

Growth

Growth Hormone, IGF-1, and Metabolism



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Contents

Foreword IV

Leading Article

- The Anabolic Effects of Insulin-like Growth Factor-1 on Skeletal Growth and Development: Lessons from Clinical and Animal Studies 31
Hayden-William Courtland, PhD, Sebastien Elis, PhD, and Shoshana Yakar, PhD.
Endocrine Division, Mount Sinai School of Medicine, New York, NY, USA
- Growth Impairment in Inflammatory Bowel Disease 41
Mary Sherlock, MB BCh BAO, MRCPI (Paediatrics) and Anne M Griffiths, MD, FRCP(C)
The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada

Citations and Editors' Notes

- IGF-1 51
- GH Receptor 53
- GH Deficiency: Genetics 54
- Prader-Willi Syndrome 57
- GH treatment 59
- Miscellaneous 62

Foreword

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The understanding of endocrinology moves forward with relentless intensity. New epidemics erupt, in the form of obesity, diabetes, and insulin-resistance syndrome; and are continually challenged by new therapeutic options, developed on a seemingly daily basis. The production of one such option, that of recombinant growth hormone (GH), has allowed a greater understanding of the disease processes involved in growth and development, although the controversy surrounding its use in therapeutics continues unabated.

Advances in the field of growth disorders continue to pose significant questions to clinicians:

- Does partial GH deficiency exist in children and/or adults?
- Explain the pathophysiology of radiation-induced GH neurosecretory dysfunction. Does it occur in adults? [1]
- How does GH replacement change levels of T4 and cortisol? [2]
- If the GH stimulation test is normal upon presentation, under what circumstances should it be repeated and when? [3]
- Is there value in the IGF-1 generation test?
- What is the best GH stimulation test and what are the target values?
- Which patients benefit from IGF-1 therapy?
- Which patients benefit from leuprolide and/or an aromatase inhibitor?

These are some examples of the dozens, perhaps hundreds of questions regarding the use of GH in adults and children and it is with many of these questions in mind that we bring you volume 2 of *Current Medical Literature – Growth*, a review journal providing commentary and analysis on the most important advances in the field of growth medicine. Each issue of this journal presents specially commissioned review articles exploring issues of current and emerging clinical importance, in addition to a systematic review of the recent international literature

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We look forward to providing you with an interesting and valuable publication and welcome your feedback and your suggestions for future content. Together, we can eliminate some concerns and improve the quality of care for children and adults in need of GH and/or IGF-1 replacement.

1. Darzy KH, Pezzoli SS, Thorner MO et al. Cranial irradiation and growth hormone neurosecretory dysfunction. *J Clin Endocrinol Metab* 2007;92:1666-72.
2. Martins MR, Doin FC, Komatsu WR et al. Growth hormone replacement improves thyroxine biological effects. *J Clin Endocrinol Metab* 2007;92:4144-53.
3. Hess O, Hujeriat Y, Wajnrach MP et al. Variable phenotypes in familial isolated growth hormone deficiency caused by a G6664A mutation in the GH-1 gene. *J Clin Endocrinol Metab* 2007;92:4387-93.

Leading Article

The Anabolic Effects of Insulin-like Growth Factor-1 on Skeletal Growth and Development: Lessons from Clinical and Animal Studies

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Skeletal growth and maintenance is complex, involving developmental regulators and metabolic hormones. However, many case studies and a large number of investigations in rodents and other species have shown unequivocally that the growth hormone (GH)–insulin-like growth factor-1 (IGF-1) pathway is the major axis controlling linear skeletal growth. This short review summarizes the main anabolic effects of the GH–IGF-1 axis on skeletal growth, while referring to clinical and mouse model studies.

GH is secreted by somatotrophs in the anterior pituitary and acts as the main regulator of IGF-1 production in the liver, which is responsible for nearly 75% of circulating IGF-1 in mice [1,2]. Upon activation of the GH receptor (GHR), signal transducer and activator of transcription 5b (STAT5b) is translocated to the nucleus and initiates *Igf-1* gene transcription. Following translation, the IGF-1 protein is secreted into the circulation [3,4]. In circulation, 95% of IGF-1 is bound to IGF-binding proteins (IGFBPs) in binary or ternary complexes with the acid labile subunit (ALS); the remaining 5% circulates free [5]. IGF-1 production by extrahepatic tissues is regulated by GH and tissue-specific factors, yet the distribution of IGF-1 among the different binding complexes is obscure. Nonetheless, it is clear that the IGF-1 receptor (IGF-1R) in

tissues is activated by free IGF-1 [6]. Once activated, the IGF-1R transmits its signal to downstream molecules, which control cellular proliferation, differentiation, and viability.

Following purification and cloning of IGF-1 and -2 almost three decades ago, expression studies have shown that both IGF-1 and -2, and the IGF-1R are ubiquitously expressed [6]. The discovery of IGFBPs and their distribution in tissues unraveled the complexity of this axis and revealed two modes of IGF-1 action:

- Endocrine/serum IGF-1, which is produced mainly by the liver and tightly regulated by GH postnatally.
- Autocrine/paracrine (tissue) IGF-1, regulated mainly by temporal and spatial tissue-specific factors.

Clinical cases of GH-IGF-1 mutations

Clinical studies of the GH–IGF-1 axis have described mutations in all pathway components (e.g. GH, GHR, STAT5B, IGF-1, IGF-1R, and ALS-binding protein). A common characteristic of these mutations is reduced IGF-1 bioactivity, which results in pre- and postnatal growth failure, as well as cognitive defects [7] and delayed bone age and physical development [8]. Clinical cases with mutations in the GHR (i.e. Laron syndrome)

are characterized by increased serum GH levels, but very low levels of IGF-1, IGFBP-3, and GH-binding protein (the extracellular domain of the GHR) in serum [9,10]. The principle defect in such patients is mutation in the binding domain of the GHR, poor activation of downstream signaling pathways, and subsequent abnormally small stature. So far, only two case reports of abnormal short stature with normal levels of GHR and serum GH-binding protein have been described [11,12]. These patients did not respond to exogenous GH treatment, despite having normal GHR. Detailed examination revealed mutations in the STAT5B transcription factor, which explained their low levels of serum IGF-1, IGFBP-3, and ALS; all of which are regulated by GH in humans.

Woods et al. describe an individual with combined prenatal and postnatal growth failure who was found to be homozygous for a deletion in the *IGF-1* gene [13] and Walenkamp et al. detail a patient, the first child of consanguineous parents, presenting with severe intrauterine and postnatal growth retardation [14]. The later subject was homozygous for a point mutation in the *IGF-1* gene, which resulted in a bio-inactive peptide and, therefore, blunted activation of IGF-1R. Only four isolated cases with mutations in the *IGF-1R* gene have been identified; a case of a compound heterozygosity for point mutations in the *IGF-1R* gene [15], a child who was heterozygous for a nonsense mutation of the *IGF-1R* gene [15], and a 13-year-old girl and her aunt (both showing intrauterine and postnatal growth retardation with increased serum IGF-1 levels), who were identified for a heterozygous mutation in exon 7 of the *IGF-1R* gene [16]. The history of intrauterine growth retardation in these individuals confirmed that abnormalities in IGF-1R function also lead to growth retardation in humans.

Currently there are no reports on mutations in the IGFBPs. However, there are already 11 described cases of mutations in the *ALS* gene [17–23]. Compound heterozygotes for mutations in the *ALS* gene present with normal serum GH levels but reduced IGF-1 and IGFBP-3 in serum. These patients

display mild short stature (–2 to –3 standard deviation), delayed puberty, and respond poorly to GH treatment. Analysis of serum IGF-1–IGFBP complexes revealed no ternary complexes and reduced levels of binary complexes with IGFBP-3.

IGF-1 and small for gestational age infants

It has been estimated that approximately 91 000 infants per year are born small for gestational age (SGA) in the US [24]. In these infants, a reduction in birth weight and/or body length may exist. The correlated health concerns include increased morbidity and mortality rates during infancy and childhood, increased risk for cardiovascular disorders [25,26], and a greater likelihood of insulin resistance/type-2 diabetes extending into adulthood [27,28]. Although the exact cause of SGA is not known, evidence supports a link to serum IGF-1 levels. Early research examining infants with SGA indicated reduced levels of IGF-1. Fetal cord sera obtained *in utero* from fetuses with growth retardation (reduced weight) were shown to have significantly lower levels of IGF-1 than sera from normal fetuses, indicating that IGF-1 may play a role during the later segment of intrauterine development [29,30].

An investigation of hormone levels in intrauterine growth-retarded (IUGR) children from birth to 2 years of age revealed significant decreases in serum IGF-1 at birth [31]. However, these levels were normal at 1 month of age and were not predictive of later growth. In this study, the authors propose that nutritional variation was the major determinant of reduced IGF-1 levels. Indeed, most children born SGA exhibit not only short stature, but also reduced lean body mass, which may result from malnutrition or low food intake [32,33]. Food intake, as assessed in 88 SGA children, was significantly lower compared with age/sex-matched controls, and correlated with low serum IGF-1 and IGFBP-3 levels [34]. Treatment with GH resulted in an increase in carbohydrate and protein intake and was associated with significant increases in lean body mass, height, and serum levels

of IGF-1 and IGFBP-3. Children who are premature and SGA show increased GH levels during infancy compared with those with SGA alone or controls [35–37]. These elevated GH levels result in GH resistance accompanied by low levels of circulating IGF-1 and IGFBP-3. Other studies have reported a genetic basis for IGF-1 deficiency resulting from deletion of the *IGF-1* gene [13], acquisition of *IGF-1* mutations [14], and existence of microsatellite markers [38]. Taken together, these studies indicate that prenatal and postnatal IGF-1 deficiency in SGA or IUGR individuals is multifactorial, and that the particular cause of the deficiency may dictate the extent to which an individual can compensate during postnatal development.

IGF-1, bone mineral density, and aging

The role of IGF-1 in adulthood and aging is an area of extensive investigation stemming from early observations regarding changes in hormone levels with age [39]. In both men and women, decreases in bone mass (the amount of bone tissue) and bone architecture accompany the aging process such that in severe cases, this age-related bone loss results in osteoporosis and places individuals at an increased risk of fracture. Risk of fracture is commonly assessed in a clinical setting by bone mineral density (BMD) scans. Thus, osteoporotic patients often have markedly reduced BMD values. Studies have shown that in both men and women (aged 30–62 years), there are significant trends of decreasing IGF-1 levels with increasing age [40,41]. Similarly, there are also significant correlations between decreases in femoral and vertebral BMD and reductions in serum IGF-1 levels in both women [40,42] and men [43,44]. In age-matched experimental groups, elderly women who suffered a femoral hip fracture had significantly lower serum IGF-1 levels than women who did not [45]. Thus, there are correlative links between IGF-1 levels, BMD, and fracture risk.

Genetic analysis of the *IGF-1* promoter indicated that the number of 192-bp microsatellites (*IGF-1* promoter

polymorphism) were correlated with increases in femoral neck BMD in elderly men and women, such that individuals without the 192-bp allele had marked decreases in BMD [46,47]. Furthermore, a follow-up study showed that women who were heterozygous, or who were lacking the 192-bp allele entirely, were at an increased risk of fracture; however, men demonstrated no significant correlations between the polymorphism and fracture risk [48]. Although these epidemiological studies do not separate the autocrine and paracrine effects of IGF-1 during aging, and BMD is used in lieu of true bone structural measurements, the evidence relating IGF-1 levels to BMD values is convincing and has resulted in numerous *in vivo* and *in vitro* studies of animal models.

GH-IGF animal models

The major changes in pre- and postnatal weight and size associated with human deficiencies in IGF-1 are suggestive of similar associations in other animal species. A survey of 526 dog breeds found that a single-nucleotide polymorphism in the *Igf-1* gene results in the substantial size variation found between small and large breeds [49]. Given that studies of large animals are costly and often time-consuming, mouse models have received a great deal of attention and, consequently, our understanding of the GH–IGF-1 axis and how it affects skeletal development is largely based on work in these experimental systems. With the development of transgenic and knockout techniques, it is now clear that mutations in components of the GH–IGF-1 axis result in growth retardation and numerous skeletal phenotypes (**Table 1**).

One of the earliest studies of the *Igf-1* gene was its deletion in mice. The investigators found that heterozygous mice were 10–20% smaller than wild-type (wt) mice and nearly all homozygous mice died within moments of birth [50]. As expected, the decrease in size of *Igf-1*^{-/-} mice resulted from a reduction in overall size of the body organs (e.g. muscle, bone) [51]. In terms of long bone linear growth, the reduction in size of *Igf-1*^{-/-} mice did not affect chondrocyte

Table 1. A summary of results from transgenic and knockout studies of the GH-IGF-1 axis in mice

	Mutant name	Serum GH/IGF-1 levels	Growth and skeletal characteristics	Ref
GH secretion	<i>dwr/dwr</i> (snell, mutation in <i>Pit-1</i> gene)	Undetectable GH, reduced IGF-1 (approximately 90%)	GR, abnormal growth plate, reduced linear growth	73, 74
	<i>dt/dt</i> (ames, mutation in <i>Prop-1</i> gene)		GR, reduced bone area and BMC	75, 76
	<i>lit/lit</i> (mutation in <i>GHRHR</i> gene)		GR (60% of adult size), reduced cortical BMD, normal trabecular bone	77
GH action	<i>Chrbp</i> ^{-/-}	Increased GH, reduced IGF-1 (approximately 90%)	GR (60% of adult size)	78
	<i>Stat5b</i> ^{-/-}		GR (males)	79
	GHA (TG)		GR (60% of adult size), four-fold increased body adiposity, reduced BMD	80 and *
	<i>Igf-1</i> ^{-/-}	Increased GH	GR (30% of adult size), reduced cortical BMD, increased trabecular BMD	50
IGF	<i>Igf-1</i> ^{+/-} (haploinsufficiency)	Reduced IGF-1 (50%)	GR (70% of adult size), reduced femoral length and areal BMD	55, 81
	<i>Igf-1</i> TG (ubiquitous expression)	Undetectable GH, increased IGF-1 (50%)	Increased body weight and organ growth, normal skeletal size and morphology	82
	<i>Igf-2</i> ^{-/-}	Normal GH and IGF-1	GR (60% of neonate size)	83
	m/m (MIDI)	Reduced IGF-1 (approximately 70%)	GR, reduced femoral length and areal BMD	57
	<i>Igf-1r</i> ^{-/-}		Lethal (neonates at 45% of WT)	61
	<i>Igf-1r</i> ^{+/-} (haploinsufficiency)		GR (90% of adult size)	84
	<i>Igfbp-1</i> ^{-/-}		Not reported	85
IGFBPs	<i>Igfbp-1</i> TG		GR, reduced skeletal mineralization	86
	<i>Igfbp-2</i> ^{-/-}		Sex-related decrease in BMD (male)	87
	<i>Igfbp-2</i> TG	Increased IGF-1 (10%)	Reduced (10%) carcass weight	88
	<i>Igfbp-3</i> ^{-/-}		No effects on body weight or linear growth noted	89
	<i>Igfbp-3</i> TG		Reduced volumetric and cortical BMD, increased resorption	90
	<i>Igfbp-4</i> ^{-/-}		GR (85% of adult size)	89
	<i>Igfbp-4</i> TG		GR	91
	<i>Igfbp-5</i> ^{-/-}		No effects on body weight or linear growth noted	89
	<i>Igfbp-5</i> TG		Sex related reduction in BMD, impaired mineralization, reduced BFR	92
	<i>Igfbp-6</i> ^{-/-}		Not reported	

	<i>Als^{-/-}</i>	Reduced IGF-1 (approximately 65%)	GR (80% of adult size), reduced volumetric and cortical BMD, reduced femoral length (10%)	93
	<i>Als</i> TG		Modest GR	94
	<i>Papp-a^{-/-}</i> (IGFBP-4 protease)		GR (60% of adult size)	95
	<i>Papp-a</i> TG		Increased body weight	96
Tissue-specific mutations	LID	Four-fold increase in GH, reduced IGF-1 (approximately 75%)	Normal growth, reduced volumetric and cortical BMD, reduced femoral length (5%)	97
	<i>Igf-1r^{-/-}</i> in OB		Normal growth, impaired mineralization	64
	<i>Igf-1^{-/-}</i> in chondrocytes		Body length, areal BMD, and BMC reduced from week 4-12	63
	<i>Igf-1</i> TG in OB		Increased volumetric and cortical BMD	66
	<i>Igf-1</i> TG in liver	Increased IGF-1 (50%)	Increased body weight and linear growth	97
	<i>Igfbp-4</i> TG in OB		Reduction bone volume and cortical BMD	98
Composite models	<i>Igf-1^{-/-}; Igf-2^{-/-}</i> (haploinsufficiency)		GR (30% of adult size)	61
	<i>Igf-1^{-/-}; Igf-1r^{-/-}</i>		Lethal (neonates at 45% of WT)	61
	<i>Igf-1^{-/-}; Igf-1r^{-/-}</i> (haploinsufficiency)		GR (30% of adult size)	61
	<i>Igf-1^{-/-}; Ghr^{-/-}</i>		GR (17% of adult size)	62
	<i>Igfbp-3-/-; 4-/-; 5^{-/-}</i>		GR (80% of adult size)	89
	<i>Igfbp-4^{-/-}; Papp-A^{-/-}</i>		GR (90% of adult size)	95
	LID <i>Als^{-/-}</i>	Six-fold increase in GH, reduced IGF-1 (approximately 90%)	GR (70% of adult size), reduced cortical and trabecular BMD	93
	<i>Igf-1^{-/-}; Igf-2</i> TG (liver expression)		GR, adults show similar body weight and length to <i>Igf-1^{-/-}</i> mice	99
<p>*Yakar S, personal note. BFR: bone formation rate; BMC: bone mineral content; BMD: bone mineral density; GH: growth hormone; GHA: GH antagonist; GHRHR: GH releasing hormone receptor; GR: growth retardation; IGF: insulin-like growth factor; IGFBPs: IGF-binding proteins; LID: liver-specific inducible deletion; MID: microphthalmia-defective iris; OB: osteoblasts; TG: transgenic mice; WT: wild-type.</p>				

proliferation, but attenuated chondrocyte hypertrophy [52,53]. However, cancellous BMD of 3-month-old *Igf-1^{-/-}* mice increased, as evidenced by decreased trabecular spacing, along with increases in trabecular number and the prevalence of a more rod-like architecture [54]. This increase in cancellous bone volume was attributed to a decrease in osteoclast activity, thereby suggesting a dual role for IGF-1 as a regulator of both anabolic (osteoblastic) and catabolic (osteoclastic) processes in bone.

Studies of *Igf-1* heterozygous mice were more feasible as most animals survived and aged normally. *Igf-1^{+/-}* mice had 50% reductions in serum and tissue IGF-1 levels, and decreased body size and BMD [55]. Their bone structure was significantly altered and by 8 months of age, cortical bone area and periosteal circumference were substantially reduced compared with WT mice [55]. The microphthalmia-defective iris (MIDI) mice, which harbor a mutant *Igf-1* allele, showed 70% reduction in circulating IGF-1 levels, decreased IGF-1 bioactivity [56], and impaired growth [57]. Treatment with exogenous IGF-1 for 3–8 weeks increased their femoral length and bone mineral content [58].

In contrast to the *Igf-1^{-/-}* mice, *Igf-2^{-/-}* mice show intrauterine growth retardation, but demonstrate catch-up growth postnatally. A comparison of *Igf-1^{-/-}* mice, *Igf-2^{-/-}* mice, and GH-deficient mice revealed that even though all strains had reductions in femoral length and BMD by 3 weeks of age, *Igf-2^{-/-}* and GH-deficient mice were able to regain BMD during puberty, while *Igf-1^{-/-}* mice were not, due to severely abrogated periosteal expansion [59]. These animal models clearly demonstrate that, while both IGF-1 and IGF-2 are important for fetal growth and development, only IGF-1 is critical for postnatal growth, at least in mice.

Deletion of the IGF-1R in mice was lethal and resulted in severe intrauterine growth retardation. This mouse model provides strong evidence that the IGF-1R is indeed the major receptor mediating IGF-1 effects during embryogenesis and postnatal development [60,61].

Recognizing the synergistic and compensatory nature of hormonal regulation, researchers have created mice with multiple gene ablations. Simultaneous disruption of the *Igf-1* and *Igf-1r* genes in mice resulted in a phenotype similar to that of *Igf-1r^{-/-}* mice, again suggesting that the actions of IGF-1 are mediated primarily via the IGF-1R [61]. On the other hand, disruption of *Igf-2* and *Igf-1r* in mice resulted in a more growth-retarded phenotype than with *Igf-1/Igf-1r* knockout mice, suggesting that some of the intrauterine functions of IGF-2 are mediated via the insulin receptor [61]. In a similar approach, both the *Ghr* and *Igf-1* genes were ablated in mice, resulting in a growth retardation more severe than in animals with just one of the two genes deleted. This indicated that both GH and IGF-1 have independent and overlapping roles in postnatal growth [62].

Tissue-specific gene alterations

With the development of tissue-specific gene inactivation (using the Cre-loxP system), our understanding of the GH–IGF-1 axis has grown markedly because:

- Most of the tissue-specific gene-inactivated models are not lethal, allowing investigation of skeletal properties in the adult mouse.
- In most models, tissue-specific gene inactivation does not cause multiple organ failure.

Therefore, direct and indirect actions on the skeleton are easier to distinguish. Targeted deletion of the mouse *Igf-1* gene in the liver (LID mice) resulted in a 75% reduction in serum IGF-1 levels, but no change in body weight, body length, or femoral length up to 6 weeks of age [1]. This study revealed that circulating IGF-1 (endocrine) was not essential for early postnatal growth and suggested that tissue IGF-1 plays a major role in development. This was clearly shown in mice with chondrocyte-specific *Igf-1* gene deletion, where body length and BMD, as well as femoral and vertebral bone periosteal circumference, were decreased [63]. Using

the Cre-loxP system, *Igf-1r* was deleted specifically in mouse osteoblasts. In sharp contrast to the systematic *Igf-1r* gene ablation (which was lethal), *Igf-1r* gene ablation in osteoblasts had no effect on body weight and size at 6 weeks of age, but resulted in marked decreases in trabecular bone volume and impaired mineralization [64]. In a reverse approach, different components of the GH-IGF system were overexpressed in a tissue-specific manner. Overexpression of IGF-1 in skeletal muscle resulted in increases in body weight and bone lengths (tibiae and femora), as well as increases in cortical area, cortical thickness, and BMD [65]. In contrast, mice overexpressing IGF-1 in osteoblasts had unchanged body weight, while bone formation rate and mineral apposition rate increased significantly by 3 weeks of age [66]. Together, these studies highlight the potential variability in body size and bone morphology that can arise from the variable effects of systemic and local IGF-1 action. Additionally, the magnitude and timing of IGF-1 action appear important in determining the skeletal phenotypes.

***In vitro* models**

Cell culture experiments have proven useful in elucidating the molecular and cellular action of IGF-1. From studies on cultured calvarial tissue from mice, researchers have made connections between IGF-1-mediated variation at the whole bone level and at the cellular level. C3H/HeJ (C3H) femora, although identical to C57BL/6J (B6) in cortical area and total area at birth, are slightly smaller in total area, and much larger in cortical area and BMD compared with B6 by 16 weeks of age [67,68]. Calvarial cultures from C3H and B6 mice (which have high and low serum and skeletal IGF-1 levels, respectively), demonstrated increased numbers of alkaline phosphatase-positive colonies in C3H cultures compared with B6 [69]. Calvariae from *Igf-1^{-/-}* mice had significant reductions in collagen synthesis suggesting an anabolic role for IGF-1 in development of the bone extracellular matrix [70]. Similarly, osteoblast cultures from

IGF-1 heterozygous mice showed a decrease in proliferation compared with control mice, as well as a 50% and 40% reduction in IGF-1 mRNA and IGF-1 protein levels, respectively [55]. Mesenchymal stem cells cultured from mouse bone marrow treated with exogenous IGF-1 were found to have increased proliferation, reduced numbers of apoptotic nuclei, and increased collagen II expression, thereby indicating a positive role for IGF-1 in the chondroinductive stage of skeletal development [71]. Ablation of the *Igf-1r* in mouse osteoblasts resulted in reduced alkaline phosphatase staining and fewer mineralized nodules in culture. These observations were in agreement with the reduced bone volume fraction and cortical thickness of *Igf-1r* heterozygous tibiae, from which the osteoblasts were obtained [72].

Conclusions

Overwhelming evidence exists to implicate IGF-1 in the regulation of bone growth and development. In mouse developmental studies, regulation of long bone length is very clear and is supported by changes in the proliferative and hypertrophic zones of the growth plate. Postnatal changes in cortical and cancellous bone properties are also well established in conjunction with changes in IGF-1 levels; however, there is tremendous variability with respect to the specific traits that change and the magnitude of these trait changes. This variability undoubtedly arises from tissue-specific differences (i.e. vertebrae vs. femora), age and gender differences, and the type of hormonal restriction placed on the system (i.e. endocrine vs. paracrine action). Thus, the full implications of IGF-1 therapy remain uncertain. Although clinical cases of IGF-1 deficiency are less common than those of GH deficiency, IGF-1 may prove useful as a therapeutic agent for improving specific aspects of postnatal bone development once future studies elucidate the local and systemic effects of IGF-1 action on bone.

Numerous studies support a role for IGF-1 in the aging process of bone. A correlation has been shown between decreased BMD and

serum IGF-1 levels, and increased fracture risk, in aging individuals. However, the clinical implications of these relationships are yet to be ascertained. This is in part because BMD measures are suggestive of only the amount of bone tissue in a given space and do not define the true mineral content or architecture of the bone. Therefore, the role of IGF-1 in matrix mineralization requires further investigation, as does its suggested dual regulatory role in both bone forming (osteoblast) and bone resorbing (osteoclast) cell populations. Similarly, while epidemiological studies and morphological traits (e.g. cortical area, cortical thickness) give an indication of fracture susceptibility, biomechanical studies are lacking in the literature and are necessary to determine the contribution of IGF-1 to bone mechanical properties. Given that the regulation of both osteoblast and osteoclast cell populations is critical in maintaining bone mass and functionality, the full implications of IGF-1 therapy remain uncertain. Future studies will enable researchers to explore this avenue by identifying the timing and regions of IGF-1 action on bone that optimize bone traits for physiological and mechanical functionality.

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Leading Article

Growth Impairment in Inflammatory Bowel Disease

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The clinical course and severity of inflammatory bowel disease (IBD) vary widely in children and in adults [1,2]. However, unique to pediatric patient populations is the potential for linear growth impairment as a complication of chronic intestinal inflammation. The challenge in treating each child or adolescent is to employ pharmacological, nutritional, and, where appropriate, surgical interventions – not only to decrease mucosal inflammation and thereby alleviate symptoms, but also to optimize growth and normalize associated pubertal development. Indeed, normal growth is a marker of therapeutic success. This review will highlight the prevalence of growth impairment in pediatric IBD, discuss its pathophysiology, and outline strategies for its prevention and management.

Normal growth and pubertal development

“Normal” children grow at very different rates. Patterns of growth and pubertal progression in young patients with IBD can only be accurately recognized as pathological if the variations in normal development of healthy children and adolescents are first appreciated.

A child’s growth is the result of both genes and environment; it appears principally mediated by hormones and nutrition. Linear growth can be represented by stature (attained height) or by the rate of growth (height velocity). A child’s attained height represents the culmination of growth in all preceding years; height velocity reflects

growth status at a particular point in time. The growth hormone–insulin-like growth factor-1 (GH–IGF-1) axis plays a pivotal role in normal postnatal growth. IGF-1 stimulates mitosis of epiphyseal chondrocytes resulting in linear bone growth. Thyroxine, cortisol, and sex steroids are also implicated in the maintenance of normal linear growth.

Linear growth velocity decreases from birth onwards, punctuated by a short period of growth deceleration prior to puberty followed by growth acceleration (the “adolescent growth spurt”) just prior to the completion of growth. As the rapid growth of infancy tails off, the steady growth of childhood predominates. Healthy children grow at a consistent rate in the range of 5–6 cm annually from 6 years of age until the onset of puberty. At puberty there is a rapid alteration in body size, shape, and composition; for a year or more height velocity approximately doubles. The age of onset of puberty, and hence of the pubertal growth spurt, varies among normal individuals and between ethnic populations. Puberty begins earlier in girls than in boys; moreover, the pubertal growth spurt occurs in mid-puberty (prior to menarche) in girls but in late puberty (after Tanner stage 4) in boys. Thus, there is quite consistently a 2-year difference in the timing of peak height velocity in girls compared with boys. In North American females, peak height velocity occurs at a mean age of 11.5 years but in males it does not occur until a mean age of 13.5 years (two standard

deviations = 1.8 years). The occurrence of menarche is an indication that linear growth is nearing completion; usually girls gain only 5–8 cm more in height within the two subsequent years.

Monitoring and assessment of growth

Standardized charts are available for graphically recording height, weight, and height velocity such that an individual child's growth can be compared with normative values [3]. Wherever possible, reference data most appropriate to the child being monitored should be utilized. An individual child's growth measurement can be represented as a percentile or as a standard deviation score (SDS) – a quantitative expression of distance from the reference population mean (50th percentile) for the same age and gender (**Figure 1**). Healthy children grow steadily along the same height percentile and hence maintain the same SDS for height from early childhood through until adulthood. Combined parental heights can be used to estimate a child's potential height:

$$\frac{(\text{Height of mother} + \text{Height of father})}{2}$$

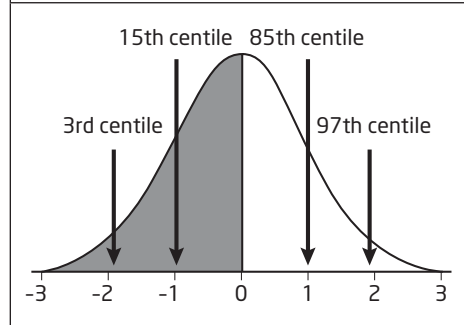
+ 2.5" for boys / -2.5" for girls

Some temporary deviation from the usual growth channel may occur if the pubertal growth spurt occurs particularly early (temporary increase in height velocity and height centile) or late (temporary decrease in height velocity and height centile).

Definitions of impaired growth

Within a large patient group, skewing of SDS for height below population reference values is suggestive of disease-associated growth impairment. The mean height SDS of a population characterized by normal growth approximates zero. Growth disturbance in an individual child is indicated by an abnormal growth rate [4]. A definition of impaired growth in terms of static height measurement, although sometimes used, may be misleading, since it is influenced by

Figure 1. Growth centiles and standard deviation (Z) scores. At any age height is distributed in a relatively normal manner in a healthy population. Z scores indicate the relative distance away from the mean for the population. A Z score of 1 is 1 standard deviation away from the mean.



parental heights. An individual child may be normally short; conversely, a previously tall child may not have increased his or her height in 2 years, but still be of average stature. A shift from higher to lower centiles on a growth chart of height attained more validly signifies growth faltering. Height velocity, expressed either as a centile or as an SDS for age and gender, is the most sensitive parameter by which to recognize impaired growth.

Growth in pediatric IBD Prevalence of growth impairment in IBD

IBD occurring during early adolescence is likely to have a major impact on nutritional status and growth owing to the very rapid accumulation of lean body mass that normally occurs at this time. Further, boys are more vulnerable to disturbances in growth than girls because their growth spurt occurs later and is ultimately longer and greater.

Crohn's disease

Several studies have characterized the growth of children with Crohn's disease who were treated in the 1980s and into the 1990s [1,5–9]. These studies are important as a benchmark of outcomes with traditional therapy. It is to be hoped that the better understanding of the

Table 1. Prevalence of linear growth impairment in pediatric Crohn's disease. Varying definitions and times of assessment (at the time of diagnosis and during follow-up) are applied.

Study [ref]	Time of assessment	Patients studied	n	Definition of linear growth impairment	Percentage with growth impairment
Baltimore, MD, USA 1961 to 1985 [5]	At diagnosis	Prepubertal (Tanner I or II)	50	Decrease in height velocity prior to diagnosis	88
Toronto, ON, Canada 1980 to 1988 [1]	During follow-up	Prepubertal (Tanner I or II)	100	Height velocity ≤ 2 SD for age for ≥ 2 years	49
Sweden 1983 to 1987 [6]	During follow-up	Population-based cohort aged <16 years at diagnosis	46	Height velocity ≤ 2 SD for age for 1 year	65
New York, NY, USA 1979 to 1989 [7]	At maturity	Children in tertiary care	38	Failure to reach predicted adult height	37
Toronto, ON, Canada 1990 to 1999 [1]	During follow-up	Prepubertal (Tanner I or II)	161	Height velocity ≤ 2 SD for age for ≥ 2 years	54
United Kingdom 1998 to 1999 [8]	At diagnosis	Population-based cohort aged <16 years at diagnosis	338	Height SDS < -1.96	13
Israel 1991 to 2003 [9]	At diagnosis	Children in tertiary care	93	Height SDS < -2.0	20

SDS: standard deviation score.

pathogenesis of growth impairment and the greater likelihood of resolution of intestinal inflammation with newer therapies may lead to enhanced growth of young patients diagnosed in the present decade.

As summarized in **Table 1**, the percentage of patients with Crohn's disease whose growth is affected varies with the time of assessment, the definition of growth impairment, and according to the nature of the population under study (tertiary referral center vs. population-based) [1,5–9]. Nevertheless, it has been consistently observed that the impairment of linear growth is common prior to the recognition of Crohn's disease as well as during the subsequent years, and that height at maturity has often been compromised [1,5–9].

At the time of diagnosis, the mean SDS for height is reduced among children with Crohn's disease as a group, compared with reference populations (**Table 2**), which is an indication of the growth retardation occurring prior to the recognition and treatment of intestinal inflammation. Data from the more recent of these studies

confirm that growth delay prior to diagnosis still occurs and remains a challenge [8,9]. A delay in epiphyseal closure allows growth to continue longer than normal. Hence, SDS for height may improve over the course of treatment when the chronic inflammation can be controlled. However, there is a paucity of population-based cohort data comparing pre-illness height centiles with final adult stature of patients with Crohn's disease that develops prior to puberty.

Ulcerative colitis

In general, at diagnosis no significant reduction is observed in height-for-age SDS among young patients with ulcerative colitis (UC) compared with the reference population. As an example, SDS for height was not reduced (mean -0.12 , 95% confidence interval [CI] -0.30 to 0.05) in 143 children and adolescents with incident UC in the British pediatric surveillance study [8].

During follow-up, growth impairment remains a less frequent complication, although relatively few studies have carefully described linear growth in UC. Hildebrand

Table 2. Mean height SDS for height in children diagnosed with Crohn's disease prior to or in early puberty (Tanner stage I or II).

Study [ref]	Patients studied	n	Mean height SDS (SD)	
			At diagnosis	At maturity
Baltimore, MD, USA 1961 to 1985 [5]	Prepubertal (Tanner I or II)	50	-0.48	Not assessed
Toronto, ON, Canada 1980 to 1988 [1]	Prepubertal (Tanner I or II)	100	-1.1 (1.3)	-0.82 (1.1)
Sweden 1983 to 1987 [6]	Population-based cohort aged < 16 years at diagnosis	46	-0.5 (1.4)	-0.4 (1.1)
Toronto, ON, Canada 1990 to 1999 [1]	Prepubertal (Tanner I or II)	161	-0.74 (1.2)	-0.70 (1.2)
United Kingdom 1998 to 1999 [8]	Population-based cohort aged < 16 years at diagnosis	338	-0.54	Not assessed
Israel 1991 to 2003 [9]	Children in tertiary care	93	-0.56 (1.16)	Not assessed

SDS: standard deviation score.

et al. observed that 11 (24%) of 45 children with UC had a height velocity < -2.0 SD over a period of more than 1 year [6]. The final attained mean height was comparable to reference population data in this study [6].

Why linear growth impairment is less common in UC than in Crohn's disease is not entirely clear. The usual colitic symptom of bloody diarrhea is more promptly investigated than the often subtle presenting symptoms of Crohn's disease, accounting at least in part for the lesser effect on growth prior to diagnosis. Disease-related differences in cytokine production may also be important.

Pathophysiology of growth impairment in IBD

As summarized in **Table 3**, several inter-related factors contribute to linear growth impairment in children with IBD. The fundamental mechanisms have recently been comprehensively reviewed [10].

Chronic caloric insufficiency

Chronic undernutrition has long been implicated and remains an important and remediable cause of growth retardation. Multiple factors contribute to malnutrition. However, a reduced intake rather than excessive losses or increased needs is the major cause of the caloric insufficiency. Disease-related anorexia may be profound;

cytokines produced by the inflamed bowel are likely to be responsible for this. Investigations in a rat model of colitis suggests that tumor necrosis factor- α (TNF- α) interacts with hypothalamic appetite pathways [10]. Significant intestinal fat malabsorption is uncommon, but leakage of protein is frequent [11]. In general, resting energy expenditure (REE) does not differ from normal in patients with inactive disease, but can exceed predicted rates in the presence of fever and sepsis. Furthermore, in comparison to comparably malnourished patients with anorexia nervosa, a lack of compensatory reduction in REE has been described in adolescents with Crohn's disease [12]. A reduction in REE is a normal biological response to conserve energy. Production of inflammatory mediators may explain the lack of REE adaptation in patients with Crohn's disease, and further augment the ongoing malnutrition.

Direct cytokine effects

A simple nutritional hypothesis fails to explain all the observations related to growth patterns among children with IBD. Direct growth-inhibiting effects of pro-inflammatory cytokines released from the inflamed intestine are at least equally as important [10]. IGF-1, produced by the liver in response to GH stimulation, is the key mediator of GH effects

Table 3. Factors contributing to growth impairment in children with Crohn's disease.

Factor	Explanation
Pro-inflammatory cytokines	Direct interference with IGF-1 mediation of linear growth
Decreased food intake	Cytokine-mediated anorexia, fear of worsening gastrointestinal symptoms
Stool losses	Mucosal damage leading to protein-losing enteropathy; diffuse small intestinal disease or resection leading to steatorrhea
Increased nutritional needs	Fever; requirements for catch-up growth
Corticosteroid treatment	Interference with growth hormone and IGF-1

IGF-1: insulin-like growth factor-1.

at the growth plate of bones. An association between impaired growth in children with Crohn's disease and low IGF-1 levels is well recognized. Early studies emphasized the role of malnutrition in suppression of IGF-1 production, but more recent studies in children with chronic inflammatory conditions and in animal models demonstrate an interleukin-6 (IL-6)-mediated reduction in circulating IGF-1, either via decreased production or increased clearance [13–15].

There is evidence that inflammatory cytokines also inhibit linear growth through pathways not involving IGF-1. Animal experiments have shown that TNF- α and IL-1 increase chondrocyte death and thus may have a deleterious effect on growth [16]. Cytokines appear to impair end-organ responsiveness to circulating testosterone, thereby compounding the effects of undernutrition in delaying progression through puberty [17].

Corticosteroid-mediated suppression of linear growth

Chronic daily corticosteroid administration in children augments the growth impairment associated with inflammatory disease. The growth suppressive effects of glucocorticoids are multifactorial, and include central suppression of GH release, decreased hepatic transcription of GH receptor such that production of IGF-1 is decreased, and decreased IGF-1 binding in cartilage [18]. Hence, exogenous corticosteroids create a state of functional GH deficiency [18].

Endocrine mediators of growth impairment

It is evident from the discussion above that reduced plasma concentrations of IGF-1, as

a result of inflammatory cytokines and/or malnutrition and/or exogenous corticosteroids, play a central role in mediating growth impairment in IBD. GH levels in response to provocative testing are normal. Thyroid gland function is normal. Sex steroids may play a role in the delayed pubertal growth spurt.

Influence of genetic factors

Given the role of inflammatory mediators in growth, it is feasible that common genetic polymorphisms that alter cytokine expression may contribute to growth impairment, rather than influencing disease susceptibility. A recent study of Israeli patients suggests that relatively common variations in the promoter region for TNF- α may have an independent effect on linear growth outcomes [19]. Similarly, data from Sawczenko et al. demonstrate a potential causal relationship between variation in the promoter region for IL-6, subsequent IL-6 expression, and a differential in linear growth impairment during active inflammation [20]. Confirmation of these, and similar findings, are awaited, and may help better elucidate the complex molecular interactions pertinent to the pathophysiology of growth impairment.

Facilitation of normal growth in IBD

The importance of prompt recognition of IBD

The clinical presentation of childhood Crohn's disease may be subtle and varied. Impairment of linear growth and concomitant delay in sexual maturation may precede the development of intestinal symptoms and dominate the presentation in some cases,

although the reasons for this are currently unclear. A prompt diagnosis is important in avoiding a long period of growth retardation. The greater the height deficit at diagnosis, the greater is the demand for catch-up growth.

The importance of monitoring growth

In caring for children with IBD, it is important to obtain pre-illness heights so that the impact of the chronic intestinal inflammation can be fully appreciated. Following diagnosis and institution of treatment, regular measurement and charting of height, together with calculation of height velocity, are central to management. A properly calibrated, wall-mounted stadiometer is required for accurate and reproducible serial measurements.

Part of the assessment of response to therapy in children with IBD is a regular analysis of whether the rate of growth is normal for age and pubertal stage and whether catch-up growth to pre-illness centiles is being achieved. Height velocity must be appraised in the context of current pubertal stage because of the variation in normal rates of growth before puberty, during puberty, and near the end of puberty. If growth and puberty appear either delayed or very advanced, radiological determination of bone age can be used to indicate the remaining growth potential.

One of the difficulties in evaluating growth in response to a therapy is the relatively long interval of time required for valid assessment. Published normal standards for height velocity throughout childhood are based on height increments during 12-month periods [21]. When growth velocity is calculated over short time periods, small errors in individual measurements are significantly magnified and the normal seasonal variation in growth is overlooked. The consensus from pediatric endocrinologists is that height velocity should be calculated over intervals no shorter than 6 months [21].

Psychosocial impact of impaired growth

Growth impairment and accompanying pubertal delay have a significant psychosocial impact on adolescents, as the physical

differences between them and their healthy peers become progressively more obvious. In the development process of a disease-specific, health-related quality of life instrument for pediatric IBD, body image issues including height and weight were among the concerns most frequently cited by adolescents with Crohn's disease [22].

Choosing therapies to optimize growth

In the management or prevention of growth impairment, attention needs to focus on treatment of gut inflammatory disease using the most appropriate pharmacological, nutritional, or surgical intervention. Key differences in management of IBD in children and young adolescents compared with adults have always included greater attention to avoidance of chronic corticosteroid therapy, more frequent use of enteral nutrition as an alternate primary therapy in Crohn's disease, and earlier consideration of resection of localized Crohn's disease and steroid-dependent UC. These strategies are all aimed at optimizing growth prior to completion of puberty. Biological therapies, specifically anti-TNF- α antibodies, have brought the management of pediatric Crohn's disease into a new era. Children whose disease remains chronically active despite the use of immunomodulatory drugs now benefit from such therapy. Ongoing monitoring of long-term safety issues will determine whether infliximab and other biological agents should be utilized earlier in pediatric treatment regimens in the future in order to improve disease-related outcomes including growth.

Anti-inflammatory treatments and effects on growth

Few interventions have been tested in the randomized controlled trial setting in children, and hence the effects of therapies on growth have seldom been rigorously assessed. The only exception is enteral nutrition as primary therapy of pediatric Crohn's disease. For most other therapies, growth outcomes have been reported only in observational studies.

Enteral nutrition

The appeal of enteral nutrition as primary therapy among pediatric patients relates to avoidance of steroids, both because of their unwanted cosmetic side effects and their propensity to interfere with growth. Amino acid-based and peptide-based formulae are administered by nocturnal nasogastric infusion, but more palatable polymeric formulae can be consumed orally, and appear comparably efficacious [23]. Open trials in children have documented endoscopic healing and decreased mucosal cytokine production following exclusive enteral nutrition [24]. Some have argued that active Crohn's disease occurring in children is more responsive than that occurring in adults, where corticosteroid therapy more often induces clinical remission [25]. However, it seems likely that other factors, such as small bowel localization and recent onset of Crohn's disease, rather than young age *per se*, influence the responsiveness of intestinal inflammation to exclusive enteral nutrition.

If enteral nutrition is to facilitate growth, remission must be maintained. One of the limitations of a liquid diet therapy has been the observed tendency for symptoms to recur promptly following its cessation. Longer term nutritional interventions, such as a cyclical exclusive enteral nutrition [26] or nocturnal supplementary enteral nutrition [27] with regular daytime diet are two strategies that have been employed to maintain remission.

Corticosteroids

Conventional corticosteroid treatment induces a rapid clinical response in most children with active Crohn's disease or UC. However, chronic daily administration of corticosteroids to control the symptoms of intestinal inflammation is clearly contraindicated in pediatric IBD because of the interference with linear growth in addition to the other unwanted long-term adverse effects common to both children and adults (**Figure 2**).

Children with moderate symptoms of active Crohn's disease localized to the ileum and/or right colon may respond to short-term treatment with controlled ileal-release

budesonide. The cosmetic effects of steroids are spared in this context, even if the overall efficacy is less than with conventional corticosteroids [28]. Studies in adults demonstrate little benefit in comparison with placebo in maintaining remission. Limited clinical experience with maintenance budesonide in children raised concerns that linear growth was impaired during therapy in spite of good weight gain [29].

Azathioprine and 6-mercaptopurine

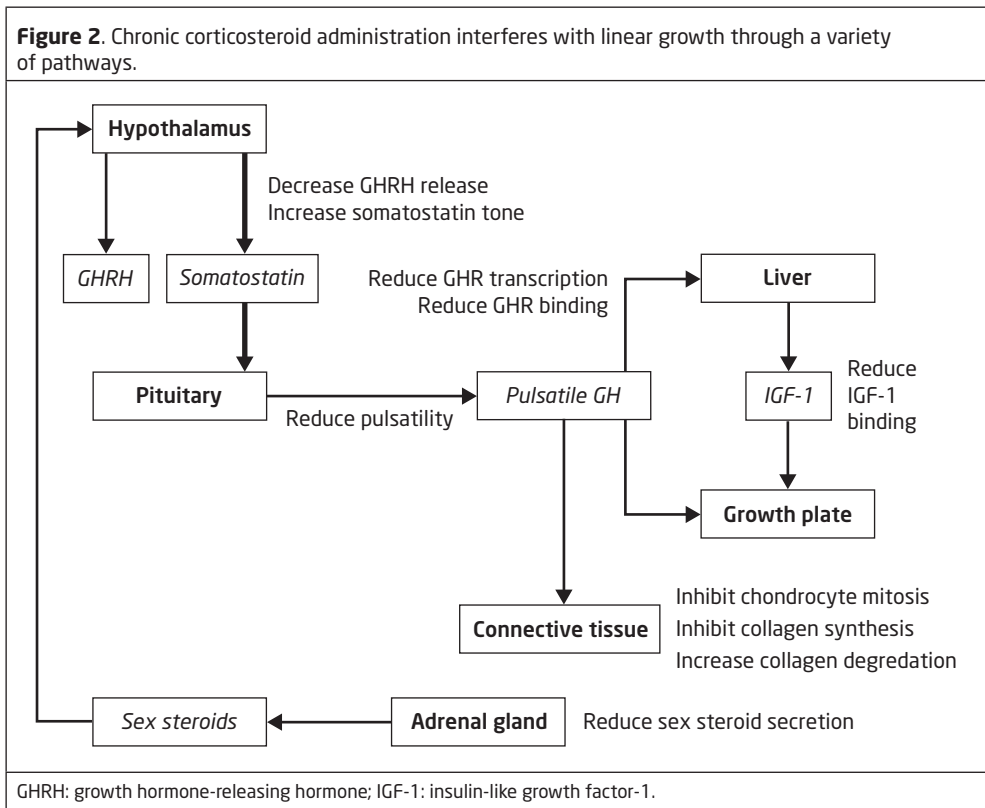
The benefits of the immunomodulatory drugs, azathioprine and 6-mercaptopurine, in maintaining clinical remission in Crohn's disease are well documented, and efficacy in preventing exacerbations of UC has also recently been re-affirmed. In a multicenter trial, newly diagnosed children with moderately severe Crohn's disease who were treated with an initial course of prednisone were randomized to receive either concomitant 6-mercaptopurine or placebo [30]. A beneficial effect on linear growth was not clearly apparent in this study in spite of the steroid-sparing effect and improved control of intestinal inflammation; this was perhaps a function of sample size and difficulties inherent in comparing growth rates among patients of varying ages and pubertal stages [21,30].

Methotrexate

Recent observational data suggested a benefit of methotrexate therapy in pediatric Crohn's disease patients who had failed to respond or proved intolerant of prior azathioprine/6-mercaptopurine treatment [31]. Improved height velocity was observed in this retrospective study.

Anti-TNF- α

Within the spectrum of pediatric Crohn's disease is a subgroup of patients with chronically active extensive disease that is not amenable to resection, and is refractory to previously available medical therapies. At the Hospital for Sick Children in Toronto (ON, Canada), such patients comprised 16–17% of all prepubertal children with Crohn's disease



diagnosed during the 1980s and 1990s [1]. These patients, as expected, were also the most likely to have sustained growth impairment.

The development of anti-cytokine therapies, such as infliximab, which have the potential to achieve mucosal healing even in otherwise treatment-refractory patients constitutes a tremendous advance. The ability of repeated infliximab infusions to sustain clinical remission is well documented in adults, and clinical experience in children is similar. Both observational [32] and clinical trial [33] data demonstrate that a beneficial effect on linear growth is observed if treatment is undertaken early enough prior to or during puberty. These observations are cause for optimism that the medical therapy for Crohn's disease available in the present decade will reduce the prevalence of sustained growth impairment in pediatric patients.

Surgery

The optimal management of young patients with IBD includes appropriate and timely

referral for intestinal resection. Sustained steroid-dependency and associated impairment of linear growth should not be tolerated in children with UC, where colectomy cures the disease and restores growth. For children with Crohn's disease, the possibility of a significant asymptomatic interval, during which normal growth and pubertal development can resume, makes intestinal resection an attractive therapeutic option, despite the likelihood of eventual disease recrudescence.

In two pediatric studies, the anatomical distribution of Crohn's disease was the most important factor influencing duration of postoperative clinical remission [34,35]. Patients with extensive ileocolonic involvement experienced an excess of early clinical recurrences (50% by 1 year) in comparison with children with preoperative disease in the terminal ileum with or without right colonic disease, or in the more proximal small intestine (50% by 5 years) [34]. Children undergoing resection because

of stenosing or fistulizing complications (e.g. bowel obstruction or intra-abdominal abscess) had delayed recrudescence of disease in comparison to those operated on simply for inflammatory symptoms that were refractory to medical therapy [34]. An early operative approach to localized disease and for complications of chronic inflammation is supported by these data [34,35]. Significant improvements in height velocity post-operatively compared with preoperatively are observed in prepubertal or early pubertal children [34,35].

Hormonal interventions

Given that corticosteroids interfere with the GH-IGF-1 axis at a number of sites (**Figure 2**), there is a small experience with the use of exogenous recombinant GH (rGH) therapy for growth failure associated with ongoing steroid therapy in a number of pediatric conditions [18]. Mauras et al. reported improvement in IGF-1 levels and height velocity in a pilot study of 10 children with Crohn's disease whose growth had been impaired in the context of steroid dependency [36]. Beyond its "anti-glucocorticoid" effects, it is possible that GH has a direct therapeutic effect in IBD. A randomized, controlled clinical trial by Slonim et al. in 2000 demonstrated a possible positive effect of GH on disease activity in adults with Crohn's disease [37]. Despite the possible benefits, GH therapy may also introduce a variety of risks and complications. GH should be considered experimental in the setting of IBD, and is still best limited to formal investigative study settings.

A period of 3–6 months of testosterone therapy, carefully supervised by pediatric endocrinologists, has been employed in boys with extreme delay of puberty; this treatment has been associated with a growth spurt. However, it must be emphasized that children requiring consideration of these adjunctive hormonal therapies should be encountered increasingly less commonly. The treatment of intestinal inflammation and assurance of adequate nutrition are of much greater importance.

Summary

An increased understanding of the mechanisms of linear growth impairment associated with chronic inflammatory disease points the way toward better management. Early recognition of Crohn's disease remains an important challenge. Following diagnosis of IBD, restoration and maintenance of a child's pre-illness growth pattern indicate success of therapy.

Current treatment regimens limit the use of corticosteroids via optimization of immunomodulatory drugs, the use of enteral nutrition in Crohn's disease, and, if necessary, surgery for UC and for intestinal complications of localized Crohn's disease. Biological agents with the potential for mucosal healing hold promise of growth enhancement even among patients with otherwise refractory disease, whose growth was previously compromised. For all interventions, there is a window of opportunity that must be taken advantage of before puberty is too advanced.

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Citations and Editors' Notes

IGF-1

Successful long-term growth hormone therapy in a girl with haploinsufficiency of the insulin-like growth factor-1 receptor due to a terminal 15q26.2→qter deletion detected by multiplex ligation probe amplification.

Walenkamp MJ, de Muinck Keizer-Schrama SM, de Mos M et al.

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J Clin Endocrinol Metab 2008;93:2421-5.

Editor's note: At the time of preparation of the present report, there had been nine previously published cases of haploinsufficiency of the insulin-like growth factor-1 (IGF-1) receptor gene (*IGF-1R*), arising from terminal deletion of the chromosome 15q region, which encompasses the gene locus. All nine cases had been identified by conventional microscopic karyotype analysis.

Here, Walenkamp et al. describe the use of the relatively new technique of multiplex ligation probe amplification, which enables detection of submicroscopic deletions according to gene copy number changes. In addition, comparative genomic hybridization utilizes microarrays of oligonucleotide probes (mostly exonic, spanning approximately 35-kb intervals across the human genome) to determine the boundaries of any identified deletions. These techniques have become part of routine clinical genetic diagnostic services in many centers, adding a new dimension to the search for genetic causes of clinical disorders such as short stature with associated features (e.g. low intelligence quotient, intrauterine growth restriction,

and/or dysmorphic features), which do not fit a clearly recognizable syndrome.

The patient was diagnosed with haploinsufficiency of the *IGF-1R* (and other adjacent genes on 15q26.2→qter), which matched the clinical picture of severe growth retardation (−3.5 standard deviation [SD] at 4.5 years) with a modest degree of antenatal growth deficiency (birth weight −3.0 SD, length −1.3 SD, head circumference −2.0 SD); normal peak GH to stimulation (25 mU/L) with unusually elevated serum IGF-1 (+2.5 SD) and IGF binding protein-3 (IGFBP-3; +0.8 SD). IGF generation tests yielded an approximately 50% increase over baseline IGF-1 after 4 days of GH (at 1 mg/m²), and a 100% increase after a further 3 days of GH (at 2 mg/m²). Having confirmed the patient's responsiveness to GH, long term treatment with GH was then given at a dose of 35–40 μg/kg/day (1 mg/m²/day). This achieved serum IGF-1 levels at approximately +3.5 SD. Furthermore, the catch-up height centile was achieved rapidly, with subsequent stabilization at approximately −2.0 SD. Puberty progressed within the normal age range and final height (157 cm; −1.6 SD) was achieved at 15 years of age. This was −1.8 SD from the target height. The authors speculate that this may reflect incomplete catch-up, which could be indicative of a persisting imbalance between IGF-1 availability and tissue-specific defects in IGF sensitivity.

IGF-1R mRNA expression, IGF-1 binding, IGF-1R autophosphorylation, and protein kinase B/Akt activation by IGF-1 were examined *in vitro* using cultured fibroblasts from the patient and compared with those from two adult "controls". Results showed

statistically insignificant lower values in the patient. The authors discuss how this may reflect tissue-specific variability, in keeping with similar insignificant *in vitro* studies from other reported cases.

Anaphylactic reaction to recombinant insulin-like growth factor-1.

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Yale University, New Haven, CT, USA.

J Pediatr Endocrinol Metab 2008;21:381-4.

Editor's note: This case report describes a significant anaphylactic reaction linked to treatment with mecasermin (Increlex: recombinant-DNA-engineered recombinant insulin-like growth factor-1 [rIGF-1]), highlighting the need for caution when introducing a new product to open use for its licensed indication. Approval of license was granted in the US based on data from five trials in just 71 pediatric patients. The patient described here had local erythema of up to 10 cm in diameter at the mecasermin injection site after the third dose. This was followed by diffuse urticaria, pruritis, respiratory distress, and tongue and pharyngeal itching at 24 h after the ninth dose. Symptoms resolved after 24 h with supportive therapy (oxygen, epinephrine, anti-histamine in a radioallergen sorbent test analysis, and steroids) under pediatric intensive care. The patient did not require intubation. One month later, a controlled intradermal challenge with mecasermin triggered local erythema and subsequent systemic responses within 15 min (lip pruritis, sneezing, and profuse rhinorrhea), which resolved with oral diphenhydramine. The patient was subsequently identified as showing immunoglobulin E responses to assorted tree nuts.

It is nearly 20 years since rIGF-1 became available for clinical research in children and adults with severe primary IGF-1 deficiency, recognized by the established clinical and biochemical features of growth hormone receptor deficiency (GHRD) or Laron syndrome, and demonstrated unresponsiveness to GH treatment owing to homozygous mutations in the GH receptor.

Using rIGF-1 as treatment for such children has proven to be of significant benefit for improving final height, but without full restoration to the height expected in the absence of GHRD. Side effects have included an expected risk of mild hypoglycemia, which could be minimized by careful attention to timing of injections and carbohydrate intake; acute hypokalemia; and disproportionate effects on tissue growth (facial dimensions and tonsillar enlargement). The approval in 2005 of rIGF-1 (as mecasermin) for the treatment of growth failure in children with severe primary IGF-1 deficiency was a welcome result after the many studies of GHRD treatment over the last 20 years. The license allows its use in children with post-receptor defects in IGF-1 production, of whom a very small number of individuals have so far been reported (*Horm Res* 2006;66:221-30). Such children have been identified by the co-existence of other clinical or immunological abnormalities, which suggests disorders of overlapping intracellular signaling pathways. With characterization of these defects at a molecular level, consideration of rIGF-1 treatment for the statural deficit is a logical progression if clinical resistance to a course of GH is demonstrated.

There are, however, a potentially much greater number of short children without recognized additional clinical features. These children would be eligible for rIGF-1 treatment on the basis of their degree of short stature (height <-3 SD) and low IGF-1 level (<-3 SD; both criteria established by US Food and Drug Administration) in the presence of normal-to-high serum GH levels, but for whom a specific defect in the IGF-1 generation pathways has not yet been identified. Cases clearly exist, but only one such patient has been reported thus far (*Acta Paediatrica* 1999;88:168-72). That child presented in early childhood as a probable case of familial short stature with height -3.5 SD, comparable to that of her mother at final height. Both were subsequently found to be heterozygous for a dominantly inherited GH receptor mutation (*Acta Paediatrica* 1999;88:168-72).

The clinical history of the patient reported here by Torjusen et al. is consistent with a

combination of constitutional delay (commonly associated with mild to severe atopic disorders) and familial short stature. The dose of GH used (50 µg/kg/day for 6 months) was greater than the standard GH replacement dose, but perhaps not sufficiently high to exclude a degree of partial GH resistance, as might occur with a heterozygous GHRD condition (*Acta Paediatrica* 1999;88:168–72).

The combination of atopy with constitutional delay is so common that careful consideration needs to be given to possible anaphylactic response to mecasermin. Prior to embarking on mecasermin treatment, care must be taken regarding the inclusion of a higher dose trial of GH, as well as molecular characterization of GH receptor status and allergy testing, including mecasermin intradermal challenge.

GH Receptor

Developmental changes in the human GH receptor and its signal transduction pathways.

Kent G, Mergelas JA, Goodyer CG.
McGill University, Montreal, QC, Canada.
J Endocrinol 2008;198:71–82.

Editor's note: The mechanisms responsible for the relative resistance of the human fetus to the high levels of circulating growth hormone (GH) present during this phase of development have thus far been difficult to elucidate. The authors of the present article have previously demonstrated reduced levels of GH receptor (GHR) in early to mid-gestation human liver compared with postnatal tissue (*Am J Physiol Endocrinol Metab* 2001;281:1213–20). In the present study, the different isoforms of GHR and major downstream signaling proteins in human fetal hepatocytes (11–19 weeks of gestation, obtained at the time of therapeutic abortion) were compared with those found in two established human adult/postnatal hepatoma cell lines (HepG2 and Huh7).

There was no significant difference in the proportions of truncated GHR_{1–279} compared with full length GHR between fetal and postnatal cells. Levels of signal transducer and activator of transcription-5B (STAT5B) were also similar between fetal and postnatal cell types. In contrast, levels of Janus kinase-2 (JAK-2), STAT1, STAT3, STAT5A (38–53%), and suppressors of cytokine signaling (SOCS) and cytokine-inducible Src homology 2 domain-containing protein (CIS) (58–76%)

signaling proteins were significantly lower in the fetal hepatocytes compared with the adult hepatic cell lines. The lower levels of SOCS and CIS proteins could be accounted for by the lower levels of the JAK-2 and STAT proteins; however, the mechanism for ontogeny of regulation of these first line signaling proteins remains to be determined.

The exon 3-deleted/full-length growth hormone receptor polymorphism did not influence growth response to growth hormone therapy over two years in prepubertal short children born at term with adequate weight and length for gestational age.

Carrascosa A, Audí L, Fernández-Cancio M et al.
Autonomous University, Barcelona, Spain.
J Clin Endocrinol Metab 2008;93:764–70.

Editor's note: In an earlier publication, Dos Santos et al. (*Nat Genet* 2004;36:720–4) proposed that the exon 3-deleted (*d3*)/full length (*fl*) growth hormone receptor (*GHR*) polymorphism was associated with variable growth response to GH treatment (the *fl/fl* genotype being less responsive than other genotypes). This suggestion was followed by a number of supporting and conflicting reports from studies in children with GH deficiency, Turner syndrome, and those small for gestational age, all of which are reviewed in the discussion section of the present article. The intrinsic growth disorders in these study cohorts of GH-treated children may have influenced the growth response.

Other factors such as cohort size and methodology for genotype assignment may have also affected the outcomes. Carrascosa et al. therefore report their retrospective analysis of this *GHR* polymorphism on the responsiveness to GH treatment in 106 short, prepubertal Spanish children (58 boys, mean age 7.8 ± 2.3 years at start of treatment between 1999 and 2005) who were of appropriate weight and length at birth. Exon 3 *GHR* genotyping yielded similar frequencies for each genotype in males and females (*GHR-d3/d3* 10 males, 8 females; *GHR-d3/fl* 23 males, 19 females; *GHR-fl/fl* 25 males, 21 females). The patients were further classified according to their peak GH response to two standard GH provocation tests, since reduced GH responsiveness might be associated with physiological compensatory increase in GH secretion. In 61% of patients the levels of GH detected by both tests were <10 ng/mL; these patients were designated GH deficient. In 26% of patients, one test was <10 ng/mL and one was >10 ng/mL; 13% scored >10 ng/mL in both tests. Serum insulin-like growth factor-1 (IGF-1) values were measured at baseline and during the 2-year treatment period.

Although there were differences in age, height, and growth response between boys and girls (girls were younger, shorter, and

had a better growth response at the start of the study), these were not associated with any difference in distribution of *GHR* genotype. Paternal, maternal, and target heights did not differ between the three categories of GH responsiveness, or between the three *GHR* genotypes for the children. Parental *GHR* genotypes were not reported. There were no differences in basal and post-treatment parameters of GH responsiveness (first and second year height velocity, height standard deviation score [SDS] attainment, IGF-1 SDS) between patient genotypes during the 2 years of study.

An additional 16 patients were excluded from this analysis as their 2-year height SDS gain was <0.5 ; this was in an attempt to exclude any patients with disorders of the GHR–IGF-1 axis other than the *GHR* polymorphism. These 16 patients had similar distribution of *GHR-d3/fl* genotype to the main study cohort and their inclusion would not have changed the overall analysis.

The authors combined the results from the several previously published studies on growth responsiveness according to *GHR* exon 3 genotype; their meta-analysis reveals no clear differences in parameters of growth according to genotype. Further, larger, and more balanced prospective studies seem the most likely way to resolve this issue.

GH Deficiency: Genetics

Influence of growth hormone (GH) receptor deletion of exon 3 and full-length isoforms on GH response and final height in patients with severe GH deficiency.

Räz B, Janner M, Petkovic V et al.

University of Bern, Bern, Switzerland.

J Clin Endocrinol Metab 2008;93:974–80.

Editor's note: The primary aim in treating growth hormone (GH)-deficient children is improving adult height, which will depend on the frequency, dosage, and duration of recombinant human GH (rhGH)

therapy. In addition to these factors, an individual's response to treatment may also be determined by genetic and epigenetic factors. A common polymorphism in the GH receptor gene (*GHR*), resulting in deletion of exon 3, has been shown to be associated with variation in the response to GH therapy.

The aim of the present study was to analyze the impact of *GHR* genotype on initial height velocity and final adult height. The study included 181 subjects with GH deficiency. Height velocity and final adult height were compared in those homozygous for the deletion of exon 3 (*GHR-d3/d3*)

and those homozygous for the full-length genotype (*GHR*-fl/fl). Height velocity in the first 2 years of therapy was significantly higher in *GHR*-d3/d3 subjects than in *GHR*-fl/fl subjects. However, there was no difference in final adult height between the two genotypes.

It is difficult to assess the full impact of this polymorphism on idiopathic short stature subjects, although the authors conclude that *GHR* genotype has a minimal impact in terms of overall responsiveness to rhGH

The endocrine phenotype in Silver-Russell Syndrome is defined by the underlying epigenetic alteration.

Binder G, Seidel AK, Martin DD et al.

University Children's Hospital, Tübingen, Germany.

J Clin Endocrinol Metab 2008;93:1402-7.

Editor's note: Recent progress in the understanding of the epigenetic mechanisms associated with Silver-Russell Syndrome (SRS) has allowed clinical diagnosis to be confirmed at a genetic level in approximately 60% of cases. Nearly 10% have a uniparental disomy of chromosome 7 (UPD7) and up to 50% have maternal duplications of chromosome 11p15 or demethylation of the imprinting control region 1 (ICR1) on 11p15, which is presumed to result in reduced fetal expression of the nearby insulin-like growth factor-2 (*IGF-2*) gene. Binder et al. have explored the relationship between these genotypes and the endocrine *IGF-1/IGF* binding protein-3 (*BP-3*) profiles, before and during growth hormone (*GH*) treatment, in 44 of the 61 SRS patients managed over an 18-year period for whom genomic DNA was available. Multiplex ligation probe-dependent amplification analysis was utilized to detect hypomethylation abnormalities at the ICR1. Short tandem repeat typing was employed to identify UPD7.

Epimutations at 11p15 were found in 19 SRS children. Five children were identified with UPD7 and two cases of small structural aberrations in 11p were observed. The remaining 18 children had no genetic defect identified. The most severe phenotype was

present in those with 11p15 abnormalities. Interestingly, the UPD7 children were significantly longer at birth but showed further loss of length (height centile), postnatally; however, the 11p15 children, showed no significant deviation from their birth length. There were also disparate patterns of *IGF-1* and *IGFBP-3* status, with the 11p15 children showing relatively high *IGF-1* and *IGFBP-3* levels compared with the UPD7 group and idiopathic small for gestational age (SGA) children. A further discrepancy became apparent during *GH* treatment, with *IGFBP-3* serum levels increasing above normal values in the 11p15 children, with only a relatively modest increase in serum *IGF-1* levels. This discordance between *IGF-1* and *IGFBP-3* responses in those with epimutations at 11p15 compared with UPD7 and other SGA children suggests the postnatal persistence of divergent mechanisms for growth failure within the genetic subgroups of SRS.

Three novel missense mutations within the LHX4 gene are associated with variable pituitary hormone deficiencies.

Pfaeffle RW, Hunter CS, Savage JJ et al.

University Children's Hospital, Leipzig, Germany.

J Clin Endocrinol Metab 2008;93:1062-71.

Editor's note: An increasing number of transcription factors (*PIT1* [*POU1F1* gene], *PRO1*, *LHX3*, *LHX4*, *PITX1*, *PITX2*, *SF1*, and *TPIT*) are recognized to be associated with anterior pituitary development, with or without effects on other parts of the brain. These factors are progressively helping in the defining and understanding of the etiology of congenital deficiencies of pituitary hormones. However, recognized mutations in these transcription factor genes contribute only a small percentage to all patients with congenital multiple pituitary hormone deficiencies. In this investigation, Pfaeffle et al. studied 253 patients (from 245 families) with growth hormone (*GH*) deficiency and evidence of at least one other pituitary hormone deficiency. Subjects were recruited from the authors' own clinical practices or from the Genetics and Neuroendocrinology

of Short Stature International Study program to explore possible associations with mutations in the *LHX4* gene sequence. This was following the first reports at the time (*Am Hum Genet* 2001;69:961–8; *Endocr J* 2007;54:637–41) that heterozygous mutations of gene encoding the *LHX4* LIM-homeodomain transcription factor were associated with congenital hypopituitarism.

The findings emphasize both the relative rarity of identifiable mutations in the *LHX4* gene as a cause of congenital hypopituitarism, and the remarkable variation in phenotype between individuals within the same family.

Just five patients (2% of the overall sample) from three families (families A, B, and C) were identified as having *LHX4* mutations. Family A were of Swiss origin. Two sisters and their father carried a heterozygous G→C transversion within exon 5 of *LHX4*, resulting in substitution of a conserved alanine residue in the recognition helix of the homeodomain with a proline residue (A210P). The index daughter was deficient in GH, thyroid stimulating hormone (TSH), adrenocorticotrophic hormone (ACTH), and gonadotropin at time of reassessment aged 20 years. Her younger sister reverted from GH deficiency to normal GH on retesting aged 19 years (peak GH 17 ng/mL, normal insulin-like growth factor-1 levels), with partial deficiency of TSH. Their father had normal stimulated GH status, with a height of 162 cm. Both girls had appearances of anterior pituitary hypoplasia with cystic lesions and normal position posterior pituitary on magnetic resonance imaging (MRI). Appearances were unchanged upon reassessment at adulthood. Family B was of Macedonian background. The affected son had GH deficiency with low free thyroxine, a small anterior pituitary and ectopic posterior pituitary at presentation aged 5 years, and a height –4.8 standard deviation. Gonadotropin insufficiency became apparent at a later date. The son had a heterozygous C→T transition, predicted to cause a change in the amino acid sequence in the LIM domains of the protein (R84C). His parents carried no mutation in the gene and there were no siblings. Family C's country of origin

was not reported. The index patient presented with neonatal hypoglycemia and jaundice, and at subsequent hospital readmission aged 2 months, had classic features of combined GH, TSH, and ACTH deficiencies. MRI showed anterior pituitary hypoplasia with ectopic posterior pituitary but no other anatomical central nervous system abnormality. Two siblings and both parents were healthy but their *LHX4* gene status was untested. Patient C had a T→G substitution, predicted to cause a missense change (L190R) in the second helix of the homeodomain. None of these patients had MRI evidence of the cerebellar hypoplasia or chiari malformation type appearances of previously studied *LHX4* mutation patients (*Am Hum Genet* 2001;69:961–8; *Endocr J* 2007;54:637–41).

The authors report the characterization of the biochemical and gene regulatory properties of the aberrant *LHX4* proteins with structural predictions, gene transcription assays, and DNA binding experiments in support of the causal effect of genotype on phenotype.

Endocrine and radiological studies in patients with molecularly confirmed CHARGE syndrome.

Asakura Y, Toyota Y, Muroya K et al.
Kanagawa Children's Medical Center,
Kanagawa, Japan.

J Clin Endocrinol Metab 2008;93:920–4.

Editor's note: Vissers et al. were the first to report on the association of mutations in the *CHD7* gene (which encodes chromodomain helicase DNA-binding protein (CHD-7)), with the clinical disorder of CHARGE syndrome (*Nat Genet* 2004;36:955–7). Subsequent studies reported the incidence of *CHD7* gene mutations to be approximately 60–70% in patients with this clinical diagnosis (*J Med Genet* 2006;43:306–14; *Am J Hum Genet* 2006;78:303–14). These, and other reports of genotype–phenotype associations in CHARGE syndrome, have been published predominantly in journals within the genetics and general pediatrics field. The present report by Asakura et al. serves to bring these observations to the

attention of clinicians and scientists within the pediatric endocrinology domain.

The relatively rare CHARGE syndrome has, for many years, been recognized as being associated with a spectrum of endocrine disorders (frequently hypogonadotropic hypogonadism, as well as growth hormone [GH] deficiency and central hypothyroidism), although these are far from being constant findings in such patients. Early reports of genotype–phenotype associations highlighted the presence of severe hearing loss and semicircular canal hypoplasia in almost all patients evaluated, together with frequent anosmia and archinencephaly. Sanlaville et al. reported these two latter features as constant findings in human fetuses with *CHD7* mutations, as well as reporting the expression of *CHD7* within the hypothalamus and pituitary during human embryonic development (*J Med Genet* 2006;3:211–7). In mice, expression of the equivalent gene, *Chd7*, has been found in the developing pituitary, although heterozygous mutations of *Chd7* have not been associated with abnormal pituitary hormone levels.

In this article, Asakura et al. report on just 15 children with a clinical diagnosis of CHARGE syndrome. *CHD7* mutation

analysis (coding region exons 2–38, including exon-intron boundaries) was available in eight patients (five male) for whom consent for DNA analysis was given. A different heterozygous *CHD7* mutation was present in each case (details of which are given in the article), six of which resulted in stop codon truncating mutations. Four boys had micropenis and/or cryptorchidism (as presumptive evidence of hypogonadotropic hypogonadism), one had GH deficiency and one had central hypothyroidism (thyroid stimulating hormone 6.7 mIU/L, free thyroxine 3.3 pmol/L). Pituitary and olfactory bulb magnetic resonance imaging appearances of these eight cases showed a “slightly low” central height of pituitary gland in three patients but otherwise normal pituitary anatomy. Olfactory sulci were “shallow, absent, or asymmetric” with hypoplastic or aplastic olfactory bulbs in all cases. Computed tomography of temporal bone in six of these eight patients revealed bilateral agenesis of the semicircular canals and dysplastic vestibules.

It is hoped that in the future, more attention will be focused on the role of *CHD7* regulation of gonadotropic function in particular, as well as on other aspects of hypothalamo-pituitary development.

Prader-Willi Syndrome

Growth hormone treatment of adults with Prader-Willi syndrome and growth hormone deficiency improves lean body mass, fractional body fat, and serum triiodothyronine without glucose impairment: results from the United States multicenter trial.

Mogul HR, Lee PD, Whitman BY et al.

New York Medical College, New York, NY, USA.

J Clin Endocrinol Metab 2008;93:1238–45.

Editor’s note: Prader-Willi syndrome (PWS) is characterized by obesity, hypotonia, hypogonadism, hyperphagia, short stature, sleep disturbances, and a neurobehavioral profile that includes cognitive deficits and

learning problems. The body composition of a PWS patient resembles that of an individual with growth hormone (GH) deficiency, including short stature and reduced lean body mass with concomitant increased fat mass. GH therapy reduces body fat, increases lean body mass, and improves final height in children, but antagonizes the action of insulin on glucose metabolism and thus increases the potential for development of diabetes. GH therapy in PWS patients is approved worldwide and is extensively used due to its benefits.

The main objective of this 12-month, open-label multicenter study was to evaluate the effectiveness and safety of GH treatment

in GH-deficient genotype-positive adults with PWS. A total of 38 subjects were eligible, and 30 completed the study (two did not start GH therapy, two were lost to follow-up, and four withdrew after 3–6 months – one due to adverse side effects). Subjects were started on a 0.2 mg/day dose of recombinant GH with monthly 0.2-mg increments, up to a maximum dose of 1.0 mg/day. The baseline characteristics of the initial study population included mean age 30.5 years, mean body mass index 34.7 kg/m², mean fasting glucose 85.3 mg/dL, and mean insulin-like growth factor-1 (IGF-1) standard deviation score –1.9.

The results show that GH therapy caused a significant increase in lean body mass (from 42.65 kg to 45.47 kg), and a reduction in percent body fat (from 42.84% to 39.95%). Fasting glucose, glycated hemoglobin, and fasting insulin levels did not show any clinically significant change. There was a progressive increase in ankle swelling, which was the only serious side effect in these patients. GH therapy also brought IGF-1 to within the normal range, without glucose impairment. Total thyroid hormone levels increased to near normalization in all subjects. There was no increase in the risk of meta-bolic syndrome.

Although GH therapy is not approved for adult PWS patients, in this study it appears to be safe and well tolerated, with no glucose impairment in any of the study participants. The authors call for more long-term studies to further establish the possible benefits and risks associated with GH therapy in PWS patients.

Sleepiness and sleep disordered breathing in Prader-Willi syndrome: relationship to genotype, growth hormone therapy, and body composition.

Williams K, Scheimann A, Sutton V et al.
Phoenix Children's Hospital, Phoenix, AZ, USA.
J Clin Sleep Med 2008;4:111-8.

Editor's note: Prader-Willi syndrome (PWS) patients suffer from excessive sleepiness, sleep-disordered breathing (SDB), and narcoleptic traits such as rapid eye movement

sleep onset periods. Growth hormone (GH) therapy in these subjects is associated with loss of body weight, increased lean body mass, and improved quality of life.

In the present study, the authors set out to identify the factors responsible for SDB in PWS patients by reviewing polysomnograms and multiple sleep latency tests. A total of 37 patients participated in the study, 16 of whom were receiving GH treatment. The patients were assessed for genotype, use and dose of GH, sleepiness score, apnea-hypopnea index score, central apnea, and periodic limb movement index.

The authors did not identify any significant relationship between the aforementioned factors and SDB in the PWS patients. Despite lower body mass indexes (BMI) in the former, there was no difference in terms of apnea-hypoxia index, central apnea frequency, oxygen nadir, or maximum carbon dioxide tension between the GH-treated and non-GH treated PWS subjects with SDB. The authors conclude that neither BMI nor underlying genetic abnormalities have predictive value in determining type or severity of SDB in PWS.

The Italian National Survey for Prader-Willi syndrome: an epidemiologic study.

Grugni G, Crinò A, Bosio L et al.
Italian Auxological Institute Foundation,
Verbania, Italy.
Am J Med Genet A 2008;146:861-72.

Editor's note: These authors studied all cases of confirmed Prader-Willi Syndrome (PWS) registered in the Italian Network for Rare Diseases over a 20-year period. A total of 425 subjects (209 male) were identified from January 1986 to June 2006 from 25 medical centers for pediatric and adult patients in Italy. The genetic defects of those studied are described in the present article. The authors present an easy-to-read graph of the percentages of those who were obese as a function of age. Under the age of 5 years approximately 20% were obese, and this percentage increased with age. Data on the use of growth hormone (GH) was obtained

for all patients. Overall, approximately half of the patients had received GH therapy. Importantly, the authors analyzed the incidence of death and the various causes, when known. In total, 18 patients died during the 20-year study period, although there was no association between GH usage and death. The authors conclude that GH therapy is safe in patients with PWS and does not affect life expectancy.

Prader-Willi syndrome: who can have growth hormone?

Stafler P, Wallis C.

Great Ormond Street Hospital, London, UK.

Arch Dis Child 2008;93:341-5.

Editor's note: The US Food and Drug Administration approved the usage of growth hormone (GH) in children with Prader-Willi Syndrome (PWS) experiencing poor growth in 2000. However, due to reports of sudden death among children with PWS receiving GH, many have discontinued its usage. Sufficient control studies analyzing mortality rates among GH treated and untreated children and young adults with PWS are currently lacking.

The present authors provide a short review of risk factors for death in PWS. They describe the respiratory complications of PWS that

are independent of GH therapy, including an account of 27 deaths in PWS patients who were GH therapy naïve. Obesity and its associated complications were more pertinent to adult deaths, whilst in children hypoventilation and upper airway infection were the main risk factors. Of the 23 deaths identified in GH-naïve children, 17 died of infections, 11 cases of which involved the respiratory tract. Five died as a result of sleep apnea or hyperventilation and aspiration. Of the 19 children with known weight status, only six were obese. GH-associated deaths mostly occurred within the first 3 months of GH therapy. Overall, 90% patients revealed a history of respiratory problems before starting GH treatment.

The authors present arguments for and against the use of GH treatment in children with PWS. Although central sleep apnea may improve with GH therapy, there is a risk of inducing upper airway obstruction through an increase in the size of structures in the upper respiratory tract in response to GH treatment. The authors state that patients with PWS need careful evaluation before commencing treatment with GH, in terms of diet; ear, nose, and throat; and the respiratory system. Finally, the authors offer a protocol for monitoring at-risk PWS patients as well as an algorithm for steps to take before prescribing GH to these patients.

GH treatment

Recombinant human growth hormone for children born small for gestational age: meta-analysis confirms the consistent dose-effect relationship on catch-up growth.

Crabbé R, von Holtey M, Engrand P et al.

Debiopharm SA, Lausanne, Switzerland.

J Endocrinol Invest 2008;31:346-51.

Editor's note: This report presents a meta-analysis of five clinical trials of growth hormone (GH) treatment in small for gestational age (SGA) children, together with two clinical trials of the Serono,

Inc. (Geneva, Switzerland) recombinant human GH (rhGH) preparation "Saizen". The focus was on the 2-year response in height standard deviation score (SDS) gain, comparing placebo with the common dosage options of 33 µg/kg/day and 67 µg/kg/day. Three cohorts of children were treated at the lower dose and nine cohorts of children were treated at the higher dose. The overall outcome was a predictive equation yielding a mean difference in height SDS gain over the first 2 years of treatment of +0.48 SDS in favor of the higher rhGH dose (approximately 2.5–3.0 cm in real terms per

patient). These findings add further impetus is added to the consideration that, in the absence of significant side effects, it may be more effective to initiate rhGH therapy for SGA children at the higher of these two doses and re-evaluate individual patient dose requirements according to growth response and serum insulin-like growth factor-1 levels at 2 years after starting GH treatment.

Systematic review: the effects of growth hormone on athletic performance.

Liu H, Bravata DM, Olkin I et al.

Santa Clara Valley Medical Center, San Jose, CA, USA.

Ann Intern Med 2008;148:747-58.

Editor's note: The use of human growth hormone (GH) to improve athletic performance has received worldwide attention. The focus has been on both the athletes who have used banned substances, as well as the ways in which these substances can be detected. GH has been occasionally called "the most anabolic substance known." However, some experts feel the benefit gained from GH use in healthy athletes is exaggerated. The present authors reviewed 44 published articles describing randomized, controlled trials in order to determine the effects of GH use on athletic performance in healthy young adults.

GH dosing regimens varied considerably among the studies. In addition, the length of treatment varied, with only three of the studies evaluating GH use for longer than 30 days. The mean dose of GH prescribed in the studies was 36 µg/kg/day (standard deviation 21 µg/kg/day).

The results included lean body mass increases in GH-treated subjects compared with those not taking GH. The reduction in fat mass with GH approached statistical significance, strength testing with the biceps or quadriceps showed no between-group difference, and basal metabolism was higher in the GH-treated groups compared with the non-GH-treated groups.

Six studies measured exercise capacity outcomes. Although exercising levels

of plasma free fatty acids and glycerol increased in those treated with GH, the exercise respiratory exchange ratio was not significantly different in GH-treated subjects compared with those not treated. In terms of safety, GH-treated participants reported higher rates of adverse events. There was soft tissue edema in 44% of GH-treated participants versus 1% in the placebo groups, as well as fatigue in 35% versus 0%, respectively. There was a higher incidence of arthralgia and carpal tunnel syndrome in those treated with GH compared with those not treated. The authors conclude that the literature does not provide sufficient evidence that use of GH enhances athletic performance, and that GH may actually hinder exercise capacity.

Response to growth hormone treatment and final height in Noonan syndrome in a large cohort of patients in the KIGS database.

Raaijmakers R, Noordam C, Karagiannis G et al.

Radboud University Nijmegen, Nijmegen, The Netherlands.

J Pediatr Endocrinol Metab 2008;21:267-73.

Editor's note: With an incidence of approximately 1 per 1000 live births, Noonan syndrome is almost six times more prevalent than Turner syndrome. Despite this, it has been difficult to co-ordinate long-term trials of growth hormone (GH) treatment through to final height. Reference growth standards are available, but unlike those for female Turner syndrome patients, the predictive value of these data sets for projected final height is not robust. Growth in Noonan syndrome is commonly associated with an inherent degree of maturational delay. Many boys have a degree of testicular dysfunction that may impact on natural progression through the pubertal growth spurt, which nonetheless will occur spontaneously or with sex steroid support in either sex. This is in contrast to the natural growth pattern of girls with Turner syndrome. Moreover, although mutations in the protein tyrosine phosphatase, non-receptor

type 11 (*PTPN11*) gene are now known to account for approximately 50% of clinically diagnosed cases of Noonan syndrome, the precision of genetic confirmation of the diagnosis is not as good as that for Turner syndrome. It has been suggested that Noonan syndrome contains an inherent element of GH resistance, since the *PTPN11* gene encodes Src homology 2-containing tyrosine phosphatase, which has a role in downstream intracellular signaling of the GH receptor. Initial early trials of GH in Noonan syndrome demonstrated short-term responsiveness and safety, but it has largely rested with open clinical management over the last 20 years or more to provide data for assessment of long-term efficacy of GH in Noonan syndrome.

The KIGS (Pfizer International Growth Study) database provided treatment response and safety data on a cohort of 402 patients who had a clinical diagnosis of Noonan syndrome (269 males). Of these, data were available on 73 patients with a full 3 years of prepubertal GH treatment, and 24 patients continued treatment until near final height. GH dosage was at a median of 0.24 mg/kg/week (range 0.17–0.77 mg/kg/week) starting at median age of 7.7 years (median height at that stage –2.86 standard deviation [SD] Tanner 1966 standards and –1.04 SD Noonan standards; thus, clearly representing a bias towards the smaller children within the Noonan phenotype). Height velocity almost doubled in the first year of treatment, declined (as would usually be expected) in the second and third years, but remained approximately 1 cm/year higher than at the start. The height SD score (SDS) increment through the first 3 years of treatment was +0.54, +0.13, and +0.13. For those patients (n=24) reaching final height after a total of between 4 and 12 years (median 7.6 years) of GH treatment, height SDS increased from median –3.28 SDS to –2.41 SDS. Thirteen of these patients had a final height below –2.0 SDS (Tanner standards). The bone age delay at the start of treatment was a median of 3.2 years, and it is unclear how much true gain in final height

was achieved as opposed to the GH response representing an acceleration of the natural tempo of growth. Notably, the first year growth response of those patients who were withdrawn from longer term GH treatment was not significantly different from those who continued with GH.

Provided the clinicians responsible for the management of this cohort of Noonan syndrome patients continue to submit the data on growth to final height, we may find, as with GH treatment for Prader–Willi Syndrome and Turner syndrome, that the cohort final heights are sufficiently and significantly different from historic reference standards to quantify the true long term benefit of GH treatment.

Evaluation of catch-up growth from orthodontic treatment and supplemental growth hormone therapy by using Z-scores.

Tsuboi Y, Yamashiro T, Ando R et al.

Okayama University, Okayama, Japan.

Am J Orthod Dentofacial Orthop 2008;133:450-8.

Editor's note: In children with growth hormone (GH) deficiency, both growth and bone age are delayed. However, the authors of the present study point out that dental age is also delayed prior to treatment. Upon GH treatment, advances in dental age, as well as craniofacial growth, are induced. The authors highlight the need for orthodontists to understand these changes.

Using Z-scores, they evaluated height and craniofacial changes in one male and one female (aged 14 and 10 years, respectively). The strength of this article is that the authors describe, step by step, the orthodontic procedures while documenting the growth parameters, which include craniofacial growth. However, only two patients were evaluated. This study emphasizes the fact that while endocrinologists are treating the growth disorder with GH, communication with the dentist and orthodontist remains important as their treatment plan could also be affected by GH therapy.

Miscellaneous

Pituitary tumors in childhood: update of diagnosis, treatment and molecular genetics.

Keil MF, Stratakis CA.

National Institutes of Health, Bethesda, MD, USA.
Expert Rev Neurother 2008;8:563–74.

Editor's note: In this easy-to-read review article, pituitary tumors in childhood are described first from an embryological point of view, and then by their histology. Craniopharyngioma, pituitary adenomas, corticotropinomas, and somatotropinomas are all discussed separately and an algorithm is presented for the evaluation of Cushing syndrome. The authors also present a section on imaging of pituitary adenomas, which includes petrosal sinus sampling and positron emission tomography scans. Finally, there is a focus on genetic conditions such as Carney complex, McCune-Albright syndrome, multiple endocrine neoplasia type-1, and familial isolated pituitary adenomas.

Three years prospective investigation of anterior pituitary function after traumatic brain injury: a pilot study.

Tanriverdi F, Ulutabanca H, Unluhizarci K et al.

Erciyes University Medical School, Kayseri, Turkey.
Clin Endocrinol (Oxf) 2008;68:573–9.

Editor's note: It is only within the last few years that the impact of traumatic brain injury (TBI) on hypothalamo-pituitary function of survivors has been recognized as a potential major contributor to the prevalence of acquired pituitary hormone deficiencies (pituitary tumors and other central nervous system tumors post-irradiation being major cause of these disorders in adulthood). Relatively short-term studies (*Am J Med* 2005;118:1416–23; *J Clin Endocrinol Metab* 2006;91:2105–11) have illustrated the pattern of early disruption in the acute recovery phase and first year post-trauma; both of which are important factors for some patients in their

initial rehabilitation. Tanriverdi et al. now report the extension of their earlier 12-month assessments to the 3-year time point in 30 patients (25 male; aged 37.2 ± 2.4 years). Seven of the 13 patients who were growth hormone (GH)-deficient at the first year had recovered after 3 years, with just one patient showing new-onset GH deficiency by that time. Five out of six patients with adrenocorticotrophic hormone (ACTH) deficiency at the 1-year assessment had recovered by the 3-year review. One patient had new-onset ACTH deficiency by that time. Those with severe rather than mild or moderate TBI were, perhaps not surprisingly, those who showed persistence of GH and ACTH deficiencies at the 3-year review. Gonadotropin and thyroid-stimulating hormone function were remarkably spared from long-term deficiencies, with resolution of dysfunction in the few showing abnormalities after the first year.

Intraindividual variation in serum thyroid hormones, parathyroid hormone and insulin-like growth factor-1.

Ankrah-Tetteh T, Wijeratne S, Swaminathan R.

St Thomas' Hospital, London, UK.
Ann Clin Biochem 2008;45:167–9.

Editor's note: A clinician's interpretation of serum hormone levels requires understanding of intraindividual variation. The authors of the present article studied such variations in thyroid-stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3), serum insulin-like growth factor-1 (IGF-1), and parathyroid hormone (PTH) levels.

Weekly blood samples were taken from 10 healthy subjects (four male) with a median age of 21 years (range 19–27 years). Samples were always taken at the same time of day (between 12:30 and 14:30). TSH was measured using the immunochemiluminometric method, and FT3 and FT4 were measured by competitive immunoassays using a Bayer Centaur analyzer (Bayer Ltd, Newbury, UK). Serum IGF-1 and

PTH were measured on the Nichols Advantage System (Nichols Institute Diagnostics, USA) by sandwich immunoassays.

The authors constructed a clear set of graphs showing the variations in each hormone level separately for each subject. The authors found FT4 and FT3 displayed the lowest intraindividual variation; however, interindividual variation was seen. Although IGF-1 had a 9.4% intraindividual coefficient of variation, caution must be taken in interpreting this as the subjects were all over the age of 19 years. PTH showed the highest variation within individuals. It is important to note that these findings may not apply to those who are on hormone replacement therapy.

Traumatic brain injury is a rarely reported cause of growth hormone deficiency.

McDonald A, Lindell M, Dunger DB et al.

University of Cambridge, Cambridge, UK.

J Pediatr 2008;152:590-3.

Editor's note: Recent studies have demonstrated that hypopituitarism, and more specifically growth hormone (GH) deficiency, is common among survivors of traumatic brain injury (TBI) who are tested several months or years following head trauma. In addition, post-traumatic anterior pituitary hormone disturbances have been demonstrated to occur at a high frequency in such patients. The age of hormone deficiency onset varies between patients, in whom GH deficiency may be isolated or occur as a component of multiple pituitary hormone deficiency syndrome. The prevalence of TBI is more marked in adults, and there are few data concerning GH deficiency in children following TBI. GH deficiency can affect both ultimate height in childhood and quality of life in adulthood.

In the present article, the authors used the KIGS (Pfizer International Growth Study) database to determine the frequency of TBI as a cause of GH deficiency. They identified a very small number of children with TBI-induced GH deficiency (n=114) compared with idiopathic GH deficiency (IGHD) patients (n=23 722). Children with

TBI as a cause of GH deficiency were older at the onset of treatment compared with IGHG patients (median age 11 years [range 5.5–15.5 years] vs. 10.3 years [range 4.4–14.5 years]). The data also showed that, compared with IGHG patients, those with TBI-induced GH deficiency had a significantly greater number of pituitary hormone deficiencies, reduced height velocity at diagnosis, reduced peak GH response to GH stimulation tests, and greater response to GH therapy (as measured by the median change in height velocity during the first year of therapy).

These results suggest that there is significant under-reporting of TBI-induced GH deficiency in children. This may be due to a number of factors, such as a lack of awareness on the part of clinicians in recognizing TBI as a cause of GH deficiency, and the slowness of onset of anterior pituitary hormone deficiencies in such patients. The authors call for prospective, longitudinal studies to address the frequency and natural history of TBI-induced GH deficiency.

Factors predicting the near-final height in growth hormone-treated children and adolescents with chronic kidney disease.

Nissel R, Lindberg A, Mehls O et al.

University Children's Hospital, Rostock, Germany.

J Clin Endocrinol Metab 2008;93:1359-65.

Editor's note: A recent study found that approximately 45% of children suffering from chronic kidney disease (CKD) presented with severe short stature following treatment by dialysis or transplantation (*Pediatr Nephrol* 2006;21:793–9). Growth hormone (GH) therapy is approved for children with CKD, given their propensity for growth failure. The impact of GH therapy on children can vary depending on the age at which GH therapy is initiated, as well as the duration of treatment.

In the present study, the authors analyzed data from the KIGS (Pfizer International Growth Study) database to assess near-final height (near-FH) in a cohort of GH-treated CKD patients. A total of 1710 children were diagnosed with CKD and enrolled for GH

treatment. Two-hundred and forty children were included in the final analysis, based on completion of at least 12 months of GH treatment and attainment of near-FH. Analysis showed that 39% of participants were prepubertal and 61% were pubertal at baseline; 45% were receiving conservative treatment for CKD, 28% were receiving dialysis (the majority of whom were on hemodialysis), and 27% were in the period following renal transplantation.

Clinical data showed that the mean age at GH therapy initiation was 13.7 ± 3.0 years, with a mean bone age of 10.4 ± 2.9 years, and a mean height standard deviation score (SDS) of -3.6 ± 1.2 . Cumulative change in height SDS was much higher in girls compared with boys (1.6 vs. 1.2). The mean near-FH was significantly different between pubertal patients with delayed puberty (-3.6), late pubertal patients (-2.9), early pubertal patients (-2.2), and prepubertal with a normal onset of puberty (-2.0).

During the first treatment year, the increase in height SDS was higher in prepubertal patients with normal onset of puberty and late pubertal patients (0.5 in both), compared with prepubertal patients with delayed onset of puberty (0.2) and with early pubertal patients (0.36; all $p < 0.01$).

The near-FH and cumulative increase in mean height SDS were significantly higher in CKD patients receiving conservative treatment compared with post-transplant patients and patients undergoing dialysis. Change in FH was positively associated with the genetic target height, duration of GH treatment, and bone age retardation at baseline.

Growth failure in children with CKD can be reversed and an improved near-FH can be achieved with GH therapy, but FH is affected by many factors, including the pubertal stage of the child, type of treatment for CKD, genetic target height, and the duration of GH therapy.

ACCREDITATION

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of the University of Kentucky College of Medicine and Remedica Medical Education and Publishing. The University of Kentucky College of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

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DISCLOSURES

Drs HW Courtland, S Elis, and S Yakar have no relevant financial interests to disclose.

Professor Griffiths has acted as a consultant for Abbott Canada, Centocor, Proctor and Gamble, and UCB Pharma; a speaker for Schering Canada and Schering-Plough, and has received research support from Schering Canada.

Dr Sherlock is supported by a fellowship from Schering-Plough, Canada.

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The Anabolic Effects of Insulin-like Growth Factor-1 on Skeletal Growth and Development: Lessons from Clinical and Animal Studies

Courtland HW, Elis S, Yakar S.

Growth: Growth Hormone, IGF-1, & Metabolism 2008;2(2):31-40.

1. GH deficiency can be best diagnosed by which of the following?
 - A. Measurements of fasting GH.
 - B. Measurements of serum IGF-2 and IGFBP-3.
 - C. Measurements of serum IGF-1.
 - D. Measurements of serum IGF-1 and IGFBP-3.
 - E. Measurements of GH and IGFBP-2.
2. Mouse models have shown that serum IGF-1 mainly affects which of the following?
 - A. Long bone linear growth and cortical bone accrual.
 - B. Cortical and trabecular bone accrual.
 - C. Cortical bone accrual.
 - D. Trabecular bone accrual.
 - E. None of the above.
3. Laron-type patients treated with GH:
 - A. Will have improved growth velocity.
 - B. Will not grow due to the inability of cells to bind IGF-1.
 - C. Will not grow because the GH receptor is inactive.
 - D. Will not grow because the ternary complex components are not secreted to circulation.
 - E. Will not grow because the GH receptor is over-expressed.
4. IGF-I accelerates growth by:
 - A. Activating the GH receptor.
 - B. Stimulating GH secretion.
 - C. Activating the IGF-1 receptor.
 - D. Stimulating STAT5B translocation to the nucleus.
 - E. Suppressing STAT5B translocation to the nucleus.
5. GH insensitivity is characterized by which of the following?
 - A. Short stature, low serum IGF-1, low serum IGFBP-3, and increased serum GH.
 - B. Short stature, low serum IGF-1, low serum IGFBP-3, and low serum GH.
 - C. Short stature, low serum IGF-1 and IGF-2, low serum IGFBP-3, and increased serum GH.
 - D. Short stature and high serum IGF-1, which increases with GH administration.
 - E. Short stature and low serum IGF-1, which increases with GH administration.
6. Patients with short stature who respond to GH may have:
 - A. Mutation in the GH receptor.
 - B. Mutation in the IGF-1 receptor.
 - C. Mutation in the STAT5B transcription factor.
 - D. A and C.
 - E. None of the above.
7. Increased risk of fracture in elderly men and women is correlated with:
 - A. Decreased BMD and increased serum IGF-1.
 - B. Decreased BMD and decreased serum IGF-1.
 - C. *IGF-1* promoter polymorphism and femoral neck BMD.
 - D. Serum IGF-1 levels only.
 - E. None of the above.
8. Which of the following statements is incorrect?
 - A. IGF-1 is the final mediator of linear growth.
 - B. GH is the treatment of choice in GH deficient patients.
 - C. IGF-1 is the treatment of choice in Laron syndrome.
 - D. IGF-1 is the only treatment for GH insensitive patients.
 - E. Growth response to IGF-1 in GH insensitive patients is higher than that following GH treatment in GH deficient patients.
9. The effect of IGF-1 on bone:
 - A. Is mediated by the IGF-1 receptor and modulated by the presence of IGFbps.
 - B. Requires somatotroph-secreted GH.
 - C. Occurs entirely postnatally.
 - D. Depend on ternary complex formation in serum.
 - E. None of the above.

10. Which of the following statements concerning osteoblast IGF-1 is correct?
 - A. It stimulates collagen synthesis.
 - B. It stimulates alkaline phosphatase expression.
 - C. It stimulates mineralization.
 - D. All of the above.
 - E. A and B only.

Growth Impairment in Inflammatory Bowel Disease

Sherlock M, Griffiths AM.

Growth: Growth Hormone, IGF-1, & Metabolism 2008;2(2):41-50.

1. Mitosis of epiphyseal chondrocytes is stimulated by which of the following?
 - A. TNF- α .
 - B. IL-1.
 - C. IGF-1.
 - D. A and B.
 - E. None of the above.
2. Which of the following statements concerning rate of growth in children is incorrect?
 - A. Growth rate is consistent in the range of 5-6 cm/year prior to puberty.
 - B. Growth rate is consistent in the range of 5-6 cm/year from age 6 to onset of puberty.
 - C. Prior to onset of puberty there is a deceleration in growth.
 - D. Prior to completion of growth, there is a period of growth acceleration.
 - E. Growth velocity should only be calculated over intervals of <6 months.
3. Which of the following values for growth rates in prepubertal children is correct?
 - A. 1-2 cm/year.
 - B. 3-4 cm/year.
 - C. 5-6 cm/year.
 - D. 7-8 cm/year.
 - E. >8 cm/year.
4. Daily corticosteroid administration:
 - A. Minimizes growth impairment associated with inflammatory disease.
 - B. Suppresses GH release.
 - C. Has no effect of hepatic GHR transcription.
 - D. Suppresses IGF-R but not IGF-1 production.
 - E. Stimulates of IL-6 production.
5. Which of the following statements regarding growth optimization in IBD is correct?
 - A. 6-mercaptopurine treatment has been associated with improved linear growth in children with CD.
 - B. Methotrexate treatment has been associated with an improved height velocity in children with CD.
 - C. Infliximab is associated with sustained clinical improved linear growth in CD children.
 - D. GH therapy should be routinely used in all IBD in patients.
 - E. B and C.
6. Which of the following statements regarding enteral nutrition is correct?
 - A. Enteral nutrition is an option that avoids use of steroids.
 - B. Amino acid based formulae are administered by nocturnal nasogastric infusion.
 - C. Exclusive enteral nutrition has been associated with reduced mucosal cytokine production.
 - D. Polymeric formulae can be administered orally.
 - E. All of the above.
7. Which of the following statements regarding impaired linear growth in UC and CD is correct?
 - A. All young patients with UC have a significant reduction in height-for-age SDS at diagnosis.
 - B. Linear growth impairment is more common in UC than in CD.
 - C. Linear growth impairment is less common in UC than in CD.
 - D. A and B.
 - E. UC patients do not achieve normal linear growth.

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Record your answers here by filling in the blank with the correct letter for the corresponding question:

The Anabolic Effects of Insulin-like Growth Factor-1 on Skeletal Growth and Development: Lessons from Clinical and Animal Studies

Courtland HW, Elis S, Yakar S. *Growth: Growth Hormone, IGF-1, & Metabolism* 2008;2(2):31-40.

1. ____ 2. ____ 3. ____ 4. ____ 5. ____ 6. ____ 7. ____ 8. ____ 9. ____ 10. ____

Growth Impairment in Inflammatory Bowel Disease

Sherlock M and Griffiths AM. *Growth: Growth Hormone, IGF-1, & Metabolism* 2008;2(2):41-50.

1. ____ 2. ____ 3. ____ 4. ____ 5. ____ 6. ____ 7. ____

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1. The activity provided new information I had not yet acquired.	1	2	3	4	5
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CML - Growth, a CME-accredited educational program, systematically identifies, evaluates, and places into clinical context the most important recent studies into the science and medicine of growth. It provides rapid access for busy specialists to a critical and clinically relevant review of the developments that will have most impact on their day-to-day practice and is designed to provide management options for clinicians to allow them to better diagnose and treat patients with growth disorders.

Each issue of *CML - Growth* will present carefully constructed leading (review) articles, written by practicing specialists, and intended to equip readers with practical knowledge of the area under discussion. These articles are commissioned to support particular educational themes identified by the Editor-in-Chief, Editorial team, and readers. This issue of *CML - Growth* presents two such leading articles.

INTENDED AUDIENCE

This activity is designed to meet the educational needs of multidisciplinary clinicians and healthcare professionals involved in the care of patients with growth disorders.

LEARNING OBJECTIVES

The Anabolic Effects of Insulin-like Growth Factor-1 on Skeletal Growth and Development: Lessons from Clinical and Animal Studies

Courtland HW, PhD, Elis S, PhD, Yakar S, PhD.
Growth: Growth Hormone, IGF-1, & Metabolism 2008;2(2):31-40.
Goal: To review recent literature concerning the effects of IGF-1 on skeletal growth and development.

Objectives: After reading this article the reader should be able to appreciate:

- The genetic components of the GH-IGF-1 axis.
- Perturbations in the GH-IGF-1 axis and their effect on growth and skeletal phenotypes.
- The importance of animal models in studying the GH-IGF-1 axis.

Growth Impairment in Inflammatory Bowel Disease

Sherlock M, MB BCH BAO MRCP (Paediatrics) and Griffiths AM, MD, FRCP(C).
Growth: Growth Hormone, IGF-1, & Metabolism 2008;2(2):41-50.
Goal: To review up-to-date literature concerning growth impairment associated with IBD.

Objectives: After reading this article the reader should be able to appreciate:

- The prevalence and pathophysiology of growth disorders in IBD.
- The importance of prompt recognition and monitoring of growth impairment in IBD.
- The importance of choosing appropriate treatments for growth impairment in IBD.

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