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Nutritional and Refractory Rickets

Prof Kamran Afzal

Department of Pediatrics,

J.N. Medical College,

AMU, Aligarh

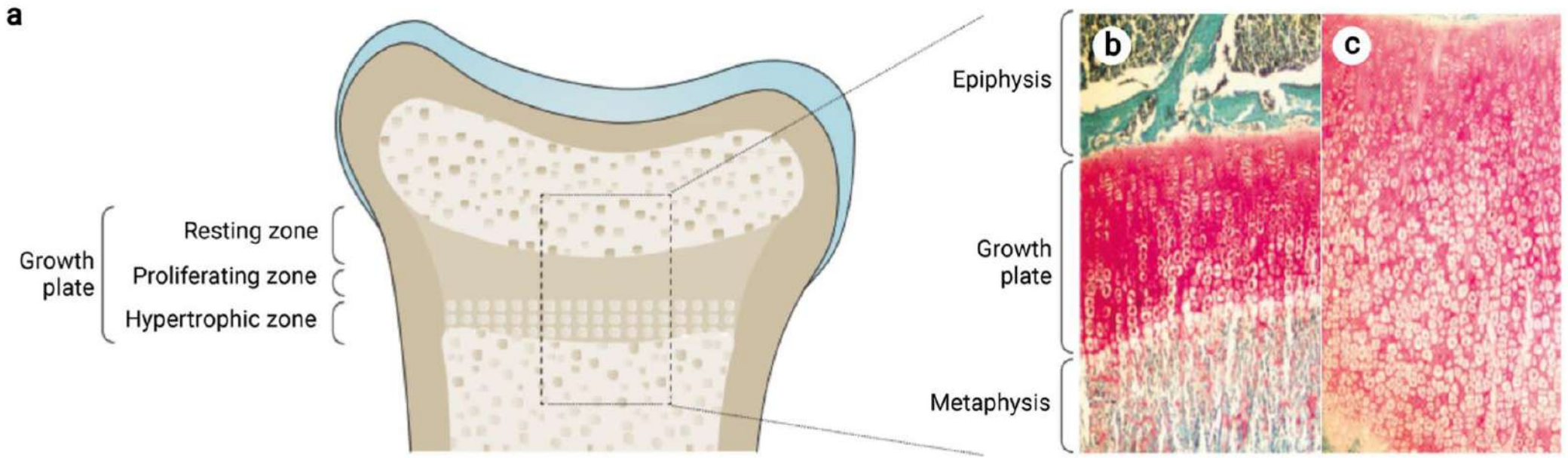
Outline

- Definition
- Morphology of growth plate in rickets
- Vitamin D metabolism
- Classification of rickets
- Nutritional rickets
- VDDR
- Phosphopenic rickets
- Diagnostic algorithm

Rickets

- Deficient mineralization can result in rickets and/or osteomalacia.
- Rickets is deficient mineralization and architectural disruption at growth plate
- Osteomalacia is impaired mineralization of the bone matrix.
- Both occur when growth plates are open; only osteomalacia when growth plates have fused
- Vitamin D deficiency most common nutritional deficiency resulting in rickets

Morphology of the growth plate in rickets

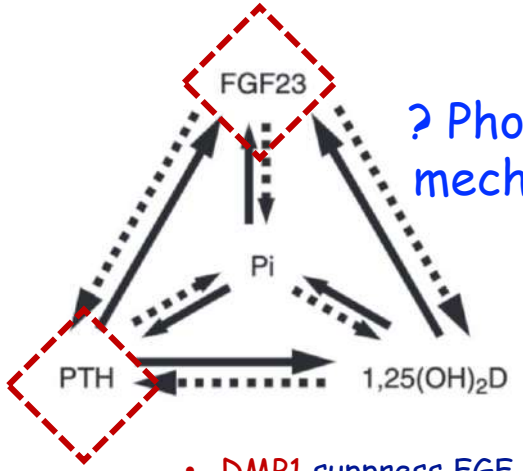


- Rickets is characterized by impaired apoptosis of hypertrophic chondrocytes, resulting in widening of the growth plates in bones and is usually associated with osteomalacia
- Growing evidence that the ultimate cause of rickets is an insufficient availability of phosphate required for terminal differentiation and mineralization of growth plate chondrocytes

Haffner, et al. Pediatric Nephrology (2022)

Regulatory mechanisms of Serum Phosphate level

- PTH and $1,25(OH)_2D$ are calciotropic hormones
- Ionized ECF calcium, primary determinant of PTH secretion
- PTH reduces Pi by internalization of Npt2a and 2c in PCT
- Pi also enhances PTH synthesis especially in CKD



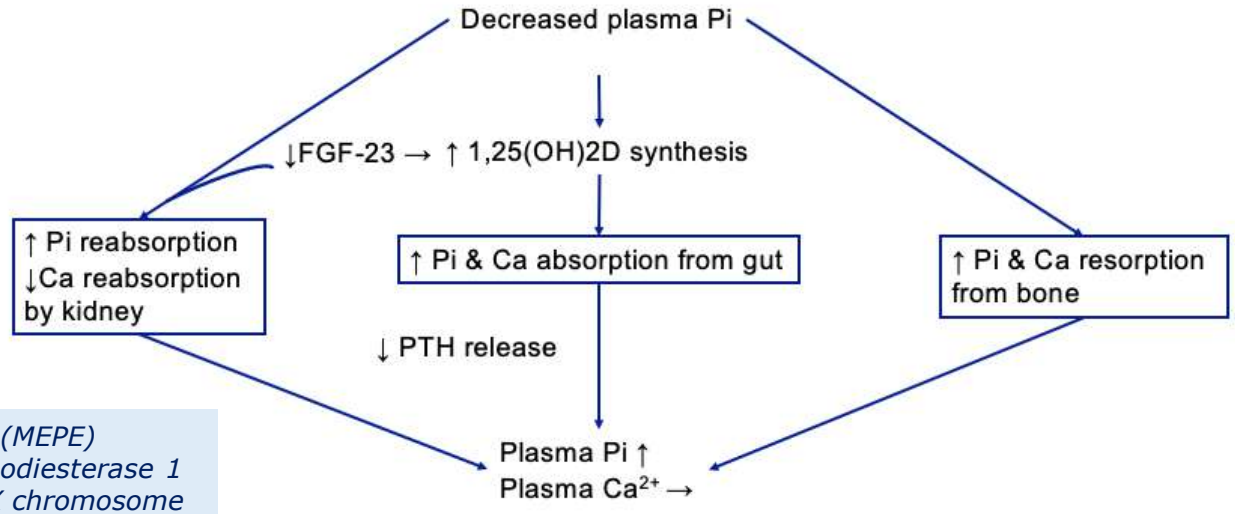
? Phosphate-sensing mechanism unknown

- DMP1 suppress FGF-23 secretion by bone
- PHEX promotes proteolysis of FGF23
- ENPP1 is required for Klotho expression

Physiologic regulators that reduce renal reabsorption

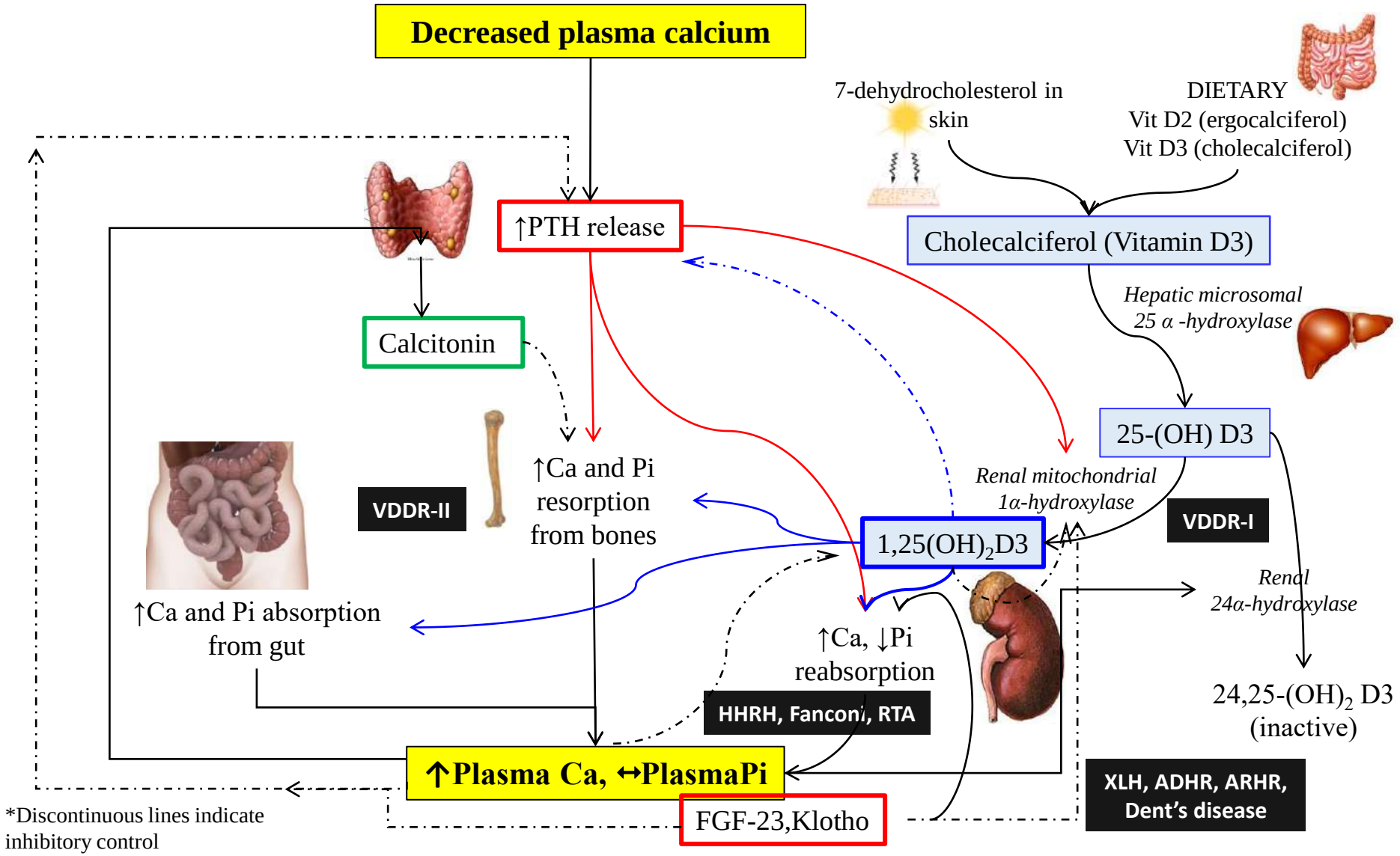
- ↑Serum phosphate concentration
- ↑ PTH
- ↑ Phosphatonins (FGF-23, FGF-7, MEPE, and sFRP-4)

Homeostatic response to hypophosphatemia



FGF: Fibroblast growth factor
sFRP: Secreted frizzled-related protein-4
DMP1 Dentin Matrix Protein 1
MEPE: Matrix extracellular phosphoglycoprotein (MEPE)
ENPP1: ectonucleotide pyrophosphatase/phosphodiesterase 1
PHEX: Phosphate regulating endopeptidase on X chromosome

Vitamin D metabolism and regulation of plasma calcium and phosphorus



Types of Rickets

- **Calcipenic rickets** results from impaired calcium availability, which is either due to reduced calcium intake and/or vitamin D deficiency (nutritional rickets) or impaired action of 1,25(OH)2D (vitamin D-dependent rickets) (VDRR))
- **Phosphopenic rickets**, also called hypophosphatemic rickets, can either be due to dietary phosphate deficiency or impaired bioavailability, FGF23-mediated renal phosphate wasting or to primary or acquired renal tubular phosphate wasting

Low Calcium intake, or Low Vitamin D	Pre-Rickets Early Osteomalacia	Rickets and Osteomalacia
No clinical signs	*No radiological signs*	*Radiological and*
Early biochemical signs	*Early clinical signs*	*clinical signs*

RISK GROUPS

PTH ↑

Urine Ca/Crea ↓

<u>Mature bone:</u>

Osteoid thickness ↑

Mineralisation Lag Time ↑

<u>Growth plate:</u>

Hypertrophic zone ↑

Mineralization ↓

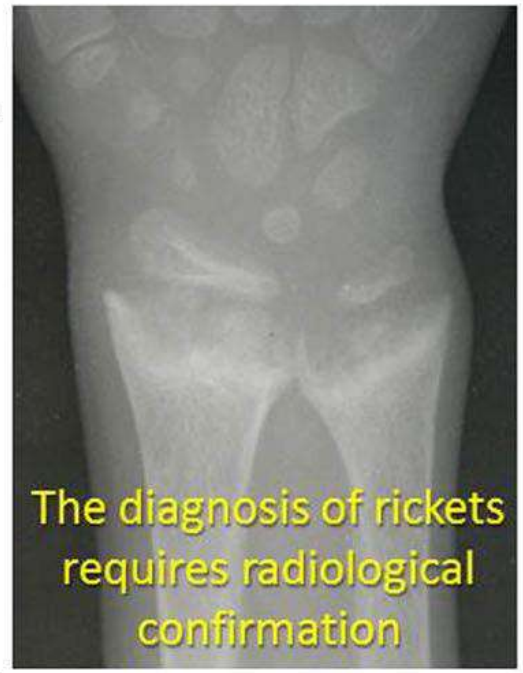
<u>Serum biochemistry:</u>

ALP and PTH ↑↑

Phosphate or Calcium ↓

<u>Urine biochemistry</u>:

Calcium/Creatinine Ratio ↓



Severity <u>and</u> duration of calcium deprivation

Types of Rickets

Calcipenic rickets

- **Vitamin D deficiency or resistance**
  - Dietary deficiency
  - Malabsorption
  - Lack of sunlight exposure
  - Defect in 25 hydroxylation of vitamin D (e.g., liver disease, medications such as phenytoin)
  - Failure of 1 hydroxylation of vitamin D due to inherent deficiency of 1 alpha hydroxylase secondary to defects in the 1 alpha hydroxylase gene (VDDR I)
  - End-organ resistance to vitamin D (VDDR II)
- **Calcium deficiency**
- **Renal rickets secondary to CKD**

Phosphopenic rickets

Renal tubular phosphate loss

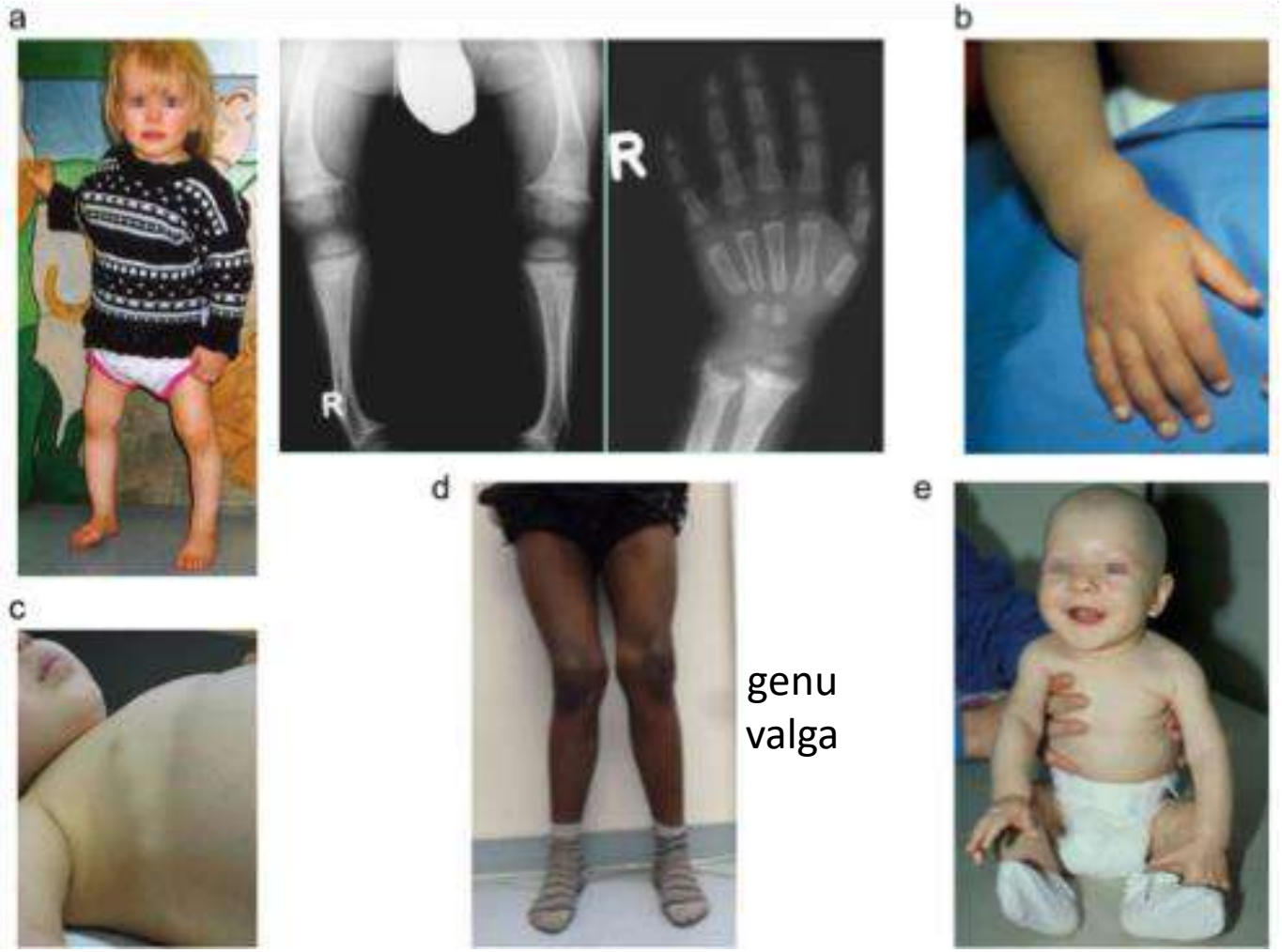
- Isolated phosphate loss secondary to genetic mutations:
  - XLHR
  - ARHR
  - ADHR
  - Hypophosphatemic rickets with hypercalciuria
- Renal Fanconi syndrome
- Dietary phosphate deficiency
- Phosphate malabsorption

Clinical features of calcipenic rickets

widening of the growth plates and metaphyseal fraying on X-rays

genu vara

rachitic rosary



genu valga

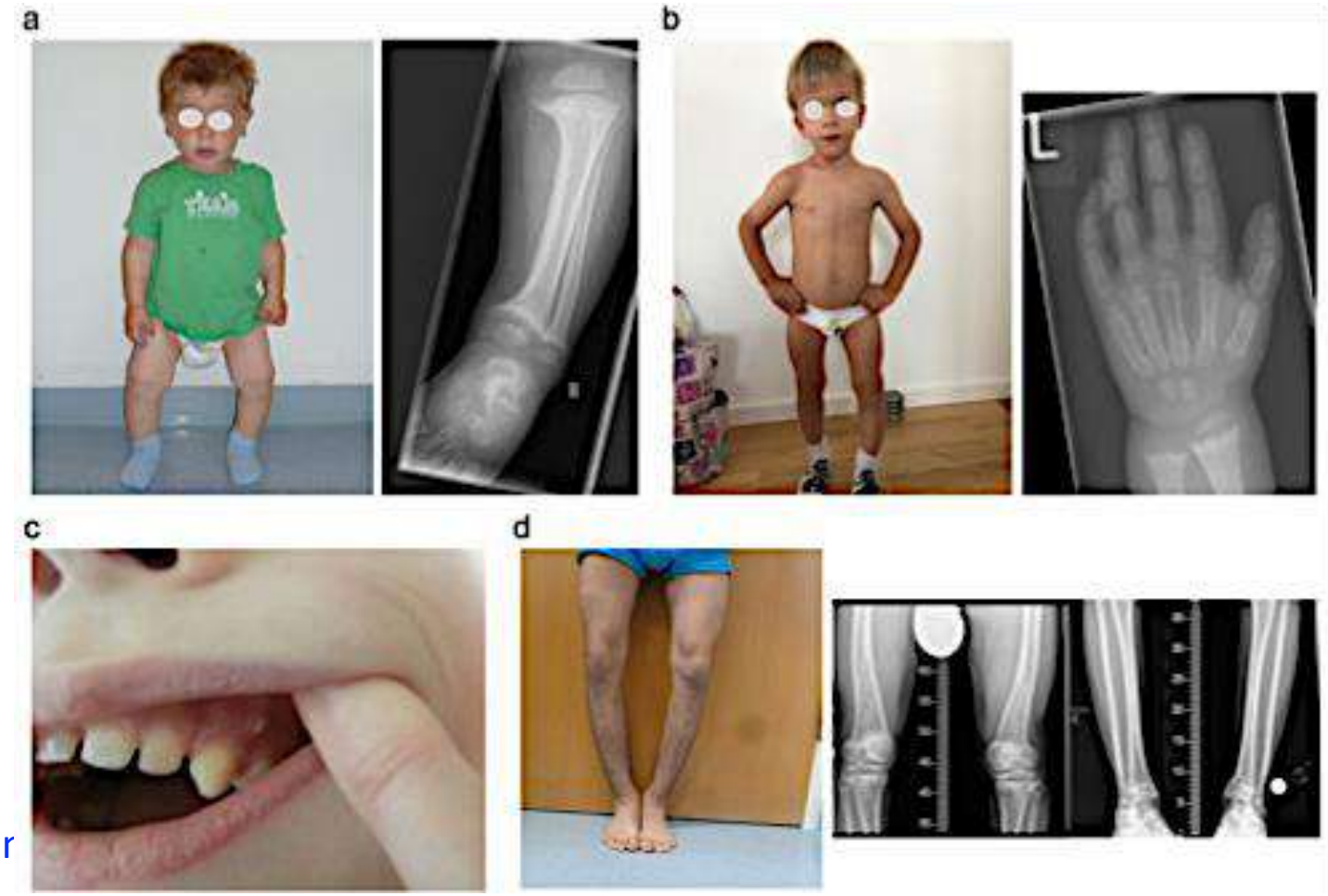
widening of the wrist

alopecia due to VDDR type 2A

Haffner, et al. Pediatric Nephrology (2022)

Clinical features of phosphopenic rickets

XLH with disproportionate short stature, genu vara, widening of growth plate and metaphyseal fraying



disproportionate short stature frontal bossing, dolichocephalus and mild signs of rickets on X-ray

Dental abscess ir XLH

genu vara and mild ricketic signs on X-ray in ARHR type 2

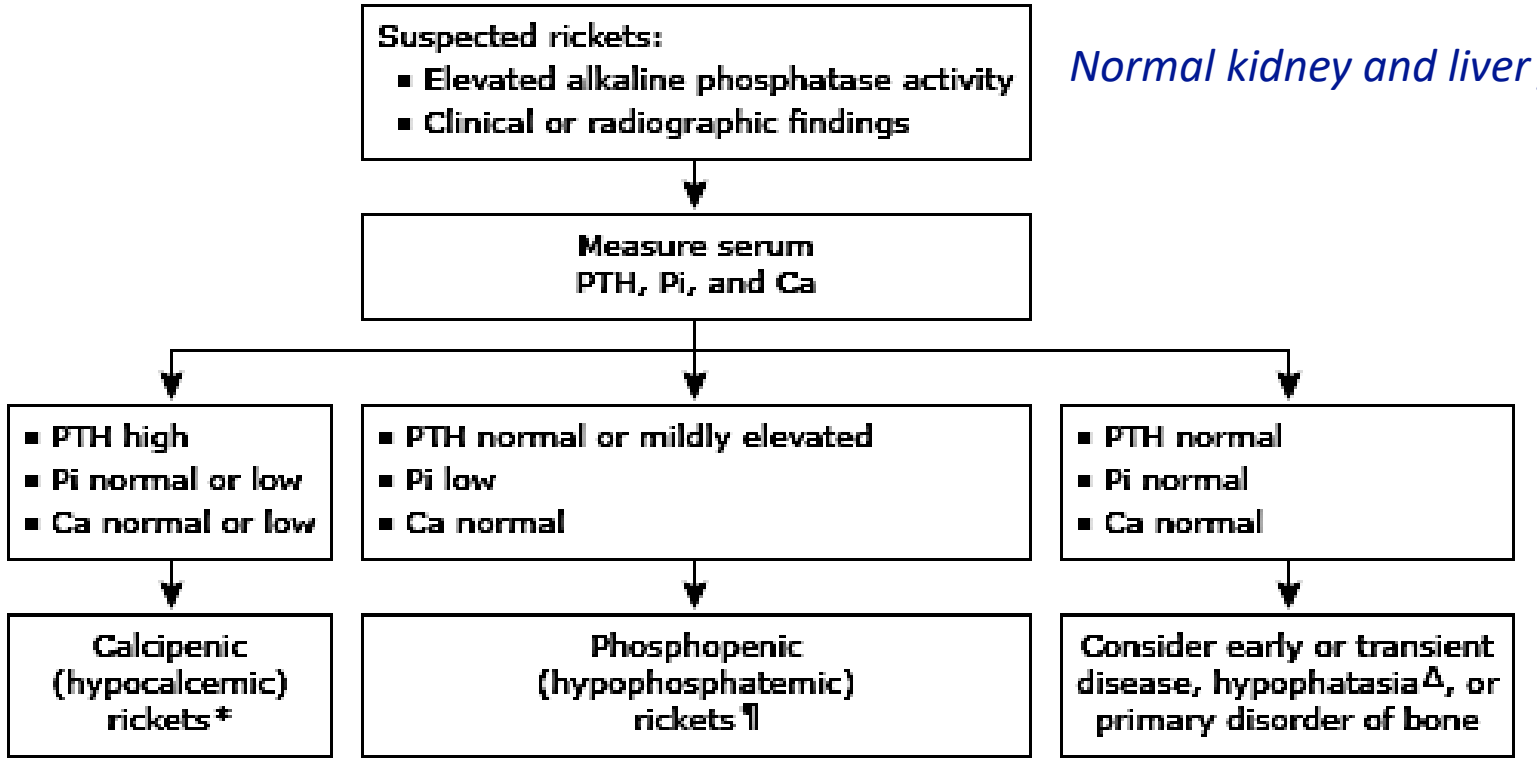
Haffner, et al. Pediatric Nephrology (2022)

Calcipenic *versus* Phosphopenic Rickets

Features	Calcipenic	Phosphopenic
Muscle weakness	+	-
Bony pain	Common	Uncommon
Extremities involved	All	Predominantly lower limbs
Tetany	±	-
Enamel hypoplasia	±	-
Dental abscess	-	±
Serum Calcium	Low/N	N
Serum phosphorus	Low	Low
Serum alkaline phosphatase	↑↑	↑/N
PTH	↑↑	↑/N
Osteopenia/osteitis	+	-

Jagtap *et al*. Indian J Endocr Metab 2012;16:177-82

Diagnostic Approach to Rickets



Normal kidney and liver function

* The diagnosis of calcipenic rickets should be confirmed by monitoring response to therapy

¶ In phosphopenic rickets, serum Pi is often very low

Δ Hypophosphatasia is accompanied by low serum alkaline phosphatase activity

Nutritional Rickets

Definition: A disorder of defective chondrocyte differentiation and mineralization of the growth plate and defective osteoid mineralization, caused by vitamin D deficiency and/or low calcium intake in children.

Severity is based on serum 25(OH)D levels and defined as

- Deficiency <12 ng/mL
- Insufficiency 12–20 ng/mL
- Sufficiency >20 ng/mL
- **Toxicity** >100 ng/mL with hypercalcemia and/or, hypercalciuria
- Levels between 50-100 ng/ml should be viewed with caution

Pathophysiology of nutritional rickets, due to vitamin D deficiency and/or dietary calcium deficiency

Reduced sunlight exposure

Dark skin, covered clothing, indoor living, excess sunscreen use

Low 25 hydroxy vitamin D

Lack of food rich in vitamin D, supplements and food fortification

Dietary deficiency

Low 1,25 dihydroxy vitamin D

Impaired intestinal calcium absorption

Drop in serum calcium below individual set point

Low dietary calcium intake

Sensed by C cells in the parathyroid gland

Secondary hyperparathyroidism

↓calcium and ↑phosphate excretion

↑ intestinal calcium absorption by increasing 1 hydroxylase activity

Stimulates osteoclasts to mobilise calcium with ongoing bone damage

Restores serum calcium by depriving body calcium stores

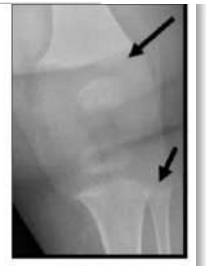
Prolonged phosphaturia

Low serum phosphate

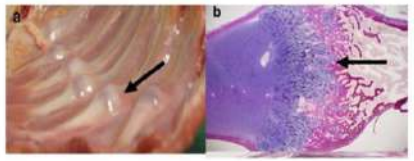
Failure of compensatory mechanisms

Low serum calcium

Hypophosphataemic complications



Rickets



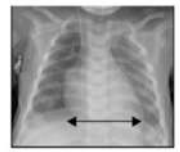
a. Rachitic rosary
b. Growth plate widening

Osteomalacia
(pink areas of un/undermineralised osteoid)

Hypophosphataemic complications

Hypocalcaemic complications

Neuromuscular irritability and Seizures



Dilated cardiomyopathy

Tetany

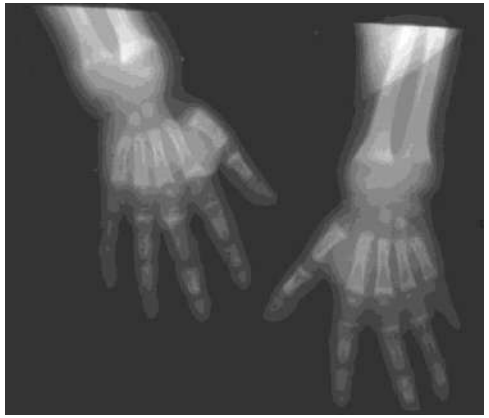
Hypocalcaemic complications

Pediatric Nephrology (2022) 37:2013–2036

Nutritional Rickets

- Osseous signs and symptoms
  - Swelling wrists and ankles,
  - Delayed fontanelle closure (normally closed by the age of 2 years)
  - Delayed tooth eruption (no incisors by 10 mo, no molars by 18 mo),
  - Leg deformity (genu varum, genu valgum, windswept deformity)
  - Rachitic rosary
  - Frontal bossing, Craniotabes
  - Bone pain, restlessness, and irritability

Nutritional Rickets



- Radiographic features
  - Splaying, fraying, cupping, and coarse trabecular pattern of metaphyses
  - Widening of the growth plate
  - Osteopenia
  - Pelvic deformities including outlet narrowing (risk of obstructed labor and death),
  - Long-term deformities in keeping with clinical deformities
  - Minimal trauma fracture

Nutritional Rickets

- Non-osseous features
  - Hypocalcemic seizure and tetany
  - Hypocalcemic dilated cardiomyopathy (heart failure, arrhythmia, cardiac arrest, death)
  - Failure to thrive and poor linear growth
  - Delayed gross motor development with muscle weakness
  - Raised intracranial pressure

Sunlight and vitamin D

- A daily sunlight exposure of 17-30 min in infants and 30-45 min in older children over 15-40% body surface area is recommended at least five times a week during noon (11AM-3PM) for preventing vitamin D deficiency
- Cutaneous vitamin D biosynthesis depends on host and environmental factors.
- Environmental factors: latitude, pollution, cloud cover and intensity of UV irradiance
- Host factors: age, skin melanin content (Fitzpatrick skin type 1 to 6, 6 being darkest) single nucleotide polymorphisms in melanin gene, body surface area exposed (clothing), lifestyle and use of sun-barrier measures as topical creams and sunscreens

Gupta P, et al. Indian Pediatrics 2021

Calcium and Vitamin D intake to prevent Vitamin D Deficiency

- **Dietary Calcium Intake to Prevent Rickets**
- 0–6 months 200 mg/day
- 6–12 months 260 mg/day
- >12 months >500 mg/day (sufficient), 300-500 mg/day (Insufficient), <300 mg/day (deficient)
- Vitamin D supplementation @ 400 IU/day is recommended in infancy
- No routine supplementation during childhood and adolescence. Estimated average requirement (EAR) of vitamin D (400-600 IU/day) should be met from sunlight and dietary sources to prevent VDD in these age-groups.

Gupta P, et al. Indian Pediatrics 2021

High-Risk Conditions Requiring Routine Vitamin D Supplementation

- Non-ambulatory states like cerebral palsy, neuromuscular disorders
- Chronic kidney disease
- Chronic liver disease
- Malabsorption syndromes
- Long-term use of glucocorticoids, antiepileptic drugs, ketoconazole
- Endocrine disorders like hyperparathyroidism
- Disorders with extensive cutaneous involvement

Gupta P, et al. Indian Pediatrics 2021
Nutritional rickets. WHO; 2019.

Treatment of nutritional rickets

- Healthy children with serum 25(OH)D < 12 ng/mL or high-risk population with level <20 ng/mL should be treated
- Children with non-osseous symptoms and AND having serum 25(OH)D level < 20 ng/mL should also be treated
- Alfa-calcidiol (1-hydroxycholecalciferol) and calcitriol are not recommended for management of nutritional rickets and VDD
- Calcium intake of 50-75 mg/kg/day (not exceeding 500 mg/day) must be ensured either through diet or supplementation
- Repeat radiographs at 4 and 12 weeks after vitamin D therapy in rickets to look for evidence of healing
- Continue therapy beyond 12 weeks if normalization of radiological or biochemical parameters (serum 25(OH) D >20-50 ng/ml). Monitor for urine calcium creatinine and renal USG

Gupta P, et al. Indian Pediatrics 2021

Treatment of nutritional rickets

- Oral treatment more rapidly restores serum 25(OH)D levels and is safer than intramuscular (IM) treatment
- Daily vs. intermittent regimes: equally efficacious; daily doses more physiological
- Dose: Vitamin D (2000 IU/day) is recommended for nutritional rickets and symptomatic vitamin D deficiency in infants, 3000 IU/day or its equivalent in weekly/monthly bolus doses may be given in children older than 1 year
- Duration of therapy: minimum of 12 weeks. Some children may require a longer treatment duration for normalization of alkaline phosphatase and serum 25(OH)D.

Gupta P, et al. Indian Pediatrics 2021

Therapy for nutritional rickets

- **Stoss therapy** with vitamin D
  - 100000-600000 IU over 1-5 days, or 60000 IU every week for 6-8 wk
  - Subsequently 400 IU of vitamin D per day.
  - In addition, all patients should receive supplements of calcium (30-75 mg/kg/d in 2-3 divided doses) for 2-4 weeks.

Treatment doses of vitamin D3 or D2 for nutritional rickets

Age	*Daily dose for 12 wk*[a]	*Alternative intermittent dose regimen*[b]	*Maintenance dose (daily)*[c]
<6 mo	2000	NA	400
6-12 mo	2000	Equivalent of 2000 IU/day may be given on a monthly or weekly basis	400
>12 mo	3000	60000 IU fortnightly (after every 2 weeks) x 5 doses	600

[a]Reassess response after 12 weeks. Ensure daily calcium intake of 50-75 mg/kg/day, not exceeding 500 mg/day. [b]In certain situations, if compliance is not good, intermittent regimens may be prescribed (in children above 6 months of age only). [c]Ensure daily intake of recommended dose through supplementation or dietary sources. Optimum duration of maintenance vitamin D therapy is not known at present

Gupta P, et al. Indian Pediatrics 2021

Vitamin D refractory rickets

- Refers to patients who fail to show evidence of radiological healing and normalization of biochemical abnormalities despite adequate therapy, as described above.
- Refractory rickets is often inherited.

Causes of Refractory Rickets

Calcium deficiency (raised parathormone levels)

- Vitamin D dependent rickets types I and II
- Chronic renal failure

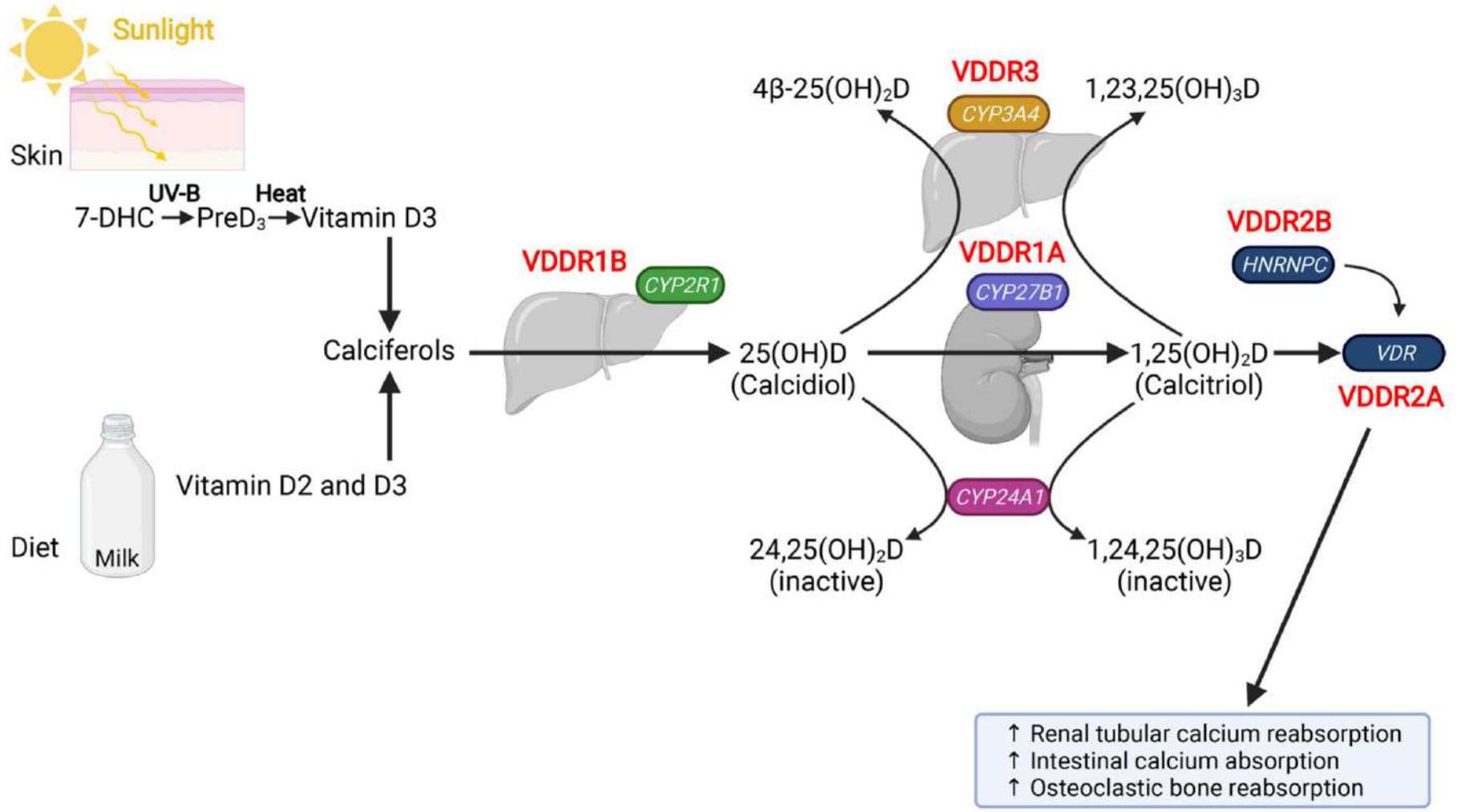
Phosphate deficiency (normal parathormone levels)

- Familial hypophosphatemic rickets: X-linked, autosomal
- Proximal renal tubular acidosis
- Fanconi syndrome
- Tumor induced
- Distal renal tubular acidosis.

Investigations for refractory rickets

- Blood levels of:
  - Ca, Pi, SAP
  - Arterial blood gases
  - Urea, creatinine, Na, K
  - iPTH
  - 25(OH)D3, 1,25 $(OH)_2D3$
- X-ray wrist , USG abdomen (nephrocalcinosis)
- Tests for phosphaturia: $FEPO_4$, TRP, $TmPO_4/GFR$
- Tests of renal acidification (for RTA): urinary pH, U-B PCO_2, $FEHCO_3$, Ammonium Chloride Loading Test
- Urine for reducing substances

Vitamin D homeostasis and hereditary causes of VDDR



Pediatric Nephrology (2022) 37:2013–2036

Vitamin D Dependent Rickets

- There are three broad categories of VDDR
- VDDR1 represents a failure to fully activate calciferols due to the inability to generate either 25(OH)D (VDDR1b) or 1,25(OH)2D (VDDR1a)
- VDDR2 is characterized by resistance to 1,25(OH)2D owing to mutations in the VDR (VDDR2a) or the presence of a nuclear ribonucleoprotein that interferes with the vitamin D receptor-DNA interaction (VDDR2b).
- VDDR3, which results from excessive inactivation of vitamin D metabolites.

VDDR 1A

- Biallelic mutations in *CYP27B1* gene (chrom 12q13.3) that encodes 25-OH-D3 -1α-hydroxylase. Greatest frequency in the French-Canadian population
- Normal at birth, problems of impaired vitamin D activity at 2–24 months.
- Hypotonia, irritability, tetany, seizures, and failure to thrive, in first few months
- Later, fractures, and typical skeletal features of rickets, impaired growth
- Biochemical: Low calcium & phosphate, elevated serum ALP and PTH
- Plasma concentrations of 1,25(OH)2D are low or even undetectable; plasma 25 (OH)D are normal or ↑

VDDR 1B

- Mutations in *CYP2R1* that decrease expression or function of enzyme 25-hydroxylase.
- There is a gene dose effect on the phenotype. Heterozygous patients also show a blunted increase of serum 25(OH)D to administration of 50,000 IU of parent vitamin D
- Hypocalcemia, secondary hyperparathyroidism and low/undetectable plasma concentrations of 25(OH)D, with reduced responsiveness to conventional doses of vitamin D
- the phenotype appears to improve with age, which may indicate acquisition of a vitamin D-independent mechanism(s) for intestinal absorption of calcium due to development of post-pubertal levels of sex hormones
- Alternatively, other CYP enzymes that possess 25-hydroxylase activity may assume greater importance with maturation.

VDDR 2A

- AR, loss-of-function mutations in the VDR gene (chrom 12q13.11) ; tissue resistance to vitamin D
- Clinical features as in other VDDR, but about 50% of patients with VDDR2a have alopecia, more severe ds.
- Alopecia develops later due to failure of normal hair follicle cycling, depends upon unliganded VDR actions
- Appear normal at birth and later develop features of vitamin D deficiency over the first 2–8 months of life.
- Low serum levels of calcium and phosphorus and elevated serum concentrations of 1,25(OH)2D, in the range of 50–1,000 pg/mL (normal in children is 30–100 pg/mL); 25(OH)D may be normal or elevated
- Children with milder forms of VDDR2a, such as those without alopecia, may have clinical and radiologic improvement with administration of high-dose vitamin D therapy that ranges from 5,000 to 40,000 IU per day of calciferol, 20–200 µg per day of calcifediol, or 17–20 mcg per day of calcitriol
- With alopecia, about half will be resistant to the highest doses of calciferols; the other half have demonstrate satisfactory calcemic responses, but require 10-times greater doses than in those with normal hair.

VDDR 2B

- VDDR2b resembles VDDR2a but is not caused by a defect in the *VDR* gene.
- The molecular defect appears to be overexpression of a nuclear protein that specifically interacts with a DNA response element that binds retinoid X receptor-VDR heterodimers.
- A heterogeneous nuclear ribonucleoproteins (hnRNPs), attenuates gene transcription via its role as hormone response element-binding proteins.
- Management of rickets is similar to that described above for VDDR2a

VDDR 3

- Increased inactivation of vitamin D metabolites caused by a gain-of-function missense mutation (p.I301T) in the gene encoding CYP3A4
- Clinical features appear similar to those of patients with VDDR1
- Reduced serum calcium and phosphorus with increased ALP and PTH
- Require high doses of calcitriol or vitamin D3 (50,000 IU daily) to maintain normal serum levels of vitamin D, PTH, calcium, and phosphorus.

Vitamin D-dependent rickets

Type	25(OH)D	1,25(OH)$_2$D	PTH	Inheritance	Gene defect (OMIM)
VDDR1A	N/I	D	I	A.R.	CYP27B1 (264700)
VDDR1B	D	D	I	A.R.	CYP2R1 (600081)
VDDR2A	N/I	N/I	I	A.R.	VDR (277440)
VDDR2B	N/I	N/I	I	A.R.	Unknown (600785) *HNRNPC*
VDDR3	D	D	I	A.D.	CYP3A4 (124010)

VDDR, vitamin D-dependent rickets, N, normal; I, increased, D, decreased; PTH, parathyroid hormone.

Levine MA (2020). Front. Pediatr. 8:315.

Suggested calciferol doses for maintenance treatment of patients with VDDR

	VDDR1A (μg per day)	VDDR1B (μg per day)	VDDR2 (μg per day)	VDDR3 (μg per day)
Vitamin D3 or D2	NI	100–200	125–1,000?*	**1,000 to?**
Calcifediol	NI	**20–50**	20–200*	50 to?
Calcitriol	**0.3–2**	0.3–2	**5–60**†	1 to?
1α (OH)D	**0.5–3**	0.5–3	**5–60**†	2 to?

In all cases, supplemental calcium is recommended as described in text. The preferred form of calciferol is noted in bold for each disorder. NI, not indicated.

**Patients with milder grades of resistance to 1,25(OH)2D (usually with normal hair) often can respond to analogs requiring 1-hydroxylation. Maximal useful doses have not been defined. Serum 1,25(OH)2D must be maintained in the range of 200–1,000 pg/mL.*

† Maximal does are limited only by cost and patient acceptance; some patients have shown no response to maximal doses tested.

Levine MA (2020). Front. Pediatr. 8:315.

Phosphopenic rickets

- Either due to dietary phosphate deficiency or impaired bioavailability, FGF23-mediated renal phosphate wasting or to primary or acquired renal tubular phosphate wasting
- **XLHR** most frequent cause of hypophosphatemic rickets, approximately 80% of all cases.
- **Dietary phosphate deficiency or impaired availability** may cause rickets, in the high-risk gp
  - very-low-birthweight infants, esp. when breast-fed and no phosphate supplements given
  - Gastrointestinal surgery or short bowel syndrome may result in low phosphate uptake.
  - Excessive use of phosphate binders or too much restriction of phosphate intake, especially in formula- fed infants suffering from CKD
- **FGF23-mediated renal phosphate wasting** is a group of disorders characterized by increased synthesis of FGF23 or reduced degradation of intact FGF23

X-linked hypophosphatemia

- X linked dominant, prevalence 4–5/100,000 children; inactivating mutations in PHEX gene (Phosphate regulating gene with Homologies to Endopeptidase on X chromosome)
- *PHEX* encodes a membrane-bound endopeptidase and is primarily expressed in bone (osteoblasts and osteocytes), and teeth (odontoblasts) and is thought to affect the expression of FGF23 rather than its degradation
- XLH constitutes 90% of familial and 70% of sporadic cases of hypophosphatemic rickets
- Clinical symptoms develop around the age of walking, resemble other rickets
- Additional features are disproportionate short stature (short legs, and preserved trunk length), dental abscesses, craniosynostosis, dolichocephalic head, and sensorineural hearing loss

X-linked hypophosphatemia

- Tooth eruption is often delayed. Mineralization of dentine is markedly impaired resulting in spontaneous endodontic abscesses and early decay of lacteal and permanent teeth
- Type 1 Chiari malformation and syringomyelia are rare, mostly asymptomatic complications of XLH, but may result in headaches and neck pain
- Adults with XLH often develop periodontitis, alveolar bone and tooth loss, enthesopathies, (ossification of the entheses, e.g., at the Achilles tendon), osteoarthritis (e.g., of the hip), and pseudofractures (characterized by cortical infraction surrounded by a thickened periosteum on X-ray) which may result in pain, reduced quality of life, and/or immobility
- **Burosumab**, a monoclonal antibody to FGF23, is an important new option for all XLH.
- It is suggested for all newly diagnosed cases and those that have failed on oral phosphate plus calcitriol therapy
- Alternative therapy: oral phosphate plus calcitriol

Autosomal-dominant hypophosphatemic rickets (ADHR)

- Rare activating pathogenic variants of FGF23 gene, prevent its proteolytic cleavage
- Incomplete penetrance, highly variable phenotype
- Patients usually become symptomatic after childhood
- Iron status is an important regulator of FGF23 metabolic pathways, and iron deficiency predisposes ADHR patients to become clinically symptomatic
- In the absence of a genetic defect, iron deficiency does not result in high FGF23 levels or phosphate wasting, because increased expression of FGF23 is matched by increased FGF23 cleavage; in patients with ADHR, the ability to increase FGF23 cleavage is impaired

Autosomal-recessive hypophosphatemic rickets (ARHR1 and 2)

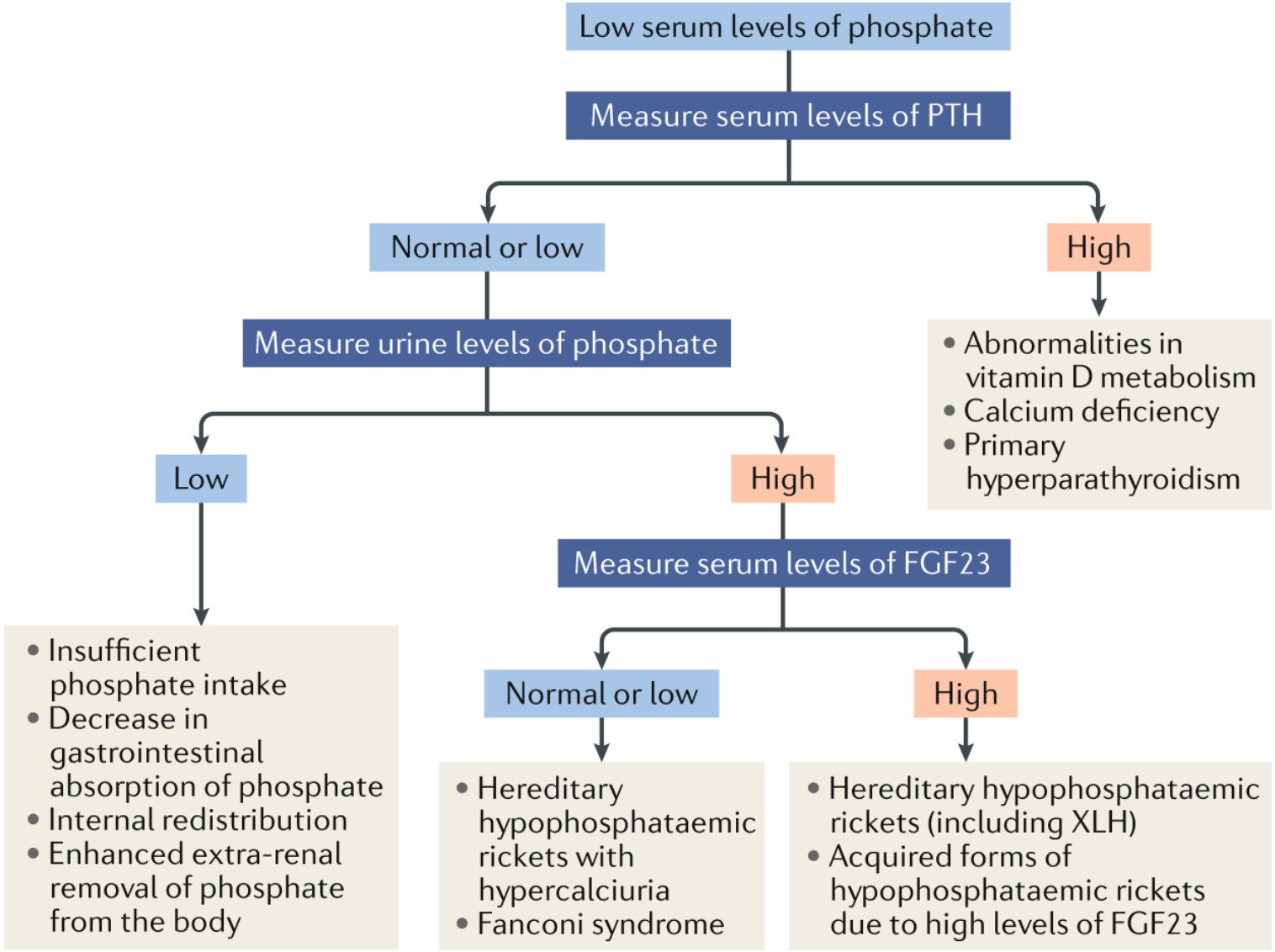
- Loss-of-function mutation of DMP1 or ENPP1 gene, both expressed in bone & teeth
- Clinical symptoms resemble those seen in XLH; onset in late infancy
- DMP1 protein plays an important role in the development of bone, cartilage and teeth, whereas ENPP1 is a regulator of bone mineralization and tissue calcification via formation of inorganic pyrophosphate (PPi).
- Mutations of ENPP1 result in marked reductions in PPi levels with consequent severe vascular mineralization known as generalized arterial calcification of infancy (GACI)
- High phenotypic heterogeneity in family members with the same ENPP1 mutations
- Patients with ARHR2 may also present with a very early onset of hearing loss

DMP1: dentine matrix acidic phosphoprotein 1
ENPP1: ectonucleotide pyrophosphatase/phosphodiesterase 1

Hypophosphatemic rickets with hypercalciuria

- HHRH is inherited as AR, gene SLC34A3, chromosome 9q34 HHRH
- Genetic mutations of the renal type 2c sodium-phosphate cotransporter.
- It is associated with high levels of vitamin D
- Rickets and/or osteomalacia is the presenting feature like XLH.
- Mild forms may present with hypercalciuria and nephrolithiasis without bone disease. Patients should be treated only with phosphorus supplementation.
- Calcitriol should not be used. Plasma calcitriol levels and urinary calcium excretion should be monitored.

Evaluation of a child with rickets presenting with hypophosphataemia



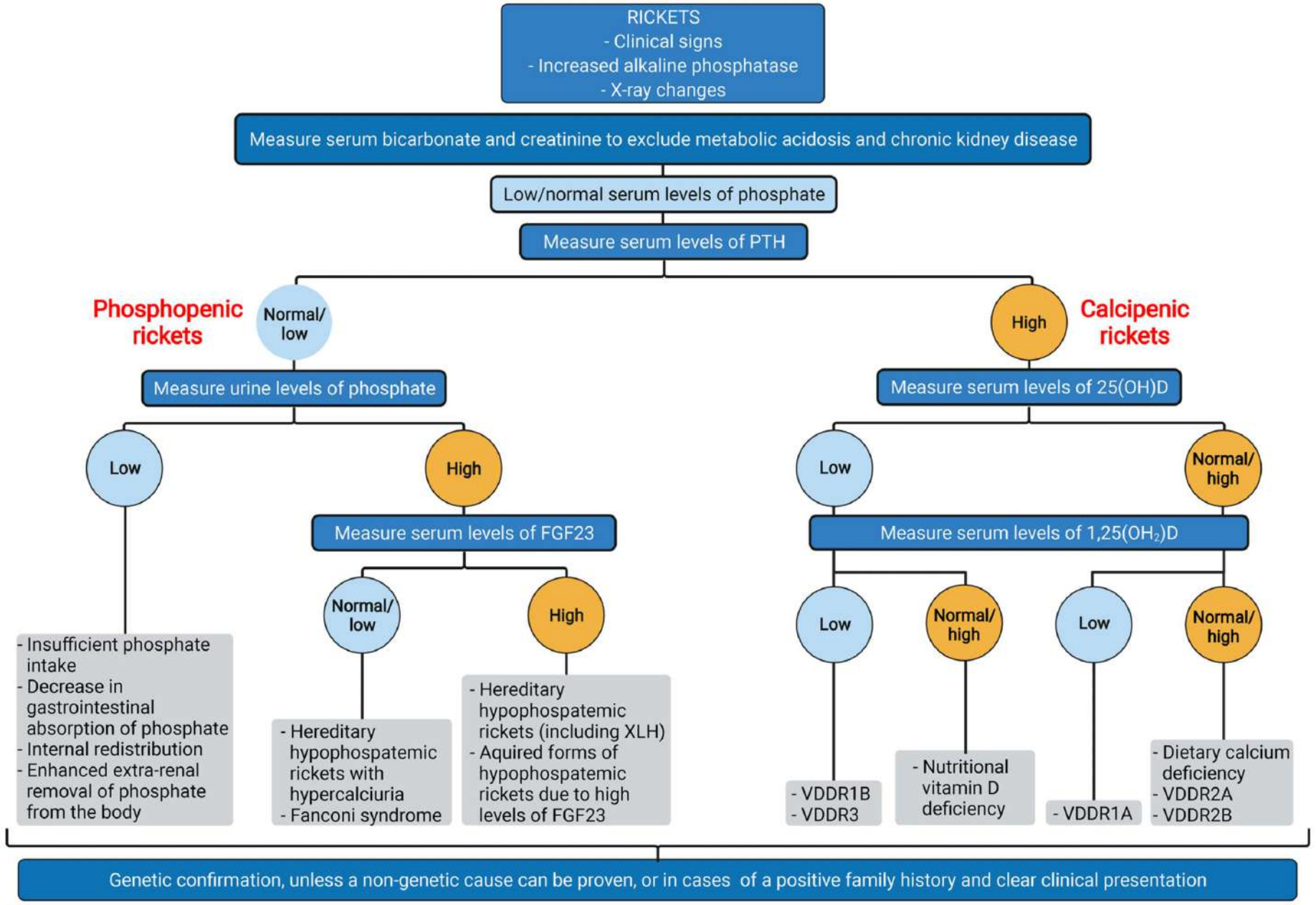
Haffner, D., *et al. Nat Rev Nephrol* **15**, 435–455 (2019)

Salient features of different types of rickets

Type	Calcium	Phosphate	Alkaline Phosphatase	PTH	25(OH)D	$1,25(OH)_2D$
Calcipenic Rickets						
Vitamin D deficiency	L or N	L or N	H or VH	H	L	variable
VDDR1	L	L or N	VH	H	N	L
VDDR2	L	L or N	VH	H	N	H
Phosphopenic rickets						
XLHR	N	L	H	N or H	N	L or N
ADHR	N	L	H	N	N	L
ARHR	N	L	H	N	N	L
HHRH	N	L	H	L or N	N	H

VDDR1: Vitamin D-dependent Rickets type 1; VDDR2: Vitamin D-dependent Rickets type 2; XLHR: X-linked Hypophosphatemic Rickets; ADHR: Autosomal Dominant Hypophosphatemic Rickets; ARHR: Autosomal Recessive Hypophosphatemic Rickets; HHRH: Hereditary Hypophosphatemic Rickets with Hypercalciuria; 25(OH)D: 25-hydroxy vitamin D; $1,25(OH)_2D$: 1,25-dihydroxy vitamin D; L: low; N: normal; H: high; VH: very high.

Recap of algorithm for the evaluation of a child presenting with rickets



Pediatric Nephrology (2022) 37:2013–2036

Summary

- Hypophosphatemia is the unifying basis for all rickets
- Calcipenic rickets require native or active vitamin D depending on the underlying pathophysiology.
- Children with X-linked hypophosphatemia should be treated with burosumab, if available.
- Alternatively, use frequent doses of oral phosphate salts in combination with active vitamin D is used
- Hypophosphatemic rickets independent of FGF23 due to selective genetic defects of renal tubular phosphate reabsorption, are treated with oral phosphate alone, since they are associated with excessive 1,25-dihydroxyvitamin D production.
- Treatment should be guided by frequent monitoring and surveillance for adverse effects