The Physiology and Mechanism of Growth

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Introduction

In the present chapter, an international group of endocrinologists were trying to select some of the most important manuscripts dealing with the physiology of growth published in the period July 1, 2019, to June 2019. We specially looked for manuscripts that shed more light on the already known mechanisms related to linear growth and those dealing with the interaction between nutrition and growth. We probably missed some important manuscripts that we did not find or could not include in our chapter because of lack of space. In our comments, we tried to explain the reasons for selecting the specific manuscripts and to highlight our own personal conclusion drawn from them. We encourage the reader to read the full manuscript whenever possible.
Key articles reviewed for this chapter

The effect of a high-calorie diet on bone growth is mediated by the insulin receptor
Wu S, Zhang Y, De Luca F
Bone 2019;122:166–175

Effects of dairy product consumption on height and bone mineral content in children: a systematic review of controlled trials
Adv Nutr 2019;10(suppl_2):S88–S96

Mechanisms by which sialylated milk oligosaccharides impact bone biology in a gnotobiotic mouse model of infant undernutrition
Proc Natl Acad Sci USA 2019;116:11988–11996

Plasma C-type natriuretic peptide: emerging applications in disorders of skeletal growth
Espiner E, Prickett T, Olney R
Horm Res Paediatr 2018;90:345–357

ASB20123: a novel C-type natriuretic peptide derivative for treatment of growth failure and dwarfism
PLoS One 2019;14:e0212680

Exogenous C-type natriuretic peptide restores normal growth and prevents early growth plate closure in its deficient rats
PLoS One 2018;13:e0204172

Prospective study of growth and bone mass in Swedish children treated with the modified Atkins diet
Svedlund A, Hallböök T, Magnusson P, Dahlgren J, Swolin-Eide D
Eur J Paediatr Neurol 2019;23:629–638

Epiphyseal growth plate architecture is unaffected by early postnatal activation of the expression of R992C collagen II mutant
Fertala J, Arita M, Steplewski A, Arnold WV, Fertala A
Bone 2018;112:42–50
Rapid early increase in body mass index is associated with impaired longitudinal growth in children with cystic fibrosis
Hak S, Arets HGM, van der Ent CK, van der Kamp HJ
Pediatric Pulmonology 2019;54:1209–1215

Bone mass development is sensitive to insulin resistance in adolescent boys
Bone 2019;122:1–7

Growth pattern of infants with gastroschisis in the neonatal period
Hall NJ, Drewett M, Burge DM, Eaton S
Clin Nutr ESPEN 2019;32:82–87

Skeletal disproportion in glucocorticoid-treated boys with Duchenne muscular dystrophy

Antibiotic perturbation of gut microbiota dysregulates osteoimmune cross talk in postpubertal skeletal development
Hathaway-Schrader JD, Steinkamp HM, Chavez MB, Poulides NA, Kirkpatrick JE, Chew ME, Huang E, Alekseyenko AV, Aguirre JI, Novince CM
Am J Pathol 2019;89:370–390

High prevalence of growth plate gene variants in children with familial short stature treated with growth hormone
J Clin Endocrinol Metab 2019;104:4273–4281

Cartilage-targeted insulin-like growth factor 1 treatment to promote longitudinal bone growth
Lui JC, Colbert M, Cheung CSF, Ad M, Lee A, Zhu, Barnes KM, Dimitrov DS, Baron J
Mol Ther 2019;27:673–680

Impact of the Ketogenic diet on linear growth in children: a single-center retrospective analysis of 34 cases
Nutrients 2019;11:1442

The Physiology and Mechanism of Growth
The effect of a high-calorie diet on bone growth is mediated by the insulin receptor
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Bone 2019;122:166–175

Background: Obese children grow faster than their normal-weight peers. Insulin resistance and hyperinsulinemia have been associated with obesity-related growth acceleration.

Methods: To determine whether obesity-associated hyperinsulinemia promotes bone growth by activating the insulin receptor (IR) in the growth plate, we generated TamCart IRfloxflox mice. The injection of 4 doses of tamoxifen in these mice (beginning at postnatal day 5th with 2 days interval between injections) resulted in the IR gene excision exclusively in the cartilage. TamCart IRfloxflox tamoxifen-treated mice (KO mice) and their IRfloxflox control littermates (C mice) at 3 weeks of age were exposed to a standard or hypercaloric (high-fat) diet for 4 weeks.

Results: At the end of study, C and KO mice fed with a high-fat diet exhibited greater weight gain than the respective strains fed with a standard diet. Body and tibial growth and growth plate height of C mice fed with high-fat diet were greater than those of standard-diet-fed C mice; however, no difference was observed between KO mice fed with standard or high-fat diet with respect to body and tibial growth and growth plate height. Circulating levels of insulin, insulin-like growth factor (IGF)-1 and leptin were significantly higher in C and KO mice exposed to high-fat diet compared to those in the same strain exposed to standard diet. Increased phosphorylation of Akt (one of the intracellular mediators of insulin action in bone) in the growth plate of C mice on high-fat diet (compared to those on standard diet) suggests that high-fat-mediated increased circulating insulin levels may directly affect growth plate function and bone growth. High-fat diet was not associated with any change of Akt phosphorylation in KO mice. In addition, in vitro studies in cultured primary chondrocytes revealed that Akt mediates the stimulatory effects of insulin on chondrocyte proliferation and differentiation.

Conclusions: In conclusion, the activation of the IR in the growth plate of mice fed with a hypercaloric diet stimulates skeletal growth and growth plate chondrogenesis.

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Comments
Insulin resistance and hyperinsulinemia are suggested to be important mechanisms involved in accelerated longitudinal growth in childhood obesity [1]. Role of insulin receptor (IR) at the growth plate, as an IGF-independent mechanism promoting growth, was studied in mice with isolated excision of the IR gene in cartilage. Both in vivo and in vitro data support this hypothesis. Namely, following a hypercaloric diet that results in insulin resistance and hyperinsulinism, growth at the level of growth plate was not increased in mice with a knockout of IR in comparison to controls. In addition, it was determined that in cultured primary chondrocytes, Akt mediates the stimulatory effects of insulin on chondrocyte proliferation and differentiation. Studies in humans are needed to further establish signaling through the IR as the mechanism involved in accelerated longitudinal growth in childhood obesity [2]. Unraveling IGF-independent mechanisms involved in bone growth is important for the development of novel therapeutic strategies in individuals with dysfunctional IGF signaling pathway and short stature.
Effects of Dairy Product Consumption on Height and Bone Mineral Content in Children: A Systematic Review of Controlled Trials


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Adv Nutr 2019;10(suppl_2):S88–S96

Background: There is a physiological basis for the roles of selected nutrients, especially proteins, calcium, and vitamin D, in growth and development, which are at a maximum during the pediatric period. Milk and dairy products are particularly rich in this group of nutrients.

Methods: The present systematic review summarizes the available evidence relating dairy product intake with linear growth and bone mineral content in childhood and adolescence.

A search was conducted in the MEDLINE (via PubMed) and SCOPUS databases following preferred reporting items for systematic reviews and meta-analyses guidelines and included intervention-controlled clinical trials with dairy products in children from January 1, 1926 to June 30, 2018.

The risk of bias for each study was assessed using the Cochrane methodology.

Results: The number of study participants, the type of study and doses, the major outcomes, and the key results of the 13 articles included in the review are reported.

Conclusions: The present systematic review shows that supplementing the usual diet with dairy products significantly increases bone mineral content during childhood. However, the results regarding a possible relation between dairy product consumption and linear growth are inconclusive.

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Mechanisms by which sialylated milk oligosaccharides impact bone biology in a gnotobiotic mouse model of infant undernutrition


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Proc Natl Acad Sci USA 2019;116:11988–11996

Background: Undernutrition in children is a pressing global health problem, manifested in part by impaired linear growth (stunting). Current nutritional interventions have been largely ineffective in overcoming stunting, emphasizing the need to obtain better understanding of its underlying
causes. Treating Bangladeshi children with severe acute malnutrition with therapeutic foods reduced plasma levels of a biomarker of osteoclastic activity without affecting biomarkers of osteoblastic activity or improving their severe stunting.

**Methods:** To characterize interactions among the gut microbiota, human milk oligosaccharides (HMOs), and osteoclast and osteoblast biology, young germ-free mice were colonized with cultured bacterial strains from a 6-month-old stunted infant and fed a diet mimicking that consumed by the donor population. Adding purified bovine sialylated milk oligosaccharides (S-BMO) with structures similar to those in human milk to this diet increased femoral trabecular bone volume and cortical thickness, reduced osteoclasts and their bone marrow progenitors, and altered regulators of osteoclastogenesis and mediators of Th2 responses. Comparisons of germ-free and colonized mice revealed S-BMO-dependent and microbiota-dependent increases in cecal levels of succinate, increased numbers of small intestinal tuft cells, and evidence for activation of a succinate-induced tuft cell signaling pathway linked to Th2 immune responses. A prominent fucosylated human milk oligosaccharide, 2’-fucosyllactose, failed to elicit these changes in bone biology, highlighting the structural specificity of the S-BMO effects. These results underscore the need to further characterize the balance between, and determinants of, osteoclastic and osteoblastic activity in stunted infants/children, and suggest that certain milk oligosaccharides may have therapeutic utility in this setting.

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**Comments**

Understanding mechanisms associated with childhood undernutrition and growth stunting is of paramount importance in the planning of successful and safe nutritional interventions. As discussed in extent in this systematic review, dairy product supplementation of diet has an important influence on bone mineral content in childhood; the effect on linear growth is, however, still debated [3]. In another study, the role of milk oligosaccharides on osteoclast and osteoblast biology was studied in experimental animals, as it was proposed from the epidemiological part of the study that alteration of the osteoclastic activity by nutritional intervention could improve decreased linear growth. Sialylated milk oligosaccharides with structures similar to those in human milk were found to increase femoral trabecular bone volume and cortical thickness, reduced osteoclasts and their bone marrow progenitors, and altered regulators of osteoclastogenesis and mediators of Th2 responses in these mice. These data shed important insights into the mechanisms of bone remodeling and growth and could have an important influence on the composition of foods used in nutritional interventions [4].

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**Plasma C-Type Natriuretic Peptide: Emerging Applications in Disorders of Skeletal Growth**

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*Horm Res Paediatr* 2018;90:345–357

**Abstract:** Although studies in experimental animals show that blood levels of C-type natriuretic peptide (CNP) and its bioinactive aminoterminal propeptide (NTproCNP) are potential biomarkers of long bone growth, a lack of suitable assays and appropriate reference ranges has limited the application of CNP measurements in clinical practice. Plasma concentrations of the processed product of proCNP, NTproCNP – and to a lesser extent CNP itself – correlate with concurrent
height velocity throughout all phases of normal skeletal growth, as well as during interventions known to affect skeletal growth in children. Since a change in levels precedes a measurable change in height velocity during interventions, measuring NTproCNP may have predictive value in clinical practice. Findings from a variety of genetic disorders affecting CNP signaling suggest that plasma concentrations of both peptides may be helpful in diagnosis, provided factors such as concurrent height velocity, feedback regulation of CNP, and differential changes in peptide clearance are considered when interpreting values. An improved understanding of factors affecting plasma levels, and the availability of commercial kits enabling accurate measurement using small volumes of plasma, can be expected to facilitate potential applications in growth disorders including genetic causes affecting the CNP signaling pathway.

**ASB20123: A novel C-type natriuretic peptide derivative for treatment of growth failure and dwarfism**

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*PLoS One 2019; 14:e0212680*

**Background:** C-type natriuretic peptide (CNP) and its receptor natriuretic peptide receptor B (NPR-B) are physiological potent positive regulators of endochondral bone growth; therefore, the CNP/NPR-B signaling pathway is one of the most promising therapeutic targets for treating growth failure and dwarfism.

**Methods:** In this article, we summarized the pharmacological properties of a novel CNP analog peptide ASB20123 as a therapeutic agent for short stature.

**Results:** ASB20123, one of the CNP/ghrelin chimeric peptides, is composed of CNP (1–22) and human ghrelin (12–28, E17D). Compared to CNP (1–22), ASB20123 showed similar agonist activity for NPR-B and improved biokinetics with a longer plasma half-life in rats. In addition, the distribution of ASB20123 to the cartilage was higher than that of CNP (1–22) after single subcutaneous (sc) injection to mice. These results suggested that the C-terminal part of ghrelin, which has clusters of basic amino acid residues and a BX7B motif, might contribute to the retention of ASB20123 in the extracellular matrix of the growth plate. Multiple sc doses of ASB20123 potently stimulated skeletal growth in rats in a dose-dependent manner, and sc infusion was more effective than bolus injection at the same dose. Our data indicated that high plasma levels of ASB20123 would not necessarily be required for bone growth acceleration.

**Conclusions:** Thus, pharmaceutical formulation approaches for sustained-release dosage forms to allow chronic exposure to ASB20123 might be suitable to ensure drug effectiveness and safety.

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Exogenous C-type natriuretic peptide restores normal growth and prevents early growth plate closure in its deficient rats

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PLoS One 2018;13:e0204172

Background: Signaling by C-type natriuretic peptide (CNP) and its receptor, natriuretic peptide receptor-B, is a pivotal stimulator of endochondral bone growth. We recently developed CNP knockout (KO) rats that exhibit impaired skeletal growth with early growth plate closure. In the current study, we further characterized the phenotype and growth plate morphology in CNP-KO rats, and the effects of exogenous CNP in rats.

Methods: We used CNP-53, an endogenous form of CNP consisting of 53 amino acids, and administered it for four weeks by continuous subcutaneous infusion at 0.15 or 0.5 mg/kg/day to 4-week old CNP-KO and littermate wild type (WT) rats.

Results: We demonstrated that CNP-KO rats were useful as a reproducible animal model for skeletal dysplasia, due to their impairment in endochondral bone growth. There was no significant difference in plasma bone-turnover markers between the CNP-KO and WT rats. At eight weeks of age, growth plate closure was observed in the distal end of the tibia and the calcaneus of CNP-KO rats. Continuous subcutaneous infusion of CNP-53 significantly, and in a dose-dependent manner, stimulated skeletal growth in CNP-KO and WT rats, with CNP-KO rats being more sensitive to the treatment. CNP-53 also normalized the length of long bones and the growth plate thickness, and prevented growth plate closure in the CNP-KO rats. Using organ culture experiment of fetal rat tibia, gene set enrichment analysis indicated that CNP might have a negative influence on mitogen activated protein kinase signaling cascades in chondrocyte.

Conclusions: Our results indicated that CNP-KO rats might be a valuable animal model for investigating growth plate physiology and the mechanism of growth plate closure, and that CNP-53, or its analog, may have the potential to promote growth and to prevent early growth plate closure in the short stature.

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Comments

Several manuscripts reported on the use of plasma C-type natriuretic peptide (CNP) as a potential therapeutic and/or diagnostic tool in growth failure including achondroplasia. CNP and its bioactive aminoterminal propeptide (NTproCNP) are potential biomarkers of long bone growth. However, lack of suitable assays and appropriate reference ranges limits the application of CNP measurements in clinical practice, for example, predicting height velocity during interventions known to affect skeletal growth in children [5]. Therapeutic use of CNP-53, an endogenous form of CNP consisting of 53 amino acids, was studied in CNP knockout rats. Continuous subcutaneous infusion of CNP-53 significantly, and in a dose-dependent manner, stimulated skeletal growth. It normalized the length of long bones and the growth plate thickness and prevented growth plate closure. These data suggest that CNP-53, or its analog, may have the potential to promote growth and to prevent early growth plate closure in the short stature [6]. Another novel therapeutic agent for skeletal growth, a chimeric peptide composed of CNP (1–22) and human ghrelin (12–28, E17D), was studied. Especially, sc infusion stimulated skeletal growth in rats. Authors propose...
that pharmaceutical formulation approaches for sustained-release dosage forms to allow chronic exposure to ASB20123 might be suitable to ensure drug effectiveness and safety [7]. These studies provide alternative approaches to achondroplasia treatment that is already in the final clinical trial phases [8].

**Prospective study of growth and bone mass in Swedish children treated with the modified Atkins diet**

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*Eur J Paediatr Neurol* 2019;23:629–638

**Background:** The modified Atkins diet (MAD) is a less restrictive treatment option than the ketogenic diet (KD) for intractable epilepsy and some metabolic conditions. Prolonged KD treatment may decrease bone mineralization and affect linear growth; however, long-term studies of MAD treatment are lacking. This study was designed to assess growth, body composition, and bone mass in children on MAD treatment for 24 months.

**Methods:** Thirty-eight patients, mean age (SD) 6.1 years (4.8 years), 21 girls, with intractable epilepsy (n = 22), glucose transporter type 1 deficiency syndrome (n = 7), or pyruvate dehydrogenase complex deficiency (n = 9) were included. Body weight, height, body mass index, bone mass, and laboratory tests (calcium, phosphorus, magnesium, alkaline phosphatase, cholesterol, 25-hydroxyvitamin D, insulin-like growth factor-I and insulin-like growth factor binding protein 3) were assessed at baseline and after 24 months of MAD treatment.

**Results:** Approximately 50% of the patients responded with >50% seizure reduction. Weight and height standard deviation score were stable over 24 months, whereas median (min – max) body mass index standard deviation score increased from 0.2 (–3.3 to 4.5) to 0.7 (–0.9 to 2.6), p < 0.005. No effects were observed for bone mass (total body, lumbar spine and hip) or fat mass.

**Conclusions:** The MAD was efficient in reducing seizures, and no negative effect was observed on longitudinal growth or bone mass after MAD treatment for 24 months.

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**Comments**

Safety is an important factor influencing the use of diets. Appropriate linear growth and increased weight are prime indicators of health in growing children. Decreased linear growth caused by dieting would limit its usefulness in most children. To this effect, a study in children with epilepsy, glucose transporter type 1 deficiency syndrome, or pyruvate dehydrogenase complex deficiency, receiving MAD (a less restrictive treatment option than the KD) as a part of their treatment, was undertaken. Reassuringly, no negative effect was observed on longitudinal growth or bone mass after 24 months of diet in this population. Nevertheless, further studies with longer duration of treatment and larger cohorts are needed to determine its safety in growing children [9, 10].
Epiphyseal growth plate architecture is unaffected by early postnatal activation of the expression of R992C collagen II mutant

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Bone 2018;112:42–50

Spondyloepiphyseal dysplasia (SED) exemplifies a group of heritable diseases caused by mutations in collagenous proteins of the skeletal system. Its main feature is altered skeletal growth. Pathomechanisms of SED include: changes in the stability of collagen II molecules, inability to form proper collagen fibrils, excessive intracellular retention of mutant molecules, and endoplasmic reticulum stress. The complexity of this pathomechanism presents a challenge for designing therapies for SED.

Our earlier research tested whether such therapies only succeed when applied during a limited window of development. Here, employing an inducible mouse model of SED caused by the R992C mutation in collagen II, we corroborate our earlier observations that a therapy must be applied at the prenatal or early postnatal stages of skeletal growth in order to be successful. Moreover, we demonstrate that blocking the expression of the R992C collagen II mutant at the early prenatal stages leads to long-term positive effects. Although, we could not precisely mark the start of the expression of the mutant, these effects are not significantly changed by switching on the mutant production at the early postnatal stages.

By demonstrating the need for early therapeutic interventions, our study provides, for the first time, empirically-based directions for designing effective therapies for SED and, quite likely, for other skeletal dysplasias caused by mutations in key macromolecules of the skeletal system.

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Comments

Studying mechanisms involved in rare bone dysplasias not only is important from the perspective of a specific bone disease but also may be applied for diagnostic and therapeutic procedure in other diseases of altered skeletal growth [11]. In the present study, timing of therapy during an individual’s development was studied. In an animal model, it was determined as successful in the long term only if it is applied at the prenatal or early postnatal stages of skeletal growth [12]. Confirming an early initiation of treatment might be of importance also in other disorders of skeletal growth, affecting not only planning of timing and modes of treatment administration but also very early diagnosis.

Rapid early increase in body mass index is associated with impaired longitudinal growth in children with cystic fibrosis

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Pediatric Pulmonology 2019;54:1209–1215

Background: Growth failure and short stature is a common consequence of children and adolescents with cystic fibrosis (CF). Previous studies have documented associations between short stat-
ure and clinical outcomes, including reduced life expectancy. It was previously thought that the underlying aetiology of growth failure in CF is due to reduced food intake/absorption and concurrent increased energy losses. More recent studies demonstrate that growth failure and poor pubertal growth spurt is still observed in contemporary cohorts of children and adolescents with CF. Recent reports also document that obesity is also seen in the CF clinic, which may be a reflection of the obesitogenic environment we live in or the over-aggressive management of nutrition. There are very few longitudinal studies of linear growth and body mass index (BMI) in CF. The aim of this study was to evaluate stature in a cohort of Dutch children with CF diagnosed clinically (born between 1997 and 2001) from 0.5 until 18 years. The secondary aim was to evaluate the associations of increase in BMI between 1 and 6 years, lung function and CF-related diabetes.

**Methods:** A retrospective study from one single centre. All subjects were diagnosed clinically and not via newborn screening. Subjects were excluded if there was another significant co-morbidity, missing height data during follow-up. All subjects had reached adult height-defined as increase in height of <0.2 cm over at least 6 months.

**Results:** Height deficits were observed at presentation in both boys and girls even after accounting for parental height (target height), which increased following diagnosis. In boys, height for age minus target height Z-scores declined during puberty, leading to reduction in adult height corresponding to 4 cm lower ($p = 0.001$) than the healthy population. In girls, height for age minus target height Z-scores declined briefly after age 8 years but increased subsequently, with adult height of only 2 cm lower ($p = 0.22$) than the healthy population. Low BMI Z-scores were observed for both boys and girls only in the first year of life. The presence of CF-related diabetes and pulmonary function were not associated with adult height. Increase in BMI Z-scores between 1 and 6 years were associated with adult height in boys (Model $R^2 = 0.176$, $r = –0.420$, $p = 0.0230$) and girls (Model $R^2 = 0.217$, $r = –0.466$, $p = 0.0019$).

**Conclusion:** Adult height deficits were still observed in boys with CF despite improvement in clinical care. Associations between increase in BMI in infancy/early childhood and adult height in CF should be addressed in future studies.

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**Comments**

In this longitudinal retrospective study, the authors document that height deficits may still be observed in males with cystic fibrosis (CF). The gender difference for growth failure has also been shown in another group of childhood chronic disease, inflammatory bowel disease (Gupta et al. Inflamm Bowel Dis 2011; 17:2318–2325; Mason et al. Horm Res Pediatr 2015;83:45–54), and this should be addressed in future studies in CF that include disease severity. Whilst statistical significant adult height deficits were documented in males with CF in this current study, it is encouraging to note that the magnitude of height deficit is only 4 cm (although the authors did not report 95% CI for the height deficit). Long-term adult height data in children with CF identified from newborn screening are now needed. The authors speculate that increase in body mass index (BMI) in infancy/early childhood may lead to increased production of adrenal androgens with associated earlier onset of puberty and therefore reduction in adult height. The associations reported in this study were obtained from univariate analysis which only explained approximately 18 and 22% of variation in adult height of males and females. Such a hypothesis needs to be proven in future studies, which take into account disease severity and nutritional status/management strategies. An alternative explanation could be that those children with more severe disease and/or nutritional issues were managed with aggressive nutritional management leading to greater increase in BMI. Optimal nutritional management in CF and impact on all health outcomes including linear growth and pulmonary function require further studies.
Bone mass development is sensitive to insulin resistance in adolescent boys

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Bone 2019;122:1–7

Background: Existing data shows that insulin may exert an osteogenic effect on bone but the relationship maybe different depending on underlying body composition. Recent studies demonstrate that osteocalcin a bone specific non-collagen protein secreted by osteoblast may influence glucose metabolism and increase insulin sensitivity. The aim of this study was to evaluate the association between insulin resistance measured by the homeostasis model of insulin resistance (HOMA-IR) and dual energy absorptiometry (DXA) bone mass in healthy children. The secondary aim was to identify if body composition, physical activity or osteocalcin may influence the association between insulin resistance and bone mass in healthy children.

Methods: Data from a 6 year longitudinal study, The Childhood Health Activity and Motor Performance School Study, Denmark (CHAMPS-study, DK) with a total of 562 healthy children (277 boys) aged between 6 and 11 years were included in this study. Subjects were included if a baseline DXA and at least one follow-up DXA together with a fasting blood sample were obtained. Fasting blood samples were analysed for glucose, insulin and osteocalcin. Physical activity was measured by accelerometers worn at least for 7 days. Maturity was defined as number of years from age at peak height velocity based on previous published equations.

Results: Mean age of subjects at baseline was 9.6 years (range 7.7–12.0 years). At baseline, 16.4% were overweight and 3.4% were obese. At follow-up, HOMA-IR was negatively associated with DXA total body less head bone mineral content (TBLH-BMC) after adjusting for maturity, sex, height and DXA bone area ($p < 0.0001$). A sex difference was identified, including in stratified analysis where HOMA-IR was negatively associated with DXA TBLH-BMC only in boys ($\beta = -31.4, p < 0.001$). Additional adjustment for weight, DXA %fat, physical activity and osteocalcin showed similar associations between HOMA-IR and DXA TBLH-BMC (boys: $\beta = -29.3, p < 0.0001$; girls: $\beta = -1.5, p = ns$).

Conclusion: In a large cohort of healthy children and adolescents, measure of insulin sensitivity with HOMA-IR was inversely associated with DXA bone mineral content, following adjustment for numerous co-variates, including physical activity and osteocalcin. This relationship however was only present in boys.

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Comments

In this cohort of healthy children, insulin sensitivity measured by homeostasis model of insulin resistance was inversely associated with dual energy absorptiometry bone mass. The intriguing association present only in boys needs to be explored in further studies. It is unclear whether this association or the strength of this association is dif-
different in children with normal body mass index and those who are overweight and obese, given that insulin levels and homeostasis model of insulin resistance were generally in the “normal” ranges in this study. In addition, the interaction of nutritional intake should be explored in further studies.

Growth pattern of infants with gastroschisis in the neonatal period
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Background: Gastroschisis is a congenital abdominal wall defect, with evidence of intestinal failure in the early neonatal period requiring supportive parenteral nutrition for weeks to months. There is however limited information on growth of infants with gastroschisis.

Methods: This study is a retrospective review of all infants with gastroschisis managed in a single neonatal surgical unit over a 4-year period. Weight at birth, 10 days post-natal (±1 day), last day of any amount of parenteral nutrition, at discharge and at outpatient follow-up were converted to Z-scores. During the period of review, parenteral nutrition policy did not change. This consisted of starting parenteral nutrition at day 2–3 (providing 100–120 kcal/day in a volume of 150 mL/kg/day). All infants were kept nil by mouth until clinical evidence of intestinal motility, whereby enteral feeds were introduced. Results were reported as mean (SD).

Results: A total of 64 infants with gastroschisis were managed in the centre during the study period, and 61 (30 males) were included in this present study (3 excluded as were initially managed in another neonatal surgical unit). Mean gestation at birth was 36.0 (2.3), mean birth weight was 2.36 kg (0.54) and mean birth weight Z-score of –0.87 (0.85). Five infants did not receive any parenteral nutrition but the rest received parenteral nutrition until a mean of 29.8 days (21.3). Mean weight Z-scores fell to –1.19 (0.92) at day 10 with a nadir of weight Z scores of –2.24 (1.13) at day 71. Discharge weight Z-score was significantly lower than birth weight Z-scores (Mean difference 0.84,\ p<0.0001) and at time of stopping parenteral nutrition (Mean difference 0.48,\ p<0.0001). Weight pattern during parenteral nutrition showed that weight Z-score fell during the first 10 days of life, with progressive increase and stabilised after 25 days of age. Weight fell following discontinuation of parenteral nutrition but stabilised approximately 30 days after.

Conclusion: This study demonstrated that despite nutritional support with parenteral nutrition, infants with gastroschisis show poor weight gain. Factors associated with weight gain and the long-term consequences should be evaluated in future studies.

Comments: This interesting report showed that current contemporary nutritional support maybe inadequate for weight gain in infants with gastroschisis. In particular, poor weight gain or weight loss appears to be common at the time of transition from parenteral nutrition to enteral feeds. Research into different nutritional support of these infants is now needed. Longer term follow-up including data on linear growth is also needed.
Skeletal disproportion in glucocorticoid-treated boys with Duchenne muscular dystrophy

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**Background:** Boys with Duchenne muscular dystrophy (DMD) are treated with long term high dose oral glucocorticoid from approximately 4–5 years, and continued to adulthood. As a result, severe growth failure and short stature are commonly seen. Significant obesity is also a problem in paediatric DMD especially at the time of loss of ambulation. Small studies in children with hemiplegic cerebral palsy showed that lower leg length maybe present. The aim of the study is to evaluate body proportions in boys with DMD treated with GC.

**Methods:** Thirty boys with DMD on glucocorticoid therapy were compared with 30 healthy aged matched children (matched to within 6 months) recruited locally. Body segments and total height were measured using dual energy absorptiometry (DXA) total body images performed on Lunar Prodigy DXA scanner. Results were reported as median (range).

**Results:** All boys with DMD have been on oral glucocorticoid for a duration of 7.1 years (1.3 to 15.2). Height Z-score was significantly lower in boys with DMD compared with controls ($p < 0.0001$) and body mass index Z-score was significantly higher ($p < 0.0001$). Fifty seven percent of controls were pre-pubertal whereas 87% of boys with DMD were pre-pubertal. Height of boys with DMD was 10.7 cm (95% CI –17.1 to –4.3) lower than healthy controls after adjusting for pubertal status. Median percentage difference of sitting height in boys with DMD compared with controls was 6.5% lower (range –24 to +6.7%), whereas median percentage difference of leg length in boys with DMD in comparison with controls was 13% lower (range –46 to +13%). Median percentage difference in femur length in DMD compared with controls was 12% lower (range –41 to +19%) and median percentage difference in tibial length in DMD compared to controls was 23% lower (range –53 to +9.4%). Similarly, greater reduction of distal long bone of the upper limb was also observed in boys with DMD.

**Conclusion:** Boys with DMD on glucocorticoid therapy had evidence of skeletal disproportion with relatively shorter leg length and greater reduction in distal long bones. The underlying aetiology of this skeletal disproportion is currently unclear.

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**Comments**

Glucocorticoid excess is not known to be associated with skeletal disproportion, although there are hardly any studies in any childhood chronic condition of glucocorticoid excess. This study utilized a method of evaluating body proportions and bone lengths using DXA total body images and opens up the opportunity to evaluate stature and bone lengths in children with immobility. Previous studies show that short stature is relatively common in boys with Duchenne muscular dystrophy (DMD) even prior to treatment with glucocorticoid when these boys are still ambulant (approximately 25% with height Z-scores lesser than –2.0). The authors raise the possibility of an inherent growth disorder associated with DMD. Obesity is a common occurrence in DMD especially during childhood and in those on glucocorticoid therapy. The interaction of obesity and nutritional intake on linear growth, stature, and body proportions should be studied in future research.
Antibiotic perturbation of gut microbiota dysregulates osteoimmune cross talk in postpubertal skeletal development

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Background: Recent research show that host gut microbiota may have an influence on pathological states of the gastrointestinal tract and also impact on distant organs (e.g., liver, brain, heart and skeleton). Throughout the lifespan, various lifestyle factors may lead to changes in gut microbiota, which includes medications like antibiotics. Pro-inflammatory immune states can suppress osteoblastic bone formation and increase bone resorption. Antibiotic administration has been shown to lead to disruption of gut microbiota leading to a pro-inflammatory hyperimmune state. The osteoimmune mechanism linking antibiotic and skeletal development is unclear. The aim of this study was to investigate the effect of antibiotic disruption of gut microbiota in mice (C57BL/6 strain) from 6 to 12 weeks.

Methods: Mice were administered antibiotics (vancomycin, imipenem/clastin and neomycin) or vehicle in drinking water from 6 to 12 weeks. Mice were euthanized at 12 weeks of age. MicroCT and histomorphometry (static and dynamic) of tibia were performed.

Results: Antibiotic therapy led to reduction in bacterial load in male and female mice but composition changes were sex dependent. Male mice treated with antibiotics showed significant increase in α-proteobacteria and γ-proteobacteria but decrease in Bacteroidetes. On the other hand, female mice treated with antibiotics showed significant increase in α-proteobacteria and decrease in Bacteroidetes and Firmicutes. Trabecular microarchitecture deficits were observed in mice treated with antibiotics at 12 weeks, with greater deficits in male mice. Antibiotic treated mice did not show any evidence of growth impairment (tibia length, growth plate chondrocyte height and zone morphology). Static and dynamic studies of bone formation on histomorphometry did not show any abnormalities in osteoblastogenesis. However, histomorphometric studies of osteoclastogenesis with TRAP-stained proximal tibia showed increased osteoclast size and number. Increased systemic inflammation was observed with antibiotic administration in the mice (increased tumour necrosis factor and chemokines, CCL3). In addition, changes in adaptive and innate immune cells were also noted in mesenteric lymph nodes and spleen.

Conclusion: This study demonstrated that broad spectrum antibiotic administration led to disruption of gut microbiota composition altering host immune response which in turn modulates the developing skeleton. Deficits in trabecular microarchitecture and increased osteoclastogenesis were observed with no impairment in linear growth.

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ence of sex steroid. The clinical implications of these results remain to be seen. In groups of children with chronic disorders requiring long-term treatment with prophylactic antibiotics, this maybe another mechanism of abnormalities in bone development.

**High prevalence of growth plate gene variants in children with familial short stature treated with growth hormone**

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**Context:** Familial short stature (FSS) is a term describing a growth disorder that is vertically transmitted. Milder forms may result from the combined effect of multiple genes; more severe short stature is suggestive of a monogenic condition. The etiology of most FSS cases has not been thoroughly elucidated to date.

**Objectives:** To identify the genetic etiology of severe FSS in children treated with growth hormone (GH) because of the diagnosis of small for gestational age or GH deficiency (SGA/GHD).

**Design, Settings and Patients:** Of 736 children treated with GH because of GHD/SGA, 33 with severe FSS (life-minimum height –2.5 SD or less in both the patient and shorter parent) were included in the study. The genetic etiology was known in 5 of 33 children prior to the study (ACAN [in 2], NF1, PTPN11, and SOS1). In the remaining 28 of 33, whole-exome sequencing was performed. The results were evaluated using American College of Medical Genetics and Genomics standards and guidelines.

**Results:** In 30 of 33 children (90%), we found at least one variant with potential clinical significance in genes known to affect growth. A genetic cause was elucidated in 17 of 33 (52%). Of these children, variants in growth plate-related genes were found in 9 of 17 (COL2A1, COL11A1, and ACAN [all in 2], FLNB, FGFR3, and insulin-like growth factor (IGF) 1R), and IGF-associated proteins were affected in 2 of 17 (IGFALS and HMGA2). In the remaining 6 of 17, the discovered genetic mechanisms were miscellaneous (TRHR, MBTPS2, GHSR, NF1, PTPN11, and SOS1).

**Conclusions:** Single-gene variants are frequent among families with severe FSS, with variants affecting the growth plate being the most prevalent.

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**Comments**

In the present study, the authors aimed to identify the genetic etiology of severe familial short stature (FSS). They classified short child (height ≤2 SD) as having FSS if at least one of his/her parents is also short (height ≤2 SD). They defined severe FSS if both the child and the shorter parent had height below –2.5 SD. It is true that more and more cases with idiopathic short stature actually are identified as suffering from different genetic variants of genes responsible for key processes that occur within the growth plate during the linear growth process. Several familial cases were already described in the literature. The surprise finding of the present manuscript is the fact that 30/33 (90%) of the children with severe FSS enrolled to the study were found to have at least one variant with potential clinical significance genes known to affect growth. It is almost like we can delete the term idiopathic familial severe short stature from our textbook and lists of potential diagnosis in our clinical practice since most cases (90%)
are not idiopathic anymore. I think it is too early to do that, and more studies in different centers and geographical areas are needed to confirm that very important and interesting finding.

Cartilage-targeted insulin-like growth factor-1 treatment to promote longitudinal bone growth
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Recombinant human growth hormone (GH) is commonly used to treat short stature in children. However, GH treatment has limited efficacy, particularly in severe, non-GH-deficient conditions such as chondrodysplasias, and potential off-target effects. Because short stature results from decreased growth plate chondrogenesis, we developed a cartilage-targeting single-chain human antibody fragment (CaAb) aiming to deliver therapeutic molecules to the growth plate, thereby increasing treatment efficacy while minimizing adverse effects on other tissues. To this end, we created fusion proteins of these CaAbs conjugated with insulin-like growth factor 1 (IGF-1), an endocrine and/or paracrine factor that positively regulates chondrogenesis. These CaAb-IGF-1 fusion proteins retained both cartilage binding and IGF-1 biological activity, and they were able to stimulate bone growth in an organ culture system. Using a GH-deficient (lit) mouse model, we found that subcutaneous injections of these CaAb-IGF-1 fusion proteins increased overall growth plate height without increasing proliferation in kidney cortical cells, suggesting on-target efficacy at the growth plate and less off-target effect on the kidney than IGF-1 alone. Alternate-day injections of these fusion proteins, unlike IGF-1 alone, were sufficient to produce a therapeutic effect. Our findings provide proof of principle that targeting therapeutics to growth plate cartilage can potentially improve treatment for childhood growth disorders.

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Comments
The authors developed an elegant and unique way to specifically deliver insulin-like growth factor (IGF)-1 to the growth plate. They also showed that the IGF-1 indeed increased growth plate and did not have an effect on other tissues (kidney). It is an important study indeed. Target-specific therapy is the desire of every physician in every specialty of medicine. Currently, physicians treating children with severe short stature with either growth hormone or IGF-1 are constantly concerned with the possible off-target short- and long-term undesired side effects. Frequently, pediatric endocrinologists treating children with GH have to consider reducing an effective dose because of too high systemic levels of IGF-1 and the concern of potential theoretical future malignancy. The described innovation of delivering the IGF-1 specifically to the growth plate where its action is needed paves the way to other targeted therapeutic options to be delivered specifically to the growth plate.
Impact of the ketogenic diet on linear growth in children: a single-center retrospective analysis of 34 cases
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Abstract: Data on the impact of the ketogenic diet (KD) on children’s growth remain controversial. Here, we retrospectively investigated the occurrence of linear growth retardation in 34 children (47% males; age range: 2–17 years) diagnosed with drug-resistant epilepsy (n = 14) or glucose transporter type 1 deficiency syndrome (n = 20) who had been treated with the KD for 12 months. The general characteristics of children with and without growth retardation were also compared. All participants received a full-calorie, traditional KD supplemented with vitamins, minerals, and citrate. Most children (80%; 11/14 in the drug-resistant epilepsy subgroup and 16/20 in the glucose transporter type 1 deficiency syndrome subgroup) treated with the KD did not show growth retardation at 12 months. Although participants with and without delay of growth did not differ in terms of baseline clinical characteristics, dietary prescriptions, or supplementation patterns, marked ketosis at 12 months tended to occur more frequently in the latter group. Altogether, our results indicate that growth retardation may occur in a minority of children treated with the KD. However, further research is required to identify children at risk and to clarify how increased ketones levels may affect endocrine pathways regulating growth during KD administration.

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Comments
Even after the present study, the question “does ketogenic diet interfere with children’s growth?” remains without a proper answer. The prospective nature of this study: mixed population, number of patients in each group, and the different age groups as well as the Tanner stage, make it difficult to draw definite conclusions from the results. So, I agree with the authors that prospective big studies are needed to answer this important question and not just for patients with drug-resistant epilepsy or glucose transporter type 1 deficiency syndrome. Many children in the world are trying different degrees of ketogenic diets for off-labeled indications, and their caregivers should know what it does to their growth during childhood and adolescence.

References


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