Rickets

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Summary

- Vitamin D in food: sequentially converted in the skin (sunlight), liver and kidneys
- Calcitriol needed for mineralization of osteoid and calcium uptake in the intestine
- Deficiency in children (epiphyseal plate still open) leads to rickets
- Deficiency in adults (epiphyseal plate closed) leads to osteomalacia
- Irregularly frayed, wide, cup-shaped distal ulna and radius, rachitic rosary, hypocalcaemia
- Pseudofractures, bone deformities, gait disturbance
- Rapid recovery after deficiency correction, except if end-organ resistance
- Do not confuse rickets with rickettsiosis

Rickets: Historical Note

For centuries, rickets – despite being common – was a mysterious disease. In 1650, Francis Glisson, a Cambridge physician published in Latin a treatise on rickets titled “De Rachitide.” Glisson’s treatise addresses the clinical features of rickets in a scientific tone, but lapses into medieval mysticism while discussing the aetiology of rickets. Glisson ascribed the aetiology of rickets to “cold distemper, that is moist and consisting of penury or paucity of and stupefaction of sprits.” Despite his affirmation of mysticism in the cause of rickets, Glisson was convinced that rickets was neither contagious nor heritable. Glisson’s suggested treatments for rickets included: cautery, incisions to draw out bad humours, blistering and ligature of soft wool around the limb to retard the return of blood. For correction of bony deformities, Glisson proposed splinting and artificial suspension of the affected infant: “The artificial suspension of the body is performed by the help of an instrument cunningly made with swathing bands, first crossing the breast and coming under the armpits, then about the head and under the chin, then receiving the hands by two handles, so that it is a pleasure to see the child hanging pendulous in the air, and moved to and fro by the spectators. This kind of exercise is thought to be many ways conducible in this affect, for it helped to restore the crooked bones, to erect the bended joints, and to lengthen the short stature of the body.”

After Glisson’s discoveries, no advances were made in the study of rickets for 2 centuries. At the turn of the 20th century, rickets was rampant among the underprivileged infants residing in industrialized cities of North in the United States and several polluted cities in Europe. In 1919,

Edward Mellanby, an English physician, conducted the earliest definitive experimental study exploring the role of diet in the aetiology and treatment of rickets. Puppies between 5 and 8 weeks of age were exposed to 1 of 4 natural diets. All 4 diets were rachitogenic after a variable period of exposure. Rickets was severe and developed easily in dogs that grew well on the rachitic diets. Neither yeast (antineuritic vitamin) nor orange juice (anti-scorbutic vitamin) hindered the development of rickets. Various foods were added to the rachitic diets and their effect on development of rickets was studied. Foods rich in fat-soluble vitamin A (cod-liver oil, butter, and whole milk) were able to prevent rickets. Mellanby postulated, “It therefore seems probable that the cause of rickets is a diminished intake of an antirachitic factor which is either fat-soluble A, or has a somewhat similar distribution to fat-soluble A. Mellanby’s work clearly established the role of diet in the cause of rickets.

McCollum was now confronted with same question faced by Mellanby, whether fat-soluble A was anti-rachitic by itself or if there was another substance with specific anti-rachitic function with similar distribution as fat-soluble A. McCollum and Mellanby were aware of F. G. Hopkins’ report that oxidation destroyed fat-soluble A. Mellanby found oxidized butter fat had lost its anti-rachitic effect, but similarly treated cod-liver oil still retained its protective action against the development of rickets. Mellanby stated “this difference can be explained by the fact that cod-liver oil contains greater quantity of antirachitic vitamin than butter, or that the destructive change takes longer time, or whether some other explanation must be sought. McCollum and his coworkers were soon able to explain the preservation of anti-rachitic function in oxidized cod-liver oil. Unlike Mellanby, they chose to explore the anti-xerophthalmic and anti-rachitic functions of oxidized butter fat and oxidized cod-liver oil. They chose “diet 3143,” which was adequately restricted with regard to fat-soluble A to cause severe rickets but still able to prevent the onset of xerophthalmia, to induce rickets in rats. Using the “line test,” the anti-rachitic potency of several fish liver oils, vegetable oils, and butter fat were tested. Oxidized cod-liver oil had lost its anti-xerophthalmic function, but still retained its calcium-depositing properties. Untreated coconut oil had no anti-xerophthalmic property, but had minimal anti-rachitic function. McCollum and his coworkers concluded that the anti-rachitic substance found in certain fats was distinct from fat-soluble vitamin A and its “specific property was to regulate the metabolism of the bones.” In the sequence of discovery of vitamins, the newly discovered antirachitic substance was the fourth; hence it was called vitamin D.

In 1890, addressing the aetiology of rickets, Palm studied the relationship between incidence of rickets and its geographical distribution and concluded that rickets was caused by lack of exposure to sunlight. Palm was able to point out that, despite a superior diet and relatively better sanitary condition, infants residing in Britain were more at risk for rickets than infants living in the tropics. Exposure to plenty of sunshine, which was the norm for infants residing in the tropics, was

responsible for their protection against rickets. Palm recommended “systematic use of sun-baths as a preventive and therapeutic measure in rickets.”

The bridging of the knowledge that photosynthesized vitamin D and vitamin D in cod-liver oil were similar was responsible for the eventual conquest of rickets. By the 1930s, the use of cod-liver oil in the treatment and prevention of rickets became common place. The eventual public health prevention initiative of fortification of milk with vitamin D led to eradication of rickets.

Source: Vitamin D, Cod-Liver Oil, Sunlight, and Rickets: A Historical Perspective; K. Rajakumar, Pediatrics Vol. 112 No. 2 Aug 2003

Vitamin D metabolism and calcium homeostasis

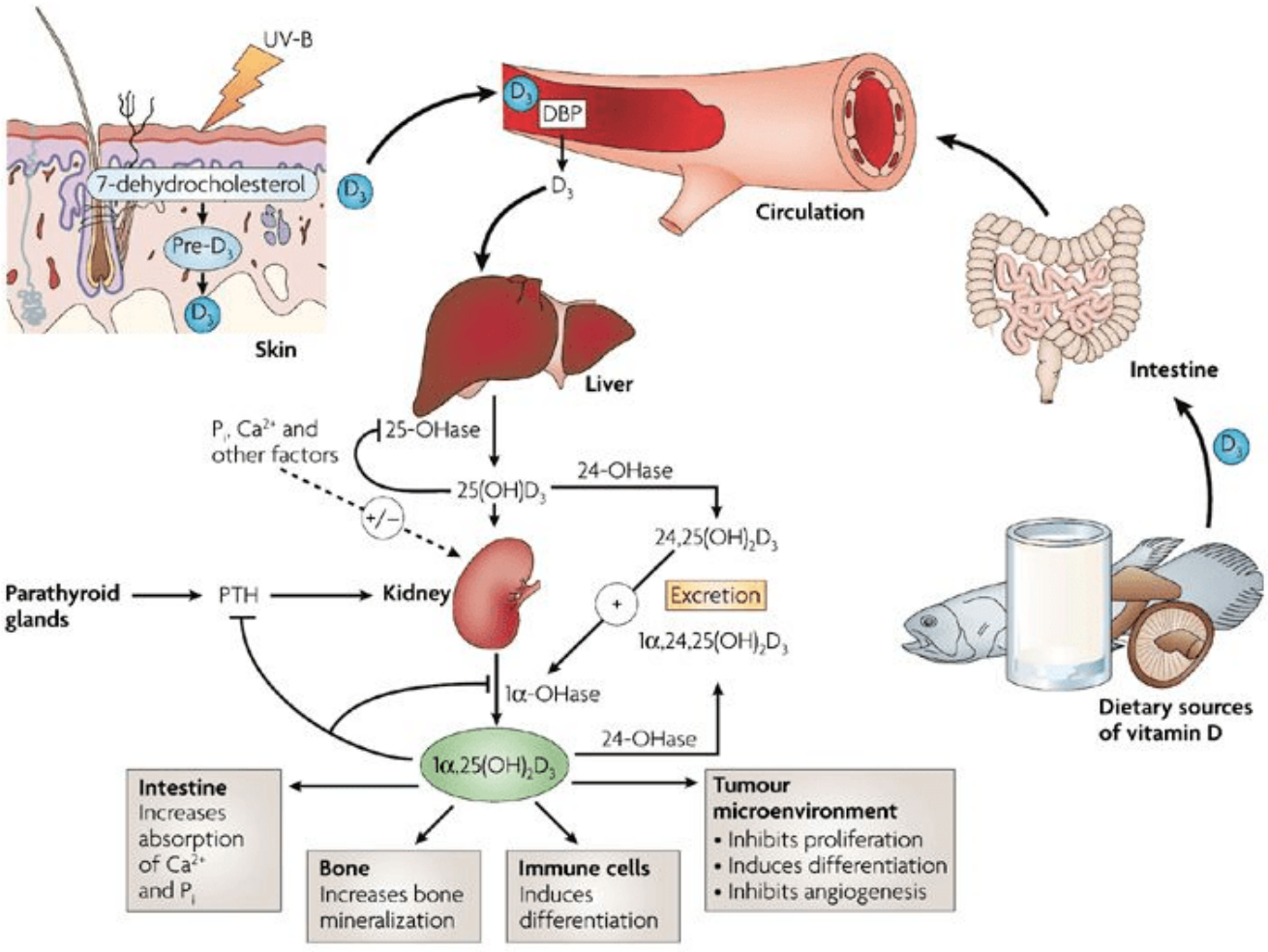

Figure: Vitamin D Metabolism (source: Nature Reviews Cancers 7, 684-700_2007)

Vitamin D is present in food as a fat-soluble provitamin. Vitamin D is regarded as a sterol, although the B ring of the molecular steroid skeleton is open. A photochemical conversion and two hydroxylations take place in the body before the final form is reached. The absorption of vitamin D is determined by the fat content of the food; by the proper functioning of the pancreas (lipase) and by the presence of sufficient bile. After absorption in the intestine, the provitamin is first transported to the skin, where a photochemical conversion takes place via ultraviolet light. Vitamin D_3 (= cholecalciferol = calciol) is formed. This compound can also be produced via UVB radiation from an endogenous precursor, 7-dehydrocholesterol or pre-vitamin D3. Sunlight breaks the B ring of the cholesterol structure to form pre-D_3. Pre-D_3 then undergoes a thermal induced rearrangement to form D_3. Continued irradiation of pre-D_3 leads to the reversible formation of lumisterol and tachysterol (isomers of pre-vitamin D_3) which can revert back to pre-D_3 in the dark. Vitamin D_3 is subsequently bound to a carrier protein and transported to the liver, where an initial hydroxylation takes place with the formation of 25-OH-D_3. In the kidneys, 25-OH-D_3 (calcidiol) is further hydroxylated to the metabolically much more active form 1,25-$(OH)_2$-D_3 (calcitriol). A similar hydroxylation takes place in the placenta. Extra-renal synthesis of 1,25-$(OH)_2$-D_3 may occur in pathological conditions, such as sarcoidosis and other granulomatous disorders.

It is important to maintain calcium concentrations at a constant level to preserve a normal neurological function, muscular contractility and bone mass. In the extracellular compartment calcium is always in equilibrium with phosphate. Their product has to remain constant, otherwise the calcium-phosphate complexes will precipitate. If calcium increases, phosphate will decrease. The biggest reservoir of those two minerals is the bone. When the calcium concentration drops, the parathyroid glands secrete the parathyroid hormone PTH. This stimulates the production of 1,25(OH)2D. The receptor of 1,25-$(OH)_2$-D_3 is located in the cytoplasm of the cell. After binding, the complex migrates to the cell nucleus where (as a transcription factor) it mediates the expression of various genes. As a result of this (1) the active absorption of calcium in the intestine is stimulated, (2) the loss of calcium through the kidneys is decreased (resorption is stimulated) with increase in phosphate excretion and (3) bone cells (osteoclasts) are stimulated to resorb bone minerals and release calcium in the extra-cellular compartment. As a result of this the calcium concentration will rise and the secretion of PTH decrease.

Rickets, causes

Rickets and osteomalacia develop when there is insufficient vitamin D, when its metabolism is

disturbed or when the tissues are resistant to its activity (e.g. mutation of the vitamin D receptor). By following the metabolic chain that leads to the active 1,25-$(OH)_2$-D_3 the various causes of osteomalacia/rickets can be visualized. For instance, the food may contain too few precursors. If there is insufficient fat in the diet, or there is insufficient bile and the fat is not absorbed (steatorrhoea), a deficiency of fat-soluble vitamins (ADEK) will occur. Prolonged treatment with cholestyramine is a risk factor. Insufficient exposure to sunlight is also an aetiological possibility. Dark-skinned people residing for a long time in the northern hemisphere are a high-risk group. This also applies to those who wear protective clothing and people who spend most of their time indoors (elderly people and Islamic women and children are high-risk groups). For instance, rickets/osteomalacia is not uncommon in Indian and Pakistani immigrants in Britain. A lack of direct sunlight and calcium (chelation of calcium by the phytates in their traditional diet and low intake of milk) contributes to the problem. There are several diseases that may be associated with vitamin D deficiency, such as chronic renal failure (lack of 1-25-$(OH)_2$-D_3 and hyperparathyroidism), hypoparathyroidism, genetic diseases such as hereditary hypophosphataemia, or vitamin D-resistant rickets.

Clinical nutrition and bone disease	
Vitamin D	Rickets, osteomalacia
Vitamin C	Scurvy
Copper	Fractures (in premature infants with parenteral nutrition)
Calcium	Osteoporosis

Vitamin D content of food (µg/100 g)

Cereals	
Grain, flours, starches	0
Milk & milk products	
Cow's milk	0.01-0.03
Human milk	0.04
Dried milk	0.21
Cream	0.1-0.28
Cheese	0.03-0.5
Yoghurt	Trace-0.04
Eggs	
Whole	1.75
Yolk	4.94
Fats and oils	
Butter	0.76
Cod liver oil	210
Margarines and spreads*	5.8-8.00
Meat & meat products	
Beef, lamb, pork, veal	Trace
Poultry, game	Trace
Liver	0.2-1.1
Fish and fish products	
White fish	Trace
Fatty fish	Trace-25
Crustacea & molluscs	Trace
Vegetables	0

* Added during production (Vitamin D_2).

Source : Holland et al 1991

Table: Vitamin D content in foods

Pathophysiology

Osteomalacia refers to a disorder in which there is abnormal bone mineralization and the ratio of mineral to matrix is diminished due to an excess of unmineralized osteoid. This in contrast to osteoporosis where there is a reduction in quantity of bone mass per unit of volume. Osteomalacia in children is known as rickets, and because of this, use of the term “osteomalacia” is often restricted to the milder, adult form of the disease.

Crystallization of minerals in osteoid requires adequate concentrations of ionized calcium and phosphate. Vitamin D influences these levels after its dihydroxylation into calcitriol (hepatic position 25 and renal position 1). When concentrations are too low crystallization does not proceed normally.

Vitamin D disrupts mineralization because it normally regulates and enhances the absorption of calcium in the intestine. A lack of vitamin D causes plasma calcium concentrations to fall. Low plasma calcium levels stimulate parathyroid hormone (PTH). PTH raises calcium concentration but also increases renal clearance of phosphate. When phosphate decreases below a critical level, mineralization cannot proceed normally. On top of this, hypophosphatemia causes a disturbed apoptosis of chondrocytes, leading to an excess of unmineralized osteoid.

Rickets in the strict sense of the term is a disease caused by any interference with the process of enchondral bone formation (calciumphospate deposition in cartilaginous bone), the cascade of events normally taking place in the epiphyseal growth plates and resulting in gain in length of long bones. In children, the abnormalities are clearest in the areas of most active growth, i.e. the epiphyses. In chronic deficiency there is resorption of trabecular and cortical bone, which is not compensated by mineralization of osteoid. Adequate treatment with vitamin D causes a rapid reversal of this situation.

Normal enchondral bone formation is resumed. In adults, the changes are similar but are not limited to the extremities of the long bones. As a consequence, the skeleton will be affected in its two main functions as the mechanical support for the other organs and the major reservoir of calcium to serve a large array of physiologic functions.

Clinical aspects

The clinical picture is one of bone deformities ranging from mild signs to very distinctive bone deformities. Clinical and radiological bone lesions predominate in the areas of rapid bone growth, namely the long bone epiphyses and the costochondral junctions. Thus the clinical manifestations are most striking at the time of greatest velocity. The maximum frequency of signs is usual found between 4-12 months with most of the signs seen in children below 18 months. Bone changes, visible on X-rays, precede clinical signs, becoming evident in the 3rd or 4th month of life (more common 6-9 months)- sometimes even at birth if the mother is severely vitamin D deficient. Bone changes in rickets are most evident at the distal ends of the radius and ulna. The bony ends lose their sharp, clear outline. They are cup-shaped and show a spotty or frayed outline. Later, the distance between the ends of the radius and ulna and the metacarpal bones appears to be increased because the noncalcified ends are invisible on the X-ray. This increase in the width of the epiphyseal cartilages can also be seen at the distal extremities of the tibia and fibula(“erlenmeyer deformity”). As healing begins, a thin white line of calcification appears at the epiphysis, becoming denser and thicker as calcification proceeds.

Kyphoscoliosis may develop and walking is delayed. Older children and adolescents experience walking as painful and in extreme cases develop bowlegs or knock-knees.

Maternal osteomalacia leads to changes in the bones of the foetus and even to tetany or seizures in the newborn (hypocalcaemia). Young infants with vitamin D deficiency are restless and sleep poorly. They have reduced mineralization of the skull (craniotabes = “wasting of the skull) and frontal bossing can be seen. On the thorax, palpable lumps develop at the costochondral junctions: costochondral beading (rachitic rosary). Harrison’s groove, corresponding to the costal insertion of the diaphragm, may be present.

In adults, osteomalacia occurs particularly in the vertebrae, pelvis and legs. Fine lines appear in the cortex: ribbon-like areas of demineralization, the so-called pseudofractures or Looser’s lines.

Histologically they consist of focal accumulations of non-calcified osteoid. Preferential localizations for pseudofractures are the lateral edge of the scapula, femur neck, medial femoral shaft, ribs and ramus pubis. Looser’s lines are usually symmetrical, extending perpendicularly to the cortex; are manifestly shorter than the diameter of the bone and display no callus formation. As the bones soften, body weight may cause bowing of the long bones, vertical shortening of the vertebrae and flattening of the pelvic bones, which narrows the pelvic outlet. This may subsequently cause difficulties in childbirth.

Rickets: clinical signs in babies

1. Aspecific restlessness and irritability
2. Head sweating
3. Skeletal signs (ricketsial thoracic rosary at 6-9 months of age). Disturbed bone maturation with wide epiphyseal plates and fraying of metaphysis. Frontal bossing and soft osseous borders of cranial vault (craniotabes) with or without widened fontanelles.
4. Delayed teething, enamel hypoplasia and numerous caries
5. Hypotonia: muscle flabby or muscle cramps (eventual seizures, tetany, laryngeal spasms)
6. Higher risk of upper respiratory tract infections due to muscle weakness and thoracic cage deformities
7. Anaemia (von Jacksch-Luzet syndrome) due to marrow space fibrosis. If severe, extramedullary production of red cells in liver and spleen can lead to hepatosplenomegaly

Human breast milk contains very little vitamin D (approx 25 IU per litre). Prolonged breast feeding by mothers who don't take extra vitamin D, followed by sudden switch to milk formula (containing lots of phosphate) can precipitate overt hungry bone syndrome, sometimes presenting with signs of acute or subacute hypocalcemia (e.g. convulsions).

Diagnosis

In the blood there is approximately 500 times more 25-OH-D_3 present than 1,25-$(OH)_2$-D_3 and the half-life of 25-OH-D_3 is 15-45 days, constituting a factual reservoir of the vitamin. As a consequence, serum level of 25(OH)D is the laboratory test ordered to indicate whether or not a person has vitamin D deficiency or insufficiency.

The half-life of 1,25-dihydroxyvitamin D is short (4 to 6 hours). The levels of this compound can remain normal (or even raised) even when a person may be vitamin D deficient, depending on the activity of the 1-alpha-hydroxylase that converts 25-hydrovitamin D to 1,25-dihydroxyvitamin D, which in turn depends on the current blood concentration of calcium, phosphate and parathyroid hormone.

Measuring the active form of vitamin D (1,25-dihydroxyvitamin D) lacks utility in the routine evaluation of suspected vitamin D deficiency.

In healthy people, normal levels are 25 to 40 ng/mL (62 to 100 nmol/L) for 25-OH-D_3 and 20 to 45

pg/mL (48 to 108 pmol/L) for 1,25-$(OH)_2$-D_3. In nutritional rickets and osteomalacia, 25-OH-D_3 levels are very low.

Hypophosphatemia and high serum alkaline phosphatase are characteristic. Calcium is low or normal, depending upon the effectiveness of parathormone (secondary hyperparathyroidism) in restoring serum calcium to normal.

It is also considered reasonable to treat at-risk persons with vitamin D supplementation without checking the level of 25(OH)D in the serum, as vitamin D toxicity is very rare.

Differential diagnosis

A review of the patient's history may suggest nutritional problems. Rickets must be distinguished from infantile scurvy (cfr. scorbutic rosary), congenital syphilis (serologic tests) and from chondrodystrophy (large head, short extremities, thick bones; normal calcium, phosphate and alkaline phosphatase levels). Frontal bossing can be a sign of congenital lues, hemolytic anemia (thalassemia's, sickle cell disease), Hurler syndrome, achondroplasia). Yaws (= Pian = Framboesia) can give rise to sabre tibia.

Osteogenesis imperfecta, cretinism, congenital dislocation of the hip, hydrocephalus and poliomyelitis should be readily distinguishable. Tetany must be distinguished from convulsions due to other causes.

Vitamin D-resistant rickets may be caused by severe renal damage, as in chronic renal tubular acidosis (e.g. Fanconi's syndrome or X-linked hypophosphataemia). Osteomalacia must be distinguished from other causes of bone decalcification, such as hyperparathyroidism, senile or postmenopausal osteoporosis; osteoporosis of hyperthyroidism, steroid use, Cushing's syndrome and atrophy of disuse.

Treatment

The World Health Organization defined an "International Unit" of vitamin D_3 as 0.025 micrograms (or one microgram = 40 IU).

Treatment usually consists of vitamin D_2 (ergocalciferol) or vitamin D_3 (cholecalciferol), in addition to dietary advice and sunlight exposure. While there is evidence that vitamin D_3 raises 25(OH)D blood levels more effectively than vitamin D_2, other evidence indicates that D_2 and D_3 are equal for maintaining 25(OH)D status. Treating vitamin D deficiency depends on the severity of the deficit. An

initial high-dosage treatment phase until the required serum levels are reached, is followed by the maintenance of the acquired levels. The lower the 25(OH)D serum concentration is before treatment, the higher is the dosage that is needed in order to quickly reach an acceptable serum level. The initial high-dosage treatment can be given on a daily (1000 IU for newborns, 1000 to 5000 IU for 1-12 months old infants and 5000 IU for patients older than 1 year) or weekly basis or can be given in form of one or several single doses orally or intramuscular (200,000 IUI), especially when there are concerns about compliance. Maintenance supplementation of 400 IU per day is recommended, with double doses for premature infants, dark-skinned infants and children residing in areas of limited sun exposure.

It is important to make sure that the children are receiving enough calcium. A daily intake of 800 mg in infants and children, and 1 g in adults, is the required minimum during the first month of treatment. Milk and dairy products can easily supply this, but when this does not seem possible, calcium supplementation must be provided.

The first radiological signs of healing will appear after 2-4 months.

Vitamin D intoxication

When accidental or intentional high doses of vitamin D are taken, the clinical picture is dominated by hypercalcaemia. The rate at which the symptoms develop depends upon the dose and duration of excess vitamin D intake. The first symptoms are anorexia, nausea, vomiting, polyuria, polydipsia and pruritus. Polyuria is secondary to a massive increase of urinary calcium excretion. Complications consist of metastatic calcifications (nephrocalcinosis!) and renal failure.

Patients sometimes complain of eye irritation. Physical examination may reveal a bandlike grey-white opacity across the corneal surface: band keratopathy. Treatment consists of stopping further administration of vitamin D and giving corticosteroids. Urinary acidification is recommended. Diuretics serve no useful purpose. Bisphosphonates such as pamidronate (an osteoclast inhibitor) may be used in extreme cases.

Prevention

With the major source of vitamin D derived from the skin, exposure to sunlight is the best prevention. In high latitude countries, supplements or fortification may be needed. Human breast milk is deficient in vitamin D (1.0 µg/L = 40 IU/L), whereas fortified cow’s milk contains ten times as much. Breastfed infants should therefore be given a supplement of vitamin D (400 IU)/day) from birth to 6 months, at

which time they are given a more diversified diet. Large doses of 200.000 IU (5 mg) can also be given every 3 months. This dose is not always well absorbed. The safest is to give daily small doses. Bottle feeds have already adjusted levels of vitamin D. Food fortification of margarine and cow’s milk has eradicated rickets in Europe and the United States.

The elderly are a particular group at risk. Many older people stay indoors most of the time and get very little exposed to sunlight. The can develop demineralization of the bone with bone pains and fractures. Daily supplements can be necessary.

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