Parathyroid and calcium metabolism disorders

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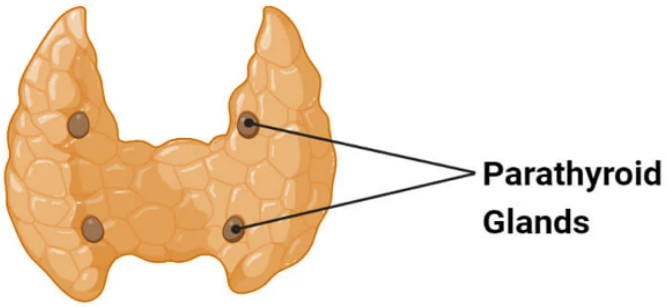
Calcium status metabolism depends of:

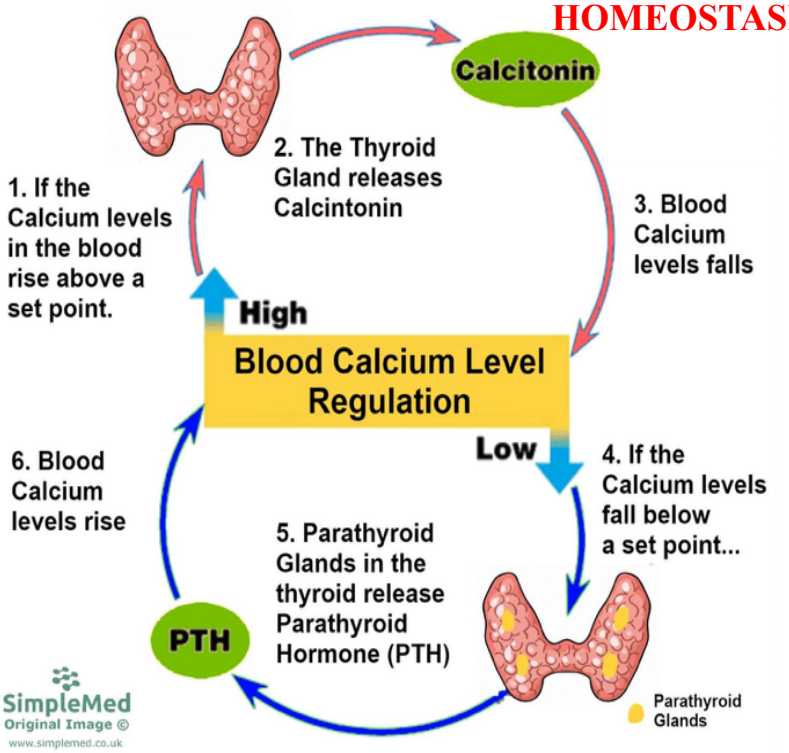
- Parathormon PTH
- Calcitonin CT
- Vitamin D; 25 OHD, 1,25 OHD
- CaSR
- Ca, ionized Ca
- Mg, PO4,

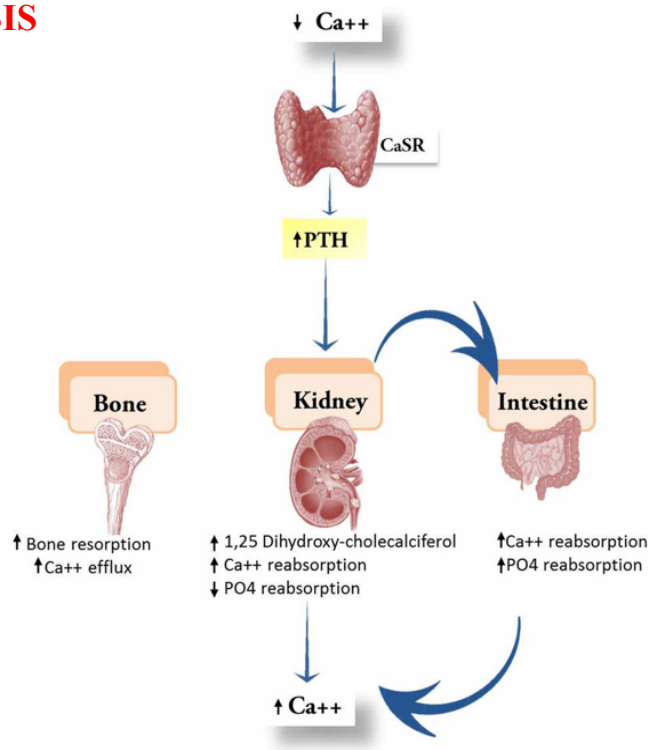
Parathyroid glands

Normal parathyroid glands are small, with overall dimensions typically averaging 5 × 3 × 1 mm and weighing less than 50 mg.

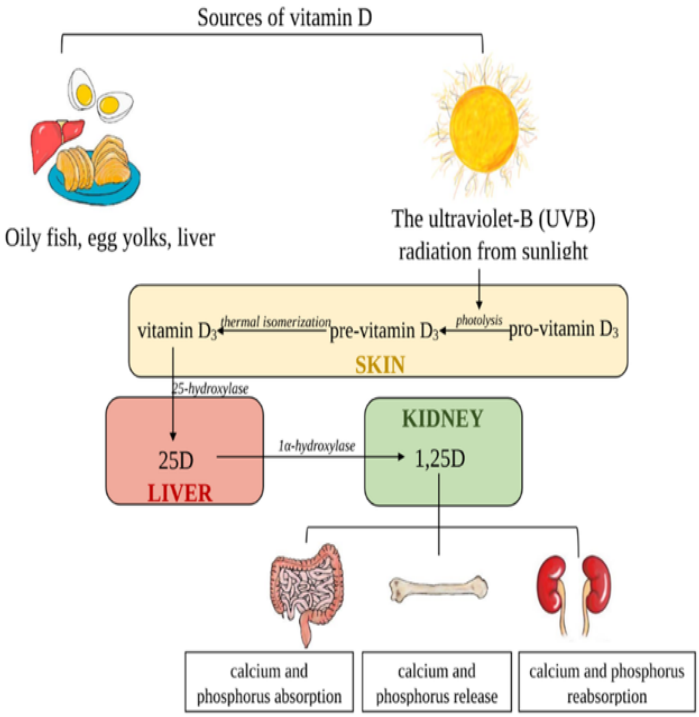


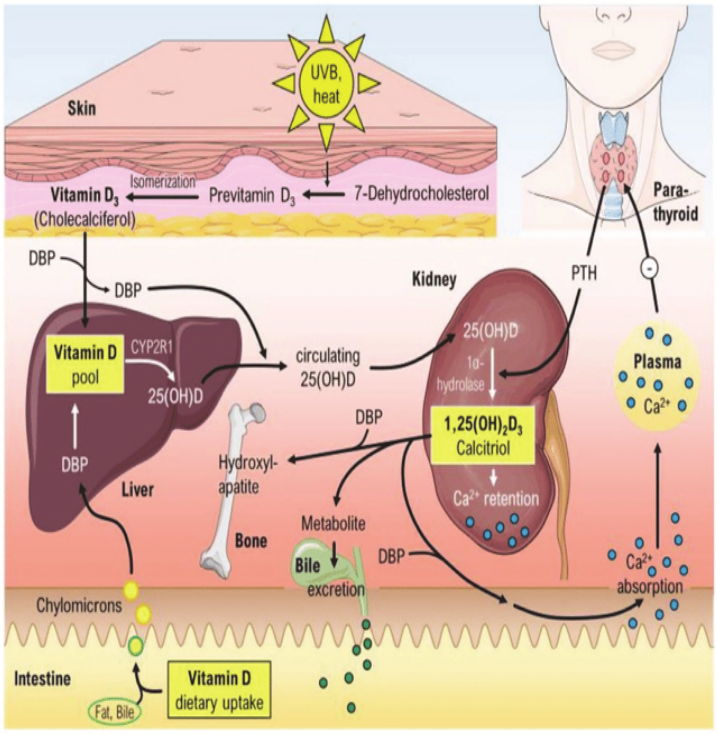
CALCIUM HOMEOSTASIS



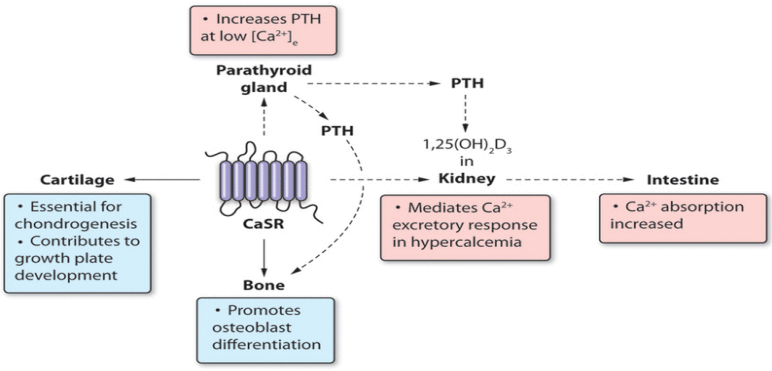


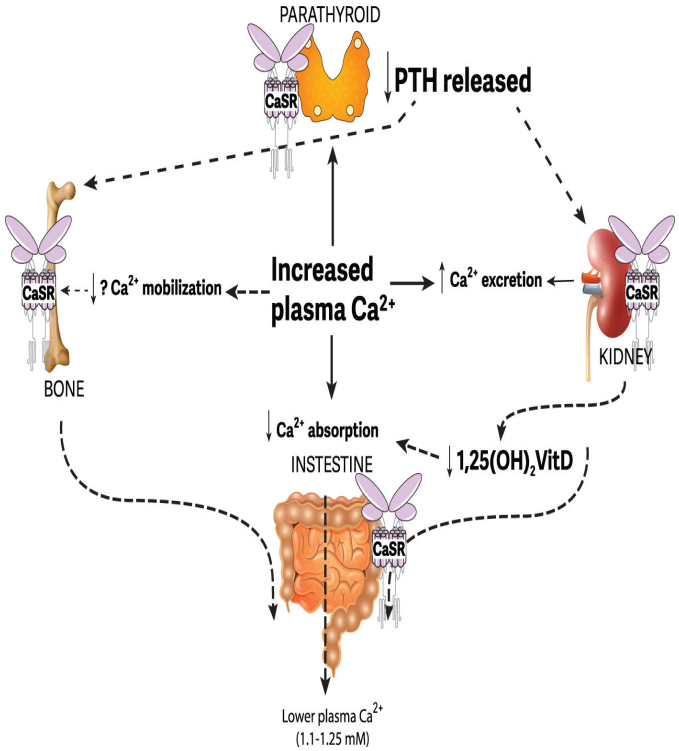
The role of vitamin D





The role of Calcium Receptor CaSR in calcium homesostasis





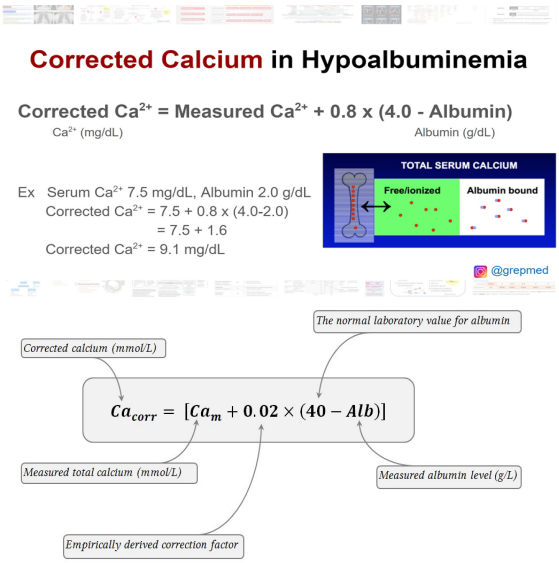
When Ca(2+) is high, the CaSR suppresses PTH synthesis and secretion, promotes its degradation, and inhibits parathyroid cellular proliferation. It has just the opposite effects on the C-cell, stimulating CT when is high. In bone, Ca(2+), acting via the CaSR, stimulates recruitment and proliferation of preosteoblasts, their differentiation to mature osteoblasts, and synthesis and mineralization of bone proteins. Conversely, inhibits the formation and activity and promotes apoptosis of osteoclasts, likely via the CaSR. These actions tend to mobilize skeletal Ca(2+) during deficiency and retain it when Ca(2+) is plentiful.

Ranges of blood Calcium and Phosphorus in children

Table 25. Age-Specific Normal Ranges of Blood Ionized Calcium, Total Calcium and Phosphorus

Age	Ionized Calcium (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)
0-5 mo	1.22-1.40	8.7-11.3	5.2-8.4
6-12 mo	1.20-1.40	8.7-11.0	5.0-7.8
1-5 y	1.22-1.32	9.4-10.8	4.5-6.5
6-12 y	1.15-1.32	9.4-10.3	3.6-5.8
13-20 y	1.12-1.30	8.8-10.2	2.3-4.5

Adapted with permission[121]; Specker.[524]
Conversion factor for calcium and ionized calcium: mg/dL × 0.25 = mmol/L.
Conversion factor for phosphorus: mg/dL × 0.323 = mmol/L.



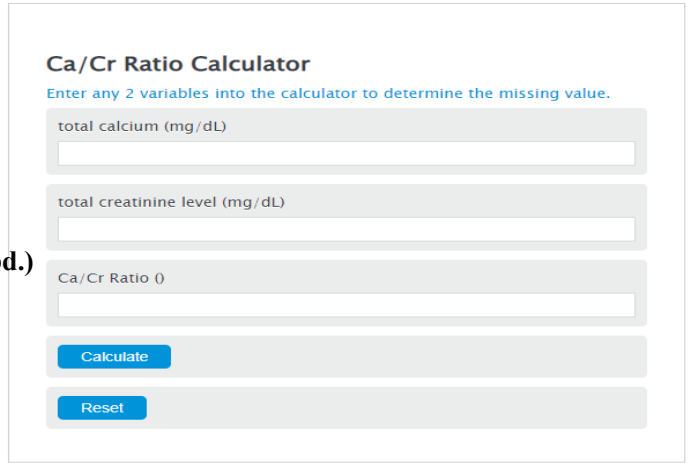
1: corrected total calcium [mg/dl] = actual calcium level [mg/dl] + (4,0 — albumin level [g/dl]) x 0,8
2: corrected total calcium [mmol/l] = actual calcium level [mmol/l] + (40 — albumin [g/l]) x 0,02

Values of the calcium-creatinine index in children, indicative of hypercalciuria

Second morning portion of urine

Age	mg Calcium/mg Creatinine
<1 year	<0.81
1–3 years	<0.53
3–5 years	<0.39
5–7 years	<0.28
>7 years	<0.21

Ca/Kr (mg/mg) in children born on time (and 35.–37. hbd.)
a) 0–6. mż. – <0,8
b) 7.–12. mż. – <0,6
c) >2. rż. – <0,21
Ca/Kr (mg/mg) in preterm 24.–34. tc.
a) <4. tż. – <1,4
b) 4.–8. tż. – <1,25
c) 8.–12. tż. – <1,0
d) 12.–20. tż. – <0,8



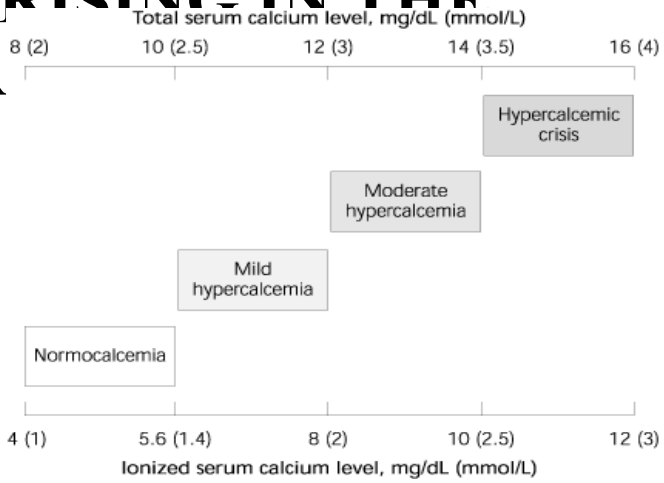
Hypercalcemia

DISORDERS ARISING IN THE PARATHYR

Abnormalities of the parathyroid glands are the most common causes of hypercalcemia.

The spectrum of parathyroid proliferative disorders includes

1. parathyroid hyperplasia,
2. parathyroid adenoma (PA),
3. atypical PA, and parathyroid carcinoma (PC).



HYPERPLASIA AND HYPERPARATHYROIDISM

1. Parathyroid hyperplasia is defined as an absolute increase in parenchymal cell mass, which occurs from the proliferation of chief cells, oncocytes, and transitional oncocytes in multiple parathyroid glands.

2. In more than 50% of cases, the enlargement of glands is symmetric.

When asymmetric, the distinction between hyperplasia and adenoma may be challenging by standard morphologic criteria alone.

Hyperparathyroidism is divided into primary, secondary, and tertiary hyperparathyroidism.

PRIMARY HYPERPARATHYROIDISM in children

1. From 80% to 85% of primary hyperparathyroidism is caused by PA (parathyroid adenoma) followed by primary parathyroid hyperplasia (15%) and PC (<5%)(parathyroid carcinoma)
2. Ectopic locations of hyperplastic parathyroid tissue have also been documented.
3. Patients with primary hyperparathyroidism have abnormal regulation of serum parathyroid hormone secretion.

Primary hyperparathyroidism is characterized by **increased serum calcium level in the setting of increased parathyroid hormone levels**.

↑↑↑ PTH and ↑↑↑ Ca total

Childhood/adolescent PHPT - parathyroid hyperplasia

Primary Hyperparathyroidism (PHPT) children

Childhood/adolescent PHPT is associated with either single parathyroid adenomas or multiple adenomas (so-called parathyroid hyperplasia).

Thus, the etiology of PHPT includes

(1) multi-gland hyperplasia resulting from germline mutations in the *MENIN*, *RET*, and *CDKN1B* (encoding p27Kip1) genes;

(2) single parathyroid adenomas that represent monoclonal neoplasms, many of which are associated with somatic mutation in *MENIN* or *PRAD1*;

(3) distinct parathyroid adenomas due to germ-line or somatic mutations in *HPRT2* (CDC 73) and which have a predisposition to parathyroid carcinoma

Neonatal severe hyperparathyroidism and familial hypocalciuric hypercalcemia

1. PHPT can present within the first few days of life as neonatal severe hyperparathyroidism **(NSHPT)**
2. NSHPT has been associated with inactivating mutations in the *CASR*
3. In most cases, neonates with NSHPT have inactivating mutations on **both *CASR* alleles**, which results in a complete or near-complete absence of functional CaSRs on parathyroid and other cells in the body.

The loss of calcium sensing leads to parathyroid hyperplasia and increased PTH secretion as well as decreased renal excretion of calcium, and consequently severe hypercalcemia ensues.

Familial hypocalciuric hypercalcemia FHH (CASR mutation)

1. Heterozygous *CASR* mutations are more commonly associated with a relatively asymptomatic form of PHPT that has been termed familial hypocalciuric hypercalcemia **(FHH),** sometimes also termed benign familial hypercalcemia.
2. FHH is therefore genetically related to NSHPT (neonatal severe hyperaparathyroidism) and its mildness is thought to represent a dose affect of the inactivating *CASR* mutations. Hence, FHH is typically an autosomal dominant condition, although very mild *CASR* mutations have been associated with an autosomal recessive form of FHH.

	FHH	MEN1	MEN2a	HPT-JT	FIHP
Tissues affected	Parathyroid	Parathyroid	MTC Pheo	Parathyroid	Parathyroid
	Kidney	Pituitary	Parathyroid	Jaw	
		Pancreas		Kidney	
Gene defect	*CaSR*	*MEN1* gene	*Ret*	*HPRT2* gene	Rarely *HPRT2* gene; most unknown
		11q13		1q25	
		**CDKN1B P27kip*			

Clinical and molecular features of genetic syndromes of primary hyperparathyroidism
FIHP = familial isolated hyperparathyroidism; FHH = familial hypocalciuric hypercalcemia; HPT-JT = hyperparathyroidism-jaw tumor; MEN = multiple endocrine neoplasia.

Clinical symptoms of hypercalcemia

At the beginning most patients are asymptomatic

- fatigue,
- mild depression, or cognitive impairment.

In longstanding increased parathyroid hormone patients may present:

- renal disorders (including nephrolithiasis and renal deficiency)
- gastrointestinal issues (including nausea/vomiting, peptic ulcer dise
- skel ures, and oste
- neur and

	Mild (corrected calcium 10.5–11.9 mg/dL)	Moderate (corrected calcium 12.0–13.9 mg/dL)	Severe (corrected calcium > 14.0 mg/dL)
Neuropsychiatric	Anxiety, depression	Cognitive dysfunction	Lethargy, confusion, stupor, coma
Gastrointestinal	Anorexia, nausea, constipation	Anorexia, nausea, constipation	Pancreatitis
Renal	Polyuria	Dehydration	Renal insufficiency, dehydration
Cardiac	Shortened QT interval	Shortened QT interval	Arrhythmia, ventricular tachycardia
Musculoskeletal	None	Weakness	Weakness

Note. Information from Inzucchi (2004); Ahmed & Hashiba (1988); Kiewiet, Ponssen, Janssens, & Fels (2004).

SECONDARY HYPERPARATHYROIDISM

Most parathyroid hyperplasia is the result of secondary hyperparathyroidism caused by

- chronic kidney disease (CKD),
- malabsorption syndrome,
- chronic inadequate sunlight exposure.

Impaired renal function leads to downregulation of the parathyroid vitamin D and calcium sensing receptors, which negatively affect mineral metabolism and result in high serum phosphate level, low serum calcium level, and vitamin D deficiency.

Parathyroid hyperplasia, cardiovascular disease, and concomitant bone

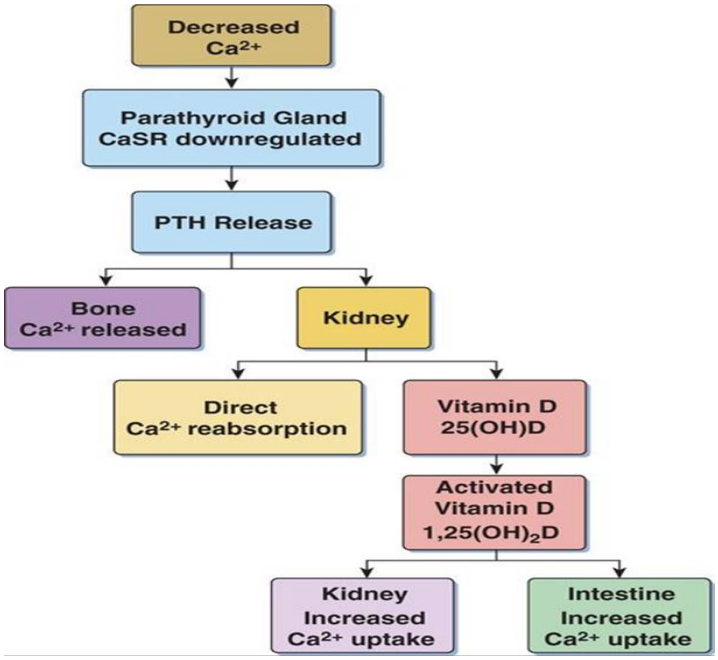
TERTIARY HYPERPARATHYROIDISM

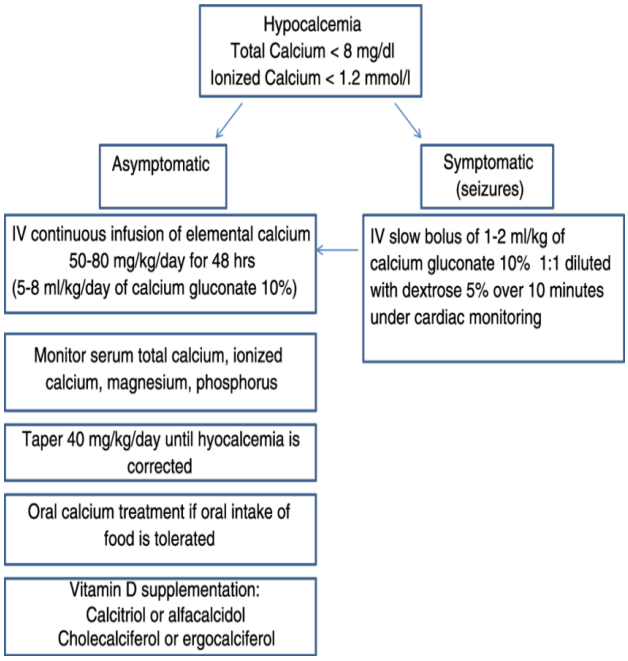
A significant proportion of patients with CKD and secondary hyperparathyroidism maintain increased levels of parathyroid hormone following kidney transplant.

This state of hyperparathyroidism is known as tertiary hyperparathyroidism.

Hypocalcemia

total calcium <8 mg/dl, ionized <1,2 mmol/l





Hypocalcemia in neonates

Early neonatal hypocalcemia 48-72 hours after birth

- Prematurity
- Birth asphyxia
- Infant of diabetc mother
- Interuterine growth retardation

Late neonatal hypocalcemia 3-7 days

- Phosphate rich cow's milk or formula feeding
- Transient hypoparathyroidism of newborn
- Magnesium deficiency
- Hypoparathyroidism

Hypocalcemia in infants and children

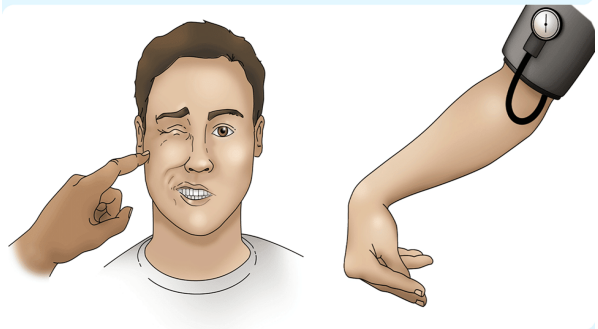
- Vitamin D deficiency
- Hypoalbuminemia
- Alkalosis
- Hypoparathyroidism
- Renal failure
- Malabsorption syndrome
- Pancreatitis
- Hungry bone syndrome
- Hypophosphatasia

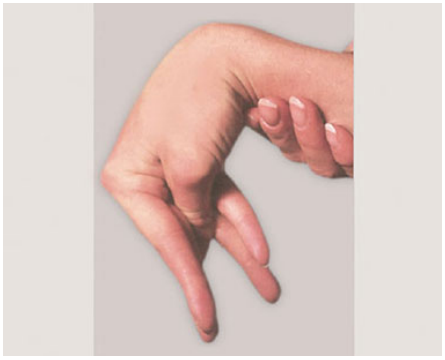
Symptoms of hypocalcemia

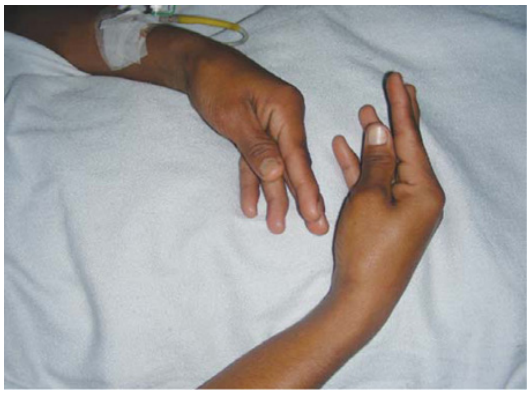
In children

1. Infant feeding problems
2. Parasthesia
3. Seizures
4. Laryngospasm
5. Tetany
6. Muscle cramps
7. Chvostek's signs
8. Trousseau's sign

Increased neuromuscular irritability
Tetany
Muscle cramping and twitching
Muscle weakness
Abdominal cramping
Laryngospasm
Bronchospasm
Central nervous system involvement
Seizures
Altered mental status
Impaired memory and concentration
Papilledema
Pseudotumor cerebri
Personality disturbances
Extrapyramidal disorders
Chvostek's sign
Trousseau's sign
Cardiac involvement
Prolonged QT interval
QRS and ST segment changes that may mimic the changes of myocardial infarction
Ventricular arrhythmias
Congestive heart failure
Cataracts
Abnormal dentition (enamel hypoplasia)







Chvostek's, Troussea'u

Hypopatathyroidism. Low levels of PTH

Causes

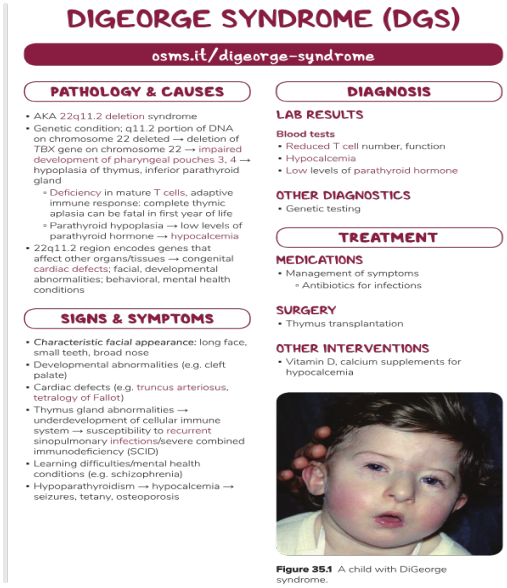
Causes of hypoparathyroidism can include:

- **Neck surgery.** This is the most common cause of hypoparathyroidism. It develops after accidental damage to or removal of the parathyroid glands during surgery. Neck surgery may be done to treat conditions of the thyroid gland, or to treat throat or neck cancer.
- **Autoimmune disease.** In some cases, the immune system attacks parathyroid tissues as if they were foreign bodies. (APS1 – mutation of AIRE gene)
- **Hereditary hypoparathyroidism.** This form can result from either being born without parathyroid glands or with glands that don't work properly. Some types of hereditary hypoparathyroidism are associated with deficiencies of other hormone-producing glands.

Hereditary hypoparathyroidism

Genetic	OMIM #
PTH biosynthesis/secretion	
Familial isolated hypoparathyroidism, autosomal recessive (chromosome 6p24.2, *GCM2*)	146200
Hypoparathyroidism, autosomal recessive (chromosome 11p15.3, *PTH*)	146200
Hypoparathyroidism, autosomal dominant (chromosome 11p15.3, *PTH*)	146200
Calcium Sensing Receptor (*CaSR*)	
Autosomal Dominant Hypocalcemia, ADH (chromosom 13q13.3-q21.1, *CaSR*)	601198
Autosomal Dominant Hypocalcemia with Bartters syndrome, ADH (chromosom 13q13.3-q21.1, *CaSR*)	601198
Parathyroid development	
22q11 deletion (chromosome 22q11, *TBX1*)	188400
Hypoparathyroidism, retardation and dysmorphism syndrome, HRDS (chromosome 1q42.3)	241410
Sanjad Sakati Syndrome	
Kenney-Caffey syndrome 1 and 2. Arab descent	244460

Hereditary DiGeorge syndrome



DIGEORGE SYNDROME (DGS)

osms.it/digeorge-syndrome

PATHOLOGY & CAUSES

- AKA 22q11.2 deletion syndrome
- Genetic condition; q11.2 portion of DNA on chromosome 22 deleted → deletion of *TBX* gene on chromosome 22 → impaired development of pharyngeal pouches 3, 4 → hypoplasia of thymus, inferior parathyroid gland
  - Deficiency in mature T cells, adaptive immune response; complete thymic aplasia can be fatal in first year of life
  - Parathyroid hypoplasia → low levels of parathyroid hormone → hypocalcemia
- 22q11.2 region encodes genes that affect other organs/tissues → congenital cardiac defects; facial, developmental abnormalities; behavioral, mental health conditions

SIGNS & SYMPTOMS

- **Characteristic facial appearance:** long face, small teeth, broad nose
- Developmental abnormalities (e.g. cleft palate)
- Cardiac defects (e.g. truncus arteriosus, tetralogy of Fallot)
- Thymus gland abnormalities → underdevelopment of cellular immune system → susceptibility to recurrent sinopulmonary infections/severe combined immunodeficiency (SCID)
- Learning difficulties/mental health conditions (e.g. schizophrenia)
- Hypoparathyroidism → hypocalcemia → seizures, tetany, osteoporosis

DIAGNOSIS

LAB RESULTS

Blood tests
- Reduced T cell number, function
- Hypocalcemia
- Low levels of parathyroid hormone

OTHER DIAGNOSTICS
- Genetic testing

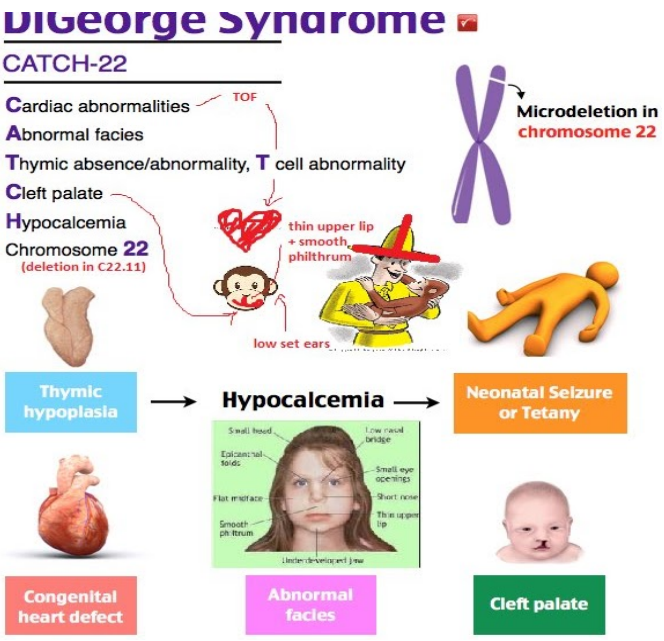
TREATMENT

MEDICATIONS
- Management of symptoms
  - Antibiotics for infections

SURGERY
- Thymus transplantation

OTHER INTERVENTIONS
- Vitamin D, calcium supplements for hypocalcemia

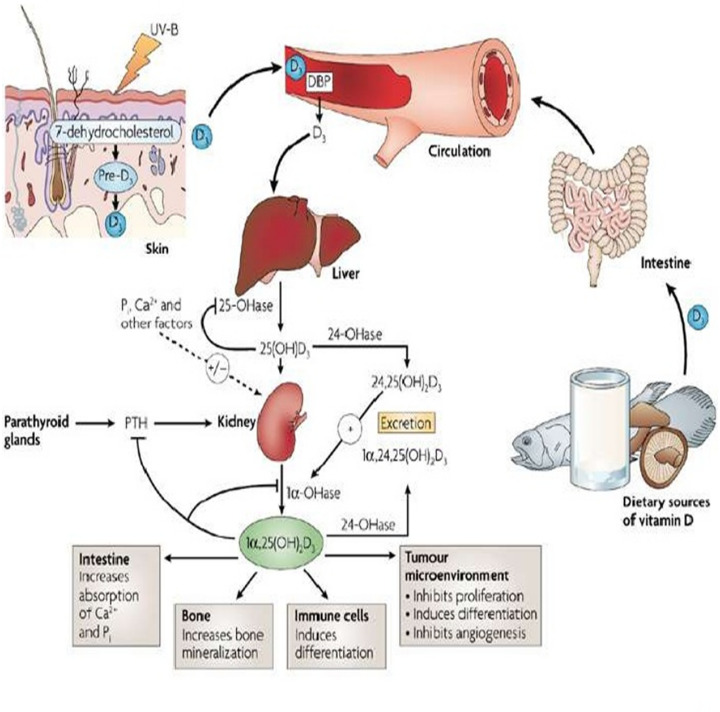
Figure 35.1 A child with DiGeorge syndrome.

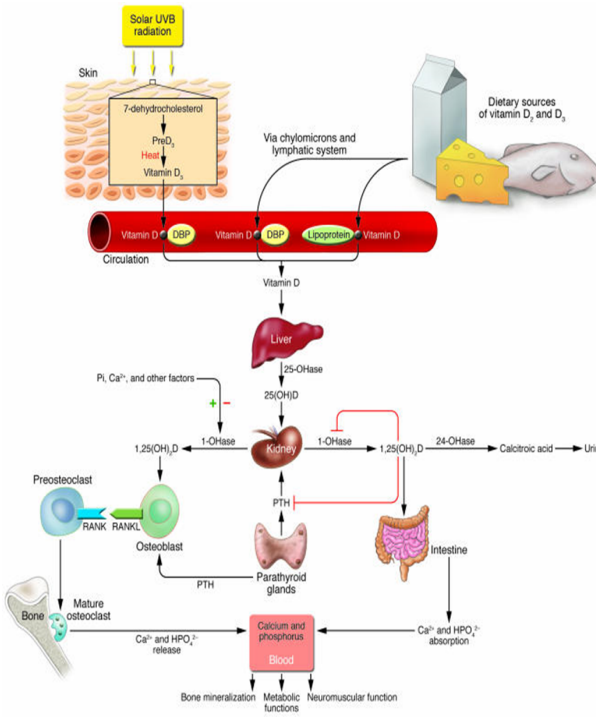


Hypocalcemia with high level of PTH

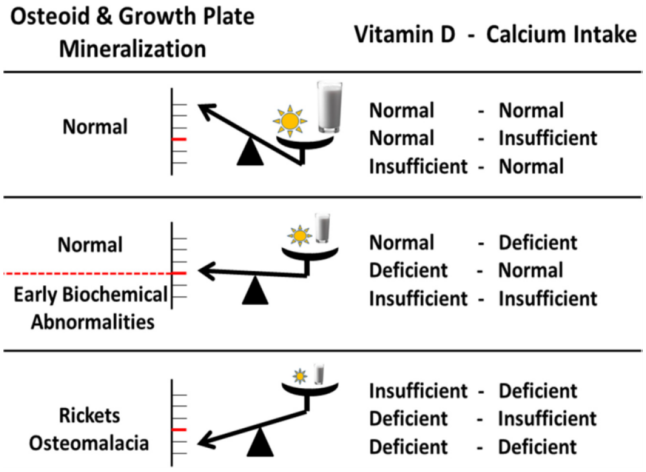
The most common

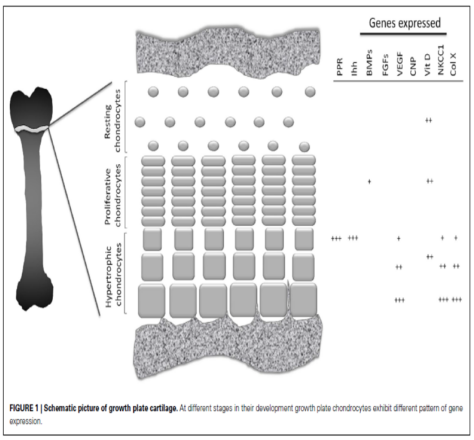
1. **Nutritional rickets; Vitamin D deficiency, calcium deficiency**
   Rickets: vitamin D-dependent and vitamin D-independent
2. Pseudoparathyroidism type 1 and type 2 (hypocalcemia and hyperphosphatemia, increased secretion of parathyroid hormone (PTH), and target tissue unresponsiveness to the biologic actions of PTH)



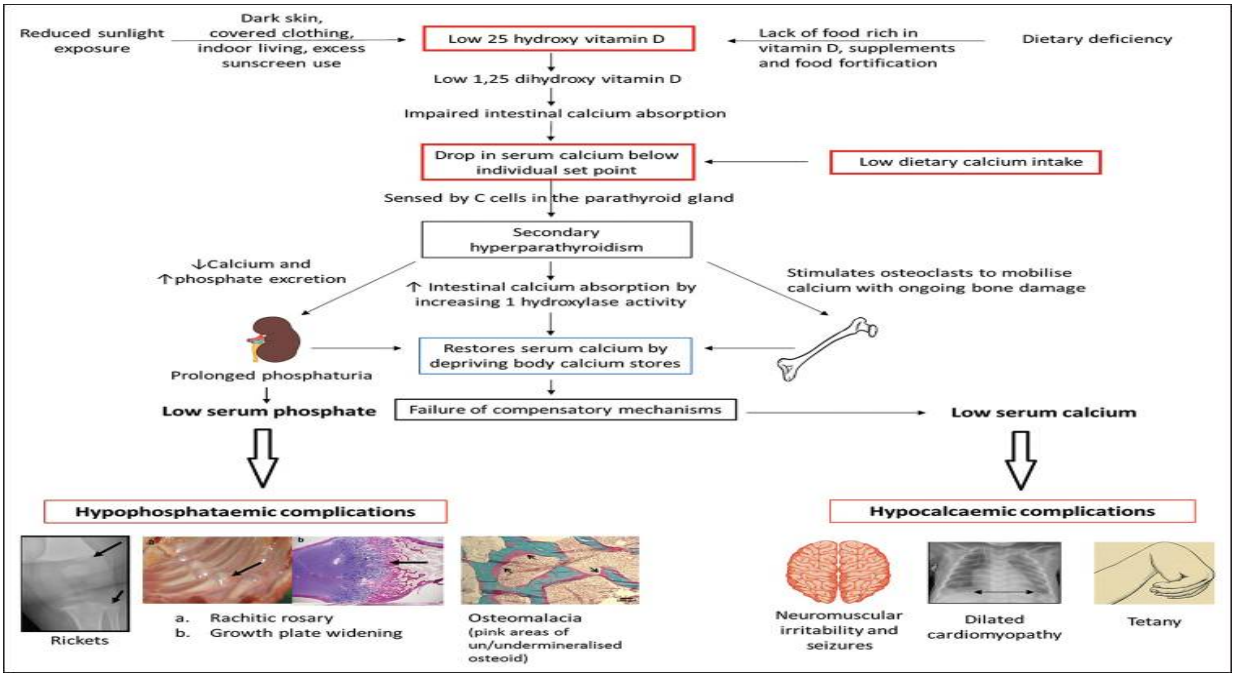


Vitamin D deficiency



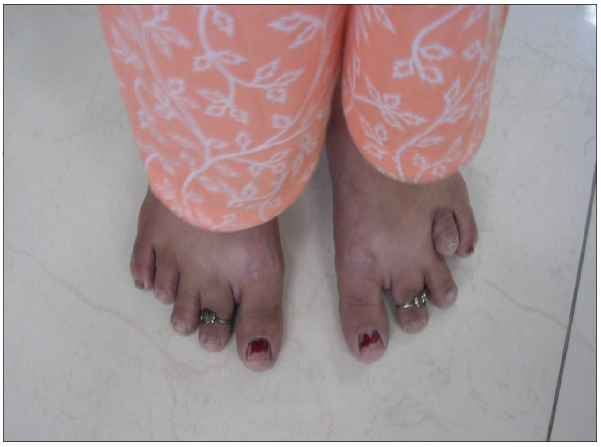


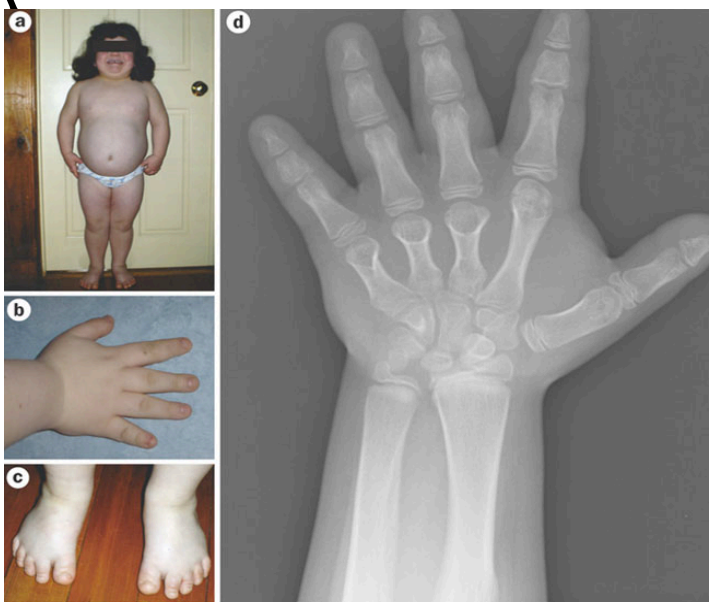
Complications of vitamin D deficiency from the foetus to the infant: One cause, one prevention, but who's responsibility? Högler W.*Best Pract Res Clin Endocrinol Metab*. 2015;29(3):385–398.(246),



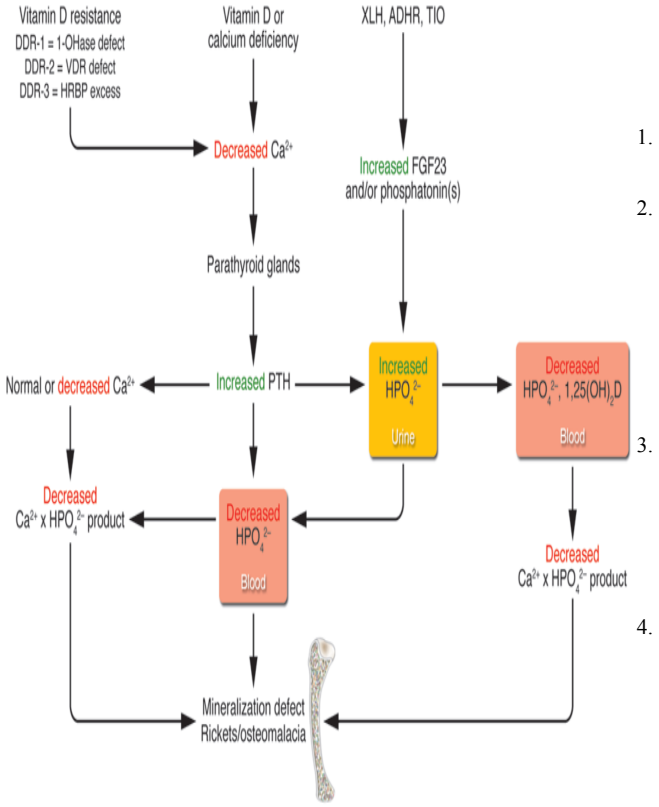
Nutritional rickets & osteomalacia: A practical approach to management.
Uday S, Högler W. Indian J Med Res. 2020 Oct;152(4):356-367.

Osteodysthrophy Albright's pseudohypoparathyroidism typ 1A





Albright hereditary osteodystrophy (AHO) is a hereditary condition due to inactivating GNAS1 gene mutation. AHO is characterized by a round face, short stature with a stocky habitus, brachydactyly, subcutaneous ossification, and dental anomalies.

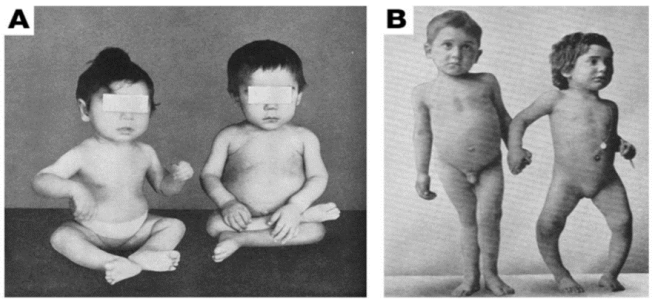


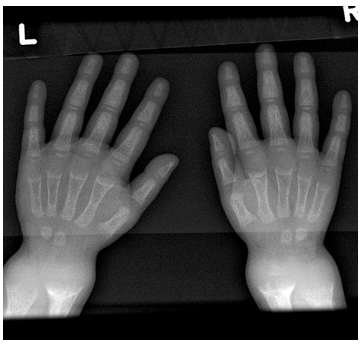
Biochemical changes in calcium and phosphorus metabolism due to vitamin D or calcium deficiency, vitamin D–resistant syndromes, or hypophosphatemic syndromes that cause rickets or osteomalacia.

1. Vitamin D and/or calcium deficiency leads to a decrease in the level of ionized calcium (Ca2+), resulting in an increase in PTH.
2. PTH increases tubular reabsorption of calcium to correct the serum calcium into the normal range, in severe the serum calcium is below normal. In addition, PTH causes phosphorus loss via the urine, resulting in a decrease in serum HPO42–. An inadequate calcium-phosphorus product (Ca+2 × HPO42–) leads to a defect in bone mineralization that causes rickets in children and osteomalacia in adults. There are various inherited and acquired disorders that can disrupt calcium and phosphorus metabolism that can also result in defective mineralization of the skeleton.
3. There are 3 inherited syndromes that cause vitamin D resistance. Vitamin D–dependent rickets type 1 (DDR-1) is due to a mutation of the 1-OHase. A mutation of the *VDR* gene results in an ineffective recognition of 1,25(OH)2D, causing DDR-2. A genetic defect that results in the overproduction of hormone response element–binding protein (HRBP) eliminates the interaction of 1,25(OH)2D with its VDR, resulting in DDR-3.
4. There are also inherited and acquired disorders that cause severe hypophosphatemia and decrease renal production of 1,25(OH)2D. The acquired disorders X-linked hypophosphatemic rickets (XLH) and autosomal dominant hypophosphatemic rickets (ADHR) are caused by the increased production or decreased destruction, respectively, of phosphatonins that include FGF23. Tumor-induced osteomalacia (TIO) is caused by the tumor's production of FGF23, which results in phosphaturia and a decrease in the renal production of 1,25(OH)2D.

Vitamin D-deficiency. Rickets.

Science in medicine. Resurrection of vitamin D deficiency and rickets
Michael F. Holick The Journal of Clinical Investigation 2006





Photograph from the 1930s of a sister (left) and brother (right), aged 10 months and 2.5 years, respectively, showing enlargement of the ends of the bones at the wrist, carpopedal spasm, and a typical "Taylorwise" posture of rickets. (**B**) The same brother and sister 4 years later, with classic knock-knees and bow legs, growth retardation, and other skeletal deformities.

Table 2

Vitamin D status and associated biochemistries: serum levels of 25(OH)D, 1,25(OH)$_2$D, Ca, HPO_4^{2-}, alkaline phosphatase (Alk. phos.), PTH, and FGF23

	25(OH) D, ng/ml	1,25(OH)2D	Ca	HPO_4^{2-}	Alk. phos.	PTH	FGF23	Skeletal disease
Vitamin D deficiency	<20	↑	↓ NL	↓	↑	↑	NL	Rickets/osteomalacia
Vitamin D insufficiency	21–29	↑ or NL	NL	NL	↑ or NL	↑ or NL	NL	↓ BMD
Vitamin D sufficiency	>30	NL	NL	NL	NL	NL	NL	None
XLH	NL	↓	NL	↓↓	↑	NL	↑ or NL	Rickets
ADHR	NL	↓	NL	↓↓	↑	NL	↑↑	Rickets
TIO	NL	↓	NL	↓↓	↑	NL	↑↑	Rickets

The upward-pointing arrows (↑ and ↑↑) indicate that the level is moderately or markedly above the normal range, respectively, and the downward-pointing arrows (↓ and ↓↓) indicate that the serum level is moderately or markedly below the normal range, respectively. NL represents levels within the normal range. BMD, bone mineral density; XLH, X-linked hypophosphatemic rickets; ADHR, autosomal dominant hypophosphatemic rickets; TIO, tumor-induced osteomalacia.

Table 1
Dietary sources of vitamin D

Source	Vitamin D content
Fortified milk	100 IU/8 oz
Fortified orange juice	100 IU/8 oz
Infant formulas	100 IU/8 oz
Fortified yogurts	100 IU/8 oz
Fortified butter	56 IU/3.5 oz
Fortified margarine	429 IU/3.5 oz
Fortified cheeses	100 IU/3 oz
Fortified breakfast cereals	~100 IU/serving
Egg yolk	~20 IU/yolk
Shiitake mushrooms, fresh	100 IU/3.5 oz
Tuna, canned	236 IU/3.5 oz
Mackerel, canned	~250 IU/3.5 oz
Sardines, canned	~300 IU/3.5 oz
Salmon, canned	~300–600 IU/3.5 oz
Salmon, fresh	~400–500 IU/3.5 oz
Shiitake mushrooms, sun-dried	1,600 IU/3.5 oz
Drisdol (vitamin D_2) liquid	8,000 IU/cc
Cod liver oil	400 IU/tsp

Table 1. *Calcium supply (sufficient intake) in age groups [7]*
Tabela 1. *Podaż wapnia (wystarczające spożycie) w grupach wiekowych [7]*

	Age Grupa wiekowa	Calcium (mg/day) Wapń (mg/d.)
Infants Niemowlęta	0–6 months 0–6 miesięcy	300
	6–12 months 6–12 miesięcy	400
Children Dzieci	1–3 years 1–3 lata	500
	4–6 years 4–6 lat	700
	7–9 years 7–9 lat	800
Adolescents Nastolatki	10–18 years 10–18 lat	1300
Adults Dorośli	19–50 years 19–50 lat	1000
	> 50 lat > 50 years	1300
Women (pregnancy, lactation) Kobiety (ciąża i laktacja)	< 19 years > 19 years < 19 lat > 19 lat	1300 1000

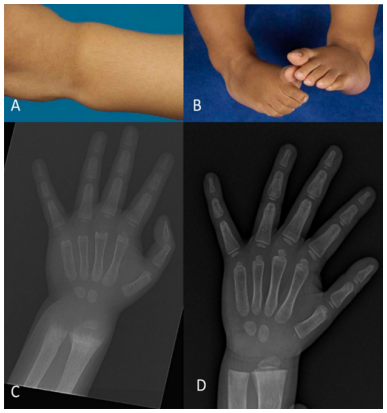
MF Holick.. The Roles of Vitamin D in Skeletal Muscle: Form, Function, and Metabolism Endocr Rev |Copyright © 2013 by The Endocrine Society

Table 3. Treatment Doses of Vitamin D for Nutritional Rickets

Age	Daily Dose for 90 Days, IU	Single Dose, IU	Maintenance Daily Dose, IU
<3 mo	2000	N/A	400
3–12 mo	2000	50 000	400
>12 mo to 12 y	3000–6000	150 000	600
>12 y	6000	300 000	600

Abbreviation: N/A, not available. Reassess response to treatment after 3 months as further treatment may be required. Ensure a daily calcium intake of at least 500 mg. For conversion from IU to μg, divide by 40.

before



after

Global Consensus Recommendations on Prevention and Management of Nutritional Rickets. Munns CF, et al. *Horm Res Paediatrics* 2016

2016

Societies
ESPE
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ASPAE
ISPAE
CSPEM
APPES
APEG
ESPGHAN

HORMONE RESEARCH IN PÆDIATRICS

Consensus Statement

Horm Res Paediatr 2016;85:83–106
DOI: 10.1159/000443136

Received: April 24, 2015
Accepted: September 17, 2015
Published online: January 6, 2016

Global Consensus Recommendations on Prevention and Management of Nutritional Rickets

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2018

POSTĘPY NEONATOLOGII 2018;24(1)

REKOMENDACJE

ZASADY SUPLEMENTACJI I LECZENIA WITAMINĄ D – NOWELIZACJA 2018 r.

VITAMIN D SUPPLEMENTATION GUIDELINES FOR POLAND – A 2018 UPDATE

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Recomendations

2023

nutrients

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Guidelines for Preventing and Treating Vitamin D Deficiency: A 2023 Update in Poland

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Assessment of Vitamin D Status and Diagnostic Criteria

7.1. It is recommended **to measure both 25(OH)D2 and 25(OH)D3, giving a total 25(OH)D serum** concentration as a measure of vitamin D status.. The diagnostics thresholds defining concentrations of serum 25(OH)D in Poland are as follows:

(1) Concentrations ≤20 ng/ml (50 nmol/L) indicate vitamin D deficiency, a state that should be immediately treated medically with the use of therapeutic dosing.

(2) Concentrations of >20 ng/ml (50 nmol/L) <30 ng/ml (75 nmol/L) reflect a suboptimal vitamin D status that calls for a moderate increase of dosing

Guidelines for Preventing and Treating Vitamin D Deficiency: A 2023 Update in Poland.

Neonates Born at Term and Infants

Preventing

(1) Age **0–6 months: 400 IU/day** (10 µg/day) of cholecalciferol from first days of life, **regardless of** the feeding method.

(2) Age **6–12 months: 400–600 IU/day (10–15 µg/day)** of cholecalciferol, **depending on** the daily amount of vitamin D consumed with meals.

(3) In term-born neonates and healthy infants calcifediol is not recommended.

Guidelines for Preventing and Treating Vitamin D Deficiency: A 2023 Update in Poland

Preterm Neonates Neonates Born at <32 Weeks of Gestation

Preventing

(1) If enteral nutrition is possible, a dose of 800 IU/day (20 µg/day) of **cholecalciferol** is recommended from the first days of life, regardless of the feeding method, during the first month of life. The intake from a diet should be calculated from the second month of life. **Calcifediol is not recommended.**

2) Supplementation should be monitored by serum 25(OH)D concentration assays, both during hospitalization (the first check-up after 4 weeks of supplementation) and/or followed up in the outpatient care.

(3) Total daily cholecalciferol dose of 1000 IU (25 µg/day) and higher may confer a risk of vitamin D overdose, especially in neonates with

Neonates 33-36 Hbd

A total of 400 IU/day (10 µg/day) of **cholecalciferol** from the first days of life, regardless of the feeding method, is recommended; **calcifediol** is not recommended.

(2) There is no need to control serum 25(OH)D concentrations routinely.

(3) Supplementation under the control of serum 25(OH)D concentration should be considered in neonates at a higher risk of vitamin D deficiency (parenteral nutrition lasting >2 weeks, ketoconazole therapy >2 weeks, anticonvulsant treatment, cholestasis, birth weight <1500 g).

Children (1–10 Years)

(1) In healthy children aged 1–3 years, supplementation should be based on cholecalciferol administration provided in a daily dose of 600 IU (15 µg/day) and, due to age-related restrictions of sunbathing, is recommended throughout the year.

(2) In healthy children aged 4–10 years sunbathing with uncovered forearms and legs for 15–30 minutes between 10 a.m. and 3 p.m. without sunscreen, starting from May until the end of September, cholecalciferol supplementation is not necessary, although still recommended and safe.

(3) If these guidelines are not fulfilled in healthy children aged 4–10 years, supplementation of cholecalciferol in dose 600–1000 IU/day (15–25 µg/day) is recommended throughout the year, based on body weight and the dietary vitamin D intake.

Adolescents (11–18 Years)

(1) In healthy adolescents, cholecalciferol as the first choice of supplementation and calcifediol as the second choice should both be used for the prevention of vitamin D deficiency.

(2) In healthy adolescents, sunbathing with uncovered forearms and legs for 30–45 minutes between 10 a.m. and 3 p.m. without sunscreen, starting from May until the end of September, cholecalciferol supplementation is not necessary, although still recommended and safe.

(3) If these guidelines are not fulfilled, supplementation based on cholecalciferol in a dose of 1000–2000 IU/day (25–50 µg/day) is recommended throughout the year, based on body weight and the dietary vitamin D intake.

(4) If the above guidelines are not fulfilled, alternative prevention based

Patients at risk vitamin D deficiency

- **In patients at risk of vitamin D deficiency , cholecalciferol or calcifediol supplementation should be implemented and followed up under the control of serum 25(OH)D concentrations, in order to achieve and maintain the optimal concentration of >30–50 ng/mL.**

- **If the assessment of serum 25(OH)D concentration is not possible in the risk groups, cholecalciferol dosing should be carried out according to the guidelines for the general population at the maximal doses for a given age group. Alternatively, calcifediol in a Daily dose of 10 µg (oral solution) may be considered for preventive management.**

- **Overweight and obesity need a special attention as this condition usually requires a double dose of cholecalciferol in relation to the doses recommended for age-matched peers with normal body weight. In obese individuals, calcifediol in a daily dose of 10 µg (oral solution) may be considered as an alternative second choice of prevention scheme.**

Treatment
Serum 25(OH)D ≤20 ng/mL—Vitamin D Deficiency

I. **From birth to 12 months of age: 2000 IU/day (50 g/day); serum 25(OH)D concentration control assay no later than 4–6 weeks after.**

II. **Age 1–10 years: 4000 IU/day (100 g/day); serum 25(OH)D concentration control no later than 6–8 weeks after.**

III. **Age 11–18 years: 4000 IU/day (100 g/day) or 7000 IU/week (175 g/week) or 10,000 IU/week (250 g/week) or 20,000 IU taken biweekly (500 g/biweekly) or 30,000 IU taken biweekly (750 g/biweekly) or 30,000 IU/month**

(1**) Verify if the previous therapy** regimen was appropriate, and correct the management accordingly (intake, dosing, compliance, type of preparation).
(2) **Therapeutic dose of cholecalciferol should be implemented immediately, based on age and body weight**.
(3) **Treatment of vitamin D deficiency should be continued for 1–3 months or until the serum 25(OH)D concentration of 30–50 ng/mL** is achieved, then it is recommended to use consecutive maintenance dose i.e., a preventive dose recommended for the general population, in relation to age and body weight.
(4**) In patients with skeletal symptoms**, metabolic bone disease, and bone mineral disorders (bone deformations, bone pain, nonspecific musculoskeletal symptoms, fatigue syndrome, and history of fragility fractures), it is necessary to assess and monitor parameters of calcium-phosphate metabolism (Ca, PO4, ALP, PTH, urine Ca/creatinine ratio), and—if available—bone mineral density with the use of DXA.
(5) For some patients with chronic diseases (obesity, malabsorption syndromes, liver diseases, chronic inflammatory diseases) or that are taking medications that interfere with hepatic cytochrome P450 (i.e., glucocorticoids, anticonvulsants, anticancer or antiretroviral drugs) a quick restoration of vitamin D deficiency is needed. For those patients, the optional use of calcifediol in therapeutic biweekly or monthly doses of 266 g (soft capsules) is reasonable, safe, and justified.
(6) After 1 to 3 months of cholecalciferol therapy, the reevaluation of serum 25(OH)D concentration should be performed.
(7) In patients receiving calcifediol in a daily dose of 10 g (oral solution), or biweekly and a monthly dose of 266 g (soft capsules) reevaluation of 25(OH)D concentration should be performed within 6–8 days, or 6–8 weeks, respectively.

Upper limits for daily cholecalciferol intake for vitamin D deficiency prophylaxis in the general population by age.

Age	Tolerable Upper Intake Level, IU/day (µg/day)
Neonates and infants aged 0–12 months	1000 (25)
Children aged 1–10 years	2000 (50)
Adolescents aged 11–18 years	4000 (100)
Adults aged 19 years and older with normal body weight	4000 (100)
Pregnant and breastfeeding women	4000 (100)
Adults aged 19 years and older with overweight or obesity	10,000 (250)