Chapter 1

Growth Hormone Axis in Skeletal Dysplasias

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Additional information is available at the end of the chapter

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Abstract

Introduction: Skeletal dysplasias, also termed as osteochondrodysplasias, are a large heterogeneous group of disorders characterized by abnormalities of bone or cartilage growth or texture. They occur due to genetic mutations and their phenotype continues to evolve throughout life. Reduced growth is a common feature.

Objective: To evaluate and discuss data about growth and growth hormone axis in patients with the main common skeletal dysplasias, such as achondroplasia, hypochondroplasia, 3M syndrome, and Leri-Weill syndrome.

Design: Evaluate retrospectively the data on growth, final height (FH), height velocity (HV), growth hormone deficiency, and growth hormone response after growth hormone (GH) treatment in patients with these disorders. However, this chapter provides an updated picture of growth hormone axis and endocrinological features in skeletal dysplasia.

Keywords: growth, growth hormone, skeletal dysplasia

1. Introduction

Skeletal dysplasias are a genetically and clinically heterogeneous group of disorders associated with generalized abnormalities in the skeleton. Collectively the birth incidence is estimated to be about 1:5000 live births [1], but it is probably underestimated due to the large amount of undiagnosed cases. The most evident clinical aspects are the skeletal abnormalities, which can anyway be associated to orthopaedic, neurologic, auditory, visual, pulmonary, cardiac, renal

and psychological complications. The clinical expression of these pathologies can range from a precocious arthropathy in otherwise healthy individuals to severe dwarfism with perinatal mortality [2].

Many different types of dysplasias have been described and classified depending on the clinical, radiological and genetic aspects. In the latest 2015 version of nosology, compared to the one of 2011, the overall number has decreased to 436 disorders, but the number of groups has increased to 42 and the number of genes to 364 [3] (**Table 1**).

Type	Composition	Distribution	Pathology	Gene	Location
I	$\alpha1[I]_2\alpha2[I]$	Dermis, bone, tendon, ligament	Osteogenesis imperfecta (OI) I, II, III, IV, VIIA. Ehler-Danlos syndrome (EDS) classic	*COL1A1, OI1, OI2, OI3, OI4, EDSC*	17q21.33
			OI II, OI III, OI IV, OI VIIB, EDS (valvular form), osteoporosis	*COL1A2*	7q21.3
II	$\alpha1[II]_3$	Cartilage, vitreous	Otospondylomegaepiphyseal dysplasia, spondyloperipheral dysplasia, osteoarthritis with mild chondrodysplasia, spondyloepiphyseal dysplasia, Stanescu type, achondrogenesis, type II or hypochondrogenesis, SMED Strudwick type, vitreoretinopathy with phalangeal epiphyseal dysplasia, Kniest dysplasia, SED congenita, Stickler syndrome, type I, epiphyseal dysplasia, multiple, with myopia and deafness, platyspondylic skeletal dysplasia, Torrance type, stickler syndrome, type I, nonsyndromic ocular, Czech ?? dysplasia	*COL2A1*	12q13.11
III	$\alpha1[III]_3$	Skin, blood vessels, intestine	Ehler-Danlos syndrome type IV	*COL3A1*	2q32.2
IV	$\alpha1[IV]_2\alpha2[IV]$ $\alpha3[IV]$ $\alpha4[IV]$ $\alpha5[IV]$ $\alpha5[IV]$, $\alpha6[IV]$	Basement membranes	Susceptibility to intracerebral, haemorrhage, porencephaly, brain small vessel disease with or without ocular anomalies, angiopathy, hereditary, with nephropathy, aneurysms, and muscle cramps Susceptibility to intracerebral haemorrhage, porencephaly	*COL4A1,POREN1, HANAC, ICH, BSVD* *COL4A2, POREN2, ICH* *COL4A3* *COL4A4* *COL4A5, ATS, ASLN*	13q34 13q34 2q36.3 2q36.3 Xq22.3

Type	Composition	Distribution	Pathology	Gene	Location
			Alport syndrome (autosomal recessive and autosomal dominant), familial benign haematuria		
			Alport syndrome, familial benign haematuria		
			Alport syndrome		
V	$\alpha1[V]_3$	Bone, dermis,	Ehler-Danlos syndrome (classic type)	*COL5A1, EDSC*	9q34.3
	$\alpha1[V]_2\,\alpha2[V]$	cornea, placenta	Ehler-Danlos syndrome (classic type)	*COL5A2, EDSC*	2q32.2
	$\alpha1[V]\,\alpha2[V]$ $\alpha3[V]$		–	*COL5A3*	19p13.2
VI	$\alpha1[VI]\,\alpha2[VI]$ $\alpha3[VI]$	Bone, dermis, cornea, cartilage	Bethlem myopathy, Ullrich congenital muscular dystrophy 1	*COL6A1, BTHLM1, UCHMD1*	21q22.3 21q22.3
	$\alpha1[VI]\,\alpha2[VI]$ $\alpha4[VI]$		Bethlem myopathy, Ullrich congenital muscular dystrophy 1	*COL6A2, BTHLM1, UCMD1*	2q37.3 3q22.1,
			Bethlem myopathy, Ullrich congenital muscular dystrophy 1, segmental isolated dystonia	*COL6A3,, DYT27, BTHLM1, UCMD1*	3p25.1 3q22.1
			–	*COL6A4*	3q22.1
			–	*COL6A5, COL29A1*	
			–	*COL6A6*	
VII	$\alpha1[VII]_2$ $\alpha2[VII]$	Dermis, bladder	Epidermolysis bullosa, Isolated toenail dystrophy	*COL7A1, NDNC8*	3p21.31
VIII	$\alpha1[VIII]_3$ $\alpha2[VIII]_3$	Dermis, brain, heart, kidney	– Corneal dystrophy	*COL8A1*	3q12.1
	$\alpha1[VIII]_2$ $\alpha2[VIII]$			*COL8A2, FECD1, PPCD2*	1p34.3
IX	$\alpha1[IX]\,\alpha2[IX]$ $\alpha3[IX]$	Cartilage, cornea, vitreous	Stickler syndrome type IV, multiple epiphyseal dysplasia	*COL9A1, EDM6, STL4COL9A2, EDM2,*	6q13 1p34.2
			Stickler syndrome type V, multiple epiphyseal dysplasia	*STL5COL9A3, EDM3, IDD*	20q13.33
			Multiple epiphyseal dysplasia with miopathy, multiple epiphyseal dysplasia		
X	$\alpha1[X]_3$	Cartilage	Metaphyseal chondrodysplasia type Schmid	*COL10A1*	6q22.1
XI	$\alpha1[XI]\,\alpha2[XI]$ $\alpha3[XI]$	Cartilage, intervertebral disc	Marshall syndrome, fibrochondrogenesis, Stickler syndrome type II	*COL11A1, STL2 COL11A2, STL3,*	1p21.1 6p21.32
			Deafness, Weissenbacher-Zweymuller syndrome, Stickler syndrome type III,	*DFNA13, DFNB53, FBCG2*	

Type	Composition	Distribution	Pathology	Gene	Location
			otospondylomegaepiphyseal dysplasia, fibrochondrogenesis		
XII	$\alpha1[XII]_3$	Dermis, tendon	Bethlem myopathy 2, Ullrich congenital muscular dystrophy 2	*COL12A1, UCMD2, BTHLM2*	6q13-q14
XIII	–	Endothelial cells, dermis, eye, heart	Congenital myasthenic syndrome	*COL13A1*	10q22.1
XIV	$\alpha1[XIV]_3$	Bone, dermis, cartilage	–	*COL14A1, UND*	8q24.12
XV	–	Capillaris, testis, kidney, heart	–	*COL15A1*	9q22.33
XVI	–	Dermis, kidney	–	*COL16A1*	1p35.2
XVII	–	Hemidesmosomes in epithelia	Generalized atrophic epidermolysis bullosa	*COL17A1, BPAG2, ERED*	10q25.1
XVIII	–	Basement membrane, liver	Knobloch syndrome	*COL18A1, KNO1*	21q22.3
XIX	–	basement membrane	–	*COL19A1, D6S228E, COL9A1L*	6q13
XX	–	Cornea	–	–	–
XXI	–	Stomach, kidney	–	*COL21A1*	6p12.1
XXII	–	Heart, retina	–	*COL22A1*	8q24.2–q24.3
XXIII	–	Brain, cornea	–	*COL23A1*	5q35.3
XXIV	–	Bone, cornea	–	*COL24A1*	1p22.3
XXV	–	Brain, heart, testis	Amyloid formation, Congenital fibrosis of extraocular muscles	*COL25A1, CLAC, CFEOM5*	4q25
XXVI	–	Testis, ovary	–	*SH2B1, SH2B, KIAA1299*	7q22.1
XXVII	–	Cartilage	Steel syndrome	*COL27A1, KIAA1870, STLS*	9q32
XXVIII	–	Dermis, sciatic nerve	Neurodegenerative disease	*COL28A1*	7p21.3

Table 1. Main common skeletal dysplasias.

2. Physiology

The human skeleton is a complex organ composed of 206 bones (126 appendicular, 74 axial and 6 ossicles). It strictly collaborates with the muscle, tendons and cartilages in order allow

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movement, mechanical support, linear growth and to protect internal organs. The bone is also involved in the calcium phosphorus metabolism and in the haematopoiesis.

The skeletal system develops from mesoderm. The mesodermal cells form the mesenchyme (embryonic connective tissue), which can differentiate into fibroblasts, chondroblasts, and osteoblasts. Initially, the mesenchyme appears uncondensed, then the cells come together to the sites of future bones and joints. How does it occur? Two mechanisms are involved, depending on the cell differentiation into osteoblasts or chondrocyte: there will be respectively a membranous or an endochondral ossification. The first one occurs especially in the calvaria of the skull, the maxilla, the mandible and in the subperiosteal bone, forming layer of long bones. The osteoblasts produce an extracellular matrix, called osteoid. Those of them which remain incorporated into the osteoid become osteocytes. Finally, the osteoid becomes mineralized, thus forming the mature bone tissue.

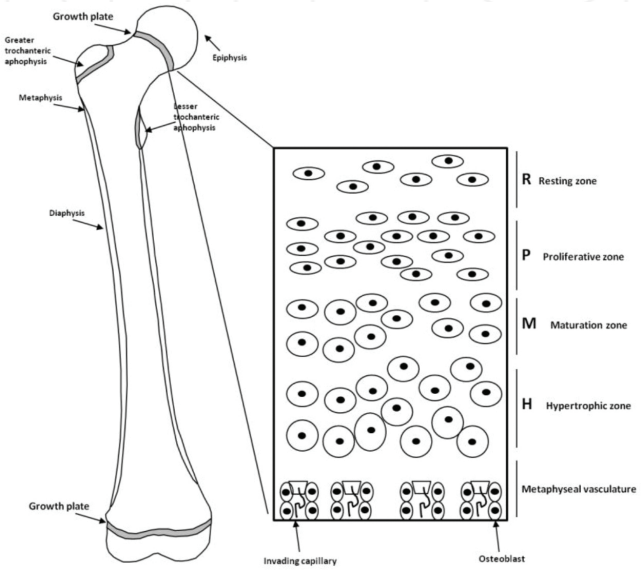

Figure 1. Anatomical representation of the femoral growth plate.

The endochondral ossification represents the mayor mechanism of formation of most of the mammalian appendicular skeleton. The first site of ossification is in the middle of the diaphysis, while the second one occurs in the epiphysis. They start from a differentiation of mesenchymal cells into chondrocytes, forming the cartilage model, which in turn, undergoes a process of proliferation, hypertrophy and degradation. Through the periosteal buds, osteoclasts (that remove the cartilage extracellular matrix (ECM)), osteoblasts (that deposit bone on cartilage remnants) and blood vessels invade the model and proceed to form the primary centre of ossification. In long bones, a secondary centre of ossification formed at each end of the cartilage model. The cartilaginous growth plate that remains between the two ossification

centres allows the linear growth until the postpubertal age, when it will be completely replaced by bone [4] (**Figure 1**). Finally, there is an appositional growth due to the periosteum's osteoblasts, leading to the formation of a bone collar that works as support for the new bone [5].

The growth plate, depending on the stage of cell's maturation, can be divided in the following zones (**Figure 1**) [6]

- The resting/germinative zone, in which the stem cells or progenitor cells continuously replace the pool of proliferative chondrocytes.
- The proliferative zone, where highly proliferating chondrocytes are disposed into column parallel to the direction of longitudinal growth and produces ECM.
- The pre-hypertrophic zone, where chondrocytes initiate the hypertrophic differentiation, characterized by IHH (Indian Hedgehog) expression (see below).
- The hypertrophic zone is constituted by enlarged chondrocytes that increase in length, thus determining the bone's lengthening; they also modify the surrounding ECM mineralizing it.
- The degeneration zone, where chondrocytes undergo rapid death before ossification.

Chondrocytes are involved in the production of the ECM, which is majorly composed by collagen. Collagens are single molecules composed by amino acid sequence of glycine-proline-X and glycine-X-hydroxyproline, where X is any amino acid other than glycine, proline or hydroxyproline. These amino acids associate into chains to form a triple helical structure. Once in the extracellular matrix, the triple helical chain undergoes several biochemical and structural modifications, becoming a fibril. The collagen family comprises 28 members that contain at least one triple-helical domain [7] and that are specifically distributed in different parts of the body. Collagens are classified in fibrillar types (I, II, III, V and XI) and non-fibrillar, depending on the structure they form in the extracellular matrix. Type I is the most expressed in the human body and with the other collagens provide mechanical strength of cartilage, bone and skin [2, 7]. Other widely represented collagens are type II (hyaline cartilage) and IV (in the basal membrane). if a mutation occurs in any of the genes encoding collagens molecules, a skeletal dysplasia can be developed.

3. Growth plate and hormones

The growth plate maturation and regulation is influenced by growth factors, local regulators and hormones (**Figure 2**). Perichondrial cells produce many different growth factors that are used as a signal to chondrocytes, but they also receive signals back from epiphyseal cells (**Figure 2**). An important role in bone formation is played by parathyroid hormone-related protein (PTHrP) and Ihh; they act directly on the differentiation and proliferation of chondrocytes and in the differentiation of osteoblast. The paracrine hormone PTHrP is expressed at high level in early proliferating chondrocytes at the end of long bones, while its receptor Pthr1 is produced at low levels by proliferating growth plate chondrocytes and at higher level in prehypertrophic cells [8]. Prehypertrophic and hypertrophic chondrocytes secrete Ihh, a

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member of the hedegehog family, which acts through the binding to receptor Patched-1 [9]. PTHrP and Ihh are connected in a feedback loop to maintain a pool of immature chondrocyte progenitors. PTHrP acts on the receptor of chondrocyte to keep them proliferating and delays the differentiation into pre-hypertrophic and hypertrophic chondrocytes. Once the cells are too far from the source of PTHrP production, in the transitional zone between proliferating and hypertrophic chondrocytes, Ihh begins to be secreted. It increases the proliferation rate and inhibits terminal differentiation of chondrocytes; moreover, it stimulates PTHrP synthesis [10]. Mutations in these two genes can cause the development of dysplasias, as for example the acrocapitofemoral dysplasia is associated with a Ihh mutation [11]. Bone morphogenetic proteins (BMPs) signal contribute to epiphyseal growth and maturation, thanks to a gradient of proteins expressed in the growth plate: BMP agonists can be found in the hypertrophic zone, while BMP antagonists in the resting zone, suggesting a role in the spatial regulation [12]. Fibroblast growth factor (FGF) signalling interact both with BMP and Ihh pathways, inhibiting chondrocyte proliferation. In fact, FGF act as antagonists of BMP signalling and negatively regulate Ihh expression, thus controlling the process of hypertrophic differentiation to the proliferation rate [13]. The role of FGF signalling is clearly demonstrated in achondroplasia, which is due to a mutation in FGF3 (fibroblast growth factor 3) receptor. Wnt signalling is then involved in chondrocytes development, differentiation and in the osteoblasts formation. The Runt family transcription factor Runx2 (runt-related transcription factor 2) and Runx3 contribute to chondrocyte hypertrophy and co-operate with TGF-β in the regulation of their maturation. TGF-β actually acts at the beginning as a stimulator of chondrocyte's differentiation, stabilizing than the epiphyseal chondrocyte in a prehypertrophic stage (**Figure 2**) [14].

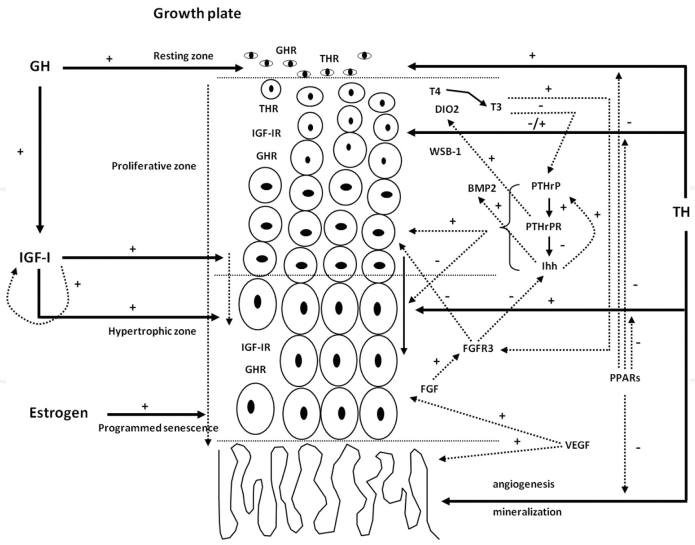


Figure 2. Main hormonal and non-hormonal actions on the growth plate. Modified by Seminara et al. [16].

Finally, the vascular endothelial growth factor seems to play a role in the epiphyseal fusion, stimulating the chondrocyte differentiation, chondrocyte survival, and the final stages of endochondral ossification. It seems to be active especially during puberty, under the stimulus of oestrogens [15]; anyway, the role it plays in oestrogen-mediated growth plate remains elusive (**Figure 2**).

As previously reported, not only growth factors but also hormones can influence bone growth. It is commonly known that sexual hormones are involved in the regulation of skeletal growth and in its maintenance. Oestrogens, especially 17β-estradiol (E2), act via the oestrogen receptor-a (ER-a); low E2 levels during sexual maturation contribute to the lengthening of the bone during the growth spurt, while high levels in the late puberty to the growth plate closure. The mechanism by which oestrogen influence bones' growth is not yet clearly understood. As oestrogens can regulate also the growth hormone-insulin growth factor-1 (GH)/IGF-1) axis, the modulation of that pathway is able to condition bone maturation: low levels of E2 increase serum GH and IGF1, enhancing the pubertal spurt [17]. Sexual hormones are mainly produced by gonads, but they can be synthetized directly in the growth plate by the aromatase or other enzymes (17β hydroxysteroid dehydrogenase, steroid sulphatase and type 1 5-α reductase) produced by the chondrocytes (**Figure 2**) [11].

Androgen stimulates bone formation linking to androgen receptor (AR) directly or as dihydrotestosterone (DHT), as well as to ER following aromatization in estradiol [18]. AR is expressed by chondrocytes and regulate their proliferation and differentiation. An increment in growth plate width after injection of testosterone directly into the growth plate of rats, support the idea that it could have a direct function. It is not well known the effect of testosterone on osteoblast cell and controversial result have been shown, anyway most *in vitro* studies indicate that androgens contribute to osteoblast progenitors proliferation, mature osteoblast differentiation and osteoblasts apoptosis inhibition (**Figure 2**) [19].

Thyroid hormones play a role in bones' growth through an action both on chondrocytes and osteoblasts. Reserve and proliferating chondrocyte in fact express thyroid hormone receptor a1 (TRa1) and TRb1, indicating that T_3 contributes directly to the epiphyseals' growth. Experiments showed that T_3 inhibits chondrocyte clonal expansion and proliferation, while stimulating chondrocyte differentiation, suggesting a role in the regulation of bone formation [20].

Studies about T_3 action on osteoblast are contradictory; anyway, it is undoubted that it contributes to stimulate osteoblast activity. In fact, T_3 promotes type I collagen synthesis and posttranscriptional modification, induces alkaline phosphatase (involved in matrix mineralization), regulates synthesis and secretion of the bone matrix proteins osteopontin and osteocalcin; it is also involved in bone remodelling enhancing the production of matrix metallopeptidase 9 (MMP-9) and -13. Furthermore, T_3 regulates IGF-1 and FGF pathways. Moreover, through the regulation of osteoprotegerine levels, T_3 can influence bone resorption (**Figure 2**) [21].

Glucocorticoids are strictly involved in growth plate regulation. Increased levels of glucocorticoids determine an inhibition of longitudinal bone's growth. It has been demonstrated that

glucocorticoids can inhibit chondrocyte proliferation, hypertrophy and cartilage matrix secretion. Glucocorticoids can affect bone also through their negative effect on muscle, influencing the normal modelling process [22]. Furthermore, glucocorticoids also slow growth plate senescence inhibiting the proliferation of the resting zone. This explains the catch up growth measured after a period of growth inhibition due to glucocorticoids excess. Once the inhibiting stimulus has been removed, the growth plates behave as "younger" growth plates, reaching the final height a bit later and more rapidly [23]. Last but not least is the role of GH and somatomedinic hormones, which will be discussed further (**Figure 2**).

4. Clinical manifestations

The main characteristic of the skeletal dysplasia is a disharmonic short stature; anyway, many other manifestations involving other organs have been described. How to recognize a dysplastic child? At first, the most important step is to examine the body proportions. Sometimes subtle degrees of the pathology could be difficult to appreciate, especially in obese or premature child.

In every child, it is essential to evaluate growth parameters such as height, weight and head circumference, but in skeletal dysplasias, these are not sufficient; it is in fact necessary to evaluate also sitting height, upper/lower segment ratio and arm span [1].

The sitting height is the distance from the vertex of the head to the surface where the child person is sitting erectly; it is used to measure the upper segment of the body. The lower segment can be calculated by subtracting the upper segment from the total height. With these parameters, it is possible to obtain the cormic index, which is the upper/lower ratio. The values of cormic index modify with age. It is important to remember that a patient with a short trunk has a decreased upper/lower segment ratio, while a short statured patient with normal trunk and relatively short limbs may have an increased upper/lower segment ratio [1]. Short trunk child could present short neck or small chest or protuberant abdomen. Depending on which part of the limb is involved, short limb dysplasias can be differentiated into three groups: rhizomelic shortening if proximal segments are involved (humerus and femur); mesomelic shortening if middle segments (radius, ulna, tibia and fibula) are involved; acromelic shortening involves distal segments as the hands and feet.

Finally, the spam arm measures the length from one fingertips to the other when arm raised parallel to the ground at shoulder height at 180° angle.

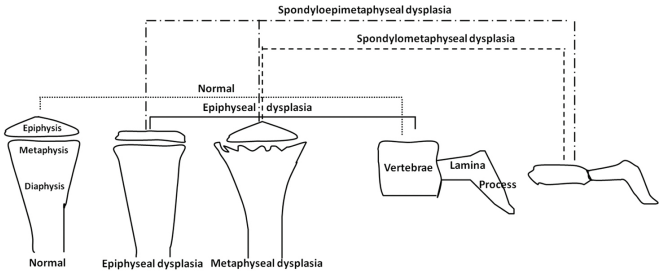
A general physical examination should always be made to detach others sign and dysmorphisms, which are useful to differentiate between numerous dysplasias. For example, the clavicular agenesis is typical of cleido-cranial dysplasia, or the blue sclera of osteogenesis imperfecta. Also facial dysmorphism can be pathognomonic: in the achondroplastic phenotype are present macrocephaly, frontal bossing, midface hypoplasia and short upturned noses; midface hypoplasia with flat nasal bridge and grey iris colour in the acrodysostosis; odontochodrodysplasia is characterized by dentinogenesis imperfecta.

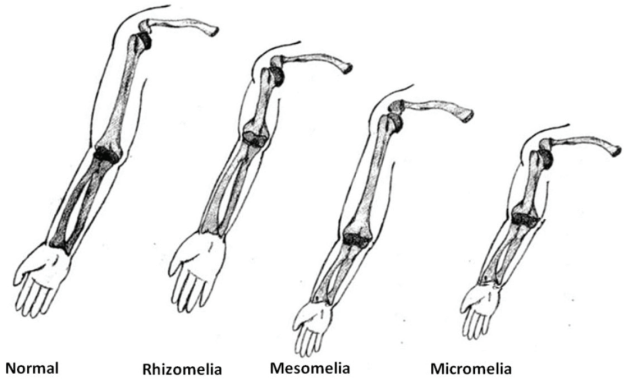
It's also important to evaluate the child during the time and repeat the physical examination to notice other manifestation involving or the skeleton, like abnormal joint mobility or angular deformities (that usually are symmetric), or other organs, depending on the role of the gene involved.

Finally, it is essential to pay serious attention to major problems associated with skeletal dysplasia; for example, there is an increased risk to develop pneumonia due to a reduced pulmonary volume secondary to the short ribs or spinal cord compression at the cervical medullar junction due to an abnormal growth of the base of the skull and the vertebral pedicles. In Larsen syndrome, a cervical spine dislocation is described and it is due to a subluxation or fusion of the vertebral bodies, usually associated with posterior vertebral arch dysraphism; the damage of the cord can cause a secondary paralysis.

5. Classification

The classification of skeletal dysplasias is based on clinical, radiographic and molecular criteria (**Figures 3** and **4**). The first international classification was established in 1969 [24]. In





Figures 3 and 4. Cartoons that show the different portions of the appendicular skeleton that manifest radiographic abnormalities aiding in the clinical classification of the skeletal dysplasias.

1992, the diseases were grouped depending on radiological similarities [25], based on the concept of families proposed by Spranger (1985). Since then, the integration of clinical and radiological aspect of skeletal dysplasia was helpful in identification of disease-related genes. Gradually, phenotypically overlapping diseases were separated in different families depending on the rearranged genes. As substantial advances have been made in molecular and genetic field, classification and nomenclature must be constantly updated. The most recent classification has been made by Bonafe et al. in Nosology and Classification of Genetic Skeletal Disorders: 2015 Revision [3].

Based on the epidemiological and clinical aspects, skeletal dysplasias can be further subdivided in order to simplify the diagnostic approach [26, 27]:

- Depending on the neonatal lethality:
  - Usually fatal
    - Achondrogenesis
    - Thanatophoric dysplasia
    - Short rib polydactyly
    - Homozygous achondroplasia
    - Camptomelic dysplasia
    - Dyssegmental dysplasia, Silverman-Handmaker type
    - Osteogenesis imperfecta, type II
    - Hypophosphatasia (congenital form)
    - Chondrodysplasia punctate (rhizomelic form)
  - Often fatal
    - Asphyxiating thoracic dystrophy (jeune syndrome)
  - Occasionally fatal
    - Ellis-van Creveld syndrome
    - Diastrophic dysplasia
    - Metatropic dwarfism
    - Kniest dysplasia
- Recognizable at birth or within first month of life:
  - Most common
    - Achondroplasia
    - Osteogenesis imperfecta (types I, III, IV)

- Spondyloepiphyseal dysplasia congenital
- Diastrophic dysplasia
- Ellis-van Creveld syndrome

◦ Less common

- Chondrodysplasia punctate
- Kniest dysplasia
- Metatropic dysplasia
- Langer mesomelic dysplasia

5.1. Radiological features

To evaluate dysplastic patients, plain films of the entire skeleton should be evaluated (**Figures 5–10**).

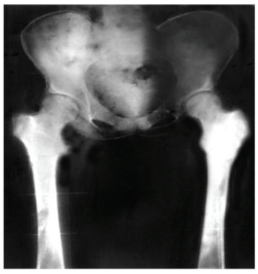


Figure 5. Achondroplasia. Squared and short ilia.

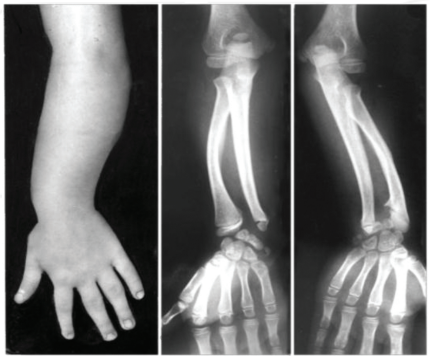


Figure 6. Leri-Weill dyschondrosteosis. Short forearms and bowing radius.

- As suggested by Amaka et al., a systematic approach to the skeletal survey has to be maintained. At first, it is important to define the anatomical localization of the abnormalities. Particularly, alteration of appendicular skeleton can involve the epiphysis, metaphysis or diaphysis; depending on the part involved, shortening of appendix is called rhizomelic, if proximal, mesomelic, if in the middle, acromelic, if distal or micromelic, if there is a generalized shortening of the limb. Finding very small epiphysis (due to a delay in ossification) or irregularly ossified epiphysis, radiologically suggest an epiphyseal dysplasia. Instead, the widening, the cortical thickening or the expansion/reduction of marrow space are characteristics of a diaphyseal dysplasia. The diagnosis of metaphyseal dysplasia is done if a widened, flared or irregular methapysis is found [28]. If even the spine is involved, these pathologies can be further differentiated in spondyloepiphyseal, spondylometaphyseal dysplasias [SMDs], or spondyloepimetaphyseal dysplasias [SEMDs] [2].

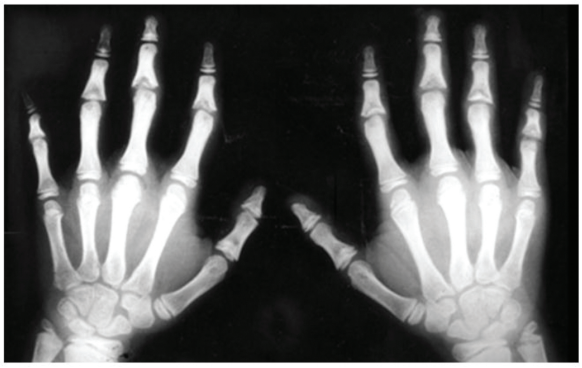


Figure 7. Trichorhinophalangeal syndrome I. Short metacarpals, especially the fourth and fifth; cone-shaped epiphyses.

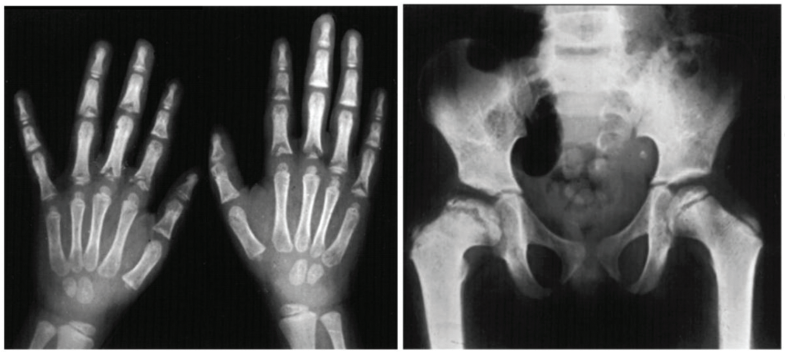


Figure 8. Trichorhinophalangeal syndrome II. Metaphyseal hooking at the proximal ends of several of the middle phalanges. Perthes-like changes in capital femoral epiphysis.

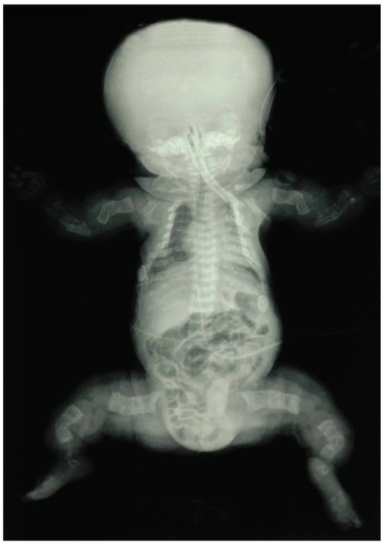


Figure 9. Type II osteogenesis imperfecta. Narrow chest. Short, broad, crumpled femora.

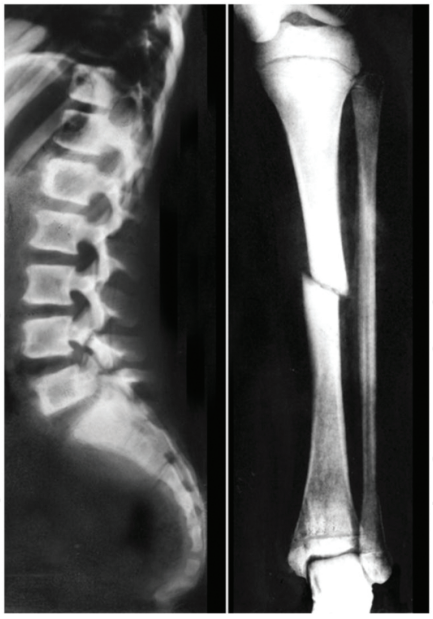


Figure 10. Pycnodysostosis. Lateral thickening of the vertebral bodies. Typical fracture of the long bone.

While examining the bones, the five "S" rules should be remembered:

- *Structure*: general appearance of bones, as alterations in bone density and their distribution
- *Shape*: certain bone shape is representative of specific pathologies (e.g. hooked vertebral bodies in mucopolysaccharidosis, horizontal trident acetabular roofs in achondroplasia).
- *Size*: size abnormalities can be absolute or relative to other bones. Bones can be described as tall, short, large, broad or hypoplastic
- *Sum*: the total number of bones; sometimes they are too many, too few or fuse (absent patella in nail-patella syndrome or absent radius in TAR syndrome, multiple epiphyseal centres in the patella I some form of diastrophic dysplasia)
- *Soft tissue*: wasting or excessive soft tissues, contractures and calcifications should be looked for, as they are involved in patient's prognosis.

The research of complications is important to have a complete picture of the patient. Fracture due to osteoporosis or osteopetrosis, atlantoaxial subluxation in mucopolysaccharidosis, progressive scoliosis are only few examples of the variety of the clinical scene [29].

The latest guideline about radiological classification of skeletal dysplasias points out four groups, as follow:

- GROUP 1: Epiphyseal dysplasias with/without spine involvement (Platyspondyly +/-);
- GROUP 2: Metaphyseal dysplasias with limb shortening/abnormal limb length;
- GROUP 3: Dysplasias with altered bone density;
- GROUP 4: Miscellaneous dysplasias, that is, those which do not typically have limb shortening or be clearly bracketed anatomically into sponylo-epi/metaphyseal dysplasias [28].

6. Growth in skeletal dysplasias

Skeletal dysplasias, as previously explained, affect both the linear growth and the body proportion; particularly, the growth of the legs and arms is often more compromised than the trunk [30], as well as we can discover in the ACH. In one-fourth of cases of skeletal dysplasias, the short growth is detectable since the prenatal age, while in the three-fourths remaining in the first two-three years of life. The final height is usually below 3 SD; here are presented the ranges of adult height for the most common dysplasis (**Table 2**).

Actually, the growth pattern of these rare pathologies has not been completely understood yet, because of the scarcity of data in the international literature. Therefore, it is difficult to establish whether the child grows under the standard centiles in a linearly way or if there are peculiar moment of important growth decrement. Furthermore, the same pathology can present with different phenotypes, even in the same family, thus causing other obstacle in the standardization of these children's growth.

However, because of many data regarding auxological longitudinal growth in many condition of bone dysplasia is lacking, knowledge on growth pattern is available only for a few skeletal dysplasias. It is interesting to note that different skeletal dysplasias seem to show similar growth pattern, as well as ACH, diastrophic dysplasia and cartilage-hair dysplasia. For example, in achondroplasia foetal growth is almost normal with a birth length ranging from −1.4 to 1.8 SD (**Figure 11**).

Condition	Adult height, cm
Achondroplasia	106–142 (mean: ♂ 132 cm and ♀ 125 cm)
Hypochondroplasia	132–147
Diastrophic dysplasia	86–122 (mean: ♂ 136 cm and ♀ 129 cm)
Metaphyseal dysplasia McKusick type	105–145 (mean: ♂ 131 cm and ♀ 123 cm)
Metaphyseal dysplasia Schmid type	130–160
Chondrodysplasia punctata Conradi-Hünermann type	130–160
Chondroectodermal dysplasia	106–153
Multiple epiphyseal dysplasia	137–155
Pyknodysostosis	130–150
Spondyloepiphyseal dysplasia congenital	84–132
Kniest dysplasia	104–145

Modified by [24].

Table 2. Ranges of adult height in the main skeletal dysplasia (irrespective of gender). Modified by [24].

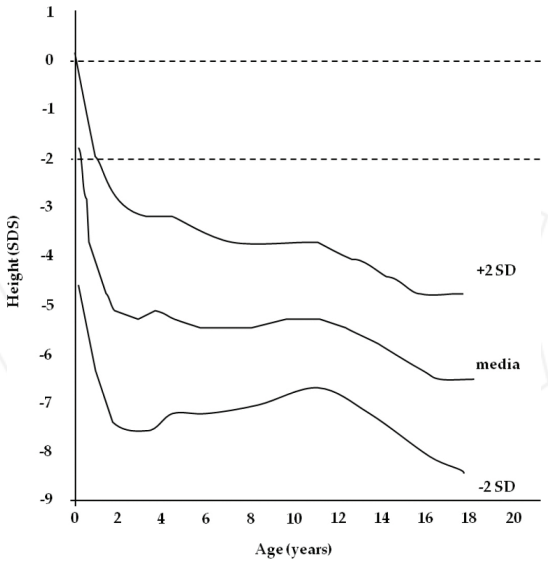


Figure 11. Mean height expressed in SDS for age in Caucasian boys and girls with achondroplasia (modified by [24]).

Hence, linear growth is fairly normal for the first postnatal months followed by a significative reduction of growth velocity and length to about –5 SD at 2 years of age. Finally, this position is maintained during the prepubertal years with a further loss during puberty (**Figure 11**).

7. Growth hormone (GH) and GH axis

The growth hormone (GH) is a polypeptide made by 191 amino acids, synthesized by somatotrope cells and stored in the anterior pituitary gland. GH is encoded by *GH1* gene situated on the long arm of chromosome 17 at position 24.2 (OMIM *139250), even if this function is regulated by a cluster of five genes strictly related. Mutations or deletions of one of these genes lead to growth hormone deficiency, resulting in short stature.

GH secretion mechanism is regulated by some hormones, principally the growth hormone releasing hormone (GHRH), the somatostatin (STT) and the Ghrelin. GHRH is a peptide produced in the hypothalamus that activates the production in and release of GH from the pituitary; GHRH binds to specific receptors, a seven transmembrane domain receptor member of the family of G-protein-coupled receptors, and located on the somatotrope cells [31]. However, STT is peptidic hormone inhibiting the release but not the GH production; STT is present in the hypothalamus but also in other part of central nervous system and in extra-nervous tissues as D-pancreatic cells, gastrointestinal cells and parafollicular thyroid cells. SST binds to a specific receptors located on the somatotrope cells, but this kind of receptors is tied to inhibitor G protein; so that way when the SST binds its receptors, it will be an inhibition of adenylate cyclase and so a decrease of c-AMP. The final result is an arrest of GH secretion from the cells.

Ghrelin, first identified in 1999 by Kojima et al. [32] is a 28 amino-acid hormone mainly synthesized in the stomach and also in the hypothalamus arcuate nucleus. Ghrelin regulation and function are very complexed, in fact it is regulated by a lot of external stimuli, such as the food intake, that decrease its secretion, instead food deprivation, hypoglycaemia and leptin administration increased this hormone [33]. Ghrelin acts directly on somatotropes cell and indirectly stimulate the release of GHRH.

GH secretion is also related to external mechanisms, such as stress, hypoglycaemia, sex hormones secretion, starvation, sleep or exercise, all condition increasing its secretion. On the contrary, other factors like hyperglycaemia, dopamine or glucocorticoid decrease it. However, many data demonstrate a bipotential action of glucocorticoid on GH secretion. In fact, while physiological level of cortisol is essential to maintain the GH axis, elevated amounts of glucocorticoid seem to increase STT levels, and so reduce GH secretion [34].

The feedback represents the most important regulatory mechanism and involves the GH, GHRH, SST and IGF-1. GH makes an auto-feedback that leads a decreased of GHRH secretion, and so that way it reduces itself. Moreover, GH stimulates SST secretion from the hypothalamus and so an ulteriore GHRH inhibition. Moreover, GHRH and SST may be able to regulate themselves reciprocally, regulating GH secretion not only acting on adenohypophysis, but also

on hypothalamus. Finally, IGF-1 operates a double feedback mechanism; from one side, it inhibits GH secretion directly, and from the other side, it acts indirectly stimulating SST secretion and inhibiting GHRH secretion [34].

During the childhood GH and thyroxine are the most relevant molecules involved in linear growth; so if there is an inadequate GH secretion linear growth slows down, and we can notice a clinical short stature, usually harmonic one. However, at puberty, the activation of the hypothalamic-gonadal axis leads to a significant increase in 24-h GH, probably because of an interaction between more factors. In fact, the presence of sex hormones causes an increase of GHRH, GH and IGF-1 secretion, a decrease of SST secretion and a reduced IGF-1 negative feedback. The result is a physiological and self-limiting hypersomatotropism that it leads to the definitive stature. In this period of life, an important increase of plasma IGF-1 concentrations was observed, leading to the growth velocity peak. Then, during puberty-adult age transition, there is a decrease of GH and IGF-1 plasma concentrations [35].

8. GH-IGF-1 axis and GH treatment in skeletal dysplasias

Most patients with skeletal dysplasia show severe short stature. Surgical therapy has been attempted to correct bone deformities, but therapy conducted to improve severe short stature has been rarely attempted. However, the optimal management of physiologically and clinically heterogeneous bone disorders requires an understanding of their medical and psychosocial complications.

Syndrome	Author	Description	Outcome and results
AAA (Triple A)	Marín S. et al. (2012), [39]	A patient with a primary growth hormone (GH) insensitivity and triple A syndrome	The treatment could have had an inhibitory effect on 11β-hydroxysteroid dehydrogenase type 1 activity
Aarskog syndrome	Darendeliler F et al. (2003), [40]	The use of GH to promote growth in children with Aarskog syndrome	No adverse events were noted
Achondroplasia (ACH)	Tanaka H. (1998), [41] Liu J et al. (2015)*, [42]	GH may be beneficial in the treatment of short stature in ACH patients with subnormal GH secretion*	This may also be introduced into the medical management of ACH
Bartter syndrome	Buyukcelik M et al. (2012), [43]	Three children with Bartter syndrome and GH deficiency (GHD)	An excellent adjunctive treatment
Cartilage-hair hypoplasia (CHH)	Harada D et al. [44]	Seven years of GH treatment suggested that GH treatment significantly improved his	GH may be considered to be an efficient treatment for CHH

Syndrome	Author	Description	Outcome and results
		disturbed bone growth and had also positive efficacy to keep growth rate	
CHARGE syndrome	Esposito A et al. (2014), [45]	GHD diagnosis. GH treatment was associated with a great improvement in growth rate and resulted in a final height appropriate to his genetic target	Without any adverse event
Costello syndrome	Blachowska E et al. (2016), [46]	In cases of documented: GHD	Only under close oncologic and cardiologic supervision
Down syndrome	Annerén G et al (1999), [47]	To study the effects of GH on linear growth and psychomotor development	GH treatment ameliorates growth velocity but not affects mental or gross motor development
	Annerén G et al. (2000), [48]	15 young children with Down syndrome treated with GH	Height SDS significantly ameliorates in Down syndrome and growth velocity declined after the stop of the treatment
	Meguri K et al. (2013)*, [49]	Twenty subjects were investigated in this study*	GH is not recommended in children with Down syndrome who have not been diagnosed with GHD. GH therapy was effective for Down syndrome short stature accompanied by GHD*
Dubowitz syndrome	Hirano T et al. (1996), [50]	A child with Dubowitz syndrome, who was found to have complete GHD	He responded to GH therapy
Ellis-van Creveld syndrome (EvC)	Versteegh FG et al. (2007), [51]	Four were GHD and four were GH sufficient	In all patients treated with GH, first year growth velocity increased. In three of the four GHD and in one GH-sufficient patient a gain in height SDS was noted
Floating-Harbor syndrome (FHS)	García RJ (2012), [52]	GH treatment led to an increase in serum IGF-1 in the upper normal range,	The growth response was modest
Hypochondroplasia (HCH)	Tanaka N et al. (2003), [53]	Comparison with ACH	Short-term GH treatment in HCH is effective to increase growth rate
IMAGe	Pedreira CC et al. (2004), [54]	A patient with isolated GHD	
Kearns-Sayre syndrome	Berio A et al. (2013) [55]	A case with partial GHD	

Syndrome	Author	Description	Outcome and results
Mandibuloacral dysplasia	Agarwal AK et al. (2008), [56]	GH therapy from the ages of 3–7 years	Did not improve the short stature
Meier-Gorlin syndrome	de Munnik SA et al. (2012), [57]		GH therapy (n = 9) was generally ineffective, though in two patients with significantly reduced IGF1 levels, growth was substantially improved by GH treatment, with 2SD and 3.8 SD improvement in height
Monosomy 18p	Schober E et al.(1995), [58]		Excellent response to GH-treatment
Netherton	Aydın BK (2014), [59]	Three patients with NS who had growth retardation associated with GHD	Responded well to GH therapy
Osteogenesis imperfecta	Antoniazzi et al. [60]	30 prepubertal children with OI (type I, IV, and III) being treated with neridronate and GH	The combined rGH-Bp treatment may give better results than Bp treatment alone, in terms of BMD, lumbar spine projected area and growth velocity, particularly in patients with quantitative defects
PHACE	Merheb M et al. (2010), [61]	Improved her growth rate	Good clinical outcome
Prader-Willi syndrome	Bakker NEJ (2015), [62] Deal CL et al. (2013)*, [63]	A randomized controlled trial and longitudinal study A systematic review*	Beneficial effect of GH treatment on health-related quality of life in children with Prader-Willi syndrome Exclusion criteria should include severe obesity, uncontrolled diabetes mellitus, untreated severe obstructive sleep apnea, active cancer, or psychosis*
Pycnodysostosis	Karamizadeh Z et al. (2014), [64]	8 children. All of the patients had GHD	Positive impact on the linear growth
RASopathies	Tamburrino F et al. (2015), [65]	Starting early during childhood, resulted in a positive height response compared with untreated patients	No significant change in bone age velocity, body proportions, or cardiovascular function was observed
Ring chromosome 15	Nuutinen M wt al. (1995), [66]	severe growth retardation is a major finding	The good growth response

Syndrome	Author	Description	Outcome and results
Ring chromosome 18	Thomas JV et al. (2006), [67]	GHD was made due to low GH levels	The hGH therapy did not improve growth velocity
SHOX deficiency Leri-Weill dyschondrosteosis, and Langer mesomelic dysplasia	Blum WF, (2013), [68] Lughetti L et al. (2010), [69]		Similar long-term efficacy as seen in girls with TS
Silver-Russell syndrome	Binder G (2013), [70]		GH improved adult height in SRS to a comparable degree
Smith-Magenis syndrome	Itoh M et al. (2004), [71] Spadoni E et al. (2004)*, [72]	GHD could be involved in sleep disturbance in SMS. GH deficiency*	After starting replacement therapy, growth has significantly improved
Three-M syndrome	Meazza C (2013), [73]	Early start of therapy	Good compliance
Trichorhinophalangeal syndrome	Marques JS et al. (2015), [74] Riedl S et al. (2004), [75]	If the growth velocity below the normal range expected for their age and sex	Increase of growth velocity*
Turner syndrome	Tai S et al. (2013), [76] Ranke MB (2015), [77]	GH treatment in Japanese children with GHD or TS resulted in increased growth over a 4-year treatment period with a favourable safety profile.	The improvements in growth declined with time
Wolf-Hirschhorn syndrome	Titomanlio L et al. (2004), [78]	A partial GHD	GH therapy should be further considered in WHS patients

Table 3. Effects of r-hGH in some genetic syndromes and disorders.

While researchers make progress in understanding the molecular mechanisms behind these disorders and identify possible therapeutic interventions in patients with skeletal dysplasia, it remains to be identified which treatments may allow a better improvement in stature. For example, for those with achondroplasia and related disorders, fibroblast growth factor receptor 3 (FGFR3) has been identified as a critical regulator of endochondral bone growth, and in these patients mutations in the coding sequence of the *FGFR3* gene have been identified [36, 37]. In these patients, several approaches to reduce FGFR3 signalling by blocking receptor activation or inhibiting downstream signals have been proposed, some promising in preclinical animal models and other in humans [38]. In this regard, more data are available on the GH-IGF-1 axis in patients with skeletal dysplasias and genetic syndrome and GH treatment (**Table 3**). So, in this section of the chapter, we try to critically evaluate the data available on the endocrine characteristics and response to GH treatment of these patients, considering the great diversity of the studies performed as well as length of observation, the sample size and GH dosage used (**Table 3**).

8.1. Achondroplasia

ACH is characterized by short-limbed dwarfism, macrocephaly with a prominent forehead and midface hypoplasia. In ACH adult, height may be 118–145 cm for men and 112–136 cm for women [79], causing considerable inconvenience in daily life and places considerable psychological problems on patients and their families [41]. In these patients, pathogenesis involves a defective endochondral ossification while periosteal and membranous ossification are normal [80].

Many data are available about the endocrine features of ACH patients. For example, Yamate et al. [81], studying 22 patients with ACH (7 males and 15 females: age range 3–12 years), reported that at study entry, the *z*-score of their height was −5.4 ± 1.2 SD, and that of their annual height gain before admission was −3.1 ± 1.3 SD. In these patients, GH response to provocative tests was normal in more than 75%: in the patients with blunted GH secretion, 80% showed subnormal response to L-Dopa stimuli, and 20% to GHRH stimuli. A 14% of patients showed a low mean GH concentration during sleep, presenting also a markedly low IGF-1 level and marked delay of bone age [81]. However, these data were confirmed by a very large study involving 42 patients with ACH, in which it was shown that some patients presented a blunted response on different GH provocation tests, whereas other patients showed a combination of a blunted response on one provocation test and low GH concentration during sleep [41]. These authors confirmed also that some of patients showed significantly lower serum IGF-1 levels, confirming the hypothesis that a subnormal GH secretion may be discovered, even if very rarely these patients exhibited severe blunted responses (with peak GH value <5 ng/ml) to more than one type of provocation test [41].

On the contrary, data suggest that ACH children showed normal thyroid function, TSH response to TRH stimulus, as well as cortisol response to insulin-induced hypoglycaemia. In these patients, the LH and FSH responses to LHRH stimulus were also commonly appropriate to Tanner stage [41, 81].

In ACH patients, data are available about the treatment with r-hGH, even if with controversial results [41, 81–84]. Data about trials have shown a variable response to treatment, even if the limited number of patients and the variability in the pubertal stage of the enrolled subjects make it very difficult to draw any final conclusions on the role of GH therapy. Yamate et al. [81] have reported a significant increase of growth velocity compared to that before GH therapy (7.2 ± 1.4 cm/year vs. 4.1 ± 0.8 cm/year) in 18 prepubertal and pubertal ACH patients after 6 months or 1 year of GH therapy at 1 IU/kg/week. However, a 6-month therapeutical trial carried out in six patients with ACH have showed that the response may to be related on pretreatment growth velocity [84], with a greater increment of growth velocity in the patients with a lower growth rate before therapy. The authors hypothesized that the variation in response to GH therapy could be related to the different ages and pubertal stages of the enrolled children [84].

In a large study involving 42 ACH patients, Tanaka et al. showed that this significative increase of height velocity during the first year of GH treatment was reduced during the second and third years of GH therapy, although the velocity was still significant than before therapy.

However, the responses to GH treatment after the second year were not uniform. In these patients, the ratios of arm span to height and sitting height to overall height were not significantly increased during GH therapy, as well as there was no significant difference in mean height velocity at the end of each year between the patients with normal or subnormal GH secretion, and between the patients treated with 0.5 IU/kg per week and those treated with 1.0 IU/kg per week GH [41]. During the treatment, the authors did not show significant changes in thyroid function tests or routine laboratory data or in spinal cord compression or narrowing of the foramen magnum [41]. However, Hertel et al. [85] confirmed that, during r-hGH treatment, the mean growth velocity increased significantly during the first year, reducing on the contrary below the baseline values during the third year of treatment [85]. The authors confirmed also that body proportion (sitting height/total height) or arm span did not show any significant change [85]. Besides, Weber et al. showed that short-term growth velocity increase in some but not all ACH prepubertal children, confirming the individual variability in the response to GH treatment [86]. In these patients, oral glucose tolerance test at the beginning and at the end of the therapy were in the normal range [86].

Therefore, the available data suggested that r-hGH may be useful in some patients with ACH in increasing the height and growth velocity. Waiting for new, more effective and specific treatments in patients with ACH, r-hGH treatment may be beneficial in the treatment of short stature in achondroplasia. About this, it will be helpful to the activation trials evaluating the response to different doses or also evaluate the combination of different, both medical and non-medical treatments.

8.2. Hypochondroplasia

Hypochondroplasia (HCH), a heterogeneous and usually mild form of chondrodystrophy, is a common cause of short stature. It often goes unrecognized in childhood and is diagnosed in adult life when disproportionate short stature becomes obvious [87]. Children with severe short stature and disproportion of the body segments usually have the mutation Asn540Lys [87].

The available data seem to demonstrate that patients with HCH respond to r-hGH treatment with an increase in spinal length and, coupled with a surgical leg-lengthening procedure, it is possible for some patients to achieve adult heights within the normal range [87]. However, GH therapy may restore the impairment of growth rate at puberty (**Figure 12**).

In fact, height SDS and height velocity SDS significantly improved during three-year treatment as compared with that before treatment and the improvement was much greater in HCH than in ACH [53].

Pinto et al. [88] showed that the over three-year treatment with r-hGH of 19 HCH children (11 with confirmed *FGFR3* mutations) showed an increase of height of 1.32 ± −1.05 SDS compared to untreated HCH individuals. However, Rothenbuhler et al. [89], evaluated HCH young children with confirmed *FGFR3* mutation treated with r-hGH over a six-year period. Their mean height SDS increased by 1.9 SDS, and trunk/leg disproportion was improved.

These results were confirmed by a meta-analysis involving 113 HCH children, administrated with median 0.25 mg/kg/week of r-hGH. In these patients, the therapy progressively improved the height and growth velocity with 12 months catch-up growth, and this improvement resulted constant until 36 months, even if the stature remained subnormal. While bone age chronologically progressed, no serious adverse events were reported [90].

Interestingly, using criteria based on the radiographic findings of decreased interpediculate distance between L1 and L5, Mullis et al. [91] identified two restriction fragment length polymorphisms (RFLP) within introns of IGF-1 (12q23) with a positive LOD score of 3.31 in some families with hypochondroplasia. The HCH children whose response to r-hGH treatment were characterized by a proportionate increase in both spinal and subischial leg length were all heterozygous for two co-inherited *IGF-I* gene RFLP alleles, indicating that *IGF-I* gene may be a candidate for explaining the variability in the response to r-hGH treatment [91].

In conclusion, patients with HCH seem to show a significative response to r-hGH therapy with an increase in spinal length and stature, and reduced the impaired growth spurt during puberty. It is important, therefore, to monitor all patients during childhood and give r-hGH treatment to those patients who fail to develop a growth spurt at puberty or showing a severe short stature.

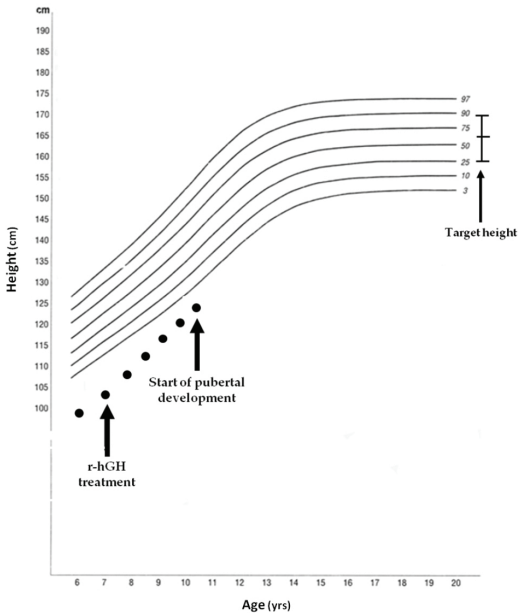


Figure 12. Effect of r-hGH therapy (the beginning is specified with the black arrow) in a female patient with a severe form of hypochondroplasia. The patients showed reduced IGF-1 and a blunted response after GH tests. You may notice the significant improvement of their stature in the short and medium term. Pubertal development onset was determined at the time of the last survey reported. *X* axis corresponds to the age of the patients expressed in years.

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8.3. Type 1 trichorhinophalangeal syndrome

Type 1 trichorhinophalangeal syndrome (TRPS1), first described by Klingmuller in 1956 and then named by Giedion in 1966, is a rare genetic condition characterized by typical craniofacial and skeletal abnormalities with short stature [92]. The patients showed commonly sparse scalp hair and lateral eyebrows, bulbous tip of the nose, long flat philtrum, thin upper vermilion border and protruding ears. Skeletal abnormalities may include cone shaped epiphyses at the phalanges, hip dysplasia and short stature [92].

In TRPS1, some patients with GH deficiency have been described. Marques et al. [74] reported a 10-year-old girl with two heterozygous nonsense *TRPS1* mutations with significantly reduced growth velocity and delayed bone age. The patient shows no response to the GH stimulation tests, thus disclosed a GH deficiency, nevertheless, after r-hGH treatment catch-up growth occurred. However, Naselli et al. [93] and Sohn et al. [94] reported four unrelated patients with TRPS1 with diagnosis of GH deficiency failuring response to r-hGH treatment, whereas Stagi et al. [95] and Sarafoglou et al. [96] reported that GH treatment was effective in improving height velocity in 4 TRPS1 patients. Finally, Merjaneh et al. [97] report a TRPS1 a family with a novel nonsense mutation in the *TRPS1* gene. In this family, the eldest sibling had a normal GH-IGF-1 axis, and bone mineral density (BMD), but he accelerated his linear growth velocity over 2 years of r-hGH (0.28 mg/kg/week) increasing the height SDS score from −2.4 to −1.4. Bone age advanced by 2.5 years during 2 years of r-hGH treatment. He remained prepubertal during treatment.

The mechanism by which GH therapy could accelerate linear growth in TRPS1 is unknown. It is interesting to note that in a cell culture model mimicking *TRPS1* mutations, IGF-1

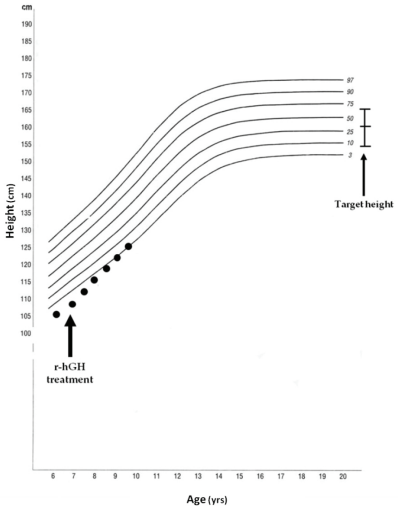

Figure 13. Effect of r-hGH therapy (the beginning is specified with the black arrow) in a female patients with type 1 Trichorhinophalangeal syndrome without GH deficiency. *X* axis corresponds to the age of the patients expressed in years.

expression was reduced by blockade of TRPS1 expression. This may suggest that the increase of IGF-1 concentrations, resulting from GH therapy, may have more effect in the growth plates of TRPS1 patients (**Figure 13**).

On the contrary, only few cases of GHD were diagnosed: a 9-year-old boy and a 10-year-old girl with TRPS2 [75, 98]. The male patient had also a TSH deficiency [99].Treatment with r-hGH was effective in both patients although their growth remained restricted. In conclusion, these data suggest performing GH stimulation tests in patients with TRPS1 or TRPS2 exhibiting a significantly reduced growth velocity and short stature. If the result is subnormal, then GH therapy should be prescribed.

8.4. Cartilage-hair hypoplasia

Cartilage-hair hypoplasia (CHH) is an autosomal recessive metaphyseal chondrodysplasia characterized by severe short-limb short stature and hypoplastic hair. The responsible gene for CHH has been identified to be *ribonuclease of mitochondrial RNA-processing* (*RMRP*) gene [99].

Bocca et al. [100] evaluated the effects of r-hGH on growth parameters and immune system in four children with CHH. The effects of treatment are more evident in patients with more severe growth retardation. However, the effects are temporary without gain in final height. However, serum immunoglobulins did not change during r-hGH treatment. On the contrary, Harada et al. [44] suggested that r-hGH treatment significantly improved the bone growth and height in CHH patients, suggesting that GH may be considered an efficient treatment for CHH. However, Obara-Moszynska et al. [101] describe another case of CHH, a girl, treated with r-hGH with a significant effect on the height gain, with an improvement from −4. to −2.98 SDS after 4 years 7 months of treatment.

In conclusion, the poor data available suggest a possible role of r-hGH in treating the severe short stature in CHH patients. However, IGF-1 and IGFBP-3 concentrations should be closely monitored during treatment, particularly because of the increased cancer risk in CHH.

8.5. Turner syndrome and short stature homeobox-containing (SHOX) gene deficiency

SHOX is the abbreviated designation for the *Short stature Homeobox-containing* gene and is localized in the pseudoautosomal region of both X and Y chromosomes [102]. *SHOX* is one of many genes that regulate longitudinal growth and SHOX deficiency, due to intragenic or regulatory region defects, cause a phenotype ranging from normal stature to mesomelic skeletal dysplasia [103].

In fact, many data showed that SHOX haploinsufficiency may be a cause of idiopathic short stature (ISS; OMIM# 604271) and the short stature of Turner syndrome (TS) patients, or Léri-Weill dyschondrosteosis (LWD; OMIM #127300), while homozygous loss of the *SHOX* gene has been related to Langer type mesomelic dysplasia (OMIM; 249700) [102].

Since discovery of *SHOX* gene in 1997, r-hGH treatment was potentially reported for growth promotion in these patients [104]. Because of SHOX deficiency represent the main cause of

short stature in TS and the r-hGH acts as an efficient and safe treatment, the same therapy in short children with *SHOX* mutation at the same dosage of TS displayed an excellent growth spurt, suggesting that growth-promoting therapy with rhGH was effective with regard to height gain in short stature due to SHOX deletions [104]. In another 2-year prospective open-label randomized study involving two cohorts of SHOX-deficient patients and a cohort of TS patients, the untreated cohort grew with a normal height velocity and unchanged height SDS, whereas the r-hGH-treated cohort grew faster and as fast as the girls with TS [105]. However, retrospective data showed also that final heights in patients with SHOX deficiency treated for more than 2 years, even if with low r-hGH dose, presented an overall gain in height of 7 cm, not different from the mean gain in height in treated TS girls [106].

In conclusion, the growth-promoting effect of GH therapy, which has been approved for growth promotion in individuals with SHOX mutations by FDA and EMEA, seems to be equal to the effect reached in TS. In many patients with SHOX deficiency, an impaired GH secretion is not uncommon. r-hGH therapy is effective in increasing height in most of these patients independent of their GH secretory status, without causing any adverse events of concern.

8.6. Osteogenesis imperfecta

Osteogenesis imperfecta (OI or brittle bone disease) is a clinically and genetically heterogeneous group of heritable disorders of connective tissue [107]. The hallmark feature of OI is represented by bone fragility with susceptibility to fracture from minimal trauma. As a consequence, these patients showed bone deformity and growth deficiency [107]. However, OI patients may show other phenotypic features, as macrocephaly, blue sclerae, dentinogenesis imperfecta, hearing loss, neurological defects and cardiopulmonary complications [108].

In these patients, genetic counselling and study are essential components of complete care for individuals with OI, as are nonsurgical (e.g. rehabilitation, bracing and splinting), surgical and pharmacological (bisphosphonates or r-hGH) management [108].

In general, many data suggest that r-hGH may have a positive effect on bone growth and bone turnover by stimulating osteoblasts, collagen synthesis and longitudinal bone growth [109]; however, in the first 6 months of r-hGH therapy in GH deficiency (GHD) patients, bone resorption is usually greater than bone formation, and there are more resorption markers [110]. Besides these actions on bone GH may show a positive action on collagen metabolism [111, 112], stimulating the IGF-1 and IGFBP-3 expression, which in turn regulates the synthesis of type I collagen [113, 114].

Besides this aspect, there is scarce data about r-hGH treatment in OI patients [115–118]. Nevertheless, in one of the first attempts to treat OI patients with r-hGH, the treated patients showed, using a bone histomorphometry study, an increase in periosteal new bone formation and intracortical bone resorption, with enhanced osteoblastic activity [119]. However, the study of GH-somatomedin axis activity in OI showed that IGF-1 serum levels are frequently in the low normal range in the most part of these patients [120, 121]. In fact, Marini et al. [115]

found a hypoactivity of this axis (without a true GH deficit) in near the half of OI patients, treating them with r-hGH or clonidine. However, some data suggest that the type IV OI children would benefit from r-hGH treatment in terms of linear growth, bone matrix synthesis and bone histomorphometric parameters [122].

In a mouse model of OI, r-hGH injections [117] increased spine and femur length, produced significant changes in densitometry parameters and ameliorated the biomechanical structural properties of bone. Accordingly, similar results are obtained in human, since r-hGH treatment seems to cause a positive effect on height growth and increase in skeletal volume and BMD, with a possible subsequent reduction in fracture. However, the combined treatment with r-hGH and neridronate positively increases BMD at the lumbar spine and wrist and significantly increases the rate of linear growth velocity, with no BA advancement; and no influence in the peripheral fracture rate [60].

8.7. Ellis-van Creveld syndrome

Ellis-van Creveld syndrome (EvC; OMIM # 225500) is a skeletal dysplasia first described in 1940 by Ellis and van Creveld [123]. EvC is characterized by ectodermal dysplasia affecting mainly the teeth and nails, chondrodysplasia of the long bones, postaxial polydactyly and congenital heart anomalies. In fact, 60% of affected individuals have a congenital cardiac defect, most commonly an atrial septum defect [124]. The entity was mapped at chromosome region 4p16 [125, 126] and subsequently the *EVC* gene was cloned [127]. A second gene (*EVC2*) located in the same chromosomal region was found to harbour mutations in some EvC patients [128].

In this syndrome, data on growth patterns are limited, but in general growth is markedly impaired [51]. Growth in EvC is known to be impaired with an estimated deviation of −2.0 to −4.5 from standard growth [51]. In most reports, only one measurement of the patient is mentioned, and few follow-up data are published. In this syndrome, the GHD and the results of GH treatment were rarely reported [129].

For example, Versteegh et al. described two subjects with EvC syndrome and GHD. In the first, a mutation in the *EVC2* gene was reported. Target height was 0.28 SDS. At age 4, a decline in growth velocity was observed, and GH provocation tests disclosed a GHD. r-hGH treatment started at 2 IU/m2 resulted in improved growth velocity. Skeletal age is approximately 1 year behind at the start of r-hGH treatment, at 11 years of age exceeded the chronological age by approximately 2 years. During therapeutic GH regimens for 11 years, patient's height increased from SDS −3.3 to −1.8. In the second patients, no mutation was detected. Target height was 0.71 SDS. GHD was ruled out by an arginine stimulation test, even if, because of a severe decline in growth velocity, treatment with e-hGH was started. During 7 months of therapy, patient's height increased from −6.0 to −5.6 SDS. Versteegh et al. [51] reported also that the evaluation of the Pharmacia Growth DataBase KIGS permits to gather data on growth and GH treatment in six other EvC patients. Four patients were diagnosed as GHD. All patients except one were treated with GH according to standard protocols. A gain in height SDS was seen in three of the four GHD patients. One GHD patient did not show an increased height SDS. Of

the GH-sufficient, one showed a gain in height SDS. In conclusion, the available data suggest that GHD can play a role in the retarded growth in at least some EvC patients.

9. General conclusions

Skeletal dysplasias are a wild and complex group of diseases due to several pathogenetic mechanisms. Up to date, even because of their rarity, available knowledge is not so large and most of this is about a very restricted number of dysplasias. Particularly, the specific aspect of the linear growth in these patients has been analysed in a very small number of studies. No specific therapy is available and supportive measures are the only helpful treatment. By the way, data presented in literature allow us to evince that in some cases a pathological GH axis can be associated to the dysplasia. So we suggest that in this patients could be useful to investigate the function of GH axis and, if defective, to start a replacement therapy with r-hGH. Clearly, GH therapy is not a target treatment for any of these dysplasias and further studies are necessary, but it could have a supportive role in the management of the auxoendocrinological growth in these disorders.

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