



Bone and growth: basic principles behind rare disorders

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Summary The heterogeneity of “rare bone disorders” can be explained by the number of molecules and regulatory pathways which are responsible for bone health and normal stature. In this article, the most important basic principles behind bone homeostasis from development to structure and regulation of the growing skeleton are summarized. The aim is to provide the reader with some theoretical background to understand the nature of the different main groups of disorders affecting bone stability, longitudinal growth and disturbances of calcium and phosphate homeostasis.

Keywords Rare bone disorder · Bone fragility · Mineralization · Bone regulation · Rare calcium disorders

Knochen und Wachstum: grundlegende Prinzipien hinter seltenen Erkrankungen

Zusammenfassung Hinter der Gruppe seltener Knochenerkrankungen steht ursächlich eine Vielzahl unterschiedlicher Regulationsmechanismen, welche auch die Heterogenität der verschiedenen Erkrankungsbilder erklärt. In diesem Artikel soll ein Überblick über grundsätzliche Aspekte der Entwicklung,

der Struktur und der Regulation des wachsenden Skelettsystems gegeben werden. Auf diese Weise sollen dem interessierten Leser die ganz unterschiedlichen seltenen Ursachen hinter erhöhter Fraktur­neigung, aber auch seltenen Wachstumsstörungen und Störungen der Mineralisation verständlich präsentiert werden.

Schlüsselwörter Seltene Knochenerkrankungen · Knochenbrüchigkeit · Mineralisation · Regulierung des Knochens · Seltene Kalziumstörungen

Introduction

The skeletal system of children is unique: Bone provides mechanical stability and at the same time allows longitudinal growth. These roles are established by rather separate “organs”, the *bony tissue* on one hand and the *cartilaginous growth plate* on the other hand. The growing bone of children and adolescents shows distinct characteristics when compared to adult bone and, as a matter of fact, growth is a process restricted to childhood and adolescence.

In this article we give an introduction on the structure and regulation of the growing skeleton with special emphasis on fundamental principles behind rare disorders of bone, growth and mineralization as a basis for their classification, diagnosis and treatments.

Bone and growth plate—basics

Development

In fetal life, limb buds appear during the 4th week of gestation, followed by rapid morphogenetic and segmentation processes. Already at the 8th week of gestation, large parts of the axial (thoracic cage, spine) and appendicular (extremities) skeleton are also mineral-

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metaphysis around HCs becomes *mineralized*, is resorbed by osteoclasts and replaced by bone (reviewed in [6]).

Regulation

Local regulatory molecules and pathways

The local regulation of bone and cartilaginous tissues is performed by a multitude of complex pathways in constant interaction with external factors such as systemic and mechanical influences (see [7]).

Bone tissue is in a continuous equilibrium of matrix formation and resorption. The coupling of the antagonistic processes is regulated by a complex system of local factors and molecular signals. A major role in intercellular communication is played by Receptor activator of nuclear factor- κ B (RANK) and its ligand (RANKL). RANK, a member of the tumor necrosis factor family, is expressed by osteoclasts. Expression of RANKL by osteoblasts induces terminal osteoclast differentiation and keeps a balance of activity between these two antagonistic cell types. Modifiers such as osteoblast-derived osteoprotegerin (OPG) interact in this regulatory system and allow adoption of the RANKL-driven coupling of osteoclasts and osteoblasts. In contrast to osteoclasts, osteoblast differentiation is mainly accomplished via three pathways: Bone morphogenetic proteins (BMPs), Wnt signaling and Notch signaling. Many skeletal conditions such as fibrodysplasia ossificans progressiva or Hajdu–Cheney syndrome are caused by direct impairment of these regulatory systems. While novel insight into the regulation of this pathway, e.g., by microRNA expression, has been gained, the complex interaction of involved pathways is still under intensive investigation [7].

With respect to the *growth plate* (GP), studies in model systems, in vitro cultures and skeletal diseases have revealed an orchestration of transcription factors, soluble proteins, receptors and extracellular matrix components that regulate cellular processes and matrix metabolism (see [8]).

Several of the main players in the context of the regulation of enchondral ossification are depicted in Fig. 1. There is a unique feedback loop between Indian hedgehog (IHH) and parathyroid hormone-related protein (PTHrP) controlling terminal differentiation of HC and thus the height of the growth plate [9]. Fibroblast growth factors (FGFs) take another essential part of growth plate regulation, which is translated into genetic conditions associated with an overactivation of differentiation via the FGF-receptor 3 such as in achondroplasia.

The molecular mechanisms behind chondrocyte hypertrophy are complex [10]. SOX9 and RUNX2, which regulate transcription of collagen type X, matrix metalloproteinase 13 (MMP-13), vascular endothelial growth factor (VEGF) and IHH genes are involved (reviewed in [8]). MMP families are regarded as the

most important degraders of ECM proteins and are known to play a part in the regulation of cell migration. VEGF, also produced by osteoclasts, appears to be the factor responsible for ingrowth of the vascular progenitor cells in the growth plate.

Local regulation of mineralization

The formation of hydroxyapatite crystals is tightly regulated to ensure sufficient matrix mineralization in hard tissues and to avoid ectopic mineralization. Pyrophosphates (PPis) represent a key regulator element being both potent inhibitors of mineralization and an essential source of phosphate for matrix formation. Secreted matrix vesicles (MV) containing PPI-degrading enzymes such as tissue-nonspecific alkaline phosphatase (TNSALP) play an essential role in the coordination of mineral nucleation [11, 12]. Short integrin-binding ligand-interacting glycoproteins (SIBLINGs) further regulate local phosphate homeostasis and link mineralization to systemic phosphate regulation, vascularization, energy metabolism, bone resorption and mechanotransduction [13].

Systemic regulation of bone and growth plate

Regulation of *bone homeostasis* via endocrine pathways is established on multiple levels [14, 15].

Parathyroid hormone (PTH) has a dual function in bone homeostasis: It supports bone formation by increasing osteoblast production and differentiation and inhibiting apoptosis, but also by locally stimulating the synthesis of IGF-I. At higher serum concentrations, PTH stimulates osteoclast formation by increasing RANKL and reducing OPG synthesis. Both the active form of *vitamin D* (1,25-(OH)₂ D), as well as its precursor (25-OH D) control bone remodeling by promoting both its formation and resorption. 25-OH D can be activated locally in osteoclasts and osteocytes via CYP27B1. Differentiation of osteocytes is directly regulated by 1,25-(OH)₂ D via vitamin D receptors (VDR). *Calcitonin* seems to directly promote osteoclasts apoptosis. It also locally stimulates the synthesis of insulin-like growth factor 1 (IGF-1), thus supporting the proliferation and differentiation of osteoblasts. Similar to the growth plate, *growth hormone* also interferes with bone remodeling by directly stimulating osteoblast production and in addition, sustaining bone formation through local stimulation of IGF-1 and IGF binding protein 3 (IGFBP-3) synthesis. *Thyroid hormone* was shown to directly act on both osteoblasts and osteoclasts but also indirectly through cytokines. It has a dual effect in osteoblasts, as it can stimulate the differentiation, but also inhibit their proliferation. T3 also seems to promote osteoclastic activity. *Estrogens* seem to play a role in controlling apoptosis in bone cells (inhibition in osteoblasts, stimulation in osteoclasts). The production and the activity of osteoclasts is inhibited by estrogens by downregulating the production of RANKL and by stimulating the synthesis of OPG. *Androgens*

were shown to indirectly downregulate osteoclastic activity by its actions on the RANKL/RANK/OPG system, thus playing a role in preserving bone mass. *Glucocorticoids* (GCs) directly and indirectly influence bone homeostasis by decreasing intestinal calcium absorption and increasing its urinary excretion. Due to the inhibition of gonadotropin secretion, it negatively influences bone formation. GC receptors were found in osteoblasts, so it has been theorized that GCs directly inhibit the formation and differentiation of osteoblasts but might also stimulate their apoptosis. Furthermore, GCs seems to sustain bone resorption by stimulating RANKL synthesis and inhibiting OPG secretion, thus promoting osteoclasts formation.

Multiple systemic hormones play a role in the regulation of the *growth plate homeostasis*, such as thyroid hormones, estrogens, vitamin D, but especially serum IGF-I and GH [16].

Estrogen receptors were found in the growth plate, the exact mode of action is still under debate although an effect on chondrocyte senescence has been proposed [17]. Many of the effects of systemic *androgens* are locally mediated via aromatization into estrogens, such as bone age maturation and growth plate fusion, but presence of androgen receptors in the growth plate also suggest direct actions. *Thyroid hormones* seem to activate the Wnt/beta-catenin signaling pathway and, as a result, stimulate the differentiation of chondrocytes. T3 is known to also promote local production of IGF-1, which in turn is involved in chondrocyte hypertrophy.

The somatomedin hypothesis had to be adjusted over time, in more recent years both direct and indirect effects of GH and IGF-I on the growth plate as well as synergistic and antagonistic effects of GH and IGF-I on metabolism and regulation of bone metabolism have been recognized [18].

Main groups of rare bone and growth disorders

Classification in subcategories of rare bone disorders can be made either according to the affected tissue component or dominating clinical symptomatology. Nosologies have increasingly moved from radiological to molecular [19] or regulatory based classifications [20].

When it comes to clinical practice, the following groups of rare bone and growth disorders are predominant:

In regard to matrix components and mechanical properties of bones, *osteoporotic* and *rachitic conditions* can be distinguished: Osteoporotic conditions are characterized by an increased bone fragility and high fracture rates, while rachitic disorders feature matrix impairment leading to decreased stiffness and development of long bone deformities. Conditions associated with increased formation of bone matrix are defined as *osteosclerotic disorders* and can lead to im-

paired biomechanical matrix properties by irregular architecture rather than by lack of synthesis.

Bone fragility disorders

Osteoporosis in pediatric patients represents a severe condition defined by impaired bone structure and increased bone fragility. Primary osteoporosis is caused by genetic deviations in bone matrix or regulator genes and has to be distinguished from secondary or acquired osteoporosis, which represent the most common cause for bone fragility in pediatrics [21]. Osteogenesis imperfecta (OI, OMIM #166200) describes a group of heterogeneous, genetic conditions and constitutes most cases of primary bone fragility. The phenotypic spectrum varies from a moderately increased fracture rate in late adulthood to perinatal death due to intrauterine fractures and deformities [22]. Mutations in collagen type I (*COL1A1* or *COL1A2*) represent the most frequent alteration in patients with OI, constituting approximately 80% of cases. Less common OI types involve regulatory genes for collagen structure, synthesis, folding, secretion and matrix organizations (Table 1).

Table 1 Simplified overview on selected clinical and genetic subtypes of osteogenesis imperfecta. Adapted from [22]

	Type	Gen	Inheritance
Non-deforming, blue sclerae	1	<i>COL1A1</i>	AD
		<i>COL1A2</i>	AD
Perinatally lethal	2	<i>COL1A1</i>	AD
		<i>COL1A2</i>	AD
		<i>CRTAP</i>	AR
		<i>LEPRE1</i>	AR
		<i>PPIB</i>	AR
Progressive deformities, blue sclerae	3	<i>COL1A1</i>	AD
		<i>COL1A2</i>	AD
		<i>BMP1</i>	AR
		<i>CRTAP</i>	AR
		<i>FKBP10</i>	AR
		<i>LEPRE1</i>	AR
		<i>PLOD2</i>	AR
		<i>PPIB</i>	AR
		<i>SERPINF1</i>	AR
		<i>SERPINH1</i>	AR
		<i>TMEM38B</i>	AR
		<i>WNT1</i>	AR
Variable severity, with sclerae	4	<i>COL1A1</i>	AD
		<i>COL1A2</i>	AD
		<i>WNT1</i>	AD
		<i>CRTAP</i>	AR
		<i>PPIB</i>	AR
		<i>SP7</i>	AR
		<i>PLS3</i>	XL
Hypertrophic callus	5	<i>IFITM5</i>	AD

AD autosomal dominant, AR autosomal recessive, XL X-linked

Sclerosing bone disorders

Sclerosing bone disorders are rare genetic conditions defined by abnormally increased deposition of mineralized matrix [23]. Most disorders are caused by pathologic mechanisms involving endochondral or intramembranous ossification, such as juveniles Paget's disease, van Buchem disease and pycnodysostosis. Despite increased bone density, some disorders are associated with increased fracture rates due to irregular bone matrix. Cranial involvement is often associated with severe neurological symptoms due to nerve compression.

Rickets and osteomalacia

Rickets are characterized by dysregulation of growth plate cartilage caused by mineral deficiency. After cessation of growth the term osteomalacia is used. While most cases of rickets are caused by vitamin D or calcium deficiency, hereditary hypophosphatemic rickets comprises a group of orphan diseases characterized by renal phosphate wasting due to dysregulation of the main endocrine regulator of phosphate handling, FGF23. X-linked hypophosphatemic rickets (XLH) represents the most common type of hypophosphatemic rickets with a prevalence of approximately 1 in 20,000 and is caused by loss-of-function of *PHEX*. In XLH, excess FGF-23 reduces renal phosphate reabsorption and vitamin D activation, resulting in chronic hypophosphatemia. Impaired growth and severe rickets are major characteristics of XLH, representing the main causes of morbidity and surgical interventions in these conditions. Onset of symptoms is commonly observed at the beginning of gait due to incremental deformities of weight bearing bones [24].

Rare disorders of PTH and vitamin D

Rare hypercalcemic disorders

Hypercalcemia can be seen in various rare genetic disorders, with different PTH levels [25, 26]: Primary hyperparathyroidism (PHPT), due to glandular hyperplasia or adenomas, is rare during childhood. Hereditary familial forms of hyperparathyroidism (HPT) are multiple endocrine neoplasia (MEN) and hyperparathyroidism-jaw tumor syndrome (HPZ-JT). The non-syndromic forms of HPT and their respective mutated genes are familial isolated hyperparathyroidism (FIHP: *MEN1*, *PTH* and *GCM2*), neonatal severe primary hyperparathyroidism (NSHPT: homozygous or compound heterozygous inactivating mutations in the *CaSR*) and familial hypocalciuric hypercalcemia (FHH: *CaSR*). The following rare disorders are associated with *low PTH levels*: Jansen metaphyseal chondrodysplasia (activating mutations in *PTHRI*), Williams Beuren syndrome (multiple gene deletions of chromosome 7q11.23) Inactivating mutations of *CYP24A1* were found in patients diagnosed

with idiopathic infantile hypercalcemia and explain the pathomechanism: vitamin D is not catabolized and it accumulates in serum, resulting in an increased intestinal calcium absorption [25–27].

Rare hypocalcemic disorders

Hypocalcemia is either caused by reduced PTH synthesis or impaired action, as well by deranged activity of *CaSR* and by disorders of vitamin D metabolism; in the pediatric population, hypocalcemia often is caused by a genetic disorder [26]. Isolated hypocalcemia can be found in agenesis (*GCM2* mutations) or in autoimmune destruction of the parathyroid glands, or in disorders leading to dysfunctional synthesis/bioactivity of PTH by PTH mutations. Some of the complex genetic pathologies and the respective genes causing hypocalcemia are DiGeorge syndrome (*TBX1* or *NEBL*), autoimmune polyglandular syndrome type 1 (*AIRE*), CHARGE syndrome (*CHD7*, *SEMA3E*), Kenney–Caffey syndrome (*TBCE*, *FAM111A*), hypoparathyroidism, sensorineural deafness and renal syndrome (*GATA3*). Familial cases, with an autosomal dominant, recessive or X-linked inheritance were also described in the literature. An impaired secretion of PTH is seen in activating mutations of the *CaSR*, as in autosomal dominant hypocalcemia type 1 (*ADH1*). Some cases present with severe hypocalcemia, while others remain asymptomatic. High serum PTH levels, due to PTH resistance, is characteristic for pseudohypoparathyroidism (PHP; new nomenclature: inactivating PTH/PTH-related protein signaling disorders iPPSD). In 4 out of the 6 iPPSDs, PTH resistance has been described so far: type 2 (includes former PHP1a and 1c) due to *Gs α* inactivating mutations, type 3 (PHP1b) caused by methylation defects of *GNAS* DMRs (differentially methylated regions), type 4 (acrodysostosis type 1) through mutations of *PRKAR1A* and type 5 (acrodysostosis type 2) caused by mutated *PDE4D* [28]. Hypocalcemia is also found in vitamin D-dependent rickets type 2, an autosomal recessive disorder caused by mutated vitamin D receptor (*VDR*), as well as in vitamin D-dependent rickets type 1, due to impaired 1- α hydroxylation (*CYP27B1* mutations).

Rare growth disorders

Both molecular and endocrine dysfunctions can lead to either attenuated or accelerated linear growth resulting in short or tall stature. Disproportionate short stature is found in most subgroups of skeletal dysplasias, but molecular defects within the growth plate or connective tissue can also lead to tall stature, e.g., in Marfan syndrome. A comprehensive survey on skeletal dysplasias is given in Walleczek et al., this issue. Severe growth disorders affecting the GH/IGF-I axis have been reviewed recently [29].

Diagnosis of rare bone and growth disorders

Bone fragility disorders

Pediatric osteoporosis is defined by a clinical significant fracture history alone or in combination with impaired bone mineral density [30]. In order to identify primary bone disorders at an early stage, a more differentiated approach including typical clinical features of osteogenesis imperfecta or hypophosphatasia has recently been proposed [31]. On suspicion, specialized clinical and lab assessment, lateral spine imaging for vertebral fractures and, if indicated, genetic analyses for OI are recommended to reduce diagnostic delays.

Rickets

Comprehensive assessment for rickets aims to distinguish vitamin D deficiency from rare genetic types such as XLH or renal causes, e.g., Fanconi syndrome. In the clinical presence of rickets, relatively normal 25(OH)D values despite increased low age specific serum phosphate values are typical findings in XLH. Further diagnostics include urinary analysis (TmP/GFR, Fanconi assessment), ALP, PTH and—if available—intact serum FGF23. All patients with suspected genetic types of hypophosphatemic rickets should undergo genetic diagnostics [24].

Growth disorders

The measurement of body proportions helps to direct diagnostics to first-line endocrine (proportional short stature) or non-endocrine reasons for short stature. Disproportionate growth disorders, together with symptoms affecting the skeletal system or connective tissue point to a genetic disorder and prompt genetic analysis and radiological investigations (see Walleczek et al. this issue and Mehany and Patsch, this issue). Comprehensive reviews on the diagnostic work-up are available [32].

Role of bone biopsy in rare bone disorders

Many clinically important conclusions have been drawn from bone biopsies during clinical studies in OI and other rare bone diseases. Sophisticated techniques help to evaluate bone material quality but also aspects of mineralization, as reviewed by Mähr et al. in this issue.

Therapies

Detailed treatment recommendations are beyond the scope of this article (we refer to Kocijan in this issue and recently published consensus guidelines). A few important principles referring to rare pediatric bone disorders are summarized as follows:

Pharmacological therapies

Bone fragility

Pharmacologic interventions for pediatric osteoporosis is predominantly based on bisphosphonates. Data derived from patient cohorts with OI could show a clear improvement of bone mineral density as well as reduction of skeletal pain. While data on bone fracture rates is not entirely clear, bisphosphonates are standard of care for pediatric patients with OI and are increasingly applied for other indications such as secondary osteoporosis, giant cell aneurysm or chronic recurrent multifocal osteomyelitis [33].

Hypophosphatemic rickets

Conventional treatment of hypophosphatemic rickets consists of oral phosphate salts and active vitamin D derivatives. Due to its short half-life time, phosphate has to be given in 3–6 doses/day, leading to frequent compliance issues. Treatment has to be initiated at optimum in the neonatal period for an optimized clinical benefit. Global approval of an FGF23 blocking antibody opened a novel therapeutic perspective for patients with XLH. Subcutaneous application of burosumab reduces renal phosphate excretion and normalizes serum phosphate in a majority of XLH patients. Nevertheless, both treatment options are only improving the phenotype with persisting growth restriction and unclear effects on dental and cranial symptoms [24].

Hyper- and hypocalcemia

Acute hypo- and hypercalcemia are emergencies and should be treated according to published recommendations [25, 26, 34]. One should take in consideration the underlying disorder when substituting calcium and vitamin D; for *CaSR* mutations, this substitution should be reserved for the symptomatic phases.

The multidisciplinary team

Most complex skeletal disorders typically affect many organ systems, thus, stressing the need for coordinated multidisciplinary care. Osteology, orthopedics, radiology, neurology and neurosurgery, functional therapies and psychology are among the main disciplines involved in long-term care for this vulnerable patient group.

Specialized orthopedic treatments are an essential component of multidisciplinary care in pediatric bone disorders. Specialized assessment, well-coordinated planning of interventions and conservative treatments have to be adapted to the conditions' characteristics and individual patient's needs (reviewed in Mindler et al. this issue, Willeger et al. this issue).

Measures of success

Initiatives such as European Reference Networks facilitated the formation of expert centers able to provide sufficient structures to ensure high-quality, cost-effective multidisciplinary care. Strong cooperation with patient groups as well as the transnational exchange and clinical studies represent key elements of future individualized patient care and will help to improve life quality and disease awareness. In this context, patient registries, definitions of measures of success by evidence-based instruments with a focus on patient reported outcomes is essential. This includes parameters of inclusion and participation, mobility, reduction of pain, comprehensive quality-of-life measures adapted to the respective condition, and identification of treatment goals.

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Conflict of interest A. Raimann, D.-A. Ertl and G. Haeusler declare that they have no competing interests.

References

- Robling AG, Bonewald LE. The Osteocyte: new insights. *Annu Rev Physiol*. 2020;82(1):485–506.
- Kim J-M, Lin C, Stavre Z, Greenblatt MB, Shim J-H. Osteoblast-osteoclast communication and bone homeostasis. *Cells*. 2020;9(9):2073. <https://doi.org/10.3390/cells9092073>.
- Udagawa N, Koide M, Nakamura M, Nakamichi Y, Yamashita T, Uehara S, et al. Osteoclast differentiation by RANKL and OPG signaling pathways. *J Bone Miner Metab*. 2020. <https://doi.org/10.1007/s00774-020-01162-6>.
- Hunziker EB. Mechanism of longitudinal bone growth and its regulation by growth plate chondrocytes. *Microsc Res Tech*. 1994;28(6):505–19.
- McKee M, Cole W. Bone matrix and mineralization. In: Glorieux F, Pettifor J, Juppner H, editors. *Pediatric Bone. Biology and Diseases*. Amsterdam: Elsevier; 2012. pp. 9–37.
- Kronenberg HM. Developmental regulation of the growth plate. *Nature*. 2003;423(6937):332–6.
- Zaidi M, Yuen T, Sun L, Rosen CJ. Regulation of skeletal homeostasis. *Endocr Rev*. 2018;39(5):701–18.
- Hallett SA, Ono W, Ono N. Growth plate chondrocytes: skeletal development, growth and beyond. *Int J Mol Sci*. 2019;20(23):6009. <https://doi.org/10.3390/ijms20236009>.
- Chung U, Lanske B, Lee K, Li E, Kronenberg H. The parathyroid hormone/parathyroid hormone-related peptide receptor coordinates endochondral bone development by directly controlling chondrocyte differentiation. *Proc Natl Acad Sci U S A*. 1998;95(22):13030–5.
- Haeusler G, Raimann A, Egerbacher M. Growth plate research. In: Pietschmann P, editor. *Principles of bone and joint research*. Berlin Heidelberg: Springer; 2017. pp. 153–71. *Learning Materials in Biosciences*.
- Golub EE. Role of matrix vesicles in biomineralization. *Biochim Biophys Acta*. 2009;1790(12):1592–8.
- Orimo H. The mechanism of mineralization and the role of alkaline phosphatase in health and disease. *J Nippon Med Sch*. 2010;77(1):4–12.
- Rowe PSN. Regulation of bone–renal mineral and energy metabolism: the PHEX, FGF23, DMP1, MEPE ASARM pathway. *Crit Rev Eukaryot Gene Expr*. 2012;22(1):61–86.
- Florencio-Silva R, Sasso GRS, Sasso-Cerri E, Simões MJ, Cerri PS. Biology of Bone tissue: structure, function, and factors that influence bone cells. *Biomed Res Int*. 2015;2015:421746. <https://doi.org/10.1155/2015/421746>.
- Siddiqui JA, Partridge NC. Physiological bone remodeling: systemic regulation and growth factor involvement. *Physiology*. 2016;31(3):233–45.
- van der Eerden BCJ. Systemic and local regulation of the growth plate. *Endocr Rev*. 2003;24(6):782–801.
- Lui JC, Nilsson O, Baron J. Growth plate senescence and catch-up growth. *Endocr Dev*. 2011;21:23–9.
- Kaplan SA, Cohen P. REVIEW: the Somatomedin hypothesis 2007: 50 years later. *J Clin Endocrinol Metab*. 2007;92(12):4529–35.
- Mortier GR, Cohn DH, Cormier-Daire V, Hall C, Krakow D, Mundlos S, et al. Nosology and classification of genetic skeletal disorders: 2019 revision. *Am J Med Genet A*. 2019;179(12):2393–419.
- Etich J, Rehberg M, Eckes B, Sengle G, Semler O, Zaucke F. Signaling pathways affected by mutations causing osteogenesis imperfecta. *Cell Signal*. 2020;76:109789.
- Saraff V, Högl W. Osteoporosis in children: diagnosis and management. *Eur J Endocrinol*. 2015;173(6):R185–97.
- Van Dijk F, Sillence D. Osteogenesis imperfecta: clinical diagnosis, nomenclature and severity assessment. *Am J Med Genet A*. 2014;164(6):1470–81.
- Boulet C, Madani H, Lenchik L, Vanhoenacker F, Amal Nath DS, de Mey J, et al. Sclerosing bone dysplasias: genetic, clinical and radiology update of hereditary and non-hereditary disorders. *Br J Radiol*. 2016;89(1062):20150349. <https://doi.org/10.1259/bjr.20150349>.
- Haffner D, Emma F, Eastwood DM, Duplan MB, Bacchetta J, Schnabel D, et al. Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. *Nat Rev Nephrol*. 2019;15(7):435–55.
- Stokes VJ, Nielsen MF, Hannan FM, Thakker RV. Hypercalcemic disorders in children. *J Bone Miner Res*. 2017;32(11):2157–70.
- Allgrove J, Shaw NJ, editors. *Calcium and Bone disorders in children and adolescents*. Book: Karger; 2015.
- Bringhurst FR, Demay MB, Kronenberg HM. Hormones and disorders of mineral metabolism. In: *Williams textbook of endocrinology*. Amsterdam: Elsevier; 2011. pp. 1277–94.
- Thiele S, Mantovani G, Barlier A, Boldrin V, Bordogna P, De Sanctis L, et al. From pseudohypoparathyroidism to inactivating PTH/PTHrP signalling disorder (IPPSD), a novel classification proposed by the EuroPHP network. *Eur J Endocrinol*. 2016;175(6):P1–17.
- Jee YH, Baron J, Nilsson O. New developments in the genetic diagnosis of short stature. *Curr Opin Pediatr*. 2018;30(4):541–7.
- Pediatric Positions. ISCD. <https://iscd.org/learn/official-positions/pediatric-positions/>. Accessed 14 Nov 2020.
- Ward LM, Weber DR, Munns CF, Högl W, Zemel BS. A contemporary view of the definition and diagnosis of osteoporosis in children and adolescents. *J Clin Endocrinol Metab*. 2020;105(5):e2088–97.
- Collett-Solberg PF, Ambler G, Backeljauw PF, Bidlingmaier M, Biller BMK, Boguszewski MCS, et al. Diagnosis, Genetics, and Therapy of Short Stature in Children: A

- Growth Hormone Research Society International Perspective. *Horm Res Paediatr*. 2019;92(1):1–14.
33. Simm PJ, Biggin A, Zacharin MR, Rodda CP, Tham E, Siarifikas A, et al. Consensus guidelines on the use of bisphosphonate therapy in children and adolescents. *J Paediatr Child Health*. 2018;54(3):223–33.
34. Davies JH. A practical approach to problems of Hypercalcaemia. *Calcium Bone Disord Child Adolesc*. 2009;16:93–114.

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