Review

Interaction Between Local Growth Plate Mechanisms and Systemic Endocrine Signals in X-Linked Hypophosphatemia (XLH) Impaired Linear Growth

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Review

Interaction Between Local Growth Plate Mechanisms and Systemic Endocrine Signals in X-Linked Hypophosphatemia (XLH) Impaired Linear Growth

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Abstract

Background/Objectives: X-linked hypophosphatemia (XLH), the most frequent heritable cause of hypophosphatemic rickets, is characterized by impaired linear growth and skeletal deformities, that can lead to disproportionate short stature. Linear growth depends on the coordinated regulation of systemic endocrine signals and local growth plate regulatory mechanisms controlling chondrocyte proliferation, differentiation, and apoptosis. This review critically discusses the molecular processes underlying growth impairment in XLH, with particular emphasis on growth plate dysfunction. **Methods:** A narrative review of experimental and clinical studies was conducted, focusing on growth plate biology, and on pathophysiology of XLH. Particular attention was given to the interaction between systemic phosphate-regulating hormones, local paracrine factors, and intracellular signaling pathways, as well as the effects of current therapeutic strategies on linear growth. **Results:** Excess fibroblast growth factor 23 (FGF23) in XLH disrupts phosphate homeostasis and vitamin D metabolism, impairing skeletal mineralization and growth plate signaling. Beyond FGF23-related dysregulation, additional FGF23-independent mechanisms directly affect growth plate chondrocyte function and extracellular matrix composition, further contributing to growth plate disorganization. Current therapeutic approaches, including conventional phosphate and active vitamin D supplementation, FGF23 inhibition with human monoclonal antibody, and combination with recombinant human growth hormone, exert heterogeneous effects on linear growth through distinct biological mechanisms. **Conclusions:** Growth impairment in XLH reflects the combined impact of alteration of calcium-phosphate metabolism, systemic endocrine dysregulation, and intrinsic growth plate dysfunctions. A better understanding of these mechanisms may facilitate the development of targeted therapeutic strategies, improving growth outcomes in individuals with XLH.

Keywords: X-linked hypophosphatemia; linear growth; fibroblast growth factor 23 (FGF23); growth plate

1. Introduction: X-linked hypophosphatemia (XLH) and linear growth

X-linked hypophosphatemia (XLH) is a metabolic bone disorder characterized by impaired phosphate homeostasis and bone mineralization. Although it represents the most common form of heritable hypophosphatemic rickets, XLH is a rare disorder, with an incidence of approximately 3.9 per 100,000 live births and a prevalence of between 1.7 and 4.8 per 100,000 individuals [1].

XLH is caused by loss-of-function mutations in the phosphate regulating endopeptidase X-linked (*PHEX*) gene, which encodes an endopeptidase expressed by osteoblasts, osteocytes, and

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odontoblasts. This enzyme plays a crucial role in regulating phosphate metabolism. An inactivation of the *PHEX* gene results in elevated circulating levels of fibroblast growth factor 23 (FGF23), a phosphaturic hormone. Excess FGF23 leads to renal phosphate wasting by reducing the expression of the sodium-phosphate cotransporters NaPi-IIa and NaPi-IIc. Furthermore, FGF23 reduces serum levels of the active form of vitamin D, 1,25-dihydroxyvitamin D (1,25$(OH)_2$D), by downregulating the expression of 25-hydroxyvitamin D-1α-hydroxylase and upregulating the expression of 24-hydroxylase [2].

Consequently, XLH is characterized by chronic hypophosphatemia due to elevated renal phosphate excretion; this is reflected by reduced tubular reabsorption of phosphate (TRP) and low tubular maximum reabsorption of phosphate per glomerular filtration rate (TmP/GFR). Additional biochemical markers include low to normal levels of 1,25$(OH)_2$D, elevated serum alkaline phosphatase (ALP) activity, and normal serum calcium and 25-hydroxyvitamin D (25-OHD) levels [3].

From a clinical perspective, XLH is characterized by a wide spectrum of manifestations that can be observed throughout an individual's lifespan. In childhood, XLH is characterized by the presence of rickets, bone deformities, impaired growth, bone pain and dental abnormalities such as recurrent tooth abscesses and periodontitis. In adults, persistent osteomalacia may lead to fractures and pseudofractures, and additional complications can develop over time, including osteoarthritis, enthesopathies, nephrocalcinosis, spinal stenosis and sensorineural hearing loss. Collectively, these conditions may result in a significant burden, impacting quality of life and physical and psychological health [1,3].

Growth impairment is a hallmark feature of XLH during childhood, and it is characterized primarily by reduced linear growth and lower limb bowing, resulting in disproportionate short stature [3]. Medical treatment has been shown to partially improve growth abnormalities, and complete correction may not be achievable, suggesting that other mechanisms besides hypophosphatemia and FGF23 excess are also involved. Affected children, as well as symptomatic or severely affected adults, are candidates for conventional treatment consisting of phosphate and active vitamin D metabolites supplementation. More recently, target therapy with burosumab, a humanized monoclonal antibody against FGF23, has become available [1,3].

This review focuses on the mechanisms underlying growth impairment in XLH, with particular emphasis on the role of systemic and local factors in growth plate dysfunction, and the impact of current therapeutic strategies on linear growth. A comprehensive understanding of the underlying pathophysiological mechanisms is essential for the development of future targeted therapies to improve growth outcomes.

In order to contextualize these pathological processes, the subsequent section provides an overview of the physiological organization and key regulatory mechanisms at the growth plate.

2. Physiology of Linear Growth

2.1. Growth Plate Structure and Function

The growth plate is a highly organized hyaline cartilage tissue that extends from the epiphysis to the metaphysis of growing long bones. It represents the primary site of bone growth through the process of endochondral ossification and is therefore a major determinant of final adult stature. The growth plate comprises chondrocytes that progressively undergo differentiation from the epiphysis to the metaphysis, giving rise to three different anatomic zones [4,5] (Figure 1):

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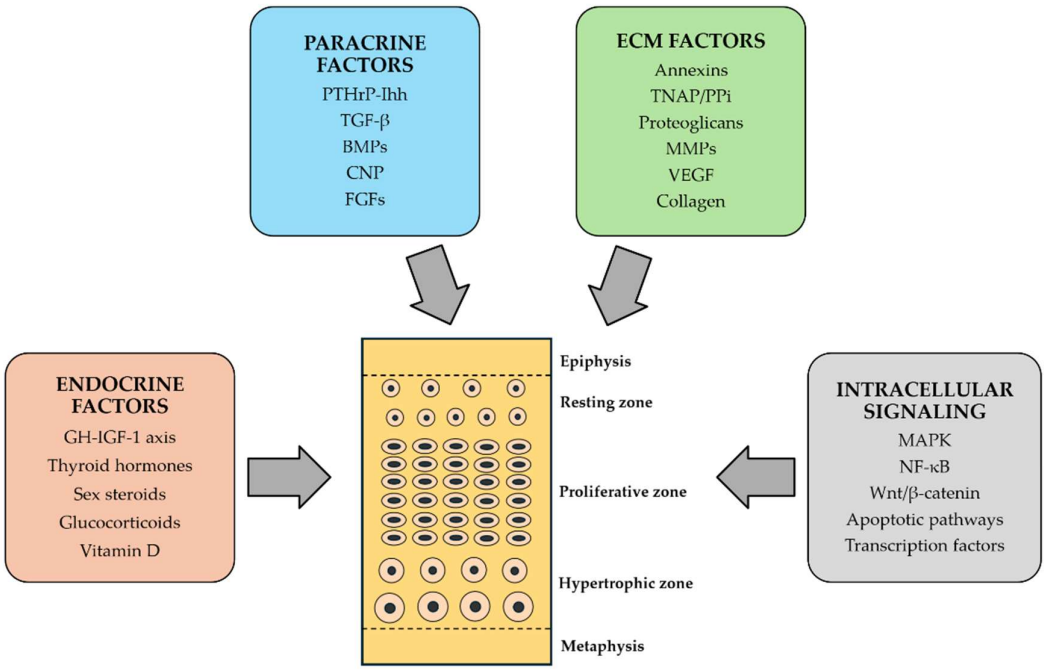

Figure 1. Schematic representation of the growth plate and the physiological mechanisms regulating linear growth. Normal linear growth relies on the coordinated regulation of growth plate chondrocyte proliferation, differentiation and apoptosis, which is finely controlled by complex interactions among endocrine and paracrine factors, extracellular molecules, and intracellular signaling pathways.

GH Growth hormone; IGF-1 Insulin-like growth factor 1; PTHrP-Ihh Parathyroid hormone-related protein-Indian hedgehog; TGF-β Transforming growth factor β; BMPs Bone morphogenetic proteins; CNP C-type natriuretic peptide; FGFs Fibroblast growth factors; ECM Extracellular matrix; TNAP Tissue-nonspecific alkaline phosphatase; PPi Pyrophosphate; MMPs Matrix metalloproteinases; VEGF Vascular endothelial growth factor; MAPK Mitogen-activated protein kinase; NF-κB Nuclear factor kappa-light-chain-enhancer of activated B cells; Wnt Wingless-related integration site.

- The resting zone is composed of progenitor cells undergoing mitosis and relatively inactive cells, embedded in an abundant extracellular matrix, and serves as a reservoir for cells entering the growth process.
- The proliferating zone is characterized by highly proliferative chondrocytes that divide along the major axis of the growing bone and organize into parallel columns, thereby driving tissue expansion.
- The hypertrophic zone consists of terminally differentiated chondrocytes, that undergo marked cellular enlargement and produce extracellular matrix consisting mainly of collagens and other non-collagenous proteins such as proteoglycans.

Linear growth is determined by the balance between chondrocyte proliferation, hypertrophic differentiation, and apoptosis, with hypertrophic enlargement playing a primary role in overall bone elongation. Alterations to these processes compromise the function of the growth plate and can lead to a wide spectrum of growth disorders and skeletal dysplasias [4,6].

Mineralization of the cartilage matrix represents a critical step in endochondral ossification. The interface between the metaphysis and the growth plate consists of a provisional zone of calcified cartilage matrix, which is subsequently resorbed and replaced by mineralized bone. In the hypertrophic zone, chondrocytes promote extracellular matrix mineralization through the release of matrix vesicles, that represent the initial sites of nucleation of hydroxyapatite [4].

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Following these processes, hypertrophic chondrocytes may then undergo apoptosis, creating space for new bone formation. Alternatively, recent evidence suggests that a subset of hypertrophic chondrocytes may survive and transdifferentiate into osteoblasts that deposit osteoid, subsequently mineralized to form mature bone tissue [4,5,7].

A final essential mechanism for cartilage resorption and bone formation involves vascular invasion from the metaphysis into the hypertrophic chondrocyte lacuna, and following recruitment of osteoclasts and chondroclasts [4,5,7].

Furthermore, growth plate dynamics are regulated by a complex interplay of factors, including hormones and local factors [4-6] (Figure 1).

2.2. Systemic Regulation of Linear Growth

Growth plate maturation and mineralization are coordinated by a complex network of systemic endocrine signals, involving growth hormone (GH) and insulin-like growth factor 1 (IGF-1), thyroid hormones, glucocorticoids, sex hormones and vitamin D [6].

2.2.1. GH - IGF-1 Axis

Growth hormone (GH) and insulin-like growth factor 1 (IGF-1) play a key role in the regulation of postnatal linear growth, whereas IGF-2 predominantly contributes to intrauterine growth [8].

Although the underlying mechanisms are not fully understood, the classical somatomedin hypothesis proposes that the effects of GH are primarily mediated by IGF-1, which is produced by the liver and circulates in a ternary complex with an IGF-binding protein (IGFBP) and the acid-labile subunit (ALS). IGF-1 exerts its effects by binding to the IGF-1 receptor (IGF-1R). In accordance with the dual effector hypothesis, GH also exerts local effects at the growth plate by directly stimulating the proliferation of resting chondrocytes and increasing the local production of IGF-1, which therefore acts as a paracrine factor [8-10]. In contrast to GH, IGF-1 has only modest effect on chondrocyte proliferation and predominantly promotes hypertrophic cells differentiation, thereby contributing to linear growth by increasing cells size rather than their number [9]. IGF-independent mechanisms directly modulated by GH include the nuclear factor kappa B (NF-κB) p65 and bone morphogenetic protein 2 (BMP-2) signaling pathways. However, the contribution of these processes to growth plate regulation remains to be fully elucidated [8].

Significantly, both GH and IGF-1 hormones also contribute to mineralization. IGF-1 acts as the main effector through several mechanisms, including the regulation of bone remodeling, osteoblast proliferation and matrix production, osteocyte survival, and vascular invasion. GH appears to support these processes mainly through indirect stimulation of local and systemic IGF-1 production [10,11].

2.2.2. Thyroid Hormones

The role of thyroid hormones in linear growth is well established. While hypothyroidism decreases linear growth and endochondral ossification, hyperthyroidism accelerates these processes by promoting the hypertrophic differentiation of growth plate chondrocytes [9].

The regulation of thyroid hormone activity in the growth plate is mediated by local type 2 deiodinase conversion of thyroxine (T4) into the biologically active form triiodothyronine (T3). Thyroid hormones exert their actions by binding to thyroid hormone receptors (TRs), with the isoform TR-α playing a major role in the regulation of linear growth and mineralization [9]. In addition, thyroid hormones contribute to systemic regulation of growth by activating the GH-IGF-1 axis [8].

2.2.3. Sex Steroids

Sex hormones play a central role in the regulation of the final stages of linear growth during puberty in both males and females [4] and are also crucial for promoting bone mineralization [12].

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The effects of estrogen on linear growth are complex. On the one hand, it enhances linear growth by stimulating the pubertal growth spurt via activation of the GH-IGF-1 axis, which increases chondrocyte proliferation and hypertrophy at the growth plate. On the other hand, estrogen accelerates growth plate maturation and epiphyseal fusion by inhibiting the proliferation of resting and proliferative chondrocytes, as well as by promoting programmed chondrocyte senescence. These alterations result in a reduction in the number and size of hypertrophic chondrocytes, progressive narrowing of the proliferative and hypertrophic zones, ultimately leading to growth plate fusion [4,6,9].

Estrogen functions within the growth plate are mediated through the activation of estrogen receptors ER-α and -β expressed in chondrocytes. In addition to systemic regulation, this hormone is also produced locally, as chondrocytes express aromatase (an enzyme that converts androgens into estrogens) and other enzymes involved in steroid metabolism [6,9].

Mutations in genes that encode ER-α or aromatase, as well as treatment with aromatase inhibitors or other causes of hypogonadism, result in delayed growth plate maturation, prolonged linear growth beyond adolescence and tall adult stature. Conversely, precocious puberty causes premature estrogen exposure and early growth plate closure, with consequent reduction in final adult height. For this reason, anti-estrogenic factors including aromatase inhibitors have been investigated as potential therapeutic strategies to increase final stature in selected cases [6,9].

Androgens also contribute to the pubertal growth spurt, mainly through their conversion to estrogens by aromatase, which is expressed in several peripheral tissues, including growth plate chondrocytes. In addition to these indirect effects, androgens also directly stimulate linear growth. In particular, dihydrotestosterone, the biologically active metabolite of testosterone, promotes chondrocyte proliferation via androgen receptor (AR)-mediated mechanisms independent of both aromatization and GH signaling [9].

2.2.4. Glucocorticoids

Glucocorticoids negatively affect linear growth, by directly inhibiting chondrocytes proliferation and inducing apoptosis [9]. In addition, excess levels impair growth plate function by inhibiting the secretion of GH and thyroid hormones [6].

The impact of these effects is evident in the growth impairment observed in children undergoing long-term high-dose glucocorticoids therapy. Discontinuing this treatment is often followed by catch-up growth, which probably reflects the preservation of chondrocyte proliferative capacity. However, prolonged exposure to glucocorticoids may lead to irreversible alterations to the growth plate resulting in short stature [9].

2.2.5. Vitamin D

Adequate calcium and phosphate levels are required for proper bone mineralization and chondrocyte maturation within the growth plate. Vitamin D contributes to systemic mineral homeostasis by upregulating epithelial transport proteins involved in intestinal calcium and phosphate absorption [9,13]. In children, vitamin D deficiency and genetic defects in its metabolism or signaling lead to rickets, characterized by expansion of the hypertrophic zone and impaired mineralization, a phenotype observed in both hypophosphatemic or hypocalcemic disorders [14].

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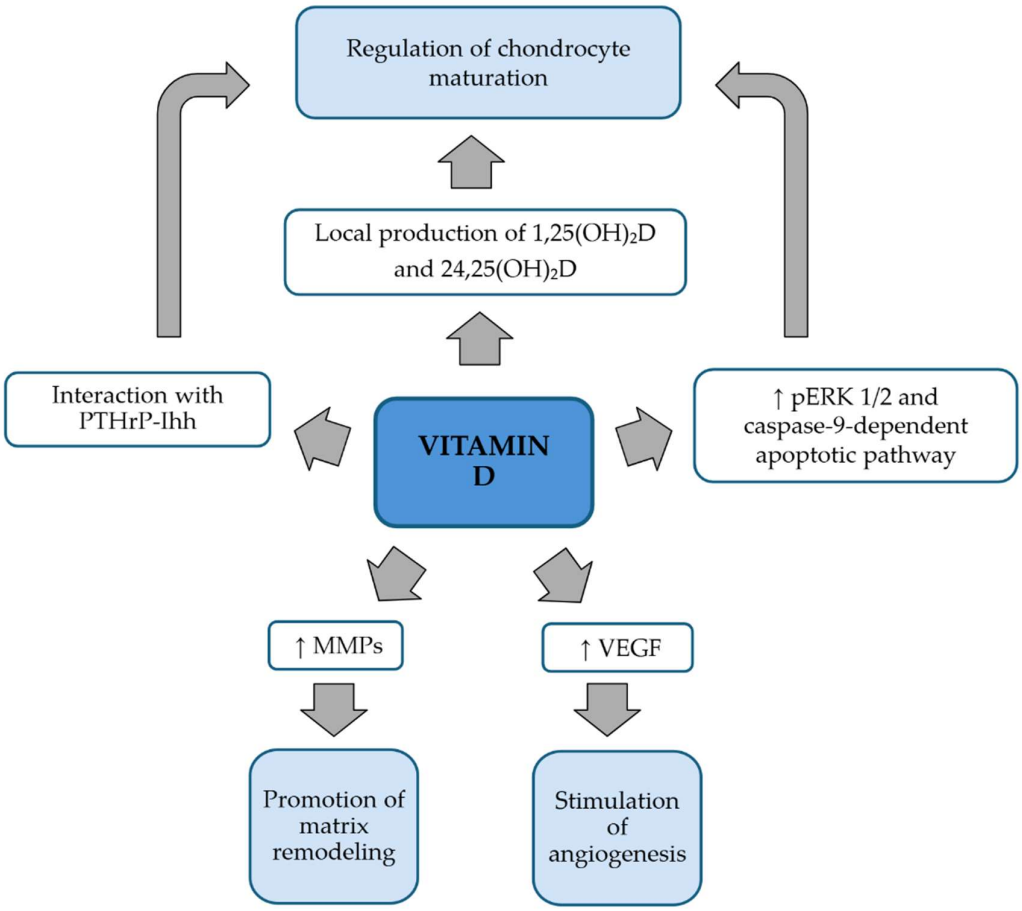

Figure 2. Local effects of vitamin D on growth plate function. In addition to systemic role in mineral homeostasis, vitamin D also regulates chondrocyte proliferation and differentiation, extracellular matrix remodeling and angiogenesis. $1,25(OH)_2D$ 1,25-dihydroxyvitamin D; $24,25(OH)_2D$ 24,25-dihydroxyvitamin D; pERK Phosphorylated extracellular signal-regulated kinase.

Vitamin D is also suggested to exert direct effects on growth plate physiology, as supported by in vitro studies (Figure 2).

Although the molecular mechanisms are not completely understood, indirect interactions with regulatory pathways such as the parathyroid hormone-related protein (PTHrP)-Indian hedgehog (Ihh) axis appear to be involved [15]. Furthermore, 1,25-hydroxylase and 24,25-hydroxylase enzymes are expressed in growth plate chondrocytes, enabling local vitamin D metabolism. Specifically, the production of 24,25-dihydroxyvitamin D ($24,25(OH)_2D$) has been implicated in chondrocyte differentiation, whereas 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) inhibits chondrocyte proliferation [9,16]. In addition, vitamin D signaling has been reported to modulate chondrocyte apoptosis, by increasing ERK (extracellular signal-regulated kinase) 1/2 phosphorylation, which in turn activates the caspase-9-dependent mitochondrial apoptotic pathway [17].

Vitamin D may also support vascular invasion and extracellular matrix remodeling by increasing chondrocyte production of vascular endothelial growth factor (VEGF), which promotes angiogenesis, and matrix metalloproteinases (MMPs), which degrades extracellular matrix components [18].

2.3. Local Regulation of Linear Growth

2.3.1. Paracrine Regulation of Growth Plate Activity

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Growth plate activity is regulated by a complex network of paracrine factors that tightly coordinate chondrocyte proliferation and hypertrophic differentiation [6,7] (Figure 3).

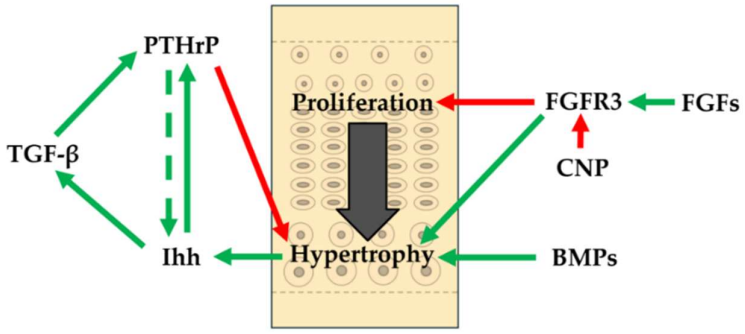

Figure 3. Paracrine regulation of growth plate activity. This process is controlled by a negative feedback loop between Indian hedgehog (Ihh), produced by hypertrophic chondrocytes, and Parathyroid hormone-related protein (PTHrP) expressed in the proliferative zone. This axis is directly modulated by TGF-β in association with paracrine factors, including FGFs, CNP and BMPs.

The central regulatory pathway is the PTHrP-Ihh signaling axis, which maintains the balance between chondrocyte proliferation and hypertrophic differentiation through a negative feedback loop within the growth plate [6]. PTHrP is produced mainly by resting zone chondrocytes and acts on proliferative chondrocytes by delaying hypertrophic differentiation. As these cells progress toward the pre-hypertrophic state, they express Ihh, which in turn stimulates PTHrP production in the resting zone, thereby sustaining the proliferative chondrocytes pool and regulating the timing of differentiation [4,6].

This feedback loop is positively regulated by several pathways. Among these, transforming growth factor-β (TGF-β), produced by perichondral cells in response to Ihh signaling, enhances PTHrP synthesis, thereby inhibiting chondrocyte hypertrophic differentiation [4]. Bone morphogenetic proteins (BMPs), members of the TGF-β superfamily, also promote hypertrophic differentiation [6]. C-type natriuretic peptide (CNP) promotes chondrocyte proliferation by activating a cyclic guanosine monophosphate (cGMP)-dependent pathway that antagonizes fibroblast growth factor receptor 3 (FGFR3) signaling [6]. Conversely, multiple fibroblast growth factors, acting through FGFR3, negatively regulate growth plate activity by inhibiting chondrocyte proliferation and accelerating their hypertrophic differentiation [6].

Moreover, inflammatory cytokines, including tumor necrosis factor (TNF), interleukin-1β (IL-1β) and interleukin-6 (IL-6), produced both systemically and locally by growth plate chondrocytes, can directly impair growth plate function and inhibit linear growth under conditions of stress or chronic inflammation [6].

2.3.2. Extracellular Matrix Regulation

Hypertrophic chondrocytes secrete a highly specialized extracellular matrix that provides structural support and serves as a template for mineralization (Figure 4).

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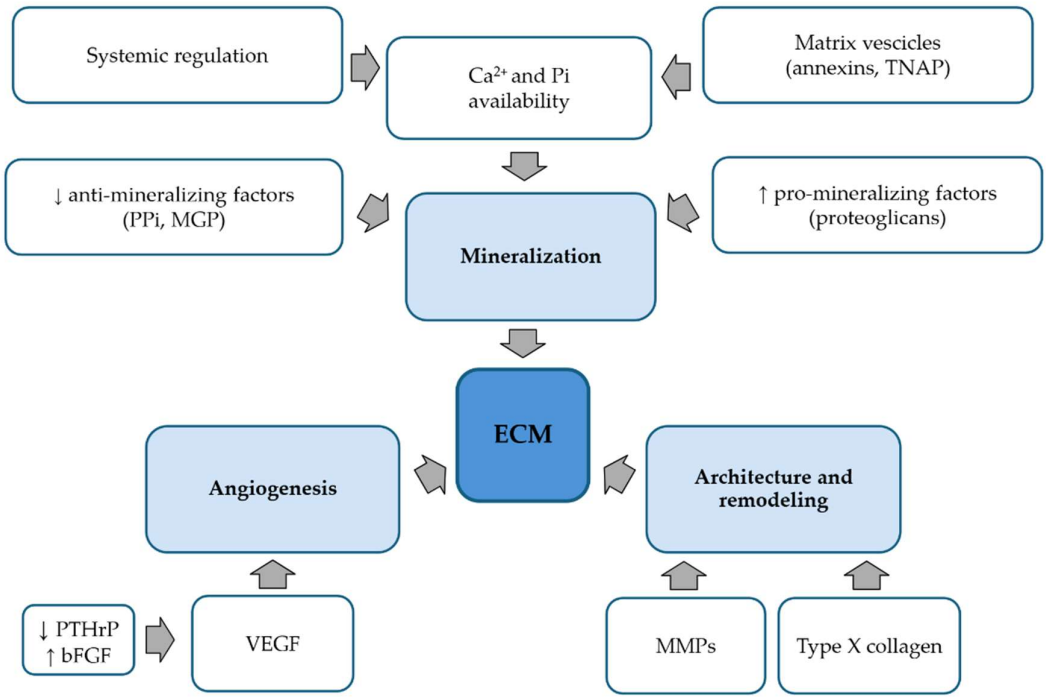

Figure 4. Physiologic regulation of extracellular matrix (ECM) structure and function at the growth plate. ECM homeostasis depends on systemic and local mechanisms ensuring balanced mineralization, vascularization and remodeling. Ca2+ Calcium; Pi Inorganic phosphate; MGP Matrix Gla protein.

Mineralization involves several complex mechanisms, whose effectiveness depends on an adequate local supply of calcium and inorganic phosphate [4,6]. Hypertrophic chondrocytes express type X collagen, which contributes to the structural organization of the matrix, and release matrix vesicles, which represent the initial sites of calcium hydroxyapatite nucleation within the hypertrophic zone. Matrix vesicles concentrate calcium and phosphate through the expression of annexins, and tissue-nonspecific alkaline phosphatase (TNAP), respectively. In particular, annexin V plays a key role in facilitating calcium internalization and crystal nucleation by interacting with types II and X collagen [4,19]. TNAP, in turn, contributes to mineralization by hydrolyzing pyrophosphate (PPi), an inhibitor of hydroxyapatite formation, into inorganic phosphate (Pi), thereby increasing extracellular phosphate pool [4,19].

The process of mineralization is regulated by a balance between pro-mineralizing and anti-mineralizing factors. For example, proteoglycans, including aggrecan, biglycan and decorin, are major components of the extracellular matrix that seem to enhance the deposition and organization of hydroxyapatite crystals by interacting with paracrine signals, such as TGF-β, and with collagen fibrils [4,6]. In contrast, inhibitors of extracellular matrix calcification, such as Matrix Gla Protein (MGP), a γ-carboxyglutamate (Gla)-containing protein, are also produced by proliferative and late hypertrophic chondrocytes in order to prevent inappropriate mineralization [4].

In addition, hypertrophic chondrocytes play a key role in modulating bone remodeling, through the release of matrix metalloproteinases (MMP-2, -9, and -13) which contribute to cleavage of type II collagen [4,19].

Vascular invasion in the growth plate is also essential for endochondral ossification. This process is primarily regulated by VEGF, which is produced by hypertrophic chondrocytes and stimulates the proliferation and migration of vascular endothelial cells to generate new blood vessels. VEGF is also necessary for recruiting and differentiating osteoclasts and chondroclasts, as well as for cartilage remodeling [4]. VEGF expression is modulated by several molecules. For instance, PTHrP and other growth factors that inhibit chondrocyte maturation may also prevent angiogenesis. Conversely, basic fibroblast growth factor (bFGF) and other mediators that promote chondrocyte hypertrophy also

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stimulate angiogenesis. MMPs also play a role in angiogenesis, though the mechanisms involved are not yet fully established [4].

2.3. 3a Intracellular Regulation of Chondrocyte Proliferation

Growth plate function is also tightly regulated by intracellular transcriptional programs that control chondrocyte differentiation, survival, and matrix synthesis. Key transcription factors include: Sex-determining region Y-box 9 (SOX-9), which regulates chondrocytes differentiation and the expression of matrix components such as collagen types II, IX and XI, and aggrecan; Core-Binding Factor Alpha 1 (CBFA-1/RUNX-2) which is a transcription regulator of chondrocyte hypertrophy and type X collagen expression [4,6]; the Short Stature Homeobox (SHOX) gene, a transcription factor predominantly expressed in the proliferative zone, where it promotes proliferation and prevents premature hypertrophic differentiation [6, 20].

These transcriptional programs are coordinated by multiple intracellular pathways that integrate extracellular signals within the growth plate [7]. The Ras-MAPK (mitogen-activated protein kinase) signaling represents a central pathway that integrates signals from several growth factors, including FGFs, CNP and EGF, thereby regulating growth plate homeostasis [6]; NF-κB signaling, activated by GH and IGF-1 through p65 (RelA) subunit, promotes cell proliferation and differentiation [6,8]; finally, Wingless-related integration site (Wnt)/β-catenin pathway contributes to chondrocyte maturation and endochondral mineralization through stabilization and nuclear translocation of β-catenin, that drives several transcriptional programs in response to extracellular Wnt ligands [7].

2.3. 3b Intracellular Regulation of Chondrocyte Apoptosis

The apoptosis of hypertrophic chondrocytes represents a key terminal step in growth plate physiology, which is essential for growth plate mineralization and remodeling. The onset of apoptosis is triggered by the intracellular activation of different signaling pathways controlled by members of the Bcl-2 (B-cell lymphoma 2) protein family and executed by caspases. The Bcl-2 protein family regulates mitochondrial outer membrane permeabilization, and includes anti-apoptotic members, such as Bcl-2, that prevent cytochrome C release from mitochondria, and pro-apoptotic members, such as BAX (Bcl-2–associated X protein), that promote cytochrome c release, leading to apoptosis [4].

The key factor in bone mineralization is the association between hypertrophic chondrocyte apoptosis and extracellular phosphate concentrations. The response to physiological levels of extracellular phosphate depends on the maturational state of chondrocytes, as more differentiated cells exhibit increased sensitivity to high phosphate levels and are therefore more prone to apoptosis. Conversely, low extracellular phosphate can reduce apoptosis and affect growth plate remodeling [4,21].

3. X-Linked Hypophosphatemia and Linear Growth

X-linked hypophosphatemia (XLH) is characterized by impaired linear growth due to alterations in growth plate's structure and functionality, under conditions of chronic hypophosphatemia and defective bone mineralization [22].

The most well-established animal model of human XLH is the Hyp mouse, which was first described in 1976 by Eva M. Eicher [23]. This mouse carries a spontaneous deletion in the PHEX gene that starts in exon 16 and extends through the 3'-untranslated region (3'-UTR), and it reproduces the clinical and biochemical features of human XLH, including hypophosphatemia and high circulating FGF23 levels [22]. Growth plates of Hyp mice exhibit decreased chondrocyte proliferation and apoptosis, as well as impaired hypertrophic differentiation. These defects are associated with the loss of chondrocyte polarity and the disruption of normal columnar architecture. Further distinctive features include defective growth plate vascularization and matrix mineralization [22,24]. The main

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pathophysiological mechanisms underlying the alterations in growth plate development and bone mineralization in XLH are summarized in Figure 5.

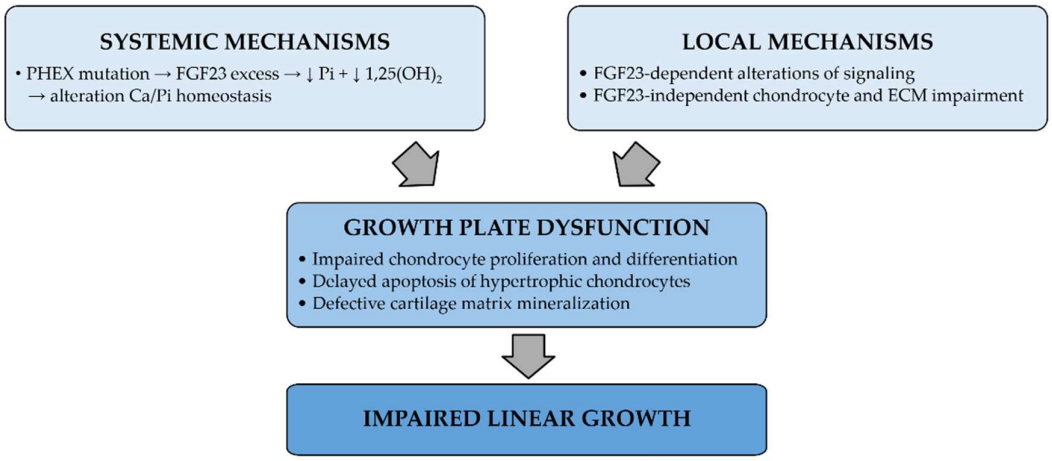

Figure 5. Pathophysiological mechanisms underlying growth retardation in X-Linked Hypophosphatemia (XLH). Loss-of-function mutations in the *PHEX* (Phosphate regulating endopeptidase X-linked) gene result in excess FGF23, which leads to chronic hypophosphatemia and impaired vitamin D metabolism. Locally, several FGF23-dependent and -independent alterations contribute to growth plate dysfunction, ultimately leading to impaired linear growth.

3.1. Systemic Mechanisms Affecting Linear Growth

3.1.1. FGF23-Mediated Hypophosphatemia

Elevated circulating FGF23 levels resulting from loss of PHEX function impair phosphate homeostasis through different mechanisms. FGF23 binds to a specific receptor (FGFR) on the basolateral surface of renal tubular cells, thereby forming a ternary complex with the co-receptor Klotho. This interaction triggers a signaling pathway that suppresses the expression of the sodium phosphate cotransporters NaPi-IIa and NaPi-IIc in proximal renal tubule cells, resulting in renal phosphate wasting. Moreover, FGF23 impairs vitamin D metabolism and suppresses PTH secretion: both mechanisms reduce circulating levels of active vitamin D ($1,25(OH)_2D$) and decrease intestinal phosphate absorption. The resulting hypophosphatemia contributes to impaired growth plate mineralization and chondrocyte function, leading to rickets and reduced linear growth [2,25]

3.1.2. Altered Vitamin D Metabolism

As mentioned above, vitamin D contributes to growth plate integrity primarily by regulating calcium and phosphate availability. In XLH, FGF23 excess leads to the inhibition of renal 1α-hydroxylase (CYP27B1) and stimulation of 24-hydroxylase (CYP24A1) expression, thereby reducing production and promoting degradation of $1,25(OH)_2D$, respectively. Consequently, intestinal phosphate and calcium absorption is reduced, with systemic consequences on mineralization and growth [25]

3.2. Local Mechanisms Affecting Growth Plate Chondrocyte Proliferation

3.2.1. FGF23 Direct Effects

Beyond its physiological role in regulating phosphate homeostasis, FGF23, when elevated, directly impacts growth plate chondrocyte function. Several studies in Hyp mice have demonstrated inhibitory effects of FGF23 on chondrocyte proliferation, mediated by FGFR3 activation in the

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presence of the co-receptor Klotho (sKL), that triggers multiple downstream pathways, including MAPK/ERK, PTHrP-Ihh and STAT1 signaling [25,26].

Elevated FGF23 levels lead to overactivation of the MAPK signaling pathway with an increased phosphorylation of ERK1/2, resulting in the expansion of the hypertrophic chondrocyte layer and disorganization of chondrocyte columns in the growth plate [26,27]. On the contrary, inhibition of this pathway through antagonism of FGF23 has been shown to improve growth plate architecture and accelerate growth [28]. Persistent ERK activation may impair chondrocyte maturation, which physiologically requires a downregulation of this pathway [28]. Accordingly, treatment with MAPK inhibitors, either alone or associated with recombinant GH, improves growth in Hyp mice compared with GH treatment alone [27], and suppression of ERK1/2 activity has also been associated with partial improvement of cartilage and skeletal abnormalities [22,24].

FGF23/sKL-induced FGFR3 activation also interferes with the PTHrP-Ihh axis, contributing to accelerated chondrocyte maturation. Although exogenous Ihh partially reverses this defect, it is not sufficient to fully restore growth plate function, suggesting that additional inhibitory mechanisms, such as activation of STAT-1 (Signal transducer and activator of transcription 1) signaling, contribute to the overall effects of FGF23 [26] (Figure 6).

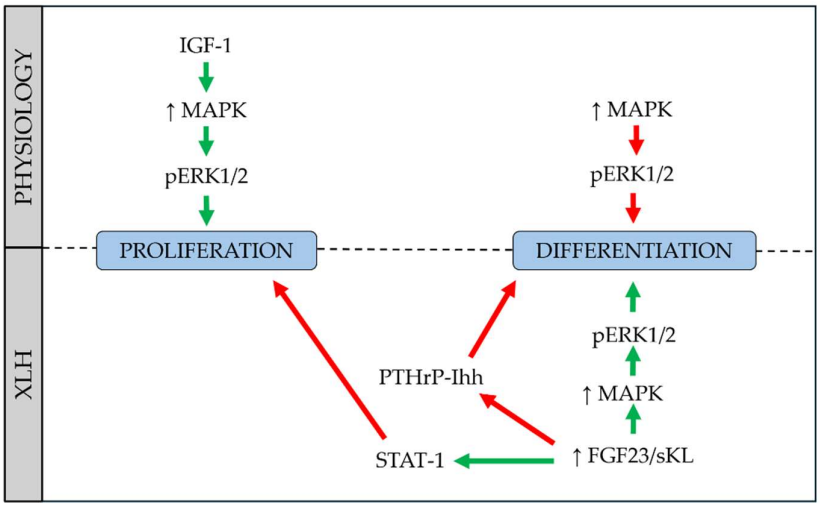

Figure 6. FGF23-mediated dysregulation of growth plate chondrocyte maturation in XLH. Under physiologic conditions, IGF-1-induced activation of MAP kinases pathways promotes chondrocyte proliferation, whereas a downregulation of this pathway is required for terminal differentiation. In XLH, persistent activation of MAPK signaling pathway by FGF23 excess contributes to enhance chondrocyte differentiation. This effect seems to be potentiated by FGF23/sKL (fibroblast growth factor 23/soluble Klotho)-mediated disruption of PTHrP-Ihh feedback loop, and STAT-1 (Signal transducer and activator of transcription 1) activation.

3.2.2. Phosphate-Regulating Endopeptidase Protein (PHEXp) Dependent Mechanisms

In addition to the effects of FGF23-mediated signaling, loss of function of PHEXp contributes to growth plate abnormalities through FGF23-independent mechanisms.

In vitro studies have demonstrated that PHEXp is normally expressed in both proliferating and hypertrophic chondrocytes, whereas it is absent in Hyp mice. This evidence suggests a direct role of PHEXp in regulating cells maturation, and its loss of function may contribute to the cartilage abnormalities observed in Hyp mice [22]. For example, a regulatory mechanism seems to involve SOX9, a crucial transcription factor for chondrogenesis, that activates PHEXp promoter in proliferative chondrocytes; however, the functional relationship between these regulators has yet to be studied [22].

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At the extracellular matrix level, PHEXp also contributes to mineralization through regulation of the release of acidic serine- and aspartate-rich MEPE (Matrix extracellular phosphoglycoprotein)-associated (ASARM) peptides [22,29] (Chapter 3.4).

3.2.3. Vitamin D Local Effects

According to in vitro evidence, vitamin D seems to directly modulate chondrocyte function[17] (Chapter 2.2.5). In line with this, vitamin D receptor (VDR)-null mice develop a rickets-like growth plate phenotype, highlighting the importance of calcitriol signaling for proper chondrocyte maturation and apoptosis [22]. Moreover, Hyp mice treated with $1,25(OH)_2D$ alone exhibit greater improvements in growth plate maturation and bone microstructure compared with those treated with anti-FGF23 antibodies, despite persistently elevated serum FGF23 levels [30].

Elevated FGF23 in XLH increases CYP24A1 (24-hydroxylase) activity, which results in enhanced degradation and reduced local availability of $1,25(OH)_2D$ in the growth plate [25]. Experimental studies on Hyp mice indicate that combined loss of CYP27B1 (1α-hydroxylase) and FGF23 genes results in rickets despite normal phosphate levels; this phenotype is prevented by administration of $1,25(OH)_2D$ [17]. Conversely, suppression of CYP24A1 in mice with elevated FGF23 levels prevents the development of rickets even in the presence of low serum phosphate and $1,25(OH)_2D$ levels. This protective effect is likely mediated by preservation of local $1,25(OH)_2D$ activity, which modulates chondrocyte proliferation through cell cycle mediators such as cyclin D1 and p21 [31].

Interestingly, $1,25(OH)_2D$ has been demonstrated to inhibit PHEX gene expression, while also potentially inducing other phosphatases, able to partially compensate for impaired PHEXp activity [17].

3.2.4. FGFs signaling dysregulation and other local mechanisms

While FGF23 exerts its effects primarily through FGFR/Klotho signaling, other FGFs overexpressed in Hyp mice, such as FGF2, -9, -18, and -21, negatively regulate chondrocyte hypertrophy and proliferation through FGFR1-4 and related pathways. Excess of FGF21, in particular, has been associated with hepatic GH insensitivity and reduced growth in Hyp mice compared to wild-type mice [22].

Beyond FGF-mediated effects, other mechanisms affect Hyp mice chondrocytes hypertrophic differentiation, including impaired cell swelling due to reduced proteoglycan synthesis, as well as reduced expression of Na-K-Cl cotransporter 1 (NKCC1) and aquaporin 1 (AQP1), which regulate ion and water fluxes, respectively [24].

3.3. Impaired Chondrocyte Apoptosis Mechanisms

A central mechanism involved in the pathogenesis of short stature in XLH is the disruption of apoptosis in hypertrophic chondrocytes. Several processes have been shown to play a role in it.

A primary factor is hypophosphatemia. Adequate extracellular phosphate levels are required for proper activation of intracellular signaling pathways, including phosphorylation of key components of the MAPK cascade, which in turn regulates the intrinsic, caspase-9-dependent mitochondrial apoptotic pathway. Consequently, reduced extracellular phosphate availability may compromise the progression of hypertrophic chondrocytes toward apoptosis [21,22].

In addition to upstream signaling defects, alterations in apoptotic processes have also been reported. For example, reduced activity of the pro-apoptotic protein caspase-3 has been observed in distal hypertrophic chondrocytes. Consistently, positivity to bromodeoxyuridine (BrdU), a marker of cell proliferation, is detected in these cells, suggesting a failure of the normal transition to apoptosis during terminal chondrocyte differentiation [24].

Collectively, these alterations result in delayed cells turnover and pathological expansion of the hypertrophic zone.

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3.4. Local Mechanisms Affecting Extracellular Matrix Structure and Mineralization

Beyond defects in chondrocyte proliferation and differentiation, XLH is characterized by impaired mineralization of the cartilage matrix and defective bone remodeling. Although hypophosphatemia is a primary contributor to defective mineralization in XLH, it is evident in both human and mouse models that phosphate supplementation alone does not fully correct rickets, indicating that local factors-contribute to these abnormalities [14,22] (Figure 7).

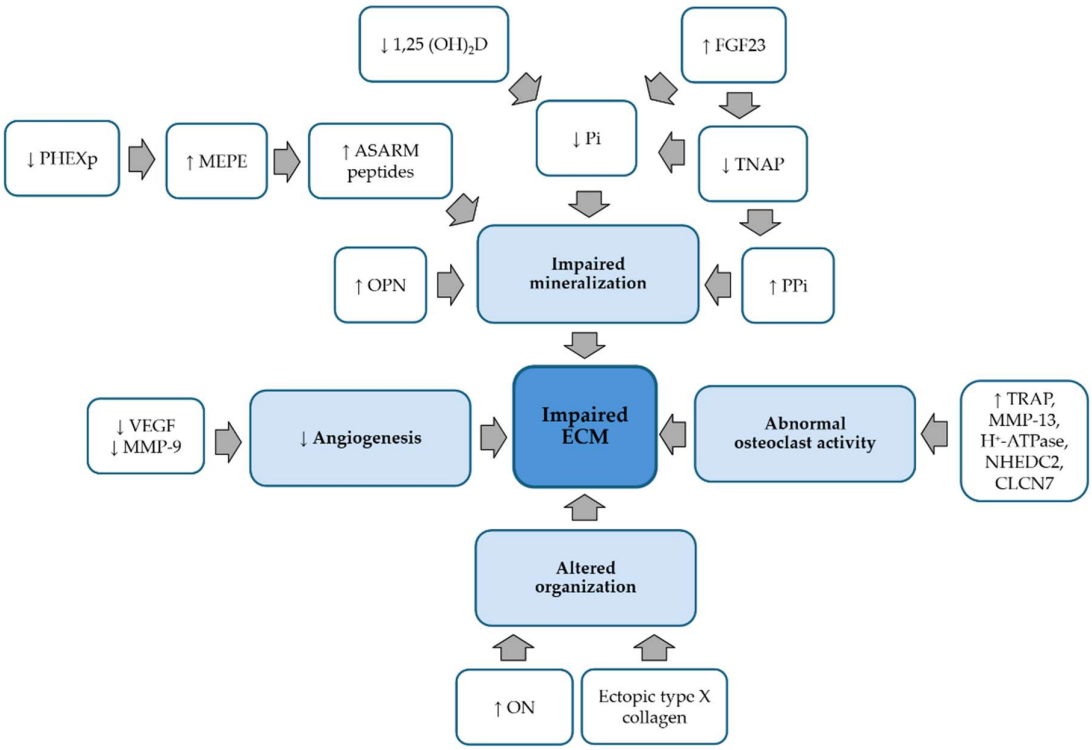

Figure 7. Impaired mineralization and organization of extracellular matrix (ECM) at the growth plate in XLH. In addition to hypophosphatemia, other local mechanisms contribute to reduced ECM mineralization, including accumulation of mineralization inhibitors. Concurrent alterations in angiogenesis, extracellular matrix organization, and osteoclast-mediated remodeling further contribute to growth plate ECM dysfunction and impaired skeletal growth. MEPE Matrix extracellular phosphoglycoprotein; ASARM Acidic serine- and aspartate-rich MEPE-associated motif; OPN Osteopontin; TRAP Tartrate-resistant acid phosphatase; NHEDC2 Na+/H+ exchanger-like domain-containing protein 2; CLCN7 Chloride voltage-gated channel 7; ON Osteonectin.

An important local mechanism involves TNAP, whose expression is negatively regulated in Hyp mice. Reduced TNAP levels result in increased extracellular PPi, a potent inhibitor of hydroxyapatite formation, as well as reduced extracellular phosphate availability [25].

Defective mineralization is further driven by dysregulation of local mineralization inhibitors, including matrix extracellular phosphoglycoprotein (MEPE), a member of the SIBLING (Small Integrin Binding Ligand N-linked Glycoprotein) family. MEPE contains an acidic serine- and aspartate-rich MEPE-associated motif (ASARM), which can be released as a phosphorylated peptide, responsible for impairing bone mineralization and phosphate uptake. Under physiological conditions, PHEXp binds MEPE and prevents ASARM release; however, in XLH, loss of PHEXp function results in elevated MEPE levels and accumulation of ASARM peptides [22,29]. Similarly, FGF23 promotes the production of osteopontin (OPN), another SIBLING family protein that inhibits hydroxyapatite crystal formation [25].

Impaired vascular invasion of the growth plate, driven by downregulation of VEGF and MMP-9, represents another key mechanism contributing to matrix impairment [22].

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In Hyp mice, altered osteoclast activity has also been observed, with a significant increase in enzymes and ion transporters involved in extracellular matrix degradation and acidification, whose regulation is essential for bone resorption [22].

Other mechanisms may affect matrix architecture, including the altered expression of matrix-related proteins in hypertrophic chondrocytes, such as increased osteonectin (ON) [22]. Ectopic type X collagen deposition due to upregulation of COL10A1 gene in Hyp osteoblasts further contributes to bone matrix disorganization [22]

3.5. Impact of Pubertal Hormonal Changes on XLH Growth Outcomes

In general, individuals with XLH experience a normal onset and progression of puberty, including a physiological growth spurt [3]. Puberty represents a critical phase for completing skeletal development and achieving adult stature. As previously mentioned, estrogen plays a central role in this process by promoting growth acceleration, while concurrently driving growth plate senescence through the progressive and irreversible depletion of resting zone chondrocytes [4].

Although pubertal development is usually preserved in XLH, impaired calcium-phosphate metabolism and other environmental factors affecting growth plate function may influence linear growth during this period, potentially attenuating the skeletal response to normal GH - IGF-1 and sex steroid signaling [32].

Final height is largely predicted by prepubertal growth. As the greatest loss of height potential occurs before the onset of puberty, patients with XLH whose linear growth is impaired from early age typically fail to reach their genetic target height. This topic is confirmed by the study of Sochett et al. describing six girls treated with conventional therapy, with a pre-existing height deficit that could not be fully compensated during puberty, despite a near-normal pubertal growth velocity [33]. In addition, impaired mineralization and suboptimal bone accrual during puberty is associated with a high risk of achieving an inadequate peak bone mass and persistent skeletal fragility [1]. As discussed below, early diagnosis and initiation of specific therapy are essential for preserving growth potential and optimizing adult height and bone health, whereas interventions initiated during puberty are likely to have a more limited impact [34].

Some clinical reports have described in the literature the impact of central precocious puberty (CPP) on coexisting rickets, including XLH [35-37]. As in children not affected by XLH, if CPP remains untreated, it may result in premature skeletal maturation and epiphyseal closure, negatively affecting final height [38]. In addition, the increased mineral demand associated with an early and rapid growth spurt may further impair skeletal mineralization and exacerbate the severity of rickets [37].

In selected cases, aromatase inhibitors, such as anastrozole, have been used to delay growth plate closure and potentially improve height outcomes in pediatric patients, by reducing estrogen exposure and prolonging the growth period. The literature describes a patient with XLH and advanced bone age who was treated with anastrozole in combination with burosumab. Pubertal height gain was maintained, and the patient's final height z-score improved to above the predicted genetic target height at 17.5 years-of age [32].

These findings underscore the importance of careful monitoring of pubertal timing and individualized treatment strategies to optimize growth and skeletal outcomes in patients with XLH.

4. Effects of Therapy on Linear Growth in X-Linked Hypophosphatemia

At present, the management of children with XLH includes conventional therapy with phosphate and active vitamin D, and the new approach with FGF23-targeting therapy with burosumab, which aim to correct the underlying abnormalities in growth plate function and bone mineralization. Other approaches, such as recombinant human growth hormone (rhGH), have also been investigated to improve linear growth and skeletal outcomes.

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4.1. Conventional Supplementation Therapy

Conventional therapy of XLH consists of oral supplementation with phosphate and active vitamin D analogues. This treatment aims to improve serum phosphate levels and bone mineralization and to support the normal differentiation of growth plate chondrocytes [3]. Beyond its role in phosphate metabolism, several cellular mechanisms have been proposed to explain the beneficial effects of $1,25(OH)_2D$ in XLH, including the modulation of signaling pathways regulating growth plate function [17] (Chapters 2.2.5 and 3.2.3).

During childhood, this therapeutic approach leads to a partial correction of skeletal deformities and modest improvement of linear growth, yielding better outcomes when treatment is introduced at an early age [3], as confirmed by retrospective studies showing significantly better growth parameters in children who started conventional therapy before the age of one [34,39]. Accordingly, international guidelines recommend initiating conventional therapy as soon as the diagnosis of XLH is confirmed [1,40,41].

Despite early initiation, however, most patients with XLH treated with phosphate and active vitamin D fail to achieve an adult stature in line with their genetic target, with a final height often remaining below -2 standard deviation scores (SDS) compared to reference populations [42,45]. Growth retardation is particularly pronounced in the first years of life, reflecting the impact of the disease on lower limb growth and associated skeletal deformities [44,45]**.** These suboptimal growth outcomes may be partly attributed to treatment-related mechanisms, including stimulation of FGF23 secretion by phosphate and active vitamin D supplementation, which may exacerbate renal phosphate wasting [1,46].

Moreover, growth response to conventional therapy is highly variable among patients even within the same family. This outcome may be influenced by genetic factors, such as vitamin D receptor promoter haplotypes, and clinical variables including disease severity as well as age at diagnosis and at treatment initiation [44,47].

4.2. Monoclonal Antibody therapy

Burosumab is a human monoclonal antibody that targets FGF23. Compared to conventional therapy, early treatment with burosumab appears to improve rickets severity and lower limb deformities, but only slightly improves height z-scores in children with XLH [1]. Moreover, discontinuation of therapy has been documented to be associated with deterioration of bone mineralization and recurrence of osteomalacia. Therefore, current guidelines recommend early initiation of burosumab and continuation of treatment until young adulthood, or at least until the completion of growth, in order to maintain disease control and ensure adequate peak bone mass accrual [1,40,48].

Burosumab exerts its effects by neutralizing FGF23, thereby improving phosphate homeostasis and supporting growth plate function [14]. In preclinical studies, treatment with an FGF23-neutralizing antibody showed to normalize growth plate structure and increase serum phosphate and $1,25(OH)_2D$ levels, with more pronounced results than conventional therapy [22]. In phase 2 and 3 clinical trials, as well as real-world studies, burosumab has demonstrated superior effects over conventional treatment on phosphate homeostasis, rickets and lower limb deformities in children with XLH, in contrast with modest improvements in linear growth [49,50].

In phase 3 clinical trials and case series studies, burosumab showed a modest catch-up growth, in particular when treatment was introduced early in age [51-53]. Nevertheless, other clinical trials and real-world studies have reported no substantial improvements in median height z-scores during follow-up, although a better evolution of linear growth was observed during burosumab treatment, preventing the early pubertal growth decline typically observed in young children with XLH [54-58].

Overall, these findings suggest modest beneficial effects of burosumab on growth in XLH; however, additional studies are needed to evaluate its long-term impact on final adult height, especially in relation to the age of onset of therapy.

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4.3. Potential Role of Recombinant Human Growth Hormone (rhGH)

Although GH deficiency is not a hallmark feature of children with XLH, rhGH has been used in some patients to improve linear growth [3,29].

In preclinical studies in Hyp mice, rhGH improved trabecular and cortical architecture and bone mineralization, but did not normalize growth plate abnormalities. Interestingly, combined inhibition of MAPK signaling pathway (similarly to burosumab FGF23 antagonism) appears to maximize GH effects by improving growth plate architecture, bone mineralization and quality [27].

Clinical outcomes in children with XLH treated with rhGH are heterogeneous. Several short-term studies have reported improvements in height z-scores and growth velocity when rhGH is used either alone [59] or in combination with conventional or burosumab therapy [55,60,61]. Persistence of growth plate abnormalities and preferential truncal growth that can be associated with rhGH therapy, raised concerns about the risk of exacerbating body disproportion and bone deformities, as reported by a few studies [62,63]. Longer studies over three years, comparing rhGH alone or in combination with conventional treatment, confirmed sustained improvements in linear growth and did not show significant worsening of body proportions [64,65]. Nevertheless, a few studies have failed to demonstrate a significant benefit on final adult height as compared with patients treated with conventional therapy alone [66,67].

The different results of these studies are also probably related to the different composition of the study populations, as the efficacy of rhGH appears to depend on various factors, including age, pubertal stage, bone metabolic control and severity of growth retardation and skeletal deformities [68].

A recent systematic Cochrane review concluded that current evidence is insufficient to support routine use of rhGH for improving linear growth, body proportions, or mineral metabolism in XLH [69]. Accordingly, current International Working Group guidelines do not recommend rhGH as a standard therapy for short stature in XLH, mainly due to limited high-quality evidence, small sample sizes, and the observational nature of most available studies [1,40]. Nevertheless, rhGH may be considered in selected cases of children who have not responded adequately to conventional therapy or burosumab [1,41].

In summary, while conventional therapy and burosumab directly target phosphate homeostasis and bone mineralization, rhGH may represent an adjunctive option in selected cases to improve linear growth. The evidence that GH treatment response is influenced by multiple clinical and genetic factors, once again underlines the importance of individualized therapeutic strategies in children affected by XLH.

5. Conclusion and Future Perspectives

Impaired linear growth in children with XLH is driven by complex mechanisms related to dysregulation of the PHEX-FGF23 axis, that also involve additional intra-growth plate and systemic endocrine pathways, leading to direct disruption of epiphyseal plate function. Alterations in chondrocyte proliferation, differentiation, and apoptosis, together with impaired extracellular matrix mineralization, ultimately result in reduced linear growth.

Evidence from both experimental models and clinical studies suggests that excess FGF23 alone does not fully account for the growth impairment observed in XLH. Rather, their findings point to a potential independent role for additional systemic, paracrine, and intracellular factors that contribute to growth plate disorganization.

Several clinical evidence underlines that burosumab is associated with more pronounced improvements in phosphate homeostasis and consequently in better linear growth and bone mineralization in comparison to conventional therapy. However, unsatisfactory and heterogeneous results regarding final height further confirm the involvement of additional molecular mechanisms that are not yet fully characterized.

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An integrated understanding of molecular mechanisms and clinical evidence will be essential to develop more targeted therapeutic strategies to improve growth outcomes in pediatric patients with XLH.

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Abbreviations

The following abbreviations are used in this manuscript:

$1,25(OH)_2D$	1,25-dihydroxyvitamin D
$24,25(OH)_2D$	24,25-dihydroxyvitamin D
25-OHD	25-hydroxyvitamin D
ALP	Alkaline phosphatase
ALS	Acid-labile subunit
ASARM	Acidic serine- and aspartate-rich MEPE-associated motif
AQP1	Aquaporin 1
BMP	Bone morphogenetic protein
CBFA-1/RUNX-2	Core binding factor alpha-1/Runt-related transcription factor 2
CLCN7	Chloride voltage-gated channel 7
CNP	C-type natriuretic peptide
CPP	Central precocious puberty
ERK	Extracellular signal-regulated kinase
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
GH	Growth hormone
GP	Growth plate
Ihh	Indian hedgehog
IGF-1	Insulin-like growth factor 1
IGF-1R	Insulin-like growth factor 1 receptor
IGFBP	Insulin-like growth factor binding protein
MAPK	Mitogen-activated protein kinase
MEPE	Matrix extracellular phosphoglycoprotein
MGP	Matrix Gla protein
MMP	Matrix metalloproteinase
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NHEDC2	Na+/H+ exchanger-like domain-containing protein 2
NKCC1	Na-K-Cl cotransporter 1
OCN	Osteocalcin
ON	Osteonectin
OPN	Osteopontin
PHEX	Phosphate regulating endopeptidase X-linked
Pi	Inorganic phosphate
PPi	Pyrophosphate
PTHrP	Parathyroid hormone-related protein
rhGH	Recombinant human growth hormone
SDS	Standard deviation score
SHOX	Short stature homeobox
SIBLING	Small integrin binding ligand N-linked glycoprotein
sKL	Soluble Klotho
SOX-9	Sex-determining region Y (SRY)-box 9
STAT-1	Signal transducer and activator of transcription 1

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TGF-β	Transforming growth factor β
TNAP	Tissue-nonspecific alkaline phosphatase
TmP/GFR	Ratio of tubular maximum phosphate reabsorption to glomerular filtration rate
TRAP	Tartrate-resistant acid phosphatase
TRP	Tubular reabsorption of phosphate
VDR	Vitamin D receptor
VEGF	Vascular endothelial growth factor
Wnt	Wingless-related integration site
XLH	X-linked hypophosphatemia

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