For this year’s yearbook, we selected papers related to growth physiology that would be helpful to practicing clinicians. They illustrate the broad range of influences on and variations in child growth. Some highlight the specific nutritional factors of non-cow milk beverage consumption by children and protein-specific effects on skeletal development in a rat model. Others looked at the growth hormone (GH) system, ranging from diagnostic and pathologic issues to non-height effects of growth hormone treatment. Another group explored the other side of the more commonly seen short stature spectrum: a variant of early puberty, a genetic cause of short stature that is associated with acceleration not deceleration of skeletal maturity (bone age), and an up-to-date review of the differential diagnoses and treatment of excessive tall stature. This is certainly not a comprehensive collection of all papers published in the past year on growth physiology and underlying mechanisms, but we hope it sufficiently highlights the nuances and richness of the field to inspire readers to explore the literature on their own.
Key articles reviewed for this chapter

Association between non-cow milk beverage consumption and childhood height
Am J Clin Nutr 2017;106:597–602

Skeletal effect of casein and whey protein intake during catch-up growth in young male Sprague-Dawley rats
Br J Nutr 2016;116:59–69

Progressive decline in height standard deviation scores in the first 5 years of life distinguished idiopathic growth hormone deficiency from familial short stature and constitutional delay of growth
Rothermel J, Lass N, Toschke C, Reinehr T
Horm Res Paediatr 2016;86:117–125

Reference values for IGF-I serum concentrations: comparison of six immunoassays
Chanson P, Arnoux A, Mavromati M, Brailly-Tabard S, Massart C, Young J, Piketty ML, Souberbielle JC; VARIETE Investigators
J Clin Endocrinol Metab 2016;101:3450–3458

Endocrine long-term follow-up of children with neurofibromatosis type 1 and optic pathway glioma
Sani I, Albanese A
Horm Res Paediatr 2017;87:179–188

The influence of growth hormone treatment on glucose homeostasis in growth hormone-deficient children: a six-year follow-up study
Horm Res Paediatr 2016;86:196–200

Growth hormone positive effects on craniofacial complex in turner syndrome
Juloski J, Dumancic J, Scepan I, Lauc T, Milasin J, Kaic Z, Dumic M, Babic M
Arch Oral Biol 2016;71:10–15

Pubertal progression and reproductive hormones in healthy girls with transient thelarche
Lindhardt Johansen M, Hagen CP, Mieritz MG, Wolthers OD, Heuck C, Petersen JH, Juul A
J Clin Endocrinol Metab 2017;102:1001–1008
Association between non-cow milk beverage consumption and childhood height

Morency ME\textsuperscript{1, 4}, Birken CS\textsuperscript{1, 5–7}, Lebovic G\textsuperscript{2, 4}, Chen Y\textsuperscript{4}, L’Abbé M\textsuperscript{1}, Lee GJ\textsuperscript{4}, Maguire JL\textsuperscript{1–7}; the TARGet Kids! Collaboration

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Am J Clin Nutr 2017;106:597–602

Background: Many parents believe that non-cow milk like soy and almond milk has health benefit over cow milk. However, non-cow milk has less protein and fat than cow milk and might have, therefore, a different effect on children’s height.

Aim: In the present study, the authors sought to determine whether there is an association between non-cow milk consumption and lower height in children and to assess whether cow milk consumption mediates the relation between non-cow milk consumption and height.

Methods: The authors conducted a cross-sectional study of 5,034 healthy Canadian children age 24–72 months who were enrolled in the Applied Research Group for Kids cohort. The primary exposure in their study was the volume of non-cow milk consumption (number of 250 mL cups per day). The primary outcome of the study was height. Multivariant linear regression was used to determine the association between non-cow milk consumption and height. A mediation analysis was conducted to determine whether cow milk consumption mediated the association between non-cow milk consumption and height.

Results: The authors found a dose-dependent association between higher non-cow milk consumption and lower height ($p < 0.0001$). They found that for each daily cup of non-cow milk consumed, children were 0.4 cm shorter. In the mediation analysis, they found that lower cow milk consumption only partially mediated the association between non-cow milk consumption and lower height. They claim that the height differences for child aged 3 years consuming 3 cups non-cow milk/day relative to 3 cups of cow milk/day were 1.5 cm.

Conclusions: The authors concluded that non-cow milk consumption was associated with lower childhood height.
The association between cow milk consumption and height gain was shown in the past in many studies [1, 2]. However, many non-cow milk beverages are produced, marketed and sold in numerous countries in the world as a milk product for children. The present study raises an important issue relevant to many parents all over the world who believe that non-cow milk beverages are better for their children’s health. Usually non-cow milk contains less protein than cow milk and does not necessarily contain all the other elements needed to support growth. Indeed, as stated by the authors the USDA MyPlate and Canadian Food Guide have acknowledged that unfortified milk alternatives do not provide the same energy, protein, vitamins or minerals found in cow milk. It is important to stress that it is not just the amount of protein which is important for linear growth but that the source of the protein might have also a crucial contribution to height gain [3]. Despite the fact we know today more than ever what a healthy diet for young children should look like, we still did not figure out the exact mechanism of the interaction between nutrition and growth, especially linear growth. Basic research exploring the mechanism and clinical well-designed prospective studies are needed to produce the ideal growth-supporting diet for the pediatric age group.

Skeletal effect of casein and whey protein intake during catch-up growth in young male Sprague-Dawley rats

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Br J Nutr 2016;116:59–69

Aim: In the present study, the authors aimed to determine whether the type of protein ingested influences the efficacy of catch-up growth and bone quality in fast growing male rats.

Methods: The authors used young male Sprague-Dawley rats who were either fed ad libitum (control group) or subjected to 36 days of 40% food restriction followed by 24 or 40 days of re-feeding with either standard rat chow or iso-energetic, iso-protein diets containing milk protein – casein or whey.

Results: Casein re-fed rats had a significant body weight and longer humerus than whey re-fed rats in the long term. The height of the epiphyseal growth plate in both casein and whey groups was greater than that of rats re-fed normal chow. They also showed that microcomputed tomography demonstrated significant differences in bone microstructure between the casein and the whey groups. Bone quality during catch-up growth depended on the type of protein ingested. The higher epiphyseal growth plate in the casein and whey re-fed-rats suggested a better growth potential with milk-based diets.

Summary: The authors concluded that whey may lead to slower bone growth with reduced weight gain and, as such, may serve to circumvent long-term complications of catch-up growth.
In this article, the authors highlighted an issue that people tend to forget. Not all proteins are alike. The contribution of different consumed proteins to linear growth might be dissimilar even when they are coming from the same source (cow milk in this study). In addition, their contribution to linear growth might not always be directly associated with their contribution to human weight and body mass index (BMI). It is therefore important to study the characteristics of each protein in the diet when height and weight are important, like in the case of growing children.

**Comments**

Progressive decline in height standard deviation scores in the first 5 years of life distinguished idiopathic growth hormone deficiency from familial short stature and constitutional delay of growth

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**Background:** Differentiating familial short stature (FSS) and constitutional delay of growth (CDG) from growth hormone deficiency (GHD) and other chronic disease can be a diagnostic challenge. The aim of this study was to determine if growth patterns in the first 5 years of life can be used to differentiate these conditions.

**Methods:** The authors studied 78 children with short stature (26 FSS, 38 CDG and 14 idiopathic GHD), and reviewed their height standard deviation scores (SDS) in the first 5 years of life.

**Results:** Height SDS was consistent between birth and 6 months of life, while height SDS decreased significantly after 6 months in GHD, FSS, and CDG. Loss of height SDS was greater in the first 2 years of life than between 2 and 5 years of life in children with CDG (–0.92 vs. –0.11; *p* = 0.003) and FSS (–0.79 vs. –0.01; *p* = 0.002). In idiopathic GHD, the loss of height SDS did not differ between the first 2 years of life and the following 3 years (–0.78 vs. –0.77; *p* = 0.821).

**Conclusion:** In children with FSS and CDG, there is a decline in height SDS in the first 2 years of life, whereas the height SDS of children with idiopathic GHD decreased almost continuously over the first 5 years of life.

**Comments**

Diagnosing GH deficiency remains a significant challenge, particularly given the poor specificity of stimulation testing [4, 5] and the high prevalence of normal variants of growth among children referred for evaluation of short stature. This study aimed to provide an additional clinical tool to differentiate children over 6 years of age with GH deficiency from FSS or CDG and puberty, namely a detailed review of growth patterns over the first 5 years of life.

The authors showed that reviewing growth trajectories over the first 5 years of life might help to distinguish children with constitutional delay in growth and puberty from those with idiopathic GH deficiency. Maximal reduction in height SDS is seen in the first 2 years of life in children with constitutional delay in growth and puberty whereas children with idiopathic GH deficiency will continue to have a reduction in height over 5 years without this early peak rate of decline. This observation may provide additional reassurance to the clinician observing the growth pattern in a child presumed to have constitutional delay in growth and puberty, hence potentially reducing the number of children undergoing GH stimulation testing.
Reference values for IGF-I serum concentrations: comparison of six immunoassays

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J Clin Endocrinol Metab 2016;101:3450–3458

Background: Different kits for measuring serum concentrations of insulin-like growth factor-I (IGF-I) can give different results for the same sample, despite a 2011 consensus calling for standardization of such assays. This study sought to establish normative data for 6 IGF-I immunoassay kits based on a large random sample of French adults [6].

Methods: Subjects were part of the French VARIETE cohort study, a prospective, national, multicenter, open and nonrandomized study of healthy adult volunteers. A total 972 subjects aged 18–90 years and with a BMI of 19–28 kg/m2 were considered. After excluding 52 subjects for abnormal values on screening laboratory tests and 11 subjects for missing data on pregnancy status or viral serology, the final 911 subjects (470 males) were stratified by gender and age groups. Serum IGF-I concentrations were measured for each sample by 6 immunoassays and converted to SDS for each technique. Bland-Altman plots assessed pairwise concordance between assays for both raw IGF-I measurements and SDS, and IGF-I SDS were further compared via the percentage of observed agreement and the weighted Kappa coefficient.

Results: Age group and gender-specific normal ranges (2.5–97.5 percentiles) were calculated for each of the 6 immunoassays. The immunoassays shared similar lower limits of the reference ranges, but their upper limits varied markedly. Pairwise concordances were moderate to good with weighted Kappa coefficient for categorized IGF-I SDS ranging 0.38–0.70 and only moderate overall (0.55).

Conclusions: Six immunoassays resulted in different reference intervals for serum IGF-I concentration despite being based on the same healthy population and showed only moderate to good agreement.

Comments: Lack of concordance among IGF-I measurements has been considered responsible in part on the reliance on different reference groups for the various tests. Because many factors affect IGF-I levels, the specific inclusion and exclusion criteria defining the “normal” reference group will impact the “normal” reference range values derived from that group. These factors include not just GH action, but age, puberty status in adolescents, gonadal status in adults (e.g., menopausal, on estrogen replacement and whether that replacement is oral or transdermal), nutrition and BMI, renal and hepatic functions, and diabetes status. The sample size of the reference population affects the calculated variance of measurements, and the non-Gaussian distribution of IGF-I values within a healthy population further complicates the calculation of reference ranges. This study demonstrated that differences persist even when different...
immunoassays are used to measure IGF-I concentrations from the same healthy population. Lack of concordance among IGF-I measurements is a major problem. Clinicians can misclassify their patients as “normal” or “abnormal” if they compare the IGF-I values measured by their local laboratory against published reference ranges that were measured by a different assay and/or based on a non-representative reference population. Further, results cannot be compared across studies because interassay variability becomes a confounding issue. This has hindered the development of evidence-based practice, and led to calls for standardization or at least harmonization of the various assays. Unfortunately, this problem is not limited to IGF-I [6, 7]; it also plagues measurement of GH [6, 7] and steroid hormone [8] levels.

**Endocrine long-term follow-up of children with neurofibromatosis type 1 and optic pathway glioma**

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_Horm Res Paediatr_ 2017;87:179–188

**Background:** Optic pathway glioma (OPG) is the most common brain tumor (7–20% of cases) that develops in children with neurofibromatosis type 1 (NF1), a multisystem neurocutaneous syndrome affecting 1 in 2,500–3,500 live births. This study sought to elucidate the causative role of tumor location on the development of hypothalamic-pituitary endocrinopathies in children with OPG from NF1.

**Methods:** Thirty-six children (18 males) with NF1 and OPG (diagnosed by MRI) who did not receive radiotherapy or surgical resection but were evaluated by university hospital endocrine clinics in London between August 1996 and May 2015 were retrospectively followed. Seventeen received only chemotherapy, 3 only decompression procedures, and 2 received both. All 36 received baseline endocrine evaluations at referral and returned every 4–6 months. Dodge criteria classified tumor location as: stage I, optic nerve alone; stage II, optic chiasm with or without optic nerve involvement; and stage III, involvement of the hypothalamus or other adjacent structures.

**Results:** During a mean follow-up of 9.1 (0.2–13.6) years, 20 (55.6%) children were diagnosed with endocrinopathies. The incidence of endocrinopathies increased with Dodge stage of the OPGs: 0/4 stage I, 12/21 (57%) stage II, and 8/11 (73%) stage III. The first endocrinopathy was found at a mean age of 7.4 (5.0–13.2) years, 2.4 (0–6.7) years after tumor diagnosis. The endocrinopathies diagnosed, in decreasing frequency, were: GHD (36%), central precocious puberty (33%), obesity with insulin resistance/impaired glucose tolerance (11%), early puberty (5.5%), GH excess (5.5%), ACTH deficiency (5.5%), hypogonadotropic hypogonadism (2.7%), and central hypothyroidism (2.7%). GHD was defined as decreased growth velocity over at least 6 months and a peak GH concentration <6.6 μg/L upon stimulation with either insulin tolerance test or glucagon. GH treatment was started in those with stable neuroradiological findings after at least 1 year of monitoring, and of those 13 patients, 9 continued to adult height by the end of the study period while 1 discontinued for worsening of previous severe scoliosis and another discontinued due to tumor progression. All 8 patients whose GH axis was reassessed at adult height had normal GH peaks on retesting.

**Conclusions:** Children with OPG due to NF1 are at high risk of developing endocrinopathies due to tumor location and thus, warrant lifelong endocrine follow-up.
It is perhaps not surprising to find hypothalamic-pituitary dysfunction to be common among children with OPGs, given the tumor location. What most surprised me in reading this paper was the transient nature of the GH excess. Two of the 36 subjects developed GH excess, defined by tall stature with increased growth velocity, high IGF-I levels, and lack of GH suppression during a 1.75 g/kg oral glucose tolerance test. GH excess was suspected in patients who were prepubertal or whose puberty was clinically and biochemically suppressed by treatment with gonadotropin releasing hormone analog (12 of the 36 subjects with OPGs developed central precocious puberty). The GH excess was suppressed by treatment with a somatostatin analog in both subjects, for 3–4 years. One stopped somatostatin analog therapy after developing acute pancreatitis, and the other upon reaching adult height. Both had normal GH secretion on testing after stopping the somatostatin analog treatment. While less common than GH deficiency among patients with OPGs and NF1 (13 of the 36 subjects in the current study), GH excess has been reported in other studies of patients with OPGs and NF1 [9, 10]. Others have also noted the transient nature of the GH excess [11]. Out of 7 patients with GH excess associated with optic pathway tumors (5 of whom had clinically diagnosed NF1, and all of whom had concurrent central precocious puberty treated with gonadotropin releasing hormone analog), only 3 continued somatostatin analog treatment for an extended period of time, and one was switched to pegvisomant (a GH receptor antagonist) due to somatostatin non-responsiveness. Five of the patients had a resolution of the GH excess with normal growth and IGF-I levels off treatment (the remaining 2 were either never treated or still on treatment at the time of study completion). Thus, this patient population offers a unique opportunity to elucidate the mechanism of the dysregulation leading to transient, excessive GH secretion.

The influence of growth hormone treatment on glucose homeostasis in growth hormone-deficient children: a six-year follow-up study

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Horm Res Paediatr 2016;86:196–200

Background: GH reduces insulin sensitivity and results in increased insulin secretion. In animal and human studies, it has been suggested that GH might also increase insulin secretion through a direct effect on the growth and function of pancreatic beta-cells. The aim of this study was to describe the insulin sensitivity using the homeostasis model assessment (HOMA-S), insulogenic index (IGI), and oral disposition index (ODI) in GHD children during GH treatment.

Methods: Ninety-nine children with GHD (62 male, 37 female; age 8.9 ± 3.5 years) were followed for a median of 6 years (range 1.5–16.2). Patients underwent an oral glucose tolerance test annually, and HOMA-S [1/(insulin (mIU/ml) × glucose (mg/dl))], IGI (Δ insulin 0–30 min / Δ glucose 0–30 min), and ODI (HOMA-S × IGI) were calculated.

Results: HOMA-S remained unchanged but an increase in IGI and ODI was observed, which became significant after 6 years of treatment (1.25 ± 1.28 vs. 2.35 ± 2.38, p < 0.05 and 0.57 ± 0.68 vs. 1.50 ± 1.92, p < 0.01, respectively).

Conclusions: GH treatment is associated with increases in the beta-cell secretory capacity of children with GH deficiency during GH treatment.
In this 6-year longitudinal study of children with GH deficiency, authors used annual oral glucose tolerance tests to explore the relationship between GH treatment and glucose homeostasis. This study challenges the perception that increased insulin secretion is simply a response to increased insulin resistance. The IGI was used to describe insulin secretion in these patients, and the authors showed that GH treatment was associated with increased insulin secretion in excess of that explained by changes in insulin resistance. This work builds on animal studies demonstrating a trophic effect of GH on pancreatic beta cells [12, 13], and suggests that this effect may also be clinically detectable in children during GH treatment.

**Growth hormone positive effects on craniofacial complex in Turner syndrome**

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Arch Oral Biol 2016;71:10–15

**Background:** Mild phenotypic features are seen in the craniofacial region of children and adults with Turner syndrome. GH treatment is approved in these patients to improve their final height. The aim of this study was to describe the effect of GH treatment on the craniofacial morphology in girls with Turner syndrome.

**Methods:** The authors performed a cross-sectional cephalometric analysis on lateral cephalograms of patients with 45 X karyotype. They included 13 girls who had received GH for at least 2 years, and 13 untreated controls who were matched for age and karyotype. Sixteen linear and angular measurements were taken from standard lateral cephalograms.

**Results:** The average age of girls included in this study was 17.3 years. In patients treated with GH, most linear measurements were significantly greater than in untreated patients. GH treatment influenced posterior face height, mandibular ramus height, total mandibular length, anterior face height, and maxillary length. There was no significant difference in the angular measurements and facial height ratio. Acromegalic features were not seen.

**Conclusions:** Long-term GH treatment has positive effects on craniofacial development in patients with Turner syndrome. The greatest effects are seen on posterior facial height and mandibular ramus. However, GH treatment does not normalize craniofacial features.

**Comments** The facial appearance of children with Turner syndrome may include a shorter and flattened cranial base, retrognathia, and a posteriorly inclined maxilla and mandible. GH can have effects on craniofacial growth, and this study used a case-control design to determine if GH treatment has a positive effect on these facial stigmata of Turner syndrome. The authors have shown that GH treatment may improve these features, mostly through effects on the mandibular ramus and posterior face height. Although
the craniofacial features did not normalize, the positive effect of GH described in this study provides additional information in discussing the potential pros and cons of GH treatment with these patients.

**Pubertal progression and reproductive hormones in healthy girls with transient thelarche**

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**Background:** This study sought to describe transient thelarche (TT), defined as breast bud appearance, regression and then reappearance, after the age of normal puberty (i.e., after age 8 years, as opposed to premature thelarche, which is similar but happens at a younger age).

**Methods:** This study included 98 healthy Caucasian girls from the longitudinal follow-up of the COPENHAGEN Puberty Study, a public school-based study of healthy children in the Copenhagen area in 2005–2006. Clinical examinations and blood sampling for hormone levels were performed every 6 months 2006–2014, and they were genotyped for FSHR and FSHB.

**Results:** TT occurred in 12 of the 98 girls, but not more than once. The median time from the first to second breast development was 1.47 years (0.88–4.09). More of the girls with TT (50%) started puberty with pubarche, as opposed to 15.4% of the 86 girls without TT. Growth velocity was slower and gonadotropin levels lower with the first (transient) thelarche than the second (permanent) thelarche, and all aspects of pubertal progression associated with the second (permanent) thelarche were normal, resembling those of girls without TT. Neither genotyping (FSHR and FSHB) nor weight/BMI distinguished girls who underwent TT versus those without.

**Conclusions:** TT is a common, peripheral (i.e., gonadotropin-independent) occurrence independent of central puberty, which progresses normally thereafter.

**Comments**

There are 2 key variables for assessing puberty: age of onset and tempo (how fast a child progresses through the various Tanner stages). Growth ceases at the end of puberty, so both variables play a role. A child can start puberty early, middle, or late and go slow, medium or fast; now add to those various combinations the possibility of TT. This study illustrates the importance of clinically monitoring an adolescent’s pubertal development in 6-month intervals to get a feel for their tempo (there are no tests to predict tempo). The risk-benefit considerations of therapeutic intervention (e.g., with a GnRH agonist) may be different for a girl with early thelarche if it turned out to be TT or followed by a slow tempo than if it were compounded by a rapid tempo.
Clinical characterization of patients with autosomal dominant short stature due to aggrecan mutations

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Background: Heterozygous mutations in the aggrecan gene (ACAN) are associated with autosomal-dominant short stature and accelerated skeletal maturation. The aim of this study was to describe the phenotypic spectrum and response to growth-promoting therapies in children with heterozygous mutations in the ACAN gene.

Methods: One hundred and three subjects (57 females, 46 males) from 20 families with heterozygous ACAN mutations were identified. Clinical information was collected through chart review.

Results: ACAN variants co-segregated with phenotype. Adults had mildly disproportionate short stature (median [range] height Z-Score –2.8 [–5.9 to –0.9]) and early growth cessation. Early-onset osteoarthritis was seen in 12 families and intervertebral disc disease in 9 families. There was no genotype-phenotype correlation between the type of ACAN mutation and joint disease. Height in children was less affected (median [range] height Z-Score –2.0 [–4.2 to –0.6]) but most children with ACAN mutations had advanced bone age (median [range] bone age – chronologic age; +1.3

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years [+0.0 to +3.7 years]). In this study population, 19 patients had received GH treatment with some increased growth velocity.

**Conclusions:** Heterozygous ACAN mutations are associated with a phenotypic spectrum ranging from mild and proportionate short stature to mild skeletal dysplasia with disproportionate short stature and brachydactyly. Early-onset osteoarthritis and degenerative disc disease is seen in many patients, suggesting dysfunction of the articular cartilage and intervertebral disc cartilage.

**Comments**
Aggrecan is a proteoglycan that plays an important role in articular and growth plate cartilage matrix and homozygous or missense mutations have been described in cases of skeletal dysplasia with severe short stature and severe joint disease [14–16]. Recently, novel heterozygous mutations in the ACAN gene have been identified as a cause of idiopathic short stature and advanced bone age with subtle skeletal abnormalities [17]. This international collaboration expands the phenotype of mutations in this gene through the detailed description of 19 different mutations in 103 subjects from 20 families. A common phenotype in affected individuals is the combination of advanced bone age with early growth cessation. Joint disease was seen in over half of this cohort, mostly presenting before 40 years of age.

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**Management of endocrine disease: diagnostic and therapeutic approach of tall stature**
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**Background:** Patients with tall stature (height above +2 SD for age and gender or more than 2 SD above mid-parental height SDS) are often referred to endocrinologists to exclude hormonal disorders.

**Methods:** Authors reviewed the differential diagnosis of tall stature and offered a practical diagnostic approach to patients with tall stature. They also discussed the limitations of current growth interrupting treatment options.

**Results:** The majority of patients with tall stature have familial tall stature or constitutional growth advancement (usually associated with obesity). Both are diagnoses of exclusion. The endocrine causes of tall stature are: GH/IGF-I excess, precocious exposure to sex steroids, prolonged growth due to delayed fusion of the growth plate (hypogonadism, aromatase deficiency, and estrogen resistance), thyrotoxicosis, and obesity. Syndromic causes include: supernumerary sex chromosome aneuploidies and monogenic forms (most notably, Marfan syndrome, Sotos syndrome, Beckwith-Wiedemann syndrome, homocystinuria and Fragile X syndrome).

**Conclusions:** Advances in genetic testing have revealed a growing list of conditions that can cause tall stature. However, now that sex steroids are no longer widely recommended to cease growth (due to short- and long-term consequences), treatment options are limited; remaining drugs are
either of poor efficacy or still considered experimental, and percutaneous epiphysiodesis (surgically attaching the epiphysis and diaphysis of a long bone) is reserved for patients with extreme tall stature >+3 SD.

**Comments**

The authors’ strong background in genetics is evident in this excellent review of multiple conditions that can cause tall stature; not only do they organize the topic by endocrine versus genetic categories of conditions, but they provide a useful table of clinical findings and disorders with which they are associated. Another approach to the topic was taken by Juan Sotos and Jesus Argente in their earlier study [18]. They categorized the differential diagnosis by pathophysiological mechanisms (excess of a growth gene [e.g., SHOX]; excess of GH; excess of growth factors [IGF-II, IGF-I, insulin]; excess or mutations of growth factor receptors; deficiency of factors needed to arrest growth [e.g., estrogen]; deficiency of factors needed to prevent bone elongation and dysmorphic proportions; alterations in genes involved in tumor suppression, cell cycle, proliferation and growth; and over-nutrition/obesity). Thus, readers can benefit from 2 excellent reviews of a large, complex topic that complement each other in approach.

**References**


