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Seminário - Paratireóide

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- **Livro Texto de Fisiologia: Glândula paratireoidiana/ metabolismo osteomineral.**
- **Holick MF. Vitamin D deficiency. N Engl J Med. 2007, 357(3):266-81.**
- **Prié D, Ureña Torres P, Friedlander G. Latest findings in phosphate homeostasis. Kidney Int. 2009, 75(9):882-9.**

I- Atividade em pequenos grupos -Temas a serem desenvolvidos no seminário:

1. Participação do hormônio paratireoidiano no controle da homeostase do cálcio e fósforo. Controle da secreção de PTH.
2. Biossíntese da forma ativa da Vitamina D. Ações da vitamina D no intestino, osso e na paratireóide.
3. Mecanismos de ação da vitamina D.
4. Conseqüências da deficiência da vitamina D, em relação ao osso.
5. A administração de 1,25(OH)2 D3 é um dos tratamentos do hiperparatireodismo secundário à insuficiência renal crônica. Explicar os mecanismos que contribuem para o hiperparatireoidismo secundário na insuficiência renal crônica, e os efeitos do tratamento com 1,25(OH)2 D3.
6. Principais fatores envolvidos no controle da homeostase do fósforo.
7. Explicar as variações do PTH e da vitamina D em uma situação de hipocalcemia e de hipofosfatemia.

II- Discussão geral dos temas

III- Avaliação individual

REVIEW ARTICLE

MEDICAL PROGRESS

Vitamin D Deficiency

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ONCE FOODS WERE FORTIFIED WITH VITAMIN D AND RICKETS APPEARED to have been conquered, many health care professionals thought the major health problems resulting from vitamin D deficiency had been resolved. However, rickets can be considered the tip of the vitamin D–deficiency iceberg. In fact, vitamin D deficiency remains common in children and adults. In utero and during childhood, vitamin D deficiency can cause growth retardation and skeletal deformities and may increase the risk of hip fracture later in life. Vitamin D deficiency in adults can precipitate or exacerbate osteopenia and osteoporosis, cause osteomalacia and muscle weakness, and increase the risk of fracture.

The discovery that most tissues and cells in the body have a vitamin D receptor and that several possess the enzymatic machinery to convert the primary circulating form of vitamin D, 25-hydroxyvitamin D, to the active form, 1,25-dihydroxyvitamin D, has provided new insights into the function of this vitamin. Of great interest is the role it can play in decreasing the risk of many chronic illnesses, including common cancers, autoimmune diseases, infectious diseases, and cardiovascular disease. In this review I consider the nature of vitamin D deficiency, discuss its role in skeletal and nonskeletal health, and suggest strategies for its prevention and treatment.

SOURCES AND METABOLISM OF VITAMIN D

Humans get vitamin D from exposure to sunlight, from their diet, and from dietary supplements (Table 1).[1-4] A diet high in oily fish prevents vitamin D deficiency.[3] Solar ultraviolet B radiation (wavelength, 290 to 315 nm) penetrates the skin and converts 7-dehydrocholesterol to previtamin D_3, which is rapidly converted to vitamin D_3 (Fig. 1).[1] Because any excess previtamin D_3 or vitamin D_3 is destroyed by sunlight (Fig. 1), excessive exposure to sunlight does not cause vitamin D_3 intoxication.[2]

Few foods naturally contain or are fortified with vitamin D. The "D" represents D_2 or D_3 (Fig. 1). Vitamin D_2 is manufactured through the ultraviolet irradiation of ergosterol from yeast, and vitamin D_3 through the ultraviolet irradiation of 7-dehydrocholesterol from lanolin. Both are used in over-the-counter vitamin D supplements, but the form available by prescription in the United States is vitamin D_2.

Vitamin D from the skin and diet is metabolized in the liver to 25-hydroxyvitamin D (Fig. 1), which is used to determine a patient's vitamin D status[1-4]; 25-hydroxyvitamin D is metabolized in the kidneys by the enzyme 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1) to its active form, 1,25-dihydroxyvitamin D.[1-4] The renal production of 1,25-dihydroxyvitamin D is tightly regulated by plasma parathyroid hormone levels and serum calcium and phosphorus levels.[1-4] Fibroblast growth factor 23, secreted from the bone, causes the sodium–phosphate cotransporter to be internalized by the cells of the kidney and small intestine and also suppresses 1,25-dihydroxyvitamin D synthesis.[5] The efficiency of the absorption of renal calcium and of intestinal calcium and phosphorus is increased in the presence of 1,25-dihy-

droxyvitamin D (Fig. 1).[2,3,6] It also induces the expression of the enzyme 25-hydroxyvitamin D-24-hydroxylase (CYP24), which catabolizes both 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D into biologically inactive, water-soluble calcitroic acid.[2-4]

DEFINITION AND PREVALENCE OF VITAMIN D DEFICIENCY

Although there is no consensus on optimal levels of 25-hydroxyvitamin D as measured in serum, vitamin D deficiency is defined by most experts as a 25-hydroxyvitamin D level of less than 20 ng per milliliter (50 nmol per liter).[7-10] 25-Hydroxyvitamin D levels are inversely associated with parathyroid hormone levels until the former reach 30 to 40 ng per milliliter (75 to 100 nmol per liter), at which point parathyroid hormone levels begin to level off (at their nadir).[10-12] Furthermore, intestinal calcium transport increased by 45 to 65% in women when 25-hydroxyvitamin D levels were increased from an average of 20 to 32 ng per milliliter (50 to 80 nmol per liter).[13] Given such data, a level of 25-hydroxyvitamin D of 21 to 29 ng per milliliter (52 to 72 nmol per liter) can be considered to indicate a relative insufficiency of vitamin D, and a level of 30 ng per milliliter or greater can be considered to indicate sufficient vitamin D.[14] Vitamin D intoxication is observed when serum levels of 25-hydroxyvitamin D are greater than 150 ng per milliliter (374 nmol per liter).

With the use of such definitions, it has been estimated that 1 billion people worldwide have vitamin D deficiency or insufficiency.[7-12,15-22] According to several studies, 40 to 100% of U.S. and European elderly men and women still living in the community (not in nursing homes) are deficient in vitamin D.[7-12,15-22] More than 50% of postmenopausal women taking medication for osteoporosis had suboptimal levels of 25-hydroxyvitamin D — below 30 ng per milliliter (75 nmol per liter).[12,22]

Children and young adults are also potentially at high risk for vitamin D deficiency. For example, 52% of Hispanic and black adolescents in a study in Boston[23] and 48% of white preadolescent girls in a study in Maine[24] had 25-hydroxyvitamin D levels below 20 ng per milliliter. In other studies, at the end of the winter, 42% of 15- to 49-year-old black girls and women throughout the United States had 25-hydroxyvitamin D levels below 20 ng per milliliter,[25] and 32% of healthy students, physicians, and residents at a Boston hospital were found to be vitamin D–deficient, despite drinking a glass of milk and taking a multivitamin daily and eating salmon at least once a week.[26]

In Europe, where very few foods are fortified with vitamin D, children and adults would appear to be at especially high risk.[1,7,11,16-22] People living near the equator who are exposed to sunlight without sun protection have robust levels of 25-hydroxyvitamin D — above 30 ng per milliliter.[27,28] However, even in the sunniest areas, vitamin D deficiency is common when most of the skin is shielded from the sun. In studies in Saudi Arabia, the United Arab Emirates, Australia, Turkey, India, and Lebanon, 30 to 50% of children and adults had 25-hydroxyvitamin D levels under 20 ng per milliliter.[29-32] Also at risk were pregnant and lactating women who were thought to be immune to vitamin D deficiency since they took a daily prenatal multivitamin containing 400 IU of vitamin D (70% took a prenatal vitamin, 90% ate fish, and 93% drank approximately 2.3 glasses of milk per day)[33-35]; 73% of the women and 80% of their infants were vitamin D–deficient (25-hydroxyvitamin D level, <20 ng per milliliter) at the time of birth.[34]

CALCIUM, PHOSPHORUS, AND BONE METABOLISM

Without vitamin D, only 10 to 15% of dietary calcium and about 60% of phosphorus is absorbed.[2-4] The interaction of 1,25-dihydroxyvitamin D with the vitamin D receptor increases the efficiency of intestinal calcium absorption to 30 to 40% and phosphorus absorption to approximately 80% (Fig. 1).[2-4,13]

In one study, serum levels of 25-hydroxyvitamin D were directly related to bone mineral density in white, black, and Mexican-American men and women, with a maximum density achieved when the 25-hydroxyvitamin D level reached 40 ng per milliliter or more.[8] When the level was 30 ng per milliliter or less, there was a significant decrease in intestinal calcium absorption[13] that was associated with increased parathyroid hormone.[10-12] Parathyroid hormone enhances the tubular reabsorption of calcium and stimulates the kidneys to produce 1,25-dihydroxyvitamin D.[2-4,6] Parathyroid hormone also activates osteoblasts, which stimulate the transformation of preosteoclasts into mature osteoclasts (Fig. 1).[1-3] Osteoclasts dissolve the mineralized collagen matrix in bone, causing os-

teopenia and osteoporosis and increasing the risk of fracture.[7,8,11,16-21]

Deficiencies of calcium and vitamin D in utero and in childhood may prevent the maximum deposition of calcium in the skeleton.[36] As vitamin D deficiency progresses, the parathyroid glands are maximally stimulated, causing secondary hyperparathyroidism.[7,9-12] Hypomagnesemia blunts this response, which means that parathyroid hormone levels are often normal when 25-hydroxyvitamin D levels fall below 20 ng per milliliter.[37] Parathyroid hormone increases the metabolism of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, which further exacerbates the vitamin D deficiency. Parathyroid hormone also causes phosphaturia, resulting in a low-normal or low serum phosphorus level. Without an adequate calcium–phosphorus product (the value for calcium times the value for serum phosphorus), mineralization of the collagen matrix is diminished, leading to classic signs of rickets in children[1,28] and osteomalacia in adults.[7,38]

Whereas osteoporosis is unassociated with bone pain, osteomalacia has been associated with isolated or generalized bone pain.[39,40] The cause is thought to be hydration of the demineralized gelatin matrix beneath the periosteum; the hydrated matrix pushes outward on the periosteum, causing throbbing, aching pain.[7] Osteomalacia can often be diagnosed by using moderate force to press the thumb on the sternum or anterior tibia, which can elicit bone pain.[7,40] One study showed that 93% of persons 10 to 65 years of age who were admitted to a hospital emergency department with muscle aches and bone pain and who had a wide variety of diagnoses, including fibromyalgia, chronic fatigue syndrome, and depression, were deficient in vitamin D.[41]

OSTEOPOROSIS AND FRACTURE

Approximately 33% of women 60 to 70 years of age and 66% of those 80 years of age or older have osteoporosis.[16,20] It is estimated that 47% of women and 22% of men 50 years of age or older will sustain an osteoporotic fracture in their remaining lifetime. Chapuy et al.[21] reported that among 3270 elderly French women given 1200 mg of calcium and 800 IU of vitamin D_3 daily for 3 years, the risk of hip fracture was reduced by 43%, and the risk of nonvertebral fracture by 32%. A 58% reduction in nonvertebral fractures was observed in 389 men and women over the age of 65 years who were receiving 700 IU of vitamin D_3 and 500 mg of calcium per day.[42]

A meta-analysis of seven randomized clinical

Figure 1 (facing page). Synthesis and Metabolism of Vitamin D in the Regulation of Calcium, Phosphorus, and Bone Metabolism.

During exposure to solar ultraviolet B (UVB) radiation, 7-dehydrocholesterol in the skin is converted to previtamin D_3, which is immediately converted to vitamin D_3 in a heat-dependent process. Excessive exposure to sunlight degrades previtamin D_3 and vitamin D_3 into inactive photoproducts. Vitamin D_2 and vitamin D_3 from dietary sources are incorporated into chylomicrons and transported by the lymphatic system into the venous circulation. Vitamin D (hereafter "D" represents D_2 or D_3) made in the skin or ingested in the diet can be stored in and then released from fat cells. Vitamin D in the circulation is bound to the vitamin D–binding protein, which transports it to the liver, where vitamin D is converted by vitamin D-25-hydroxylase to 25-hydroxyvitamin D [25(OH)D]. This is the major circulating form of vitamin D that is used by clinicians to determine vitamin D status. (Although most laboratories report the normal range to be 20 to 100 ng per milliliter [50 to 250 nmol per liter], the preferred range is 30 to 60 ng per milliliter [75 to 150 nmol per liter].) This form of vitamin D is biologically inactive and must be converted in the kidneys by 25-hydroxyvitamin D-1α-hydroxylase (1-OHase) to the biologically active form — 1,25-dihydroxyvitamin D [$1,25(OH)_2D$]. Serum phosphorus, calcium, fibroblast growth factor 23 (FGF-23), and other factors can either increase (+) or decrease (–) the renal production of $1,25(OH)_2D$. $1,25(OH)_2D$ decreases its own synthesis through negative feedback and decreases the synthesis and secretion of parathyroid hormone by the parathyroid glands. $1,25(OH)_2D$ increases the expression of 25-hydroxyvitamin D-24-hydroxylase (24-OHase) to catabolize $1,25(OH)_2D$ to the water-soluble, biologically inactive calcitroic acid, which is excreted in the bile. $1,25(OH)_2D$ enhances intestinal calcium absorption in the small intestine by interacting with the vitamin D receptor–retinoic acid x-receptor complex (VDR-RXR) to enhance the expression of the epithelial calcium channel (transient receptor potential cation channel, subfamily V, member 6 [TRPV6]) and calbindin 9K, a calcium-binding protein (CaBP). $1,25(OH)_2D$ is recognized by its receptor in osteoblasts, causing an increase in the expression of the receptor activator of nuclear factor-κB ligand (RANKL). RANK, the receptor for RANKL on preosteoclasts, binds RANKL, which induces preosteoclasts to become mature osteoclasts. Mature osteoclasts remove calcium and phosphorus from the bone, maintaining calcium and phosphorus levels in the blood. Adequate calcium (Ca^{2+}) and phosphorus (HPO_4^{2-}) levels promote the mineralization of the skeleton.

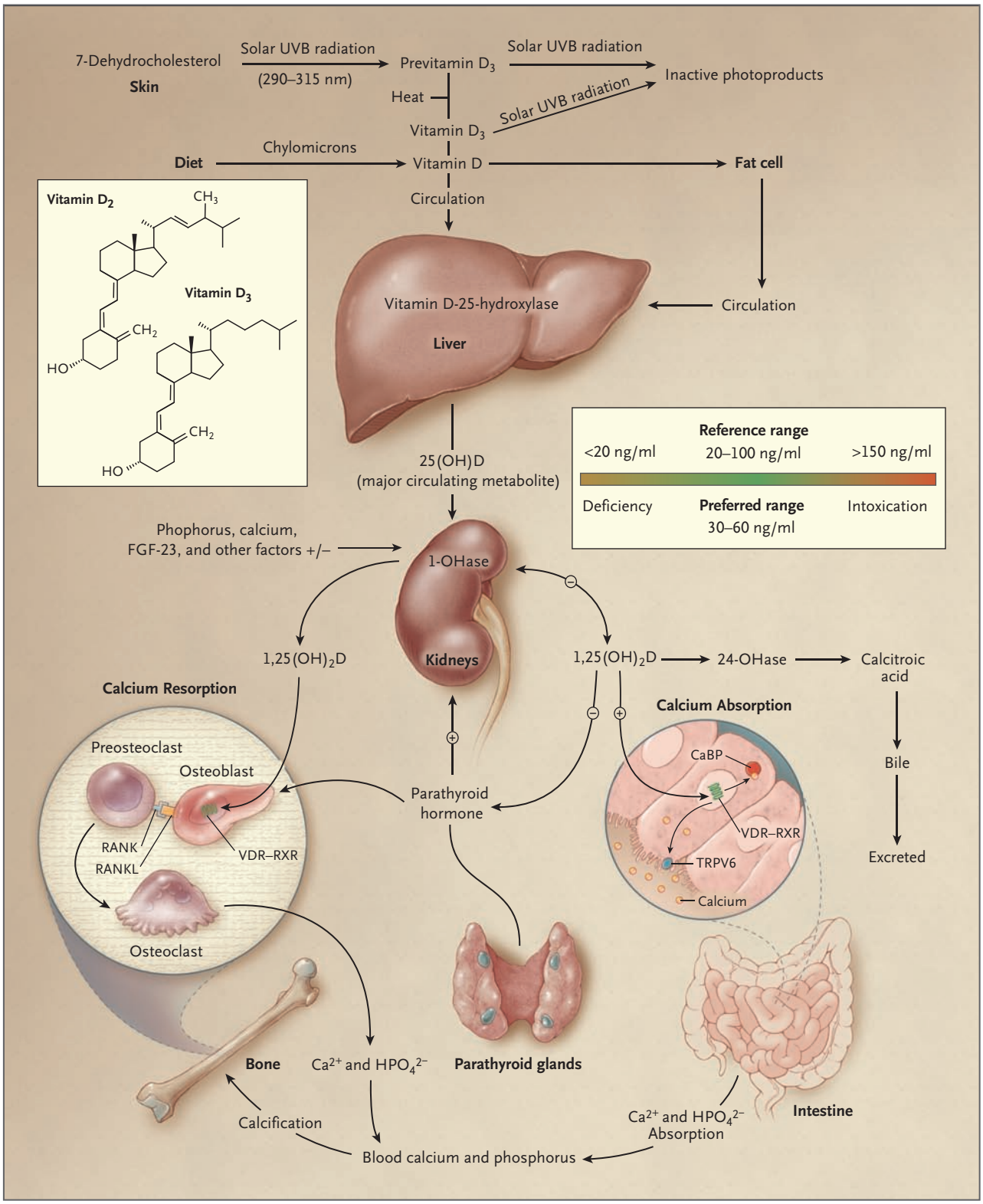

Table 1. Dietary, Supplemental, and Pharmaceutical Sources of Vitamins D_2 and D_3.*

Source	Vitamin D Content
Natural sources	
Salmon	
Fresh, wild (3.5 oz)	About 600–1000 IU of vitamin D_3
Fresh, farmed (3.5 oz)	About 100–250 IU of vitamin D_3 or D_2
Canned (3.5 oz)	About 300–600 IU of vitamin D_3
Sardines, canned (3.5 oz)	About 300 IU of vitamin D_3
Mackerel, canned (3.5 oz)	About 250 IU of vitamin D_3
Tuna, canned (3.6 oz)	About 230 IU of vitamin D_3
Cod liver oil (1 tsp)	About 400–1000 IU of vitamin D_3
Shiitake mushrooms	
Fresh (3.5 oz)	About 100 IU of vitamin D_2
Sun-dried (3.5 oz)	About 1600 IU of vitamin D_2
Egg yolk	About 20 IU of vitamin D_3 or D_2
Exposure to sunlight, ultraviolet B radiation (0.5 minimal erythemal dose)†	About 3000 IU of vitamin D_3
Fortified foods	
Fortified milk	About 100 IU/8 oz, usually vitamin D_3
Fortified orange juice	About 100 IU/8 oz vitamin D_3
Infant formulas	About 100 IU/8 oz vitamin D_3
Fortified yogurts	About 100 IU/8 oz, usually vitamin D_3
Fortified butter	About 50 IU/3.5 oz, usually vitamin D_3
Fortified margarine	About 430 IU/3.5 oz, usually vitamin D_3
Fortified cheeses	About 100 IU/3 oz, usually vitamin D_3
Fortified breakfast cereals	About 100 IU/serving, usually vitamin D_3
Supplements	
Prescription	
Vitamin D_2 (ergocalciferol)	50,000 IU/capsule
Drisdol (vitamin D_2) liquid supplements	8000 IU/ml
Over the counter	
Multivitamin	400 IU vitamin D, D_2, or D_3‡
Vitamin D_3	400, 800, 1000, and 2000 IU

* IU denotes international unit, which equals 25 ng. To convert values from ounces to grams, multiply by 28.3. To convert values from ounces to milliliters, multiply by 29.6.
† About 0.5 minimal erythemal dose of ultraviolet B radiation would be absorbed after an average of 5 to 10 minutes of exposure (depending on the time of day, season, latitude, and skin sensitivity) of the arms and legs to direct sunlight.
‡ When the term used on the product label is vitamin D or calciferol, the product usually contains vitamin D_2; cholecalciferol or vitamin D_3 indicates that the product contains vitamin D_3.

trials that evaluated the risk of fracture in older persons given 400 IU of vitamin D_3 per day revealed little benefit with respect to the risk of either nonvertebral or hip fractures (pooled relative risk of hip fracture, 1.15; 95% confidence interval [CI], 0.88 to 1.50; pooled relative risk of nonvertebral fracture, 1.03; 95% CI, 0.86 to 1.24). In studies using doses of 700 to 800 IU of vitamin D_3 per day, the relative risk of hip fracture was reduced by 26% (pooled relative risk, 0.74; 95% CI, 0.61 to 0.88), and the relative risk of nonvertebral fracture by 23% (pooled relative risk, 0.77; 95% CI, 0.68 to 0.87) with vitamin D_3 as compared with calcium or placebo.[8] A Women's Health Initiative study that compared the effects of 400 IU of vitamin D_3 plus 1000 mg of calcium per day with placebo in more than 36,000 postmenopausal women confirmed these results, reporting an increased risk of kidney stones but no benefit with respect to the risk of hip fracture.

The Women's Health Initiative study also showed that serum levels of 25-hydroxyvitamin D had little effect on the risk of fracture when levels were 26 ng per milliliter (65 nmol per liter) or less. However, women who were most consistent in taking calcium and vitamin D_3 had a 29% reduction in hip fracture.[43] Optimal prevention of both nonvertebral and hip fracture occurred only in trials providing 700 to 800 IU of vitamin D_3 per day in patients whose baseline concentration of 25-hydroxyvitamin D was less than 17 ng per milliliter (42 nmol per liter) and whose mean concentration of 25-hydroxyvitamin D then rose to approximately 40 ng per milliliter.[8]

Evaluation of the exclusive use of calcium or vitamin D_3 (RECORD trial) showed no antifracture efficacy for patients receiving 800 IU of vitamin D_3 per day.[44] However, the mean concentration of 25-hydroxyvitamin D increased from 15.2 ng per milliliter to just 24.8 ng per milliliter (37.9 to 61.9 nmol per liter), which was below the threshold thought to provide antifracture efficacy.[8] Porthouse and colleagues,[45] who evaluated the effect of 800 IU of vitamin D_3 per day on fracture prevention, did not report concentrations of 25-hydroxyvitamin D. Their study had an open design in which participants could have been ingesting an adequate amount of calcium and vitamin D separate from the intervention. This called into question the conclusion that vitamin D supplementation had no antifracture benefit.[8]

MUSCLE STRENGTH AND FALLS

Vitamin D deficiency causes muscle weakness.[1,7,8,28] Skeletal muscles have a vitamin D receptor and may require vitamin D for maximum function.[1,8]

Performance speed and proximal muscle strength were markedly improved when 25-hydroxyvitamin D levels increased from 4 to 16 ng per milliliter (10 to 40 nmol per liter) and continued to improve as the levels increased to more than 40 ng per milliliter (100 nmol per liter).[8] A meta-analysis of five randomized clinical trials (with a total of 1237 subjects) revealed that increased vitamin D intake reduced the risk of falls by 22% (pooled corrected odds ratio, 0.78; 95% CI, 0.64 to 0.92) as compared with only calcium or placebo.[8] The same meta-analysis examined the frequency of falls and suggested that 400 IU of vitamin D_3 per day was not effective in preventing falls, whereas 800 IU of vitamin D_3 per day plus calcium reduced the risk of falls (corrected pooled odds ratio, 0.65; 95% CI, 0.4 to 1.0).[8] In a randomized controlled trial conducted over a 5-month period, nursing home residents receiving 800 IU of vitamin D_2 per day plus calcium had a 72% reduction in the risk of falls as compared with the placebo group (adjusted rate ratio, 0.28%; 95% CI, 0.11 to 0.75).[46]

NONSKELETAL ACTIONS OF VITAMIN D

Brain, prostate, breast, and colon tissues, among others, as well as immune cells have a vitamin D receptor and respond to 1,25-dihydroxyvitamin D, the active form of vitamin D.[1-4,6] In addition, some of these tissues and cells express the enzyme 25-hydroxyvitamin D-1α-hydroxylase.[1-3,6]

Directly or indirectly, 1,25-dihydroxyvitamin D controls more than 200 genes, including genes responsible for the regulation of cellular proliferation, differentiation, apoptosis, and angiogenesis.[1,2,47] It decreases cellular proliferation of both normal cells and cancer cells and induces their terminal differentiation.[1-3,6,47] One practical application is the use of 1,25-dihydroxyvitamin D_3 and its active analogues for the treatment of psoriasis.[48,49]

1,25-Dihydroxyvitamin D is also a potent immunomodulator.[2-4,6,50] Monocytes and macrophages exposed to a lipopolysaccharide or to *Mycobacterium tuberculosis* up-regulate the vitamin D receptor gene and the 25-hydroxyvitamin D-1α-hydroxylase gene. Increased production of 1,25-dihydroxyvitamin D_3 result in synthesis of cathelicidin, a peptide capable of destroying *M. tuberculosis* as well as other infectious agents. When serum levels of 25-hydroxyvitamin D fall below 20 ng per milliliter (50 nmol per liter), the monocyte or macrophage is prevented from initiating this innate immune response, which may explain why black Americans, who are often vitamin D–deficient, are more prone to contracting tuberculosis than are whites, and tend to have a more aggressive form of the disease.[51] 1,25-dihydroxyvitamin D_3 inhibits renin synthesis,[52] increases insulin production,[53] and increases myocardial contractility (Fig. 2).[54]

LATITUDE, VITAMIN D DEFICIENCY, AND CHRONIC DISEASES

CANCER

People living at higher latitudes are at increased risk for Hodgkin's lymphoma as well as colon, pancreatic, prostate, ovarian, breast, and other cancers and are more likely to die from these cancers, as compared with people living at lower latitudes.[55-65] Both prospective and retrospective epidemiologic studies indicate that levels of 25-hydroxyvitamin D below 20 ng per milliliter are associated with a 30 to 50% increased risk of incident colon, prostate, and breast cancer, along with higher mortality from these cancers.[56,59-61,64] An analysis from the Nurses' Health Study cohort (32,826 subjects) showed that the odds ratios for colorectal cancer were inversely associated with median serum levels of 25-hydroxyvitamin D (the odds ratio at 16.2 ng per milliliter [40.4 nmol per liter] was 1.0, and the odds ratio at 39.9 ng per milliliter [99.6 nmol per liter] was 0.53; $P \leq 0.01$). Serum 1,25-dihydroxyvitamin D levels were not associated with colorectal cancer.[61] A prospective study of vitamin D intake and the risk of colorectal cancer in 1954 men showed a direct relationship (with a relative risk of 1.0 when vitamin D intake was 6 to 94 IU per day and a relative risk of 0.53 when the intake was 233 to 652 IU per day, $P<0.05$).[56] Participants in the Women's Health Initiative who at baseline had a 25-hydroxyvitamin D concentration of less than 12 ng per milliliter (30 nmol per liter) had a 253% increase in the risk of colorectal cancer over a follow-up period of 8 years.[62] In a study

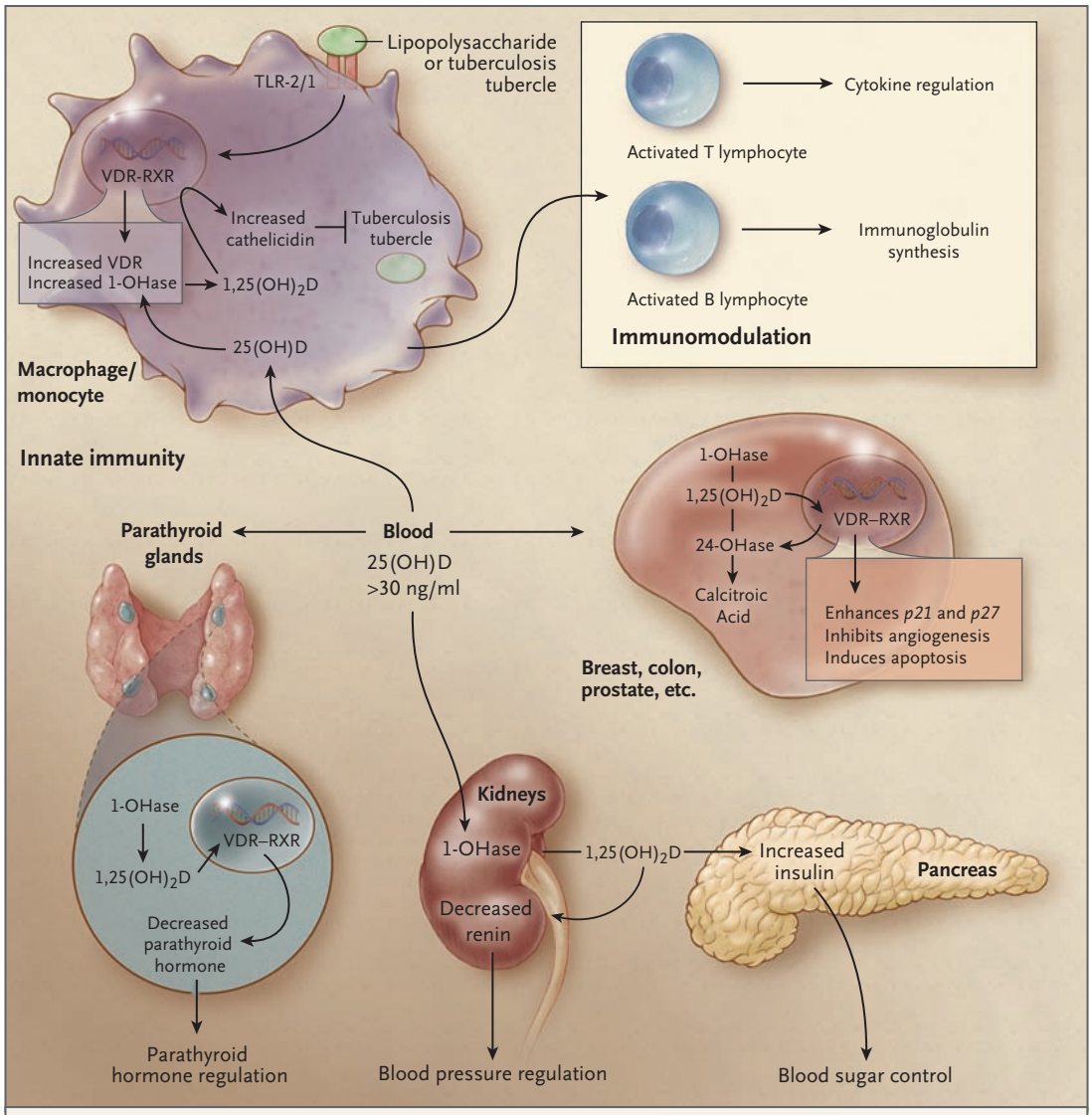

Figure 2. Metabolism of 25-Hydroxyvitamin D to 1,25-Dihydroxyvitamin D for Nonskeletal Functions.

When a macrophage or monocyte is stimulated through its toll-like receptor 2/1 (TLR2/1) by an infectious agent such as *Mycobacterium tuberculosis* or its lipopolysaccharide, the signal up-regulates the expression of vitamin D receptor (VDR) and 25-hydroxyvitamin D-1α-hydroxylase (1-OHase). A 25-hydroxyvitamin D [25(OH)D] level of 30 ng per milliliter (75 nmol per liter) or higher provides adequate substrate for 1-OHase to convert 25(OH)D to its active form, 1,25 dihydroxyvitamin D [1,25$(OH)_2$D]. 1,25$(OH)_2$D travels to the nucleus, where it increases the expression of cathelicidin, a peptide capable of promoting innate immunity and inducing the destruction of infectious agents such as *M. tuberculosis*. It is also likely that the 1,25$(OH)_2$D produced in monocytes or macrophages is released to act locally on activated T lymphocytes, which regulate cytokine synthesis, and activated B lymphocytes, which regulate immunoglobulin synthesis. When the 25(OH)D level is approximately 30 ng per milliliter, the risk of many common cancers is reduced. It is believed that the local production of 1,25$(OH)_2$D in the breast, colon, prostate, and other tissues regulates a variety of genes that control proliferation, including *p21* and *p27,* as well as genes that inhibit angiogenesis and induce differentiation and apoptosis. Once 1,25$(OH)_2$D completes the task of maintaining normal cellular proliferation and differentiation, it induces expression of the enzyme 25-hydroxyvitamin D-24-hydroxylase (24-OHase), which enhances the catabolism of 1,25$(OH)_2$D to the biologically inert calcitroic acid. Thus, locally produced 1,25$(OH)_2$D does not enter the circulation and has no influence on calcium metabolism. The parathyroid glands have 1-OHase activity, and the local production of 1,25$(OH)_2$D inhibits the expression and synthesis of parathyroid hormone. The 1,25$(OH)_2$D produced in the kidney enters the circulation and can down-regulate renin production in the kidney and stimulate insulin secretion in the beta islet cells of the pancreas.

of men with prostate cancer, the disease developed 3 to 5 years later in the men who worked outdoors than in those who worked indoors.[63] Pooled data for 980 women showed that the highest vitamin D intake, as compared with the lowest, correlated with a 50% lower risk of breast cancer.[64] Children and young adults who are exposed to the most sunlight have a 40% reduced risk of non-Hodgkin's lymphoma[65] and a reduced risk of death from malignant melanoma once it develops, as compared with those who have the least exposure to sunlight.[66]

The conundrum here is that since the kidneys tightly regulate the production of 1,25-dihydroxyvitamin D, serum levels do not rise in response to increased exposure to sunlight or increased intake of vitamin D.[1-3] Furthermore, in a vitamin D–insufficient state, 1,25-dihydroxyvitamin D levels are often normal or even elevated.[1,3,6,7] The likely explanation is that colon, prostate, breast, and other tissues express 25-hydroxyvitamin D-1α-hydroxylase and produce 1,25-dihydroxyvitamin D locally to control genes that help to prevent cancer by keeping cellular proliferation and differentiation in check.[1-3,47,56,58] It has been suggested that if a cell becomes malignant, 1,25-dihydroxyvitamin D can induce apoptosis and prevent angiogenesis, thereby reducing the potential for the malignant cell to survive.[2,3,7,67] Once 1,25-dihydroxyvitamin D completes these tasks, it initiates its own destruction by stimulating the *CYP24* gene to produce the inactive calcitroic acid. This guarantees that 1,25-dihydroxyvitamin D does not enter the circulation to influence calcium metabolism (Fig. 1).[1-4] This is a plausible explanation for why increased sun exposure and higher circulating levels of 25-hydroxyvitamin D are associated with a decreased risk of deadly cancers.[56-65]

AUTOIMMUNE DISEASES, OSTEOARTHRITIS, AND DIABETES

Living at higher latitudes increases the risk of type 1 diabetes, multiple sclerosis, and Crohn's disease.[68,69] Living below 35 degrees latitude for the first 10 years of life reduces the risk of multiple sclerosis by approximately 50%.[69,70] Among white men and women, the risk of multiple sclerosis decreased by 41% for every increase of 20 ng per milliliter in 25-hydroxyvitamin D above approximately 24 ng per milliliter (60 nmol per liter) (odds ratio, 0.59; 95% CI, 0.36 to 0.97; P=0.04).[71] Women who ingested more than 400 IU of vitamin D per day had a 42% reduced risk of developing multiple sclerosis.[72] Similar observations have been made for rheumatoid arthritis[73] and osteoarthritis.[74]

Several studies suggest that vitamin D supplementation in children reduces the risk of type 1 diabetes. Increasing vitamin D intake during pregnancy reduces the development of islet autoantibodies in offspring.[53] For 10,366 children in Finland who were given 2000 IU of vitamin D_3 per day during their first year of life and were followed for 31 years, the risk of type 1 diabetes was reduced by approximately 80% (relative risk, 0.22; 95% CI, 0.05 to 0.89).[75] Among children with vitamin D deficiency the risk was increased by approximately 200% (relative risk, 3.0; 95% CI, 1.0 to 9.0). In another study, vitamin D deficiency increased insulin resistance, decreased insulin production, and was associated with the metabolic syndrome.[53] Another study showed that a combined daily intake of 1200 mg of calcium and 800 IU of vitamin D lowered the risk of type 2 diabetes by 33% (relative risk, 0.67; 95% CI, 0.49 to 0.90) as compared with a daily intake of less than 600 mg of calcium and less than 400 IU of vitamin D.[76]

CARDIOVASCULAR DISEASE

Living at higher latitudes increases the risk of hypertension and cardiovascular disease.[54,77] In a study of patients with hypertension who were exposed to ultraviolet B radiation three times a week for 3 months, 25-hydroxyvitamin D levels increased by approximately 180%, and blood pressure became normal (both systolic and diastolic blood pressure reduced by 6 mm Hg).[78] Vitamin D deficiency is associated with congestive heart failure[54] and blood levels of inflammatory factors, including C-reactive protein and interleukin-10.[54,79]

VITAMIN D DEFICIENCY AND OTHER DISORDERS

SCHIZOPHRENIA AND DEPRESSION

Vitamin D deficiency has been linked to an increased incidence of schizophrenia and depression.[80,81] Maintaining vitamin D sufficiency in utero and during early life, to satisfy the vitamin D receptor transcriptional activity in the brain, may be important for brain development as well as for maintenance of mental function later in life.[82]

LUNG FUNCTION AND WHEEZING ILLNESSES

Men and women with a 25-hydroxyvitamin D level above 35 ng per milliliter (87 nmol per liter) had

Table 2. Causes of Vitamin D Deficiency.*

Cause	Effect
Reduced skin synthesis	
Sunscreen use — absorption of UVB radiation by sunscreen[1-3,7,85]	Reduces vitamin D_3 synthesis — SPF 8 by 92.5%, SPF 15 by 99%
Skin pigment — absorption of UVB radiation by melanin[1-3,7,85]	Reduces vitamin D_3 synthesis by as much as 99%
Aging — reduction of 7-dehydrocholesterol in the skin[2,7,85]	Reduces vitamin D_3 synthesis by about 75% in a 70-year-old
Season, latitude, and time of day — number of solar UVB photons reaching the earth depending on zenith angle of the sun (the more oblique the angle, the fewer UVB photons reach the earth)[1-3,85]	Above about 35 degrees north latitude (Atlanta), little or no vitamin D_3 can be produced from November to February
Patients with skin grafts for burns — marked reduction of 7-dehydrocholesterol in the skin	Decreases the amount of vitamin D_3 the skin can produce
Decreased bioavailability	
Malabsorption — reduction in fat absorption, resulting from cystic fibrosis, celiac disease, Whipple's disease, Crohn's disease, bypass surgery, medications that reduce cholesterol absorption, and other causes[86,87]	Impairs the body's ability to absorb vitamin D
Obesity — sequestration of vitamin D in body fat†	Reduces availability of vitamin D
Increased catabolism	
Anticonvulsants, glucocorticoids, HAART (AIDS treatment), and antirejection medications — binding to the steroid and xenobiotic receptor or the pregnane X receptor[1-3,7,88]	Activates the destruction of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D to inactive calcitroic acid
Breast-feeding	
Poor vitamin D content in human milk[1,33,89]	Increases infant risk of vitamin D deficiency when breast milk is sole source of nutrition
Decreased synthesis of 25-hydroxyvitamin D	
Liver failure	
Mild-to-moderate dysfunction	Causes malabsorption of vitamin D, but production of 25-hydroxyvitamin D is possible[2,3,6,7,90]
Dysfunction of 90% or more	Results in inability to make sufficient 25-hydroxyvitamin D
Increased urinary loss of 25-hydroxyvitamin D	
Nephrotic syndrome — loss of 25-hydroxyvitamin D bound to vitamin D–binding protein in urine	Results in substantial loss of 25-hydroxyvitamin D to urine[2,3,6,91]
Decreased synthesis of 1,25-dihydroxyvitamin D	
Chronic kidney disease	
Stages 2 and 3 (estimated glomerular filtration rate, 31 to 89 ml/min/1.73 m^2)	
Hyperphosphatemia increases fibroblast growth factor 23, which decreases 25-hydroxyvitamin D-1α-hydroxylase activity[5,6,91-94]	Causes decreased fractional excretion of phosphorus and decreased serum levels of 1,25-dihydroxyvitamin D
Stages 4 and 5 (estimated glomerular filtration rate <30 ml/min/1.73 m^2)	
Inability to produce adequate amounts of 1,25-dihydroxyvitamin D[2,3,6,91-96]	Causes hypocalcemia, secondary hyperparathyroidism, and renal bone disease

a 176-ml increase in the forced expiratory volume in 1 second.[83] Children of women living in an inner city who had vitamin D deficiency during pregnancy are at increased risk for wheezing illnesses.[84]

CAUSES OF VITAMIN D DEFICIENCY

There are many causes of vitamin D deficiency, including reduced skin synthesis and absorption of vitamin D and acquired and heritable disorders of

Table 2. (Continued.)

Cause	Effect
Heritable disorders — rickets	
Pseudovitamin D deficiency rickets (vitamin D–dependent rickets type 1) — mutation of the renal 25-hydroxyvitamin D-1α-hydroxylase gene (*CYP27B1*)[1-3,97]	Causes reduced or no renal synthesis of 1,25-dihydroxyvitamin D
Vitamin D–resistant rickets (vitamin D–dependent rickets type 2) — mutation of the vitamin D receptor gene[1-3]	Causes partial or complete resistance to 1,25-dihydroxyvitamin D action, resulting in elevated levels of 1,25-dihydroxyvitamin D
Vitamin D–dependent rickets type 3 — overproduction of hormone-responsive-element binding proteins[98]	Prevents the action of 1,25-dihydroxyvitamin D in transcription, causing target-cell resistance and elevated levels of 1,25-dihydroxyvitamin D
Autosomal dominant hypophosphatemic rickets — mutation of the gene for fibroblast growth factor 23, preventing or reducing its breakdown[1-3,5,6,92]	Causes phosphaturia, decreased intestinal absorption of phosphorus, hypophosphatemia, and decreased renal 25-hydroxyvitamin D-1α-hydroxylase activity, resulting in low-normal or low levels of 1,25-dihydroxyvitamin D
X-linked hypophosphatemic rickets — mutation of the *PHEX* gene, leading to elevated levels of fibroblast growth factor 23 and other phosphatonins[1-3,5,6,92]	Causes phosphaturia, decreased intestinal absorption of phosphorus, hypophosphatemia, and decreased renal 25-hydroxyvitamin D-1α-hydroxylase activity, resulting in low-normal or low levels of 1,25-dihydroxyvitamin D
Acquired disorders	
Tumor-induced osteomalacia — tumor secretion of fibroblast growth factor 23 and possibly other phosphatonins[1-3,5,6,92,99]	Causes phosphaturia, decreased intestinal absorption of phosphorus, hypophosphatemia, and decreased renal 25-hydroxyvitamin D-1α-hydroxylase activity, resulting in low-normal or low levels of 1,25-dihydroxyvitamin D
Primary hyperparathyroidism — increase in levels of parathyroid hormone, causing increased metabolism of 25-hydroxyvitamin D to 1,25-hydroxyvitamin D[2,3,6]	Decreases 25-hydroxyvitamin D levels and increases 1,25-dihydroxyvitamin D levels that are high-normal or elevated
Granulomatous disorders, sarcoidosis, tuberculosis, and other conditions, including some lymphomas — conversion by macrophages of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D[100]	Decreases 25-hydroxyvitamin D levels and increases 1,25-dihydroxyvitamin D levels
Hyperthyroidism — enhanced metabolism of 25-hydroxyvitamin D	Reduces levels of 25-hydroxyvitamin D

* UVB denotes ultraviolet B, SPF sun protection factor, and HAART highly active antiretroviral therapy.
† There is an inverse relationship between the body-mass index and 25-hydroxyvitamin D levels.[2,7,85]

vitamin D metabolism and responsiveness.[2,3,6] Table 2 lists causes and effects of vitamin D deficiency.

VITAMIN D REQUIREMENTS AND TREATMENT STRATEGIES

CHILDREN AND ADULTS

Recommendations from the Institute of Medicine for adequate daily intake of vitamin D are 200 IU for children and adults up to 50 years of age, 400 IU for adults 51 to 70 years of age, and 600 IU for adults 71 years of age or older.[101] However, most experts agree that without adequate sun exposure, children and adults require approximately 800 to 1000 IU per day.[1-3,8,15,16,20,102,103] Children with vitamin D deficiency should be aggressively treated to prevent rickets (Table 3).[1,28,105-107] Since vitamin D_2 is approximately 30% as effective as vitamin D_3 in maintaining serum 25-hydroxyvitamin D levels,[117,118] up to three times as much vitamin D_2 may be required to maintain sufficient levels. A cost-effective method of correcting vitamin D deficiency and maintaining adequate levels is to give patients a 50,000-IU capsule of vitamin D_2 once a week for 8 weeks, followed by 50,000 IU of vitamin D_2 every 2 to 4 weeks thereafter (Table 3).[2,7,9] Alternatively, either 1000 IU of vitamin D_3 per day (available in most pharmacies) or 3000 IU of vitamin D_2 per day is effective.[2,7,102,103] Strategies such as having patients take 100,000 IU of vitamin D_3 once every 3 months have been shown to be effective in maintaining 25-hydroxyvitamin D levels at 20 ng per milliliter or higher and are also effective in reducing the risk of fracture.[119]

BREAST-FED INFANTS AND CHILDREN

Human milk contains little vitamin D (approximately 20 IU per liter), and women who are vitamin D–deficient provide even less to their breast-

Table 3. Strategies to Prevent and Treat Vitamin D Deficiency.*

Cause of Deficiency†	Preventive and Maintenance Measures to Avoid Deficiency	Treatment of Deficiency
Children		
Breast-feeding without vitamin D supplementation[28,33,89,104] — up to 1 yr	400 IU of vitamin D_3/day,[1,28,104] sensible sun exposure,[1] 1000–2000 IU of vitamin D_3/day is safe,[1,2,27,75] maintenance dose is 400–1000 IU of vitamin D_3/day[1,2,104]	200,000 IU of vitamin D_3 every 3 mo,[1,105] 600,000 IU of vitamin D intramuscularly, repeat in 12 wk[106]; 1000–2000 IU of vitamin D_2 or vitamin D_3/day[1,107] with calcium supplementation
Inadequate sun exposure[24,29-31,108] or supplementation,[1,28,104-107] dark skin[23] — 1 through 18 yr	400–1000 IU vitamin D_3/day,[1,104,107] sensible sun exposure, 1000–2000 IU of vitamin D_3/day[1,108] is safe,[1,27,75,104,107] maintenance dose is 400–1000 IU of vitamin D/day[1,75]	50,000 IU of vitamin D_2 every wk for 8 wk[1,9]‡
Adults		
Inadequate sun exposure[7,15] or supplementation,[7-20] decreased 7-dehydrocholesterol in skin because of aging (over 50 yr)[7]	800–1000 IU of vitamin D_3/day,[1-3,8,16,21,42] 50,000 IU of vitamin D_2 every 2 wk or every mo,[7,9] sensible sun exposure[7,15,109,110] or use of tanning bed or other UVB radiation device (e.g., portable Sperti lamp),[111-114] up to 10,000 IU of vitamin D_3/day is safe for 5 mo,[27] maintenance dose is 50,000 IU every 2 wk or every mo[7,9]‡	50,000 IU of vitamin D_2 every wk for 8 weeks[9]; repeat for another 8 wk if 25-hydroxyvitamin D <30 ng/ml‡
Pregnant or lactating (fetal utilization,[33] inadequate sun exposure[33,89] or supplementation[33,89])	1000–2000 IU of vitamin D_3/day,[33,89] 50,000 IU of vitamin D_2 every 2 wk, up to 4000 IU of vitamin D_3/day is safe for 5 mo,[33,89] maintenance dose is 50,000 IU of vitamin D_2 every 2 or 4 wk[9]‡	50,000 IU vitamin D_2 every wk for 8 wk[115]; repeat for another 8 wk if 25-hydroxyvitamin D <30 ng/ml‡
Malabsorption syndromes (malabsorption of vitamin D,[2,3,86,87] inadequate sun exposure[2,3,6,7] or supplementation[2,3,6,7])	Adequate exposure to sun or ultraviolet radiation,[7,113] 50,000 IU of vitamin D_2 every day, every other day, or every wk,† up to 10,000 IU of vitamin D_3/day is safe for 5 mo,[27] maintenance dose is 50,000 IU of vitamin D_2 every wk‡	UVB irradiation (tanning bed or portable UVB device, e.g., portable Sperti lamp),[111-114] 50,000 IU of vitamin D_2 every day or every other day‡
Drugs that activate steroid and xenobiotic receptor,[88] and drugs used in transplantation[116]	50,000 IU of vitamin D_2 every other day or every week, maintenance dose is 50,000 IU of vitamin D_2 every 1, 2, or 4 wk‡	50,000 IU of vitamin D_2 every 2 wk for 8–10 wk, or every wk if 25-hydroxyvitamin D <30 ng/ml‡
Obesity[2,7]	1000–2000 IU of vitamin D_3/day, 50,000 IU of vitamin D_2 every 1 or 2 wk, maintenance dose is 50,000 IU of vitamin D_2 every 1, 2, or 4 wk‡	50,000 IU of vitamin D_2 every wk for 8–12 wk; repeat for another 8–12 wk if 25-hydroxyvitamin D <30 ng/ml‡
Nephrotic syndrome[2,3,6,7,91-94]	1000–2000 IU of vitamin D_3/day, 50,000 IU of vitamin D_2 once or twice/wk,[2,94] maintenance dose is 50,000 IU of vitamin D_2 every 2 or 4 wk[2]‡	50,000 IU of vitamin D_2 twice/wk for 8–12 wk[2,94]; repeat for another 8–12 wk if 25-hydroxyvitamin D <30 ng/ml‡
Chronic kidney disease§		
Stages 2 and 3	Control serum phosphate,[6] 1000 IU of vitamin D_3/day, 50,000 IU of vitamin D_2 every 2 wk,[91,94] maintenance dose is 50,000 IU of vitamin D_2 every 2 or 4 wk; may also need to treat with an active vitamin D analog when vitamin D sufficiency is obtained‡	50,000 IU of vitamin D_2 once/wk for 8 wk[91,94]; repeat for another 8 wk if 25-hydroxyvitamin D <30 ng/ml‡
Stages 4 and 5	1000 IU of vitamin D_3/day,[51] 50,000 IU of vitamin D_2 every 2 wk, need to treat with 1,25-dihydroxyvitamin D_3 or active analogue‡	0.25–1.0 μg of 1,25-dihydroxyvitamin D_3 (calcitriol)[2,6,91,93,94] by mouth twice a day or one of the following: 1–2 μg of paricalcitriol IV every 3 days,[6,91,93,94] 0.04–0.1 μg/kg IV every other day initially and can increase to 0.24 μg/kg, 2–4 μg by mouth three times/wk,[6,91,93,94] or doxecalciferol[6,91,93,94] 10–20 μg by mouth three times/wk or 2–6 μg IV three times/wk

Table 3. (Continued.)

Cause of Deficiency†	Preventive and Maintenance Measures to Avoid Deficiency	Treatment of Deficiency
Adults		
Primary or tertiary hyperparathyroidism	800–1000 IU of vitamin D_3/day, 50,000 IU of vitamin D_2 every 2 wk (serum calcium levels will not increase),[115] maintenance dose is 50,000 IU of vitamin D_2 every 2 or 4 wk‡	50,000 IU of vitamin D_2 once a wk for 8 wk; repeat for another 8 wk if 25-hydroxyvitamin D <30 ng/ml
Granulomatous disorders and some lymphomas	400 IU of vitamin D_3/day, maintenance dose is 50,000 IU of vitamin D_2/mo‡	50,000 IU vitamin D_2 once a wk for 4 wk or every 2 to 4 wk, need to keep 25-hydroxyvitamin D between 20 and 30 ng/ml (level above 30 ng/ml can result in hypercalciuria and hypercalcemia)‡

* These recommendations are based on published literature and the author's personal experience. IV denotes intravenously. To convert the values for 25-hydroxyvitamin D to nanomoles per liter, multiply by 2.496.
† For the specific mechanism of deficiency, see Table 2.
‡ The goal is to achieve concentrations of 25-hydroxyvitamin D at about 30 to 60 ng per milliliter. Physicians should use these guidelines in combination with their clinical judgment according to the circumstances.
§ In stages 2 and 3 of chronic kidney disease, the estimated glomerular filtration rate is 31 to 89 ml per minute per 1.73 m^2; in stages 4 and 5, the estimated rate is <30 ml per minute per 1.73 m^2.

fed infants.[33,89] Lactating women given 4000 IU of vitamin D_3 per day not only had an increase in the level of 25-hydroxyvitamin D to more than 30 ng per milliliter but were also able to transfer enough vitamin D_3 into their milk to satisfy an infant's requirement.[89]

In Canada, to prevent vitamin D deficiency, current guidelines recommend that all infants and children receive 400 IU of vitamin D_3 per day (Table 3).[104]

PATIENTS WITH CHRONIC KIDNEY DISEASE

In patients with any stage of chronic kidney disease, 25-hydroxyvitamin D should be measured annually, and the level should be maintained at 30 ng per milliliter or higher, as recommended in the Kidney Disease Outcomes Quality Initiative guidelines from the National Kidney Foundation.[6,91,93,94] It is a misconception to assume that patients taking an active vitamin D analogue have sufficient vitamin D; many do not. Levels of 25-hydroxyvitamin D are inversely associated with parathyroid hormone levels, regardless of the degree of chronic renal failure.[2,6,93-96] Parathyroid glands convert 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, which directly inhibits parathyroid hormone expression.[6,93-96,120] Patients with stage 4 or 5 chronic kidney disease and an estimated glomerular filtration rate of less than 30 ml per minute per 1.73 m^2 of body-surface area, as well as those requiring dialysis, are unable to make enough 1,25-dihydroxyvitamin D and need to take 1,25-dihydroxyvitamin D_3 or one of its less calcemic analogues to maintain calcium metabolism and to decrease parathyroid hormone levels and the risk of renal bone disease (Table 3).[6,91,93,94]

MALABSORPTION AND MEDICATION

Patients with mild or moderate hepatic failure or intestinal fat-malabsorption syndromes, as well as patients who are taking anticonvulsant medications, glucocorticoids, or other drugs that activate steroid and xenobiotic receptor, require higher doses of vitamin D (Table 3).[7,88] Exposure to sunlight or ultraviolet B radiation from a tanning bed or other ultraviolet B–emitting device is also effective.[7,113,115]

SUNLIGHT AND ARTIFICIAL ULTRAVIOLET B RADIATION

Sensible sun exposure can provide an adequate amount of vitamin D_3, which is stored in body fat and released during the winter, when vitamin D_3 cannot be produced.[7,15,85,108-110] Exposure of arms and legs for 5 to 30 minutes (depending on time of day, season, latitude, and skin pigmentation) between the hours of 10 a.m. and 3 p.m. twice a week is often adequate.[2,7,108-110] Exposure to one minimal erythemal dose while wearing only a bathing suit is equivalent to ingestion of approximately 20,000 IU of vitamin D_2.[1,2,7,85] The skin has a great capacity to make vitamin D_3, even in the elderly, to reduce the risk of fracture.[109-111] Most tanning beds

emit 2 to 6% ultraviolet B radiation and are a recommended source of vitamin D_3 when used in moderation.[111-113,115] Tanners had robust levels of 25-hydroxyvitamin D (approximately 45 ng per milliliter [112 nmol per liter]) at the end of the winter and higher bone density as compared with nontanners (with levels of approximately 18 ng per milliliter [45 nmol per liter]).[112] For patients with fat malabsorption, exposure to a tanning bed for 30 to 50% of the time recommended for tanning (with sunscreen on the face) is an excellent means of treating and preventing vitamin D deficiency (Table 3).[113] This reduces the risk of skin cancers associated with ultraviolet B radiation.

VITAMIN D INTOXICATION

Vitamin D intoxication is extremely rare but can be caused by inadvertent or intentional ingestion of excessively high doses. Doses of more than 50,000 IU per day raise levels of 25-hydroxyvitamin D to more than 150 ng per milliliter (374 nmol per liter) and are associated with hypercalcemia and hyperphosphatemia.[1-3,27,121,122] Doses of 10,000 IU of vitamin D_3 per day for up to 5 months, however, do not cause toxicity.[27] Patients with chronic granulomatous disorders are more sensitive to serum 25-hydroxyvitamin D levels above 30 ng per milliliter because of macrophage production of 1,25-dihydroxyvitamin D, which causes hypercalciuria and hypercalcemia.[1-3,100] In these patients, however, 25-hydroxyvitamin D levels need to be maintained at approximately 20 to 30 ng per milliliter to prevent vitamin D deficiency and secondary hyperparathyroidism (Table 3).[1-3,100]

CONCLUSIONS

Undiagnosed vitamin D deficiency is not uncommon,[1-3,6-20,123] and 25-hydroxyvitamin D is the barometer for vitamin D status. Serum 25-hydroxyvitamin D is not only a predictor of bone health[8] but is also an independent predictor of risk for cancer and other chronic diseases.[8,54,59-64,71-75,83-85] The report that postmenopausal women who increased their vitamin D intake by 1100 IU of vitamin D_3 reduced their relative risk of cancer by 60 to 77% is a compelling reason to be vitamin D–sufficient.[124] Most commercial assays for 25-hydroxyvitamin D are good for detecting vitamin D deficiency. Radioimmunoassays measure total 25-hydroxyvitamin D, which includes levels of both 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3. Some commercial laboratories measure 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3 with liquid chromatography and tandem mass spectroscopy and report the values separately. As long as the combined total is 30 ng per milliliter or more, the patient has sufficient vitamin D.[7,14,27] The 1,25-dihydroxyvitamin D assay should never be used for detecting vitamin D deficiency because levels will be normal or even elevated as a result of secondary hyperparathyroidism. Because the 25-hydroxyvitamin D assay is costly and may not always be available, providing children and adults with approximately at least 800 IU of vitamin D_3 per day or its equivalent should guarantee vitamin D sufficiency unless there are mitigating circumstances (Table 2).

Much evidence suggests that the recommended adequate intakes are actually inadequate and need to be increased to at least 800 IU of vitamin D_3 per day. Unless a person eats oily fish frequently, it is very difficult to obtain that much vitamin D_3 on a daily basis from dietary sources. Excessive exposure to sunlight, especially sunlight that causes sunburn, will increase the risk of skin cancer.[125,126] Thus, sensible sun exposure (or ultraviolet B irradiation) and the use of supplements are needed to fulfill the body's vitamin D requirement.

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Latest findings in phosphate homeostasis

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The kidney is a key player in phosphate balance. Inappropriate renal phosphate transport may alter serum phosphate concentration and bone mineralization, and increase the risk of renal lithiasis or soft tissue calcifications. The recent identification of fibroblast growth factor 23 (FGF23) as a hormone regulating phosphate and calcitriol metabolism and of klotho has changed the understanding of phosphate homeostasis; and a bone–kidney axis has emerged. In this review, we present recent findings regarding the consequences of mutations affecting several human genes encoding renal phosphate transporters or proteins regulating phosphate transport activity. We also describe the role played by the FGF23–klotho axis in phosphate homeostasis and its involvement in the pathophysiology of phosphate disturbances in chronic kidney disease.

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The control of serum phosphate concentration is mandatory to avoid the occurrence of severe metabolic disorders. Several lines of evidences indicate that hyperphosphatemia decreases life expectancy.[1–3] Hypophosphatemia is also associated with bone demineralization and increased risk of renal stone occurrence.[4] Our knowledge of the mechanisms that govern phosphate homeostasis has been greatly improved during the recent years following the identification of mutations in several genes encoding for renal phosphate transporters or associated proteins, and by the discoveries of a new hormone, the fibroblast growth factor 23 (FGF23), and the multi-function protein klotho. The disruption or the overexpression of the genes encoding these proteins in mice, and the identification of mutations in human have emphasized their central role in human phosphate physiology and in the pathophysiology of phosphate disorders in chronic kidney disease.

THE CENTRAL ROLE OF THE KIDNEY IN PHOSPHATE HOMEOSTASIS

Phosphate is filtered at the glomerulus then reabsorbed almost exclusively in the proximal tubule. The amount of phosphate reabsorbed by the proximal tubule is hormonally regulated and determines, in subjects with normal renal function or moderately reduced glomerular filtration rate, serum phosphate levels. Two type 2 sodium phosphate co-transporters, NPT2a (SLC34A1) and NPT2c (SLC34A3), are expressed at the apical domain of renal proximal tubular cells and reabsorb phosphate from the glomerulus filtrate (Figure 1).[5,6] The targeted disruption of the NPT2a gene in mice and the loss-of-function mutations in the human NPT2a gene increase urinary phosphate excretion, induce hypophosphatemia and are both associated with renal stone occurrence and/or bone demineralization confirming the key role played by this carrier in phosphate homeostasis.[7–9] Patients with renal stones and a seven amino-acid heterozygous deletion in NPT2a exhibited an ability of the kidney to reabsorb phosphate similar to that observed in patients affected with renal stones in the past who did not have this mutation, questioning its role in the patient phenotype.[10] However, this lack of difference can be explained by significant differences of serum parathyroid hormone (PTH) concentrations between the two groups. Although the phenotype of mice with NPT2c gene disruption has not

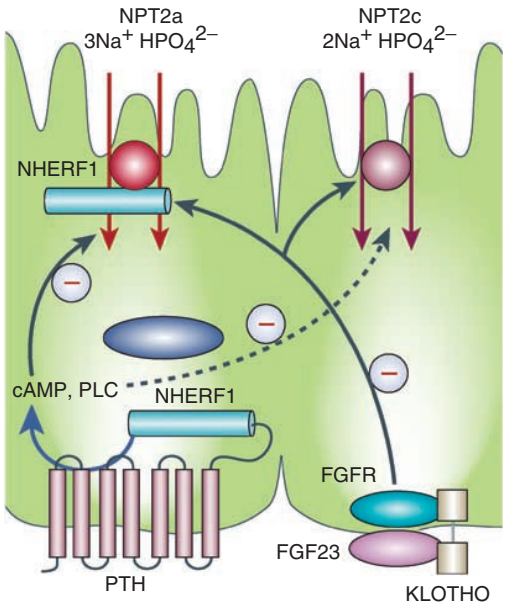

Figure 1 | Proteins involved in renal phosphate reabsorption. Phosphate is reabsorbed in the proximal tubular cells through two sodium phosphate cotransporters, NPT2a and NPT2c, the activity of which is controlled by two hormones; the parathyroid hormone (PTH) and the fibroblast growth factor 23 (FGF23). PTH binds to the PTH type1 receptor (PTHR1) and induces the retrieval of NPT2a from the brush border membrane. Its effect on NPT2c is uncertain. FGF23 decreases the expression of both sodium phosphate cotransporters. NHERF1 binds to NPT2a and type 1 PTH receptor (PTH1R). Mutations in all these proteins have been identified in humans with impaired renal phosphate reabsorption.

yet been published, mutations in the human NPT2c gene is responsible for the hereditary hypophosphatemic rickets with hypercalciuria, a disorder close to that observed in patients with NPT2a mutations.[11–14]

NPT2a and NPT2c have similar affinities for phosphate but differ by several features. First, their stoichiometry for sodium ion: NPT2a carries three sodium ions with phosphate, whereas NPT2c carries only two.[5,15,16] Second, the hormonal regulation of these two sodium phosphate cotransporters is not identical (see below). Third, studies carried out in rats suggest that NPT2c is preferentially expressed before weaning ages, its expression decreasing thereafter.[15] These differences may explain why the defect in NPT2a function cannot be compensated by NPT2c in later life: although the renal expression of NPT2c is increased in NPT2a−/− mice, they still exhibit a profound defect of renal phosphate transport.[17]

The expression of a third type 2 sodium phosphate cotransporter mRNA, NPT2b (SLC34A2), has been reported in the kidney.[18,19] This transporter is also expressed in lung and small intestine.[19] Intestinal expression of NPT2b is upregulated by calcitriol,[19,20] which may mediate the stimulation of intestinal phosphate absorption by calcitriol treatment. The tubular localization of NPT2b in the kidney and its role in renal phosphate reabsorption is unknown. In lung, NPT2b seems to play a central role in the reabsorption of phosphate released from phospholipid cleavage. Indeed, mutations of this transporter in humans lead to lung calcifications.[21] Serum phosphate concentration and renal phosphate transport did not seem to be altered in these patients under normal phosphate diet.

Two other types of sodium phosphate cotransporters, type 1 and type 3, are expressed in the kidney. NPT1 (SLC17A1) is expressed at the apical membrane of proximal tubular cells and in the liver; it is a nonspecific anionic carrier whose physiological role regarding phosphate homeostasis is still unknown.[22,23]

Type 3 phosphate transporter family is composed of PiT1 (SLC20A1) and PiT2 (SLC20A2). These proteins, initially identified as retrovirus receptors, transport phosphate with a high affinity.[24,25] They are widely expressed, which suggests that they may play an important role in supplying cells with phosphate rather than playing a key role in the regulation of phosphate balance at the body level.[24] Overexpression of PiT1 in cultured vascular smooth muscle cells grown in a high phosphate-rich medium increases cellular calcifications, suggesting that PiTs could be involved in the mechanisms leading to pathological vascular and soft tissue calcifications such as those observed in uremic patients.[26]

The molecules and the mechanisms leading to the reabsorption of phosphate from the lumen to the proximal tubule cells have almost been completely elucidated; however, scarce information exist regarding the phosphate transport at the basolateral side of the proximal tubular cell as well as the phosphate transport in other nephron sites, namely in the distal tubule.

HORMONAL CONTROL OF RENAL PHOSPHATE TRANSPORT

Parathyroid hormone and its signaling pathway

Parathyroid hormone binds to type 1 PTH receptor in proximal tubular cells, stimulates cAMP synthesis and phospholipase C pathway and decreases renal phosphate transport. It is well established that PTH induces the retrieval of NPT2a from proximal tubular cell brush border membrane (Figure 1).[27] The effect of PTH on NPT2c expression differs according to the animal models studied. Although NPT2c is expressed in the renal brush border membrane from proximal tubular cells of NPT2a−/− mice,[17] infusion of PTH in these animals fails to further decrease renal phosphate transport[28,29] suggesting that PTH cannot lower NPT2c expression in this model. By contrast, in thyroparathyroidectomized rats, administration of PTH markedly decreases NPT2c expression in renal brush border membrane vesicles.[30]

To properly exert its physiological role, NPT2a needs to be correctly located at the cellular membrane. Several data indicate that the correct targeting of NPT2a to the apical membrane and the control of its retrieval by PTH require the presence of the sodium–proton exchanger regulatory factor 1 (NHERF1). NHERF1 belongs to the PDZ domain protein family. It contains two PDZ domains that bind to the carboxy-terminal end of NPT2a and type 1 PTH

receptor.[31,32] The targeted disruption of NHERF1 gene in mouse results in a phenotype similar to that observed in NPT2a$^{-/-}$ mice, due to the decrease in NPT2a expression in the renal brush border membranes of proximal tubular cells.[33] The mechanism underlying the decrease in NPT2a in NHERF1$^{-/-}$ mice is complex and may associate abnormal targeting and increased PTH-induced retrieval from the brush border membrane. Sodium phosphate transport is decreased in NHERF1$^{-/-}$ renal proximal tubule cells in primary culture by comparison with their wild-type counterpart, this may be associated with a lower NPT2a membrane abundance[34] suggesting that NHERF1 is mandatory for proper sorting of NPT2a. In contrast, experiments performed on the kidney slices showed no difference of phosphate transport between wild-type and NHERF1−/− mice.[35] These latter results suggest that the defect in renal phosphate transport of NHERF1−/− mice requires the presence of an extrarenal factor. This factor may be PTH itself. Indeed, in the presence of NHERF protein, the synthesis of cAMP in response to PTH is inhibited in PS120 cells and in opossum kidney cells.[32,36] Interestingly, it has been known for many years that the truncation of the carboxy-terminal region of type 1 PTH receptor, which is the site of NHERF–type 1 PTH receptor interaction, enhanced cAMP synthesis but not phospholipase C in response to PTH.[37] The levels of urinary cAMP excretion in NHERF1$^{-/-}$ mice has not been reported, so it is unknown if an increase in cAMP synthesis in response to PTH in the proximal tubule may account for the decrease in NPT2a apical expression. However, we have very recently identified mutations in the PDZ2 and the inter region domain of NHERF1 in humans with renal phosphate loss and nephrolithiasis or bone demineralization.[38] Urinary cAMP excretion was increased in these patients, contrasting with normal serum PTH concentration and undetectable PTH-related peptide levels. Experiments performed in cultured renal cells showed that these mutations increased PTH-induced cAMP synthesis resulting in a specific inhibition of renal phosphate transport.

Fibroblast growth factor 23

The main role of PTH in adults is to maintain constant serum ionized calcium concentration, not serum phosphate concentration. PTH regulates calcium release from bone, and calcium reabsorption in the kidney, and in turn ionized calcium concentration controls PTH secretion through the calcium sensor. PTH increases urinary phosphate excretion, but a direct role of phosphate on PTH secretion is difficult to assess as manipulations of phosphate levels modify ionized calcium concentration. Hypophosphatemia with inappropriate urinary phosphate excretion can occur in the absence of hyperparathyroidism, suggesting the existence of non-PTH phosphaturic factors. These factors have been only recently identified. The FGF23 is the better characterized of these factors and we begin to understand its physiological role (Figure 2). FGF23 is a 251 amino-acid peptide synthesized by bone cells, namely osteocytes and osteoblasts,[39–41] in response

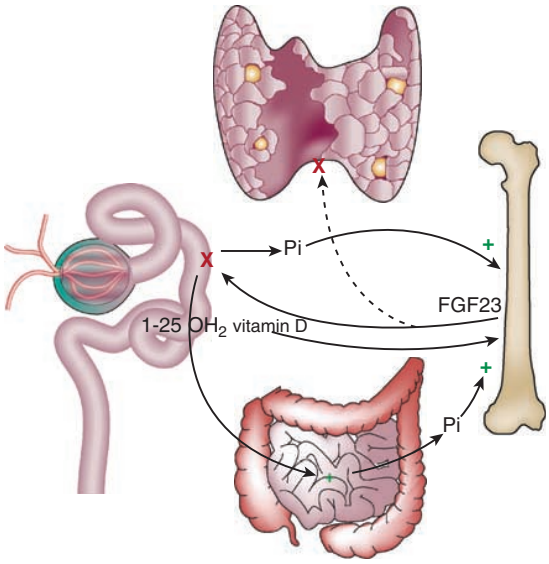

Figure 2 | FGF23 and the bone–kidney axis. The fibroblast growth factor 23 (FGF23) is synthesized by bone in response to an increase in serum phosphate concentration. FGF23 controls renal phosphate transporter activity and calcitriol synthesis by the proximal tubule and intestinal phosphate absorption through calcitriol level. FGF23 may also alter parathyroid gland functions.

to high phosphate intake, hyperphosphatemia or an increase in serum calcitriol concentration.[42–48] When recombinant FGF23 is injected in animals, it induces a rapid and marked inhibition of renal phosphate reabsorption resulting in severe hypophosphatemia, bone demineralization, and low serum calcitriol concentration. FGF23 decreases NPT2a and NPT2c mRNA and protein expression in the kidney. It also inhibits 1-α hydroxylase expression in the renal proximal tubule and stimulates the 24 hydroxylase, the enzyme that converts calcitriol and 25-OH vitamin D into inactive metabolites.[49–57] Infusion of FGF23 decreases the intestinal absorption of phosphate by inhibiting NPT2b expression, which further lowers serum phosphate concentration.[54] This effect on NPT2b is mediated by the reduction of calcitriol levels, as it is abolished in mice with disrupted vitamin D receptor gene.[58] Recent findings suggest that FGF23 may control PTH synthesis and secretion. Injection of FGF23 in animals rapidly decreases PTH secretion within 10 min through the MAPK pathway;[59] it also inhibits PTH gene expression in parathyroid glands.[59] Furthermore, at variance with its effect in renal proximal tubule, FGF23 dose-dependently increases 1-α hydroxylase expression in bovine parathyroid cells,[60] which may contribute to reduce PTH gene transcription.

The disruption of FGF23 gene in mouse is associated with hyperphosphatemia, elevated renal phosphate reabsorption, hypercalcemia, low serum PTH levels, high concentrations of circulating calcitriol, soft tissue calcifications, accelerated senescence, and pulmonary emphysema.[61–63] Similarly, administration of inactivating monoclonal antibodies anti-FGF23 results in hyperphosphatemia and high serum calcitriol levels.[64]

The active form of FGF23 is the 32 kDa intact peptide, which normally circulates in the plasma of normal subjects. A still unidentified enzyme inactivates FGF23 by cleavage between amino acids 176 and 179, which results in two peptides that can be detected in the plasma. It is unknown if FGF23 is metabolized at a specific site in the body, in particular, although serum FGF23 concentration increases with the decrease in glomerular filtration rate (see below), the role of the kidney in FGF23 degradation is not known. A correct glycosylation of the peptide is important for intact FGF23 stability. Indeed, mutations in the glycosylation sites of FGF23 or inactivating mutations of UDP-*N*-acetyl-α-D-galactosamine/polypeptide *N*-acetylgalactosaminyltransferase 3 gene (*GALNT3*), the enzyme responsible for FGF23 *O*-glycosylation, increase intact FGF23 degradation and result in tumoral calcinosis or hyperostosis–hyperphosphatemia syndrome.[65–72] In these disorders, intact FGF23 plasma concentration are low, contrasting with elevated levels of the carboxy-terminal peptide.

The development of soft tissue calcifications in FGF23-deficient disorders can be induced by the hyperphosphatemia or the elevated serum calcitriol concentration. The double knockout of FGF23 and 1-α hydroxylase in mice or that of FGF23 and vitamin D receptor results in a normal phenotype and normal survival, suggesting that the overproduction of calcitriol is harmful in the absence of FGF23.[62,63,73] However, in these mice, serum phosphate concentration is respectively low or normal, which can contribute to the normalization of the phenotype. Selective normalization of serum phosphate or calcitriol concentrations by diet show that normal serum phosphate concentration fully rescues the phenotype of FGF23$^{-/-}$ mice, including mortality and soft tissue calcifications, whereas, in hyperphosphatemic animals with normal calcitriol levels, vascular calcifications and survival were improved but not normalized.[74] Normalization of serum phosphate concentration in patients with tumoral calcinosis has a marked beneficial effect on soft tissue calcifications.[69]

Klotho and FGF receptors

The observations that FGF23 can bind with low affinity to multiple FGF receptors, and that inactivation or overexpression of FGF23 result in disorders that alter calcium phosphate homeostasis led to look for an FGF23-specific receptor. Indeed, dysfunctions of FGFs or their receptors are associated with abnormal fetal development or cancer occurrence without modification of calcium or phosphate balance. Interestingly, mice with an insertional disruption of the klotho gene by a transgene resulting in a hypomorphic allele, exhibit a phenotype similar to that of FGF23-null mice.[61,75] The complete targeted disruption of klotho gene led to an identical phenotype.[76] Klotho gene encodes a 1014-amino-acid long protein with a long extracellular NH2 extremity, a single pass transmembrane domain, and a short intracellular carboxy-terminal region. The extracellular domain is composed of two homologous regions named KL1 and KL2. Klotho is expressed at the cell surface but is also present in the plasma as two secreted forms. One of the secreted forms of klotho results from the shedding of klotho from the cell surface. This form is made up of the KL1 and KL2 domains. The second secreted form of klotho is due to an alternative RNA splicing in exon 3 that gives a protein of 549 amino acids containing only the KL1 domain. Several data converge to show that klotho is important for FGF23 function. The transmembrane and the KL1–KL2 secreted forms of klotho binds to FGF23.[77,78] Injection of an anti-klotho antibody that abrogates klotho–FGF23 interaction in mice reproduces the disorders of klotho and FG23-null mice.[78] Klotho binds to multiple FGF receptors increasing the affinity of FGF receptors for FGF23.[77,78] The klotho–FGF receptor–FGF23 complex activates the phosphorylation of ERK1/2 and FGF receptor substrate.[77,78] In klotho-deficient or inactivated mice, serum-intact FGF23 concentration is increased but is ineffective in controlling serum phosphate levels.[79] In summary, klotho is a co-receptor that specifically increases the sensitivity of FGF receptors to FGF23.

Klotho is expressed in a limited number of organs: kidney, brain, the pituitary gland, the parathyroid gland, ovary, testis, skeletal muscle, duodenum, and pancreas.[59,75] Surprisingly, in the kidney, klotho is not expressed in the proximal tubule but, instead, in the distal tubule.[80] To date, the mechanism by which FGF23 decreases renal phosphate transporter expression and 1-α-hydroxylase and 24-hydroxylase expression in the renal proximal tubule is unknown. The role of klotho in the renal distal tubule seems to be independent of FGF23.

Co-immunoprecipitation studies indicate that soluble klotho can bind FGF23;[64,78] however, the function of the circulating forms of klotho remains to be established.

Klotho isoform that contains KL1 and KL2 has a weak β-glucuronidase activity.[81] Addition of the extracellular domain of klotho on cells expressing the calcium ion channel TRPV5 increases calcium entry. This effect is reproduced by a β-glucuronidase and is due to the retention of TRPV5 in the plasma membrane.[82] The physiological signification of these findings is not completely understood.

Overexpression of klotho in mice significantly extends lifespan, represses insulin and insulin-like growth factor signaling, and increases manganese-superoxide dismutase expression, which reduces oxidative stress.[83,84] The calcium–phosphate balance in these mice has not been reported.

ALTERATION OF THE FGF23–KLOTHO AXIS IN HUMAN DISEASES

Role of FGF23 in chronic kidney diseases

Serum-intact FGF23 concentration increases early when glomerular filtration rate declines.[85,86] In chronic kidney disease, serum FGF23 concentration is correlated with serum phosphate concentration and urinary fractional excretion of phosphate, and inversely correlated with serum calcitriol and PTH concentrations.[85,87,88] The early increase in FGF23 levels in chronic kidney disease prevents hyperphosphatemia, by decreasing phosphate absorption in the renal proximal tubule and in the intestine; however, by inhibiting the

1-α-hydroxylase activity, FGF23 may also generate a secondary hyperparathyroidism.[85] The increase in serum-intact FGF23 concentration in chronic kidney disease may also be partially due to impaired FGF23 degradation; however, the role of the kidney in FGF23 cleavage has not been established. High levels of FGF23 concentrations are associated with accelerated degradation of glomerular filtration rate in non-diabetic patients with chronic kidney disease independently of other factors.[89] In dialysis patients, serum FGF23 concentration is markedly increased and predicts the future development of refractory hyperparathyroidism.[90,91] PTH-induced phosphate release from bone may stimulate FGF23 production in dialysis patients, which in turn controls PTH secretion. Higher levels of serum FGF23 may be necessary to control serum PTH and phosphate concentration in patients who will develop refractory hyperparathyroidism. It is unknown if klotho expression decreases in the PTHs as observed in the kidney, and if this mechanism might also be implicated in the genesis of refractory hyperparathyroidism.

In the absence of refractory hyperparathyroidism, we have found no correlation between serum FGF23 concentration and bone mineralization density at several skeletal sites in a population of hemodialysis patients, suggesting the lack of direct effect of FGF23 on bone.[88]

Increased serum FGF23 concentrations in dialysis patient are also associated with increased mortality within the first year of hemodialysis.[92]

The increased production of FGF23 during the dialysis period may result in an autonomous secretion of FGF23 in some patients. This phenomenon may explain persistent high serum FGF23 levels and the hypophosphatemia observed in many patients following successful renal transplant.[93]

Various genetic disorders with abnormal serum FGF23 concentrations responsible for hypo or hyperphosphatemia are shown in Table 1.

Involvement of klotho in pathology

The expression of the membrane and KL1 forms of klotho is decreased in the kidney in patients with chronic renal failure but has not been reported in other organs.[94] The consequences of this decrease on FGF23 action in the kidney are uncertain.

In humans, klotho polymorphisms have been associated with longevity and the risk of cardiovascular calcifications, and with bone mineral density in postmenopausal women.[95–101]

Klotho is expressed in ovary; recently, the levels of mRNA KL1 form of klotho in epithelial ovarian cancer have been associated with poor survival prognosis in this context.[102] The role of KL1 klotho in cancer requires further elucidation, as KL1 has also antitumoral properties, it can suppress IGF type 1 receptor autophosphorylation,[83] but can also facilitate tumor by stimulating angiogenesis and inhibiting apoptosis.[103–106]

Table 1 | Genetic disorders associated with inappropriate renal phosphate reabsorption and serum phosphate concentration in human

Disorder	Serum phosphate concentration	Mutated gene	Mechanism	FGF23 concentration
Autosomal dominant hypophosphatemic rickets	Low	FGF23	Increased stability of FGF23	Increased
X-linked hypophosphatemia	Low	PHEX	Unknown	Increased
Autosomal recessive hypophosphatemia	Low	DMP1	Unknown	Increased
McCune-Albright syndrome	Low	GNAS	Hypersecretion of FGF23 by bone cells	Increased
Familial tumoral calcinosis hyperostosis–hyperphosphatemia syndrome	High	FGF23	Glycosylation defect, instability of FGF23	Intact: low c-terminal: increased
	High	GALNT3	Glycosylation defect, instability of FGF23	Intact: low c-terminal: increased
	High	Klotho	Resistance to FGF23	Intact: increased
Hypophosphatemia with hyperparathyroidism	Low	Translocation t(9,13)(q21.13;q13.1)	Increased klotho abundance in plasma	Increased
Hypophosphatemia with renal lithiasis or bone demineralization	Low	NPT2a	Defect of phosphate transport	Normal
	Low	NPT2c	Defect of phosphate transport	Normal
	Low	NHERF1	Increased responsiveness of renal proximal tubule to PTH	Normal

FGF23, fibroblast growth factor 23; NHERF1, sodium–proton exchanger regulatory factor 1; PTH, parathyroid hormone.

OTHER BONE-DERIVED PHOSPHATURIC FACTORS

The matrix extracellular phosphoglycoprotein (MEPE) is 525-amino-acid protein expressed in bone. Its cleavage releases an acid-rich motif peptide (ASARM) located in the carboxy-terminal part of MEPE. ASARM peptide is an inhibitor of bone mineralization. Administration or over-expression of MEPE induces renal phosphate leak, hypophosphatemia, and bone demineralization.[107–109] The increased levels of ASARM and MEPE peptides and of FGF23 have been reported in humans with X-linked hypophosphatemia, and in Hyp mice, two disorders due to mutations in Phex gene (phosphate regulating gene with homologies to endopeptidases on the X chromosome) have been reported.[53,110–112] The phosphaturic effect of MEPE may be mediated by FGF23 questioning the role of MEPE as a phosphaturic factor. The release of ASARM from MEPE would decrease PHEX expression and activity,[113–115] which would inhibit bone mineralization and increase FGF23 secretion by a still unidentified mechanism.[53,87,116] This view is consistent with the inability of MEPE gene disruption to reverse the phenotype of Hyp mice.[116]

As MEPE, dentin matrix protein 1 belongs to the SIBLING (small integrin-binding ligand N-linked glycoproteins) protein family. Humans with mutation in dentin matrix protein 1 gene and dentin matrix protein 1-null mice exhibit hypophosphatemia, increased excretion of phosphate in urine and increased FGF23 plasma concentration.[117,118] The mechanism by which inactivation of dentin matrix protein 1 increases FGF23 expression remains to be determined.

CONCLUSION

Our knowledge of the mechanisms that participate to maintain serum phosphate concentration within the normal range has greatly improved during the past few years. The pathophysiology and consequences of disorders with inadequate renal phosphate reabsorption have been elucidated. The understanding of the genesis of secondary hyperparathyroidism in chronic kidney disease has been modified. Its treatment and prevention will probably benefit from the development of new drugs, interfering with phosphate transporters, hormonal receptors, or associated proteins.

DISCLOSURE

All the authors declared no competing interests.

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