Turkish Archives of Pediatrics

REVIEW
DOI: 10.5152/TurkArchPediatr.2023.23050

Approach to Rickets: Is It Calciopenic or Phosphopenic?

Sema Nilay Abseyi, Zeynep Şıklar

Department of Pediatric Endocrinology, Ankara University Faculty of Medicine, Ankara, Turkey

ABSTRACT

Rickets is a childhood disorder of decreased mineralization of bone tissue. It is either calciopenic or phosphopenic, according to the deficient mineral. Calcium, phosphate, and vitamin D metabolism should be known to understand the pathophysiology of rickets. A deficiency of calcium or vitamin D can be caused by several conditions. These conditions lead to defective osteoid mineralization, impaired chondrocyte differentiation, and apoptosis in the growth plate, resulting in clinical and radiological findings of rickets. Rickets developing as a result of vitamin D deficiency is the most frequently encountered form. Vitamin D-dependent rickets classification is made according to genetic abnormalities of enzymes that are involved in vitamin D metabolism. Phosphopenic rickets is divided mainly into 2 categories that are FGF23 related or not. A systemic approach that includes a detailed history, physical examination, and laboratory evaluation is required when performing a diagnostic evaluation. Vitamin D and calcium supplementation should be used to treat nutritional rickets. To prevent rickets and its morbidities, vitamin D prophylaxis in the newborn period is suggested. High dose of vitamin D3, 1.25(OH)2D, and calcium are treatment choices in vitamin D-dependent rickets according to its subgroup. If conventional treatment consisting of phosphate and calcitriol is ineffective in the treatment of phosphopenic rickets, Burosumab is the new treatment option.

Keywords: Rickets, Vitamin D, Calcium metabolism, FGF23

INTRODUCTION

Rickets is a cartilage growth plate disorder in children caused by insufficient mineralization of bone tissue due to deficiency of calcium, phosphate, vitamin D, or other cofactors. According to the mineralization deficiency that causes rickets, it is divided into 2 main forms "calciopenic" and "phosphopenic" (Figure 1).[1] It is important to know the mechanism of vitamin D, calcium, and phosphate well to make a complete evaluation of rickets cases.

VITAMIN D, CALCIUM, AND PHOSPHATE MECHANISM

Two different precursor molecules make up the source of vitamin D. The first of these is cholecalciferol (vitamin D3), synthesized from the skin. The second form is ergocalciferol (vitamin D2) which can be used as a source of vitamin D by taking it into the body through plants, drugs, or food enriched with vitamin D.[2-4]

Approximately 90%-95% of vitamin D synthesis takes place in the skin under the influence of sunlight. The B-ring of 7-dehydrocholesterol (pro-vitamin D3) is broken by the nonenzymatic photolysis effect of ultraviolet B (290-315 nm wavelength) rays in the epidermis. As a result, pre-vitamin D3 is formed. Then, with the effect of heat, 2 different double bonds are formed between the carbon atoms in the broken B ring and the synthesis of vitamin D3 takes place.[5]

Corresponding author:
Zeynep Şıklar
✉ zeynepsklr@gmail.com
Received: March 3, 2023
Accepted: April 4, 2023
Publication Date: July 11, 2023

Cite this article as: Abseyi SN, Şıklar Z. Approach to rickets: Is it calciopenic or phosphopenic? *Turk Arch Pediatr.* 2023;58(5):458-466.

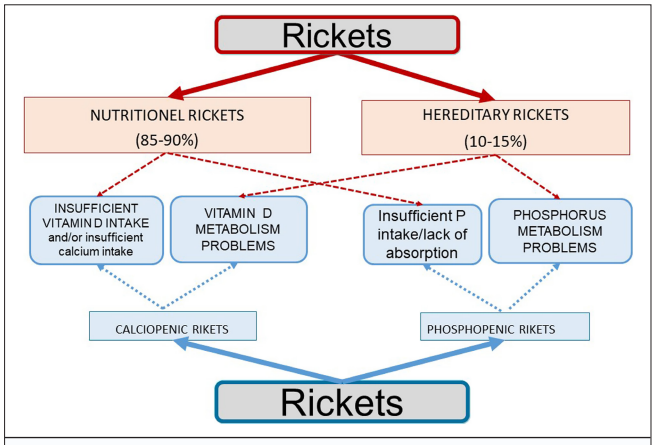

Figure 1. Classification of rickets.

Vitamin D3 synthesized in the skin is released into the systemic circulation, and most of all forms (85%-88%) are transported in serum by binding to vitamin D binding protein, and the remainder (12%-15%) bound to albumin. Vitamin D3 transported to the liver is first converted to 25-hydroxy vitamin D3 (25OHD) by the enzyme cytochrome P450 25-hydroxylase. 25OHD is the main circulating form of vitamin D and is the parameter that gives the best information about the body's vitamin D pool. Its half-life is about 15-20 days.[6,7] Studies have found that the major enzyme responsible for 25-hydroxylation in the body is CYP2R1.[2,5]

The final step of active vitamin D formation is mediated by the 1α-hydroxylase enzyme encoded by the *CYP27B1* in the kidney proximal tubules.[2,5] Factors controlling 1α-hydroxylation activity in the kidney are parathyroid hormone (PTH), calcium, and phosphorus. While hypocalcemia, increased PTH, and hypophosphatemia increase active vitamin D production through renal 1α-hydroxylase enzyme activation, hypercalcemia, fibroblast growth factor 23 (FGF23), and active vitamin D itself exert an inhibitory effect on active vitamin D synthesis via the 1α-hydroxylase enzyme. Active vitamin D increases the synthesis of FGF23 from osteoblasts. FGF23 suppresses the 1α-hydroxylase enzyme and increases the activity of the 24-hydroxylase enzyme. In addition, hypercalcemia inhibits 1α-hydroxylase by suppressing PTH and hyperphosphatemia by increasing FGF23.[2,5,8]

Inactivation of vitamin D occurs through the 24-hydroxylase enzyme encoded by the *CYP24A1* gene.[5] 24-hydroxylase is a critical enzyme that protects the body from the excessive accumulation and possible intoxication of vitamin D.[9]

Vitamin D has important effects on calcium-phosphorus metabolism and bone health. One of the most important functions of vitamin D is to increase the absorption of calcium from the intestines. The absorption of phosphate, another important molecule for bone mineralization, occurs mostly in the jejunum and is actively under the influence of vitamin D.[5] This absorption occurs via the sodium-phosphate cotransporter IIb (NaPi IIb).[10]

Most of the calcium reaching the renal tubules is absorbed from the proximal and distal tubules, and about 1%-2% is excreted in the urine. Phosphate reabsorption takes place under the control of vitamin D by sodium-dependent phosphate carrier proteins (NaPi-IIa and NaPi-IIc) in proximal tubular cells.[5,11]

More than 99% of total calcium is found in bone tissue as a calcium-phosphate complex, while the remaining <1% is distributed between the intracellular and extracellular compartments. Ionized calcium balances the calcium pool in the intra cellular–extracellular space and plays an important role in bone metabolism. This balance is achieved by the cooperation of various hormones (PTH and vitamin D) and the organs they affect (kidney, bone, and intestinal system).[8,12]

Vitamin D receptor (VDR) is a member of the nuclear receptor superfamily, involved in regulating the physiological actions of 1α,25$(OH)_2$D3. Vitamin D receptor requires heterodimeric partner retinoid X receptor (RXR) and co-activators for its functions. The ligand binding triggers the functional association of VDR with RXR, and this heterodimeric complex initiates the activation of target genes.[13]

Calciopenic Rickets

Calciopenic rickets is a disorder that can occur due to vitamin D and/or calcium deficiency or vitamin D resistance. These conditions lead to deterioration in the growth plate and osteoid mineralization, impaired chondrocyte differentiation and apoptosis in the growth plate, and an increase in osteoid tissue, resulting in clinical and radiological findings of rickets.[14] Rickets developing as a result of vitamin D deficiency is a form of nutritional rickets. Although a lack of calcium or phosphorus intake can also cause nutritional rickets, it is most commonly caused by insufficient vitamin D intake. For this reason, when nutritional rickets is mentioned, "rickets due to vitamin D intake deficiency" is understood.[14]

Nutritional rickets due to vitamin D deficiency is most common between the ages of 4 months and 3 years. It is more common in girls and in the winter season. Its frequency varies according to features such as age, gender, season, skin color, weight, and region of residence. Today, its incidence is increasing in both high-income and low-income countries. Although different methodologies have been used, its frequency is reported as 2.9/100 000 in Canada, 4.9/100 000 in Australia, 7.5/100 000 in the United Kingdom, and 24/100 000 in the United States.[8] In our country, the frequency of nutritional rickets has been reported to be between 1.6% and 19% in previous years.[15] 25OHD levels were found below normal in more than 18% of infants in the neonatal intensive care unit.[16] In school-age children, the frequency of vitamin D deficiency was found to be over 17% in the spring.[14]

Pathogenesis

Vitamin D is necessary for the absorption of calcium from the gut, its mobilization to the bone, and bone mineralization. Vitamin D deficiency is defined in 3 periods.[14] First, intestinal calcium absorption decreases and serum calcium level decreases in parallel with insufficient vitamin D and/or calcium intake. In the later period, PTH increases (secondary hyperparathyroidism), osteoclastic activity, and normal levels of serum calcium are tried to be maintained. As plasma calcium rises, hypophosphatemia and an increase in

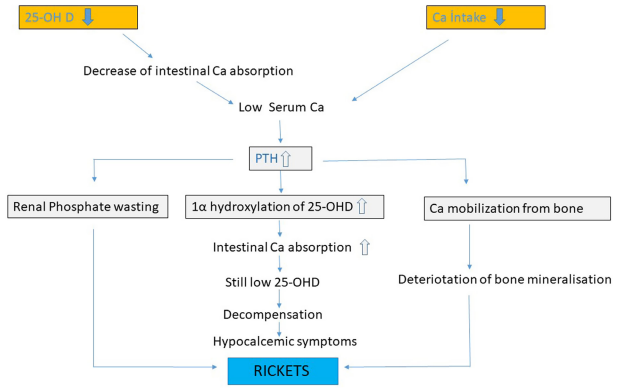

Figure 2. Pathophysiology of nutritional rickets.

alkaline phosphatase (ALP) are observed. During this period, $1\alpha,25(OH)_2D3$ levels are preserved and may even be high. If the vitamin D level decreases further, the third period is started. While PTH and ALP increase even more, hypophosphatemia and hypocalcemia develop together with phosphaturia (Figure 2).[14]

Linear growth in childhood is associated with the activity of the cartilage growth plate located in the epiphysis of long bones. Chondrocytes in the proliferative region of the growth plate divide and organize into columns parallel to the growth direction of the bones. In this region, hypertrophic chondrocytes then differentiate and form the hypertrophic region. These cells undergo apoptosis and differentiate into osteoblasts and form spaces between them, allowing vessels and osteoprogenitor cells that will form the bone matrix in the future to migrate to this region.[8] If the enchondral matrix is insufficiently mineralized, cartilage tissue increases, the growth plate thickens, and the ends of long bones (especially weight-bearing) deteriorate, resulting in rachitic deformities. During the formation and differentiation of the periosteal and endosteal surfaces of trabecular bone and cortical bone tissue, osteoid formation occurs by osteoblasts.[1]

In case of vitamin D deficiency, insufficiency, or ineffectiveness of vitamin D (nutritional or genetic), serum levels of calcium and phosphorus, which play an important role in bone metabolism, decrease. As a result, rickets develops in open cartilage growth plates. In the same situation, a problem called osteomalacia develops in adults.[1] In this case, vitamin D increases bone resorption through VDR signaling in osteoblasts and provides calcium transfer from bone to blood, which leads to deterioration in bone mineralization.[5,12] Rickets clinically manifests itself with skeletal deformities.[1]

Histologically, chondrocyte differentiation and maturation are impaired as a result of insufficient calcification of the cartilage growth plate. Trabecular bone is the region of bone that is particularly poorly mineralized as a result of low phosphate. Inadequate mineralization of osteoid tissue may develop as a result of calcium, phosphate, or vitamin D deficiency in the diet, insufficient absorption of these nutrients from the intestine, impaired metabolism or effect of vitamin D, impaired ALP production and function, and impaired renal retention of calcium or phosphorus.[1]

RISK FACTORS FOR NUTRITIONAL RICKETS DUE TO VITAMIN D DEFICIENCY

Maternal Factors

Vitamin D Deficiency

- Dark-colored skin (vitamin D synthesis) is related to the degree of exposure to sunlight, especially ultraviolet (UV) B rays. Exposure to the sun for 10-15 minutes between 10:00 AM and 03:00 PM in spring and summer in those with light skin color provides sufficient vitamin D synthesis from the skin. However, those with dark skin need to be exposed to sunlight 6-10 times longer than those with light skin.[4,17]
- Closed clothing style and the colors of the clothes used;
- Long winter and autumn seasons at high latitudes;
- Other factors that block UV rays (continuously living in closed environments (such as a home, or office), being unable to go outside due to disability, air pollution, constantly cloudy-closed air, and using sunscreen with high protection factor);
- Insufficient vitamin D intake in the diet.

DIET CONTAINING INSUFFICIENT CALCIUM (POVERTY, MALNUTRITION, AND VEGAN DIET)

Infant/Child-Related Factors

- Neonatal vitamin D deficiency secondary to maternal vitamin D deficiency;
- Insufficient vitamin D supplementation in infant nutrition;
- Extended breastfeeding without starting complementary feeding from 6 months;
- Closed clothing style;
- Winter and autumn seasons at high latitudes;
- A diet containing insufficient calcium (poverty, malnutrition, vegan diet).

Vitamin D-Dependent Rickets

Vitamin D-dependent rickets (VDDR) occurs when there is a problem in the synthesis of 25(OH)D, or $1\alpha,25(OH)_2D3$, or resistance at the VDR. There are different types. As a result of biallelic mutations in the *CYP27B1* gene encoding 1-alpha hydroxylase in VDDR type 1A, $1\alpha,25(OH)_2D3$ cannot be synthesized at a sufficient level.[18] This form is the most common type of VDDR, and its prevalence has been reported as 1-5/10 000.[19]

In VDDR type 1B, there is a deficiency in 25 hydroxylations of vitamins D2 and D3 as a result of a mutation in the *CYP2R1* gene. In other words, there is a deficiency in 25(OH)D synthesis.[18]

Signal transmission at the VDR is impaired in VDDR types 2A and 2B. While there is a mutation in the receptor in VDDR type 2A, VDR signal transmission is impaired as a result of the heterogeneous nuclear ribonucleoprotein C (*HNRNPC*) mutation in type 2B. In VDDR type 3, which is a very rare form, the inactivation of vitamin D metabolites is increased as a result of a mutation in the *CYP3A4* gene. Clinical findings are similar to VDDR type 1A. They do not respond to conventional dose vitamin D treatment.[20]

The cases of VDDR are clinically and biochemically similar to nutritional rickets. Findings in VDDR1A often occur in early

infancy (first 2 years of age). Clinically, it presents with typical signs of rickets, hypotonia, irritability, growth retardation, tetany due to hypocalcemia, and convulsions. Fractures are seen in cases that cannot be diagnosed early.[19,21]

The characteristic of VDDR 1B, which has similar findings, is the amelioration of clinical findings over time in some cases. In VDDR types 2A and 2B, hypocalcemia can be severe during infancy. Normal VDR function is necessary for the hair follicle cycle. Therefore, alopecia can be seen in patients with VDDR types 2A and 2B with VDR resistance.[21] In cases with alopecia, eyebrows are often absent, and some of them also do not have eyelashes. Patients with defects in DNA binding or loss of heterodimeric interactions with RXR develop alopecia. However, alopecia does not develop in patients with ligand-binding or co-activator-binding mutations.[13] Clinical findings are more serious in cases accompanied by alopecia.[18]

Phosphopenic Rickets

FGF23-Mediated Hypophosphatemia

FGF23 is produced especially by osteocytes, and while increasing renal phosphorus excretion, it decreases the effectiveness of vitamin D (by decreasing 1 alpha hydroxylation and increasing 24 hydroxylations). Various problems can cause FGF23-mediated hypophosphatemia and subsequent hypophosphatemic rickets. The most common cause of FGF23-mediated hypophosphatemia is "X-linked hypophosphatemia (XLH)."[22]

X-Linked Hypophosphatemic Rickets

XLH is caused by an X-linked dominant mutation of the phosphate-regulating endopeptidase X-linked (*PHEX*) gene. Sporadic PHEX variants occur commonly. *PHEX* inactivation increases *FGF23* expression, resulting in decreased tubular phosphorus reabsorption and hypophosphatemia. $1\alpha,25(OH)_2D3$ levels are low/normal.[22]

Clinical findings are variable, even among siblings. Usually, signs of rickets begin to develop months after birth. Especially bending of the lower extremities and short stature are noteworthy. Dental abscesses are common. Chiari malformation, craniosynostosis, and sensorineural hearing loss are additional findings seen in childhood. Muscle weakness, bone pain, bone deformities, gait abnormalities, osteoarthritis, enthesopathy, and pseudofractures are seen in patients with XLH in adulthood. Osteomalasic pseudofractures may go unrecognized and are more common than those reported in skeletal surveys. It is an important finding that bone density is not low.[22]

Autosomal Dominant Hypophosphatemic Rickets

In autosomal dominant hypophosphatemic rickets (ADHR), a mutation that affects the protein cleavage site of FGF23 results in a decrease in its degradation, resulting in hypophosphatemic rickets. Its proteolytic degradation is a mechanism that limits the increase in FGF23 protein level. N-acetyl-galactosaminyltransferase 3 (encoded by *GALNT3*) plays a role in preventing this degradation. If *GALNT3* is effective, it reduces the proteolysis of FGF23 by making O-glycosylation of intact FGF23.[22]

Clinical signs can occur at any age. In some, it is seen in early childhood, while in some, it can occur in adolescence or even adulthood. In addition, spontaneous remission and recurrences can be seen in cases.[22]

There is an important link between ADHR and iron deficiency. If iron levels are normal, ADHR will not occur. FGF23 expression and levels are higher in those with iron deficiency. Although *FGF23* expression is increased only in those with iron deficiency, intact FGF23 level is normal because proteolysis is normal. However, if there is an additional decrease in FGF23 proteolysis, the FGF23 level will be even higher. As a result, hypophosphatemic rickets will occur in the presence of iron deficiency in patients with ADHR. Iron replacement in patients with ADHR normalizes FGF23 levels and serum phosphorus levels.[23]

On the other hand, administration of iron infusion (especially carboxymaltose or poly maltose compounds of iron) causes an acute decrease in FGF23 proteolysis in those without *FGF23* mutation. This is manifested by an increase in intact FGF23 levels and a decrease in serum phosphorus.[24]

Autosomal Recessive Hypophosphatemic Rickets

Mutations in dentin matrix protein 1 (*DMP1*), ectonucleotide pyrophosphatase/phosphodiesterase 1 (*ENPP1*), and family with sequence similarity 20, member C (*FAM20C*) genes cause autosomal recessive hypophosphatemic rickets (ARHR).[22]

DMP1 is a protein expressed in bones and teeth, and hypophosphatemic rickets develops with an increase in *FGF23* gene expression in its deficiency. *DMP1* expression is also increased by FAM20C. FAM20C also increases FGF23 phosphorylation, making it more resistant to proteolysis. As a result, in FAM20C deficiency, both FGF23 gene expression increases and FGF23 proteolysis decreases. Consequently, the development of hypophosphatemia is inevitable. *FAM20C* mutation causes Raine syndrome (cerebral calcifications, osteosclerosis of long bones, facial and acral dysmorphism, and dental decay) together with hypophosphatemic rickets.[22]

Interestingly, ENPP1 deficiency is responsible for 2 different diseases: Generalized arterial calcification of infancy (GACI) and ARHR. Nearly half of GACI cases die in early infancy. Autosomal recessive hypophosphatemic rickets develops later in surviving cases. Some cases do not show symptoms in infancy and are diagnosed with direct hypophosphatemic rickets findings.[13,22]

In the *ENPP1* mutation, pyrophosphate production from adenosine triphosphate is reduced, leading to vascular calcification. Despite the low pyrophosphate level, bone mineral density does not increase. On the contrary, a decrease in mineralization is observed with an increase in FGF23 level.[22]

Other Causes of FGF23-Mediated Hypophosphatemic Rickets

Tumor-induced osteomalacia or oncogenic osteomalacia is one of the rare paraneoplastic syndromes. It is a condition that can present with bone pain, muscle weakness, and fractures, often resulting from excessive FGF23 secretion from small mesenchymal tumors. Increased FGF23 causes hypophosphatemia and phosphopenic rickets. It is usually seen after 30 years in adults and is rare in the childhood age group.[25]

Fibrous dysplasia lesions seen in bone tissue may express FGF23. In some cases, hypophosphatemia and rickets may develop.[22]

Fibroblast growth factor receptor 1 (*FGFR1*) activating mutations can cause a disorder called osteoglophonic dysplasia, characterized by rhizomelia, craniofacial anomalies, focal skeletal lesions, and hypophosphatemia. In cutaneous skeletal hypophosphatemia syndrome, which is a neuroectodermal disorder, hypophosphatemia may be found within its systemic findings.[22]

Non-FGF23–Mediated Renal Hypophosphatemia

Chronic hypophosphatemia and hypophosphatemic rickets may develop in cases where phosphorus loss is high as a result of various defects in the renal tubules.[26] One of them is Hereditary hypophosphatemic rickets with hypercalciuria (HHRH). The underlying pathology in HHRH is the presence of a recessive mutation in the solute carrier family 34-member 3 (*SLC34A3*) gene, which encodes renal sodium-dependent phosphate cotransporter 2c (NaP2c). As a result of chronic renal phosphate loss, rickets/osteomalacia, muscle weakness, bone pain, and limb deformities develop. In some cases, skeletal deformities may not be prominent due to the residual activity of NaP2c cotransporters. An important feature of the cases is hypercalciuria which may be accompanied by hypercalcemia as well as rickets findings. Production of $1\alpha,25(OH)_2D3$ is increased in patients with the *SLC34A3* mutation, as FGF23 is not elevated. A high $1\alpha,25(OH)_2D3$ level also causes excessive calcium absorption from the intestines and hypercalciuria. Renal stones and nephrocalcinosis may develop due to hypercalciuria. In some cases, hypercalcemia may worsen with vitamin D replacement. Therefore, before deciding on the use of vitamin D in a patient with hypophosphatemic rickets, hypercalciuria should be controlled, and the diagnosis of HHRH should be excluded.[22,26]

Other renal tubular pathologies that cause hypophosphatemia include Dent's disease, cystinosis, and tyrosinemia. In these cases, the presence of Fanconi syndrome findings (renal losses of amino acids, glucose, bicarbonate, and other solutes) in addition to hypophosphatemia is guiding the differential diagnosis.[22]

Evaluation of the Patient with Rickets

The diagnosis of rickets is based on typical clinical symptoms, radiological findings, and laboratory findings. A systemic approach that includes a detailed history, physical examination, and laboratory evaluation is required when performing a diagnostic evaluation.[21] Nutritional rickets due to vitamin D deficiency should be sought first in a child with signs of rickets, and then genetic causes should be sought. Diagnosing nutritional rickets with only biochemical tests will lead to wrong treatment options.[17]

In the patient's anamnesis, findings such as nutritional characteristics, presence of vitamin D replacement, onset time of symptoms and signs, risk factors that may cause vitamin D deficiency, short stature, characteristics of deformities, accompanying alopecia, and dental deformities should be questioned. Short individuals in the family, orthopedic problems, and the presence of consanguineous marriage should also be questioned. Identification of similar patients in the family history is a warning of the presence of genetically inherited rickets. However, a negative family history does not exclude genetic causes.[17] It should be kept in mind that classical rickets findings may not be evident in cases at an early age (0-3 months), and these cases may present mostly with hypocalcemic seizures.[1,27]

Lack of vitamin D replacement, low calcium diet intake, gastrointestinal surgery, and use of drugs that affect calcium and/or vitamin D metabolism suggest the diagnosis of nutritional rickets. However, in addition to the main pathology, there may be insufficient vitamin D and/or calcium intake in genetically caused rickets.[14]

In the physical examination, height and sitting height measurements of the cases should be taken, whether the trunk and extremities are proportional, the presence of deformities in the extremities, and accompanying findings should be evaluated.[21] Since rickets is a disease of the growing bone, clinical findings, and bone deformations of the fastest-growing body regions are more evident at any age.[17]

Presence of large fontanelles and craniotabes in early childhood (>first 3 months), later frontal bossing, enlargement of wrists and ankles, delayed closure of anterior fontanelle, delayed tooth eruption, tooth enamel hypoplasia, rachitic rosary in the thorax, leg deformities (genu valgum, genu varum or a combination of both, "windswept"—valgus deformity of one leg and varus deformity of the other), bone pain, irritability, and short stature are among the findings detected on examination.[17]

Nonskeletal findings include tetany, hypocalcemic seizures, delayed gross motor development due to muscle weakness, dilated cardiomyopathy due to hypocalcemia, and increased intracranial pressure.[8,17]

In cases with hypophosphatemic rickets, especially bending of the lower extremities, craniosynostosis, and dental abscesses draw attention. Clinically, seizures due to hypocalcemia, tetany, and hypotonia may develop in cases with nutritional rickets and VDDR, while hypocalcemia is not observed in hypophosphatemic rickets.[21]

Laboratory and Imaging

In a patient with suspected rickets based on the history and clinical findings, serum Ca, P, ALP levels, PTH, and 25(OH)D levels are checked first to support the diagnosis. In addition, creatinine, bicarbonate, $1\alpha,25(OH)_2D3$, plasma FGF23 (if possible), and renal tubular functions are the tests that will be required in the differential diagnosis of rickets. A diagnostic approach algorithm is given (Figure 3).

Serum phosphate level tends to be lower in hypophosphatemic rickets than in calciopenic rickets. Since normal phosphate levels are high in the first month of life and gradually decrease toward adulthood, normal levels should be evaluated according to age. Determination of tubular maximum reabsorption of Pi per glomerular filtration rate (TmP/GFR) indicates phosphorus excretion in cases with rickets. TmP/GFR will be found to be decreased in both calciopenic and phosphopenic rickets as there is renal phosphate loss. To determine the renal Fanconi syndrome, the presence of glycosuria and proteinuria should be checked in the urinalysis. Urine Ca/Cr should also be checked for the differential diagnosis of hypophosphatemic rickets with hypercalciuria. Ca level is often low in patients with

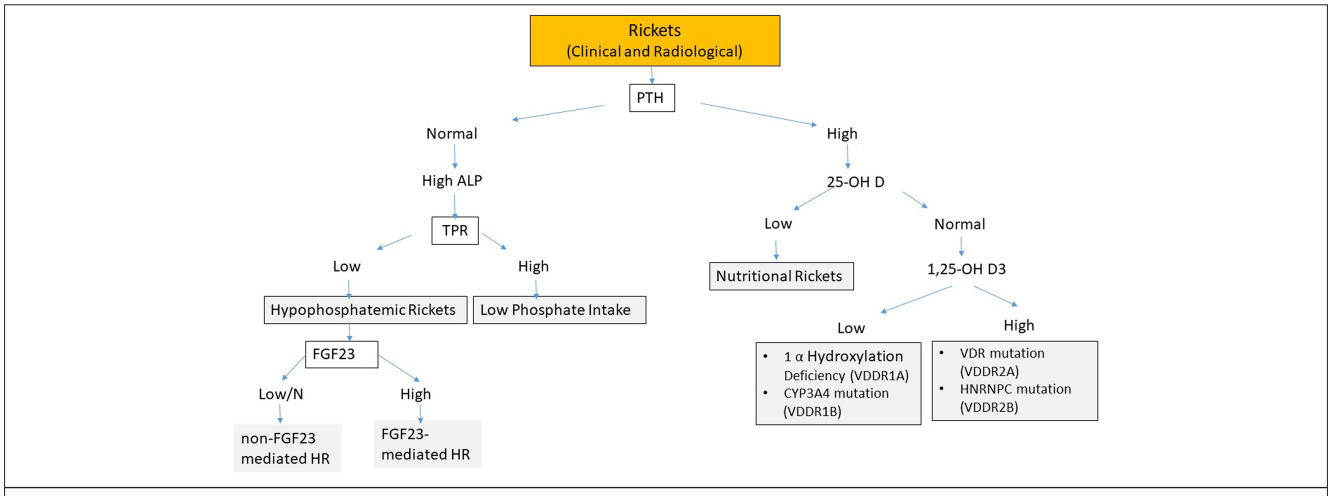

Figure 3. Diagnostic algorithm of rickets.

calciopenic rickets. However, in the early stages of rickets, it can be compensated by the calcium released from the bone as a result of the PTH effect. Calcium is usually normal in phosphopenic rickets.[21]

Serum ALP levels are high in all forms of rickets. Since serum ALP levels vary according to age, it should be checked whether they are within normal limits according to age and gender. In calciopenic rickets, the ALP level may increase up to 10 times the upper limit of normal, while the increase is more moderate (up to 1-3 times) in hypophosphatemic rickets.[21]

Parathyroid hormone is increased especially in calciopenic rickets and is usually normal in hypophosphatemic form. However, since the 1,25(OH)D vitamin level is low, mild PTH increases may be encountered. PTH is suppressed in hypophosphatemic rickets with hypercalcemia.[18]

The main circulating form of vitamin D is 250HD3, and its half-life is 2-3 weeks, indicating both vitamin D intake and endogenous production. For these reasons, it is the best indicator of vitamin D levels in the body.[27] Since the half-life of the biologically active form (Calcitriol) is as short as 4-6 hours, it is not suitable for ideal measurement. Different reference values have been determined by different endocrine communities over the years. According to the latest global consensus report, 250HD is defined as deficiency if it is below 12 ng/mL (30 nmol/L), and as insufficiency, if it is between 12 and 20 ng/mL (30-50 nmol/L). If the level is above 20 ng/mL (50 nmol/L), it is considered sufficient.[17] Secondary hyperparathyroidism usually develops when the 250HD level is less than 20 ng/Ml.[27] Toxicity was defined as hypercalcemia, hypercalciuria, suppressed PTH, and a 250HD level of >100 ng/mL.[17]

Routine vitamin D levels are not recommended in healthy children if there is no risk factor for vitamin D deficiency.[17,28]

Nutritional rickets due to vitamin D deficiency is divided into 3 stages according to biochemical findings.[4,14] (Table 1).

Serum 25(OH)D level is low in cases with nutritional rickets as well as in VDDR types 1B and type 3. However, since vitamin D deficiency may be present in the general population, serum 25(OH)D vitamin levels may be found to be low in hypophosphatemic rickets cases.[21]

Table 1. Biochemical Stages of Nutritional Rickets

	Ca	P	ALP	PTH	25(OH)D	1,25(OHD)
Stage 1	N/↓	N	N/↑	N/↑	↓	N
Stage 2	N	↓	↑	↑/↑↑	↓↓	N/↓
Stage 3	↓/↓↓	↓↓	↑↑	↑↑↑	↓↓↓	↓

ALP, alkaline phosphatase; Ca, calcium; P, phosphorus.

Measurement of FGF23 levels, if possible, is very helpful in the diagnosis of FGF23-induced hypophosphatemic rickets. However, if the plasma centrifugation time is delayed, its level decreases, and it can be falsely measured as normal/low.[21]

Radiologically, changes are detected, especially in rapidly growing bones (hand and ankle, knee). The earliest rachitic change is the loss of the demarcation line between the metaphysis and the growth plate. Later, as rickets progresses, "disorganization of the growth plate with cupping, splaying, formation of cortical spurs and stippling," and deformities are observed.[21] Metaphyseal enlargement, irregularity, enlargement of the growth plate, osteopenia in long bones, stress fractures, increased risk of fracture, especially in those with severe radiological findings, and pelvic deformities that may cause obstetric problems may be seen.[8,17]

A scoring system developed by Thacher can also be used in the radiological evaluation of rickets severity. In this scoring system, radiological changes are scored using knee and wrist radiographs.[29]

TREATMENT

Nutritional Rickets Treatment

Although vitamin D level is below the limit and even vitamin D deficiency is present, calcium absorption is normal in many people and rickets does not develop, bone mineralization does not change, and very few develop secondary hyperparathyroidism. A daily intake of 500 mg of calcium can prevent the development of rickets, even though it is low in vitamin D.[28] Therefore, vitamin D treatment should be considered, especially

Table 2. Vitamin D Treatment Doses in Nutritional Rickets due to Vitamin D Deficiency[18]

	Daily Doses (IU)	A Single Dose (IU)	Daily Maintenance Dose
Vitamin D treatment doses in nutritional rickets			
<3 months	2000	–	400
3-12 months	2000	50 000	400
12 months to 12 years	3000-6000	150 000	600
>12 years	6000	300 000	600

*A concomitant daily calcium intake of 500 mg is recommended regardless of age.

in patients with low vitamin D levels, secondary hyperparathyroidism, and radiologically confirmed rickets.[30]

Since there is not enough data on single-dose treatment in the first 3 months, it is not recommended by consensus. For the first 3 months, a minimum of 2000 IU/day (50 pg/day) has been recommended as a vitamin D treatment dose (Table 2).[17] In a study in which a single dose of 300 000 and 600 000 IU vitamin D therapy was compared, hypercalcemia and/or hypercalciuria were observed in a few cases using 600 000 IU.[31] Oral therapy improves 250HD more quickly than intramuscular therapy. Treatment can be done with vitamin D2 or vitamin D3 and a similar effect is observed. Vitamin D3 may be preferred in a single high-dose treatment due to its long half-life.[17] The major drawbacks of high-dose vitamin D use are the increased risk of severe hypercalcemia and consequent hypercalciuria and kidney stone formation. However, in many studies, it has been shown that the use of high-dose vitamin D at the beginning of treatment is safe, except for a few rare cases.[31]

To prevent the hungry bone syndrome, 500 mg/day of oral calcium should be given routinely with diet or with vitamin D as a drug supplement, regardless of age and weight.[17]

Prophylaxis

It has been shown that 400 IU/day of vitamin D3 given to newborns is sufficient for rickets prophylaxis.[32] Regardless of the diet, 400 IU/day of vitamin D is recommended to be given from birth to one year of age to prevent rickets.[17] An average level of 16 ng/mL can be achieved by oral daily intake of 600 IU of vitamin D in healthy individuals aged 1-70 years.[28]

According to current studies, routine vitamin D supplementation is not recommended for children over the age of 2 who do not have risk factors and do not have chronic diseases related to calcium and vitamin D, even if vitamin D is below the normal value.[28] Since vitamin D has a wide treatment range, side effects are not expected for sufficient vitamin D (400-600 IU/day).[18] For preterm infants weighing less than 1500 grams, the recommended daily total intake is 800-1000 IU/day for the first few months of life. Again, 500-1000 IU/day of vitamin D prophylaxis is recommended for those with risk factors, especially for winter months.[28]

Although vitamin D deficiency is more common in obese children, prophylaxis is controversial if there are no risk factors for them. Approximately 90% of the daily vitamin D requirement is provided by sunlight, and the amount of this synthesis varies according to the sunbathing time and season. For the synthesis of vitamin D, it is recommended that the head and arms be exposed to sunlight for 10-15 minutes at least twice a week, without using sunscreen, between 10:00 AM and 03:00 PM in the April-September period. Foods meet 10% of the vitamin D requirement, and the consumption of sea fish such as salmon and eggs is recommended. Outdoor activities should be encouraged as they support both vitamin D levels and bone mineralization.[28] Adequate calcium intake is also important in rickets prophylaxis (Table 3).

Prevention of congenital rickets: pregnant women, especially those at risk of vitamin D deficiency, should take 600 IU/day vitamin D supplements. This amount will prevent increased cord blood ALP levels, neonatal hypocalcemia, and congenital rickets and ensure normal dental enamel formation. The calcium needs of pregnant women are similar to nonpregnant women.[17,33]

Treatment in Vitamin D-Dependent Rickets Cases

In VDDR type 1A, a lifelong physiologic dose of $1\alpha,25(OH)_2D3$ should be given in 2 doses per day. In the first 3-6 months of the treatment, the dose is given a little higher, as bone remineralization will be rapid and the need for calcium will be high (Hunger bone phenomenon). Another option is to give alphacalcidiol (once a day), which is converted to $1\alpha,25(OH)_2D3$ in the liver. Treatment with 25(OH) vitamin D (calcifediol) is appropriate in VDDR type 1B. Otherwise, a physiological dose of $1\alpha,25(OH)_2D3$ or a pharmacological dose of vitamin D2 or vitamin D3 can be given. In both VDDR 1A and 1B cases, 50 mg/kg/day of elemental calcium should be given to meet the calcium requirement in the early stages of treatment. Serum PTH and calcium levels should be kept in the mid-normal range.[18]

In those diagnosed with VDDR type 2A, high-dose oral calcium (5-6 g/m^2 of elemental calcium) in the first few months of life can provide normocalcemia. In some cases, intravenous calcium infusion may be required. Treatment is similar in VDDR type 2B. It is preferred to use calcitriol or alfacalcidol as a vitamin D preparation. Other options are the administration of vitamin D3, vitamin D2, or 25(OH)D3. Very high doses may be required to achieve normocalcemia. In cases responding to high-dose calcitriol, adding 1000 mg of elemental calcium per day is useful. In some cases, it may not respond to high-dose calcitriol and high-dose (6 g/day) oral calcium. IV calcium

Table 3. Recommended Daily Calcium Intakes[4,18]

Age	Calcium Intake (mg/day)
0-6 months	200
6-12 months	260
1-3 years	700
4-8 years	1000
9-13 years	1300
14-18 years	1300

infusion (1000 mg/day, >12 hours) is given in these cases. In cases of VDDR type 2A, since intestinal calcium absorption will improve at puberty, the need for calcium may decrease. PTH should be kept close to upper-normal levels in the follow-up.[18]

In VDDR type 3, high-dose vitamin D2 or D3 can provide normocalcemia and treatment of cases.[18]

Phosphopenic Rickets Treatment

First of all, it is important to ensure adequate phosphorus intake if there is phosphopenic rickets due to a lack of intake or gastrointestinal problems. Conventional treatment or burosumab treatment is used in phosphopenic rickets with FGF23 excess. Conventional treatment includes a combination of oral phosphate and calcitriol. Phosphate is started at 20-60 mg/kg/day. The dose should not be exceeded 80 mg/kg/day, as it generally has gastrointestinal side effects and may cause secondary hyperparathyroidism. Calcitriol is started at 20-30 ng/kg/day. Treatment is continued at a level that will not cause hypercalciuria and keep the PTH level normal. The treatment goal is to improve rickets signs and bring the ALP level to near-normal levels. Since renal phosphate loss will not improve, normalization of serum phosphorus levels should not be targeted in conventional treatment.[18,22] Since the half-life is short and renal losses continue, phosphate and calcitriol treatments should be given in multiple doses during the day. Only oral phosphate is used in cases with phosphopenic rickets that are not mediated by FGF23 and go with hypercalciuria. In these cases, calcitriol is not given because $1\alpha,25(OH)_2D3$ levels are high and hypercalciuria is present.[22]

FGF23-mediated rickets cases may be affected to varying degrees, and some cases respond well to conventional treatment.[34] It is recommended that burosumab treatment should be considered in children with XLH aged 1 year or older (or from 6 months, as approved in some countries, such as the USA) and in adolescents with radiographic evidence of bone disease,[22,35] The indications that were recommended in the 2019 guidelines are overt bone disease (active rickets on plain radiography) and disease that is refractory to conventional therapy (bone pain, failure to correct ALP, or worsening growth), serious side effects due to conventional treatment (nephrocalcinosis, hyperparathyroidism), the presence of associated complications such as pseudofractures and an inability to adhere to conventional treatment.[22,35,36]

Burosumab is a monoclonal antibody that binds FGF23 and inhibits its activity—approved by the FDA and EMA as monotherapy for hypophosphatemic rickets. It is the only drug that can be used for the mechanism of the disease. Burosumab is mechanistically inappropriate when FGF23 concentrations are low and are contraindicated in moderate to severe kidney disease.[22] Studies have shown that it increases TmP/GFR and improves serum phosphorus and $1\alpha,25(OH)_2D3$ levels. Conventional therapy should be discontinued 1 week before burosumab administration. The dose is started at 0.8 mg/kg subcutaneously every 2 weeks. The dose can be increased up to 2 mg/kg to maintain serum phosphorus levels at low-moderate normal levels. Periodic measurement of serum phosphorus at peak and through time points is important to monitor burosumab. If serum phosphorus is elevated, regardless of treatment modality, the doses should decrease. Worsening kidney function or nephrocalcinosis also prompts dose decreases.[22] Burosumab treatment is well-tolerated, with minor injection site reactions, pain in the extremities, fever, rash, myalgia, and headaches reported.[36]

A phase III study including children aged 1–12 years demonstrated that burosumab was superior to conventional therapy in improving, among many parameters, serum phosphate and $1\alpha,25(OH)_2D3$, radiographic rickets findings and length/height Z-score at week 64.[37] In children with XLH, burosumab administration for 160 weeks improved phosphate homeostasis and rickets and was well-tolerated.[38]

In conclusion, the diagnosis of rickets is based on the presence of typical clinical, biochemical, and radiological findings. Nutritional rickets due to vitamin D deficiency, calciopenic type, is the most common form. However, with the provision of adequate vitamin D and calcium intake in children, the nutritional frequency will decrease and genetically caused rickets will begin to attract attention more frequently. X-linked hypophosphatemic rickets has an important place among phosphopenic rickets in our country. Although there are common features in clinical and laboratory findings, there are differences according to the type of rickets, and paying attention to these will provide a more accurate diagnosis.

Adequate calcium intake and normal vitamin D levels are required in all patients with rickets in treatment. While nutritional rickets can be easily treated with replacement, VDDRs may require high-dose vitamin D or vitamin D analogs and parenteral calcium supplementation, depending on the underlying pathology. Phosphopenic rickets is often FGF23 dependent, and burosumab is a good treatment option if conventional therapy is ineffective. It may also require additional treatment specific to the underlying disease.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – Z.Ş., S.N.A.; Design – Z.Ş.; Supervision – Z.Ş.; Resources – Z.Ş., S.N.A.; Materials – Z.Ş., S.N.A.; Data Collection and/or Processing – Z.Ş., S.N.A.; Analysis and/or Interpretation – Z.Ş., S.N.A.; Literature Search – Z.Ş., S.N.A.; Writing – S.N.A., Z.Ş.; Critical Review – Z.Ş., S.N.A.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: This study received no funding.

REFERENCES

1. Root AW, Levine MA. Disorders of mineral metabolism. Abnormalities of mineral homeostasis in the newborn, infant, child and adolescent. In: Sperling MA, Majzoub JA, Menon RK, Stratakis CA, eds. *Sperling Pediatric Endocrinology*. Elsevier: Philadelphia; 2020: 705-813.
2. Bikle D, Christakos S. New aspects of vitamin D metabolism and action- addressing the skin as source and target. *Nat Rev Endocrinol*. 2020;16(4):234-252. [CrossRef]

3. Houghton LA, Vieth R. The case against ergocalciferol (vitamin D2) as a vitamin supplement. *Am J Clin Nutr*. 2006;84(4):694-697. [CrossRef]
4. Castano L, Madariaga L, Grau G, García-Castaño A. 25(OH)Vitamin D Deficiency and Calcifediol Treatment in Pediatrics. *Nutrients*. 2022;14(9):25. [CrossRef]
5. Bikle DD, Feingold KR, Anawalt B, et al. *Vitamin D: Production, Metabolism and Mechanisms of Action*. South Dartmouth, MA: MDText.com, Inc; 2000. Endotext [internet]. Published online December 31, 2021.
6. Stoffers AJ, Weber DR, Levine MA. An update on vitamin D Deficiency in the twenty-first century: nature and nurture. *Curr Opin Endocrinol Diabetes Obes*. 2022;29(1):36-43. [CrossRef]
7. Heaney RP, Horst RL, Cullen DM, Armas LA. Vitamin D3 distribution and status in the body. *J Am Coll Nutr*. 2009;28(3):252-256. [CrossRef]
8. Gentile C, Chiarelli F. Rickets in children: an update. *Biomedicines*. 2021;9(7):738. [CrossRef]
9. Herrmann M. Assessing vitamin D metabolism - four decades of experience. *Clin Chem Lab Med.*, 2023;61(5):880-894. [CrossRef]
10. Miller WL, Imel EA. Rickets, vitamin D, and Ca/P metabolism. *Horm Res Paediatr*. 2022;95(6):579-592. [CrossRef]
11. Peacock M. Phosphate metabolism in health and disease. *Calcif Tissue Int*. 2021;108(1):3-15. [CrossRef]
12. Peacock M. Calcium metabolism in health and disease. *Clin J Am Soc Nephrol*. 2010;5(suppl 1):S23-S30. [CrossRef]
13. Kashyap J, Kumari N, Ponnusamy K, Tyagi RK. Hereditary Vitamin D-Resistant Rickets (HVDRR) associated SNP variants of vitamin D receptor exhibit malfunctioning at multiple levels. *Biochim Biophys Acta Gene Regul Mech*. 2023;1866(1):194891. [CrossRef]
14. Orbak Z. Nutrisyonel Raşitizm. In: Darendeliler F, Aycan Z, Kara C, Özen S, Eren E, eds. *Çocuk Endokrinolojisi ve Diyabet*. İstanbul: İstanbul Tıp Kitabevleri; 2021:1852-1860.
15. Hatun Ş, Ozkan B, Bereket A. Vitamin D deficiency and prevention: Turkish experience. *Acta Paediatr*. 2011;100(9):1195-1199. [CrossRef]
16. Fedakâr A. Vitamin D deficiency, prevalence and treatment in neonatal period. *Endocr Metab Immune Disord Drug Targets*. 2019;19(6):866-873. [CrossRef]
17. Munns CF, Shaw N, Kiely M, et al. Global consensus recommendations on prevention and management of nutritional rickets. *J Clin Endocrinol Metab*. 2016;101(2):394-415. [CrossRef]
18. Haffner D, Leifheit-Nestler M, Grund A, Schnabel D. Rickets guidance: part II-management. *Pediatr Nephrol*. 2022;37(10):2289-2302. [CrossRef]
19. Kaygusuz SB, Alavanda C, Kirkgoz T, et al. Does genotype-phenotype correlation exist in vitamin D-dependent rickets type IA: report of 13 new cases and review of the literature. *Calcif Tissue Int*. 2021;108(5):576-586. [CrossRef]
20. Mantoanelli L, de Almeida CM, Coelho MCA, et al. Vitamin D-dependent rickets Type 3: a case report and systematic review. *Calcif Tissue Int*. 2023;112(4):512-517. [CrossRef]
21. Haffner D, Leifheit-Nestler M, Grund A, Schnabel D. Rickets guidance: part I-diagnostic workup. *Pediatr Nephrol*. 2022;37(9):2013-2036. [CrossRef]
22. Ackah SA, Imel EA. Approach to hypophosphatemic rickets. *J Clin Endocrinol Metab*. 2022;108(1):209-220. [CrossRef]
23. Imel EA, Liu Z, Coffman M, Acton D, Mehta R, Econs MJ. Oral iron replacement normalizes fibroblast growth factor 23 in iron-deficient patients with autosomal dominant hypophosphatemic rickets. *J Bone Miner Res*. 2020;35(2):231-238. [CrossRef]
24. Wolf M, Rubin J, Achebe M, et al. Effects of iron isomaltoside vs ferric carboxymaltose on hypophosphatemia in iron-deficiency anemia: two randomized clinical trials. *JAMA*. 2020;323(5):432-443. [CrossRef]
25. Jiajue R, Ni X, Jin C, et al. Early discrimination between tumor-induced rickets/osteomalacia and X-linked hypophosphatemia in Chinese children and adolescents: a retrospective case-control study. *J Bone Miner Res*. 2021;36(9):1739-1748. [CrossRef]
26. Stürznickel J, Heider F, Delsmann A, et al. Clinical spectrum of hereditary hypophosphatemic rickets with hypercalciuria (HHRH). *J Bone Miner Res*. 2022;37(8):1580-1591. [CrossRef]
27. Saggese G, Vierucci F, Prodam F, et al. Vitamin D in pediatric age: consensus of the Italian Pediatric Society and the Italian Society of Preventive and Social Pediatrics, jointly with the Italian Federation of Pediatricians. *Ital J Pediatr*. 2018;44(1):51. [CrossRef]
28. Reinehr T, Schnabel D, Wabitsch M, et al. Vitamin D supplementation after the second year of life: joint position of the Committee on Nutrition, German Society for Pediatric and Adolescent Medicine, and the German Society for Pediatric Endocrinology and Diabetology. *Mol Cell Pediatr*. 2019;6(1):3. [CrossRef]
29. Thacher TD, Fischer PR, Pettifor JM, Lawson JO, Manaster BJ, Reading JC. Radiographic scoring method for the assessment of the severity of nutritional rickets. *J Trop Pediatr*. 2000;46(3):132-139. [CrossRef]
30. Grossman Z, Hadjipanayis A, Stiris T, et al. Vitamin D in European children-statement from the European Academy of Paediatrics (EAP). *Eur J Pediatr*. 2017;176(6):829-831. [CrossRef]
31. Cesur Y, Caksen H, Gündem A, Kirimi E, Odabaş D. Comparison of low and high dose of vitamin D treatment in nutritional vitamin D deficiency rickets. *J Pediatr Endocrinol Metab*. 2003;16(8):1105-1109. [CrossRef]
32. Zittermann A, Pilz S, Berthold HK. Serum 25-hydroxyvitamin D response to vitamin D supplementation in infants: a systematic review and meta-analysis of clinical intervention trials. *Eur J Nutr*. 2020;59(1):359-369. [CrossRef]
33. Orbak Z, Karacan M, Doneray H, Karakelleoglu C. Congenital rickets presenting with hypocalcaemic seizures. *West Indian Med J*. 2007;56(4):364-367.
34. Şıklar Z, Turan S, Bereket A, et al. Nationwide Turkish cohort study of hypophosphatemic rickets. *J Clin Res Pediatr Endocrinol*. 2020;12(2):150-159. [CrossRef]
35. Mughal MZ, Baroncelli GI, de Lucas-Collantes C, et al. Burosumab for X-linked hypophosphatemia in children and adolescents: opinion based on early experience in seven European countries. *Front Endocrinol (Lausanne)*. 2022;13:1034580. [CrossRef]
36. Trombetti A, Al-Daghri N, Brandi ML, et al. Interdisciplinary management of FGF23-related phosphate wasting syndromes: a Consensus Statement on the evaluation, diagnosis, and care of patients with X-linked hypophosphatemia. *Nat Rev Endocrinol*. 2022;18(6):366-384. [CrossRef]
37. Imel EA, Glorieux FH, Whyte MP, et al. Burosumab versus conventional therapy in children with X-linked hypophosphatemia: a randomized, active-controlled, open-label, phase 3 trial. *Lancet*. 2019;393(10189):2416-2427. [CrossRef]
38. Linglart A, Imel EA, Whyte MP, et al. Sustained efficacy and safety of burosumab, a monoclonal antibody to FGF23. *J Clin Endocrinol Metab*. 2022;107(3):813-824. [CrossRef]