BMJ Best Practice

Rickets

Straight to the point of care

Last updated: May 13, 2025

Table of Contents

Summary

Rickets is deficient mineralisation at the growth plate of long bones, resulting in faltering growth. If the underlying condition is not treated, bone deformity occurs, typically causing bowed legs and thickening of the ends of long bones.

Rickets only occurs in growing children before fusion of the epiphyses, and typically affects the wrists, knees, and costochondral junctions.

Rickets occurs primarily as a result of a nutritional deficiency of vitamin D, but can be associated with nutritional deficiencies of calcium or phosphorus. Hypophosphataemic rickets is a common genetic cause of rickets.

The mainstay of treatment is to correct vitamin D deficiency and to ensure adequate calcium intake.

Vitamin D deficient rickets can be prevented in many cases by ensuring that children and pregnant women have sufficient vitamin D and calcium intake.

Definition

Rickets refers to changes caused by deficient mineralisation at the growth plate of long bones. Osteomalacia refers to impaired mineralisation of the bone matrix. Rickets and osteomalacia usually occur together while the growth plates are open. Rickets only occurs in growing children before fusion of the epiphyses; osteomalacia can occur after the growth plates have fused.[1] [2]

Rickets can manifest in childhood at the distal forearm, knee, and costochondral joints, as these are sites of rapid bone growth, where large quantities of calcium and phosphorus are required for mineralisation.[3] Characteristic features include widening of the bones at the wrists and knees, bowing of the legs, spine deformities, fractures, bone pain, and dental abnormalities.[4]

Epidemiology

In a community-based population in the US, the incidence of nutritional rickets in children younger than 3 years was 24.1 per 100,000 for the decade beginning in 2000.[8] Nutritional rickets is associated with black and South Asian ethnicity, and with breastfeeding.[4] [8][9] [10] The peak incidence of rickets is between 6 and 23 months, with a further peak among adolescents aged 12 to 15 years.[11]

Globally, nutritional deficiencies are the leading cause of rickets, followed by vitamin D-dependent, vitamin D-resistant, and renal rickets. Surprisingly, in the sunniest areas of the world, rickets is still a major health problem. Reasons for this may include sociocultural factors (such as burka-wearing practices, an increase in sedentary lifestyles, less time spent outdoors), foods unfortified with vitamin D, and diets low in calcium.[12] [13] Increased skin pigmentation is associated with reduced capacity to synthesise colecalciferol. Increased sunscreen use has also been implicated in vitamin D deficiency.[14]

Of the genetic causes of rickets, the most common is X-linked hypophosphataemic rickets, with a prevalence of 1 in 20,000.[6] The prevalence of X-linked hypophosphataemic rickets is estimated to be between 16 per million and 50 per million.[6] [15] In children presenting with a new diagnosis of rickets, vitamin D deficiency and X-linked hypophosphataemic rickets are diagnosed at similar rates. Other genetic causes (mutations in vitamin D 25-hydroxylase or 1-alpha-hydroxylase enzymes or in the vitamin D receptor, or autosomal dominant and autosomal recessive hypophosphataemic rickets) are very rare.

Aetiology

Vitamin D metabolism is dependent on sunlight and enzymatic conversion in the liver and kidneys. Ultraviolet light converts 7-dehydrocholesterol to colecalciferol (vitamin D3). Colecalciferol may also be obtained from the diet. Colecalciferol is converted to calcidiol (25-hydroxyvitamin D) by vitamin D 25-hydroxylase in the liver. Calcidiol is converted to calcitriol (1,25-dihydroxyvitamin D) by 1-alpha-hydroxylase in the kidney. Ergocalciferol (vitamin D2) is obtained from the diet and is metabolised in a similar manner as colecalciferol.[4]

Causes of calcium-deficient rickets include nutritional or malabsorptive vitamin D deficiency, a defect of 1-alpha-hydroxylase, dysfunction of the vitamin D receptor, dietary calcium deficiency, or chronic renal failure resulting in decreased renal vitamin D synthesis.[5]

The main reasons for inadequate vitamin D supply in infants from Western countries are prolonged breastfeeding without vitamin D supplementation and concomitant avoidance of sun exposure. Genetic factors and air pollution have been implicated in vitamin D deficiency in Indian children.[13] At latitudes above 40º north or south, no effective synthesis of colecalciferol occurs in winter months, so deficiency is more common.[9] [16]

Phosphate-deficient rickets is almost always caused by renal phosphate wasting. Genetic hypophosphataemic rickets, oncogenic hypophosphataemic rickets, and rickets associated with McCune-Albright syndrome result from excessive blood levels of fibroblast growth factor-23 (FGF-23), a hormone (secreted by osteoblasts, osteoclasts, and osteocytes) that decreases phosphate reuptake in the kidney. Hereditary hypophosphataemic rickets with hypercalcuria, Fanconi syndrome, and renal tubular acidosis type II are caused by mutations in ion transporter genes.[6] [17] Nutritional deficiency of phosphate is a rare cause of rickets. Phosphate is abundant in most diets but may not be sufficient in growing infants, or it may be precipitated in the stomach by antacids.[5]

Medications that can cause calcium and phosphorus deficiency include loop diuretics and corticosteroids, and phenytoin can cause target organ resistance to calcitriol.[4]

Pathophysiology

Growth plate thickness is determined by chondrocyte proliferation and hypertrophy, vascular invasion, and conversion into primary bone spongiosa. Mineral deficiency prevents the normal process of bone mineral deposition. If mineral deficiency (whether calcium or phosphate) occurs at the growth plate, growth slows and there is delayed bone age. This condition is called rickets. Poor mineralisation of trabecular bone, resulting in a greater proportion of unmineralised osteoid, is the condition of osteomalacia. Rickets is found only in growing children before fusion of the epiphyses, whereas osteomalacia is present at all ages. All rickets patients have osteomalacia, but not all patients with osteomalacia have rickets. If the underlying condition does not improve, bone deformity occurs.[3][5]

In calcium-deficient rickets, the primary defect results from lack of vitamin D, or lack of vitamin D effect. This results in decreased calcium absorption in the gut.[18] This reduction in calcium absorption increases parathyroid hormone secretion, which acts to preserve blood calcium levels by 1) activating bone resorption, 2) decreasing renal calcium loss, 3) increasing renal phosphate loss, and 4) increasing vitamin D activation by upregulating the vitamin D 1-alpha-hydroxylase enzyme in the kidney. The combination of decreased calcium and phosphate availability results in rickets.

In phosphate-deficient rickets, the primary defect causes severe renal phosphate wasting. Decreased phosphate availability results in rickets.

Classification

Causes of rickets[3][5] [6]

1. Calcium-deficient rickets with secondarily elevated parathyroid hormone levels (sometimes referred to as hypocalcaemic rickets):

- Lack of vitamin D due to
    - Decreased sun exposure
    - Dietary-deficient intake
    - Malabsorption
    - Liver disease (affects conversion of colecalciferol to calcidiol)
    - Anticonvulsant drugs (phenytoin may cause target organ resistance to calcitriol)
    - Renal osteodystrophy
    - Type I or pseudovitamin D-deficient rickets occurs because of a defect in 1-alpha-hydroxylase, the enzyme responsible for the conversion of 25-hydroxyvitamin D into the active metabolite.
- End-organ resistance
    - Very rare autosomal recessive disorder associated with end-organ resistance to calcitriol, usually caused by mutations in the gene encoding the vitamin D receptor. This is called type II vitamin D-dependent rickets.
- Dietary calcium deficiency.

2. Phosphate-deficient rickets (without secondarily elevated parathyroid hormone levels) may be caused by:

- Renal phosphate wasting
    - Genetic hypophosphataemic rickets
        - X-linked hypophosphataemic rickets
        - Autosomal dominant hypophosphataemic rickets
        - Autosomal recessive hypophosphataemic rickets
        - McCune-Albright syndrome
        - Hereditary hypophosphataemic rickets with hypercalcuria
        - Fanconi syndrome
        - Renal tubular acidosis (type 2/proximal)
    - Oncogenic hypophosphataemia
- Phosphate deficiency from poor intake or malabsorption.

Case history

Case history #1

A 24-month-old girl has faltering growth and an unusual gait. She has bowed legs, thick wrists, and dental caries. Her weight (8 kg) and height (72.5 cm) are below the 3rd percentiles for her age. Her diet consists predominantly of breastfeeding 5 times daily. The patient's antenatal, delivery, and post-natal history are unremarkable. She lives with her parents. Laboratory studies reveal elevated total alkaline phosphatase and elevated intact parathyroid hormone level. The 25-hydroxyvitamin D level is decreased. Plain x-rays of the patient's knees and wrists demonstrate osseous changes including metaphyseal cupping and flaring, epiphyseal irregularities, and widening of the physeal plates.

Case history #2

A 13-year-old girl presents to the emergency department with 4-day history of knee pain. She cannot recall any injury to account for her symptoms. She has localised tenderness of the distal femur with no swelling, warmth, or erythema. The knee joint itself is unremarkable, with no effusion and full range of movement. Plain x-rays of the knee show generalised reduced bone density with cortical thinning, coarse trabecular pattern, and a Looser's zone (pseudofracture). Blood testing shows hypocalcaemia, low levels of vitamin D, elevated levels of parathyroid hormone, and high levels of alkaline phosphatase. Liver and renal chemistries are otherwise unremarkable.

Other presentations

Other presentations of rickets include hypoplasia of the dental enamel; delay in the closure of the fontanelles; parietal and frontal bossing; craniotabes (soft skull bones); rachitic rosary (enlargement of the costochondral junction, visible as beading along the anterolateral aspects of the chest); and a Harrison's groove, caused by the muscular pull of the diaphragmatic attachments to the lower ribs. Hypocalcaemic rickets may affect the musculoskeletal system, with decreased muscle tone, leading to delayed achievement of motor milestones, and result in predisposition to infections. Hypocalcaemia may also present with carpopedal spasms, tetany, or seizures.[4][5]

Hypophosphataemic rickets has highly variable clinical characteristics and may not be diagnosed until adulthood. Adults may present with short stature, osteomalacia, bowed legs, lower leg pain, arthritis, stress fractures, dental caries, dental abscesses, and calcification of the tendons and ligaments (enthesopathy).[7]

Approach

Information about the child's diet should include specifics of vitamin D and calcium intake. Sunlight exposure should be noted. Review of systems should focus on growth and orthopaedic concerns.

Clinical

Rickets is characterised by delayed growth, bone pain, and bone deformity. The type of deformity depends on the biomechanical situation of the extremities at the time when the structural weakness develops. Bone deformities of the forearms and posterior bowing of the distal tibia can occur in infants, whereas exaggerated physiological bowing of the legs (genu varum) is a finding in toddlers who have started walking. Older children may have valgus or windswept (valgus deformity of one leg and varus deformity of the other) deformities of the legs.[4] [5] [24] Metaphyseal widening can be seen adjacent to the major joints as well as along the costochondral joints, creating the 'rachitic rosary'.

Signs and symptoms of hypocalcaemia, such as muscle cramps, muscle weakness, numbness, paraesthesias, carpopedal spasm, tetany, and seizures may be present in hypocalcaemic rickets.[4]

Malnutrition manifested as rickets. Note the bowed legs and enlarged right wrist

CDC

Malnutrition manifested as rickets. Note the bowed legs and knees

CDC

Laboratory

Traditional rickets is caused by a quantitative or qualitative lack of vitamin D. Serum levels of calcium, phosphorus, calcidiol, alkaline phosphatase, parathyroid hormone (PTH), urea nitrogen, and creatinine are all measured initially. Calcitriol (1,25-dihydroxyvitamin D) is the active form of vitamin D, but calcidiol (25-hydroxyvitamin D) is preferred for testing as it has a longer half-life and is found at much higher levels in the serum. Urine calcium and phosphorus are also tested initially.[4]

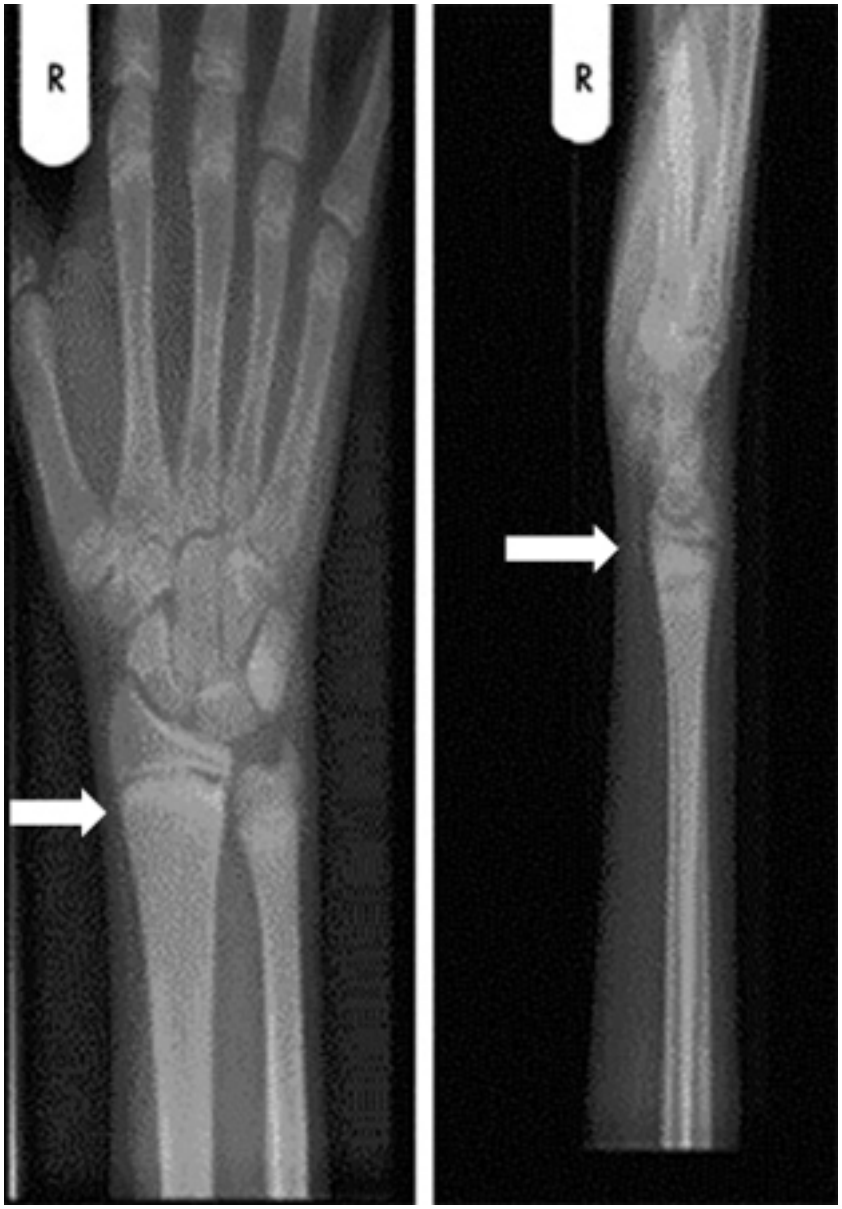
The most common laboratory findings in nutritional rickets (due to vitamin D deficiency) are decreases in serum calcium, serum phosphorus, calcidiol, calcitriol, and urinary calcium, with elevated serum PTH and alkaline phosphatase and urinary phosphorus. Rickets is unlikely if both serum inorganic phosphorus and PTH levels are normal.[4] [5]

Hypophosphataemic rickets is caused by renal phosphate wasting. Serum phosphate levels are low and urine phosphate levels are high. Serum alkaline phosphatase levels will be elevated. Serum levels of calcium, PTH, calcidiol, and calcitriol are normal in hypophosphataemic rickets. Vitamin D deficiency is common and can complicate the presentation of hypophosphataemic rickets. Vitamin D deficiency must be corrected before the diagnosis of hypophosphataemic rickets can be made. A low percent tubular reabsorption of phosphate (TRP) in the absence of vitamin D deficiency is diagnostic of hypophosphataemic rickets.[25]

Imaging

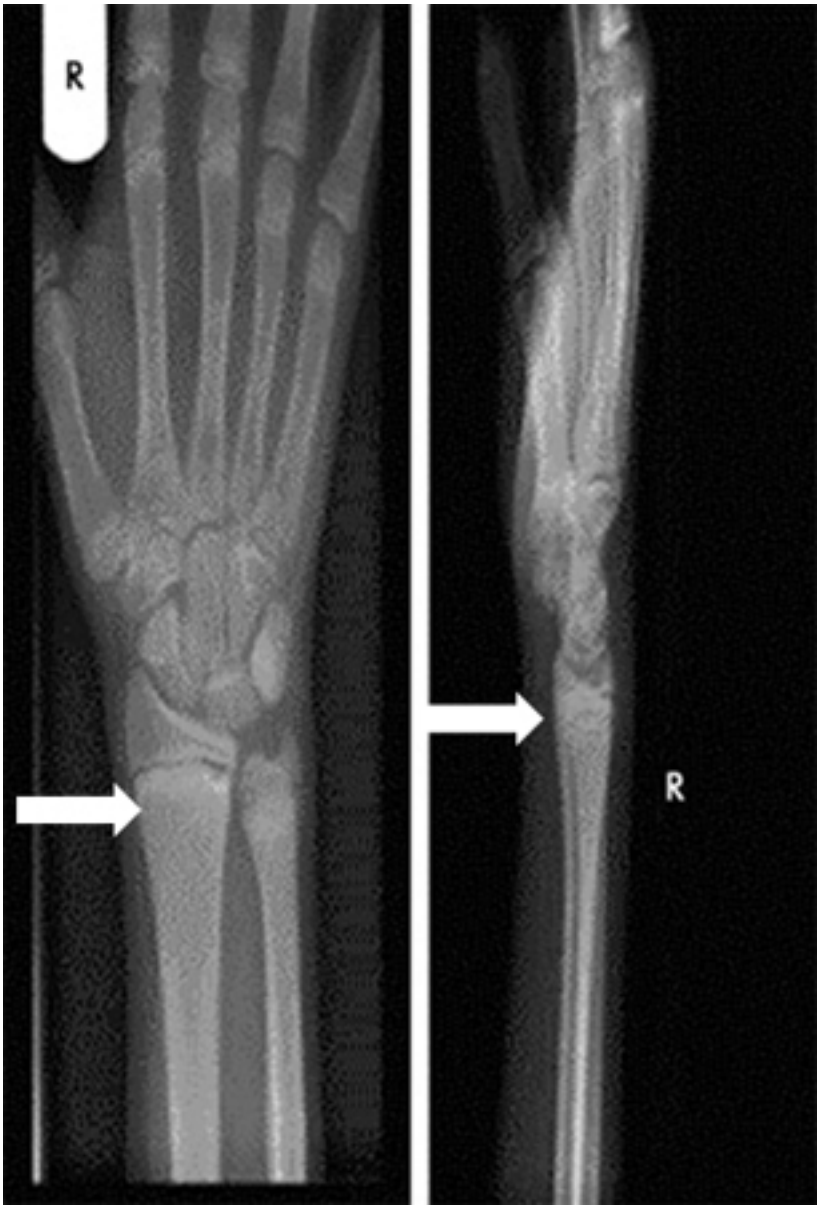
An x-ray of a long bone showing cupping, splaying, and fraying of the metaphysis is required for diagnosis. Widening of the epiphyseal plate and loss of definition of the zone of provisional calcification at the epiphyseal/metaphyseal interface are the early signs of rickets.

The distal ulna is the site that best demonstrates the early signs of impaired mineralisation, and the metaphyses above and below the knees are more useful sites in older children.[4]



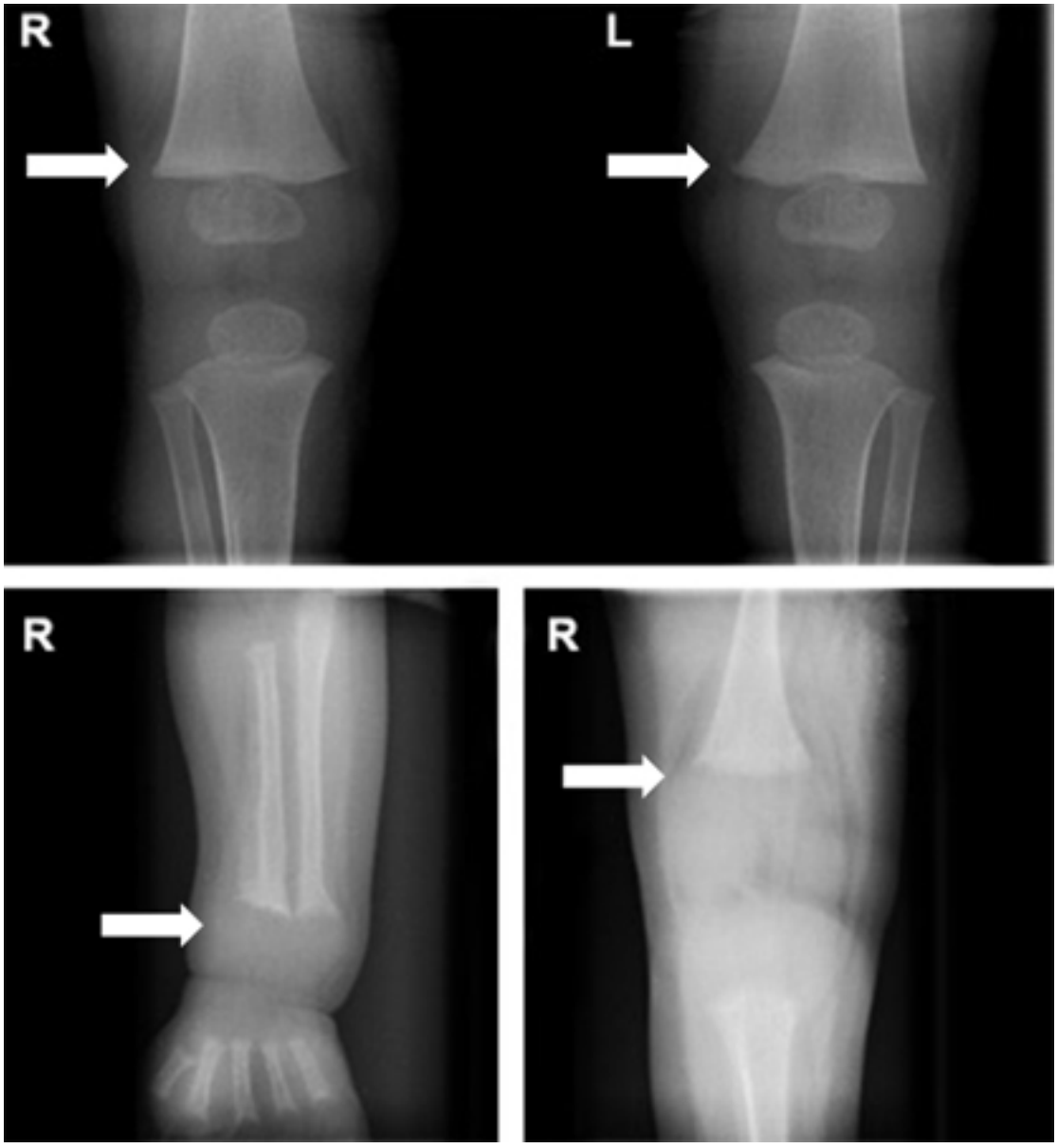
Right wrist of a patient with vitamin D deficient rickets before treatment. His right wrist x-ray showed sclerotic and widened end plates of the radius and ulna (arrows)

Seerat I, Greenberg M. Hypocalcaemic fit in an adolescent boy with undiagnosed rickets. BMJ Case Reports 2010; doi:10.1136/bcr.10.1136/bcr10.2008.1153



Right wrist of a patient with vitamin D deficient rickets after treatment (arrows)

Seerat I, Greenberg M. Hypocalcaemic fit in an adolescent boy with undiagnosed rickets. BMJ Case Reports 2010; doi:10.1136/bcr.10.1136/bcr10.2008.1153



Bony changes (arrows) before (bottom panels) and after (top panel) treatment of rickets

Bangalore H, Bisht S, Inusa B. Rickets and tracheobronchomalacia.

BMJ Case Reports 2009; doi:10.1136/bcr.01.2009.1422

History and exam

Key diagnostic factors

presence of risk factors (common)

- Key factors include inadequate exposure to sunlight, age <18 months, breastfeeding, inadequate calcium and phosphate intake, and positive family history.

Other diagnostic factors

bone pain (common)

- May be associated with pseudofractures or insufficiency fractures.[3]

growth faltering (common)

- Faltering growth is a common presentation of rickets.[4]

delayed achievement of motor milestones (common)

- Consider rickets in children presenting with developmental delay.[4]

bony deformities (common)

- Such as bowlegs.[4]

Malnutrition manifested as rickets. Note the bowed legs and knees

CDC

muscle weakness (common)

- May be due to hypocalcaemia or hypophosphataemia.[4]

carpopedal spasm (uncommon)

- May be seen associated with hypocalcaemia.

numbness or paresthesias (uncommon)

- May be seen in association with hypocalcaemia.

tetany (uncommon)

- May be seen associated with hypocalcaemia.

hypocalcaemic seizures (uncommon)

- Can be a manifestation of rickets associated with hypocalcaemia.[4]

Risk factors

Strong

age 6 to 23 months

- The peak incidence of rickets is between 6 and 23 months, with a further peak among adolescents aged 12 to 15 years.[11]
- Onset of rickets can only occur while epiphyseal plates have not yet closed.[12]

inadequate sunlight exposure

- Living in latitudes above 40º north or south, or sociocultural factors (such as burka-wearing practices, an increase in sedentary lifestyles, less time spent outdoors) result in reduced synthesis of colecalciferol by the skin.[9] [16] Increased sunscreen use has also been implicated.[14]

breastfeeding

- Breast milk is deficient in vitamin D. Without nutritional supplementation, rickets is possible.[3]

calcium deficiency

- Inadequate intake of calcium can lead to insufficient bone mineralisation. Breast milk contains limited amounts of calcium, but cows' milk is a richer source.[4] In societies without a tradition of milk-drinking, calcium intake is often <300 mg daily. The net absorption of calcium and other minerals is limited by other food substances such as phytate, present in most cereals.[3]

phosphate deficiency

- Inadequate intake of phosphorus can lead to insufficient bone mineralisation. Phosphorus is abundant in most diets but may not be sufficient in rapidly growing low-birth-weight babies. Phosphate may be precipitated in the stomach by antacids.[3]

family history of rickets

- A family history of short stature, orthopaedic abnormalities, poor dentition, alopecia, and parental consanguinity may signify inherited rickets.[4]

antacids, loop diuretics, corticosteroids, or anticonvulsants

- Phosphate may be precipitated in the stomach by aluminium-containing antacids.[4] Other medicines that can cause calcium and phosphorus deficiency include loop diuretics and corticosteroids, and phenytoin can cause target organ resistance to calcitriol.[4]

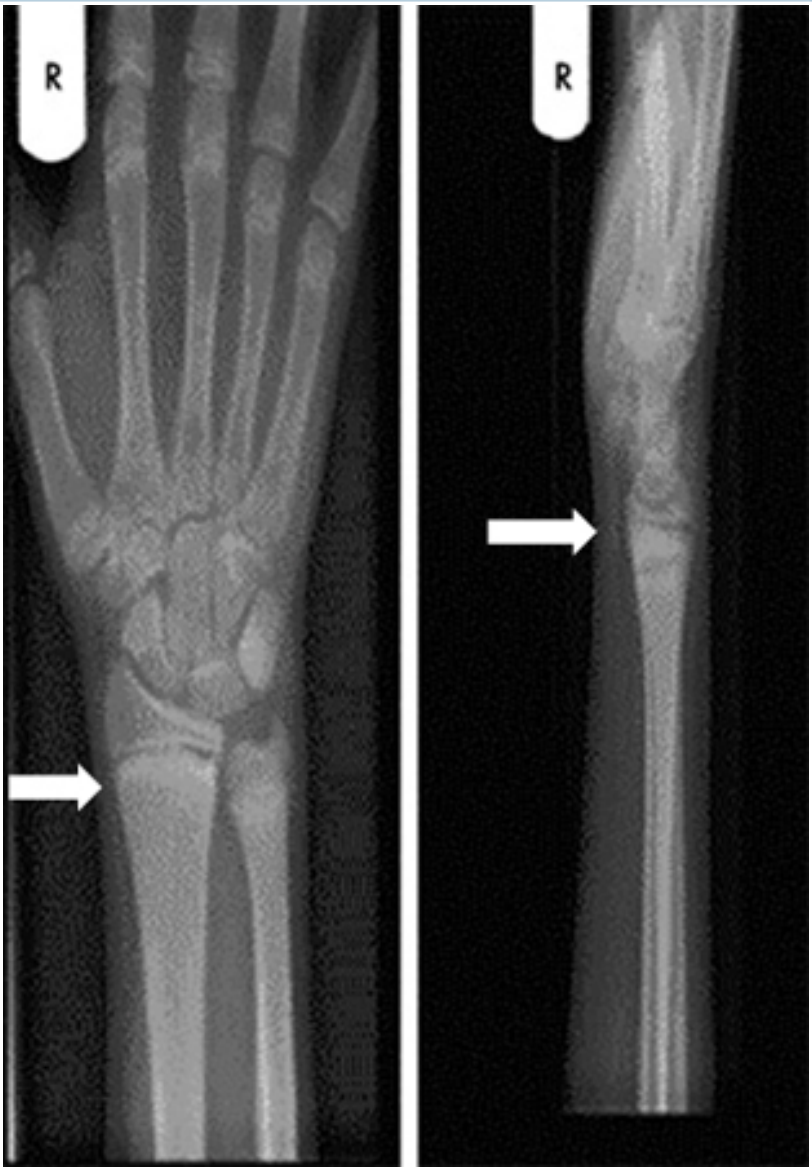
Weak

darker skin complexion

- Increased skin pigmentation may require increased exposure to sunlight to allow adequate conversion of 7-dehydrocholesterol to colecalciferol.[3]

Investigations

1st test to order

Test	Result
x-ray of a long bone • X-rays of knees and wrists are taken when rickets is suspected.[4]  *Right wrist of a patient with vitamin D deficient rickets before treatment. His right wrist x-ray showed sclerotic and widened end plates of the radius and ulna (arrows)* *Seerat I, Greenberg M. Hypocalcaemic fit in an adolescent boy with undiagnosed rickets. BMJ Case Reports 2010; doi:10.1136/bcr.10.1136/bcr10.2008.1153*	**widening of the epiphyseal plate, loss of definition of the zone of provisional calcification at the epiphyseal/metaphyseal interface, cupping, splaying, and fraying of the metaphysis; Looser's zone (pseudofracture)**
serum calcium • Normal values 2.3 to 2.7 mmol/L; as low as 1.9 mmol/L in neonatal period.[3][5]	**may be decreased in hypocalcaemic rickets; normal in hypophosphataemic rickets**

Test	Result
serum inorganic phosphorus • Normal values vary with age. • Neonatal period: 1.6 to 3.0 mmol/L; adolescence: 0.9 to 1.5 mmol/L.[3][5]	**may be decreased in hypocalcaemic rickets; decreased in hypophosphataemic rickets**
serum parathyroid hormone level • Normal values vary with age and method: 1 to 6 picomoles/L.[3][5]	**high with hypocalcaemic rickets and normal with hypophosphataemic rickets**
25-hydroxyvitamin D levels (calcidiol) • Calcitriol (1,25-dihydroxyvitamin D) is the active form of vitamin D, but calcidiol (25-hydroxyvitamin D) is preferred for testing as it has a longer half-life and is found at much higher levels in the serum. • Normal values >25 nanomoles/L (>10.0 nanograms/mL).[3]	**low in vitamin D-deficient rickets, usually <25 nanomoles/L (<10 nanograms/mL); normal in genetic forms of hypocalcaemic rickets and in hypophosphataemic rickets**
alkaline phosphatase and liver function tests • Levels vary with age. High alkaline phosphatase may represent a high bone turnover state.[5] Liver and biliary tract disease can cause abnormal vitamin D metabolism.[4]	**alkaline phosphatase is elevated in rickets**
serum creatinine and urea • Kidney disease causes abnormal calcium and phosphorus regulation and impaired synthesis of calcitriol.[4]	**raised in rickets caused by kidney disease**
urinary calcium and phosphorus • Serum and urine values are used to calculate percent tubular reabsorption of phosphate (TRP). Low TRP is diagnostic of hypophosphataemic rickets in the absence of vitamin D deficiency.[26] TRP is normally >80%.[25]	**urinary calcium is decreased and urinary phosphorus is increased in hypocalcaemic rickets; urinary calcium is normal and urinary phosphorus is high in hypophosphataemic rickets**

Other tests to consider

Test	Result
1,25-dihydroxyvitamin D levels (calcitriol) • Normal values 43 to 139 picomoles/L; up to 250 picomoles/L in pre-term babies.[3][5] • Calcitriol may be normal, low, or high in relation to the reference range. Serum calcitriol concentration is inappropriately low for the prevailing phosphate level in patients with X-linked hypophosphataemic rickets (hypophosphataemia typically stimulates calcitriol synthesis), and very low in type I vitamin D-dependent rickets (pseudovitamin D-deficient rickets). In patients with type II vitamin D-dependent rickets (end-organ resistance to calcitriol), serum calcitriol concentration is usually very high.	**typically normal or elevated in hypocalcaemic rickets as a result of parathyroid hormone action; usually normal in hypophosphataemic forms of rickets**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Hypophosphatasia	• An autosomal recessive disorder that radiographically resembles rickets. • This is an inborn error of metabolism in which activity of the tissue-non-specific (liver/bone/kidney) alkaline phosphatase is deficient.[5]	• Defined by low serum alkaline phosphatase activity. • Large quantities of phosphoethanolamine are found in the urine.
Metaphyseal dysostoses	• Includes Jansen and Schmid types of metaphyseal dysostosis and Pyle's disease. • Bowing of the legs, short stature, and a waddling gait.[5]	• Absence of abnormalities of low serum levels of calcium and phosphate, alkaline phosphatase activity, or vitamin D metabolites.
Blount syndrome	• Condition that causes osteochondrosis of the tibia, resulting in bowing of the legs. May be related to obesity.	• Absence of abnormalities of low serum levels of calcium and phosphate, alkaline phosphatase activity, or vitamin D metabolites.
Benign hyperphosphatasia	• A benign condition of elevations of serum alkaline phosphatase levels. May be transient or permanent.	• Absence of radiological findings of rickets.
Chronic renal failure	• Chronic renal failure can cause a rickets-like clinical picture, but this is rarely a presenting finding.	• Abnormal renal function tests.

Criteria

Radiological diagnostic requirements[3]

Rickets is diagnosed by the presence of x-ray findings including long bone cupping, splaying, and fraying of the metaphyseal areas. Looser's zones (pseudofractures) may also be seen in areas of decreased calcification where major arteries cross bone.

Biochemical diagnostic requirements[26]

An elevated alkaline phosphatase level is present in active rickets and normal in recovering rickets of any aetiology. A low 25-hydroxyvitamin D level in the presence of active rickets defines vitamin D deficient rickets. A low percent tubular reabsorption of phosphate (TRP) in the absence of vitamin D deficiency is diagnostic of hypophosphataemic rickets.

Approach

Symptomatic hypocalcaemia is a medical emergency and requires hospitalisation. Hypocalcaemic seizures and/or cardiovascular instability require an intensive care environment and intravenous calcium infusion.

Calcitriol may be useful in vitamin D deficiency with hypocalcaemia until calcium levels are normalised. Calcitriol is also recommended for type I vitamin D-deficient rickets, type II vitamin D-resistant rickets, and familial or X-linked hypophosphataemic rickets.[4] [27]

Calcium-deficient rickets (sometimes referred to as hypocalcaemic rickets)

Vitamin D deficiency

- The mainstay of treatment for infants and children with nutritional rickets is to correct vitamin D deficiency and to ensure adequate calcium intake.[1]
- Patients respond well to calcium supplements and oral vitamin D2 (ergocalciferol) or vitamin D3 (colecalciferol). Vitamin D2 is the US Food and Drug Administration (FDA)-approved treatment for vitamin D deficiency, although studies have shown that vitamin D3 is more effective. Vitamin D3 is substantially less expensive than vitamin D2. Patients who do not respond should be evaluated for vitamin D-resistant rickets. Many successful dosing regimens exist
- Alternative treatment protocols include:
    - A high dose of oral vitamin D2 given as a single dose (Stoss therapy)
    - A single, high dose of vitamin D2 given intramuscularly, a practical alternative if malabsorption makes oral vitamin D2 ineffective.
- Serum calcium, phosphorus, alkaline phosphatase, and urinary calcium-to-creatinine ratio are measured periodically in children who are being treated for vitamin D deficiency. X-rays are used to document the healing of rachitic lesions.[4] [27]

Calcium deficiency

- Oral calcium and vitamin D2 at recommended daily values are used to treat calcium-deficiency rickets.[27] [28]

Pseudovitamin D-deficient rickets

- A physiological dose of calcitriol generally promotes complete healing of the bone disease and resolution of the biochemical abnormalities. Treatment is continued at this dose until the bone is healed.
- The aim of therapy is to maintain serum levels of calcium, phosphorus, and alkaline phosphatase within normal limits.[27]

Vitamin D resistance

- Severe vitamin D-resistant rickets presents in the first few weeks of life with symptomatic hypocalcaemia, requiring intravenous calcium support.
- Every patient receives a 6-month trial of therapy with supplemental calcium and vitamin D2 or calcitriol. Where available, alfacalcidol can be used in place of calcitriol.[29]
- If the abnormalities of the syndrome do not normalise in response to this treatment, clinical remission might be achieved by administering high-dose oral calcium or a long-term intravenous infusion of calcium into a central vein (intracaval infusion).
- Patients undergoing therapy are evaluated initially at least once a week.

- Serum calcium, phosphorus, alkaline phosphatase, creatinine, 1,25-dihydroxyvitamin D, parathyroid hormone, and the urinary calcium-to-creatinine ratio are measured.[27]

Hypophosphataemic rickets

Treatment varies according to cause.[26]

Hypophosphataemic rickets (X-linked, autosomal dominant, autosomal recessive, McCune-Albright syndrome)

- The treatment of hypophosphataemic rickets is complex and has serious potential adverse effects. Patients should be managed by experienced practitioners.
- Oral phosphate salts are used to replace renal phosphate losses and heal the rickets. The goal of treatment is not to normalise serum phosphate, but rather to heal the rickets.
- High-dose oral phosphate salts can inhibit gastrointestinal absorption of calcium, resulting in an increase of parathyroid hormone (PTH) and worsening of the phosphate losses.
- Calcitriol is used to counteract the decrease in calcium absorption. Underdosing results in hyperparathyroidism. Overdosing can cause hypercalciuria, nephrocalcinosis, and, in the long term, renal failure. Where available, alfacalcidol can be used in place of calcitriol.[30]
- Burosumab, a fibroblast growth factor-23 (FGF-23) blocking monoclonal antibody, is a second-line therapeutic option for patients with X-linked hypophosphataemia (XLH). In the US, burosumab is approved for the treatment of XLH in children 6 months of age and older. In Europe, burosumab is authorised for the treatment of XLH in children 1 year of age and older with radiographic evidence of bone disease.
- Burosumab is given subcutaneously. Adverse effects include hypersensitivity reactions, injection site reactions, extremities pain, and headaches.[30] Hyperphosphataemia and nephrocalcinosis are potential adverse effects, but were not seen in the children in the clinical trials.
- Although patients with XLH may benefit from burosumab, there are many patients who can be treated successfully with phosphate salts and calcitriol. Consensus guidelines recommend considering burosumab for patients with XLH who have radiographic evidence of overt bone disease that is refractory to conventional therapy, or for patients who experience complications or are unable to adhere to conventional therapy.[30]
- Treatment monitoring requires frequent determinations of serum calcium, phosphorus, PTH, alkaline phosphatase, and urine calcium-to-creatinine ratio.
- Renal ultrasounds are needed to screen for nephrocalcinosis.
- X-rays are used to monitor the rickets.
- In children, burosumab increases serum phosphate levels, reduces alkaline phosphatase levels, and improves the radiological features of rickets.[31] In adults, it normalises phosphate levels in 94% of patients and improves fracture healing and histomorphometric signs of osteomalacia.[32] [33] [34]

Hereditary hypophosphataemic rickets with hypercalciuria

- Treatment is with high-dose oral phosphate salts alone.

Tumour-induced osteomalacia

- Primary treatment is the resection of the associated tumour. However, incomplete resection, recurrence, or metastases of tumours can preclude definitive therapy.
- In such cases, calcitriol alone or combined with phosphate salts completely heals or significantly improves the attendant bone disease and biochemical and histological abnormalities. This is

because patients with oncogenic osteomalacia have similar clinical, biochemical, and radiological characteristics to patients with X-linked hypophosphataemic rickets.

- Where available, alfacalcidol can be used in place of calcitriol.[35] Use of alfacalcidol for tumour-induced rickets may be off-label in some countries.

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute (summary)		
symptomatic hypocalcaemia		
	1st	**in-hospital admission and treatment**

Ongoing		(summary)
calcium-deficient rickets: vitamin D deficiency		
	1st	calcium and vitamin D supplementation
calcium-deficient rickets: calcium deficiency		
	1st	calcium and vitamin D supplementation
calcium-deficient rickets: pseudovitamin D deficiency		
	1st	calcitriol or alfacalcidol
calcium-deficient rickets: vitamin D resistance		
	1st	calcium and vitamin D supplementation
	adjunct	high dose oral or intracaval calcium
hypophosphataemic rickets: X-linked		
	1st	phosphate salts plus calcitriol or alfacalcidol
	2nd	burosumab
hereditary hypophosphataemic rickets with hypercalciuria		
	1st	phosphate salts
hypophosphataemic rickets: tumour-induced		
	1st	tumour removal
	adjunct	calcitriol or alfacalcidol with or without phosphate salts

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute

symptomatic hypocalcaemia

1st **in-hospital admission and treatment**

» Symptomatic hypocalcaemia is a medical emergency and requires hospitalisation. Hypocalcaemic seizures and/or cardiovascular instability require an intensive care environment and intravenous calcium infusion.

Ongoing

calcium-deficient rickets: vitamin D deficiency

1st **calcium and vitamin D supplementation**

Primary options

» calcium: children: 45-65 mg/kg/day orally given in 4 divided doses
Dose refers to elemental calcium.

--AND--

» ergocalciferol: children: consult specialist for guidance on initial dose, adjust dose according to response
-or-
» colecalciferol: children: consult specialist for guidance on initial dose, adjust dose according to response

» Most patients respond well to calcium supplements and oral vitamin D2 (ergocalciferol) or vitamin D3 (colecalciferol). Vitamin D2 is the US Food and Drug Administration (FDA)-approved treatment for vitamin D deficiency, although studies have shown that vitamin D3 is more effective. Vitamin D3 is substantially less expensive than vitamin D2.

» Alternative treatment protocols include: high dose of oral vitamin D2 given as a single dose (Stoss therapy); or a single high dose of vitamin D2 given intramuscularly (a practical alternative if malabsorption makes oral vitamin D2 ineffective). However, parenteral vitamin D2 is not currently available in the US.

calcium-deficient rickets: calcium deficiency

1st **calcium and vitamin D supplementation**

Primary options

» calcium: children: 45-65 mg/kg/day orally given in 4 divided doses
Dose refers to elemental calcium.

-and-
» ergocalciferol: children: consult specialist for guidance on initial dose, adjust dose according to response

» Oral calcium and vitamin D2 at recommended daily values are used to treat calcium-deficiency rickets.[27] [28]

calcium-deficient rickets: pseudovitamin D deficiency

Ongoing

1st **calcitriol or alfacalcidol**

Primary options

» calcitriol: children: consult specialist for guidance on initial dose, adjust dose according to response

OR

» alfacalcidol: children: consult specialist for guidance on initial dose, adjust dose according to response

» Occurs due to a defect in 1-alpha-hydroxylase, the enzyme that is responsible for the conversion of 25-hydroxyvitamin D into the active metabolite. A physiological dose of calcitriol generally promotes complete healing of the bone disease and resolution of the biochemical abnormalities. Treatment is continued at this dose until the bone is healed.

» The aim of therapy is to maintain serum levels of calcium, phosphorus, and alkaline phosphatase within normal limits.[27] Where available, alfacalcidol can be used instead of calcitriol.

calcium-deficient rickets: vitamin D resistance

1st **calcium and vitamin D supplementation**

Primary options

» calcium: children: 45-65 mg/kg/day orally given in 4 divided doses
Dose refers to elemental calcium.

--AND--

» ergocalciferol: children: consult specialist for guidance on initial dose, adjust dose according to response
-or-
» calcitriol: children: consult specialist for guidance on initial dose, adjust dose according to response
-or-
» alfacalcidol: children: consult specialist for guidance on initial dose, adjust dose according to response

» Every patient receives a 6-month trial of therapy with supplemental calcium and vitamin D2 or, in more severe cases, calcitriol. Where available, alfacalcidol can be used in place of calcitriol.[29]

MANAGEMENT

Ongoing

adjunct **high dose oral or intracaval calcium**

Treatment recommended for SOME patients in selected patient group

Primary options

» calcium carbonate: children: consult specialist for guidance on initial dose, adjust dose according to response

OR

» calcium gluconate: children: consult specialist for guidance on initial dose, adjust dose according to response

» In patients for whom the abnormalities of the syndrome do not normalise in response to oral calcium and vitamin D, clinical remission might be achieved by administering high-dose oral calcium or a long-term intravenous infusion of calcium into a central vein (intracaval infusion). Long-term intravenous administration is via an indwelling intracaval catheter.

hypophosphataemic rickets: X-linked

1st **phosphate salts plus calcitriol or alfacalcidol**

Primary options

» calcitriol: children: consult specialist for guidance on initial dose, adjust dose according to response
-or-
» alfacalcidol: children: consult specialist for guidance on initial dose, adjust dose according to response
--AND--
» sodium phosphate/potassium phosphate: children: consult specialist for guidance on initial dose, adjust dose according to response

» Regimen includes a period of titration to achieve a maximum dose of calcitriol and phosphate salts. Where available, alfacalcidol (1a-hydroxyvitamin D) can be used in place of calcitriol, with the same dosing range.

2nd **burosumab**

Primary options

» burosumab: children ≥6 months of age and <10 kg body weight: 1 mg/kg subcutaneously every 2 weeks initially, adjust dose according

MANAGEMENT

Ongoing

to response, maximum 2 mg/kg/dose (90 mg/dose) every 2 weeks; children ≥6 months of age and >10 kg body weight: 0.8 mg/kg subcutaneously every 2 weeks initially, adjust dose according to response, maximum 2 mg/kg/dose (90 mg/dose) every 2 weeks
Minimum starting dose is 10 mg.

» A second-line therapeutic option for patients with X-linked hypophosphataemia (XLH). In the US, burosumab is approved for the treatment of XLH in children 6 months of age and older. In Europe, burosumab is authorised for the treatment of XLH in children 1 year of age and older with radiographic evidence of bone disease.

» Burosumab is given subcutaneously. Adverse effects include hypersensitivity reactions, injection site reactions, extremities pain, and headaches.[30] Hyperphosphataemia and nephrocalcinosis are potential adverse effects, but were not seen in the children in the clinical trials.

» Although patients with XLH may benefit from burosumab, there are many patients who can be treated successfully with phosphate salts and calcitriol. Consensus guidelines recommend considering burosumab for patients with XLH who have radiographic evidence of overt bone disease that is refractory to conventional therapy, or for patients who experience complications or are unable to adhere to conventional therapy.[30]

» In children, burosumab increases serum phosphate levels, reduces alkaline phosphatase levels, and improves the radiological features of rickets.[31] In adults, it normalises phosphate levels in 94% of patients and improves fracture healing and histomorphometric signs of osteomalacia.[32] [33] [34]

hereditary hypophosphataemic rickets with hypercalciuria

1st **phosphate salts**

Primary options

» sodium phosphate/potassium phosphate: children: consult specialist for guidance on initial dose, adjust dose according to response

» Treatment is with high-dose phosphorus alone.

hypophosphataemic rickets: tumour-induced

MANAGEMENT

Ongoing

1st **tumour removal**

» Surgical removal of the tumour can cure rickets.

adjunct **calcitriol or alfacalcidol with or without phosphate salts**

Treatment recommended for SOME patients in selected patient group

Primary options

» calcitriol: children: consult specialist for guidance on initial dose, adjust dose according to response

OR

» alfacalcidol: children: consult specialist for guidance on initial dose, adjust dose according to response

OR

» calcitriol: children: consult specialist for guidance on initial dose, adjust dose according to response
-or-
» alfacalcidol: children: consult specialist for guidance on initial dose, adjust dose according to response

--AND--

» sodium phosphate/potassium phosphate: children: consult specialist for guidance on initial dose, adjust dose according to response

» In patients for whom tumour resection is not possible because of recurrence or metastasis, calcitriol alone (or combined with phosphate salt supplementation) completely heals the attendant bone disease or significantly improves the biochemical and histological abnormalities. Where available, alfacalcidol can be used in place of calcitriol.[35] Use for tumour-induced rickets may be off-label in some countries.

Emerging

Recombinant human growth hormone

Final height may be reduced in patients with X-linked hypophosphataemia. In one small non-randomised trial, administration of recombinant human growth hormone (rhGH) to children with X-linked hypophosphataemic rickets resulted in a sustained increase in age-standardised height during 2 years of treatment. Pre-pubertal children responded better to rhGH than pubertal children.[36] In an earlier 3 year randomised controlled open-label study, growth hormone improved linear growth, without progression of body disproportion, in short children with X-linked hypophosphataemia.[37] Follow-up analysis of the open label study found that growth hormone treatment did not significantly increase adult height in this group of short children with X-linked hypophosphataemia.[37] [38] One systematic review did not show enough high-certainty evidence to recommend the use of rhGH in children with X-linked hypophosphataemia.[39]

Calcitonin

One report noted that a single subcutaneous injection of salmon calcitonin could reduce FGF-23 levels (a hormone that decreases phosphate reuptake in the kidney) in adults (n=7) with X-linked hypophosphataemic rickets.[40] A subsequent 3 month randomised trial of 21 patients with X-linked hypophosphataemia found no effect of nasally administered salmon calcitonin on circulating levels of FGF-23.[41]

Paricalcitol

Prevention of hyperparathyroidism is important in the ongoing management of X-linked hypophosphataemia. One controlled trial reported a reduction in parathyroid hormone levels in adults with X-linked hypophosphataemia who were randomised to receive paricalcitol daily for one year.[42]

Primary prevention

Pregnant women should receive 600 to 1000 units/day of vitamin D daily during the second and third trimesters. When vitamin D deficiency is identified during pregnancy, most experts agree that 1000 to 2000 units/day of vitamin D is safe.[19] Vitamin D supplementation for infants may be more effective at reducing vitamin D deficiency in populations at higher risk of deficiency than supplementation for the lactating mothers (low certainty evidence).[20]

The American Academy of Pediatrics recommends that all infants have a minimum intake of 400 units/day of vitamin D beginning soon after birth. The US Institute of Medicine recommends vitamin D RDAs of 600 units/day for ages 1 to 70 years and 800 units/day for ages 71 years and older.[21] The recommended US daily allowance of elemental calcium is up to 1300 mg/day for adolescents, with recommended requirements going down after peak bone growth.[22] Endocrine Society expert panel guidance recommends empirical vitamin D supplementation between the ages of 1 and 18 years to aid prevention of nutritional rickets.[23] Recommendations on daily intake lack consensus; see Vitamin D deficiency for further information on supplementation.

Secondary prevention

The American Academy of Pediatrics recommends all infants have a minimum intake of 400 units/day of vitamin D beginning soon after birth to age 12 months. Children and adults aged >1 year should have at least 600 units/day of vitamin D.[21] [28]

Infants of patients with familial hypophosphataemic rickets require frequent monitoring for hypophosphataemia and raised serum alkaline phosphatase, so that early diagnosis can be made and treatment started.[4]

Patient discussions

Parents are advised to give vitamin D supplements to infants who are exclusively breastfed, and encouraged to feed older children a diet with adequate calcium and vitamin D content. Parents may need sun protection advice so that their children receive adequate sunlight exposure without increasing risks of skin damage and malignancy.[4]

FOLLOW UP

Monitoring

Monitoring

All patients require careful monitoring of serum calcium, phosphorus, calcidiol, and alkaline phosphatase levels. Monitoring of the urine can detect changes in calcium and phosphorus levels, and in the urinary calcium-to-creatinine ratio, which indicates hypercalciuria. Abnormal fluctuations in serum or urine values may require adjustment to the dose of medicine. Within 1 week after initiation of treatment, biochemical changes (a rise in the levels of phosphorus and calcium) and radiographic changes may be evident, and physical examination findings revert to normal within 6 months.[4]

Less common types of rickets will probably need subspeciality consultation to assist with ongoing management.[4]

Additional monitoring

Patients with vitamin D resistance require monitoring of 1,25-dihydroxyvitamin D, parathyroid hormone (PTH), and the urinary calcium-to-creatinine ratio evaluated at least every week initially.

Patients with hypophosphataemic rickets require monitoring of PTH levels and monitoring for nephrocalcinosis.

Disease resolution

After resolution of active medical disease, surgical therapy may be considered if deformities are severe.

Complications

Complications	Timeframe	Likelihood
hungry bone syndrome due to vitamin D therapy	**short term**	**low**
Worsening of hypocalcaemia after the start of vitamin D therapy for hypocalcaemic rickets may occur. Consider supplementing the breastfed infant with calcium during the first few days of therapy, to prevent the possibility of hypocalcaemia and seizures attributed to hungry bones.[1]		
treatment-related hypercalcaemia and its effects (nephrocalcinosis, intra-ocular calcifications)	**short term**	**low**
Possible adverse effects of vitamin D therapy include hypercalciuria, hypercalcaemia, nephrocalcinosis, and intra-ocular calcifications. Checking the urinary calcium-to-creatinine ratio and kidney function (i.e., serum creatinine) at follow-up visits is important. Renal ultrasound and ophthalmological consultation (slit-lamp examination) may be performed in patients with hypercalciuria or hypercalcaemia.[1][4]		

Prognosis

Calcium-deficiency rickets: vitamin D deficiency

Most children with vitamin D-deficient rickets will respond well to vitamin D and calcium, although response rates are higher with intramuscular than with oral treatment.[4]

Calcium-deficiency rickets: calcium deficiency

Calcium supplementation leads to relief of bone pain within 1 month, with improved mobility. Wrist enlargement may resolve within 6 months, although knee deformity may not resolve spontaneously.[44]

Calcium-deficiency rickets: pseudovitamin D deficiency

A physiological dose of calcitriol generally promotes complete healing of the bone disease and resolution of the biochemical abnormalities.

Calcium-deficiency rickets: vitamin D resistance

Not all patients respond to oral treatment, but metabolic and bone abnormalities may improve with intravenous calcium.[45]

Hypophosphataemic rickets: X-linked, autosomal dominant, autosomal recessive, McCune-Albright syndrome

Many patients have impaired growth and bone healing despite treatment. Outcomes are better when treatment is started in early infancy, but skeletal development remains abnormal and early growth deficits may be permanent.[46] [47]

Hereditary hypophosphataemic rickets with hypercalciuria

Patients may respond to treatment. Spontaneous improvement in the renal phosphate-wasting defect has been reported in later life.[48]

Hypophosphataemic rickets: tumour-induced

Surgical removal of the tumour can cure rickets, but not all children have a complete response.[47]

Management of deformity

Untreated rickets can cause permanent bone deformity and lead to stunted growth. Surgical intervention may be necessary to repair severe bony abnormalities.[4]

Diagnostic guidelines

Europe

Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia (https://www.nature.com/articles/s41581-019-0152-5)

Published by: Nature Review Nephrology **Last published:** 2019

International

Global consensus recommendations on prevention and management of nutritional rickets (https://academic.oup.com/jcem/article/101/2/394/2810292)

Published by: Endocrine Society **Last published:** 2016

Treatment guidelines

Europe

Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia (https://www.nature.com/articles/s41581-019-0152-5)

Published by: Nature Reviews Nephrology **Last published:** 2019

North America

Global consensus recommendations on prevention and management of nutritional rickets (https://academic.oup.com/jcem/article/101/2/394/2810292)

Published by: Endocrine Society **Last published:** 2016

Vitamin D - screening and supplementation during pregnancy (https://www.acog.org/clinical/clinical-guidance/committee-opinion)

Published by: American College of Obstetricians and Gynecologists **Last published:** 2011 (re-affirmed 2021)

A clinician's guide to X-linked hypophosphatemia (https://onlinelibrary.wiley.com/doi/full/10.1002/jbmr.340)

Published by: American Society for Bone and Mineral Research **Last published:** 2011

Evaluation, treatment, and prevention of vitamin D deficiency (https://www.endocrine.org/guidelines-and-clinical-practice/clinical-practice-guidelines)

Published by: Endocrine Society **Last published:** 2011

Dietary reference intakes for calcium and vitamin D (http://nationalacademies.org/hmd/reports/2010/dietary-reference-intakes-for-calcium-and-vitamin-d.aspx)

Published by: Institute of Medicine **Last published:** 2010

Asia

Prevention and treatment of vitamin D and calcium deficiency in children and adolescents (https://iapindia.org/publication-recommendations-and-guidelines)

Published by: Indian Academy of Pediatrics **Last published:** 2017

Rickets: standard treatment guidelines (https://iapindia.org/publication-recommendations-and-guidelines)

Published by: Indian Academy of Pediatrics **Last published:** 2022

REFERENCES

Key articles

- American College of Obstetricians and Gynecologists. ACOG committee opinion no. 495: vitamin D: screening and supplementation during pregnancy. Jul 2011 [internet publication]. Full text (https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2011/07/vitamin-d-screening-and-supplementation-during-pregnancy)

- Munns CF, Shaw N, Kiely M, et al. Global consensus recommendations on prevention and management of nutritional rickets. J Clin Endocrinol Metab. 2016 Feb;101(2):394-415. Full text (https://academic.oup.com/jcem/article/101/2/394/2810292) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/26745253?tool=bestpractice.bmj.com)

References

1. Pettifor JM. Rickets and vitamin D deficiency in children and adolescents. Endocrinol Metab Clin North Am. 2005 Sep;34(3):537-53, vii. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16085158?tool=bestpractice.bmj.com)

2. Pitt MJ. Rickets and osteomalacia are still around. Radiol Clin North Am. 1991 Jan;29(1):97-118. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/1985332?tool=bestpractice.bmj.com)

3. Elder CJ, Bishop NJ. Rickets. Lancet. 2014 May 10;383(9929):1665-76. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/24412049?tool=bestpractice.bmj.com)

4. Nield LS, Mahajan P, Joshi A, et al. Rickets: not a disease of the past. Am Fam Physician. 2006 Aug 15;74(4):619-26. Full text (https://www.aafp.org/afp/2006/0815/p619.html) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16939184?tool=bestpractice.bmj.com)

5. Chesney RW. Bone structure, growth, and hormonal regulation. In: Behrman RE, Kliegman RM, Jenson HB, eds. Nelson textbook of pediatrics, 17th ed. Philadelphia, PA: Saunders; 2004.

6. Alizadeh Naderi AS, Reilly RF. Hereditary disorders of renal phosphate wasting. Nat Rev Nephrol. 2010 Nov;6(11):657-65. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/20924400?tool=bestpractice.bmj.com)

7. Beck-Nielsen SS, Brusgaard K, Rasmussen LM, et al. Phenotype presentation of hypophosphatemic rickets in adults. Calcif Tissue Int. 2010 Aug;87(2):108-19. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/20524110?tool=bestpractice.bmj.com)

8. Thacher TD, Fischer PR, Tebben PJ, et al. Increasing incidence of nutritional rickets: a population-based study in Olmsted County, Minnesota. Mayo Clin Proc. 2013 Feb;88(2):176-83. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/23374621?tool=bestpractice.bmj.com)

9. Weisberg P, Scanlon KS, Li R, et al. Nutritional rickets among children in the United States: review of cases reported between 1986 and 2003. Am J Clin Nutr. 2004 Dec;80(6 Suppl):1697S-705S. Full text

(https://academic.oup.com/ajcn/article/80/6/1697S/4690514) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15585790?tool=bestpractice.bmj.com)

10. Julies P, Lynn RM, Pall K, et al. Nutritional rickets under 16 years: UK surveillance results. Arch Dis Child. 2020 Jun;105(6):587-92. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31949032?tool=bestpractice.bmj.com)

11. World Health Organization. Nutritional rickets: a review of disease burden, causes, diagnosis, prevention and treatment. November 2019 [internet publication]. Full text (https://www.who.int/publications/i/item/9789241516587)

12. Holick MF. Resurrection of vitamin D deficiency and rickets. J Clin Invest. 2006 Aug;116(8):2062-72. Full text (https://www.jci.org/articles/view/JCI29449) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16886050?tool=bestpractice.bmj.com)

13. Gupta P, Dabas A, Seth A, et, al. Indian Academy of Pediatrics revised (2021) guidelines on prevention and treatment of vitamin D deficiency and rickets. Indian Pediatr. 2022 Feb 15;59(2):142-58. Full text (https://www.indianpediatrics.net/feb2022/142.pdf) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34969941?tool=bestpractice.bmj.com)

14. Diehl JW, Chiu MW. Effects of ambient sunlight and photoprotection on vitamin D status. Dermatol Ther. 2010 Jan-Feb;23(1):48-60. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/20136908?tool=bestpractice.bmj.com)

15. Rafaelsen S, Johansson S, Ræder H, et al. Hereditary hypophosphatemia in Norway: a retrospective population-based study of genotypes, phenotypes, and treatment complications. Eur J Endocrinol. 2016 Feb;174(2):125-36. Full text (https://www.doi.org/10.1530/EJE-15-0515) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/26543054?tool=bestpractice.bmj.com)

16. Bandeira F, Griz L, Dreyer P, et al. Vitamin D deficiency: a global perspective. Arq Bras Endocrinol Metabol. 2006 Aug;50(4):640-6. Full text (http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0004-27302006000400009&lng=en&nrm=iso&tlng=en) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17117289?tool=bestpractice.bmj.com)

17. Prié D, Friedlander G. Genetic disorders of renal phosphate transport. N Engl J Med. 2010 Jun 24;362(25):2399-409. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/20573928?tool=bestpractice.bmj.com)

18. Chanchlani R, Nemer P, Sinha R, et al. An overview of rickets in children. Kidney Int Rep. 2020 Jul;5(7):980-90. Full text (https://www.doi.org/10.1016/j.ekir.2020.03.025) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/32647755?tool=bestpractice.bmj.com)

19. American College of Obstetricians and Gynecologists. ACOG committee opinion no. 495: vitamin D: screening and supplementation during pregnancy. Jul 2011 [internet publication]. Full text (https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2011/07/vitamin-d-screening-and-supplementation-during-pregnancy)

20. Tan ML, Abrams SA, Osborn DA. Vitamin D supplementation for term breastfed infants to prevent vitamin D deficiency and improve bone health. Cochrane Database Syst Rev. 2020 Dec

11;12:CD013046. Full text (https://www.doi.org/10.1002/14651858.CD013046.pub2) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/33305822?tool=bestpractice.bmj.com)

21. Ross AC, Manson JE, Abrams SA, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab. 2011 Jan;96(1):53-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/21118827?tool=bestpractice.bmj.com)

22. Palacios C. The role of nutrients in bone health, from A to Z. Crit Rev Food Sci Nutr. 2006;46(8):621-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17092827?tool=bestpractice.bmj.com)

23. Demay MB, Pittas AG, Bikle DD, et al. Vitamin D for the prevention of disease: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2024 Jul 12;109(8):1907-47. Full text (https://academic.oup.com/jcem/article/109/8/1907/7685305) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/38828931?tool=bestpractice.bmj.com)

24. Dobrescu MO, Garcia AC, Robert M. Rickets. CMAJ. 2006 Jun 6;174(12):1710. Full text (http://www.cmaj.ca/content/174/12/1710.1.long) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16754897?tool=bestpractice.bmj.com)

25. Payne RB. Renal tubular reabsorption of phosphate (TmP/GFR): indications and interpretation. Ann Clin Biochem. 1998 Mar;35(Pt 2):201-6. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9547891?tool=bestpractice.bmj.com)

26. Carpenter TO, Imel EA, Holm IA, et al. A clinician's guide to X-linked hypophosphatemia. J Bone Miner Res. 2011 Jul;26(7):1381-8. [Erratum in: J Bone Miner Res. 2015 Feb;30(2):394.] Full text (https://onlinelibrary.wiley.com/doi/full/10.1002/jbmr.340) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/21538511?tool=bestpractice.bmj.com)

27. Drezner MK. Osteomalacia and rickets. In: Goldman L, Ausiello D, eds. Cecil textbook of medicine, 22nd ed. Philadelphia, PA: Saunders Publishing; 2004:1555-62.

28. Munns CF, Shaw N, Kiely M, et al. Global consensus recommendations on prevention and management of nutritional rickets. J Clin Endocrinol Metab. 2016 Feb;101(2):394-415. Full text (https://academic.oup.com/jcem/article/101/2/394/2810292) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/26745253?tool=bestpractice.bmj.com)

29. Andary R, El-Hage-Sleiman AK, Farhat T, et al. Hereditary vitamin D-resistant rickets in Lebanese patients: the p.R391S and p.H397P variants have different phenotypes. J Pediatr Endocrinol Metab. 2017 Apr 1;30(4):437-44. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28301319?tool=bestpractice.bmj.com)

30. Haffner D, Emma F, Eastwood DM, et al. Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. Nat Rev Nephrol. 2019 Jul;15(7):435-55. Full text (https://www.doi.org/10.1038/s41581-019-0152-5) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31068690?tool=bestpractice.bmj.com)

31. Imel EA, Glorieux FH, Whyte MP, et al. Burosumab versus conventional therapy in children with X-linked hypophosphataemia: a randomised, active-controlled, open-label, phase 3 trial. Lancet.

2019 Jun 15;393(10189):2416-27. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31104833?tool=bestpractice.bmj.com)

32. Carpenter TO, Imel EA, Ruppe MD, et al. Randomized trial of the anti-FGF23 antibody KRN23 in X-linked hypophosphatemia. J Clin Invest. 2014 Apr;124(4):1587-97. Full text (https://www.jci.org/articles/view/72829) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/24569459?tool=bestpractice.bmj.com)

33. Zhang X, Imel EA, Ruppe MD, et al. Pharmacokinetics and pharmacodynamics of a human monoclonal anti-FGF23 antibody (KRN23) in the first multiple ascending-dose trial treating adults with X-linked hypophosphatemia. J Clin Pharmacol. 2016 Feb;56(2):176-85. Full text (https://accp1.onlinelibrary.wiley.com/doi/full/10.1002/jcph.570) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/26073451?tool=bestpractice.bmj.com)

34. Imel EA, Zhang X, Ruppe MD, et al. Prolonged correction of serum phosphorus in adults with X-linked hypophosphatemia using monthly doses of KRN23. J Clin Endocrinol Metab. 2015 Jul;100(7):2565-73. Full text (https://academic.oup.com/jcem/article/100/7/2565/2829602) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/25919461?tool=bestpractice.bmj.com)

35. Florenzano P, Gafni RI, Collins MT. Tumor-induced osteomalacia. Bone Rep. 2017 Dec;7:90-97. Full text (https://www.doi.org/10.1016/j.bonr.2017.09.002) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29021995?tool=bestpractice.bmj.com)

36. Rothenbuhler A, Esterle L, Gueorguieva I, et al. Two-year recombinant human growth hormone (rhGH) treatment is more effective in pre-pubertal compared to pubertal short children with X-linked hypophosphatemic rickets (XLHR). Growth Horm IGF Res. 2017 Oct;36:11-15. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28822957?tool=bestpractice.bmj.com)

37. Živičnjak M, Schnabel D, Staude H, et al. Three-year growth hormone treatment in short children with X-linked hypophosphatemic rickets: effects on linear growth and body disproportion. J Clin Endocrinol Metab. 2011 Dec;96(12):E2097-105. Full text (https://www.doi.org/10.1210/jc.2011-0399) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/21994957?tool=bestpractice.bmj.com)

38. Meyerhoff N, Haffner D, Staude H, et al. Effects of growth hormone treatment on adult height in severely short children with X-linked hypophosphatemic rickets. Pediatr Nephrol. 2018 Mar;33(3):447-56. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29058153?tool=bestpractice.bmj.com)

39. Smith S, Remmington T. Recombinant growth hormone therapy for X-linked hypophosphatemia in children. Cochrane Database Syst Rev. 2021 Oct 7;10(10):CD004447. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004447.pub3/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34618915?tool=bestpractice.bmj.com)

40. Liu ES, Carpenter TO, Gundberg CM, et al. Calcitonin administration in X-linked hypophosphatemia. N Engl J Med. 2011 Apr 28;364(17):1678-80. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/21524226?tool=bestpractice.bmj.com)

REFERENCES

41. Sullivan R, Abraham A, Simpson C, et al. Three-month randomized clinical trial of nasal calcitonin in adults with X-linked hypophosphatemia. Calcif Tissue Int. 2018 Jun;102(6):666-70. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29383408?tool=bestpractice.bmj.com)

42. Carpenter TO, Olear EA, Zhang JH, et al. Effect of paricalcitol on circulating parathyroid hormone in X-linked hypophosphatemia: a randomized, double-blind, placebo-controlled study. J Clin Endocrinol Metab. 2014 Sep;99(9):3103-11. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/25029424?tool=bestpractice.bmj.com)

43. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2011 Jul;96(7):1911-30. Full text (https://academic.oup.com/jcem/article/96/7/1911/2833671) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/21646368?tool=bestpractice.bmj.com)

44. Oginni LM, Sharp CA, Badru OS, et al. Radiological and biochemical resolution of nutritional rickets with calcium. Arch Dis Child. 2003 Sep;88(9):812-7. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12937108?tool=bestpractice.bmj.com)

45. Malloy PJ, Hochberg Z, Tiosano D, et al. The molecular basis of hereditary 1, 25-dihydroxyvitamin D3 resistant rickets in seven related families. J Clin Invest. 1990 Dec;86(6):2071-9. Full text (https://www.jci.org/articles/view/114944/pdf) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/2174914?tool=bestpractice.bmj.com)

46. Mäkitie O, Doria A, Kooh SW, et al. Early treatment improves growth and biochemical and radiographic outcome in X-linked hypophosphatemic rickets. J Clin Endocrinol Metab. 2003 Aug;88(8):3591-7. Full text (https://academic.oup.com/jcem/article/88/8/3591/2845268) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12915641?tool=bestpractice.bmj.com)

47. de Menezes Filho H, de Castro LC, Damiani D. Hypophosphatemic rickets and osteomalacia. Arg Bras Endocrinol Metabol. 2006 Aug;50(4):802-13. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17117305?tool=bestpractice.bmj.com)

48. Econs MJ, McEnery PT. Autosomal dominant hypophosphatemic rickets/osteomalacia: clinical characterization of a novel renal phosphate-wasting disorder. J Clin Endocrinol Metab. 1997 Feb;82(2):674-81. Full text (https://academic.oup.com/jcem/article/82/2/674/2823552) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9024275?tool=bestpractice.bmj.com)

Images

Figure 1: Malnutrition manifested as rickets. Note the bowed legs and enlarged right wrist

CDC

Figure 2: Malnutrition manifested as rickets. Note the bowed legs and knees

CDC

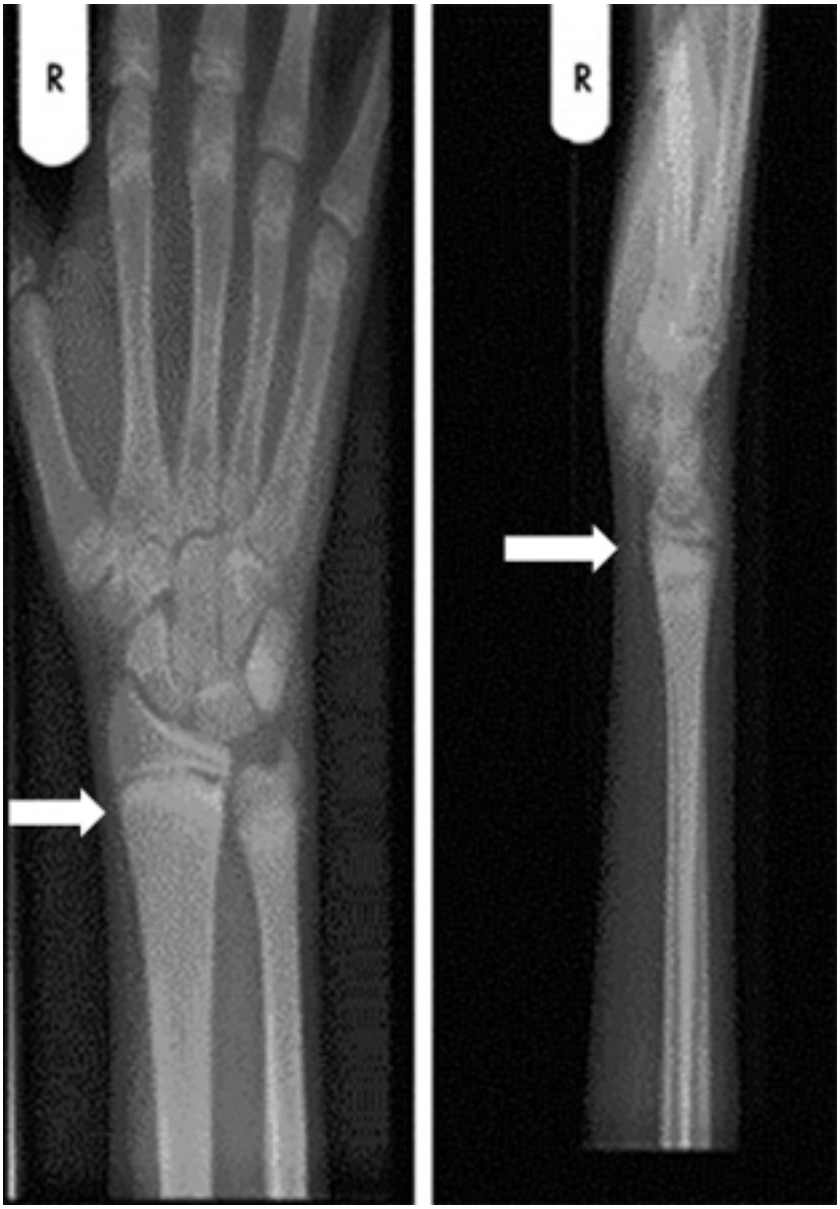


Figure 3: Right wrist of a patient with vitamin D deficient rickets before treatment. His right wrist x-ray showed sclerotic and widened end plates of the radius and ulna (arrows)

Seerat I, Greenberg M. Hypocalcaemic fit in an adolescent boy with undiagnosed rickets. BMJ Case Reports 2010; doi:10.1136/bcr.10.1136/bcr10.2008.1153

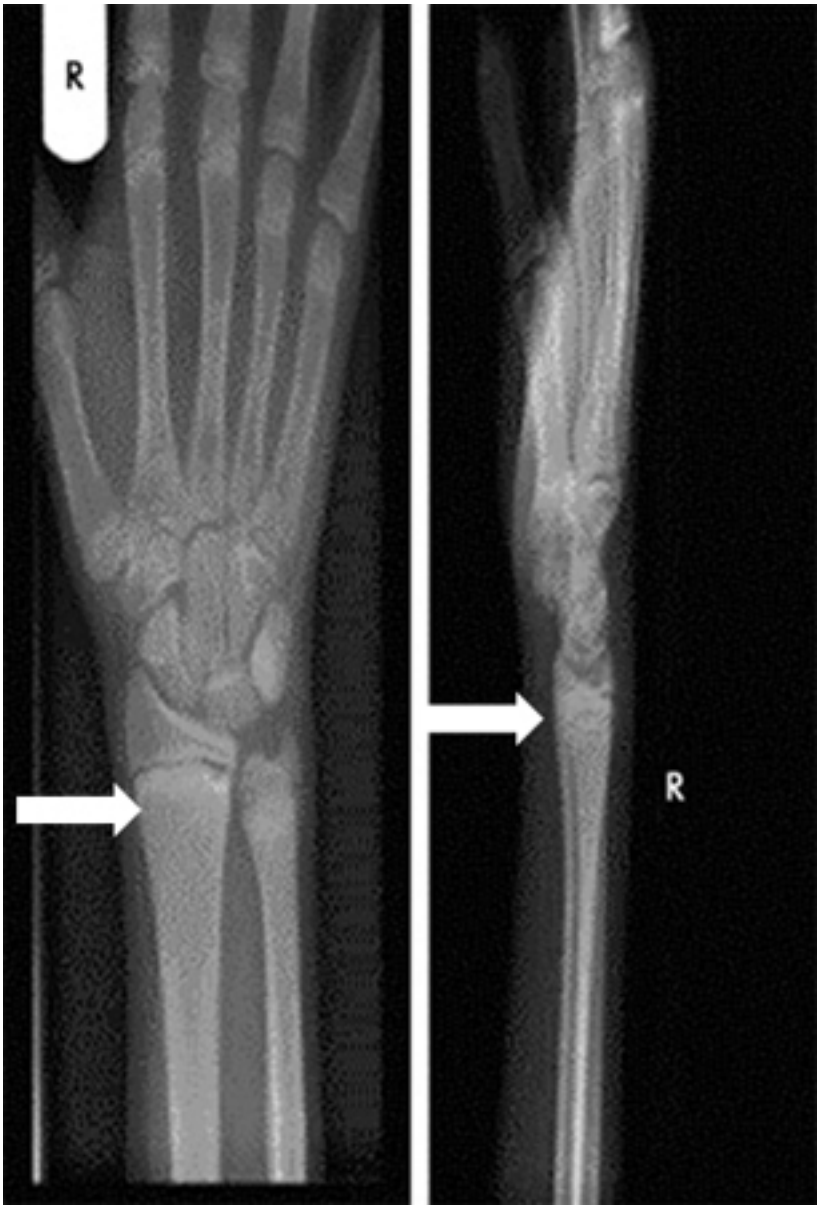


Figure 4: Right wrist of a patient with vitamin D deficient rickets after treatment (arrows)

Seerat I, Greenberg M. Hypocalcaemic fit in an adolescent boy with undiagnosed rickets. BMJ Case Reports 2010; doi:10.1136/bcr.10.1136/bcr10.2008.1153

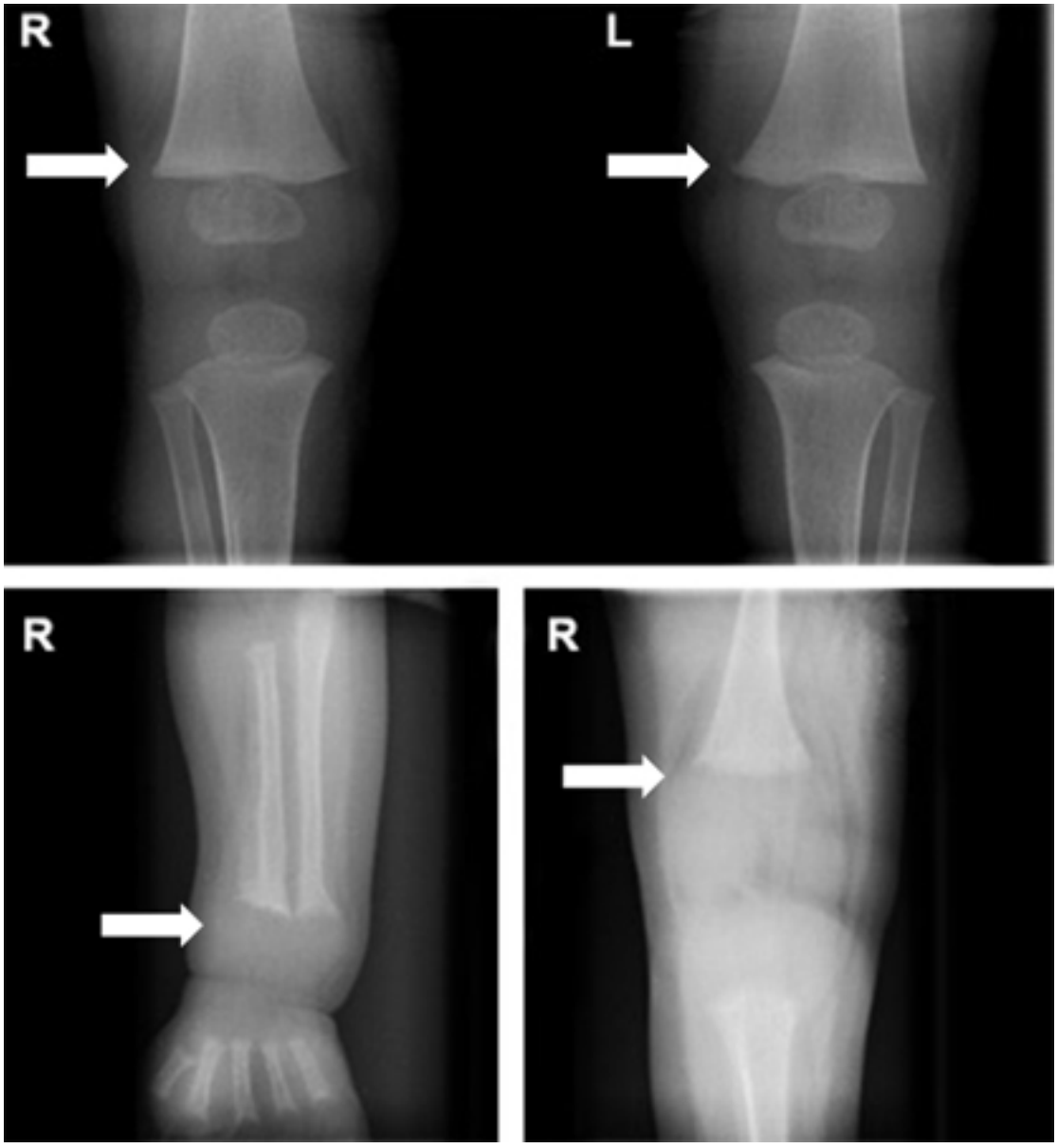


Figure 5: Bony changes (arrows) before (bottom panels) and after (top panel) treatment of rickets

Bangalore H, Bisht S, Inusa B. Rickets and tracheobronchomalacia. BMJ Case Reports 2009; doi:10.1136/bcr.01.2009.1422

Disclaimer

BMJ Best Practice is intended for licensed medical professionals. BMJ Publishing Group Ltd (BMJ) does not advocate or endorse the use of any drug or therapy contained within this publication nor does it diagnose patients. As a medical professional you retain full responsibility for the care and treatment of your patients and you should use your own clinical judgement and expertise when using this product.

This content is not intended to cover all possible diagnosis methods, treatments, follow up, drugs and any contraindications or side effects. In addition, since such standards and practices in medicine change as new data become available, you should consult a variety of sources. We strongly recommend that you independently verify specified diagnosis, treatments and follow-up and ensure it is appropriate for your patient within your region. In addition, with respect to prescription medication, you are advised to check the product information sheet accompanying each drug to verify conditions of use and identify any changes in dosage schedule or contraindications, particularly if the drug to be administered is new, infrequently used, or has a narrow therapeutic range. You must always check that drugs referenced are licensed for the specified use and at the specified doses in your region.

Information included in BMJ Best Practice is provided on an “as is” basis without any representations, conditions or warranties that it is accurate and up to date. BMJ and its licensors and licensees assume no responsibility for any aspect of treatment administered to any patients with the aid of this information. To the fullest extent permitted by law, BMJ and its licensors and licensees shall not incur any liability, including without limitation, liability for damages, arising from the content. All conditions, warranties and other terms which might otherwise be implied by the law including, without limitation, the warranties of satisfactory quality, fitness for a particular purpose, use of reasonable care and skill and non-infringement of proprietary rights are excluded.

Where BMJ Best Practice has been translated into a language other than English, BMJ does not warrant the accuracy and reliability of the translations or the content provided by third parties (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages). BMJ is not responsible for any errors and omissions arising from translation and adaptation or otherwise.Where BMJ Best Practice lists drug names, it does so by recommended International Nonproprietary Names (rINNs) only. It is possible that certain drug formularies might refer to the same drugs using different names.

Please note that recommended formulations and doses may differ between drug databases drug names and brands, drug formularies, or locations. A local drug formulary should always be consulted for full prescribing information.

Treatment recommendations in BMJ Best Practice are specific to patient groups. Care is advised when selecting the integrated drug formulary as some treatment recommendations are for adults only, and external links to a paediatric formulary do not necessarily advocate use in children (and vice-versa). Always check that you have selected the correct drug formulary for your patient.

Where your version of BMJ Best Practice does not integrate with a local drug formulary, you should consult a local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing before prescribing.

Interpretation of numbers

Regardless of the language in which the content is displayed, numerals are displayed according to the original English-language numerical separator standard. For example 4 digit numbers shall not include a comma nor a decimal point; numbers of 5 or more digits shall include commas; and numbers stated to be less than 1 shall be depicted using decimal points. See Figure 1 below for an explanatory table.

BMJ accepts no responsibility for misinterpretation of numbers which comply with this stated numerical separator standard.

This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

Our full website and application terms and conditions can be found here: Website Terms and Conditions.

Contact us

+ 44 (0) 207 111 1105
support@bmj.com

BMJ
BMA House
Tavistock Square
London
WC1H 9JR
UK

Contributors:

// Authors:

Carlos Palacio, MD, MPH, FACP

Professor of Medicine
Associate Program Director, Internal Medicine Residency, Department of Medicine, University of Florida College of Medicine, Jacksonville, FL
DISCLOSURES: CP declares that he has no competing interests.

Firas Warda, MD

Endocrinology Fellow
Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, University of Florida College of Medicine, Jacksonville, FL
DISCLOSURES: FW declares that he has no competing interests.

// Acknowledgements:

Professor Carols Palacio and Dr Firas Warda would like to gratefully acknowledge Dr Robert Olney, a previous contributor to this topic.
DISCLOSURES: RO declares that he has no competing interests.

// Peer Reviewers:

Phil Fischer, MD

Professor of Pediatrics
Mayo Clinic, Rochester, MN
DISCLOSURES: PF declares that he has no competing interests.

Zulf Mughal, MD

Consultant in Paediatric Bone Disorders
Department of Paediatric Endocrinology, Royal Manchester Children's Hospital, UK
DISCLOSURES: No disclosures

Arshag Mooradian, MD

Professor of Medicine
University of Florida College of Medicine, Jacksonville, FL
DISCLOSURES: AM declares that he has no competing interests.