puberty and increasing growth velocity, while concomitantly increasing senescence of the growth plate cells leading to epiphyseal closure (16). Prismatic, seminal cases of fully virilized young men actively growing to very tall heights well into their late 20s, with mutations in the estrogen receptor causing estrogen insensitivity (17), or mutations in the aromatase gene causing estrogen deficiency (18), helped better decipher the mechanisms of growth plate closure. The most abundant estrogen receptor (ER) in bone is ERα (19), and the signaling pathways of ERs are complex, some ligand-dependent and some ligand-independent, the latter effects influenced by circulating growth factors. Estrogens appear to be critical in endochondral ossification of the growth plate (resting, proliferative, and hypertrophic zones). Investigators studying proximal tibia of female mice with ERα knock outs (KO), for example, showed increased growth plate height compared with wild-type mice, and prolonged sustained longitudinal bone growth in the KOs (19), similar to the estrogen resistant man (17). This is true also in the ERα collagen-specific KOs (19). Estradiol (E_2) accelerates fusion of the growth plate in rabbits by advancing senescence of the growth plate via proliferative exhaustion of the chondrocytes (20), and estrogen decreases resting zone chondrocytes and increases structural senescence (20, 21). Estrogen administration results in epiphyseal closure in aromatase deficient men (22). In aggregate, a plethora of work both in experimental animals and humans have convincingly shown that it is indeed estrogen, mediated via ERα, that is the principal regulator of epiphyseal fusion in boys and girls.

Androgens and Growth

Administration of testosterone in males and estrogen in girls causes significant augmentation of GH production as measured by frequently sampled, pulsatile GH in children (10, 12). These effects on GH are blocked in boys by tamoxifen—an estrogen receptor blocker (13)—and administration of a nonaromatizable androgen (oxandrolone) results in no detectable increase in GH production (12). However, even nonaromatizable androgens can stimulate growth (23, 24), suggesting that androgens *per se* can promote linear growth, likely by their anabolic effects at the epiphyseal growth plate (21, 25, 26). Androgens may stimulate longitudinal bone growth via the androgen receptor by modulation of the hypertrophic zone differentiation and chondrocyte proliferation (26).

Etiologies of Short Stature

Short stature and/or growth deceleration can occur associated with a long list of conditions, and often poor growth may be the first clinical manifestation of some of these. Hormonal deficiencies or insensitivity are obligatory causes to exclude, but skeletal dysplasias (overt and subtle), chronic illnesses such as inflammatory bowel disease, and genetic/syndromic causes are all in the differential diagnosis. Although in-depth discussion of these is beyond the scope of this review, endocrine-related etiologies and syndromes that cause short stature amenable to hormonal treatment are here briefly discussed, particularly in the context of peripubertal presentation.

Endocrine Causes

In general, endocrine causes of short stature are characterized by marked growth deceleration and often a pudgy phenotype, as GH is lipolytic; hence, its deficiency, when severe, allows for excess fat accumulation. Pituitary disorders, brain tumors (pre- or posttreatment), traumatic brain injury, infiltrative diseases of the brain, optic nerve hypoplasia, midline brain and facial defects, and history of cranial irradiation are all considerations associated with GH deficiency. However, family history of severe short stature is important, as many genetic disruptions to the GH axis have also been identified, including defects in all components of the pathway such as mutations in the GHRH receptor or in the GH gene, or in pituitary transcription factors (eg, HESX1, LHX3, LHX4, PROP-1, PIT-1 (POUF1), ROBO1, BMP4), leading to GH deficiency often combined with other pituitary deficiencies. GH receptor mutations (Laron syndrome) and postreceptor defects in growth hormone action (JAK/Stat5b) leading to GH insensitivity can also be causative; also IGF-1 and IGF-1 receptor defects, ALS deficiency, and PAPPA-2 mutations may all result in poor growth. Hypothyroidism, regardless of etiology, and cortisol excess, either pituitary, adrenal, or exogenous, can also

Table 1. Organic/genetic etiologies of short stature amenable to treatment with growth-promoting therapies

Structural CNS & pituitary disease
Brain/pituitary tumors (both malignant and benign [craniopharyngioma]), cranial irradiation, traumatic brain injury, infiltrative brain disorders, septo-optic dysplasia (SOD) and hypopituitarism (de Morsier syndrome), anatomical midline brain defects, interrupted pituitary stalk
Comment: Associated with either with isolated GH deficiency (IGHD), or multiple pituitary hormone deficiencies.
Diagnosis: Low GH, low IGF-1, abnormal brain MRI. Responsive to GH.
Genetic defects in GH production
Mutations in GHRH receptor gene (known as IGHD4 and/or dwarfism of Sindh (27, 28)); GH1 gene (IGHD1A and 1B, IGHD2 [AD]); pituitary transcription factors (eg, HESX1 [SOD], LHX3, LHX4, PROP-1, POUF1 [PIT-1] [AR/AD], SOX3 [X-linked], BMP4, ROBO1) *[omim.org entry #618157; #262400; #612781; #173100; #182230; #221750; #262700; #262600; #613038; #312000; #112262; #620303]*
Comment: Isolated GHD or combined anterior pituitary hormone deficiencies can occur, especially with defects in pituitary transcription factors. Other reported findings include C-spine abnormalities and deafness (LHX3), Chiari malformation and cerebellar defects (LHX4), intellectual deficits and hypogammaglobulinemia (SOX3), eye and ear malformations (BMP4), neuronal/cardiac/renal developmental defects (ROBO1)
Diagnosis: Low GH, low IGF-I, thyroid, cortisol and gonadotropin deficiencies are possible. Targeted gene sequencing indicated. Responsive to GH, except children with IGHD1A who develop binding antibodies against GH.
Genetic defects in GH sensitivity
Mutations in GH receptor gene (Laron syndrome); post GH receptor signaling (JAK/Stat5b); IGF-1 gene.
Comment: Frontal bossing, midline hypoplasia (Laron syndrome), severe postnatal growth failure, immunodeficiency (JAK/Stat5b), Intrauterine growth retardation (IUGR), developmental disability, deafness (IGF-I gene mutation) (29-31).
Diagnosis: High/normal GH, low IGF-I, targeted gene sequencing *[omim.org entry #262500; #245590; #608747]*. Responsive to IGF-1 therapy.
Genetic defects affecting IGF-1 availability
Mutations in ALS gene; PAPPA-2 (3, 32).
Comment: Mild growth deficits (ALS deficiency); postnatal growth failure, long fingers and toes (PAPPA-2)
Diagnosis: Normal GH, low IGF-I, low ALS concentration (ALS deficiency), but poor response to GH (limited experience); high GH, high total IGF-1, low free IGF-1 (PAPPA-2). Responsive to IGF-1.
Genetic defects in IGF-1 sensitivity
Mutations in IGF-1 receptor (33)
Comment: IUGR
Diagnosis: High/normal GH, high IGF-I. Limited data, unlikely to be responsive to IGF-1.
Genetic syndromes associated with short stature
Turner syndrome (45× and related karyotypes); SHOX deficiency; Noonan syndrome (PTNP11, Ras-MAPK associated genes); Prader Willi (PW) syndrome (70% absence of paternal expression of 15q11.2-q13)
Comment: May have extensive comorbidities such as primary ovarian failure, aortopathy, bicuspid aortic valve, dysmorphic features, horseshoe kidneys and others (Turner syndrome); Madelung deformity, Leri-Weill malformation (SHOX deficiency); pulmonary stenosis, dysmorphic features, can be inherited AD (Noonan syndrome); hypotonia at birth, cryptorchidism, dysmorphic features, poor feeding/FTT, followed by hyperphagia, obesity later in childhood, hypogonadism (PW syndrome). (34, 35)
Diagnosis: Chromosomes (Turner syndrome), targeted gene sequencing (SHOX deficiency), chromosome microarray (Noonan syndrome, PW syndrome), methylation studies (PW syndrome). All variably responsive to GH. *[omim.org entry #312865, #127300, #163950, #176270]*
Skeletal dysplasias
Hypochondroplasia, achondroplasia
Comment: Disproportionate short stature
Diagnosis: Targeted gene sequencing. [omim.org entry #146000; #100800]. Achondroplasia may respond to CNP therapy (6)

Abbreviations: ALS, acid labile subunit; CNP, C-type natriuretic peptide; FTT, failure to thrive; GH, growth hormone; GHD, growth hormone deficiency; GHRH, growth hormone-releasing hormone; IGF-1, insulin-like growth factor 1.

significantly stunt growth. Careful history, physical exam, anthropometry (arm span, upper/lower segment ratio, sitting height/height ratio, and head circumference) and proper biochemical assays (IGF-1, IGFBP-3, GH responses to stimuli, thyroid and cortisol levels), chromosomes or targeted genetic sequencing, and brain imaging work-up (as appropriate) would be diagnostic. Those conditions affecting GH production will be sensitive to GH therapy, whereas those with GH insensitivity and inability to respond to IGF-1 will not respond to GH, but some would in theory respond to recombinant IGF-1, a drug available for this purpose (Table 1).

Syndromes Commonly Associated With Short Stature Responsive to Treatment

As shown in Table 1, there is a host of genetic conditions that are associated with short stature or an abnormal growth pattern. Several are amenable to treatment, and clinical trials have been conducted that have led to Food and Drug Administration (FDA) approval for the use of growth-promoting therapies, including Turner syndrome, Noonan syndrome, and Prader Willi syndrome, SHOX haploinsufficiency, and children born small for gestational age (SGA). Skeletal dysplasias are a large heterogeneous group of genetic skeletal malformation syndromes characterized mostly by abnormal endochondral but normal periosteal ossification. The most commonly known of these conditions targeted for intervention are achondroplasia and hypochondroplasia, both caused by allelic variant mutations in fibroblast growth factor receptor 3 (FGFR3). CNP has been used in prepubertal children with achondroplasia with modest but positive results, resulting in the FDA approval of the use of a CNP analogue to promote growth in these children (6).

Nonsyndromic Disorders of Growth

There are special populations that represent a challenge for the pediatric endocrinologist, particularly during the

peripubertal years when the window for potential intervention begins to close as puberty approaches, discussed below.

Constitutional Delay of Growth and Maturation

Constitutional delay of growth and maturation (CDGM) is a term often used to describe children with short stature and delayed onset of puberty, but no evidence for systemic disease or hormonal dysfunction. These children's growth is believed to be a normal variant and patients usually attain normal adult height, although much later than their peers, but often within the lower part of their mid-parental target height zone (36, 37). However, the designation of CDGM or "late bloomer" as colloquially known, is largely subjective and not based on well-defined diagnostic criteria, most likely representing a heterogenous group of disorders. From a physiological standpoint, the delayed growth and tempo of puberty can result in reduced peak bone mass (38-40) and, depending on the severity of the growth delay, adult short stature. Children with CDGM are typically underweight for height and often have a family history of CDGM, suggestive of an underlying, intrinsic problem in energy intake and energy utilization (41-43). Most children with CDGM begin to deviate from the normal growth curve before 2 years of age, subsequently grow at a relatively normal velocity, and then have a delayed pubertal growth spurt (41). The pattern of growth is strikingly similar to that of malnourished children (42-46), suggesting that CDGM may lie in the spectrum of nutritional dwarfing because of an imbalance in caloric intake and energy expenditure. Using double-labeled water studies, we have shown that boys with CDGM have higher rates of overall energy expenditure compared with age-matched and size-matched controls (47). This increased metabolism may result in impaired growth. In boys, when old enough (>13 years) and still prepubertal on examination, testosterone, alone and in combination with the aromatase inhibitor (48) oxandrolone (no longer available in the United States), and GH (49), have all been used to manage CDGM. If young (<12 years) and prepubertal, these children can respond well to GH. However, follow-up studies we conducted using GH and nutritional supplements did not further improve the growth of these youngsters compared with GH alone (49).

CDGM is hence a diagnosis of exclusion that can only be made retrospectively, that is, in children followed longitudinally and eventually entering puberty late and reaching the mid-parental target height at an older age. Regrettably, not infrequently, parents and children are reassured that they will be "late bloomers" by their providers, then puberty arrives, epiphyses fuse, and the child ends up substantially below mid-parental height. Given that those < −2 SDS also may fit the diagnostic criteria for idiopathic short stature (discussed below), GH therapy should at least be considered and discussed. Whether one continues treatment to adult height, or only until child is at a taller percentile on track with mid-parental height needs to be individualized.

Idiopathic Short Stature and Normal Variant Familial Short Stature

Idiopathic short stature (ISS) is defined as a height below −2 SD of the mean for age- and sex-matched controls in the absence of any endocrine, metabolic, musculoskeletal, or other diagnosis. This designation represents a heterogeneous group of disorders in which no specific etiology for the short stature can be elicited, similar to the heterogeneity of those children born SGA. In the past few years, numerous conditions previously classified as ISS have been identified as genetic conditions (50, 51). Recent examples of this misclassification, include heterozygous mutations in aggrecan (ACAN), for example, which have been identified in families with apparent ISS presenting with otherwise unexplained accelerated bone maturation, often with forms of osteochondritis (52, 53), and mutations in the Indian hedgehog (IHH) gene which codifies an important paracrine regulator of endochondral ossification (54); both can result in adult short stature.

Genome-wide studies indicate that the majority of the variation in adult height is explained by several hundred genetic variations, each with a small effect (55). However, in a small proportion of the population, short stature is caused by specific genetic variations with larger effect. In a study of 565 individuals with unexplained short stature, whole-exome sequencing was performed in 200 subjects and was able to identify a genetic cause in 21% of syndromic cases and in 14% of those with apparent ISS (56). Epigenetic changes, such as increased methylation of promoter regions for the IGF-1 gene, are predicted to reduce the individual's sensitivity to GH and contribute to ISS (57). Targeted sequencing for genes related to the growth cascade is hence important to perform before the diagnostic label of ISS is given.

Similarly, *Familial Short Stature* has been a common diagnosis used for children < −2 SD below the mean height for age but within familial genetic target range in an otherwise healthy child. This term, however, should be avoided, since just because something is familial does not make it normal, and a child of very short parents forces the discussion as to the etiology of the growth retardation in the parents themselves. If indeed no identifiable pathology is diagnosed in the child, and parents are of different racial/ethnic backgrounds in particular, the term *Normal Variant Familial Short Stature* may be more appropriate. Strictly speaking, there is considerable overlap with the ISS designation besides the family history for short stature. The importance of the need for routine monitoring for the possibility of unrecognized underlying conditions that cause disease needs to be underscored. It is reasonable to anticipate that as genetic testing becomes more widely available and cost-effective, it will increasingly be used to identify genetic causes of short stature in a significant proportion of these children and even their families.

Therapeutic Options in Peripubertal Years

As detailed in Fig. 1, treatment of any of these conditions discussed here depends on the underlying diagnosis. The peripubertal years, however, often present a significant challenge to balance the proposed intervention against a rapidly changing sex steroid milieu, regardless of etiology. An x-ray of the left hand and wrist for bone age determination is a useful adjunct to the clinical assessment of time available for growth. Often, initially delayed bone ages > 1 year from chronology can rapidly advance as the child sexually develops, and predicted adult heights that were comforting and seemingly on-target to achieve mid-parental height become significantly compromised in some children. Hence, assessment of the tempo of bone age acceleration becomes an important tool in treatment selection and treatment monitoring.

Recombinant Human Growth Hormone

Recombinant human GH (somatropin) is the primary treatment option for short stature in children with defects in the GH pathway causing GH deficiency. GH has a long-standing

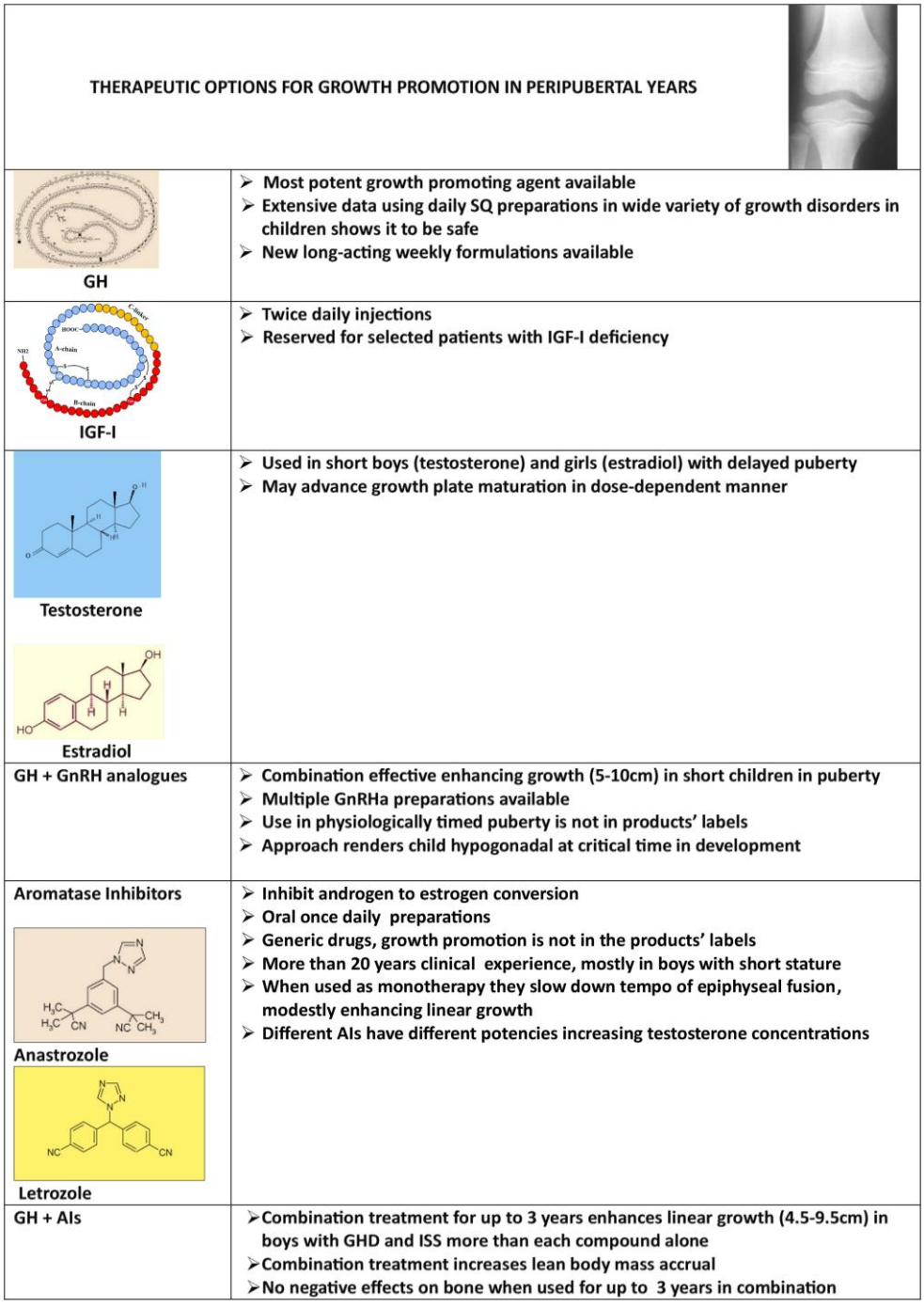

Figure 1. Therapeutic options for growth promotion in growth-retarded peripubertal children, including GH, IGF-1, sex steroids (testosterone, estradiol), GH/GnRH analogues, aromatase inhibitors, and GH/aromatase inhibitors (see reference (16)).

record of efficacy and safety with normalization of linear growth, especially if started early in childhood. The more profoundly GH-deficient these children are, the more sensitive they are to GH treatment. Net gains in height can be substantial and well established, often with normalization of their growth patterns altogether (58, 59). In children without documented GH deficiency, such as those with ISS, children born SGA with failure to catch up, Turner syndrome, Noonan syndrome, Prader Willi syndrome, monogenic short stature related to SHOX haploinsufficiency, and any other condition of poor growth not related to GH deficiency *per se* in which GH is used, responses tend to be more heterogenous (35). Conventional FDA-approved GH doses used in GH deficiency range on average from 0.2 to 0.3 mg/kg/week given as a daily subcutaneous injection; lower doses are often used in other countries. In conditions not associated with GH deficiency, doses often need to be higher—up to 0.48 mg/kg/week, such as in SGA and ISS—to achieve a meaningful clinical response. We have studied the safety and efficacy of high doses of GH (up to 0.7 mg/kg/week) in GH-deficient children during puberty in an attempt to mimic the significant increase in GH production rates during this period of development (60). We

observed faster growth and ultimately taller height using higher doses, but responses increasing height were clearly not linear; that is, doubling the dose did not result in doubling of the growth velocity compared to standard dose, and IGF-1 concentrations were ~40% higher using this approach. High-dose GH use in GH-deficient children in puberty received FDA approval; however, this approach is costly, and should be reserved for those most growth retarded at the start of treatment. Close monitoring of IGF-1 levels to keep those < 2 SD above the mean is recommended.

Long-Acting GH Formulations

New *long-acting* formulations of GH have been studied over the last decade. Different technologies to manipulate drug half-life have been produced including depot formulations, PEGylated formulations, noncovalent albumin binding GH, and GH fusion proteins. To date, there are currently 3 formulations approved by the FDA in the United States for use in growth promotion in GH-deficient children: somapacitan (age 2.5 years and older) (61), lonapegsomatropin (age 1 year and older) (62, 63), and somatrogon (3 years and older) (64, 65). Theoretically, this is a welcomed therapeutic advancement, as weekly injections are expected to decrease patient burden of daily injections, particularly in adolescent patients who often become principally in charge of their own dosing. Improved adherence, increased acceptance, and greater tolerability could all potentially improve treatment outcomes. No significant short-term side effects have been reported using these preparations and immunogenicity has been very low (65). However, although many of the children have been followed for several years and many have entered puberty during long-term surveillance, these new preparations were studied largely in prepubertal children at study entry. Given dosing is *per kg* of body weight, treatment during puberty requires careful monitoring and dose titration to maintain IGF-1 concentrations within normal range. A potential pitfall to consider is transient exposure to high GH and IGF-1 concentrations, which may vary depending upon the chemical design used to prolong GH action. Long-term impact on metabolism, optimal therapeutic dosing and monitoring, and immunogenicity of long-acting GH products require long-term surveillance studies (66-68). Although not FDA-approved at the time of this review paper, studies are underway using long-acting preparations of GH in a variety of other disorders of growth such as Turner syndrome, Noonan syndrome, children with ISS, and children born SGA.

Recombinant IGF-1

Recombinant human IGF-1 is the recommended treatment for children with severe primary IGF-1 deficiency, a rare group of conditions due to mutations in the GH receptor, post-GH receptor signaling pathway, or IGF-1 gene (69). Patients with proven gene defects that cause GH insensitivity could start directly on IGF-1 replacement. IGF-1 (mecasermin [Increlex®]) is available as subcutaneous injections, approved by the FDA in doses starting at 40 µg/kg/dose and titrated up to 120 µg/kg/dose given twice daily. The FDA had previously approved IGF-1 in combination with IGFBP-3 (mecasermin rinfabate) as replacement therapy; however, the product was withdrawn from the US market due to patent issues although it may be made available through an FDA IND process.

Sex Steroids

Estrogen increases GH production rates in puberty (70) and low doses in particular have been found to be growth-promoting (71). Androgens also increase GH production (10, 11) but this is mediated via aromatization to estrogens (12, 13). In children with poor growth and relative hypogonadism, such as those suspected of having CDGM, administration of androgens to boys and estrogens to girls in low doses has been practiced in an attempt to boost growth and trigger secondary sexual characteristics (feminization/virilization) without causing accelerated fusion of the growth plates. Girls with Turner syndrome, particularly in those diagnosed late in the peripubertal years, are often quite short and have been shown to benefit from GH therapy (34). However, since most have primary gonadal failure, estrogen is also needed, the latter introduced by age 12 years and in low doses in order to cause breast development and feminization to develop while allowing room still for linear growth (34). This is a fine balance that requires careful monitoring of bone age advancement. Oxandrolone, a nonaromatizable androgen, has been shown to promote growth in both boys and girls (23, 24), an effect likely to be directly on the epiphyseal growth plates. However, oxandrolone has been recently withdrawn from the US market in 2023 and is no longer commercially available.

GH Plus Gonadotropin Hormone Releasing Hormone Analogues

Once sex steroids production begins and the physical changes of puberty—thelarche in girls, testicular enlargement in boys—are observed, the window available for growth is limited. For the children starting the process at a very short stature in particular, that is, those < −2 SDS in height, the pubertal growth spurt is not enough for attainment of normal adult height within their mid-parental height. Growth spurts are highly variable and the sex steroids that drive the growth spurt also cause epiphyseal fusion. In most children identified with severe short stature between 10 and 14 years, puberty is commonly physiologically timed and not precocious. One approach to promote growth when time is running out is to suppress puberty altogether using gonadotropin hormone releasing hormone (GnRH) analogues while co-treating with GH. This strategy, considered off-label use, has been shown successful in a multiplicity of clinical situations associated with poor linear growth when the children are in physiologic puberty, with net gains of 5 to 10 cm in adult height (Table 2). GnRH analogue use combined with GH use has not been associated with permanent detrimental effects on bone in children (85-89), nor on psychosocial function (90, 91). Use of GnRH analogues as monotherapy to promote growth in normally timed puberty, however, should be discouraged, as it may have a negative impact on bone mineralization (92). This approach to increase adult height while the child is in puberty requires at least 2 to 3 years of combined treatment and is one we use mostly in girls with profoundly retarded growth. When suppressing *physiologically* timed puberty, risk/benefit assessment and willingness to postpone pubertal development need to be openly discussed prospectively with these young patients and their families.

Aromatase Inhibitors

Over the last 20 years blockers of aromatase, oral drugs marketed for the treatment of postmenopausal women with breast

Table 2. Impact of GH and sex steroid modulation on height gain

Gain in height in children using combination GH/GnRHa					
Condition	**Reference**	**Age (y)**	**R × Length (y)**	**Actual/predicted height gain (cm)**	**Height SDS**
GHD	Mericq (72)	14.3	3	+ 3.3 GH, +12.3 GH/GnRHa	−4.0 baseline, −2.7 GH, −1.3 GH/GnRHa
SGA	Lem (73)	12.2	2	+ 13.6 (F), +10.9 (M)	N/A
SGA/ISS	Kamp (74)	11.4-12.2	3	+8.0 (F), +10.4 (M)	N/A
SHOX	Scalco (75)	11.8	1.4-5.8	N/A	−2.3 baseline, −1.7 GH/GnRHa
CPP	Pucarelli (76)	9.9	2-4	+2.3 GH +8.2 GH/GnRHa	N/A
Gain in height in male children using aromatase inhibitors					
CDGM	Wickman (48)	15.1	1	+5.1 T/Letrozole No gain T/Placebo	N/A
ISS	Hero (77)	9-14.5	2	+5.9 Letrozole No gain Placebo	−2.3 baseline,+0.7 p Rx −2.4 baseline, −2.4 p Rx
GHD	Mauras (78)	14.1	2-3	+4.5/+6.7 (2/3 y) GH/anastrozole +1.0/+1.0 (2/3 y) GH/Placebo	−1.4/−1.5 baseline, +0.77 taller p anastrozole vs placebo
ISS	Mauras (79)	14.1	2-3	+5.2 AI[a], +7.6 GH, +9.5 GH/AI*	−2.2, −2.4, −2.3 baseline −1.73, −1.43, −1.25 (2 y)
ISS	Rothenbuhler (80)	15.2	11.5 mo 19 mo	+4.1 GH +8.3. GH/Anastrozole	−1.7 baseline, −1.8 p Rx −1.8 baseline, −1.1 p Rx
GHD/ISS	Miller (81)	12.1/10.76	2 y	N/A GH/AI	−0.99/−1.04 baseline −0.40/−0.65 p Rx
CDGM	Salehpour (82)	12.6-14.6	2 y	+6.1 Letrozole +1.9 Oxandrolone +1.4 Placebo	−2.91 baseline, −2.27 p Rx −3.0 baseline, −2.37 p Rx −2.88 baseline, −2.86 p Rx
FMPP	Leschek (83)	4.9	7.3 y	+8.9 Testolactone/ Anastrozole/ Spironolactone	−1.5 baseline, −0.3 p Rx
Gain in height in girls with early puberty using GnRHa + Aromatase Inhibitor					
CPP	Papadimitriou (84)		2 y	+1.92 GnRH +7.51 GnRHa/AI	+0.31 SDS +1.21 SDS

Abbreviations: AI, aromatase inhibitor; CDGM, constitutional delay of growth and maturation; CPP, central precocious puberty; FMPP, familial male-limited precocious puberty; GH, growth hormone; GHD, growth hormone deficiency; GnRH, gonadotropin hormone releasing hormone; GnRHa, gonadotropin hormone releasing hormone analogue; ISS, idiopathic short stature; p, post; SGA, small for gestational age; T, testosterone.
[a]anastrozole/letrozole.

cancer, have been studied to promote linear growth in boys, a topic we recently extensively reviewed (16). Given that the process of epiphyseal fusion in children is estrogen-driven, the availability of aromatase inhibitors (AIs) enables the selective blockade of estrogen production while allowing continued virilization in pubertal boys. Aromatase P450 (estrogen synthetase), a product of the CYP19 gene located on chromosome 15, catalyzes the conversion of C19 androgens (testosterone and androstenedione) to estrogens (estradiol and estrone) and is expressed in multiple tissues, including ovary, adipose tissue, liver, muscle, bone, syncytiotrophoblast, and breast tumors. Three such oral products are now available in generic form and all potently block tissue aromatase: anastrozole (1 mg) achieves 96.7% blockade, letrozole (2.5 mg) > 99.1% blockade, and exemestane (25 mg) 97.9% blockade (93-96). Anastrozole and letrozole are reversible aromatase blockers that mostly undergo hepatic metabolism and are administered orally without regard to food. Exemestane, a steroid, is a competitive analogue of androstenedione that irreversible blocks tissue aromatase, its absorption is affected by fat contents; hence, it must be administered with food. We have studied pharmacokinetics and pharmacodynamics of both anastrozole and exemestane (97, 98) in young male subjects, and overall, these are comparable to data reported in postmenopausal women. We assessed the impact of full GnRH axis suppression with a GnRH analogue vs an AI (anastrozole) in physiologic studies using infusions of stable isotopes of leucine to measure whole-body protein kinetics in healthy young men in their 20s (99). When we only suppressed the estrogen, instead of estrogen and testosterone, there were no detectable decreases in whole-body protein synthesis rates as compared with the catabolic

effects observed when we suppressed testosterone production, suggesting that, at least during the window of the experiments, there was lack of catabolic effect by the AI.

AIs have been successfully used to promote linear growth both as monotherapy and in combination with GH in boys with constitutional growth delay, GH deficiency, ISS, and in boys with constitutive activations of the LH receptor (testotoxicosis) (Table 2). Boys with short stature and delayed puberty (CDGM) at a mean age of 15 years, were treated with testosterone and either an AI (letrozole) or placebo for 12 months showing an increase in adult height prediction based on bone age of +5.1 cm vs no increase in the placebo-treated group (48). The theoretical advantage of the approach is that it permits full virilization of the boys without causing premature bone fusion by testosterone. The same investigators used letrozole (2.5 mg) vs placebo in 31 boys aged 9 to 14.5 years with ISS, of whom 27 of the 31 were considered prepubertal at study entry (77). Although initially they reported an increase in height potential in the AI group, there were no differences in adult height between the groups when followed much later (100), suggesting that administration of an AI as monotherapy is not useful to promote growth in prepuberty.

We have performed 2 randomized controlled trials using AIs in fully pubertal males. One in very short GH-deficient boys (n = 52, height SDS −2.3, mean age 14 years) treated with GH and anastrozole vs GH and placebo up to 3 years (78). Bone age advancement was markedly slower in the GH/AI group compared to GH/placebo, with net gains in predicted adult height of +4.5/+6.7 cm in the GH/anastrozole group vs +1.0/+1.0 cm in the GH/placebo group after 24/36 months. We subsequently did a comparator study using AIs alone (anastrozole and letrozole), GH alone, vs combination AI/GH for up to 3 years in 76 fully pubertal boys with ISS (mean age 14 years, height SDS −2.3 SDS) who had residual height potential with bone age ≤ 14 years (79). Participants were followed for 12 additional months after study drug discontinuation to assess their near-adult height. Gains at near-final height were 5.2 cm, 7.6 cm, and 9.5 cm with AI, GH, combination treatment respectively compared with CDC-based data on growth in boys with height SDS of −2 SD (Table 2). Miller et al (81) investigated real-world use of AIs in a retrospective, observational database (ANSWER program) and reported height outcomes of 142 very short pubertal boys (GH-deficient, or ISS, height SDS −2.0 or −2.2, respectively) naïve to GH therapy who were in puberty. After 2 years of treatment with combination AI/GH height outcomes were −0.40 and −0.65 SDS for the GH-deficient and ISS groups, respectively. Table 2 summarizes available studies.

Safety profile of AIs has been strong; IGF-1 concentrations do not increase significantly with AI monotherapy, whereas they increase as expected with the GH and GH/AI combination. Testosterone is higher with AIs but still within normal pubertal range, particularly with anastrozole (78, 79). All documented metrics of bone health, dual-energy x-ray absorptiometry (DXA) scans, including lateral spine assessed for disc space narrowing, wedging, compression, and irregularities, and bone surveys were not different among groups (79). Use of AI in combination with GH has been shown to promote a favorable body composition by increasing lean body mass when compared to treatment with GH or AI alone (79). In our own extensive clinical experience using this class of drugs, we monitor bone age advancement every 6 months and we use AIs mostly in combination with GH and in normally timed puberty. We also prefer not to exceed the time window of our own studies, that is, up to 3 years. We also obtain a DXA before initiation of an AI and again after 2 years. Results on quality-of-life surveys have been encouraging using combination AI/GH (101). Data on sperm counts and fertility with AI use have also been reassuring (see reference (16) for extensive review).

Limited data exist on the use of AIs for growth promotion in girls with normal puberty. Given the expected increase in androgens, the potential disruption of natural puberty and feminization by blocking estrogens, and the theoretical concern of ovarian cyst formation driven by the rise in gonadotropins that ensues, we do not recommend their use in girls (16). One of the few studies on AI use to date in otherwise early pubertal girls is by Papadimitriou et al (84). They studied 40 girls randomized to either monthly GnRH analogue alone or with anastrozole for 2 years, to suppress both gonadal and adrenal estrogen, and reported an increased in predicted adult height gain at 24 months of +1.21 ± 0.45 SDS (7.51 cm) with combination treatment vs +0.31 ± 0.37 SDS (1.92 cm) with leuprorelin alone. No virilization and a good safety profile were reported. However, ultrasounds to assess ovarian morphology were not performed. More studies in this patient population are needed.

C-Natriuretic Peptide

C-natriuretic peptide (CNP) is another important regulator of longitudinal bone growth that acts through natriuretic peptide receptor B (NPR2). CNP signaling via NPR2 in chondrocytes inhibits the mitogen-activated protein kinase signaling pathway by downregulating FGFR3 signaling. Gain-of-function mutations in the *FGFR3* gene result in achondroplasia and hypochondroplasia. The CNP analog vosoritide has recently been approved for treatment of achondroplasia in children, and it has yielded good results (6). Longer-acting preparations are under study (102). Studies thus far have been in prepubertal children; hence, data on effects in pubertal children are lacking. There are ongoing research studies using CNP analogs in different types of genetic short stature and Turner syndrome; long-term data will be needed to assess if efficacy and safety in these conditions justifies treatment.

Summary

Growth is a complex process in which nutrition, hormones, and genetic and environmental factors play important roles. Enhanced molecular knowledge on the genetics of the growth cascade, and greater availability of accurate genetic testing have improved our understanding of the molecular basis of short stature and underlying cellular mechanisms, enhancing phenotype/genotype correlations. When these children first present for evaluation in the peripubertal years, it poses a therapeutic challenge, given the limited window for intervention, regardless of the etiology of the short stature. Differences between chronological age and bone age can disappear during puberty and limit the impact of growth-promoting agents; hence, starting any growth-promoting agent in children with poor growth close to, or in the midst of puberty, must take into consideration the inexorable impact of sex steroids on the epiphyseal growth plate. GH remains the staple of

treatment not only in disorders of the GH axis, but in syndromes such as Turner, Noonan, Prader Willi, children born SGA, and SHOX haploinsufficiency, all FDA-approved indications for use of GH. Long-acting preparations of GH are quickly changing the landscape in patients that need GH, with approvals for use in GH-deficient children, and ongoing investigations for use in multiple other indications. Androgens and estrogens can be growth-promoting but can also accelerate growth plate closure. Co-treatment with GH and GnRH analogues is a viable consideration, particularly in girls, to promote growth in the peripubertal years, with promising results when used for at least 2 years. Data on the co-treatment with GH and AIs in boys with GH deficiency and ISS have accumulated for the last 20+ years, making them a strong alternative for use in short boys in puberty. Although this class of drugs is generic and not in the products' labels, enough information has accumulated on their safety and efficacy, considered a legitimate practice when using off-label products in children (103). We recommend that bone ages are obtained every 6 months in short children progressing through puberty and consideration given to halting or decreasing estrogen production in children whose adult height is compromised, particularly in combination with GH. Although these approaches have been shown to be effective and safe, they deserve individualized and careful consideration and detailed discussion with the families.

Disclosures

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Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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