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Vitamin D Metabolism and Rickets in Domestic Animals: A Review

K. E. Dittmer[1] and K. G. Thompson[1]

Abstract

Rickets and osteomalacia are increasing in prevalence in people because of cultural practices, breast-feeding, decreased sun exposure, and increased sunscreen usage. Several hereditary forms of rickets owing to either renal phosphate wasting or defects in vitamin D metabolism are also reported in people. Rickets is well recognized in domestic animals, but published reports are not always supported by microscopic findings, and diagnoses based on clinical signs and radiology are unreliable. Most cases in domestic animals are caused by dietary deficiency of either vitamin D or phosphorus, but occasional inherited forms are reported in pigs, sheep, cats, and dogs. There is variation between species in susceptibility to dietary vitamin D and phosphorus deficiency and in the ability to manufacture vitamin D in their skin. A number of mouse models have been discovered or created to study human skeletal diseases and skeletal homeostasis. With the discovery that vitamin D is involved in not only calcium and phosphorus homeostasis but also in the immune system and cancer, there is great potential for new and existing animal models to generate valuable information about vitamin D and its many functions. This review presents an overview of vitamin D metabolism and rickets in domestic and laboratory animals and makes comparisons where appropriate with the disease in humans.

Keywords

bone, rickets, vitamin D, phosphorus, genetic diseases

Rickets is a classic metabolic bone disease of humans and animals, first described in the first and second centuries.[158,165] With the discovery that vitamin D could prevent rickets, the prevalence of this disease in developed countries plummeted; however, it still occurs. In fact, the prevalence of rickets and vitamin D insufficiency is increasing in people of all ages in the developed world, due in part to decreased sunlight exposure and widespread sunscreen usage.[88] The disease is well recognized in animals, but published reports are uncommon and sometimes confusing.

The pathogenesis of rickets involves impaired mineralization of physeal and epiphyseal cartilage during endochondral ossification and of newly formed osteoid. Most cases in domestic animals are caused by dietary deficiency of either vitamin D or phosphorus, but occasional inherited forms are reported.[109,200] Osteomalacia is caused by a failure of newly formed osteoid to mineralize, but it occurs in adults after closure of growth plates.[109]

In this article, we review vitamin D metabolism and rickets, with reference to the disease in domestic animals but presenting comparison with the disease in humans where appropriate.

Biology of Vitamin D

Activation of Vitamin D

Vitamin D is available from two sources: isomerization of 7-dehydrocholesterol (7-DHC) in the skin to vitamin D_3 following exposure to ultraviolet light or from ingestion of vitamin D_2 or D_3 in the diet. Only a few foods, including cod liver oil and fatty fish such as salmon and sardines, naturally contain high concentrations of vitamin D_3.[49] Vitamin D_2 is present in certain plants owing to conversion of ergosterol to vitamin D_2 by ultraviolet light.[40]

Ultraviolet light in the 270- to 315-nm range is required for the conversion of 7-DHC in the skin to previtamin D_3, which then undergoes thermal isomerization to vitamin D_3 over the course of 3 days.[87,100] The formation efficiency of vitamin D_3 in the skin is influenced by skin pigmentation and ultraviolet light intensity.[13,87] Melanin vies with 7-DHC for ultraviolet photons, and a longer time in sunlight is required for maximum previtamin D_3 formation in dark-skinned animals.[87] The intensity of ultraviolet light that reaches the skin of the animal depends on latitude and altitude. Ultraviolet radiation is less at higher latitudes, particularly during winter, when daylight hours are low.[159,213] When the altitude of the sun is less

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than 35°, as occurs during winter at latitudes of 31° or higher, there is insufficient penetration of ultraviolet light to convert 7-DHC to previtamin D_3.[13] At high altitude, ultraviolet radiation may be intense, and animals may be exposed to excessive or prolonged exposure to sun.[90] In these situations, previtamin D_3 photoisomerizes to the biologically inert tachysterol and lumisterol, which are sloughed off with keratinocytes during normal skin turnover.[87]

Species vary in their ability to form vitamin D_3 in their skin. For example, exposure of dogs and cats to ultraviolet light does not significantly increase dermal vitamin D_3 concentration.[92] In contrast, similar irradiation of rats leads to a 40-fold increase in vitamin D_3.[92] This presumably relates to the presence of 7-DHC-Δ^7-reductase, an enzyme capable of degrading 7-DHC, in the skin of cats.[145] Not surprisingly, a study in Australia demonstrated that, unlike other species, dogs did not show seasonal variation in serum 25-hydroxyvitamin D (25(OH)D) concentrations.[115] In their natural state, dogs and cats would have satisfied their vitamin D requirements from ingesting the fat, liver, and blood of their quarry, but pet dogs and cats now rely on dietary supplements.[92] Most herbivores are able to produce vitamin D_3 in response to ultraviolet irradiation of the skin, as indicated by the higher concentrations of serum vitamin D_3 in shorn sheep than in unshorn sheep.[29,81] Llamas and alpacas have been found to be highly susceptible to vitamin D deficiency. These camelids have evolved with a thick hair coat and pigmentation to protect them against the intense solar radiation present in their natural environment in the high Andes.[25,82,209] When transferred to lower altitudes or higher latitudes where solar radiation is much lower, serum vitamin D concentrations in llamas and alpacas decline to low levels, especially during winter.[182,211]

Once vitamin D_3 is formed in the skin, it preferentially binds to vitamin D–binding protein in the capillaries of the dermis, and it is either stored in fat or transported to the liver.[87] Whether obtained from sun exposure or diet, vitamins D_2 and D_3 are biologically inactive and must undergo two hydroxylation reactions to be activated.[49] Figure 1 shows the steps involved in the conversion of vitamin D to its active form: 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$). The 25-hydroxylation occurs mainly in the liver, whereas the second 1α-hydroxylation takes place in the kidneys. Vitamin D becomes biologically active only after the second hydroxylation is complete.

Hepatic 25-hydroxylation. A number of hepatic cytochrome P450s have been postulated as carrying out 25-hydroxylation of vitamin D, including CYP27A1, CYP3A4, CYP2R1 and CYP2J3,[162] and this step in vitamin D metabolism is largely unregulated. Because of its strong association with vitamin D–binding protein, $25(OH)D_3$ is stable and is the main form of vitamin D in circulation.[100] The concentration of 25(OH)D in serum is proportional to dietary intake and is therefore a useful measure of dietary consumption and/or skin production.[87]

Renal 1α-hydroxylation. The next step in the process of vitamin D activation depends on the plasma ionized calcium concentration. If plasma ionized calcium concentration is low, renal 1α-hydroxylation of 25(OH)D occurs to produce the active form of vitamin D ($1,25(OH)_2D_3$), but if the calcium concentration is adequate, 25(OH)D undergoes 24-hydroxylation to an inactive metabolite.[100] The renal 1α-hydroxylase (CYP27B1) is also regulated by parathyroid hormone (PTH), calcitonin, and feedback inhibition by $1,25(OH)_2D_3$. When plasma ionized calcium is low, PTH may directly stimulate the 1α-hydroxylase gene promoter or indirectly stimulate renal 1α-hydroxylase mRNA production and activity via cAMP pathways.[21,147,171] However, when plasma ionized calcium concentrations are normal, calcitonin is thought to upregulate renal 1α-hydroxylase production of $1,25(OH)_2D_3$.[147,226] The feedback inhibition of 1α-hydroxylase by $1,25(OH)_2D_3$ is mostly due to inhibition of PTH and the cAMP pathways.[21]

Plasma phosphate concentration is also involved in the control of $1,25(OH)_2D_3$ production. Low plasma phosphate concentration induces renal 1α-hydroxylase activity independent of either PTH or calcium concentrations.[5,68] High plasma phosphate concentration inhibits $1,25(OH)_2D_3$ formation through the activity of the phosphatonins, fibroblast growth factor 23, and secreted frizzled-related protein 4.[12]

Catabolism Pathways

The two main pathways responsible for the catabolism of active vitamin D are catalyzed by CYP24.[9] The first involves C-24 oxidation to calcitroic acid,[100] whereas the second involves conversion of $1,25(OH)_2D_3$ to $1,25(OH)_2D_3$-26,23-lactone via a 23-hydroxylation.[162] The *CYP24* gene contains two vitamin D–responsive elements (VDREs) in its promoter. These elements allow $1,25(OH)_2D_3$ to upregulate *CYP24* expression via the vitamin D receptor (VDR) and stimulate its own catabolism.[43,227] PTH and plasma phosphate concentrations are also involved in the control of the catabolic pathways.[192,193,228] When serum ionized calcium concentrations are normal and PTH is suppressed, CYP24 activity and expression increase such that 25(OH)D is converted to the much-less-potent 24,25-dihydroxyvitamin D_3, and $1,25(OH)_2D_3$ is catabolized.[193,227,228] However, low plasma phosphate concentration decreases CYP24 expression and activity, thus reducing $1,25(OH)_2D_3$ catabolism.[192,221]

The Vitamin D Receptor

The VDR is a member of the family of type II nuclear receptors for steroid hormones. These receptors require heterodimerization with retinoid X receptors (RXRs) to increase their affinity for the ligand—in this case, $1,25(OH)_2D_3$.[7,163] The VDR protein contains four main domains: ligand binding, heterodimerization with the RXR, binding of VDREs, and enlistment of coregulators.[49] In the nucleus, VDR-RXR-$1,25(OH)_2D_3$ binds to specific sequences called VDREs present in the promoter area of the target gene.[78,96] Nuclear coactivators and transcription factors, positive and negative, interact with the VDR-RXR-$1,25(OH)_2D_3$ to augment or repress $1,25(OH)_2D_3$ gene transcription activation.[49,164] For further description of the

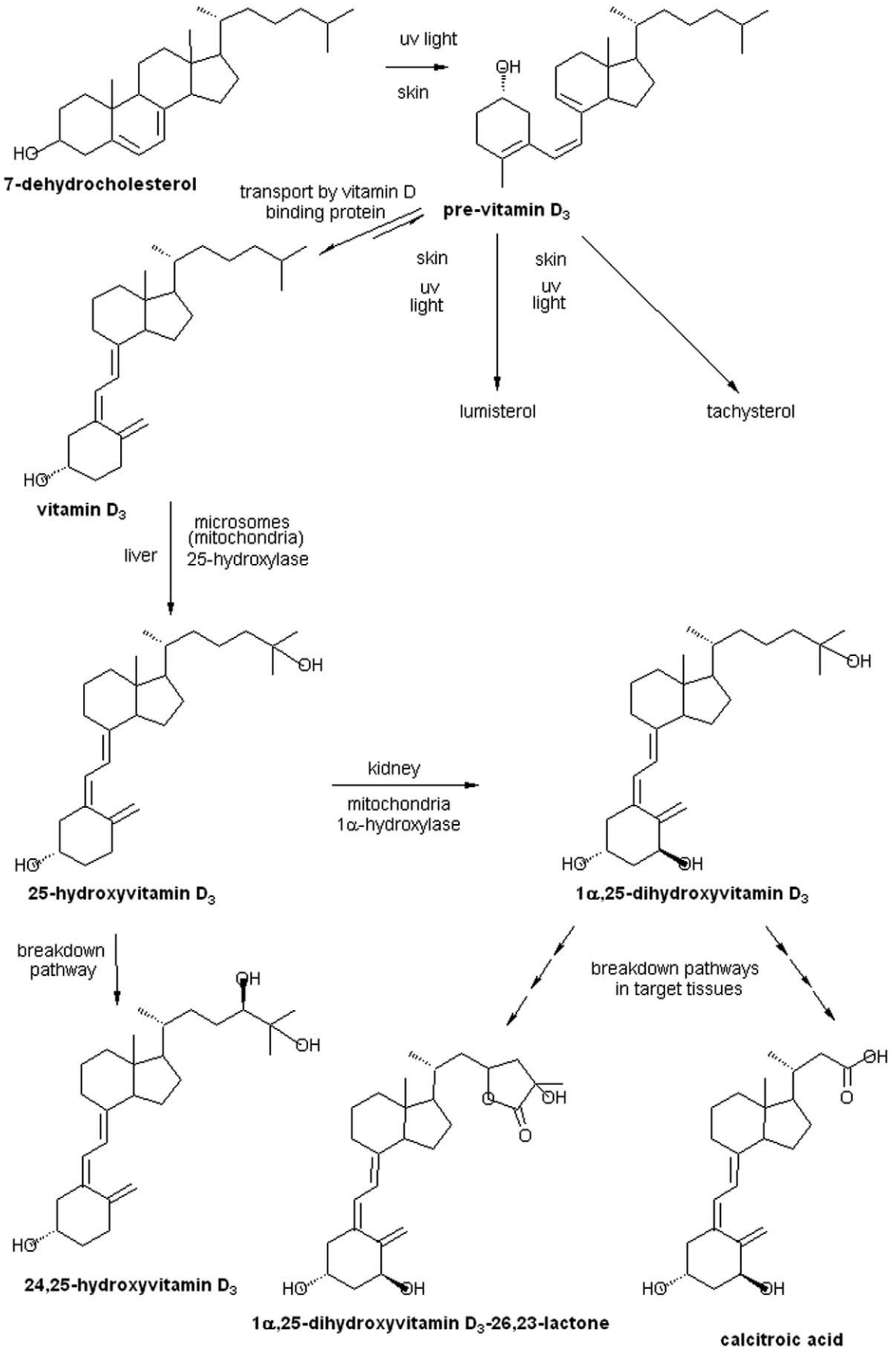

Figure 1. Vitamin D synthesis, activation, and breakdown: Exposure of 7-dehydrocholesterol in the skin to ultraviolet irradiation leads to thermal isomerization to vitamin D_3, which is transported by vitamin D–binding protein to the liver. Vitamin D_3 25-hydroxylation occurs in the

molecular signaling of $1,25(OH)_2D_3$, we refer to the reviews by Dusso et al[49] and Haussler et al.[78]

Functions of Vitamin D

The main target organs for vitamin D are the intestine, bone, kidney, and parathyroid glands.[49] With PTH, the primary function of vitamin D is to maintain plasma ionized calcium and phosphate concentrations within narrow physiological limits.

Intestine. In the intestine, $1,25(OH)_2D_3$ promotes active uptake and transcellular transport of calcium. The epithelial calcium channel, transient receptor potential vanilloid 6 (TRPV6), transports calcium into the cell where it binds to calbindin D and is transported across the cell.[190] A Ca^{2+} ATPase (PMCA1b) and Na^+/Ca^{2+} exchanger (NCX1) then discharges calcium into the bloodstream.[18] Paracellular transport of calcium down an electrochemical gradient also occurs.[207] TRPV6 and calbindin are upregulated by $1,25(OH)_2D_3$, thereby increasing intestinal calcium absorption,[86,143] whereas high blood calcium concentrations provide negative feedback on the numbers of TRPV6 channels, thereby reducing intestinal calcium absorption.[86] TRPV6 and calbindin may also be induced, independent of vitamin D and blood calcium concentrations, by high dietary and intestinal calcium concentrations.[207]

Active phosphate absorption in the intestine may also be increased by $1,25(OH)_2D_3$, which leads to increased expression of the Na-P_i transporter and altered intestinal cell membrane lipid composition.[113,222]

Bone remodeling. In the skeleton, $1,25(OH)_2D_3$, in association with PTH, promotes mobilization of calcium from bone stores to maintain ionized blood calcium concentration within a narrow range.[89] This is thought to be achieved by stimulation of RANKL (receptor activator for NF-κB ligand) and increased osteoclastogenesis.[3] RANKL, a surface ligand on osteoblasts, can bind either to osteoclasts via RANK (receptor activator for NF-κB) or to a decoy receptor called osteoprotegerin (OPG).[189] When RANKL binds to RANK, it induces differentiation and maturation of osteoclast progenitor cells to osteoclasts.[191] RANKL is stimulated by $1,25(OH)_2D_3$ via VDREs on the RANKL promoter, thereby inducing osteoclastogenesis, resorption of bone, and mobilization of calcium.[108] OPG production is inhibited by $1,25(OH)_2D_3$.[110] If RANKL binds to OPG, osteoclastogenesis and bone resorption is inhibited.[19]

Bone growth and mineralization. It is uncertain whether vitamin D affects bone growth and mineralization directly or indirectly by altering calcium and phosphate concentrations in the extracellular fluid via intestinal uptake of calcium.[189] If ionized calcium and phosphate concentrations are within the physiological range, $1,25(OH)_2D_3$/VDR is apparently not essential for mineralization of osteoid.[152] However, osteoblasts and chondrocytes express both 25-hydroxyvitamin D-1α-hydroxylase and VDR,[187] and both calcium and $1,25(OH)_2D_3$, independent of the VDR, are thought to be required for normal growth plate development.[73,152] Juvenile mice with inactivation of the VDR in chondrocytes have impaired vascular invasion and decreased osteoclast numbers, leading to a transient increase in the density of the primary spongiosa.[136,187] Similarly, mice with chondrocyte-specific inactivation of 1α-hydroxylase also have impaired vascular invasion and increased neonatal bone volume, in addition to increased width of the hypertrophic zone of the growth plate.[149] These mouse models suggest an intracrine role for $1,25(OH)_2D_3$ in endochondral ossification, over and above the endocrine role of keeping serum calcium and phosphate within normal limits.

Parathyroid glands. The VDR and $1,25(OH)_2D_3$ are not essential for controlling PTH production, but they do work in conjunction with calcium.[49,73] Deficiency of vitamin D results in hypocalcemia, which leads to parathyroid hyperplasia and secondary hyperparathyroidism.[144] Conversely, $1,25(OH)_2D_3$ suppresses parathyroid cell growth by decreasing growth factors (transforming growth factor–epidermal growth factor receptor growth loop) and increasing known inhibitors of cell growth (cyclin-dependent kinase inhibitors p21 and p27).[50] This is the physiological basis behind the use of active vitamin D in treating people for secondary hyperparathyroidism in end-stage chronic renal disease.[220] In addition, active vitamin D has been shown to upregulate calcium-sensing receptor expression by binding to VDREs on the calcium-sensing receptor gene promoter, leading to increased sensitivity of the parathyroid gland to plasma ionized calcium and decreased PTH secretion.[24,28]

Kidney. The main role of $1,25(OH)_2D_3$ in the kidney is to control its own production by inhibition of renal 1α-hydroxylase and stimulation of CYP24 (24-hydroxylase).[49] Whether $1,25(OH)_2D_3$ has any direct effect on renal filtration of calcium and phosphate is controversial, given that its effects are clouded by its actions on PTH and intestinal calcium and phosphate absorption.[49] Calcium transport across renal epithelial cells is similar to that which occurs across intestinal epithelial cells. The epithelial calcium channel (TRPV5) is present on the apical cell membrane of cells in distal convoluted tubules and collecting ducts of the kidney and transports calcium into the cell.[190] Calbindin-D_{28K} transports calcium across the renal tubular cell, and the calcium transporters PMCA1b and NCX1 on the basolateral cell membrane release calcium into the bloodstream.[17] PTH, $1,25(OH)_2D_3$, and estrogen may all independently induce upregulation of TRPV5, calbindin-D_{28K},

Figure 1. (continued). liver by cytochrome P450, which is followed by transport to the kidney and 1α-hydroxylation in the proximal convoluted tubules to produce 1,25-dihydroxyvitamin D_3, the active form of vitamin D. Also included are the breakdown pathways catalyzed by CYP24 cytochromes. Isomerization of 7-dehydrocholesterol also produces tachysterol and lumisterol, which are biologically inert and are sloughed off in keratinocytes during normal skin turnover.

PMCA1b, and NCX1 gene expression.[17,84,85,206] PTH-dependent calcium transport in distal convoluted tubules may also be accelerated by $1,25(OH)_2D_3$.[66] Renal tubular reabsorption of phosphate is increased by $1,25(OH)_2D_3$ when PTH is present, but this is unlikely to be a direct effect on the kidney.[49]

Other Effects

Vitamin D has also been shown to have other endocrine and autocrine/paracrine roles in multiple cell types and organs. Vitamin D may protect against cancer and possibly even treat cancer by suppression of cell growth.[69,111,229] In one study, serum vitamin D concentration and the incidence of some cancers were shown to be inversely related, although many confounding factors were present.[39] Vitamin D may also have a role in the immune system; it may be involved in prevention of cardiovascular disease, hypertension, and diabetes mellitus; and it may aid in treatment of rheumatoid arthritis, inflammatory bowel disease, psoriasis, and multiple sclerosis.[15,100,146,229]

Toxicity

In spite of its many beneficial effects, an excess of vitamin D is toxic, causing widespread soft tissue mineralization secondary to persistent hypercalcemia and hyperphosphatemia.[148] Affected animals show severe gastrointestinal signs, hypertension, heart rhythm abnormalities, neurological signs (eg, seizures), and, eventually, death.[75,148,154] This underlies the use of cholecalciferol as a pesticide in some countries. The pathogenesis of cholecalciferol toxicity is not completely understood, because serum $1,25(OH)_2D_3$ concentrations are usually normal whereas serum 25(OH)D concentrations are 10 to 20 times greater than the normal range.[174] It is possible that high concentrations of 25(OH)D activate the VDR and stimulate gene transcription of vitamin D–responsive genes or that the high concentration of all vitamin D metabolites overwhelms the vitamin D–binding protein, leading to release of free $1,25(OH)_2D_3$, which then enters the cell and stimulates gene transcription.[99]

Pathology of Rickets

The characteristics of rickets are similar in all species. Lesions are typically most severe in the fastest-growing bones, including the radius, the tibia, and the metacarpals and metatarsals.[60,150] On radiographic and postmortem examination, widening of the physeal growth plate is the most archetypal change.[60,109,156] Other abnormalities seen radiographically may include metaphyseal flaring, thinning of the cortex, poor mineralization of the skeleton, and pathological fractures.[48,109,139,156] In addition, postmortem examination may reveal irregular thickening of the physeal cartilage, erosion of articular cartilage due to collapse of subchondral bone, and spontaneous fractures.[60,150,197] Enlargement of costochondral junctions, the so-called rachitic rosary, is also a classic lesion of rickets that may be seen on radiographic or postmortem examination.[60,139]

Impaired provisional calcification of cartilage at sites of endochondral ossification leads to the accumulation of hypertrophic chondrocytes, resulting in thickened and irregular growth plates with islands and tongues of chondrocytes extending into the metaphyses.[60,197,200] Similar changes occur beneath articular epiphyseal cartilage complexes in the expanding epiphyses of young animals.[200] Other microscopic changes may include thick osteoid seams lining trabeculae and disorganization or absence of the primary spongiosa.[150,160,200] One of the early pioneers of research into rickets, Sir Arnold Theiler, regarded the pathognomonic change as "the presence of osteoid tissue in quantities surpassing normal physiological limits."[198(p 1145)] Hemorrhage and signs of trauma may be seen in the metaphysis and primary spongiosa because of damage to weakened trabeculae of poorly mineralized bone.[16,200,201]

Rickets in Humans

Nutritional Causes

In the developed world, nutritional rickets has been reemerging as a disease problem; in Third World countries, it never went away and is thought to be one of the five most common diseases of children.[2,77] Medical writings from the first and second centuries described the classical bone deformities associated with rickets, and in the mid–17th century, Daniel Whistler and Francis Glisson wrote the first detailed medical reports.[158,165] It was not until the industrial revolution, however, that rickets became an epidemic.[158,165] In 1909, histological evidence of rickets was an incidental finding in 96% of children who died at less than 18 months of age.[165] At that time rickets was associated with heavy air pollution, urbanization, overcrowding, and inadequate diet.[158] Experimental work in the early 20th century confirmed the efficacy of the traditional remedy for treating rickets, cod liver oil, and eventually, vitamin D was named in 1922 as the agent responsible for preventing the disease.[158,165]

Rickets in humans is seen most commonly either during infancy or at puberty, corresponding to periods of maximal growth.[216] The common clinical signs in humans include craniotabes, skeletal deformities (eg, bowed or knock-kneed legs), rachitic rosary, delayed eruption of teeth, and enamel hypoplasia.[161,216] Low to normal calcium and phosphate concentrations, high PTH concentration, high alkaline phosphatase activity, low $25(OH)D_3$, and normal to high $1,25(OH)_2D_3$ concentrations (if adequate vitamin D is present) are typically seen in the serum of children with nutritional rickets.[109,161,216]

In developed countries, nutritional rickets is most often associated with exclusive breast-feeding.[34,157,158,204] Although vitamin D readily passes into it, breast milk is low in vitamin D (reported values of 4 to 40 IU/liter)[117,167] and does not supply an infant's daily requirements (200 to 400 IU/liter).[117,214] The vitamin D metabolites, $25(OH)D_3$ and $1,25(OH)_2D_3$, pass poorly into breast milk. Most breast-fed infants acquire vitamin D through sunlight exposure; however, this is affected by such factors as skin pigmentation,[87] the amount of skin exposed to sunlight,[138] air pollution,[1] latitude,[159,213] cloud cover,[214] and

sunscreen usage.[137] In a review of reports on nutritional rickets from 1986 to 2003 in the United States, 83% of children with rickets were African American or other dark-skinned races, and 96% were breast-fed.[214]

In the United Kingdom and Northern Europe, rickets is most common in infants and children of either Asian or Afro-Caribbean origin.[76,91,93,155] In these communities, risk factors include latitude, vegetarianism, consumption of chapattis or flatbread, traditional clothing, and social customs with limited exposure to sunlight.[8,155,158] Vegetarian diets and flatbreads typically contain high concentrations of phytates and dietary fiber, which may lead to vitamin D deficiency when combined with low calcium intake and limited exposure to the sun.[8,158]

The elderly and housebound are also at risk, and although clinical osteomalacia is not common in this age group, its $25(OH)D_3$ concentrations are frequently low.[22,140,215] Elderly people generally spend more time indoors, and aged human skin has reduced ability to produce vitamin D following exposure to ultraviolet light.[128]

Food allergies are considered a possible risk factor for nutritional rickets.[63,95] Allergies to hens' eggs, cows' milk, and peanuts are the most common and may lead to parents' giving their children diets that are nutritionally unbalanced.[63,151] Soy milk is a common substitute for cows' milk in allergic individuals, but it is low in calcium, phosphorus, magnesium, and vitamin D.[95] Such a diet is unsuitable as a complete food for infants and may lead to the development of rickets.[63,95] Gastrointestinal disease or cholestatic liver disease may also lead to the development of rickets and osteomalacia because of malabsorption, impaired 25-hydroxylase activity, changes in enterohepatic circulation, intestinal unresponsiveness to vitamin D, and excessive fecal loss of vitamin D.[134,181]

Genetic Causes

A number of heritable causes of rickets and osteomalacia have been identified and are most commonly due to a defect in either vitamin D metabolism or renal tubular function.[218]

Heritable diseases associated with renal phosphate wasting include X-linked hypophosphatemic rickets (XLH), autosomal dominant hypophosphatemic rickets, autosomal recessive hypophosphatemic rickets, and hereditary hypophosphatemic rickets with hypercalciuria.[58,168] These diseases, as well as tumor-induced osteomalacia, are characterized by hypophosphatemia, renal inorganic phosphate wasting, rickets, and inappropriately low to normal $1,25(OH)_2D_3$ concentrations.[14,168,218]

XLH has an X-linked dominant mode of inheritance, and with one in 20,000 people affected, it is the most common form of hereditary rickets in humans.[14] In addition to the microscopic changes of rickets, "halos" of unmineralized osteoid surround individual osteocytes (hypomineralized periosteocytic lesions), a lesion considered pathognomonic for this disease.[218] The genetic mutation that causes XLH has been isolated to the *PHEX* gene on chromosome 22 in the human genome.[47] *PHEX* stands for "phosphate-regulating gene with homologies to endopeptidases on the X-chromosome," and it produces a protein that has homology with membrane-bound metalloproteinases.[47,172] No single predominant mutation in *PHEX* causes XLH, and in mutational analysis of patients with XLH, 18 mutations in *PHEX* were found.[94] The mechanism by which PHEX mutations cause XLH has yet to be elucidated.[94] One hypothesis is that a circulating factor that is degraded or processed by PHEX influences phosphate reabsorption in the kidney. Candidates for the circulating factor are known as phosphatonins and include fibroblast growth factor 23 (FGF23), matrix extracellular phosphoglycoprotein, and secreted frizzled-related protein 4.[12,14,168] The mechanism of vitamin D dysfunction is unknown, although phosphatonins like FGF23 do inhibit $1,25(OH)_2D_3$ production.[176] A similar mechanism is behind tumor-induced osteomalacia in humans, where the production of the same phosphatonins by mesenchymal tumors (mixed connective tissue type) leads to renal phosphate wasting and osteomalacia.[12,62]

Autosomal dominant hypophosphatemic rickets is less common than XLH. Mutations in the gene for FGF23 on chromosome 12 are believed to be the cause of autosomal dominant hypophosphatemic rickets.[196] Such mutations induce loss of a cleavage site on FGF23, leading to an increase in its activity and consequent phosphaturia, hypophosphatemia, and rickets.[6,123,178]

Three families have been identified with autosomal recessive hypophosphatemic rickets.[166] The patients had renal phosphate wasting and elevated FGF23 concentrations.[126] Mutations were found in the gene for dentin matrix protein 1 (DMP1), a noncollagenous bone protein.[58,126]

Hereditary hypophosphatemic rickets with hypercalciuria is characterized by autosomal recessive inheritance and was first described in a Bedouin family.[205] In contrast to other hypophosphatemias, $1,25(OH)_2D_3$ is elevated, possibly explaining the hypercalciuria.[168,205] The disease occurs as a result of a single nucleotide deletion in the gene coding for the NaP_i-IIc protein (a renal Na-P_i cotransporter), truncating the protein in patients homozygous for the deletion.[11]

Vitamin D–dependent rickets type I (VDDR I) or pseudovitamin D–deficiency rickets is an autosomal recessive disorder caused by a failure to convert $25(OH)D_3$ to $1,25(OH)_2D_3$,[65] most likely because of a defect in renal 25-hydroxyvitamin D_3-1α-hydroxylase.[65,106] Affected individuals have normal serum $25(OH)D_3$ concentrations and low $1,25(OH)_2D_3$ concentrations.[218] The defect in VDDR I involves the *CYP27B1* gene (encoding 25-hydroxyvitamin D_3-1α-hydroxylase) on chromosome 12q13.3, and a number of mutations in the gene have been detected in affected individuals.[67,107,212,225]

Hereditary vitamin D–resistant rickets (HVDRR), or vitamin D–dependent rickets type II, was first described in 1978, with patients showing hypocalcemia, secondary hyperparathyroidism, and high serum $1,25(OH)_2D_3$ concentrations.[23,135] Patients were normal at birth owing to transplacental calcium flux between the mother and fetus, but skeletal changes and hypocalcemia were evident from 2 to 8 months of age.[122] Approximately 75% of affected individuals are born to consanguineous parents.[133] Partial to total alopecia—including eyebrows and, in some cases, eyelashes—is present in 70 to

Table 1. Selected Models of Metabolic Bone Disease in Mice and Rats[a]

Mouse Model	
Hyp[52]	
Human disease equivalent	X-linked hypophosphatemic rickets
Abnormalities	Hypophosphatemia, rickets, dwarfism, inappropriately normal plasma ($1,25(OH)_2D_3$), high fractional excretion of phosphate
Gy[127]	
Human disease equivalent	X-linked hypophosphatemic rickets
Abnormalities	Hypophosphatemia, rickets, circling, inner ear abnormalities, increased plasma ($1,25(OH)_2D_3$), increased renal phosphate loss
FGF23 knockout[177]	
Abnormalities	Growth retardation, shortened life span, hyperphosphatemia, increased renal phosphate reabsorption, increased plasma ($1,25(OH)_2D_3$), focal osteomalacia
1α-hydroxylase knockout[38,153]	
Human disease equivalent	Vitamin D–dependent rickets type I
Abnormalities	Rickets, growth retardation, hypocalcemia, low plasma ($1,25(OH)_2D_3$), high plasma ($25(OH)D_3$), hyperparathyroidism
VDR null or $VDR^{-/-}$[26,121]	
Human disease equivalent	Hereditary vitamin D–resistant rickets
Abnormalities	Alopecia, rickets, hypocalcemia, hypophosphatemia, hyperparathyroidism
VDR/RXR_γ knockout[223]	
Abnormalities	Growth retardation, rickets, more severe bone abnormalities than $VDR^{-/-}$, hypocalcemia, alopecia
Cyp24a1 (24-hydroxylase) knockout[188]	
Abnormalities	Death of 50% of progeny at less than 3 weeks because of high plasma ($1,25(OH)_2D_3$) and hypercalcemia, accumulation of unmineralized osteoid at sites of intramembranous ossification
24-hydroxylase transgenic rats[103]	
Abnormalities	Constitutive expression of 24-hydroxylase, albuminuria, hyperlipidemia, atherosclerosis, urinary loss of vitamin D–binding protein and 25(OH)D, decreased plasma ($24,25(OH)_2D_3$)
DMP1 knockout	
Human disease equivalent	Autosomal recessive hypophosphatemic rickets
Abnormalities	Rickets, osteomalacia, elevated fibroblast growth factor 23, hypocalcemia, hypophosphatemia, inappropriately normal plasma ($1,25(OH)_2D_3$), mineralization defects, defective osteoblast to osteocyte differentiation and maturation
Vitamin D–binding protein knockout[173]	
Abnormalities	On a vitamin D–replete diet, mice are normal; on a vitamin D–deficient diet, mice develop secondary hyperparathyroidism and rickets; and on a diet excessive in vitamin D, mice are resistant to the development of hypercalcemia.
Ca^{2+}-sensing receptor knockout[70]	
Abnormalities	Rickets, dwarfism, hypercalcemia, hypophosphatemia, hyperparathyroidism

[a] VDR, vitamin D receptor; RXR, retinoid X receptor.

80% of affected individuals.[133] The disease occurs because of either hormone-binding defects or DNA-binding defects of the VDR.[133] A third group of defects was originally thought to comprise defective receptor translocation to the nucleus,[80,217] but recent work has shown that this defect is the result of constitutive overexpression of heterogeneous nuclear riboprotein and its competition with the VDR-RXR complex for binding to the VDRE.[31,32]

Animal Models of Rickets

A number of mouse models have been discovered or created to study human skeletal diseases. Table 1 summarizes some of these, with a selection of other models that have been created to study the function of different hormones and proteins involved in skeletal homeostasis.

Mouse Models

Two naturally occurring models of hypophosphatemic rickets due to renal phosphate wasting have been described in mice: the Gy mouse and Hyp mouse.[52,127] Both are characterized by hypophosphatemia, rickets, normal to high $1,25(OH)_2D_3$, and increased renal phosphate loss. The Gy mouse also has inner ear abnormalities that lead to circling.[127] The phenotype

observed in the Hyp mouse is the result of excessive FGF23 concentrations due to inactivating mutations in *PHEX*.[124]

Four strains of *VDR* null mice have been developed. The Tokyo strain has exon 2 of the *VDR* gene removed (exon 2 encodes the first of two zinc fingers involved in DNA binding),[26] and the Boston strain has exon 3 removed (which encodes the second zinc finger).[121] Two other strains also have a missing first zinc finger.[54,208] The disease in all strains is phenotypically similar to HVDRR in humans.[26] Affected mice are normal at birth but become hypocalcemic and hypophosphatemic and develop hyperparathyroidism by 21 days of age.[121] The *VDR*-null mice develop rickets and osteomalacia by day 35.[121] *VDR*-null mice also develop progressive alopecia, commencing at around 4 weeks of age and becoming complete by 100 days.[41,121] *VDR*-null mice fed a diet high in calcium (2.00%), phosphorus (1.25%), and lactose from day 18, before the development of serum biochemical changes, do not develop rickets and osteomalacia but still become alopecic,[120] which suggests that the VDR is not required for the prevention of hyperparathyroidism or for normal skeletal homeostasis.[41]

The *DMP1*-knockout mouse is a model for autosomal recessive hypophosphatemic rickets. These mice have renal phosphate wasting, elevated FGF23, and inappropriately normal serum $1,25(OH)_2D_3$ concentrations.[58,126] DMP1 is thought to promote mineralization of osteoid, and it may be required for differentiation of osteoblasts into osteocytes.[58] DMP1 also leads to upregulation of FGF23 by an unknown pathway.[125]

Nonhuman Primates

New World monkeys may also be used as a model for HVDRR. The marmoset (*Callithrix jacchus*) in particular requires a diet high in vitamin D_3 for normal growth. Concentrations of $1,25(OH)_2D_3$ in marmosets are 4 to 10 times higher than those in rhesus monkeys or humans, suggesting relative end-organ resistance to $1,25(OH)_2D_3$.[179,224] Recent evidence has suggested that this resistance to $1,25(OH)_2D_3$ in marmosets is not due to the VDR but instead to overexpression of a VDR-independent VDRE-binding protein, which interferes with vitamin D–regulated transactivation.[33,35] Marmosets also have high circulating glucocorticoid concentrations and are resistant to high levels of glucocorticoids, suggesting that the species may be resistant to a variety of steroid hormones, not just $1,25(OH)_2D_3$.[179]

Sheep and Goats

Rickets is uncommon in sheep, and until recently, all reported cases had been nutritional in origin. Fitch and Ewer both performed extensive investigations into rickets in sheep in the 1940s and 1950s.[57,59-61] In New Zealand, rickets occurred most commonly in the South Island in winter, in association with the feeding of greenfeed oats to growing lambs approaching 1 year of age. Although calcium and phosphorus levels were adequate,[57] the crops contained high concentrations of carotene, which has been shown to antagonize the action of vitamin D on the intestine and bone.[74,97,169] Although rickets is most common in sheep fed cereal crops, the disease may occur in lambs grazing pasture, Italian ryegrass, choumoellier, and turnips.[57] Such feeds also have high concentrations of carotenes; however, cereal crops may be more rachitogenic because of the higher availability of carotene.[74]

Naturally occurring rickets is also uncommon in sheep in the United Kingdom,[16,55,142,150] but outbreaks associated with high latitude, low sunshine hours, and poor-quality pasture low in phosphorus have occurred in Scotland.[16,150] In Ireland, rickets has occurred in sheep fed oats in winter months and, in northern England, in sheep grazing lush ryegrass swards over winter, most likely because of the rachitogenic effect of carotenes.[37,142]

Clinical signs of rickets in sheep include stiff gait, lameness, enlarged joints (particularly, the radiocarpal), bowed or bent legs, and loss of condition or poor weight gain.[16,37,48,56,60,150,210] Rickets is most commonly seen in recently weaned animals because of the rapid growth at this age and their dependence on pasture or crops.[16,150]

Sheep have a seasonal trough in serum 25(OH)D concentrations in late winter, owing to fleece cover and reduced exposure to ultraviolet light.[184] This is exacerbated by the demands of pregnancy.[184,185] The serum vitamin D concentration of lambs has been shown to be closely related to the vitamin D concentration of the dam.[184,185] Lambs at 3 to 4 weeks predominantly rely on milk, which may have low vitamin D concentrations if the vitamin D status of the dam is inadequate.[210]

An unusual outbreak of rickets was described in lambs of 3 to 4 weeks of age in Oregon.[210] Because ewes' milk may be low in vitamin D, vitamin D deficiency was considered the most likely cause of the outbreak. Although rickets was not confirmed histologically, the clinical signs, low 25(OH)D concentrations, and positive response to treatment with cholecalciferol suggest that vitamin D deficiency was the likely cause of the bone deformities.[210]

Skeletal lesions resembling rickets were reported in goat kids fed artificial milk intended for calves on a large commercial farm in the Netherlands.[42] Physeal changes were not present microscopically, but the authors described broad osteoid seams in the primary and secondary spongiosa. The synthetic calf milk had a calcium:phosphorus ratio of 0.83:1.00, which was considered low. Given the absence of growth plate changes in this case and the adequate phosphorus concentration of the diet, a diagnosis of nutritional secondary hyperparathyroidism should be considered. Formation of poorly mineralized woven bone is a feature of fibrous osteodystrophy and may resemble osteoid seams in some circumstances.[200]

Recently, a form of rickets with autosomal recessive inheritance has been described in Corriedale sheep from New Zealand.[44,46,202] The clinical signs resembled rickets in other species and included decreased growth rate, thoracic lordosis, and angular limb deformities. Lesions at necropsy included segmental thickening of the physes, collapse of subchondral bone of the humeral head (Fig. 2), thickened cortices, and enthesophytes around distal limb joints.[46,202]

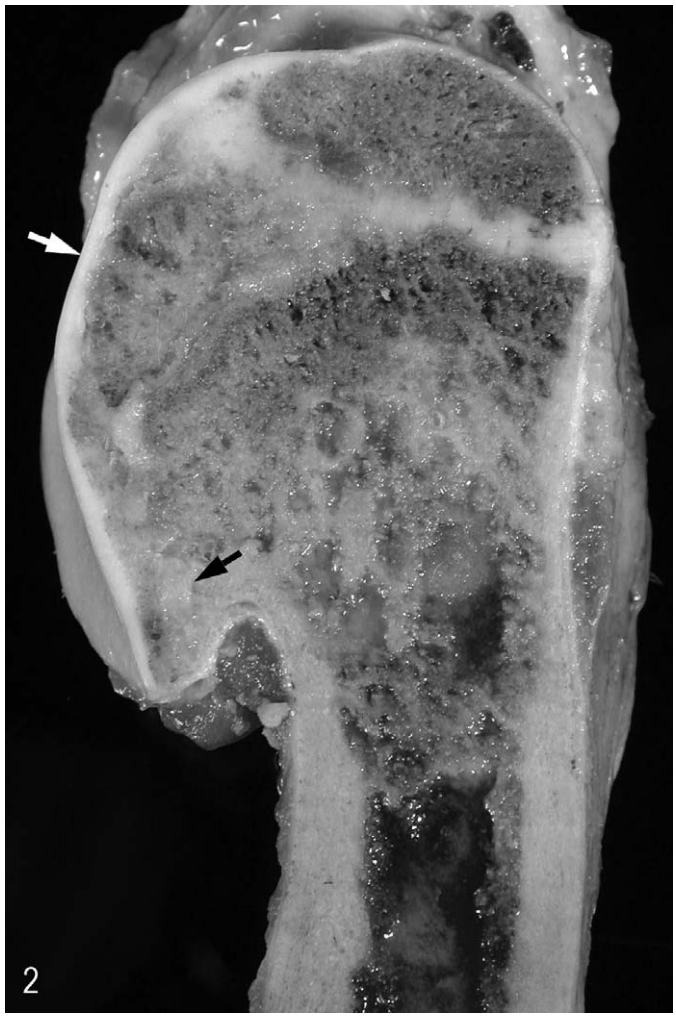

Figure 2. Proximal humerus; 1-year-old Corriedale sheep with inherited rickets, showing flattening of the humeral head and separation of articular cartilage from collapsed subchondral bone (white arrow). Also note the segmental thickening of the physis (black arrow), thickened metaphyseal trabeculae, and thickened cortices.

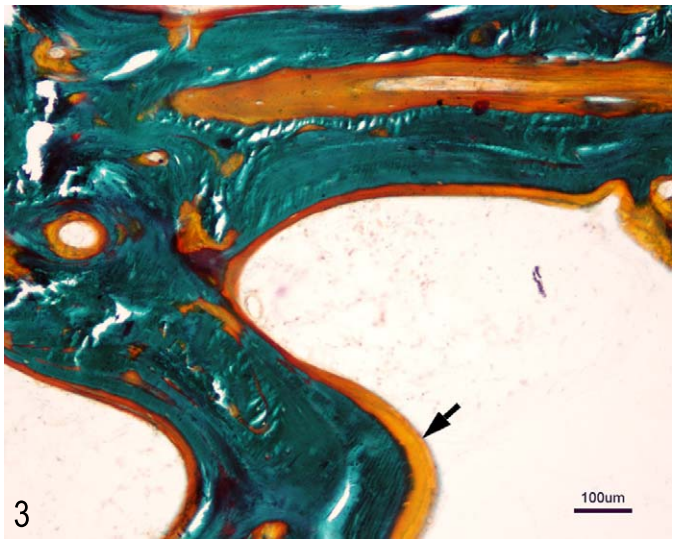

Figure 3. Rib; 2-year-old Corriedale sheep with inherited rickets, showing unmineralized osteoid seams lining trabeculae (black arrow) and cortical resorption cavities. Goldner's trichrome method. Bar = 100 μm.

Microscopically, there was persistence of hypertrophic chondrocytes at sites of endochondral ossification, inappropriate and excessive osteoclastic resorption, microfractures, and wide unmineralized osteoid seams lining trabeculae (Fig. 3) and filling secondary osteons.[46] Although initial biochemistry results suggest a defect in the VDR analogous to HVDRR of humans,[202] subsequent in vitro studies on cultured skin fibroblasts showed that the VDR was normal. The genetic defect in Corriedale sheep may be different from those currently described in humans and animals to date.

Cattle

There are few published reports of naturally occurring rickets in cattle, and no inherited forms have been described. The earliest published investigations on rickets and osteomalacia in cattle were conducted by Sir Arnold Theiler and colleagues in South Africa.[198,199] In their studies, phosphorus deficiency was shown to be the basis of a syndrome characterized by osteophagia, stiff gait, lameness, swollen joints, and sometimes spontaneous fracture.[198] Vitamin D deficiency was not considered a contributing factor, because of the abundant sunshine available in South Africa.[198] A similar syndrome reported in the Northern Territory of Australia was referred to as *stiffs, creeps*, or *peg-leg*. The disease occurred during periods of drought; osteophagia was a feature; and phosphorus deficiency was considered the cause.[170]

Cattle are considered more susceptible than sheep to phosphorus deficiency.[200] In a 10-year trial investigating the effect of phosphorus deficiency in cattle, the main skeletal changes were osteoporosis and osteomalacia.[180] When dietary phosphorus was less than 6 g per day, loss of body condition occurred, as did lameness, abnormal stance, spontaneous fractures, reproductive failure, and hypophosphatemia. Clinical recovery occurred within 6 months once the dietary phosphorus deficiency was corrected.[180]

One published report involved 4 yearling bullocks housed inside and fed oats, sugar beet pulp, barley, hay, and raw potatoes.[186] The cows on the farm also showed signs of fluorosis, which may have contributed to the development of rickets in the yearlings. Fluoride stimulates bone formation, increasing skeletal demand for calcium and perhaps exacerbating vitamin D deficiency.[105,112] Rickets has also been reported in children in areas of India with water containing high fluoride levels.[105]

A similar skeletal disease was reported in Sweden, in fattening bulls kept indoors and fed a concentrated diet with high levels of phosphorus.[101] The clinical, biochemical,

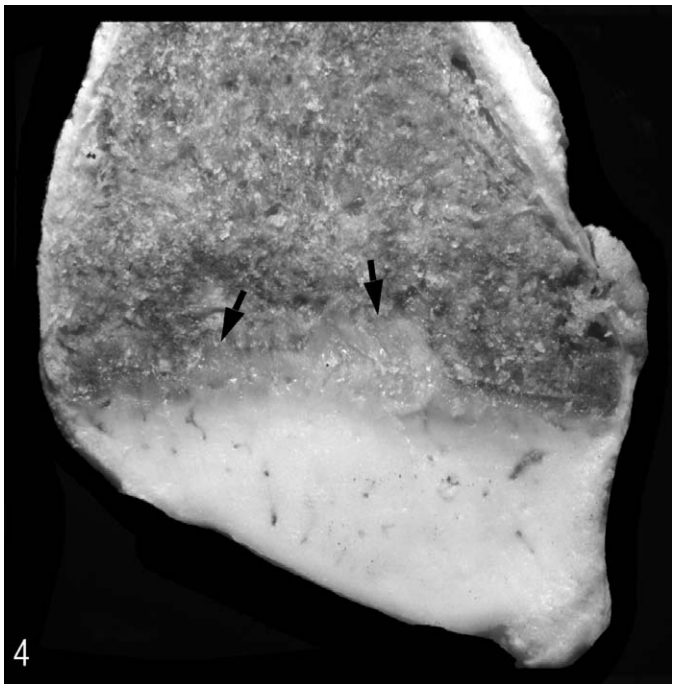

Figure 4. Costochondral junction; 1-year-old steer with tongues of cartilage (black arrows) extending into the metaphysis of a costochondral junction.

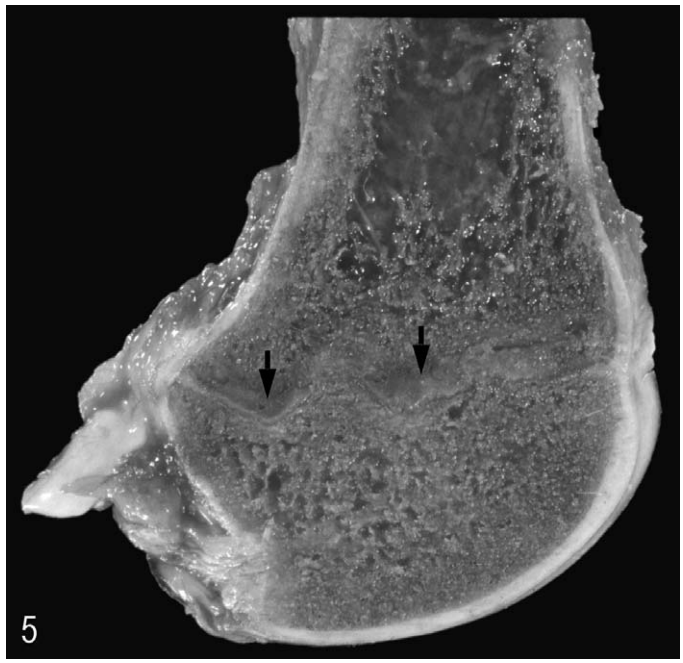

Figure 5. Distal femur; 5-month-old alpaca with rickets, showing segmental physeal thickening (black arrows).

and radiological changes were consistent with rickets, and histologically there were features of fibrous osteodystrophy and rickets. This combination would be expected in vitamin D deficiency, which leads to low calcium and subsequent secondary hyperparathyroidism.

In New Zealand, rickets was reported in yearling Angus steers fed a swede crop over winter. Affected cattle had poor growth rate and lameness that became severe when moved from the crop onto hill country grazing land.[201] Steers developed vertebral fractures leading to posterior paralysis, and rickets (Fig. 4) was confirmed histologically.[201] The phosphorus concentration of the crop, when combined with the low dry matter content, was inadequate to supply daily phosphorus requirements.[201]

Llamas and Alpacas

Since being transported from the Andes to other parts of the world, llamas and alpacas have been found to be highly susceptible to rickets. A peak in the incidence of rickets in crias occurs from January to March in the Northern Hemisphere.[211] In this study, crias born in autumn/winter had lower vitamin D concentrations and were more likely to develop rickets than were those born in summer.[211] The reason may be that these animals receive less vitamin D via the placenta or colostrum because of the low level of solar radiation at that time of year,[182] and a young cria's diet consists substantially of milk, which is low in vitamin D.[211] Interestingly, alpacas appear to be more susceptible to rickets than sheep. In an outbreak in New Zealand, alpacas became hypophosphatemic and developed rickets during winter months (Fig. 5), whereas lambs grazing the same pasture with the alpacas showed no signs of phosphorus deficiency.[82]

Horses

Rickets is rare in horses and appears to occur less frequently than in other domestic species.[53] Experimentally, Shetland ponies deprived of sunlight and dietary vitamin D showed irregularly widened physes on radiographs, consistent with rickets.[53] Compared to other animal species, horses have higher serum calcium concentrations and lower serum 25(OH)D and $1,25(OH)_2D_3$ concentrations.[20,131,183] In fact, the vitamin D metabolite concentrations—25(OH)D and $1,25(OH)_2D_3$—in horses are lower than those at which rickets occurs in other animals,[20] suggesting a species variation and perhaps indicating different mechanisms for calcium and phosphate metabolism in horses. This is possibly reflected in the fact that a large proportion of calcium in the horse is excreted via the kidney into the urine, as evidenced by the large amount of calcium carbonate crystal present in the urine of horses.[51]

Pigs

Piglets grow rapidly and are weaned early, making them susceptible to rickets if their diet contains inadequate vitamin D.[200] In intensive pig farming where animals are housed in a controlled environment, vitamin D requirements of the pig are usually supplied by the diet.[200]

An outbreak of rickets affecting 82 pigs was described on a small fattening unit in Scotland.[156] The pigs were emaciated and had difficulty rising; they also had bowed forelegs, joint swellings, and pain on moving. Folding and erosion of articular cartilage and enlargement of long bone metaphyses and costochondral junctions were seen radiographically and during postmortem examination.[156] Microscopic changes were consistent with rickets and nutritional secondary hyperparathyroidism.[156] A similar case was reported on a semi-intensive pig farm in New Zealand where the pigs were fed a diet with no vitamin supplement.[203] A combination of nutritional secondary hyperparathyroidism and rickets were seen histologically, with myelofibrosis and multifocal thickening of physes.[203] No further cases were seen once fat-soluble vitamins (including vitamin D) were added to the diet.[203]

A genetic form of rickets similar to VDDR I in humans was originally described in pigs in 1962, and a strain (the Hannover) was bred with the syndrome. Pigs affected with VDDR I are used as a model for the same disease in humans.[64] From 3 to 8 weeks of age, piglets with VDDR I develop progressive hypocalcemia and hypophosphatemia, leading to secondary hyperparathyroidism and rickets.[64,219] Concentrations of $1,25(OH)_2D_3$ in the blood were low but significantly above zero, whereas concentrations of $25(OH)D_3$ and PTH were high.[64,104,219] Calcium-binding protein concentrations in the plasma and intestine were reduced, and no 25-hydroxyvitamin D_3-1α-hydroxylase and 24-hydroxylase activity was found in renal homogenates.[64]

At the molecular level, VDDR I in the Hannover pig is associated with one of two different deletions in the *P450C1* coding region.[30] One involves a deletion of 173 base pairs and the other, a deletion of 329 base pairs, both of which lead to a frame shift mutation and a premature stop codon.[30] The result produces conformational changes that make the enzyme ineffectual owing to loss of the heme-binding region and other domains.[30] The authors hypothesized that a mRNA processing error may have caused the deletions, given that they occurred at mRNA processing sites.[30]

Dogs

There are few reports of naturally occurring rickets in dogs and cats, and the disease is considered rare.[10] Carnivores are unlikely to suffer from phosphorus deficiency given that phosphorus concentrations in meat are relatively high, and although they may not manufacture vitamin D in their skin, adequate levels of which are added to commercial rations.[92,145,200] Dogs and cats fed predominantly meat- or offal-based rations without vitamin D supplements develop fibrous osteodystrophy rather than rickets, owing to nutritional secondary hyperparathyroidism.[200]

In the last 20 years, there have been three reports of rickets in dogs from Australia. Two involved litters of Greyhound pups and the other, a 12-week-old Collie.[118,132] The Collie and one litter of Greyhounds were reared on a diet of milk and meat. The other Greyhound litter had an unreliable dietary history.[118,132] The age at presentation ranged from 10 weeks for the Collie to 14 weeks for one of the Greyhound litters.[118,132] Clinical signs and radiographic changes in all dogs were considered to be consistent with rickets, but the diagnosis was not confirmed histologically. Serum 25(OH)D concentrations were measured in one Greyhound litter and found to be low.[132] The low concentration of vitamin D in milk, with the low maternal vitamin D status and the rapid growth of Greyhound pups, is thought to have predisposed these litters to rickets,[132] but the possibility of fibrous osteodystrophy due to nutritional secondary hyperparathyroidism, either as an associated or a primary problem, was not excluded.

Rickets was reported in a Shetland Sheepdog diagnosed with acute renal failure at 10 weeks of age and fed a low phosphate renal failure diet.[141] Ten weeks later, the dog presented with varus deformities of the forelimbs, failure to grow, and prominent metaphyses, and radiographically, it had widened physes.[141] The renal failure diet had low protein and phosphate levels, which were inadequate for growth. Replacement of the diet with one specific for growing puppies led to resolution of clinical signs.[141]

In a recent report, VDDR I and suspected nutritional secondary hyperparathyroidism were diagnosed in an 8-month-old Shetland Sheepdog with diffuse osteopenia and myelopathy fed an organic premix and raw ground beef.[195] The term *vitamin D–dependent rickets type I* was used incorrectly in this case, given that this form of rickets is associated with a genetic defect in the activity of renal 1α-hydroxylase, rather than with a deficient diet. Rickets was diagnosed on the basis of low normal 25(OH)D,[45] but no growth plate changes were present radiographically,[195] so nutritional secondary hyperparathyroidism by itself may have been a more appropriate diagnosis.[45]

HVDRR has been recently reported in a Pomeranian dog[119] that had hypocalcemia, hyperparathyroidism, and skeletal abnormalities consistent with rickets. The dog's serum 25(OH)D was low, whereas $1,25(OH)_2D_3$ was increased, suggesting a VDR defect. In this case, a frame shift mutation was found in the VDR, which lead to a premature stop codon and termination of protein translation.[119]

A possible inherited form of VDDR I was diagnosed in a Saint Bernard in Australia.[98] Serum calcium concentration was within normal limits; phosphorus concentration was low; and plasma PTH concentration was increased. Radiographs showed changes consistent with rickets. The authors considered a 25-hydroxyvitamin D-1α-hydroxylase enzyme deficiency to be the most likely cause of the clinical signs seen in this dog,[98] but serum 25(OH)D and $1,25(OH)_2D_3$ concentrations were not measured and a diagnosis of VDDR I was not confirmed.

Cats

Naturally occurring rickets is rare in cats. Cats experimentally fed a vitamin D–deficient diet developed clinical signs of rickets after 4 and 5 months.[4] The diagnosis of rickets was not confirmed histologically and was based on radiographic changes and increased serum alkaline phosphatase concentrations, which are not specific for rickets.

There has been one confirmed report of VDDR I and several reports of possible HVDRR in cats,[71,72,79,175,194] but the diagnosis has not always been supported by adequate biochemical data or histology. In one case, confirmation of a diagnosis of HVDRR was obtained with skin biopsies for fibroblast culture to examine $1,25(OH)_2D_3$ receptor binding, but genetic analysis was not performed.[72] A 731delG mutation in the *CYP27B1* (1α-hydroxylase) gene was detected in the case of VDDR I.[71] Other reported cases appeared similarly. Most affected kittens presented at around 4 months of age, perhaps reflecting the time required for kittens born with normally mineralized bones to develop signs of vitamin D deficiency.[83] This assumes that transplacental calcium transport in cats does not require vitamin D. The kittens showed different responses to treatment, as seen in humans with HVDRR, presumably due to different defects in the VDR.[133]

Reptiles

Metabolic bone disease is common in captive reptiles and typically manifests as a combination of fibrous osteodystrophy and osteomalacia in young actively growing animals.[36,129,130] Factors associated with metabolic bone disease include dietary calcium deficiency, unbalanced calcium:phosphorus ratio in the diet, or inadequate exposure to ultraviolet light, leading to vitamin D deficiency.[130]

The vitamin D endocrine system of reptiles appears to be similar to that of mammals.[114] In the wild, reptiles have ample opportunity for sun basking, but in captivity, they may not have adequate exposure to natural light—for instance, iguanas held under ultraviolet lamps were shown to possess lower plasma vitamin D concentrations than iguanas exposed to natural light.[116] The materials of the cage in which reptiles are kept may also attenuate ultraviolet light from lamps or natural light to below wavelengths required for vitamin D synthesis in the skin.[27] In the wild, reptiles alter their basking time, not only for thermoregulatory reasons, but also because of the vitamin D content of their diet.[102] Chameleons given a diet low in vitamin D spent increased time basking compared to those fed a diet with adequate vitamin D.[102]

Conclusion

Vitamin D is intimately involved in calcium and phosphate homeostasis, and it plays a crucial role in bone formation and remodeling. Deficiency of vitamin D in its active form, whether due to environmental or genetic factors, may result in rickets or osteomalacia secondary to hypocalcemia and hypophosphatemia. The hypocalcemia may also lead to hyperparathyroidism and concurrent fibrous osteodystrophy.

Although the gross and histologic lesions of rickets are characteristic, many reports of this disease in domestic animals are based on clinical signs and radiology and are thus questionable. Osteomalacia may be underdiagnosed in domestic animals because of the insensitivity of radiographs and an inability to reliably detect bone pain. It is important that veterinary pathologists be aware of variations among species in their susceptibility to rickets and osteomalacia and thereby use objective criteria to confirm diagnoses.

Although vitamin D has long been recognized for its role in preventing rickets and osteomalacia in people and domestic animals, recent research has indicated that it may have important roles beyond the maintenance of a healthy skeleton. There is considerable potential for new and existing animal models to reveal further information about vitamin D metabolism and to investigate its possible involvement in immunity and cancer prevention.

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